Welcome to the latest issue of Cardiology Research Review.

In this issue we report biological proof of the concept of renal denervation in patients with uncontrolled hypertension, and a retrospective study of the mortality benefits of mechanical vs bioprosthetic heart valves. A Canadian study looks at the incidence of sudden cardiac arrest during competitive sports, a meta-analysis compares the clinical effectiveness of CTCA and functional stress testing in patients with suspected coronary artery disease, a NZ study finds that reporting cardiomegaly based on chest x-ray findings is inaccurate, and remote heart rhythm sampling using the AliveCor heart monitor proves to be useful for AF screening in ambulatory patients. The issue finishes with probably the most controversial finding of the year: PCI did not improve exercise time compared with a placebo procedure in patients with medically treated angina and severe coronary stenosis.

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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Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED)

Authors: Townsend R et al.

Summary: The sham-controlled SPYRAL HTN-OFF MED study evaluated the effects of renal denervation on uncontrolled hypertension in the absence of antihypertensive medications. 80 patients with uncontrolled hypertension who were drug-naïve or had discontinued their antihypertensive medications were enrolled at 21 centres in the USA, Europe, Japan, and Australia. Patients underwent renal angiography before being randomised to renal denervation or a sham control group. The primary end-point was change in 24-h blood pressure at 3 months. Office and 24-h ambulatory blood pressure decreased significantly from baseline to 3 months in the renal denervation group but no significant changes were seen in the control group.

Comment: Interventional renal artery denervation appeared to offer a treatment alternative for arterial hypertension. But then a major randomised trial failed to demonstrate a benefit of the intervention while doubts around drug adherence and other technical issues remained. The presented study went back a step and treated patients with renal artery denervation that were not on antihypertensive drugs but had hypertension. It is a randomised, sham-controlled trial with adaptions in the technique as well. Overall it showed a significant drop in blood pressure and provided biological proof of the principle of renal artery denervation. This might lead to a reassessment of the method and I guess an adaptation of previous trials. Persistence might pay off in the end.

Reference: Lancet 2017;390(10108):2160-70

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.
Mechanical or biologic prostheses for aortic-valve and mitral-valve replacement

Authors: Goldstone A et al.

Summary: This study compared long term outcomes associated with mechanical and bioprosthetic heart valves in patients who underwent primary aortic-valve replacement (AVR) or mitral-valve replacement (MVR) between 1996 and 2013 in California. From 1996 through 2013, the use of bioprosthetic valves increased from 11.5% to 51.6% for AVR and from 16.8% to 53.7% for MVR. For AVR, receipt of a bioprosthetic valve was associated with higher 15-year mortality than a mechanical valve in patients aged 45–54 years (hazard ratio [HR], 1.23; p=0.03) but not in patients aged 55–64 years. For MVR, a bioprosthetic valve was associated with higher mortality than a mechanical valve among patients aged 40–49 years (HR, 1.88; p<0.001) and 50–69 years (HR, 1.16; p=0.01). The incidence of reoperation was significantly higher with a bioprosthetic valve than with a mechanical valve. Patients who received mechanical valves had a higher cumulative incidence of bleeding (and stroke in some age groups) than those who received a bioprosthetic valve.

Comment: Over the years the balance between bioprosthetic and mechanical heart valves has shifted towards the bioprosthetic ones both in absolute numbers and also through lowering the age when bioprosthetic valves are felt to be appropriate. This retrospective study re-investigated the background of this strategy; the primary end-point was mortality. The study demonstrated a benefit of mechanical aortic valves up to age 55, but there was no difference between 55 and 64 years. In comparison, mechanical mitral valves were associated with less mortality in patients under 70. The authors in particular challenge the increasing use of bioprosthetic mitral valves in ‘younger’ patients (<70). Over the age of 55 the choice of an aortic valve prostheses will be driven by patient factors as there was no mortality difference in this group.


