Cardiology Practice Review™

Making Education Easy

Issue 21 - 2022

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Abbreviations used in this issue:

PBAC = Pharmaceutical Benefits Advisory Committee
RHD = rheumatic heart disease
TGA = Therapeutic Goods Administration

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Welcome to the 21st issue of Cardiology Practice Review.

This Review covers news and issues relevant to clinical practice in cardiology. It will bring you the latest updates, both locally and from around the globe, in relation to topics such as new and updated treatment guidelines, changes to medicines reimbursement and licensing, educational, medicolegal issues, professional body news and more. And finally, on the back cover you will find our COVID-19 resources for Cardiologists and a summary of upcoming local and international educational opportunities including workshops, webinars and conferences.

We hope you enjoy this Research Review publication and look forward to hearing your comments and feedback.

Kind Regards,

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Editor

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Clinical Practice

Changes to recommended management of borderline RHD in Australia

Borderline rheumatic heart disease (RHD) is defined as 'echocardiographic features which are abnormal but do not fulfil criteria for the diagnosis of RHD'. It is thought that borderline RHD represents a combination of normal variations in cardiac echocardiography findings and early RHD pathology. A diagnosis of borderline RHD is restricted to people aged ≤20 years, because in individuals older than 20 years, minor age-related or degenerative changes may overlap with what is defined as borderline RHD on echocardiography.

Previously in Australia, secondary prophylaxis was not routinely recommended for borderline RHD. It could be considered, however, for individuals with a history of acute rheumatic fever (ARF) or a family history of rheumatic valve surgery, or if the family preferred treatment. However, new evidence from the 2021 GOAL study found that Ugandan children and adolescents with borderline RHD who received secondary prophylaxis for two years after diagnosis were significantly less likely to develop structural heart changes on echocardiography when compared to those that did not receive prophylaxis. An Australian expert assessment group reviewed these results and agreed that the benefits of secondary prophylaxis for borderline RHD are now relevant in the Australian setting. In response to the GOAL study Australian guidelines for managing borderline RHD in Australia have changed.

Updated recommendations

Individuals aged 20 years and younger who have no documented history of ARF, are diagnosed with borderline RHD on echocardiogram and who live in a high-risk setting should receive secondary prophylaxis for a minimum of two years following diagnosis. Medical review and repeat echocardiogram should be conducted at 1-2 years after diagnosis, and again 1-2 years after ceasing secondary prophylaxis. High risk settings include:

- People living in an ARF-endemic setting.
- Aboriginal and/or Torres Strait Islander peoples living in rural or remote settings.
- Aboriginal and/or Torres Strait Islander peoples, and Māori and/or Pacific Islander peoples living in metropolitan households affected by crowding and/or lower socioeconomic status.
- People with a personal history of ARF.

https://tinyurl.com/2uwaxjas

The relevance of symptoms in CVD: A scientific statement from the AHA

Symptoms of six common cardiovascular diseases (CVD) — acute coronary syndromes, heart failure, valvular disorders, stroke, rhythm disorders, and peripheral vascular disease — often overlap and may vary over time and by sex, the American Heart Association (AHA) notes in a new scientific statement. CVD symptoms can profoundly affect quality of life, and a clear understanding of them is critical for effective diagnosis and treatment decisions. Evaluating CVD symptoms can be challenging due to their subjective nature. Symptoms may go unrecognised or unreported if people don't think they are important or are related to an existing health condition.

ACS — Chest pain and associated symptoms

Chest pain is the most frequently reported symptom of ACS and has often been described as substernal pressure or discomfort and may radiate to the jaw, shoulder, arm, or upper back. The most common co-occurring symptoms are dyspnoea, diaphoresis, unusual fatigue, nausea, and light headedness. Women are more likely than men to report additional symptoms outside of chest pain. As a result, symptoms other than chest pain have often been labelled as atypical. However, this may have been due to the lack of women included in the clinical trials from which the symptoms were derived.

Heart failure

In HF, dyspnoea is the classic symptom and a common reason to present for medical care. However, early, more subtle symptoms should be recognised. These include gastrointestinal symptoms such as upset stomach, nausea, vomiting, and loss of appetite; fatigue; exercise intolerance; insomnia; pain (chest and otherwise); mood disturbances (primarily depression and anxiety); and cognitive dysfunction. Women with HF report a higher burden of physical symptoms, are more likely to have depression and anxiety, and report a lower quality of life compared to men with HF. It is important to account for dyspnoea by using probing questions.

