

Cardiology Research Review™

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Issue 43 - 2011

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Welcome to the latest issue of Cardiology Research Review.

Highlights this month include a finding that lower salt intake is associated with higher cardiovascular mortality. If confirmed, current recommendations for salt intake in the general population may need rethinking. We also report research that validates the recommendation that most patients with valvular heart disease don't need prophylactic antibiotics for dental surgery. And a sigh of relief for ARB advocates, we've included a large meta-analysis that refutes the concern that they increase the risk of MI.

We hope you find this issue interesting and look forward to hearing your comments.

Kind regards,

Associate Professor John Amerena
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Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion

Authors: Stolarz-Skrzypek K et al for the European Project on Genes in Hypertension (EPOGH) Investigators

Summary: This population-based cohort study examined the association between urinary sodium excretion and various health outcomes. 3681 individuals without cardiovascular disease (CVD) were followed for a median 7.9 years; 2096 participants were normotensive at baseline. The CVD death rate during follow-up decreased with increasing tertiles of 24-h urinary sodium excretion: 4.1% in the low (mean 107 mmol/24h), 1.9% in the medium (mean 168 mmol/24h), and 0.8% in the high excretion group (mean 260 mmol/24h; $p < 0.001$ for trend). This inverse association remained significant in multivariable-adjusted analyses. Baseline sodium excretion was not predictive of total mortality or fatal plus nonfatal CVD events. The rate of incident hypertension during follow-up was 27.0% in the low, 26.6% in the medium, and 25.4% in the high sodium excretion group. Multivariable-adjusted analyses showed that a 100-mmol increase in sodium excretion during follow-up was associated with a 1.71mm Hg increase in SBP ($p < 0.001$) but no change in DBP. In conclusion, lower sodium excretion was associated with higher CVD mortality in this cohort study.

Comment: The relationship between increased salt and changes in SBP is well established but that increased salt intake does not increase the risk of HT was unexpected in this study. It was also unexpected that the lowest sodium intake was associated with the highest CV mortality which supports the long held belief by Laragh et al. that high renin states increase CV risk. If these provocative findings can be reproduced it may dramatically change our recommendations about salt intake for the general population.

Reference: JAMA 2011;305(17):1777-1785
<http://jama.ama-assn.org/content/305/17/1777.abstract>

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Patterns and intensity of medical therapy in patients undergoing percutaneous coronary intervention

Authors: Borden W et al

Summary: This observational study investigated the impact of the COURAGE trial findings on the use of optimal medical therapy (OMT; antiplatelet agent, β -blocker and statin) in patients with stable angina undergoing PCI. Of 467,211 patients evaluated, 37.1% underwent PCI before and 62.9% underwent PCI after publication of the COURAGE trial. 44.2% of patients received OMT before PCI and 65.0% of patients received OMT at discharge after PCI ($p<0.001$). OMT was used prior to PCI in 43.5% of patients before COURAGE and 44.7% of patients after COURAGE. The use of OMT at discharge after PCI was 63.5% before COURAGE and 66.0% after COURAGE. In conclusion, OMT practice patterns in patients with stable CAD undergoing PCI changed little after publication of the COURAGE trial.

Comment: The COURAGE trial showed that a trial of optimal medical therapy in patients with stable CAD was reasonable as there was no mortality disadvantage in delaying PCI. In the US it appears that these findings were not taken up widely as the use of even a liberal definition of OMT in patients undergoing PCI did not change after publication. It would be interesting to see if this pattern was also seen in Australia where perhaps there is a less aggressive approach to PCI.

Reference: *JAMA* 2011;305(18):1882-1889
<http://jama.ama-assn.org/content/305/18/1882.abstract>

Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study

Authors: Thornhill M et al

Summary: In 2008 the National Institute for Health and Clinical Excellence (NICE) released a guideline recommending the cessation of antibiotic prophylaxis before invasive dental procedures for patients at risk of infective endocarditis. This study evaluated the impact of the NICE guideline. When prescribing data for the 12 months before the introduction of the guideline were compared with prescribing data for the period 14–25 months after the introduction of the guideline, antibiotic prophylaxis prescriptions decreased from a mean 10,277 prescriptions per month to a mean 2292 prescriptions per month (-78.6% ; $p<0.001$). There was no evidence of a significant change in the trend in the number of deaths from infective endocarditis seen prior to the guideline. In conclusion, prescribing of antibiotic prophylaxis fell by 78.6% after introduction of the NICE guideline but was not accompanied by a large increase in the incidence of infective endocarditis.

