Cardiology Research Review™

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Issue 119 - 2019

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Abbreviations used in this issue:

CAD = coronary artery disease; **CV** = cardiovascular; **HR** = hazard ratio; **LDL** = low-density lipoprotein; **PCI** = percutaneous coronary intervention; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **RCT** = randomised controlled trial.

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Welcome to the latest issue of Cardiology Research Review.

In this issue, dietary cholesterol and eggs are again under the spotlight for their association with CV disease, the Cholesterol Treatment Trialists' Collaboration looks at the value of statins in the elderly, and a multinational cohort study revisits the debate about optimal sodium intake. UK researchers report that survival after a diagnosis of heart failure has only modestly improved in the 21st century, bempedoic acid treatment shows promise as add-on therapy in patients with hypercholesterolaemia not responding sufficiently to statins, and US researchers report that canakinumab is not cost-effective for secondary prevention in patients with prior MI.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

Associate Professor John Amerena

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Associations of dietary cholesterol or egg consumption with incident cardiovascular disease and mortality

Authors: Zhong V et al.

Summary: This study determined the association of dietary cholesterol and eggs with incident CV disease and all-cause mortality. Individual participant data were pooled from 6 prospective US cohorts (n=29,615). During a median follow-up of 17.5 years there were a total of 5400 CV disease events and 6132 all-cause deaths. The associations of dietary cholesterol or egg consumption with incident CV disease and all-cause mortality were monotonic. Each additional 300mg of dietary cholesterol consumed per day was associated with a higher risk of incident CV disease (adjusted HR, 1.17) and all-cause mortality (adjusted HR, 1.18). Each additional half egg per day was also associated with a higher risk of incident CV disease (adjusted HR, 1.06) and all-cause mortality (adjusted HR, 1.08). The associations between egg consumption and CV disease and all-cause mortality were no longer significant after adjustment for dietary cholesterol consumption.

Comment: Not surprisingly these data show that increased intake of cholesterol and eggs is associated with increased risk of CV disease in a US population. I still wonder how much of this association with eggs is due to accompanying food and cooking methods, such as frying eggs with bacon, sausages and hash browns etc (more so than the eggs themselves), and whether poached or boiled eggs would have the same risk, which was not explored in this analysis.

Reference: JAMA 2019;321(11):1081-95

Abstract

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Efficacy and safety of statin therapy in older people

Authors: Cholesterol Treatment Trialists' Collaboration

Summary: This meta-analysis examined the efficacy and safety of statin therapy in older people. A total of 28 RCTs of statins (n=186,854) were included. Participants were divided into six age groups (≤55 years, 56–60 years, 61–65 years, 66–70 years, 71–75 years, and >75 years). 14,483 participants (8%) were aged >75 years at randomisation, and median follow-up duration was 4.9 years. Meta-analysis of individual participant data showed that statin therapy significantly reduced major vascular events and major coronary events in all age groups. Proportional reductions diminished slightly with age, but the trend did not reach statistical significance. The reduction in major vascular events in patients with pre-existing vascular disease was similar across all age groups.

Comment: There is ongoing debate as to the benefits of statin therapy in the elderly (>75 years), especially for primary prevention. This meta-analysis suggests that there are benefits in older patients, with a reduction in major vascular events primarily in those with established CV disease. This will be explored in more detail in the Australian-led STAREE study which is just about to start recruitment.

Reference: Lancet 2019;393(10170):407-15
Abstract

RESEARCH REVIEW — The Australian Perspective Since 2007

Joint association of urinary sodium and potassium excretion with cardiovascular events and mortality

Authors: O'Donnell M & Mente A

Summary: This multinational cohort study evaluated the association of urinary sodium and potassium excretion (as surrogate measures of intake) with CV events and mortality. The cohort comprised 103,570 people from urban and rural communities in 18 high-, middle-, and low-income countries. Morning fasting urine samples were used to estimate 24h urinary sodium and potassium excretion. A 6-category variable for joint sodium and potassium excretion was used: sodium excretion <3 g/day (low), 3–5 g/day (moderate), and >5 g/day (high), together with potassium excretion either greater/equal or less than the median (2.1 g/day). Multivariable Cox regression analysis found a J-shaped association of sodium excretion, and an inverse association of potassium excretion, with death and CV events during a median follow-up of 8.2 years. For joint sodium and potassium excretion categories, the lowest risk of death and CV events was seen in the group with moderate sodium excretion and higher potassium excretion. Compared with this group, the combinations of low potassium and low sodium excretion (HR, 1.23) and low potassium and high sodium excretion (HR, 1.21) were associated with the highest risk.