Valvular heart disease

Valvular heart disease is a common cause of HF, with symptoms generally indistinguishable from other HF causes. Rheumatic heart disease is still prevalent in low- and middle-income countries, with population aging and cardiomyopathies now the main cause of valve disease. In the absence of acute severe valve dysfunction, patients typically have a prolonged asymptomatic period, followed by a period of progressive symptoms. Symptoms of aortic valve disease can differ between women and men. Aortic stenosis can be silent for years, then as it progresses, women experience dyspnoea and exercise intolerance more often than men. Women are also more likely to be frail and to have a higher NYHA class (III/IV) than men. Men are more likely to report chest pain.

Stroke

Classic stroke symptoms (face drooping, arm weakness, speech difficulty), in addition to nonclassic symptoms, such as partial sensory deficit, dysarthria, vertigo, and diplopia, should be considered for activating a stroke response team. Women with stroke are more likely to present with nonfocal symptoms (e.g., headache, altered mentality, and coma/stupor) than men. Post-stroke screening should include assessment for anxiety, depression, fatigue, and pain.

Rhythm disorders

Cardiac arrhythmias, such as atrial fibrillation (AF), atrial flutter, supraventricular tachycardia, bradyarrhythmia, and ventricular tachycardia, present with common symptoms. Palpitations are a hallmark of many cardiac arrhythmias. The most common cardiac arrhythmia, AF, may present with palpitations or less specific symptoms (fatigue, dyspnoea, dizziness) that occur with a broad range of rhythm disorders. Chest pain, dizziness, presyncope/syncope, and anxiety occur less frequently in AF. While palpitations are considered a typical AF symptom, some patients with new-onset AF may present with nonspecific symptoms or no symptoms. Women and younger patients with AF usually have palpitations, whereas men are more commonly asymptomatic. Older age also increases the likelihood of a nonclassic or asymptomatic presentation of AF.

Peripheral vascular disease

Classic claudication occurs in about one third of patients with peripheral arterial disease (PAD) and is defined as calf pain that occurs in one or both legs with exertion (walking), does not begin at rest, and resolves within 10 minutes of standing still or rest. However, non-calf exercise pain is reported more frequently than classic claudication symptoms. Women with PAD are more likely to have non-classic symptoms or an absence of symptoms. Evaluating symptoms at rest, during exercise, and during recovery can help with classifying symptoms as ischaemic or not. PAD with symptoms is associated with an increased risk for myocardial infarction and stroke, with men at higher risk than women.

Similar to PAD, peripheral venous disease (PVD) can be symptomatic or asymptomatic. Clinical classification of PVD includes symptoms such as leg pain, aching, fatigue, heaviness, cramping, tightness, restless legs syndrome, and skin irritation.

https://tinyurl.com/yaw2jk9c

National Lipid Association scientific statement on statin intolerance: A new definition and key considerations for ASCVD risk reduction in the statin intolerant patient

The US National Lipid Association has published a scientific statement with a new definition for statin intolerance and key considerations for ASCVD risk reduction in the statin intolerant patient.

Statin intolerance is defined as one or more adverse effects associated with statin therapy which resolves with dose reduction or discontinuation and can be classified as a complete inability to tolerate any dose of a statin or partial intolerance with inability to tolerate the dose necessary to achieve therapeutic objectives. To classify a patient statin intolerant, a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage.

The statement notes that although statins are generally well tolerated, statin intolerance occurs in 5% to 30% of patients and contributes to reduced statin adherence, as well as higher risk for adverse cardiovascular outcomes. The statement acknowledges the importance of identifying modifiable risk factors for statin intolerance and recognises the possibility of a "nocebo" effect, which refers to the patient expectation of harm leading to perceived side effects.

To identify a tolerable statin regimen, the statement recommends that clinicians consider employing a number of different strategies (a different statin, dose, and/or dosing frequency). Nonstatin therapy may be necessary for patients who cannot achieve therapeutic objectives with lifestyle and maximal tolerated statin therapy, and in these cases, therapies with evidence from randomised controlled trials showing reduced cardiovascular events are recommended (ezetimibe and PCSK 9 inhibitors). In high and very high-risk patients who are statin intolerant, nonstatin therapy should be initiated while further attempts are made to identify a tolerable statin in order to limit exposure to increased levels of atherogenic lipoproteins.

https://tinyurl.com/47xn7tmj

Evaluation of the incremental value of a coronary artery calcium score beyond traditional cardiovascular risk assessment

