Cardiology Research Review™

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Making Education Easy

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In this issue:

Welcome

Welcome to the first edition of Cardiology Research Review, a unique Hong Kong publication bringing you some of the most important and recent Cardiology research from around the world.

While we all need to keep up to date with the latest research, most of us are very short on time. We aim to make this easier by selecting ten articles of interest, and for each I have provided my commentary on relevance to practice. Links to the website abstracts are also included so you can form your own opinions.

If you have colleagues who will also find the Review useful please feel free to forward on, and encourage them to subscribe on the Research Review site – www.researchreview.hk

Highlights in this first edition include the benefits of treating very elderly people with hypertension, the results of the PURE study that compared the use of proven secondary prevention drugs in urban and rural communities in countries at various stages of economic development, the use of PPIs may be a marker of increased risk as opposed to cause-and-effect, and an interesting study of bariatric surgery in morbidly obese patients.

I hope you find the review informative, and welcome your feedback and comments.

Kind Regards

Prof Bryan Yan

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Immediate and late benefits of treating very elderly people with hypertension: results from active treatment extension to Hypertension in the Very Elderly randomised controlled trial.

Authors: Beckett N et al for the HYVET Study Group

Summary: This 1-year open label extension of the Hypertension in the Very Elderly Trial (HYVET) assessed the benefits of antihypertensive treatment in very elderly patients. Patients taking double-blind treatment at the end of HYVET were eligible to enter the extension phase; 1682 of them participated and were given an antihypertensive regimen of sustained release indapamide 1.5mg (plus perindopril 2–4 mg if required) with target BP <150/80mm Hg. After 6 months the BP difference between the 2 groups (patients previously receiving antihypertensives vs placebo) was 1.2/0.7mm Hg. No significant differences were seen in the incidence of stroke or cardiovascular (CV) events when people previously treated with active drug were compared with those previously receiving placebo, but significant differences were seen for total mortality (hazard ratio 0.48, 95% CI 0.26–0.87; p=0.02) and CV mortality (hazard ratio 0.19, 95% CI 0.04–0.87; p=0.03). In conclusion, sustained reductions in total and CV mortality reinforce the benefits of antihypertensive treatment in the very elderly.

Comment: Hypertension remains the leading cause of cardiovascular risk and mortality worldwide and prevalence is continuously increasing in the elderly population. Given the rapid rise in the number of people living beyond their 80s, it is important to know whether or not to continue pharmacotherapy for hypertension for these patients. The extension phase of the HYVET trial reinforces conclusion drawn from its earlier results as well as several other studies (e.g. SYST-EUR, CONVINCE, VALUE) that treatment of hypertension is beneficial in the elderly and should be pursued. However, in clinical practice, the more difficult task lies in maintaining adherence, monitoring and managing side-effects of antihypertensive therapy in the very elderly patients.

Reference: BMJ2012;344:d7541

http://dx.doi.org/10.1136/bmj.d7541

Independent commentary by Bryan Yan, Associate Professor, Division of Cardiology, Department of Medicine & Therapeutics, Chinese University of Hong Kong; Interventional Cardiologist, Prince of Wales Hospital, Hong Kong. **For full bio CLICK HERE.**

Subclinical atrial fibrillation and the risk of stroke

Authors: Healey J et al for the ASSERT Investigators

Summary: This study evaluated whether subclinical episodes of rapid atrial rate detected by implanted devices are associated with an increased risk of ischaemic stroke in patients with no other evidence of AF. 2580 patients with hypertension and no history of AF who had recently received a pacemaker or defibrillator device were included. Patients were monitored for 3 months to detect episodes of subclinical atrial tachyarrhythmias (atrial rate >190 beats/min for > 6 min) then followed for a mean 2.5 years. 10.1% of patients were found to have subclinical atrial tachyarrhythmias. These were associated with an increased risk of clinical AF (hazard ratio 5.56, 95% CI 3.78–8.17; p<0.001) and ischaemic stroke or systemic embolism (hazard ratio 2.49, 95% CI 1.28–4.85; p=0.007) during follow-up. The population attributable risk of stroke or systemic embolism associated with subclinical atrial tachyarrhythmias was 13%. In conclusion, subclinical atrial tachyarrhythmias occurred frequently in patients without clinical AF and were associated with an increased risk of ischaemic stroke or systemic embolism.