Comment: The debate regarding the optimal sodium intake continues. Previous studies from this group have shown that high and low salt intakes increase CV risk, and these data confirm this but also show that high potassium intake is protective. This being the case perhaps our focus should also be on increasing dietary potassium as well as keeping salt intake to a moderate level.

Reference: BMJ 2019;364:l772
Abstract

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Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017

Authors: Taylor C et al.

Summary: This UK cohort study estimated trends in survival rates for people diagnosed with heart failure in primary care from 2000 to 2017. Primary care data for 55,959 patients aged ≥45 years with a new diagnosis of heart failure and 278,679 age- and sex-matched controls were extracted from the Clinical Practice Research Datalink for the period 2000–2017, and linked with mortality data. Overall, 1-, 5-, and 10-year survival rates increased over time to 80.8%, 48.2%, and 26.2%, respectively. Improvement in survival was greater for patients not requiring hospitalisation around the time of diagnosis (5.3 vs 2.9 years, p<0.001). A deprivation gap was evident between people who were least deprived and those who were most deprived (median survival, 11.1 vs 8.7 years; p<0.001).

Comment: This large cohort study shows that even with the best available therapy heart failure has a terrible prognosis with 81%, 48% and 26% survival at 1, 5 and 10 years, respectively, despite best available therapy, and with worse outcomes in the socially disadvantaged. Although survival rates have improved over time, heart failure still represents a huge public health problem as it is resource intensive and is likely to increase with the aging of the population. Incremental benefit of new therapies over traditional treatment has been disappointing, apart from Entresto®, so it is imperative we try and get all patients diagnosed with heart failure on evidence-based treatment, and that further research is undertaken.

Reference: BMJ 2019;364:l223
Abstract

Safety and efficacy of bempedoic acid to reduce LDL cholesterol

Authors: Ray K et al., for the CLEAR Harmony trial

Summary: The CLEAR Harmony trial investigated the long-term safety and efficacy of bempedoic acid in patients with hypercholesterolaemia who were also taking guideline-recommended statin therapy. 2230 patients with LDL cholesterol ≥70 mg/dl despite taking maximally tolerated statin therapy were randomised 2:1 to receive add-on bempedoic acid or placebo for 1 year. At week 12, bempedoic acid reduced mean LDL cholesterol by 19.2 mg/dl (–16.5% from baseline; p<0.001 vs placebo). The incidence of adverse events did not differ significantly between groups, but the incidence of adverse events leading to discontinuation was higher in the bempedoic acid group (10.9% vs 7.1%), as was the incidence of gout (1.2% vs 0.3%).

Comment: Many patients with atherosclerotic CV disease do not reach target levels despite ezetimibe and maximally tolerated doses of statins, which places them at increased risk for CV events. PCSK9 inhibitors are an option in this situation but their prohibitive cost means their use is severely restricted in Australia. Bempedoic acid appears to be a safe and efficacious cholesterol-lowering agent, but there is no outcome data yet. Whether it will become available before outcome studies are published is not clear, but there is a precedent with ezetimibe which was available for years with only efficacy and safety data.

Reference: N Engl J Med 2019;380:1022-32
Abstract

Mendelian randomization study of *ACLY* and cardiovascular disease

Authors: Ference B et al.

Summary: ATP citrate lyase is an enzyme in the cholesterol biosynthesis pathway, upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the statin target. This mendelian randomisation study determined whether genetic inhibition of ATP citrate lyase has the same effect on LDL cholesterol levels as genetic inhibition of HMGCR. Genetic scores were constructed that were composed of independently inherited variants in the genes encoding ATP citrate lyase (*ACLY*) and HMGCR to create instruments that mimic the effect of ACYL inhibitors and HMGCR inhibitors. 654,783 patients were included in the study, 105,429 of whom had a major CV event. *ACLY* and *HMGCR* scores were associated with similar patterns of changes in plasma lipid and lipoprotein levels and with similar effects on the risk of CV events per 10-mg/dl decrease in LDL cholesterol. Neither lifelong genetic inhibition of ATP citrate lyase nor lifelong genetic inhibition of HMGCR was associated with an increased risk of cancer.

Comment: This interesting study shows that in patients with genetic abnormalities that lower cholesterol levels to similar levels seen with statins and bempedoic acid, there is a reduction in CV events. This bodes well for the outcome studies with bempedoic acid (see above) and is consistent with the "lower is better" mantra.

