Cardiology RESEARCH REVIEW™

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Issue 101 – 2022

In this issue:

Abbreviations used in this issue

AF = atrial fibrillation
CABG = coronary artery bypass graft
CAD = coronary artery disease
CoDE-HF = Collaboration for the Diagnosis and Evaluation of Heart Failure
COVID-19 = coronavirus disease 2019
CTCA = computed tomography coronary angiography
HF = heart failure
HR = hazard ratio
MI = myocardial infarction
MRI = magnetic resonance imaging
NSTEMI = non-ST-elevation MI
NT-proBNP = N-terminal pro-B-type natriuretic peptide
PDAY = Pathobiologic Determinants of Atherosclerosis in Youth
PCI = percutaneous coronary intervention
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Welcome to the latest issue of Cardiology Research Review.

In this issue we report a number of big data trials. Researchers in England analyse millions of patients following COVID and vaccination to put myocarditis into perspective, the DISCHARGE investigators find that CTCA works well to work up chest pain, and an analysis of the CARDIA study finds that risk factors can lead to onset of atherosclerosis at a young age. Also in this issue, a longitudinal Swedish study reports that ischaemic heart disease matters much less in cardiac arrest these days (surprisingly), an Australian study supports extending invasive management to selected elderly patients with NSTEMI, and an analysis of UK Biobank data adds to the negative press about salt and CVD.

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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Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection

Authors: Patone M et al.

Summary: This English study investigated the risk of hospitalisation or death from myocarditis, pericarditis or cardiac arrhythmias after adenovirus (ChAdOx1; n=20,615,911) or messenger RNA-based (BNT162b2 or mRNA-1273; n=17,999,580) COVID-19 vaccines or a positive SARS-CoV-2 test (n=3,028,867) between Dec 2020 and Aug 2021 in people aged ≥16 years. It was estimated that there were an extra 2, 1 and 6 myocarditis events per 1 million people vaccinated with ChAdOx1, BNT162b2 and mRNA-1273, respectively, in the 28 days after a first dose, an extra 10 events per 1 million vaccinated in the 28 days after a second dose of mRNA-1273, and an extra 40 events per 1 million patients in the 28 days after a positive SARS-CoV-2 test. Increased risks of pericarditis and cardiac arrhythmias were seen after a positive SARS-CoV-2 test, but not after COVID-19 vaccination (except for an increased risk of arrhythmia after a second dose of mRNA-1273).

Comment: This is one of those *Nature Medicine* papers containing enormous amounts of UK data. 38,615,491 patients vaccinated against COVID and 3,028,867 with a positive COVID test were analysed. Of this combined group, 1615 had an admission for myocarditis, 1574 for pericarditis and 385,508 for arrhythmia. In a very condensed summary, post COVID the myocarditis incidence was 40 extra per million, compared to vaccination with 1–10 per million. Pericarditis and arrhythmia risks were not elevated post vaccination, but elevated after COVID. However, these were presentations leading to admissions, not necessarily all the patients with difficult to characterise chest pains and palpitations that we have been seeing. But it puts the post-vaccination symptoms in context with those from actual COVID disease, and overall myocarditis and pericarditis incidence was low (0.00007%).

Reference: Nat Med 2022;28(2):410-22
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.

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CT or invasive coronary angiography in stable chest pain

Authors: The DISCHARGE Trial Group

Summary: The DISCHARGE trial compared the utility of CTCA and invasive coronary angiography (ICA) as initial diagnostic imaging strategies for guiding the treatment of patients with stable chest pain. 3561 patients (56.2% female) who had an intermediate pretest probability of obstructive CAD and were referred for ICA at 1 of 26 European centres were included. Major adverse cardiovascular events (MACE) occurred in 2.1% of patients randomised to CTCA and 3.0% of patients randomised to ICA (HR 0.70, 95% CI 0.46–1.07; p=ns). Major procedure-related complications occurred in 0.5% and 1.9% of patients in the respective groups (HR 0.26, 95% CI 0.13–0.55), and 8.8% and 7.5% of patients in the respective groups had angina during the final 4 weeks of follow-up (odds ratio 1.17, 95% CI 0.92–1.48).

Comment: Different paths are taken for the workup of stable chest pain; this study compared CTCA to ICA as initial tests. The primary end-point was the prevention of MACE. 3561 patients with intermediate pretest probability were randomised in 26 European centres. While MACE did not differ between CTCA and ICA, there were significantly more adverse events in the ICA group. 22.3% of CTCA patients underwent consecutive ICA. CTCA patients had less PCI (10.8% vs 14.4%) or CABG surgery (2.2% vs 3.5%). Overall, a CTCA-first strategy compared favourably with ICA, preventing MACE at a similar level but with less adverse outcomes. Functional testing was not the subject of this study.