This systematic review and meta-analysis investigated the value of combining a CVD risk score with coronary artery calcium score (CACS) compared with CVD risk score alone for assessing cardiovascular status and risk. A database search identified six eligible cohort studies (n=17,961) in primary prevention populations that used one of the CVD risk calculators recommended by national guidelines (Framingham Risk Score, QRISK, pooled cohort equation, NZ PREDICT, NORRISK, or SCORE), and reported incremental discrimination with CACS for estimating the risk of a future cardiovascular event. Among participants classified as being at low risk by the CVD risk score and reclassified as intermediate or high risk by CACS, 85.5–96.4% did not have a CVD event during follow-up ranging from 5.1–10.0 years. Among participants classified as being at high risk by the CVD risk score and reclassified as low risk by CACS, 91.4–99.2% did not have a CVD event during follow-up. Overall, the gains in discrimination by CACS were at best modest (gain in C statistic was 0.036, 95% CI 0.020–0.052). The authors conclude that CACS may have a role for refining risk assessment in selected patients, but which patients would potentially benefit remains unclear.

https://tinyurl.com/5n84p483

Incidence, risk factors, natural history, and hypothesised mechanisms of myocarditis and pericarditis following COVID-19 vaccination: Living evidence syntheses and review

This review aimed to synthesise evidence on incidence rates and risk factors for myocarditis and pericarditis after mRNA vaccination against COVID-19 based on 46 studies. The incidence of myocarditis after vaccination was highest in adolescent and young adult males aged 12-17 years (50-139 cases per million) and 18-29 years (28-147 cases per million). Amongst girls and boys aged 5-11 years and women aged 18-29 years, myocarditis incidence with BNT162b2 (Pfizer/BioNTech) could be <20 cases per million. Among those aged 18-29 years, myocarditis incidence was higher after mRNA-1273 (Moderna) versus Pfizer vaccination. Incidence of myocarditis or pericarditis after a second dose of mRNA vaccine may be lower when administered ≥31 days versus ≤30 days after the first dose. In men aged 18-29 years, the dosing interval may need to be increased to ≥56 days to reduce myocarditis or pericarditis incidence. Most (>90%) myocarditis cases involved men with a median age of 20-30 years and with symptom onset 2-4 days after a second dose (71-100%). Most cases (≥84%) were admitted to hospital for a short duration (2-4 days). Over a longer-term follow-up (3 months; n=38), persistent echocardiogram abnormalities, and ongoing symptoms or a need for drug treatments or restriction in activities was observed in >50% of patients. The authors concluded that while most cases of myocarditis are mild and self-limiting, data on children and some severe cases of myocarditis are limited.

https://tinyurl.com/2436b7mw

Regulatory News

PBAC recommendations

The PBAC made the following recommendations at its July meeting. Of note, none of these products are listed on the PBS yet.

- Extending the existing PBS listings for **evolocumab** (Repatha®) for hypercholesterolaemia, to include patients who have a LDL-C between 1.8 and 2.6 mmol/L despite optimised treatment with statins and ezetimibe, and to allow initial prescribing by any medical practitioner in consultation with a specialist physician. The PBAC recommended that these changes flow on to **alirocumab** listings, at established pricing relativities with evolocumab.
- The PBS listing of **vericiguat** (Verquvo®) as an Authority Required for the initial restriction and an Authority Required for the continuing restriction, for the treatment of symptomatic (NYHA class II, III or IV) chronic heart failure in patients with a reduced ejection fraction (LVEF <45%) and who are stabilised after a recent decompensation heart failure event requiring hospitalisation and/or intravenous diuretic therapy.

https://tinyurl.com/bdzcrksk

TGA: Implementing conservation methods during the tenecteplase shortage

Last month, we reported that the TGA has been advised of a shortage of tenecteplase (Metalyse) injection until the end of 2023, due to manufacturing constraints. Tenecteplase is used to treat thrombolysis in the immediate period following myocardial infarction. The TGA has now published recommendations for clinicians to implement conservation methods during the shortage. Usage of tenecteplase must be reduced by at least 35% nationally or tenecteplase stock will be exhausted in Australia by the end of 2022. Tenecteplase supply must be prioritised for settings where there are no alternatives. Clinicians are asked to adopt the following recommendations from the beginning of October 2022. Prior to this, Boehringer Ingelheim will increase stock of alteplase (Actilyse) to allow for the increased use of alteplase in place of tenecteplase for some indications.

Clinical recommendations

- Tenecteplase should be prioritised for:
  - pre-hospital thrombolysis (e.g., ambulance services)
  - small rural and remote facilities/hospitals, including Aboriginal health services.
- Alteplase should be used in metropolitan and larger regional hospitals to conserve tenecteplase for the above settings.
- Any out-of-date tenecteplase products should be set aside and not disposed of pending further decisions on potential expiry date extensions.

https://tinyurl.com/czwbyxhs

TGA alert: Quinapril contamination with low levels of *N*-nitroso-quinapril

The TGA has been advised that very low levels of the nitrosamine impurity *N*-nitroso-quinapril have been detected in Australian quinapril products including when quinapril has been combined with hydrochlorothiazide. This issue also affects quinapril products and quinapril with hydrochlorothiazide supplied internationally.

