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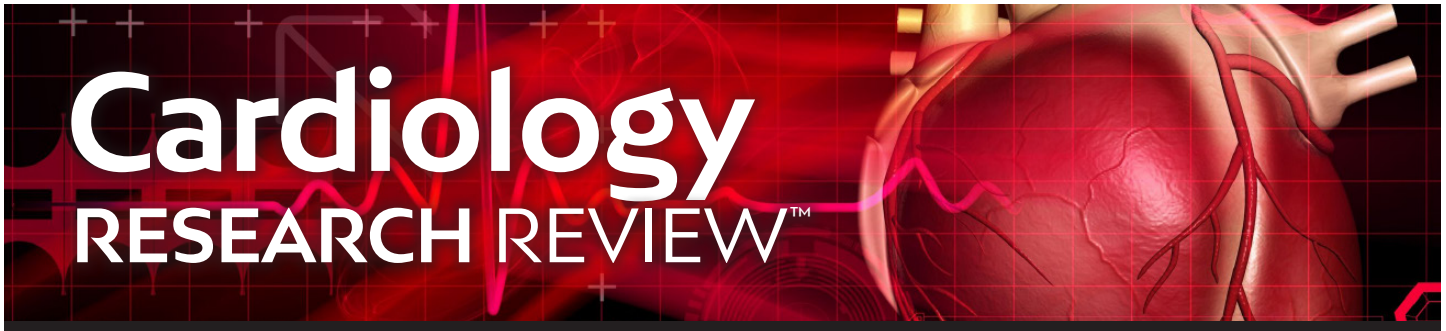

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Issue 96 – 2021

In this issue:

Welcome to the latest issue of Cardiology Research Review.

In this issue, we report that detection of AF and the right timing for initiation of oral anticoagulants remains a challenge, more options for treating heart failure with preserved ejection fraction are becoming apparent, and salt substitutes and a polypill might simplify the treatment of hypertension.

I hope you find these and the other selected articles interesting and look forward to receiving any feedback you may have.

Kind regards,

Professor Alexander Sasse
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Implantable loop recorder detection of atrial fibrillation to prevent stroke (the LOOP study)

Authors: Svendsen JH et al.

Summary: The Danish LOOP study investigated whether AF screening using an implantable loop recorder (ILR) and subsequent use of oral anticoagulants if needed can prevent stroke in high-risk individuals. 6004 individuals (aged 70–90 years) without AF but with at least 1 risk factor for stroke (hypertension, diabetes, previous stroke, or heart failure) were randomised 1:3 to ILR monitoring or usual care (control group). Oral anticoagulants were recommended in the ILR group if AF persisted for ≥6 min. During a median follow-up of 64.5 months, AF was diagnosed in 31.8% of patients in the ILR group and 12.2% in the control group (HR 3.17, 95% CI 2.81–3.59; p<0.0001). Oral anticoagulants were initiated in 29.7% of patients in the ILR group and 13.1% of patients in the control group (HR 2.72, 95% CI 2.41–3.08; p<0.0001). The primary outcome of first stroke or systemic arterial embolism occurred in 4.5% and 5.6% of patients in the respective groups (p=NS), and major bleeding occurred in 4.3% and 3.5% of patients, respectively (p=NS).

Comment: There are a number of papers coming out using ILRs to monitor for arrhythmia, in particular AF. Here patients in sinus rhythm but with at least 1 stroke risk factor were randomised to ILR or usual care. The cut off to start anticoagulation was AF for longer than 6 min. Unsurprisingly, more patients were diagnosed with AF in the ILR group (31.8% vs 12.2%) and consequently more patients were on oral anticoagulants in the ILR group (29.7% vs 13.1%). However, the rate of stroke was not significantly different between groups (4.5% vs 5.6%, p=0.11). So, ILR will find more AF but the threshold to initiate oral anticoagulants remains unclear.

Reference: Lancet 2021; published online Aug 29
Abstract

Abbreviations used in this issue

ACS = acute coronary syndrome
AF = atrial fibrillation
ANZACS-QI = All NZ ACS Quality Improvement
BP = blood pressure
COVID-19 = coronavirus disease 2019
CVD = cardiovascular disease
ECG = electrocardiogram
HFpEF = heart failure with preserved ejection fraction
HR = hazard ratio
LVEF = left ventricular ejection fraction
TAVI = transcatheter aortic valve implantation
SGLT2 = sodium-glucose co-transporter 2

Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP)

Authors: Svennberg E et al.