Comment: The recommendation that most patients with valvular heart disease do not need prophylactic antibiotics for dental surgery was received with a large degree of scepticism as this was entrenched in the medical literature. It appears that this policy has been implemented widely in the UK without an increase in endocarditis, reinforcing the validity of this advice although on-going surveillance would be prudent.

Reference: *BMJ* 2011;342:d2392
<http://www.bmj.com/content/342/bmj.d2392.full.pdf>

Cardiology Research Review

Independent commentary by Associate Professor John Amerena, Cardiologist and Director of the Geelong Cardiology Research Unit.



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Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials

Authors: Bangalore S et al

Summary: This meta-analysis and trial sequential analysis (TSA) evaluated cardiovascular outcomes associated with angiotensin receptor blockers (ARBs). A literature search for randomised clinical trials of ARBs (compared with placebo or active treatment) that enrolled at least 100 patients for at least 1 year found 37 trials (n=147,020) with a total follow-up of 485,166 patient-years. Pooled data analysis found that ARBs did not increase the risk of MI, death, cardiovascular death, or angina pectoris when compared with controls, but reduced the risk of stroke (relative risk [RR] 0.90, 95% CI 0.84–0.98), heart failure (RR 0.87, 95% CI 0.81–0.93), and new onset diabetes (RR 0.85, 95% CI 0.78–0.93). TSA showed firm evidence for relative risk reduction of stroke (mean 10%) vs placebo only, and a relative risk reduction of heart failure (mean 10%) and new onset diabetes (mean 10%) vs controls (placebo/active treatment). In conclusion, this analysis refutes the hypothesis that ARBs increase the risk of MI and shows that, compared with controls, ARBs reduce the risk of stroke, heart failure, and new onset diabetes.

Comment: There has been lingering concern that ARBs increase the risk of MI since the initial papers that raised this concern several years ago. This large meta-analysis effectively refutes this and supports the large clinical benefit seen with this class in numerous clinical trials.

Reference: *BMJ* 2011; 342:d2234
<http://www.bmj.com/content/342/bmj.d2234.abstract>

Proton pump inhibitor use and risk of adverse cardiovascular events in aspirin treated patients with first time myocardial infarction: nationwide propensity score matched study

Authors: Charlot M et al

Summary: This retrospective study investigated the risk of adverse cardiovascular events associated with proton pump inhibitors (PPIs) in patients taking aspirin for first time MI. Administrative data from all hospitals in Denmark were reviewed for all aspirin-treated patients who survived 30 days after a first MI between 1997 and 2006. Clopidogrel recipients were excluded. The combined endpoint (recurrent MI, stroke or cardiovascular death) occurred in 16.9% of 19,925 patients reviewed. In patients who received a PPI, the hazard ratio for the combined endpoint was 1.46 (95% CI 1.33–1.61; p<0.001) based on the time dependent Cox proportional hazard model and 1.61 (95% CI 1.45–1.79; p<0.001) based on the propensity score matched model. In conclusion, treatment with a PPI was associated with an increased risk of adverse cardiovascular events in patients taking aspirin for first time MI.

Comment: It has been postulated that some PPIs reduce the effect of clopidogrel in secondary prevention after ACS due to competition for metabolism by the CYP system, but this is still controversial. This is the first report that suggests that there is an adverse interaction between PPIs and aspirin, which is not metabolised by the cytochrome system, implying perhaps that PPIs have an adverse effect in their own right. Until more information is available it would be wise to only use PPIs after ACS when there is a definite indication rather than for prophylaxis.