Reference: N Engl J Med 2022;386:1591-1602
Abstract

PDAY risk score predicts cardiovascular events in young adults

Authors: Gidding SS et al.

Summary: The CARDIA study used the PDAY risk score to predict atherosclerotic cardiovascular disease (ASCVD) events in young adults. Cardiovascular risk data, coronary artery calcium (CAC) scores, and ASCVD data were collected for 5004 young adults at age 18 and 30 years, with 30-year follow-up. Each standard deviation increase in PDAY score at each examination was significantly associated with future ASCVD. Hazard ratios (per standard deviation) increased from 1.74 to 2.04 from year 0 to year 15, and C-statistics ranged from 0.771 to 0.794. CAC measurement at age 33–45 years improved risk prediction only if the score was zero.

Comment: Another risk score, this one predicts atherosclerosis in under 40-year-olds. In a very unusual approach, the PDAY score is based on postmortem data of men and women who died accidentally. The score was applied to 5004 patients originally recruited in 1985–1986 and was tested to see if it predicted ASCVD in mid-life. Measured were age, high-density lipoprotein (HDL) and non-HDL cholesterol, hypertension, male gender, male obesity and smoking, though they were weighted differently. When CAC scoring was added to the assessment, it produced only a small improvement in ASCVD risk prediction. The paper is very complex, but the score seems to work. Personally I was again reminded that these (partially) preventable risk factors have a relevant effect even at a young age.

Reference: Eur Heart J 2022;43(30):2892-900
Abstract

Trends in survival after cardiac arrest: A Swedish nationwide study over 30 years

Authors: Jerkeman M et al.

Summary: This analysis of the Swedish cardiopulmonary resuscitation registry evaluated trends in characteristics, management, and survival after out-of-hospital cardiac arrest (OHCA) or in-hospital cardiac arrest (IHCA). 106,296 cases of OHCA where resuscitation was attempted were reported in 1990–2020 and 30,032 cases of IHCA where resuscitation was attempted were reported in 2004–2020. 30-day survival after OHCA increased from 5.7% in 1990 to 10.1% in 2011 and remained unchanged thereafter. Odds ratios for 30-day survival in 2017–2020 versus 1990–1993 were 2.17 overall, 2.36 for men, and 1.67 for women. Bystander cardiopulmonary resuscitation (CPR) increased from 30.9% to 82.2%. The odds ratio for 30-day survival after IHCA in 2017–2020 versus 2004–2007 was 1.18, with the probability of survival increasing by 46.6% in 2011–2020. Approximately 90% of survivors of OHCA and IHCA had no or mild neurological sequelae.

Comment: Sweden has been running a national registry on cardiac arrests since 1990, and this paper describes developments in OHCAs and IHCAs in a health system that is quite comparable to that of New Zealand. By its nature the paper is mostly descriptive. Survival of patients has improved significantly, at least for patients with shockable rhythm (from 14.4% to 35.8%). Women make up about one-third of cardiac arrests and their outcomes tend to be worse. 30-day survival increased by a factor of 2.2 after OHCA and 1.2 after IHCA, in particular men and younger patients had the most improvements. Myocardial ischaemia as the main cause reduced drastically from 67% to 28%. Rates of bystander CPR have also markedly changed from 31% to 82%. This study provides a wealth of data to guide future policy decisions.

Reference: Eur Heart J 2022; published online Aug 4
Abstract

Effect of MRI-guided fibrosis ablation vs conventional catheter ablation on atrial arrhythmia recurrence in patients with persistent atrial fibrillation

Authors: Marrouche NF et al.

Summary: The multicentre DECAAF II trial investigated the efficacy and safety of MRI-guided fibrosis ablation in patients with persistent AF. 843 patients with symptomatic or asymptomatic persistent AF who were undergoing AF ablation at 44 centres in 10 countries were randomised to pulmonary vein isolation (PVI) plus MRI-guided atrial fibrosis ablation (n=421) or standard PVI alone (n=422). Delayed-enhancement MRI was performed in both groups before ablation to assess baseline atrial fibrosis and 3 months after ablation to assess ablation scar. The primary end-point (time to first atrial arrhythmia recurrence after the 90-day blanking period post-ablation) did not differ significantly between groups (43.0% of fibrosis-guided PVI patients and 46.1% of PVI-only patients). Patients in the fibrosis-guided PVI group had a higher rate of safety outcomes (2.2% vs 0%; p=0.001). Six patients in the fibrosis-guided ablation + PVI group had an ischaemic stroke compared with none in PVI-only group.

