Cardiology RESEARCH REVIEW™

Making Education Easy

Issue 1 – 2019

In this issue:

Abbreviations used in this issue

ACS = acute coronary syndrome
AF = atrial fibrillation
ANZACS-QI = All NZ Acute Coronary Syndrome Quality Improvement
ARIC = Atherosclerosis Risk in Communities
BP = blood pressure
CABG = coronary artery bypass grafting
CAD = coronary artery disease
ECG = electrocardiogram
ESC = European Society of Cardiology
HFrEF = heart failure with reduced ejection fraction
HR = hazard ratio
IHD = ischaemic heart disease
MI = myocardial infarction
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation MI

Welcome to the latest issue of Cardiology Research Review.

In this issue, a UK cohort study reports that fish eaters and vegetarians have less IHD than meat eaters, and an analysis of the ARIC cohort reports that sustained hypertension in mid-life increases the risk of subsequent dementia. The THEMIS study investigates the benefits of adding ticagrelor to aspirin in patients with stable coronary disease and diabetes, the AFIRE study reports no benefit from adding antiplatelet medication to rivaroxaban in AF patients with stable coronary disease, and Italian researchers make generous assumptions regarding global climate change and MI risk. We also report the results of 2 significant trials (DAPA-HF and ISAR-REACT 5) that were presented recently at ESC 2019.

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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Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up

Authors: Tong T et al.

Summary: This analysis of the EPIC-Oxford study examined the risk of IHD and stroke in meat eaters, fish eaters, and vegetarians over an 18-year period. 48,188 adults without a history of IHD, stroke, angina or cardiovascular disease were classified into 3 distinct dietary groups: meat eaters (n=24,428), fish eaters (consumed fish but no meat; n=7506), and vegetarians (including vegans; n=16,254). During 18.1 years of follow-up, 2820 cases of IHD and 1072 cases of total stroke were recorded. After adjusting for sociodemographic and lifestyle confounders, fish eaters and vegetarians had 13% and 22% lower rates of IHD, respectively, than meat eaters ($p<0.001$). The associations for IHD were partly attenuated after adjustment for high cholesterol, high BP, diabetes, and body mass index. In contrast, vegetarians had 20% higher rates of total stroke (ischaemic and haemorrhagic) than meat eaters. The associations for stroke did not attenuate after adjustment for disease risk factors.

Comment: Recently there were a number of papers circulating about diet and cardiovascular health. This UK study followed participants over about 18 years, divided into meat eaters, fish eaters and vegetarians. In the end 28,364 of 48,188 participants were left with repeat measurements. 73% remained vegetarians to the end but were counted as vegetarians for the main analysis. Cardiovascular outcomes were derived from National Health Service coding. Per 1000 patients, vegetarian patients had 10 less counts of IHD but 3 more cases of stroke than meat eaters. This particular pattern was not necessarily reproducible in other studies which makes interpretation difficult. An explanation of why vegetarians would have more strokes is not available.

Reference: BMJ 2019;366:l4897

Abstract

Association of midlife to late-life blood pressure patterns with incident dementia

Authors: Walker K et al.

Summary: This analysis of the ARIC cohort examined the association of mid- to late-life BP patterns with subsequent dementia. 4761 participants were enrolled during midlife (1987–1989) and followed-up over 6 visits through 2016–2017. 516 (11%) incident dementia cases occurred during follow-up. The dementia incidence rate (per 100 person-years) was 1.31 for participants with normotension in midlife and late-life; 1.99 for midlife normotension and late-life hypertension; 2.83 for midlife and late-life hypertension; 2.07 for midlife normotension and late-life hypotension; and 4.26 for midlife hypertension and late-life hypotension. Participants in the midlife and late-life hypertension group and in the midlife hypertension and late-life hypotension group had a significantly increased risk of subsequent dementia than those who remained normotensive (HRs, 1.49 and 1.62, respectively). Irrespective of late-life BP, sustained hypertension in midlife was associated with dementia risk (HR, 1.41).

Comment: 4761 patients were initially screened for hypertension in 1987–1989 when they were about 50 years old. Patients were placed in 5 groups according to BP control. Follow up included neurocognitive evaluation. 11% progressed to dementia, another 17% developed mild cognitive impairment. Those with hypertension in midlife and either hyper- or hypotension in late-life had a significantly increased risk of developing dementia when compared to patients with normalised BP. Similar studies have shown comparable results, highlighting the need to optimise BP control throughout mid- and late-life.