Reference: *BMJ* 2011;342:d2690
<http://www.bmj.com/content/342/bmj.d2690.full.pdf>

Randomized trial of stents versus bypass surgery for left main coronary artery disease

Authors: Park S-J et al

Summary: This study compared the use of PCI and CABG for left main CAD. 600 patients with unprotected left main coronary artery stenosis were randomised 1:1 to undergo CABG or PCI with sirolimus-eluting stents and were followed for 2 years. After 1 year, the primary composite endpoint of major adverse cardiac or cerebrovascular events occurred in 26 patients in the PCI group and 20 patients in the CABG group (cumulative event rate, 8.7% vs 6.7%; absolute risk difference, 2.0 percentage points; 95% CI -1.6 to 5.6; p=0.01 for noninferiority). After 2 years, cumulative event rates were 12.2% and 8.1% in the respective groups (hazard ratio with PCI, 1.50; 95% CI 0.90–2.52; p=0.12). Ischaemia-driven target-vessel revascularisation was more common in the PCI group (cumulative event rate 9.0% vs 4.2%; hazard ratio 2.18; 95% CI 1.10–4.32; p=0.02). In conclusion, PCI with sirolimus-eluting stents was noninferior to CABG with respect to major adverse cardiac or cerebrovascular events in patients with unprotected left main coronary artery stenosis, but the noninferiority margin was too wide for the results to be clinically directive.

Comment: Despite the authors claiming noninferiority for unprotected LM stenting compared with surgery in this small study, there were strong trends in the wrong direction for MACE and ischaemia driven revascularisation in the stenting group at 1 and 2 years after the procedure. Bypass surgery should still be the first choice for LM disease with stenting considered only for patients unfit for an operation.

Reference: *N Engl J Med* 2011;364:718-1727
<http://www.nejm.org/doi/full/10.1056/NEJMoa1100452>

Effects of sugar-sweetened and sugar-free cocoa on endothelial function in overweight adults

Authors: Njike V et al

Summary: This study evaluated the effects of daily intake of sugar-free and sugar-sweetened cocoa beverages on endothelial function in overweight volunteers. 44 adults (BMI 25–35 kg/m²) were randomised to a treatment sequence comprising sugar-free cocoa beverage, sugar-sweetened cocoa beverage, and sugar-sweetened cocoa-free placebo. Each beverage was administered daily for 6 weeks, separated by a 4-week washout period. Compared with placebo, sugar-free cocoa improved flow-mediated dilation (FMD) by 3.2% (95% CI 1.8–4.6; p<0.001) and sugar-sweetened cocoa improved FMD by 2.3% (95% CI 0.9–3.7; p=0.002). The improvement in FMD tended to be greater after consumption of sugar-free versus sugar-sweetened cocoa. Cocoa ingestion had no effects on other biomarkers of cardiac risk and did not alter BMI. In conclusion, daily cocoa ingestion improves endothelial function without affecting other markers of cardiac risk.

Comment: There has been great interest in the lay press as to the cardiovascular benefits of chocolate, whose principle ingredient is cacao. This interesting study suggests a mechanism by which cacao consumption improves vascular function, although it appears the beneficial effect on endothelial function may be attenuated by sucrose.

Reference: *Int J Cardiol* 2011;149(1):83-88
<http://dx.doi.org/10.1016/j.ijcard.2009.12.010>

Novel antiplatelet drug revacept (dimeric glycoprotein VI-Fc) specifically and efficiently inhibited collagen-induced platelet aggregation without affecting general hemostasis in humans

Authors: Ungerer M et al

Summary: This phase I study evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of the antiplatelet agent revacept in humans. 30 healthy male volunteers received a single IV dose of revacept 10, 20, 40, 80, or 160mg. The serum concentration–time courses of each dose were concentration- and time-dependent and showed narrow variation. Revacept dose-dependently inhibited collagen-induced platelet aggregation (for up to 48h at lower doses and for 7 days at higher doses) but had no effects on ADP- or thrombin receptor activating peptide-dependent platelet aggregation. Revacept had no significant effects on bleeding time. There were no relevant drug-related adverse events or laboratory changes, or changes in BP, HR, or ECG parameters. In conclusion, revacept is a safe and well-tolerated compound that causes specific, dose-related inhibition of platelet aggregation.

