Cardiology RESEARCH REVIEW™

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Issue 106 – 2023

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Abbreviations used in this issue
BMI = body mass index
BP = blood pressure
CV = cardiovascular
ECG = electrocardiogram
HFpEF = heart failure with preserved ejection fraction
HR = hazard ratio
LVEF = left ventricular ejection fraction
OR = odds ratio
SGLT2 = sodium glucose co-transporter 2
WHO = World Health Organization

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Welcome to the latest issue of Cardiology Research Review.

In this issue, an analysis of data from the Cardiovascular Health Study finds that physical activity (especially higher-intensity exercise) can reduce the risk of conduction disease, a Mayo Clinic study suggests that smartwatches might be useful screening tools for detecting heart failure, and US investigators report that common dietary supplements are unlikely to reduce lipids and inflammatory biomarkers in patients at risk for atherosclerotic CV disease. Also in this issue, an Australian study shows that troponin testing in the ambulance might speed up chest pain diagnosis and avoid burdening our emergency departments.

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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Lifestyle habits associated with cardiac conduction disease

Authors: Frimodt-Møller EK et al.

Summary: This analysis of data from the Cardiovascular Health Study examined the association between baseline characteristics (including lifestyle habits) and cardiac conduction disease. 5050 adults aged ≥65 years with annual 12-lead ECGs obtained over a 10-year period were included. Prevalent conduction diseases at baseline included first-degree atrioventricular block (n=257), left anterior fascicular block (n=99), left posterior fascicular block (n=9), right bundle branch block (BBB; n=193), left BBB (n=76), and intraventricular block (n=102). Older age, male sex, larger BMI, hypertension, and coronary heart disease were associated with a higher prevalence of conduction diseases at baseline, whereas white race and more physical activity were associated with a lower prevalence. During a median 7-year follow-up, 1036 patients developed incident conduction disease. Older age, male sex, larger BMI, and diabetes were each associated with incident conduction disease. Greater physical activity (HR 0.91, 95% CI 0.84–0.98; p=0.017) was associated with a reduced risk, while smoking and alcohol were not significantly associated with risk.

Comment: Which lifestyle habits increase the risk of cardiac conduction disease? This prospective study recruited 5050 participants; 669 of them (13.2%) had baseline conduction disease. 1036 patients (23.6%) developed conduction disease (median follow-up 7 years). Older age, male sex, a larger BMI, and diabetes were associated with a higher risk of incident conduction disease. Smoking and alcohol did not have an effect. Physical activity in a dose-dependent manner came with a reduced risk of conduction disease; in particular, higher-intensity exercise markedly reduced risk of future conduction disease (p=0.002). Apparently the first study of its kind, it shows that even the more severe forms of conduction disease can, to a degree, be mitigated by lifestyle behaviour.

Reference: Eur Heart J 2023;44(12):1058-66
Abstract

Prospective evaluation of smartwatch-enabled detection of left ventricular dysfunction

Authors: Attia ZI et al.

Summary: This Mayo Clinic study investigated the use of a smartwatch to identify left ventricular dysfunction. 2454 patients (mean age 53 years, 56% female) from 46 US states and 11 countries sent 125,610 smartphone ECGs via an iPhone app to a secure data platform for analysis. 421 participants had at least one watch-classified sinus rhythm ECG within 30 days of an echocardiogram, of whom 16 (3.8%) had an ejection fraction ≤40%. The artificial intelligence (AI) algorithm detected patients with low ejection fraction with an area under the curve of 0.885 (95% CI 0.823–0.946) when using mean prediction within 30 days of an echocardiogram, and 0.881 (95% CI 0.815–0.947) when using the closest ECG relative to the echocardiogram that determined the ejection fraction.

Comment: AI algorithms are applied to ECG (AI-ECG) for a number of diagnostic reasons, but can they detect left ventricular systolic dysfunction (LVSD) and be used as a screening tool? Based on a previous study using a 12-lead AI-ECG, the algorithm was adapted to a single-lead Apple Watch ECG. Users of a health app were contacted and in the end 2454 volunteered to upload their ECGs. 421 patients happened to have had an echo in the past 30 days, and 16 (3.8%) had significant LVSD which the AI-ECG algorithm detected with a sensitivity of 68.8–87.5% and a specificity of 80.7–83.7% depending on cut-off. The authors summarised as "*AI-ECG models in geographically dispersed populations at lower cost using patients' own devices*". Ring any bells?

Reference: Nat Med 2022;28(12):2497-2503
Abstract

Comparative effects of low-dose rosuvastatin, placebo, and dietary supplements on lipids and inflammatory biomarkers

Authors: Laffin LJ et al.