Comment: This study showed for the first time that silent atrial fibrillation (AF) in patients with pacemakers is associated with significant increased risk of stroke. A number of important issues are raised. Firstly, there a lot of patients with pacemakers and it is unclear what to do about this silent AF because unlike clinical AF, these episodes are usually much shorter in duration and asymptomatic and only detectable by the device. Secondly, the prevalence of silent AF in the population of patients without pacemakers is not known and whether it may account for some proportion at least of cryptogenic strokes is also unclear. What remains to be determined is whether this risk could be reduced with anticoagulation. Until clinical trials targeting this population with short, asymptomatic episodes of high atrial rate are done, there is no evidence for treatment with warfarin or other anticoagulants.

Reference: N Engl J Med 2012;366:120-129

http://www.nejm.org/doi/full/10.1056/NEJMoa1105575

Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from PLATO.

Authors: Goodman S et al

Summary: This subgroup analysis of the PLATO trial examined the relationship between proton pump inhibitor (PPI) use and 1-year rate of cardiovascular events in patients with ACS randomised to clopidogrel or ticagrelor. The rates of cardiovascular events (cardiovascular death, MI or stroke) were higher in patients taking PPIs (n=6539) than in those not taking PPIs (n=12,060) at randomisation in both the clopidogrel group (adjusted hazard ratio 1.20, 95% CI 1.04–1.38) and the ticagrelor group (hazard ratio 1.24, 95% CI 1.07–1.45). Patients on non-PPI gastrointestinal drugs had similar primary endpoint rates compared to those taking PPIs, but patients not taking any gastric therapy had a significantly lower rate. In conclusion, the association between PPI use and adverse cardiovascular events found in the PLATO trial may be due to confounding, with PPI use perhaps being a marker for, rather than a cause of, higher rates of cardiovascular events.

Comment: Although it is well established that proton pump inhibitors (PPI) interfere with the metabolism of clopidogrel, it is still unclear what the clinical impact of this is, and there is much confusion as to whether PPIs and clopidogrel should be co-administered. The one randomized study that has been conducted on this subject, COGENT, found no clinical interaction in terms of cardiovascular events between the PPI omeprazole and clopidogrel. In this study, the finding that use of a PPI was associated with higher rates of cardiovascular events in both clopidogrel and ticagrelor patients is likely due to confounding. The fact that you are on a PPI is likely a marker for increased risk rather than a true cause-and-effect relationship. Given PPIs are not known to interfere with the metabolism of ticagrelor, it may not be PPI per se but potentially the association between PPI use and a higher-risk patient which is supported by the paradoxically higher rates of bleeding in PPI-treated patients. Therefore, current practice of prescribing PPI for patients on clopidogrel or ticagrelor at high risk of gastrointestinal bleeding should not be altered.

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http://tinyurl.com/7qylt62

Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey

Authors: Yusuf S et al on behalf of the PURE Study Investigators

Summary: The PURE study assessed the use of secondary prevention drugs (antiplatelet drugs, beta-blockers, ACE inhibitors or ARBs, and statins) in patients with a history of cardiovascular (CV) disease. 153,996 adults were recruited from urban and rural communities in countries at various stages of economic development. Rates of previous CV disease and use of proven effective secondary preventive drugs and BP-lowering drugs were evaluated using standardised questionnaires. Overall, few individuals with CV disease took secondary prevention drugs. Use was highest in high-income countries and lowest in low-income countries, and decreased in line with reduction of country economic status (p trend <0.0001 for every drug type). Only 11.2% of patients in high-income countries received no drugs, compared with 80.2% in low-income countries. Drug use was higher in urban than rural areas (p<0.0001), with greatest variation in poorest countries. Country-level factors such as economic status had more of an impact on rates of drug use than individual-level factors. In conclusion, use of secondary prevention medications is low worldwide, especially in low-income countries and rural areas.