Reference: JAMA 2019;322(6):535-45
Abstract

Ticagrelor in patients with stable coronary disease and diabetes

Authors: Steg P et al., for the THEMIS Steering Committee and Investigators

Summary: The THEMIS study investigated whether adding ticagrelor to aspirin improves outcomes in diabetic patients with stable CAD. 19,220 patients aged ≥50 years who had stable CAD and type 2 diabetes mellitus were randomised in a double-blind design to receive either ticagrelor plus aspirin or placebo plus aspirin for a median 39.9 months. The incidence of ischaemic cardiovascular events was lower in the ticagrelor group than in the placebo group (7.7% vs 8.5%; p=0.04), but the incidences of major bleeding (2.2% vs 1.0%; p<0.001) and intracranial haemorrhage (0.7% vs 0.5%; p=0.005) were higher. The incidence of fatal bleeding did not differ significantly between groups (0.2% vs 0.1%). Permanent treatment discontinuation was more common in ticagrelor recipients (34.5% vs 25.4%).

Comment: 19,220 diabetic patients that had established CAD (per angiogram with or without intervention) and no previous MI were randomised to aspirin in comparison to aspirin and ticagrelor. These patients were considered high risk and the question was whether or not more potent antiplatelet medication would prove to be useful. The result was in keeping with previous similar studies. The dual antiplatelet medication reduced the incidence of MI (HR, 0.84, 95% CI 0.71–0.98) and stroke (HR, 0.80; 95% CI 0.64–0.99) but not cardiovascular death. However, the more potent dual combination therapy was associated with 2.3 times as many serious bleeding events. To simplify, the combination prevented 93 strokes and MIs at the expense of 106 more serious bleeding events.

Reference: N Engl J Med 2019;381:1309-20
Abstract

Myocardial viability and long-term outcomes in ischemic cardiomyopathy

Authors: Panza J et al.

Summary: This long-term follow-up of the STITCH trial evaluated whether assessment of myocardial viability in patients with ischaemic cardiomyopathy can predict outcomes after surgical revascularisation. 601 patients with CAD that was amenable to CABG and who had left ventricular ejection fraction (LVEF) ≤35% had myocardial viability assessed using single-photon-emission computed tomography (SPECT), dobutamine echocardiography, or both. Patients were then randomised to undergo CABG plus medical therapy or to receive medical therapy alone. During a median 10.4-year follow-up, the incidence of death (primary end-point) was lower in the CABG plus medical therapy group than the medical therapy alone group (adjusted HR, 0.73). However, there was no significant interaction between the presence or absence of myocardial viability and the beneficial effect of CABG.

Comment: The original STITCH trial on myocardial viability was published years ago, followed by a 10-year follow up in this paper. Patients had LVEF of 35% or less and underwent coronary revascularisation and/or medical therapy. Viability at the time was assessed using mostly SPECT and stress echo. Overall, CABG did better than medical therapy (HR, 0.73, 95% CI 0.6–0.9). However the presence of viability was not associated with an improved survival. The authors concluded that the concept of viability predicting a prognostic benefit from revascularisation is not confirmed. This fairly general conclusion discarding the concept of viability might just be a bit early, after all we have pretty much abandoned the clinical methods applied in this trial in favour of using cardiac magnetic resonance imaging (MRI) and late gadolinium enhancement. But large trials on MRI and myocardial viability are lacking.

Reference: N Engl J Med 2019;381:739-48
Abstract

Antithrombotic therapy for atrial fibrillation with stable coronary disease

Authors: Yasuda S et al., for the AFIRE Investigators

Summary: The multicentre AFIRE study evaluated the use of antithrombotic therapy in patients with AF and stable CAD. 2236 patients with AF who had undergone PCI or CABG more than 1 year earlier or who had angiographically confirmed CAD not requiring revascularisation were randomised in an open-label design to receive rivaroxaban alone or in combination with a single antiplatelet agent. The primary efficacy end-point was a composite of stroke, systemic embolism, MI, unstable angina requiring revascularisation, or death from any cause. Rivaroxaban monotherapy was non-inferior to combination therapy for the primary efficacy end-point, and superior to combination therapy for the primary safety end-point of major bleeding. However, the trial was stopped early because of increased mortality in the combination therapy group.

Comment: Essentially, the question of this trial was whether or not rivaroxaban (as a representative of non-vitamin K antagonist oral anticoagulants) is sufficient for AF patients that also have stable CAD, or if an additional antiplatelet drug is required. Allocation was randomised but open-label, 2236 patients were randomised. The trial was stopped early due to a clear signal of increased mortality in the combination therapy group. Not only was mortality increased, there was also no benefit in preventing major cardiovascular events, and bleeding events were increased as well. There appears no benefit in adding antiplatelet medication to rivaroxaban in stable CAD and AF.

Reference: N Engl J Med 2019;381:1103-13
Abstract

Association between inpatient echocardiography use and outcomes in adult patients with acute myocardial infarction

Authors: Pack Q et al.