Abstract

Sudden cardiac arrest during participation in competitive sports

Authors: Landry C et al., for the Rescu Investigators

Summary: This Canadian study examined the occurrence of sudden cardiac arrest during participation in sports activities. The Rescu Epistry cardiac arrest database was reviewed to identify all out-of-hospital cardiac arrests that occurred during sports activities in 2009–2014 in individuals aged 12–45 years. 74 sudden cardiac arrests occurred during participation in a sport; of these, 16 occurred during competitive sports and 58 occurred during non-competitive sports. The incidence of sudden cardiac arrest during competitive sports was 0.76 cases per 100,000 athlete-years; 43.8% of the athletes survived. Among the competitive athletes, two deaths were attributed to hypertrophic cardiomyopathy but none to arrhythmogenic right ventricular cardiomyopathy. Three cases of sudden cardiac arrest were considered to have been potentially identifiable if the athletes had undergone pre-participation screening.

Comment: We encourage our patients to be engaged in sports, at the same time we are alerted when someone comes to harm during sports, or even has a sudden cardiac death. The questions are what is the cause and how could we prevent it? Data collection is difficult but the authors made use of a comprehensive registry in Canada. They looked at individuals aged 12–45 years who had cardiac arrest during sport activities. Competitive race events and soccer appeared to be associated with the greatest number of cardiac arrests. In non-competitive athletes it was gym workouts and running. Interestingly, hypertrophic and arrhythmogenic right ventricular cardiomyopathies were uncommon, only very few of the arrests could have been predicted previously or captured on screening. Interestingly, the main reason for an arrest in the group aged 35–45 years was an ischaemic event. The article contains a very interesting analysis but concludes that wide-ranging screening programmes would be unlikely to significantly reduce these tragic events.


Abstract
Coronary computed tomography angiography vs functional stress testing for patients with suspected coronary artery disease

Authors: Foy A et al.

Summary: This systematic review and meta-analysis compared the clinical effectiveness of CTA and functional stress testing for patients with suspected coronary artery disease. A search of PubMed and MEDLINE identified 13 randomised clinical trials that compared CTA (n=10,319) with functional stress testing (n=9,777) that were suitable for inclusion. During a mean follow-up of 18 months there were no significant differences between CTA and functional stress testing cohorts for mortality or cardiac hospitalisation. However, CTA was associated with a reduced incidence of MI (0.7% vs 1.1%; risk ratio [RR], 0.71) and an increased incidence of invasive coronary angiography (11.7% vs 9.1%; RR, 1.33) and revascularisation (7.2% vs 4.5%; RR, 1.86). Patients receiving CTA were also more likely to receive a diagnosis of new coronary artery disease and to have started aspirin or statin therapy.

Comment: CTCA is probably the most practical answer. The inherent variations in practice. And then the three authors have coronary angiograms leading to more interventions. It was unclear what the risk of more interventions was and how this would influence results. Also, the use of the device highly acceptable. It seems like an approach that we should consider.


Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation

Authors: Halcox J et al.

Summary: The REHEARSE-AF study examined the use of the AliveCor heart monitor attached to a WiFi-enabled device to obtain remote electrocardiograms (iECGs) in ambulatory patients. 1001 patients aged ≥65 years with a CHADS-VASc score ≥2 who were free from AF were randomised to the iECG arm or routine care. iECGs were acquired twice weekly for 1 year onto a secure server and were read by an automated AF detection algorithm, a CHADS-VASc score ≥2 who were free from AF were randomised to the iECG arm or routine care. iECGs were acquired twice weekly for 1 year onto a secure server and were read by an automated AF detection algorithm, a cardiologist and/or a consultant cardiologist. 19 patients in the iECG group were diagnosed with AF over the 12-month study period compared with 5 in the routine care group (hazard ratio, 3.9; p=0.007) at a cost per AF diagnosis of $US10,780. Most iECG patients were satisfied with the device, and found it easy to use without restricting activities or causing anxiety.

Comment: You are concerned that your patient might have AF, but it is difficult to track their symptoms, their episodes are too infrequent for a Holter, and they have risk factors. How about using their smartphone for a little help? This randomised 1-year trial attached the AliveCor device to the patient’s smartphone, recorded an ECG twice a week, and compared it with standard care. The monitoring device found almost 4 times as many patients with AF compared to standard care. 42% of the newly diagnosed patients had symptomatic. Within the year of the trial there was no difference in clinical outcome. Study participants found the use of the device highly acceptable. It seems like an approach that we should consider.