Comment: A convincing hypothesis, the amount of atrial scarring should affect the outcome in AF ablation. Here 44 centres enrolled 843 patients and measured atrial scar with MRI. They then randomised patients to standard PVI or fibrosis-guided PVI. Arrhythmia recurrence rates were 46% in the standard PVI group and 43% in the fibrosis-guided PVI group, so not different (p=0.63). Hence fibrosis-guided ablation is not recommended by the authors. However, my comment would be that (1) fibrosis measurement via MRI is not as easy/reproducible as these trials make you believe, and (2) it does not necessarily disprove the fibrosis to AF link, but rather shows – yet again – that the type of PVI does not matter so much.

Reference: JAMA 2022;327(23):2296-305
Abstract

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Generalizability of the EAST-AFNET 4 trial: Assessing outcomes of early rhythm-control therapy in patients with atrial fibrillation

Authors: Dickow J et al.

Summary: The EAST-AFNET 4 trial demonstrated the clinical benefits of early rhythm-control (ERC) therapy in patients with new-onset AF and concomitant cardiovascular conditions. This study evaluated the generalisability of the EAST-AFNET 4 findings in routine practice. 109,739 patients with newly diagnosed AF were identified from a US administrative database and classified as receiving ERC (AF ablation therapy or antiarrhythmic drug therapy) within the first year after AF diagnosis (n=27,106) or not receiving ERC (control group, n=82,633). 72.9% of patients met inclusion criteria for EAST-AFNET 4. Cox proportional hazards regression analysis showed that ERC was associated with a reduced risk of the primary composite outcome of all-cause mortality, stroke, or hospitalisation for HF or MI (HR 0.85, 95% CI 0.75–0.97; p=0.02). Results were largely consistent between patients who were eligible for EAST-AFNET 4 trial inclusion and those who were not.

Comment: The EAST-AFNET 4 trial had previously suggested a benefit for ERC in AF, including early ablation (in 25%) or medical rhythm control strategies. These study results were analysed by retrospective review of US data. 27,106 patients would qualify as ERC treatment compared to 82,633 receiving usual AF care; patients were grouped according to whether they met original EAST-AFNET 4 criteria. The primary outcome was a composite of all-cause mortality, stroke, or hospitalisation with the diagnoses of HF or MI, and the ERC had a better outcome compared to usual care (HR 0.85, 95% CI 0.75–0.97), although mortality was not affected in the 2.6-year follow-up. While the patients were not randomised to the 2 groups (leading to a certain bias) the authors feel their data support the EAST-AFNET 4 results suggesting an early strategy for rhythm control in AF.

Reference: J Am Heart Assoc 2022;11(11):e024214
Abstract

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Development and validation of a decision support tool for the diagnosis of acute heart failure

Authors: Lee KK et al.

Summary: This meta-analysis and modelling study evaluated the diagnostic performance of NT-proBNP thresholds for acute HF and developed a decision support tool (CoDE-HF) that combined NT-proBNP levels with clinical characteristics to determine the probability of acute HF. Of 10,369 patients with suspected acute HF who participated in 14 trials, 43.9% had an adjudicated diagnosis of acute HF. An NT-proBNP threshold of 100 pg/ml achieved optimal rule-out criteria, and an NT-proBNP threshold of 1000 pg/ml achieved optimal rule-in criteria. However, performance was poor in certain patient subgroups. The CoDE-HF decision tool used NT-proBNP concentrations as a continuous measure together with objective clinical variables known to be associated with acute HF (age, estimated glomerular filtration rate, haemoglobin, body mass index, heart rate, blood pressure, peripheral oedema, chronic obstructive pulmonary disease, and ischaemic heart disease). It had excellent diagnostic performance across all patient subgroups, and ruled in and ruled out acute HF more accurately than use of NT-proBNP thresholds alone.

Comment: While the use of NT-proBNP is well established in the diagnosis of HF, this study evaluated the performance of NT-proBNP for the diagnosis of acute HF in different subgroups. Essentially they did a meta-analysis but went back to patient-level data on 10,369 patients. A NT-proBNP threshold of 100 pg/ml achieved the best rule-out results with a negative predictive value of 97.8% and a sensitivity of 99.3%. For rule-in a threshold of 1000 pg/ml was seen as optimal with a positive predictive value of 74.9% and specificity of 76.1%. Both cut-offs worked less well in older patients. From the data a decision tool (CoDE-HF) was developed by incorporating and weighing clinical factors. It apparently performed well and further prospective studies are planned to see if CoDE-HF can guide clinical decisions.