Summary: This retrospective US study evaluated the association between use of inpatient echocardiography and outcomes in adults with acute MI. 98,999 patients hospitalised for acute MI at 397 hospitals were included in the analysis. 69,652 (70.4%) patients underwent at least 1 transthoracic echocardiogram; the median hospital risk-standardised rate of echocardiography was 72.5%. In models that adjusted for hospital and patient characteristics, no differences were found in inpatient mortality or 3-month readmissions between the highest and lowest quartiles of echocardiography use. However, hospitals with the highest rates of echocardiography had slightly longer mean lengths of stay (0.23 days) and higher mean costs ($US3164) per admission than hospitals in the lowest quartile of use.

Comment: The provision of left ventricular assessment per echo in patients with MI is not only a class I guideline indication but also a key performance indicator for ANZACS-QI. This retrospective audit of hospital coding data in the US analysed about 100,000 patients, 70.4% had an echocardiogram after a MI. There were some US specific results regarding insurance status and types of hospital but overall having had an echo post MI does not improve mortality or 3-month readmission. There was a weak association of echo with the use of angiotensin converting-enzyme inhibitors and angiotensin receptor blockers. The authors suggested parameters when an echocardiogram might be deferred e.g. low level troponin increase or no changes to the 12-lead ECG in stable non-STEMI patients.

Reference: JAMA Intern Med 2019;179(9):1176-85
Abstract

Impact of telemedicine interventions on mortality in patients with acute myocardial infarction

Authors: Marcolino M et al.

Summary: This systematic review and meta-analysis evaluated the impact of telemedicine interventions on mortality after acute MI. A search of various databases identified 30 non-randomised controlled and 7 quasi-experimental studies (n=16,960) that were suitable for inclusion. Meta-analysis of the data showed that telemedicine was associated with reduced in-hospital mortality compared with usual care (relative risk [RR], 0.63). Door-to-balloon time was consistently reduced (mean difference, −28 min), but showed large heterogeneity. 30-day mortality (RR, 0.62) and long-term mortality (RR, 0.61) were also reduced by telemedicine, with moderate heterogeneity.

Comment: Telemedicine in the treatment of MI represents current practice and is being expanded across NZ with the implementation of the STEMI pathway. Telemedicine in this case means ECG transmission and pre-hospital communication. This meta-analysis looked at 37 studies across the globe assessing 16,960 patients and comparing telemedicine to usual care. The main finding was a reduction of MI-related mortality from 8.4% with usual care to 4.9% using telemedicine (HR, 0.63; 95% CI 0.55–0.72). These findings are remarkably clear and highlight that STEMI coordination via telemedicine leads to tangible benefits in patient care.

Reference: Heart 2019;105(19):1479-86
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.

Climate changes and ST-elevation myocardial infarction treated with primary percutaneous coronary angioplasty

Authors: Versaci F et al.

Summary: This Italian study evaluated the impact of seasonal changes on daily rates of primary PCI in patients with acute MI. Details for 4132 primary PCIs and 6880 days were retrospectively collected in 3 high-volume Italian institutions with different geographical features. Overall, adjusted analysis showed that higher minimum atmospheric pressure in the previous 3 days was associated with lower risk of PCI (p=0.030). PCI rates in winter were increased by lower mean temperature (p=0.002) and lower rainfall (p=0.049). In spring, greater changes in atmospheric pressure in the previous 3 days were associated with increased risk of PCI (p=0.032), with similar effects in summer for minimum temperature on the same day (p=0.040).

Comment: In this issue we have to do something with climate change. This study conducted in Italy analysed weather data for MI presentations leading to primary PCI; 4132 cases were collected. Overall weather effects were comparatively small with hazard ratios ranging from 0.97 to 0.99. Cold winter days had the biggest impact. The authors also found that the weather 3 days before presentation played a role. Changes in atmospheric pressure 3 days before in spring and same day temperature changes in summer also had an influence. The authors then extrapolated their data to global climate change and an increased future risk of MI, both assumptions may be a bit generous.

Reference: Int J Cardiol 2019;294:1-5
Abstract

Ticagrelor or prasugrel in patients with acute coronary syndromes

Authors: Schüpke S et al., for the ISAR-REACT 5 Trial Investigators

Summary: The multicentre, open-label ISAR-REACT 5 trial compared the efficacies of ticagrelor and prasugrel in 4018 patients with ACS for whom invasive evaluation was planned. During 1 year of follow-up, a primary end-point event (death, MI, or stroke) occurred in 9.3% of patients in the ticagrelor group and 6.9% in the prasugrel group (HR, 1.36; p=0.006), and definite or probable stent thrombosis occurred in 1.3% and 1.0% of patients in the respective groups. The incidence of major bleeding did not differ significantly between groups.