As a precautionary measure, Pfizer Australia has paused supply of their quinapril products while this issue is investigated. In addition, all batches of Accupril and Accuretic/Aquinaretic tablets have been recalled from pharmacies that were identified as containing unacceptable levels of *N*-nitroso-quinapril.

Health professionals should be aware that there may be limited availability of quinapril and quinapril with hydrochlorothiazide products due to the current shortage. Alternative hypertension management may include one of the multiple other single ingredient ACE inhibitors or other alternatives.

https://tinyurl.com/26z73skd

News in Brief

Acute rheumatic fever and rheumatic heart disease in Australia

The Australian Institute of Health and Welfare has published an epidemiological overview of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) in Australia. Between 2016 and 2020, the number and rate of ARF notifications increased, from 60 per 100,000 in 2016 to 69 per 100,000 in 2020. The rate of new RHD diagnoses increased, and 80% of people newly diagnosed with RHD did not have a previous diagnosis of ARF. Fourteen percent of people had severe RHD at the time of their diagnosis. The median age at RHD diagnosis was 23 years, and females had higher rates for RHD in all age groups, excluding 0-4 years.

https://tinyurl.com/yckxjec3

Comparative efficacy of novel antidiabetic drugs on CV and renal outcomes in patients with diabetic kidney disease

This systematic review and network meta-analysis assessed the comparative effectiveness of sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors in patients with diabetic kidney disease. SGLT2 inhibitors significantly reduced the risk of the kidney-specific composite outcome by 26% (HR 0.74) and 36% (HR 0.64) compared with GLP-1 receptor agonists and DPP-4 inhibitors, respectively. The risk of major adverse cardiovascular events was significantly reduced with SGLT2 inhibitors (by 18%, HR 0.82) and GLP-1 receptor agonists (by 18%, HR 0.82), compared with DPP-4 inhibitors. SGLT2 inhibitors significantly reduced the risk of hospitalisation for heart failure by 28% (HR 0.72) and 41% (HR 0.59) compared with GLP-1 receptor agonists and DPP-4 inhibitors, respectively.

https://tinyurl.com/ye58wssm

Targeted hypothermia vs targeted normothermia in survivors of cardiac arrest

This systematic review and meta-analysis evaluated the use of targeted hypothermia in patients with coma after cardiac arrest. A search of MEDLINE, EMBASE, and Cochrane databases through July 2021 identified 8 randomised trials (n=2927) that were suitable for inclusion. The mean targeted temperature in the hypothermia arms varied from 31.7°C to 34°C. There were no significant differences between hypothermia and normothermia groups in terms of long-term mortality, rates of favourable neurological outcome, in-hospital mortality, bleeding, sepsis, or pneumonia. Ventricular arrhythmias were more common with hypothermia (risk ratio 1.36, 95% CI 1.17–1.58). After exclusion of the TTM2 trial, hypothermia had a favourable neurological outcome compared with normothermia (risk ratio 1.45, 95% CI 1.17–1.79). In the end, the meta-analysis calls for further randomised trials.

https://tinyurl.com/446jzvvk

COVID-19 Resources for Cardiologists

CSANZ https://tinyurl.com/y3xp272
ACC https://tinyurl.com/y68aud3a
ESC https://tinyurl.com/wn3fsts

Conferences, Workshops and CPD

Please click on the links below for upcoming local and international Cardiology meetings, workshops and CPD.
ACRA https://tinyurl.com/y4yj8xb5
CSANZ https://tinyurl.com/3mwt5ttr
Cardiac Skills Australia https://tinyurl.com/zkzlelb
Heart Foundation https://tinyurl.com/y34smdoz
Australian Centre for Heart Health https://tinyurl.com/e2yjcreu
ACC https://tinyurl.com/y2khytpz
AHA https://tinyurl.com/zajc9a7
ESC Congresses and Events https://tinyurl.com/y6ko68yf
ESC Education https://tinyurl.com/y3zkjp3o

Research Review Publications

Acute Coronary Syndrome Research Review
with Professor John French
http://tinyurl.com/gos7bqt

Atrial Fibrillation Research Review
with Dr Andre Catanchin
http://tinyurl.com/gpvl4dv

Cardiology Research Review
with Associate Professor John Amerena
http://tinyurl.com/gpxu6bl

Heart Failure Research Review
with Professor John Atherton, Professor Andrew Coats and Dr Mark Nolan
http://tinyurl.com/hxxrsv6

Interventional Cardiology Research Review
with Conjoint Professor Craig Juergens
http://tinyurl.com/h3h3wcp

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