Summary: The Swedish STROKESTOP trial investigated whether systematic screening for AF could reduce mortality and morbidity in an older population compared with no screening. 28,768 older adults (aged 75–76 years) without a history of AF were randomised to an AF screening group or a control group. Those in the AF screening group were asked to record ECGs intermittently for 14 days. Treatment with oral anticoagulants was offered if AF was detected. The primary end-point was a composite of ischaemic or haemorrhagic stroke, systemic embolism, bleeding leading to hospitalisation, and all-cause death. During a median follow-up of 6.9 years, significantly fewer primary end-point events occurred in the intervention group than in the control group (31.9% vs 33.0%; HR 0.96, 95% CI 0.92–1.00; p=0.045).

Comment: This trial intensively screened 75–76 year-old adults for AF over a period of 2 weeks compared with a control group (usual care). Patients with AF were started on oral anticoagulants and followed for 5 years. In the end more than 28,000 patients were enrolled. There was a marginal benefit for the screened group regarding the composite end-point (HR 0.96, 95% CI 0.92–1.00), and fewer ischaemic strokes (HR 0.92), but no difference in other individual end-points (mortality, embolism, dementia etc). The number needed to screen to prevent 1 stroke was 91. This trial is a few years old, maybe using more modern screening tools would improve outcome but it quantifies the benefit of screening programmes for AF.

Reference: Lancet 2021; published online Aug 29
Abstract

Empagliflozin in heart failure with a preserved ejection fraction

Authors: Anker SD et al., for the EMPEROR-Preserved Trial Investigators

Summary: The EMPEROR-Preserved trial investigated the efficacy of the SGLT2 inhibitor empagliflozin in patients with HFpEF. 5988 patients with class II–IV heart failure and LVEF >40% were randomised to receive empagliflozin 10mg or placebo once daily in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalisation for heart failure. During a median 26.2 months of follow-up, a primary outcome event occurred in 13.8% of patients in the empagliflozin group compared with 17.1% in the placebo group (HR 0.79, 95% CI 0.69–0.90; p<0.001). The between-group difference was mainly due to a decrease in hospitalisations for heart failure in the empagliflozin group (HR 0.73, 95% CI 0.61–0.88; p<0.001). The effects of empagliflozin were similar in patients with or without diabetes. Adverse events reported with empagliflozin included uncomplicated genital and urinary tract infections and hypotension.

Comment: More data from SGLT2 inhibitors and diabetes drugs in the treatment of heart failure, specifically in the difficult-to-treat version with preserved ejection fraction. 5988 symptomatic HFpEF patients with or without diabetes were randomised to empagliflozin 10mg or placebo; although 33% actually had a moderate reduction in LV function. The follow-up was 26 months, by which time 13.8% of the empagliflozin patients had reached the primary end-point of death or hospitalisation compared to 17.1% (HR 0.79, CI 0.69–0.90; p=0.0003). There was no mortality difference. The empagliflozin group had a slower decline of renal function. Uncomplicated genital infections were more frequent with empagliflozin. It will be interesting to see how this will further influence heart failure guidelines.

Reference: N Engl J Med 2021;385:1451-61
Abstract

Effect of salt substitution on cardiovascular events and death

Authors: Neal B et al.

Summary: This open-label, cluster-randomised trial investigated the effects of salt substitution on cardiovascular and safety outcomes in individuals with a history of stroke or aged ≥60 years with hypertension. 20,995 individuals from 600 villages in rural China were included. The villages were randomly assigned in a 1:1 ratio to an intervention group (participants used a salt substitute comprising 75% NaCl and 25% KCl) or a control group (participants used 100% NaCl). Participants were followed up for a mean 4.74 years. The rate of stroke was lower with the salt substitute than with regular salt (rate ratio 0.86, 95% CI 0.77–0.96; p=0.006), as were the rates of major cardiovascular events (rate ratio 0.87, 95% CI 0.80–0.94; p<0.001) and death (rate ratio 0.88, 95% CI 0.82–0.95; p<0.001). The rate of serious adverse events attributed to hyperkalaemia was not significantly higher with the salt substitute.

Comment: This study is a bit unusual, but made it in the NEJM. In a 1:1 ratio participants over 60 years and with hypertension in Chinese villages were given a salt substitute (75% NaCl, 25% KCl) compared to regular diet. Mean follow-up was 4.7 years, the primary outcome was stroke, and the secondary outcome was cardiovascular events. The rate of fatal or nonfatal stroke events was significantly lower in the salt substitute group than in the regular salt group, with a very similar result for prevention of cardiovascular events. There were no relevant serious side effects from the KCl substitute, although slightly more hyperkalaemia. This is a seemingly simple intervention with a relevant result.

Reference: N Engl J Med 2021;385(12):1067-77
Abstract

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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 with 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 (<140/90 mm 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 intervention group.