Reference: BMJ 2022;377:e068424
Abstract

Invasive versus conservative management in patients aged ≥85 years presenting with non-ST-elevation myocardial infarction

Authors: Kunniardy P et al.

Summary: This retrospective cohort study in Australia compared outcomes after invasive versus conservative management of NSTEMI in elderly patients. Outcomes for 1052 patients aged ≥85 years who presented to a tertiary centre with NSTEMI in 2008–2018 were analysed. 99 (9.4%) patients underwent early coronary angiography (they tended to be younger, male, and live independently without mobility or cognitive issues). Overall, 47% of patients died during a mean follow-up of 1.3 years. Cox regression analysis adjusted for age, premorbid functional status, cognition and cardiovascular risk factors showed that invasive management was the strongest predictor of survival (HR 0.47, 95% CI 0.26–0.85; p=0.01). Invasive management was associated with a trend to increased risk of in-hospital bleeding (6.1% vs 2.6%; p=0.054) but there was no significant between-group difference in stroke (2.0% vs 3.8%; p=0.37).

Comment: Acute coronary syndrome pathways were initially quite restrictive regarding invasive management of elderly patients. Concerns were comorbidity and the ability to benefit compared to the risk. This Australian study retrospectively analysed patients 85 years or older presenting with NSTEMI. They found 1052 patients and (only) 9.4% underwent invasive management – these patients being younger, having less comorbidity and being more likely male. After a follow-up of 1.3 years, 47% of patients had died. After trying to adjust for cofounders by statistical means the invasive management was the strongest predictor for survival (HR 0.47, p=0.01). Bleeding increased from 2.6% to 6.1% with invasive management, but the rate of stroke did not differ between groups. While this study does not replace a randomised trial it supports extending invasive management to selected elderly patients with NSTEMI.

Reference: Intern Med J 2022;52(7):1167-73
Abstract

Rivaroxaban monotherapy vs combination therapy with antiplatelets on total thrombotic and bleeding events in atrial fibrillation with stable coronary artery disease

Authors: Naito R et al.

Summary: This post hoc secondary analysis of the AFIRE trial evaluated the use of rivaroxaban alone or in combination with antiplatelet therapy in patients with AF and CAD. 2215 patients with AF and stable CAD who had undergone PCI or CABG surgery at least 1 year earlier or who had angiographically confirmed CAD not requiring revascularisation were randomised to receive rivaroxaban alone or in combination with antiplatelet therapy. 12.2% of patients in the rivaroxaban monotherapy group and 19.2% in the combination therapy group had a thrombotic, bleeding, or fatal event during a median follow-up of 24.1 months. Mortality rates were 3.7% and 6.6% in the respective groups. Overall, rivaroxaban monotherapy was associated with a lower risk of total events compared with combination therapy (HR 0.62, 95% CI 0.48–0.80; p<0.001).

Comment: AF and recent stents frequently cause concerns about anticoagulation, however this paper looks at the patients that are medically managed with stable CAD and concomitant AF. Rivaroxaban monotherapy was compared to rivaroxaban with antiplatelet medication by randomising a total of 2215 patients either way. The primary end-point was a composite of thrombotic, bleeding, and fatal events. In these patients with stable CAD, rivaroxaban monotherapy was associated with less adverse events (12.2% vs 19.2%) and a lower mortality rate (3.7% vs 6.6%). Overall the findings support giving rivaroxaban alone instead of in conjunction with antiplatelet medication in this group of patients with stable CAD. Whether this is a class effect for non-vitamin K antagonist oral anticoagulants was not tested by the study.

Reference: JAMA Cardiol 2022;7(8):787-94
Abstract

Type of stressor and medium-term outcomes after Takotsubo syndrome: What becomes of the broken hearted? (ANZACS-QI 59)

Authors: Looi J-L et al.