Summary: This single-centre prospective trial investigated the effects of six common dietary supplements on low-density lipoprotein (LDL) cholesterol levels, compared with low-dose rosuvastatin and placebo. 190 adults with LDL cholesterol 70–189 mg/dl and an increased 10-year risk of atherosclerotic CV disease were randomised to rosuvastatin 5 mg/day, placebo, fish oil, cinnamon, garlic, turmeric, plant sterols, or red yeast rice extract for 4 weeks. The primary end-point was the percent change in LDL cholesterol from baseline to day 28. Treatment with rosuvastatin significantly decreased LDL cholesterol levels compared with placebo (–35.2%; p<0.001) and all six supplements (p<0.001). None of the dietary supplements decreased LDL cholesterol levels compared with placebo.

Comment: From a cardiologist point of view, supplements to help with lipid lowering are somehow weirdly popular, though not even inexpensive. But how do they (fish oil, cinnamon, garlic, turmeric, plant sterols, red yeast rice) compare to moderate dose statin (rosuvastatin 5mg) and placebo? Patients were randomised to just one of these compounds, about 25 in each group. Percent change in LDL cholesterol from baseline was the primary end-point, and the secondary end-point was high-sensitivity C-reactive protein (hs-CRP). The result is quite clear, rosuvastatin reduced LDL cholesterol by 37.9%, all the others didn't, or rather were no different from placebo. High-density lipoprotein cholesterol and hs-CRP were not affected by any of the substances used. Small numbers, but relatively clear results.

Reference: J Am Coll Cardiol 2023;81(1):1-12
Abstract

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Chest pain management using prehospital point-of-care troponin and paramedic risk assessment

Authors: Dawson LP et al.

Summary: This economic evaluation investigated whether prehospital point-of-care troponin (Tn) testing and paramedic risk stratification of patients with chest pain could result in cost savings compared with existing care pathways. 188,551 patients in Victoria, Australia, who were attended by an ambulance for acute chest pain without ST-segment elevation were included. Decision tree models were used to estimate costs for three pathways: (1) existing care; (2) paramedic risk stratification and point-of-care Tn testing without prehospital discharge; or (3) prehospital discharge and referral to a virtual emergency department (ED) for low-risk patients. Estimated annualised infrastructure and staffing costs for the point-of-care Tn pathways (assuming a 5-year device life span) were $AU2.27 million for the pathway without prehospital discharge and $AU4.60 million for the pathway with prehospital discharge. Total annual cost using prehospital point-of-care Tn and paramedic risk stratification was lower than existing care both without prehospital discharge ($AU6.45 million cost savings) and with prehospital discharge ($AU42.84 million cost savings).

Comment: Chest pain. What if the ambulance does a rapid Tn test? This paper from Australia performed a modelling study with pre-hospital Tn testing, comparing standard practise (model 1), prehospital Tn test without prehospital discharge (model 2), and prehospital Tn test with prehospital discharge (model 3). The cost savings are quite high: $AU6.5 million for model 2 and between $AU43 million and $AU72 million for model 3. Implementation costs varied, with annual costs between $AU1 million and $AU2.3 million over 5 years. The study aimed to prove the financial concept, so safety remains to be confirmed in a prospective study. But looking at the situation in EDs in NZ, maybe this might be something to watch out for.

Reference: JAMA Intern Med 2023;183(3):203-11
Abstract

Ionising radiation and cardiovascular disease

Authors: Little MP et al.

Summary: This systematic review and meta-analysis investigated the association between ionising radiation exposure and CV disease. A search of PubMed, Medline, Embase, Scopus, and Web of Science Core collection databases identified 93 studies that were suitable for inclusion. Relative risk per Gy increased for CV disease overall (excess relative risk per Gy, 0.11; 95% CI 0.08–0.14). However, interstudy heterogeneity was noted. For ischaemic heart disease and all CV disease, risks were larger per unit dose for lower dose (inverse dose effect) and for fractionated exposures (inverse dose fractionation effect). Population-based excess absolute risks ranged from 2.33% per Gy in England and Wales to 3.66% per Gy in Germany (largely reflecting the underlying rates of CV disease mortality in these populations).

Comment: What is the effect of ionising radiation on CV disease? Never mind that there are large variations in source of radiation, how could we even measure the effect? This meta-analysis reviewed the risks of radiation-associated CV disease that have been observed in therapeutically- or diagnostically-exposed cohorts. However, the first five pages of the paper deal with the difficulties in aligning the studies. The exposure to radiation was graded in steps from <0.5Gy to >5Gy. The main outcome was that radiation exposure was associated with a generally significant meta-excess relative risk per Gy for all CV disease. Inflammatory mechanisms are thought to play a role but were not investigated; also this meta-analysis did not establish causality. Nevertheless, even <0.5Gy exposure was associated with an increase in CV disease.