Reference: Circulation 2017;136:1784-94

Is cardiomegaly on chest radiograph representative of true cardiomegaly

Authors: McKee J & Ferrier K

Summary: This cross-sectional observational study compared cardiac size on chest x-ray (CXR) to that on echocardiography to determine the accuracy of CXR for detecting true cardiomegaly. CXR and echocardiogram reports were reviewed for 244 patients after non-ST segment elevation MI (NSTEMI). 39 patients were reported to have cardiomegaly on CXR and 22 of them also had cardiomegaly on echo (true positive rate of 56% and false positive rate of 44%). 55 patients were reported to have cardiomegaly on echo, but 33 (60%) of these patients did not have cardiomegaly identified on CXR. Sensitivity of CXR to identify cardiomegaly was 40% and specificity was 91%, with a positive predictive value of 56% and negative predictive value of 84%.

Comment: CXRs are common on admission, are reasonably fast and arguably inexpensive tests. But the determination of heart size and cardiomegaly has been reasonably static using CXR while other imaging modalities are able to define heart size taking variables such as age, gender, ethnicity and height/weight into account. The results of this study speak for themselves. CXRs are not very sensitive to detect true cardiomegaly, however if an enlarged heart is detected in the setting of an NSTEMI an echo – already indicated according to current guidelines – will give you the answer. Another message that could be inferred is that using x-ray as a screening tool for cardiomyopathy does not appear to be helpful. In fact it would be interesting to see how many patients referred for an echo with cardiomegaly actually have relevant cardiac enlargement or dysfunction.


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Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation

Authors: Cannon C et al., for the RE-DUAL PCI Steering Committee and Investigators

Summary: The RE-DUAL trial examined the use of dual antithrombotic therapy with dabigatran after PCI in patients with AF. 2725 patients with AF who had undergone PCI were randomised to receive triple therapy with warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and aspirin (for 1–3 months), or dual therapy with dabigatran 110mg or 150mg plus a P2Y12 inhibitor. The primary end-point was a major or clinically relevant non-major bleeding event during a mean follow-up of 14 months. The incidence of the primary end-point was 15.4% in the 110mg dual-therapy group vs 26.9% in the triple-therapy group (hazard ratio [HR], 0.52; p<0.001), and 20.2% in the 150-mg dual-therapy group vs 25.7% in the corresponding triple-therapy group (HR, 0.72; p<0.001). The incidence of the composite efficacy end-point (thromboembolic events, death, or unplanned revascularisation) did not differ significantly between the triple-therapy group and the two dual-therapy groups combined.

Comment: AF is common, coronary interventions are common. The dilemma is the balance between bleeding and stent complications leading to frequent discussions and concerns around what drugs to combine and the duration of treatment. The end-point in this trial was bleeding. It compared a triple therapy including warfarin with a dual therapy of dabigatran, clopidogrel and/or ticagrelor. Comparing the 110mg dabigatran group to warfarin the incidence of bleeding was 15.4% vs 26.9%, and comparing the 150mg dabigatran group to warfarin the incidence of bleeding was 20.2% vs 25.7%. Statistical parameters indicated a significant benefit for the dabigatran combinations. The secondary end-point ensured that there was no difference in revascularisation or coronary complications. The results demonstrated non-inferiority for the dual combination with dabigatran. While this has not made it into the guidelines the results might help us to simplify treatment in this group and importantly reduce the risk of bleeding.


Incidence of previously undiagnosed atrial fibrillation using insertable cardiac monitors in a high-risk population

Authors: Reiffel J et al.

Summary: The REVEAL AF study used an insertable cardiac monitor to determine the incidence of AF in patients at high risk for but without previously known AF. 446 patients with a CHADS2, score of 3 or greater (or 2 with at least 1 additional risk factor) were enrolled; approximately 90% of them had nonspecific symptoms potentially indicative of AF, such as fatigue, dyspnea, and/or palpitations. 385 patients (86.3%) received an insertable cardiac monitor and were observed for 26.9% in this group and importantly reduce the risk of bleeding.