Summary: This NZ study compared outcomes in patients with Takotsubo syndrome (TS) triggered by acute physical or emotional stressors. Of 632 patients presenting with TS in 2006–2018 (mean age 65 years, 95.9% female), 27.4% had an associated acute physical stressor, 46.4% had an emotional stressor and 26.2% had no evident stressor. In-hospital mortality was similar in the respective groups (1.7%, 1.2%, and 0.3%). During a median 4.4 years of follow-up post-discharge, mortality was higher in TS patients with physical stress (HR 4.46, 95% CI 3.10–6.42) or MI (HR 4.23, 95% CI 3.81–4.70) than in patients without known cardiovascular disease (CVD). However, mortality in patients with TS associated with emotional stress or no stressor was similar to that in patients without known CVD. Recurrence was similar in the 3 groups.

Comment: TS is a regional cardiomyopathy triggered by stress, but does the type of stress affect the outcome? Stressors were categorised as emotional or acute physical illness. 632 patients (96% female) were enrolled in this NZ study, 27.4% had a physical, 46.4% an emotional and 26.2% no apparent stressor. Following discharge and compared to a reference group with no presumed CVD, patients with MI and TS with physical stressor had a similar mortality risk (HR 4.5 and 4.2); TS with emotional or no stressor had a mortality similar to the no-CVD group (HR 1.11 and 1.08). Recurrence rate (6.4%) was not affected by the type of stressor. Mortality in the physical stress TS patients seemed to be driven by non-cardiac causes.

Reference: Heart Lung Circ 2022;31(4):499-507
Abstract

Age at menopause and risk of heart failure and atrial fibrillation

Authors: Shin J et al.

Summary: This nationwide cohort study in Korea evaluated the impact of premature or early menopause on the risk of HF and AF. Reproductive histories were collected for 1,401,175 postmenopausal women enrolled with the Korean National Health Insurance Service. 42,699 (3.0%) women developed HF and 44,834 (3.2%) developed AF during a mean follow-up of 9.1 years. Multivariable Cox proportional hazard models found that women with premature menopause were at increased risk for HF (HR 1.33, 95% CI 1.26–1.40) and AF (HR 1.09, 95% CI 1.02–1.16) compared with women without premature menopause. There was a significantly increasing trend in HRs for the risk of both HF and AF in women aged 45–49, 40–44, and <40 years at menopause compared with women aged ≥50 years at menopause (p-trend <0.001).

Comment: Two chronic heart diseases, HF and AF, but how are they affected by premature menopause (<40 years of age)? The study enrolled 1,401,175 postmenopausal women in Korea via their public health records. Mean follow up was 9.1 years. Women with premature menopause more commonly presented with HF (HR 1.33) and AF (HR 1.09, both p<0.001); when adjusted for cofounders the statistical relation did not change much. Also, when comparing different age groups of menopause onset, early onset had significantly higher rates of AF and HF. The findings in this study are clear and well presented. Maybe age at menopause should be a routine part of risk assessment and taken into account more often for clinical decisions.

Reference: Eur Heart J 2022; published online Aug 4
Abstract

Adding salt to foods and hazard of premature mortality

Authors: Ma H et al.

Summary: This analysis of UK Biobank data investigated whether adding salt to food increases the risk of premature mortality. 501,379 individuals completed a questionnaire on the frequency of adding salt to food (but not adding salt to cooking) at baseline and were followed up for a median 9.0 years, during which time 18,474 premature deaths occurred. Multivariable hazard ratios for all-cause premature mortality across the increasing frequency of adding salt to foods were 1.00 (reference), 1.02 (95% CI 0.99–1.06), 1.07 (95% CI 1.02–1.11), and 1.28 (95% CI 1.20–1.35) (p-trend <0.001). The association was significantly modified by fruit and vegetable intake. Compared with the never/rarely group, always adding salt to foods decreased life expectancy by 1.50 years in 50-year-old females and by 2.28 years in 50-year-old males.

Comment: Salt and CVD, there are quite a few publications coming out lately. Here 501,379 patients enrolled in the UK Biobank had filled out a salt questionnaire, describing salt use as 'never/rarely', 'sometimes', 'usually' and 'always'. This was backed up by sodium urine analysis and follow-up questionnaires. Median follow-up was 9 years. Mortality was increased in the 'usually' (HR 1.07, 95% CI 1.02–1.11) and 'always' (HR 1.28, 95% CI 1.20–1.35) groups – all groups were extensively adjusted for cofounders. The mortality was more often from CVD in these groups, including a higher frequency of strokes. However, the association between salt and mortality was not shown in patients with body mass index >30 kg/m^2. High intakes of potassium-containing vegetables and fruits attenuated the salt effect. 'Sometimes' adding a bit of salt seems ok, but 'usually' doing it not so much.

Reference: Eur Heart J 2022;43(30):2878-88
Abstract