Reference: BMJ 2023;380:e072924
Abstract

Dapagliflozin in heart failure with improved ejection fraction: A prespecified analysis of the DELIVER trial

Authors: Vardeny O et al.

Summary: This prespecified analysis of the DELIVER trial investigated the efficacy of dapagliflozin in patients with heart failure with improved ejection fraction (HFimpEF). Of a total of 6263 DELIVER participants with symptomatic heart failure and LVEF >40%, 1151 (18%) had HFimpEF (LVEF had previously improved from ≤40% to >40%). Participants were randomised to receive dapagliflozin 10mg or placebo daily and the primary outcome was a composite of CV death or worsening heart failure. Dapagliflozin reduced the primary composite outcome in patients with HFimpEF (HR 0.74, 95% CI 0.56–0.97) to a similar extent as in individuals with ejection fraction consistently >40% (HR 0.84, 95% CI 0.73–0.95).

Comment: Now what is HFimpEF? Essentially it means LVEF was previously <40% but has now improved. However, actual data about what to do with HFimpEF remains limited. SGLT2 inhibitors have been established as one of four pillars of heart failure therapy. This paper analyses subgroups from DELIVER with HFimpEF (n=1151), randomised to dapagliflozin or placebo. Dapagliflozin reduced the primary composite end-point in HFimpEF to a similar extent as patients with LVEF consistently over 40%. The dapagliflozin effect was fairly consistent throughout subgroups. Safety and tolerability was also not different. Overall, the study suggests that patients with HFimpEF that remain symptomatic benefit from the addition of an SGLT2 inhibitor to their medication.

Reference: Nat Med 2022;28(12):2504-11
Abstract

Cardiovascular risk factor prevalence, treatment, and control in US adults aged 20 to 44 years, 2009 to March 2020

Authors: Aggarwal R et al.

Summary: This study used National Health and Nutrition Examination Survey data to determine changes in the prevalence and management of CV risk factors (hypertension, diabetes, hyperlipidaemia, obesity, and tobacco use) from 2009 through March 2020 in US adults aged 20–44 years. Analysis of data for 12,924 individuals showed that from 2009 to 2020 the prevalence of hypertension increased from 9.3% to 11.5%, diabetes increased from 3.0% to 4.1%, obesity increased from 32.7% to 40.9%, and hyperlipidaemia decreased from 40.5% to 36.1%. Black adults had high rates of hypertension across the study period (16.2% in 2009/10 and 20.1% in 2017/20), and Mexican Americans had significant increases in hypertension (from 6.5% to 9.5%) and diabetes (from 4.3% to 7.5%) over time. The percentage of young adults treated for hypertension who achieved BP control did not change significantly, while glycaemic control among young adults receiving treatment for diabetes remained suboptimal throughout the study period (45.5% in 2009/10 and 56.6% in 2017/20).

Comment: This is one of those papers to quote for talks and presentations, and it has some nice graphs as well. The trends of CV risk factor prevalence and the likely implications for future manifestation of CV disease – admittedly from the US. 12,924 participants, 20–44 years old, 2009 to 2020. Trends in CV risk factors were similar between men and women. Hypertension (9.3% to 11.5%), diabetes (3.0% to 4.1%) and obesity (32.7% to 40.9%) increased. Hyperlipidaemia decreased, smoking did not change. In the US context there were differences within the ethnical background as well – black adults had more often hypertension, and Mexican more commonly diabetes. Treatment rates were felt to be low, around 53.7% for hypertension, 54.5% for diabetes. Different US context, but CV disease is not going away any time soon.

Reference: JAMA 2023;329(11):899-909
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. **For full bio CLICK HERE.**

Rate-adaptive atrial pacing for heart failure with preserved ejection fraction: The RAPID-HF randomized clinical trial

Authors: Reddy YNV et al.

Summary: The RAPID-HF trial investigated whether implanting and programming a pacemaker for rate-adaptive atrial pacing improves exercise performance in patients with HFpEF and chronotropic incompetence. 29 patients (mean 66 years, 45% female) underwent pacemaker implantation and were randomised to atrial rate responsive pacing versus no pacing for 4 weeks, followed by a 4-week washout period and then crossover for an additional 4 weeks. The primary end-point was oxygen consumption ($\dot{V}o_2$) at anaerobic threshold ($\dot{V}o_2$,AT). In the absence of pacing, peak $\dot{V}o_2$ and $\dot{V}o_2$,AT were both significantly correlated with peak exercise heart rate. Pacing increased heart rate during low-level and peak exercise, but there was no significant change in $\dot{V}o_2$,AT, peak $\dot{V}o_2$, patient-reported health status, or N-terminal pro-brain natriuretic peptide levels.