Comment: This study raises an alarming message to the fact that despite rapid advances in the treatment of cardiovascular diseases and dissemination of published therapeutics guidelines, simple, readily available and effective preventive drugs such as aspirin and statins are grossly underused globally. This therapeutic gap is even more apparent between affluent and underdeveloped nations and between city and rural populations. The economic status of the country may account for about two-thirds of the variations in drug use, whereas individual factors such as age, sex, co-morbidities accounted for a third. Even in the highest-income countries in the survey, only one-half to two-thirds of people with a history of myocardial infarction or stroke were taking either aspirin or statins. There is a false assumption that physicians will prescribe in accordance to well established guidelines but many "real world" barriers such as national prosperity and availability of healthcare prevent effective delivery of preventive therapy. One of the biggest hurdles is the fact that most healthcare systems in the world do not have an organized approach to secondary prevention. Efforts should focus on national policies and structured healthcare systems to improve the penetration of secondary-prevention cardiovascular therapies.

Reference: The Lancet 2011;378(9798):1231-1243

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)61215-4/abstract

Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects

Authors: Eerenberg E et al

Summary: This randomised, crossover study evaluated the potential of prothrombin complex concentrate (PCC) to reverse the anticoagulant effects of rivaroxaban and dabigatran. 12 healthy male volunteers received rivaroxaban 20mg twice daily or dabigatran 150mg twice daily for 2.5 days, followed by either a single bolus of 50 IU/kg PCC (Cofact) or a similar volume of saline. After a washout period, the procedure was repeated with the other anticoagulant. Rivaroxaban induced a significant prolongation of the prothrombin time that was immediately and completely reversed by PCC ($p<0.001$). The endogenous thrombin potential was inhibited by rivaroxaban and normalised with PCC ($p<0.001$). Dabigatran increased the activated partial thromboplastin time, ecarin clotting time, and thrombin time. Administration of PCC did not restore these coagulation tests. In conclusion, PCC reversed the anticoagulant effect of rivaroxaban but not dabigatran in healthy subjects at the dose used in this study.

Comment: Novel oral anticoagulants such as dabigatran, rivaroxaban and apixaban have advantages over warfarin including no need for laboratory monitoring, less drug-drug interactions and less food-drug interactions. However, there are concerns about what action to take if excessive bleeding occurs on these agents because specific reversal agents are not available. Already, bleeding events with dabigatran have prompted safety advisories in Japan and Australia and have led to labeling updates in Europe and the US focusing on the need for monitoring renal function, since renal impairment can increase bleeding risk. There is no established guideline on the management of patients who are bleeding or require emergent surgery. Recently, some expert opinion guidance for reversing the anticoagulant effect of the new oral anticoagulants recommended routine supportive care, activated charcoal if drug ingestion was within a couple of hours, and hemodialysis if feasible for dabigatran. New hemostatic agents such as prothrombin complex concentrate may be considered for reversal of factor Xa inhibitors.

Reference: Circulation 2011;124:1573-1579

http://circ.ahajournals.org/content/124/14/1573.abstract

Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy

Authors: Tardif J-C et al on behalf of the SHIFT Investigators

Summary: This SHIFT echocardiographic substudy evaluated the effects of ivabradine on LV remodelling in patients with chronic heart failure (HF). In SHIFT, patients with LVEF ≤35% and resting heart rate ≥70 beats/min were randomised to receive ivabradine or placebo in addition to regular HF therapy. 411 patients who had complete echocardiographic data at baseline and 8 months were evaluated in this substudy. Ivabradine significantly decreased LV end-systolic volume index (LVESVI) compared with placebo ($p<0.001$) independently of beta-blocker use, HF aetiology, and baseline LVEF. Ivabradine also improved LV end-diastolic volume index ($p=0.002$) and LVEF ($p< 0.001$) compared with placebo. The incidence of CV mortality or hospitalisation for worsening HF (the SHIFT primary composite outcome) was higher in patients with LVESVI above the median (59 mL/m^2) at baseline (hazard ratio 1.62, 95% CI 1.03–2.56, $p=0.04$). In conclusion, ivabradine reverses cardiac remodelling in patients with HF and LV systolic dysfunction.