Comment: The polypill, again. This Australian study used low dosages (quarter) of irbesartan, amlodipine, indapamide and bisoprolol compared to control full strength irbesartan, plus extra anti-hypertensives if required. It was double-blinded, enrolled nearly 600 patients and the outcome was office BP after 12 weeks. Although patients in the control group required more additional medication (40% vs 15%), BP control in the intervention group was better. In a subgroup of patients that carried on with randomised treatment beyond 12 weeks, up-titration was less common in the polypill group but BP control was still better at 52 weeks. Yet again another trial showing the advantages of a polypill approach for the treatment of hypertension.

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

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Association of alcohol consumption with morbidity and mortality in patients with cardiovascular disease

Authors: Ding C et al.

Summary: This meta-analysis of data from 3 large-scale cohorts and 12 published studies investigated the association between alcohol consumption and prognosis in individuals with pre-existing CVD. Data were analysed for a total of 48,423 participants in the UK Biobank Study, the Health Survey for England, the Scottish Health Survey, and 12 published studies. Alcohol consumption was associated with all of the assessed outcomes (all-cause mortality, CVD mortality, and subsequent cardiovascular events) in a J-shaped manner relative to current non-drinkers. Risk reduction was greatest at 7 g/day for all-cause mortality (relative risk [RR] 0.79, 95% CI 0.73–0.85), 8 g/day for CVD mortality (RR 0.73, 95% CI 0.64–0.83), and 6 g/day for cardiovascular events (RR 0.50, 95% CI 0.26–0.96), and remained significant up to 62 g/day, 50 g/day, and 15 g/day, respectively. No significantly elevated risks were found at higher levels of drinking.

Comment: Combining UK Biobank registry data with a meta-analysis, this paper examined the association between alcohol intake and subsequent cardiovascular events – in the end analysing about 48,000 patients. As usual these kinds of studies are based on questionnaires followed by grouping patients accordingly. A J-shaped association of alcohol with cardiovascular events was confirmed. A protective effect peaked at about 7g alcohol per day and was present up to 62 g/day (all-cause mortality); however the peak alcohol consumption demonstrating a reduction in cardiovascular events in patients with known cardiovascular disease was lower at 15 g/day (1 standard NZ drink contains 10g alcohol). Gender differences are mentioned but not particularly specified, the reader being directed to supplementary files. This result is in line with other studies, but keep in mind there are some cardiovascular conditions such as AF that are much more sensitive to alcohol.

Reference: BMC Med 2021;19(1):167
Abstract

Association between transcatheter aortic valve replacement for bicuspid vs tricuspid aortic stenosis and mortality or stroke among patients at low surgical risk

Authors: Makkar RR et al.

Summary: This registry-based cohort study compared outcomes after TAVI for bicuspid versus tricuspid aortic stenosis in patients at low surgical risk. 37,660 patients enrolled in the Society of Thoracic Surgeons (STS)/American College of Cardiology Transcatheter Valve Therapies Registry from June 2015 to October 2020 who underwent bicuspid or tricuspid TAVI with a balloon-expandable valve and who were at low surgical risk (STS risk score <3%) were included in the analysis. Coprimary outcomes were 30-day and 1-year mortality and stroke. 3168 propensity-matched pairs of low surgical risk patients with bicuspid or tricuspid aortic stenosis were analysed. There were no significant between-group differences for 30-day or 1-year mortality or for 30-day or 1-year stroke. There were also no significant differences between bicuspid and tricuspid groups in procedural complications, valve haemodynamics, and moderate or severe paravalvular leak.

Comment: Many TAVI trials excluded patients with bicuspid aortic valves (BAVs), but 15–29% of patients with severe aortic stenosis are presumed to have a BAV. This trial evaluated patients with presumed low risk undergoing TAVI (Edwards SAPIEN®) by propensity matching BAV to tricuspid aortic valve patients. The result is pretty straightforward: 30-day and 1-year outcomes were not different. The haemodynamics of implanted valves were also not different. BAV patients were about 7 years younger and hence had favourable 1-year unadjusted mortality data. While this evidence is not randomised it appears to show that, in selected cases, BAVs have similar outcomes to tricuspid aortic valves.

Reference: JAMA 2021;326(11):1034-44
Abstract

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The impact of a national COVID-19 lockdown on acute coronary syndrome hospitalisations in New Zealand (ANZACS-QI 55)

Authors: Chan DZ et al.