Reference: N Engl J Med 2019;380:1033-42
Abstract

Reinfarction in patients with myocardial infarction with nonobstructive coronary arteries (MINOCA)

Authors: Nordenskjöld A et al.

Summary: This observational study determined the mechanisms and prognosis for reinfarction in patients with MI with non-obstructive coronary arteries (MINOCA). 570 patients with MINOCA who were hospitalised in Sweden due to recurrent MI were evaluated. 340 of them underwent a new coronary angiography, and 47% had evidence of obstructive CAD. Male sex, diabetes, peripheral vascular disease, elevated creatinine levels, and ST elevation at presentation were more common in patients with MI with obstructive CAD than in patients with recurrent MINOCA. Mortality during a median follow-up of 38 months did not differ between patients with or without obstructive CAD.

Comment: Once a patient has had MINOCA it would be reasonable to assume that recurrent MI would not be associated with CAD. This study would suggest this is not the case. 50% of patients in this situation had marked progression of CAD, so that a remote history of MINOCA should not obviate the need for angiography (with or without PCI) in patients who present with recurrent acute coronary syndrome.

Reference: Am J Med 2019;132(3):335-46
Abstract

Cost-effectiveness of canakinumab for prevention of recurrent cardiovascular events

Authors: Sehested T et al.

Summary: This study evaluated the cost-effectiveness of adding the anti-inflammatory monoclonal antibody canakinumab to standard of care for the secondary prevention of major CV events. A hypothetical cohort of post-MI patients with a high-sensitivity C-reactive protein (CRP) level ≥2 mg/L was constructed. Patients received canakinumab 150mg every 3 months plus standard of care, compared with standard of care alone. A state-transition Markov model was used to estimate costs and outcomes over a lifetime horizon from a US health care sector perspective (using the canakinumab market price of $US73,000 per year). Adding canakinumab to standard of care increased life expectancy from 11.31 to 11.36 years, quality-adjusted life-years (QALYs) from 9.37 to 9.50, and costs from $US242,000 to $US1,074,000, yielding an incremental cost-effectiveness ratio of $US6.4 million per QALY gained. The price would have to be reduced by more than 98% to meet the $US100,000 per QALY willingness-to-pay threshold.

Comment: The CANTOS study was a pivotal proof of concept study that showed that in patients with CV disease and inflammation (as measured by CRP), treatment with the interleukin-6 inhibitor canakinumab was associated with a reduction in CV events but not CV or all-cause mortality. Unfortunately its cost is prohibitive, as shown in this study, so it is unlikely to ever be used in clinical practice unless there is a large reduction in its cost.

Reference: JAMA Cardiol 2019;4(2):128-35
Abstract

Efficacy and safety of aspirin for primary prevention of cardiovascular events

Authors: Mahmoud A et al.

Summary: This meta-analysis evaluated the efficacy and safety of aspirin for primary prevention of CV events. A search of various electronic databases identified 11 RCTs of aspirin vs placebo (or control) involving a total of 157,248 patients without established atherosclerotic disease. Meta-analysis of the data showed that aspirin was not associated with a lower incidence of all-cause mortality during a mean follow-up of 6.6 years. However, aspirin was associated with an increased risk of major bleeding (relative risk, 1.47; p<0.0001) and intracranial haemorrhage (relative risk, 1.33; p=0.001).

Comment: Recent studies such as ASPREE, ARRIVE and ASCEND were unable to demonstrate a benefit of aspirin in the elderly without overt CV disease and in high CV risk individuals, and in ASCEND there was no net benefit even in a diabetic population. This meta-analysis confirms these findings so that the general consensus is now that aspirin should be not recommended in patients for primary prevention, and used only in those who have had a CV event.