Comment: The SHIFT trial, first reported last year, showed an 18% reduction in the primary end point of cardiovascular death/heart-failure hospitalization with ivabradine vs placebo. The echocardiography substudy of the SHIFT trial, which included 611 patients, is one of the largest echo substudies on reverse remodeling in heart failure. Left ventricular ejection fraction was significantly increased by 3% in the ivabradine group vs. placebo. The benefits in remodeling occurred in parallel to lowering of resting heart rate which was known to have positive effects on remodeling as shown in beta-blocker studies. Of note, ivabradine was effective only in the subset of patients who were in sinus rhythm and had a heart rate above 70. Whether the same effects would have achieved if more patients were on recommended higher doses of beta blockers is unclear. However, these results support the use of ivabradine in addition to established heart-failure therapies if patients with a raised resting heart rate and are in sinus rhythm.

Reference: Eur Heart J 2011:32;2507–2515

http://dx.doi.org/10.1093/eurheartj/ehr311

Blood pressure targets recommended by guidelines and incidence of cardiovascular and renal events in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET)

Authors: Mancia G et al

Summary: This study evaluated the cardiovascular and renal benefits associated with BP targets (<140/90 or <130/80mm Hg) in patients at high cardiovascular risk participating in the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET). Patients were grouped according to the proportion of visits before an event in which they had BP <140/90 or <130/80mm Hg. A progressive increase in the proportion of visits in which target BP was reached was associated with a reduction in the risk of stroke, new onset of microalbuminuria or macroalbuminuria, and return to normoalbuminuria in albuminuric patients, but not MI or HF. The risk of CV events was reduced by increasing the frequency of BP control to <140/90mmHg, but not to <130/80mmHg. In conclusion, the more frequent achievement of the recommended BP targets led to cerebrovascular and renal protection in patients at high CV risk, but did not increase cardiac protection.

Comment: The present analyses from ONTARGET suggested that tighter blood pressure control to <130/80 mm Hg conferred additional protection against stroke and renal disease but not myocardial infarction or heart failure in high risk patients. These findings are relevant to the ongoing debate on optimal blood pressure targets for high-risk patients but more evidence is needed from prospective randomized trials. The authors suggested that guidelines for the management of hypertension should revise their targets for high-risk patients because lowering blood pressure to <130/80 mmHg conferred no greater cardiac protection than achieving a target of <140/90 mmHg and that guidelines might differ in different populations with different patterns of vascular disease. For example, in many parts of Asia, where stroke presents the greatest burden, tighter blood pressure control may be advocated.

Reference: Circulation 2011;124:1727-1736

http://circ.ahajournals.org/content/124/16/1727.abstract

Bariatric surgery and long-term cardiovascular events

Authors: Sjöström L et al

Summary: This analysis of data from the ongoing Swedish Obese Subjects (SOS) study investigated the association between bariatric surgery, weight loss and cardiovascular events. Long-term outcomes of 2010 obese participants who underwent bariatric surgery between 1987 and 2001 were compared with those of 2037 matched obese controls who received usual care in the Swedish primary health care system. Median follow-up was 14.7 (range 0–20) years. Bariatric surgery was associated with a reduction in cardiovascular deaths during follow-up (adjusted hazard ratio 0.47; 95% CI 0.29–0.76; p=0.002) and a reduction in the incidence of first time MI or stroke (adjusted hazard ratio 0.67; 95% CI 0.54–0.83; p<0.001). In conclusion, bariatric surgery reduced cardiovascular deaths and cardiovascular events compared with usual care in obese adults.

Comment: Many parts of the developed and developing world including Asia are facing an obesity epidemic. One of the most important risks of obesity is the development of cardiovascular disease. Furthermore, obesity can cause diabetes which in turn can contribute to cardiovascular disease. Over the years, bariatric surgery has gained in popularity and the demand is rapidly growing. In this large study, patients in the bariatric surgery group compared with those in the control group had lower rates of cardiovascular deaths, myocardial infarction or stroke but the absolute difference between groups was small, even after long 14.7-year follow-up. It may seem intuitive that controlling obesity should result in less cardiovascular disease but the benefits of bariatric surgery were not that straightforward. Interestingly, the benefits observed from bariatric surgery were not related to weight loss which suggested some other factor was involved. Perhaps patients motivated enough to undergo bariatric procedures were more adherent with medical treatments or pursue a healthier lifestyle independent of their body mass index (BMI). Since BMI did not predict who will gain cardiovascular benefits, perhaps it is time for an update on current guidelines for bariatric surgery which is based on a patient's BMI. It is also important to identify which patients are most likely to benefit most from bariatric surgery because the expected health benefits may be small and not necessarily exceed the risks of the surgery for obese patients who are otherwise healthy.