Comment: This study was presented at the ESC in Paris. It directly compares the use of ticagrelor (with pre-loading) to prasugrel (with loading after the angiogram or after randomisation) in patient with ACS. Approximately 2000 patients were enrolled in each group, and 84% underwent PCI. Dual antiplatelet therapy was continued for 1 year. A primary end-point event (death from any cause, MI, or stroke) at 1 year after randomisation occurred more often in the ticagrelor group, the HR compared to prasugrel was 1.36 (95% CI 1.09–1.70). Bleeding was not different between the two drugs. The impact of this trial will require a detailed analysis, however it shows that there can be benefits in the (all too rare) head-to-head comparisons of current drugs (think non-vitamin K antagonist oral anticoagulants).

Reference: N Engl J Med 2019;381:1524-34
Abstract

Complete revascularization with multivessel PCI for myocardial infarction

Authors: Mehta S et al., for the COMPLETE Trial Steering Committee and Investigators

Summary: This analysis of the COMPLETE trial investigated whether PCI of nonculprit lesions further reduces the risk of cardiovascular death or new MI in STEMI patients undergoing PCI of the culprit lesion. 4041 patients with STEMI and multivessel CAD who had undergone successful culprit-lesion PCI were randomised to receive complete revascularisation with PCI of angiographically significant nonculprit lesions, or no further revascularisation. At a median follow-up of 3 years, the first coprimary outcome (a composite of cardiovascular death or new MI) had occurred in 7.8% of patients in the complete-revascularisation group compared with 10.5% in the culprit-lesion-only PCI group (HR, 0.74; p=0.004). The second coprimary outcome (a composite of cardiovascular death, new MI, or ischaemia-driven revascularisation) occurred in 8.9% and 16.7% of patients in the respective groups (HR, 0.51; p<0.001). For both coprimary outcomes, the benefit of complete revascularisation was consistently observed regardless of the intended timing of nonculprit-lesion PCI (either during or after the index hospitalisation).

Comment: In acute PCI for MI, should just the culprit artery be revascularised or should non-culprit lesions in vessels >2.5mm also be treated? About 4000 patients were randomised to either treatment. Lesions were rated as relevant when they were more than 70% stenosed or had a fractional flow reserve of 0.80 or less. Cross-over occurred in about 5% of patients. Mean follow-up was over 3 years. Mortality or new MI in patients with complete revascularisation was significantly lower (HR, 0.74), almost entirely driven by new MI. Mortality alone and heart failure (New York Heart Association class IV) were not prevented with complete revascularisation. In summary, complete revascularisation during the hospital stay or shortly thereafter led to a significant reduction of ischaemic cardiac events.

Reference: N Engl J Med 2019;381:1411-21
Abstract

Dapagliflozin in patients with heart failure and reduced ejection fraction

Authors: McMurray J et al., for the DAPA-HF Trial Committees and Investigators

Summary: The DAPA-HF trial investigated the effects of the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin in patients with established HFrEF. 4744 patients with New York Heart Association class II–IV heart failure and an ejection fraction ≤40% were randomised to receive dapagliflozin 10mg once daily or placebo, in addition to recommended therapy. During a median follow-up of 18.2 months, 16.3% of patients in the dapagliflozin group and 21.2% in the placebo group had worsening heart failure (HR, 0.74; p<0.001); a first worsening heart failure event occurred in 10.0% and 13.7% of patients in the respective groups (HR, 0.70). 9.6% of patients in the dapagliflozin group and 11.5% in the placebo group died from cardiovascular causes (HR, 0.82). Findings in patients with diabetes were similar to those in patients without diabetes.

Comment: Over the last few years there have been a number of promising heart failure drug trials and this was one of the major trials at ESC 2019 in Paris. Dapagliflozin, an SGLT2 inhibitor, was trialled in this randomised, controlled trial to demonstrate its previously noted effect on heart failure. It enrolled patients with HFrEF, mean left ventricular ejection fraction 31%, and median N-terminal pro-brain natriuretic peptide level 1428 pg/ml. Dapagliflozin did better regarding the primary composite end-point but also improved on the end-point of cardiovascular death. While SGLT2 inhibitors are in principle diabetes drugs, the benefits on the primary end-point were independent of diabetes at baseline. Dapagliflozin was apparently well tolerated and overall it was felt to offer a new approach to treat heart failure. Options in heart failure are improving, and we will have to see where SGLT2 inhibitors fit in the current heart failure protocol.

Reference: N Engl J Med 2019; published online Sep 19
Abstract