Summary: This study used data from the ANZACS-QI registry to evaluate the impact of a nationwide lockdown on ACS hospitalisations in NZ. All patients admitted to hospital with ACS who underwent coronary angiography during the lockdown (23 March – 26 April 2020) were compared with those admitted during equivalent weeks in 2015–2019. Ambulance attendances and regional community troponin-I testing during lockdown were also assessed. Hospitalisations for ACS were lower during the 5-week lockdown (rate ratio 0.72, 95% CI 0.61–0.83; p=0.003), due mainly to fewer admissions for non-ST-segment elevation ACS (NSTE-ACS; p=0.002). Door-to-balloon times for ST-segment elevation myocardial infarction (STEMI) were comparable in lockdown and non-lockdown periods. For NSTE-ACS, there was an increase in percutaneous revascularisation (59% vs 49%; p<0.001) and a decrease in surgical revascularisation (9% vs 15%; p=0.005). There were fewer ambulance attendances for cardiac arrests during lockdown, but attendances for suspected ACS were comparable.

Comment: Based on the national ANZACS-QI database the impact of the first NZ COVID-19 lockdown was analysed. The circumstances of the lockdown were very specific with a relatively strict lockdown but in comparison a low number of COVID-19 cases and hospitalisations. The number of STEMI presentations and treatment parameters were essentially unchanged. Non-STEMI presentations were reduced by 31%, and unstable angina by 46%. Ambulance attendances were reduced by 12%. Community troponin-I testing was significantly reduced by 38%. As the burden of COVID was low, changes are likely to be partially behavioural but also a true decline of at least NSTE-ACS is possible.

Reference: Lancet Reg Health West Pac 2020;5: 100056
Abstract

Difference in prognosis between continuation and discontinuation of a 5-month cardiac rehabilitation program in outpatients with heart failure with preserved ejection fraction

Authors: Morita H et al.

Summary: This study evaluated clinical outcomes in outpatients with HFpEF or non-HFpEF who did or did not complete a 5-month cardiac rehabilitation (CR) programme. 173 outpatients with HF who participated in a 5-month CR programme were enrolled. Patients were grouped according to whether they had HFpEF (mean LVEF 63%) or non-HFpEF (mean 31%), and whether or not they completed the CR programme. Clinical outcomes at 5 months were compared among the groups. The rates of all-cause death and hospital admissions in patients in both the HFpEF and non-HFpEF groups who completed CR were significantly lower than those in patients who discontinued the programme. All-cause death and hospital admissions in each group were independently associated with continuation of the CR programme.

Comment: CR is well established. What sets this study apart is looking at HFpEF patients with predominantly diastolic dysfunction as well as the duration of CR of up to 5 months. The comparison group was patients with LVEF <50%, and an internal control served patients that discontinued CR early. The full 5 months of CR was beneficial in both groups, highlighted by a marked difference in the end-points of death and readmission (HFpEF, p=0.0084; non-HFpEF, p=0.0126). The study was only observational but seems to suggest that HFpEF patients benefit similarly from CR, and that CR needs a certain period of time to be successful.

Reference: J Clin Med 2021;10(15):3306
Abstract

Independent commentary by Professor Alexander Sasse

Professor Alexander Sasse is Consultant Cardiologist and Clinical Director of the Cardiology Department at Wellington Hospital/CCDHB. His clinical interests include the various modalities of cardiac imaging, structural heart disease and intervention, general cardiology and the prevention of stroke. He went to Medical School in Bonn and did his training at the RWTH Aachen (Germany) and has been a Cardiologist since 2004. In 2007 he moved to Wellington and has been there since. 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.

Angiography after out-of-hospital cardiac arrest without ST-segment elevation

Authors: Desch S et al., for the TOMAHAWK Investigators

Summary: The TOMAHAWK trial evaluated the benefits of early coronary angiography and revascularisation in 554 patients with successfully resuscitated out-of-hospital cardiac arrest of possible coronary origin. Patients were randomised to undergo either immediate coronary angiography (immediate-angiography group) or initial intensive care assessment with delayed or selective angiography (delayed-angiography group). None of the patients had evidence of ST-segment elevation on post-resuscitation ECG. By 30 days, 54.0% of patients in the immediate-angiography group and 46.0% in the delayed-angiography group had died (HR 1.28, 95% CI 1.00–1.63; p=0.06). The composite of death or severe neurological deficit occurred more frequently in the immediate-angiography group (64.3% vs 55.6%).

Comment: What to do after successful cardiac arrest resuscitation … immediate angiography and intervention or intensive care and delayed invasive assessment and treatment? 554 patients in multiple centres were randomly assigned. 96% in the immediate group had an angiogram compared with 62% in the delayed group; the median delay was 47h. The prevalence of coronary artery disease was 60.7% (immediate) and 72.1% (delayed). There was no difference regarding mortality at 30 days. There was also no difference regarding a number of secondary end-points including stroke, length of stay and safety end-points. In the absence of ST elevation this trial did not show a benefit in immediate invasive management of cardiac arrest.

Reference: N Engl J Med 2021; published online Aug 29
Abstract

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