Comment: AF is already quite common in the older population, but this paper suggests there might even be significantly more undiagnosed patients out there. This prospective study reports on the results from implanted cardiac monitors in patients in presumed sinus rhythm with a CHADS2, score of 3 or greater. Interestingly, 6 months was the cut-off for calling an arrhythmia AF. After 18 months, 23.3% patients were newly diagnosed with AF, about half of them ended up with oral anticoagulation. But if you measured up to 30 months, 40% of patients were diagnosed with AF. Comparing these data with the other study presented in this review (using smartphones for AF detection) there seems to be an epidemic of undiagnosed AF out there. Are we underdiagnosing/undertreating? More dependable data on outcomes of this extensive AF screening would be helpful.


Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke

Authors: Mas J-L et al., for the CLOSE Investigators

Summary: The CLOSE study investigated the use of patent foramen ovale (PFO) closure in patients with cryptogenic stroke. 663 patients who had had a recent stroke attributed to PFO and had an associated atrial septal aneurysm or large interatrial shunt were randomised 1:1:1 to transcatheter PFO closure plus long-term antplatelet therapy (PFO closure group), antplatelet therapy alone, or oral anticoagulation alone. Patients with contraindications to anticoagulants or to PFO closure were randomly assigned to the prescriptive non-contraindicated treatment. The primary end-point was a thromboembolic event, death, or unplanned revascularisation. During a mean follow-up of 5.3 years, the risk of stroke was significantly lower among those assigned to PFO closure combined with antplatelet therapy than among those assigned to antplatelet therapy alone (hazard ratio, 0.03; p<0.001). PFO closure was associated with an increased risk of AF.

Comment: PFO closure in the context of stroke has been a surprisingly controversial topic for some. While 2017 brought 3 major publications on interventional PFO closure, the presented paper (CLOSE) is one of them. It is a French, non-industry funded multicentre, randomised, open-label trial comparing interventional PFO closure to oral anticoagulation and antplatelet therapy. The primary outcome was stroke. No stroke occurred in the closure group, but 14 patients on antplatelet therapy had another stroke (p<0.001). After device closure 4.6% had a brief episode of AF without recurrence through the remainder of the follow-up. 5.9% had procedural complications, none resulted in disability or death. In the oral anticoagulation vs antplatelet therapy groups there were 3 and 7 strokes, respectively. The rate of serious complications throughout the duration of the study did not differ between the groups. Together with the data from Gore-REDUCE and long-term RESPECT data the message for PFO closure is clear: rule out other causes of a stroke, assess for risks such as sepal aneurysm and large shunt and then CLOSE it.


Percutaneous coronary intervention in stable angina (ORBITA)

Authors: A-Lanree R et al.

Summary: The ORBITA study determined the effects of PCI on symptoms in patients with stable angina. 230 patients with severe (>70%) single-vessel stenosis received 6 weeks of medication optimisation. They then underwent pre-randomisation assessments before 200 patients were randomised 1:1 to undergo PCI or a placebo procedure. The primary end-point (change in exercise time during cardiopulmonary exercise testing) did not differ significantly between groups at 6 weeks.

Comment: Probably the most controversial paper of the year. The patient has stable angina, should we use medicine or stents to treat it? The authors of this study designed a rigorous-appearing protocol even including a placebo procedure. To cut right to the results of the study, it seems to have a negative result, which has been plastered all over the media. While I encourage you to read the original paper here are some thoughts around it. The primary end-point was not survival/mortality or MI or an assessment of ischaemic burden. The end-point was exercise time after 30 days. Other end-points were angina questionnaires. Interestingly, the dobutamine stress echo results did show a significant improvement after PCI. Then there are questions around selection bias and difficulties with recruitment for the study. Do the patients that went into the study represent all patients considered for PCI, or was this a less severe subgroup that was pre-selected through referral or patient pre-conception. And then there was criticism around just including 200 patients. Just a few thoughts. So while the double-blinded approach makes a lot of sense and while medical therapy for stable angina certainly is reasonable this study might just lead to more questions than answers.

Reference: Lancet 2017; published online Nov 2