Reference: JAMA 2012;307(1):56-65

http://jama.ama-assn.org/content/307/1/56.abstract

Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction

Authors: Keller T et al

Summary: This study assessed the diagnostic performances of a highly sensitive troponin I (hsTnI) assay and a contemporary troponin I (cTnI) assay in the diagnosis of acute MI. 1818 patients with suspected ACS had 12 biomarkers including hsTnI (level of detection, 3.4 pg/mL) and cTnI (level of detection, 10 pg/mL) measured on admission and again after 3 and 6 hours. 22.7% of patients were diagnosed as having acute MI. When a diagnostic cut-off value at the 99th percentile was used, hsTnI level at admission had a sensitivity of 82.3% and a negative predictive value of 94.7%; cTnI at admission had a sensitivity of 79.4% and a negative predictive value of 94.0%. Using the 99th percentile diagnostic cut-off value combined with the serial change in troponin level over 3 hours, the positive predictive value for hsTnI increased from 75.1% at admission to 95.8% after 3 hours, and for cTnI increased from 80.9% at admission to 96.1% after 3 hours. In conclusion, the serial change in hsTnI or cTnI in the 3 hours after admission may facilitate an early diagnosis of acute MI.

Comments: Cardiac troponin I and T testing has become the cornerstone for diagnosis of myocardial infarction and is useful for risk assessment and management of suspected acute coronary syndrome patients. The development of highly sensitive troponin assays allows measurement of troponin concentrations at and below the current 99th percentile of a healthy population. The clinical implication of the study included that (1) patients with symptoms suggestive of acute coronary syndrome can be rapidly evaluated within 3 hours; (2) immeasurable troponin concentrations at 3 hours can rule out myocardial infarction (MI); (2) an increase of 200% or more in troponin concentration at 3 hours confirms diagnosis of MI; (3) Elevated troponin at first blood draw but no change by 3 hours indicates it is probably not an MI but is worth following up on, as the patient is still at increased risk.

Reference: JAMA 2011;306(24):2684-2693

http://jama.ama-assn.org/content/306/24/2684.abstract

Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data

Authors: Heneghan C et al for the Self-Monitoring Trialist Collaboration

Summary: This meta-analysis evaluated the value of self-monitoring of oral anticoagulation. 11 randomised trials with data for 6417 participants and 12,800 person-years of follow-up were identified from a search of Embase (1980–2009) and Medline (1966–2009). Primary outcomes were time to death, first major haemorrhage, and first thromboembolic event. Patients who were self-monitoring their oral anticoagulation had a significant reduction in thromboembolic events (hazard ratio 0.51; 95% CI 0.31–0.85) but not major haemorrhagic events or death compared with patients who were not self-monitoring. Participants in the self-monitoring group who were <55 years had a marked reduction in thrombotic events (hazard ratio 0.33, 95% CI 0.17–0.66), as did those with mechanical heart valve (hazard ratio 0.52, 95% CI 0.35–0.77). There were no significant adverse events associated with self-monitoring in the very elderly. In conclusion, self-monitoring of oral coagulation is a safe option for suitable patients of all ages.

Comment: Patients who self-tested and adjusted their doses had significantly lower rates of thromboembolic events suggested that patients should be given the opportunity and provided the training to undertake self-management. The most striking reductions in risk were seen in patients younger than 55 years and in those taking anticoagulation because of a mechanical heart valve. A possible explanation could be that younger patients, especially those with mechanical heart valves, are highly aware of thromboembolic risks, more motivated and are therefore prepared to manage their medical treatments. This strategy of self-monitoring was considered safe even in the very elderly over 85 years of age. However, the uptake of self-testing and self-monitoring has remained low. However, the availability of newer anticoagulation agents such as dabigatran and rivaroxaban that do not require monitoring at all may render this strategy moot.

Reference: The Lancet 2012;379(9813):322-334

http://dx.doi.org/10.1016/S0140-6736(11)61294-4