Comment: Patients with HFpEF not uncommonly have chronotropic incompetence (this paper quotes more than 50%) so why not implant a pacemaker? In this study, 29 HFpEF patients had chronotropic incompetence and received a pacemaker, the outcome was exercise performance ($\dot{V}o_2$max). At the randomisation visit the pacemaker in half the patients was programmed to increased programmed heart rate, continued for 4 weeks, followed by another test. Then programming back to baseline and the third test after another 4 weeks ('wash-out'). Pacing increased low-level exercise heart rate by 16/min, at higher levels by 14/min. However, there was no relevant effect on outcomes across all parameters. As expected, pacemaker implantation was associated with adverse events in 21%. In the end, pacing patients with HFpEF and chronotropic incompetence (over 4 weeks) was not beneficial.

Reference: JAMA 2023;329(10):801-9
Abstract

Endovascular ultrasound renal denervation to treat hypertension: The RADIANCE II randomized clinical trial

Authors: Azizi M et al., for the RADIANCE II Investigators and Collaborators

Summary: The RADIANCE II trial investigated the efficacy and safety of ultrasound renal denervation in patients with hypertension resistant to treatment. At 37 centres in the US and 24 centres in Europe, 1038 patients aged 18–75 years who had hypertension despite taking up to two antihypertensive medications and who had ambulatory BP ≥135/85mm Hg and <170/105mm Hg after a 4-week medication washout were randomised 2:1 to undergo ultrasound renal denervation or a sham procedure, and abstained from antihypertensive medications for 2 months where possible. The reduction in daytime ambulatory systolic BP at 2 months (primary outcome) was greater with ultrasound renal denervation than with the sham procedure (mean –7.9 vs –1.8mm Hg; p<0.001).

Comment: Renal denervation for the treatment of arterial hypertension keeps coming back. Here sham-controlled, randomised (2:1) and all hypertensive medications discontinued 4 weeks before treatment. Renal denervation was done via an ultrasound system (also sponsor of the study); n=150 treatment, 74 sham procedure. The primary efficacy outcome was the mean change in daytime ambulatory systolic BP at 2 months, which dropped significantly by 7.9mm Hg (SD 11.6mm Hg) compared to the sham procedure group (–1.8mm Hg; SD 9.5mm Hg). Similar changes were replicated in a number of secondary end-points. Follow-up showed no relevant renal artery stenosis (>70%) following denervation. The benefit of this study is the absence of BP medication as well as a comparison to a sham procedure, giving us an idea of what to expect from renal artery denervation – at least in the study group population.

Reference: JAMA 2023;329(8):651-61
Abstract

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Impact of electrically assisted bicycles on physical activity and traffic accident risk

Authors: Haufe S et al.

Summary: This observational study in Germany evaluated the impact of e-bikes compared with conventional cycling on reaching the WHO target for physical activity (at least 150 min of moderate-to-vigorous physical activity [MVPA] per week). Study participants (1250 e-bikers and 629 conventional bike users) were given activity trackers to assess time, distance and heart rate when cycling over four consecutive weeks. Questionnaires were used to assess traffic accidents over 12 months. The proportion of participants reaching 150 min of MVPA per week was higher for conventional bike users than for e-bike users (35.0% vs 22.4%; p<0.001). Multiple regression models adjusted for age, sex, comorbidities and bike usage patterns showed that the odds of reaching the physical activity target were lower for e-biking than for conventional biking (OR 0.56, 95% CI 0.43–0.72).

Comment: How do e-bikes compare to regular bikes for CV fitness? 1250 e-bikers and 629 conventional cyclists volunteered for this study. Bike activity and heart rate were recorded, and the end-point was a WHO standard for exercise (150 min of moderate exercise/week, or 75 min of vigorous exercise/week). E-bike riders were older, had higher BMI and more comorbidities. Conventional bikers rode overall 25 min/week longer and 70 min/week longer in moderate or vigorous exercise zones. Accidents occurred more often in the e-bike group (p=0.039). E-bikers were more likely to replace car rides. Overall, conventional bikers more often achieved WHO standards for exercise, but the two groups represent different populations and some e-bikers might otherwise not get on a bike at all.

Reference: BMJ Open Sport Exerc Med 2022;8(4): e001275
Abstract