Reference: Eur Heart J 2019;40(7):607-17
Abstract

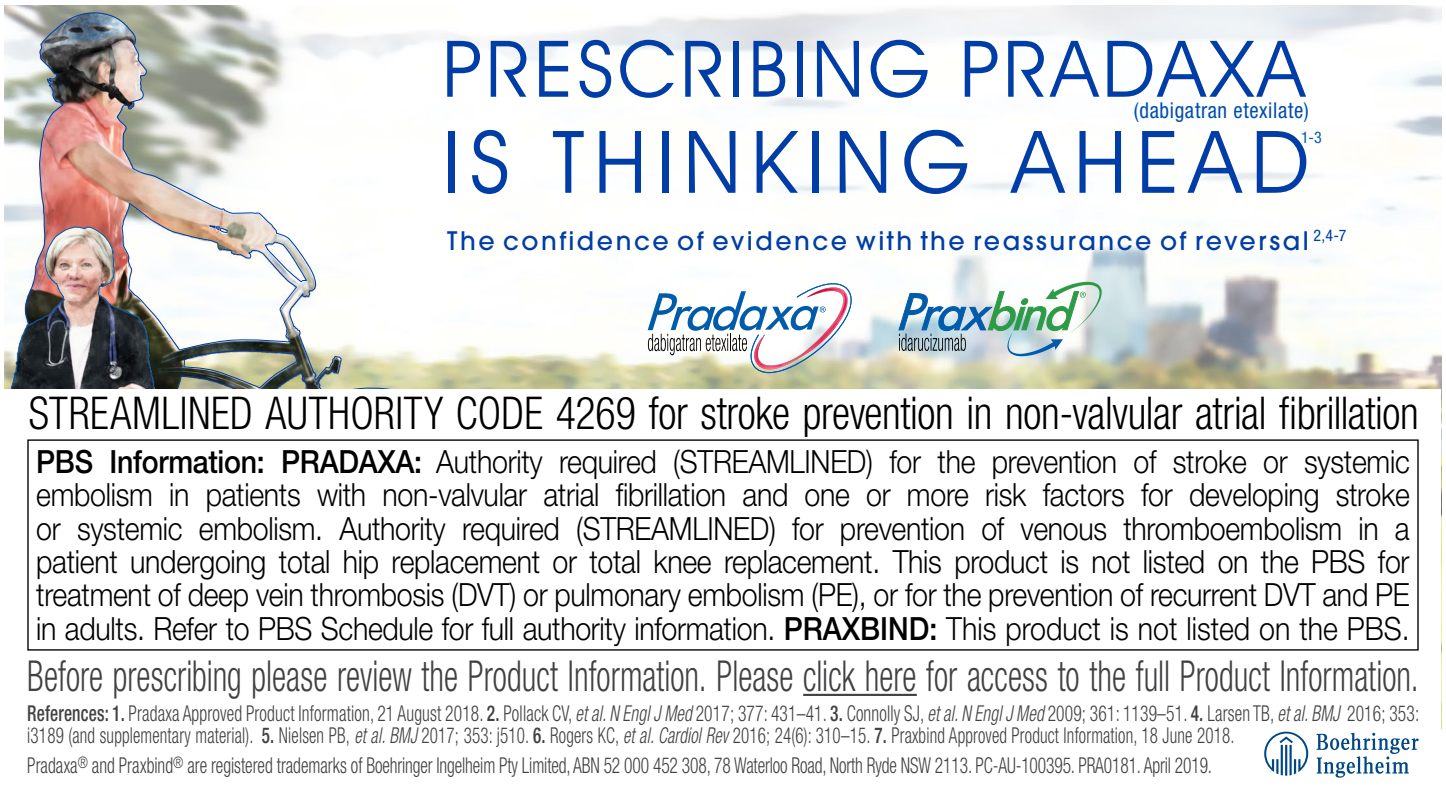
Levels of evidence supporting American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines, 2008-2018

Authors: Fanaroff A et al.

Summary: This study determined the level of evidence (LOE) supporting current guideline recommendations from the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC). The number of recommendations and the distribution of LOE A (supported by data from multiple RCTs or a single, large RCT), LOE B (supported by data from observational studies or a single RCT), and LOE C (supported by expert opinion only) were determined for each guideline document. Across 26 current ACC/AHA guidelines, 8.5% of recommendations were classified as LOE A, 50.0% as LOE B, and 41.5% as LOE C. Across 25 current ESC guideline documents, 14.2% of recommendations were classified as LOE A, 31.0% as LOE B, and 54.8% as LOE C. When comparing current guidelines with prior versions, the proportion of recommendations that were LOE A did not increase in either ACC/AHA or ESC guidelines.

Comment: Although we try to practice evidence-based medicine, this study suggests that many of the guidelines that are used to direct decisions we have to make in clinical practice are based on consensus opinion from key opinion leaders and experts. Given that most of the older drugs we use in cardiology are off-patent, and the cost of clinical trials, it is unlikely that trials will be undertaken to prove the benefits of traditional treatments e.g. diuretics, but all new therapies will need to have RCT data before being accepted as legitimate treatment options.

Reference: JAMA 2019;321(11):1069-80
Abstract



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