Comment: There is intense research being undertaken to find new antiplatelet therapies that decrease platelet aggregation but do not increase bleeding, as has been seen with the P2Y₁₂ inhibitors where greater efficacy has been associated with increased bleeding. Oral platelet thrombin receptor antagonists have potential in this regard, and are being studied in clinical trials of ACS and chronic CV disease at present. It seems that revacept may also have these properties but it is unlikely to have much impact unless an oral preparation is available.

Reference: *Circulation* 2011;123:1891-1899
<http://circ.ahajournals.org/cgi/content/abstract/123/17/1891>

Treatment and outcomes in patients with myocardial infarction treated with acute β -blocker therapy: results from the American College of Cardiology's NCDR[®]

Authors: Kontos M et al

Summary: This US registry study investigated the acute use of beta-blockers in patients with MI. Data for 34,661 patients who received acute (≤ 24 hours) beta-blocker treatment for ST-elevation MI (STEMI) or non-STEMI (non-STEMI) at 291 participating US hospitals were reviewed. Patients were stratified according to the presence of risk factors for shock: age >70 years, symptoms >12 hours (STEMI patients), SBP <120 mm Hg, and HR >110 beat/min on presentation. 45% of STEMI and 63% of non-STEMI patients were found to have at least 1 high-risk variable. In-hospital complications including cardiogenic shock and mortality increased as the number of risk factors for shock increased. Very early beta-blocker use in the emergency department significantly increased the risk of shock compared with later treatment (but within 24h). In conclusion, early beta-blocker treatment should be avoided in patients with acute MI.

Comment: The timing of instituting beta-blockade after MI has been largely empiric. This study suggests that very early beta-blockade (<24 hrs) is associated with adverse outcomes, especially in the sickest patients. It would therefore seem wise to delay introducing these potentially lifesaving agents at least for 24 hrs after MI, or until the patient is haemodynamically stable.

Reference: *Am Heart J* 2011;161(5):864-870
[http://www.ahjonline.com/article/S0002-8703\(11\)00076-7/abstract](http://www.ahjonline.com/article/S0002-8703(11)00076-7/abstract)

The incidence of bradyarrhythmias and clinical bradyarrhythmic events in patients with acute coronary syndromes treated with ticagrelor or clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) Trial: results of the Continuous Electrocardiographic Assessment Substudy

Authors: Scirica B et al for the PLATO Investigators

Summary: This PLATO substudy investigated the incidence of bradyarrhythmias in 2908 hospitalised patients treated with ticagrelor or clopidogrel for acute coronary syndromes (ACS). Patients underwent 7-day continuous ECG recordings within 24h of symptom onset and again 1 month later. The principal safety endpoint was the incidence of ventricular pauses lasting at least 3 s. At the initial ECG, 5.8% of ticagrelor and 3.6% of clopidogrel recipients had ventricular pauses ≥ 3 s (relative risk 1.61; $p=0.006$). After 1 month, ventricular pauses ≥ 3 s were less common and no significant differences were seen between treatment groups (2.1% and 1.7%, respectively). Most of the additional ventricular pauses reported with ticagrelor at the first cECG assessment were asymptomatic, nocturnal and originated from the sino-atrial node (66%). The incidences of bradyarrhythmic adverse events did not differ between groups. In conclusion, ticagrelor caused more ventricular pauses than clopidogrel in patients with ACS but there were no apparent clinical consequences.

Comment: Ticagrelor, a potent oral reversible P2Y₁₂ inhibitor, has been accepted by many regulatory authorities and has recently been approved by the TGA in Australia. Bradyarrhythmias were detected in the early studies with the agent and in the pivotal PLATO trial (in which ticagrelor showed significant benefits over clopidogrel in ACS), but these generally occurred early after its institution and did not translate into clinical events or the need for pacing.

Reference: *J Am Coll Cardiol* 2011;57:1908-1916
<http://content.onlinejacc.org/cgi/content/abstract/57/19/1908>



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