Winter 2024

GP Connect

Supporting best practice in cardio-metabolic health

Sydney Cardiology

From the editor – Dr Gunjan Aggarwal

Specialising in general adult cardiology and non-invasive cardiac imaging, particularly echocardiography and cardiac computed tomography (CT).

Welcome to the winter edition of GP Connect 2024. This issue provides updates on the management of Heart Failure with reduced LV ejection fraction (HFrEF), cardiovascular disease associated with climate change, and the proposed mechanisms of action of SGLT2 inhibitors.

SGLT2 inhibitors have proven to be revolutionary in the management of patients with diabetes, chronic kidney disease, and all types of congestive heart failure. They are an important part of the therapeutic armamentarium of all cardiologists. Although they started out as diabetes medications, they have now become important cardiovascular drugs. Dr James Wong provides updates on the potential mechanisms of action of SGLT2 inhibitors, and the benefits associated with these drugs in heart failure, atherosclerosis, and kidney disease.

In this issue Dr Martin Brown provides an update on new therapeutic developments in HFrEF, including the four pillars of heart failure therapy, as well as the role of newer drugs such as omecamtiv mecarbil and vericiguat in patients with persistent symptoms of HFrEF.

Dr Fiona Foo thoroughly discusses the effects of climate change and air pollution on cardiovascular disease and various strategies to help identify and manage the impacts on patient health. I hope you enjoy this winter edition of GP Connect.

In this issue

Access past issues

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All Sydney Cardiology clinics have emergency appointments available for same-day referrals.

Click here to contact your local clinic directly for assistance.

We remain available as always to provide continued care to you and your patients in any way possible.

Thank you for your continued support,

Dr Gunjan Aggarwal.

Why are cardiologists interested in diabetic medications?

Dr James Wong

Specialising in general cardiology, prevention of coronary artery disease and hypertension.

Have you noticed how diabetic drugs have affected cardiac management lately? It is not for want of managing diabetes - cardiologists are very happy to leave this to diabetologists, but the bottom line is that sodium glucose cotransporter 2 (SGLT2) inhibitors such as empagliflozin and dapagliflozin used to treat diabetes also reduce major adverse cardiac events. The GLP1 receptor agonists also have prognostic benefits, but that is another story.

What are SGLT2 Inhibitors?

SGLT2 inhibitors were developed to treat type 2 diabetes mellitus (T2DM). The SGLT2 is expressed in the proximal renal tubule and mediates reabsorption of about 90% of the filtered glucose load. SGLT2 inhibitors promote renal glucose excretion and modestly lowers elevated blood glucose levels, blood pressure and weight.

Looking beyond diabetes – how it started

In the EMPA-REG outcome trial in 2015, empagliflozin showed promising results in patients with T2DM and atherosclerotic cardiovascular disease (ASCVD). When added to standard care, it significantly reduced the risk of major adverse cardiac events by 14%, cardiovascular death by 38%, all cause death by 32%, and hospitalisation for heart failure by 35% compared to placebo.

This caught the attention of heart failure doctors. Diabetes alone shortens life by 6-18 years. The combination of diabetes and heart failure is particularly bad prognostically with up to 50% mortality rate within a year and 75% at two years.

Following the EMPA-REG trial, evidence has continued to support SGLT2 inhibitors as effective heart failure therapy, regardless of the presence of diabetes. These agents seem to prevent macro and microvascular complications offering lifetime benefits.

Currently SGLT2 inhibitors are recommended as the 'fourth pillar' in heart failure management, alongside RAAS inhibition (ACE inhibitor or angiotensin receptor blocker or ARNI), a beta-blocker and a mineralocorticoid inhibitor – without requirement of the patient having diabetes. This applies to heart failure with reduced ejection fraction (HFref) and heart failure with preserved ejection fraction (HFpef).

How do SGLT2 inhibitors work?

Empagliflozin and dapagliflozin are once-daily oral medications. SGLT2 inhibitors work by exerting pleiotropic metabolic and direct cardioprotective and nephroprotective effects. They reduce inflammation, oxidative stress, fibrosis, intraglomerular hypertension and sympathetic nervous system activation and may improve mitochondrial function and myocardial efficiency (see Table 1 and Figure 1).

What are the precautions?

- All patients with type I diabetes mellitus
- The presence of T2DM with prior diabetes ketoacidosis (DKA) or a condition predisposing to DKA (e.g. pancreatic insufficiency, drug or alcohol addiction, prolonged fasting)
- Volume depletion or symptomatic hypotension
- eGFR < 20ml/min/1.73m2, end stage kidney disease or rapidly declining kidney function
- History of complicated urinary tract infection or genitourinary infections
- Presence of risk factors for foot amputation (e.g. neuropathy, foot deformity, vascular disease, previous foot ulceration)

Table 1. Lessons learned on presumed mechanisms of SGLT2i activity

SGLT2i and heart failure	
1.	Osmotic diuresis and natriuresis reduce cardiac overload
a.	Greater reductions of interstitial fluid compared with other diuretic agents
2.	Direct cardiac effects:
a.	Inhibits NHE-1
b.	SGLT2i reduce CaMKII (reduces sarcoplasmic Ca^{++} leak to improve contractility)
c.	Possible increase in phosphorylation levels of myofilament regulatory proteins
d.	Possible epigenetic modification
3.	Reduction of sympathetic nervous system overdrive
4.	Possible improvement in myocardial efficiency
5.	Improved oxygen delivery through stimulation of renal EPO secretion
6.	Reduction in inflammation can lead to activiation of adenosine monophosphate-activated protein kinase
7.	Reduction of oxidative stress (leads to improved mitochondrial function)
8.	Metabolic decrease in:
a.	HbA1c
b.	Blood pressure
c.	Body weight
d.	Vascular stiffness

SGLT2i and atherosclerosis	
1.	Reduction in inflammation
2.	Reduction in epicardial fat and noxious signals including leptin and RAAS
3.	Reduction in oxidative stress
4.	Improved endothelial function
5.	Cardioprotective effects by shifting circulating vascular progenitor cell toward M2 polarisation
6.	Reduction in uric acid
7.	Possible improvement of NAFLD
8.	Metabolic decrease in:
a.	HbA1c
b.	Blood pressure
c.	Body weight

NOTE: SGLT2i in atherosclerosis shows small increases of LDL-C which can result in unknown clinical implications

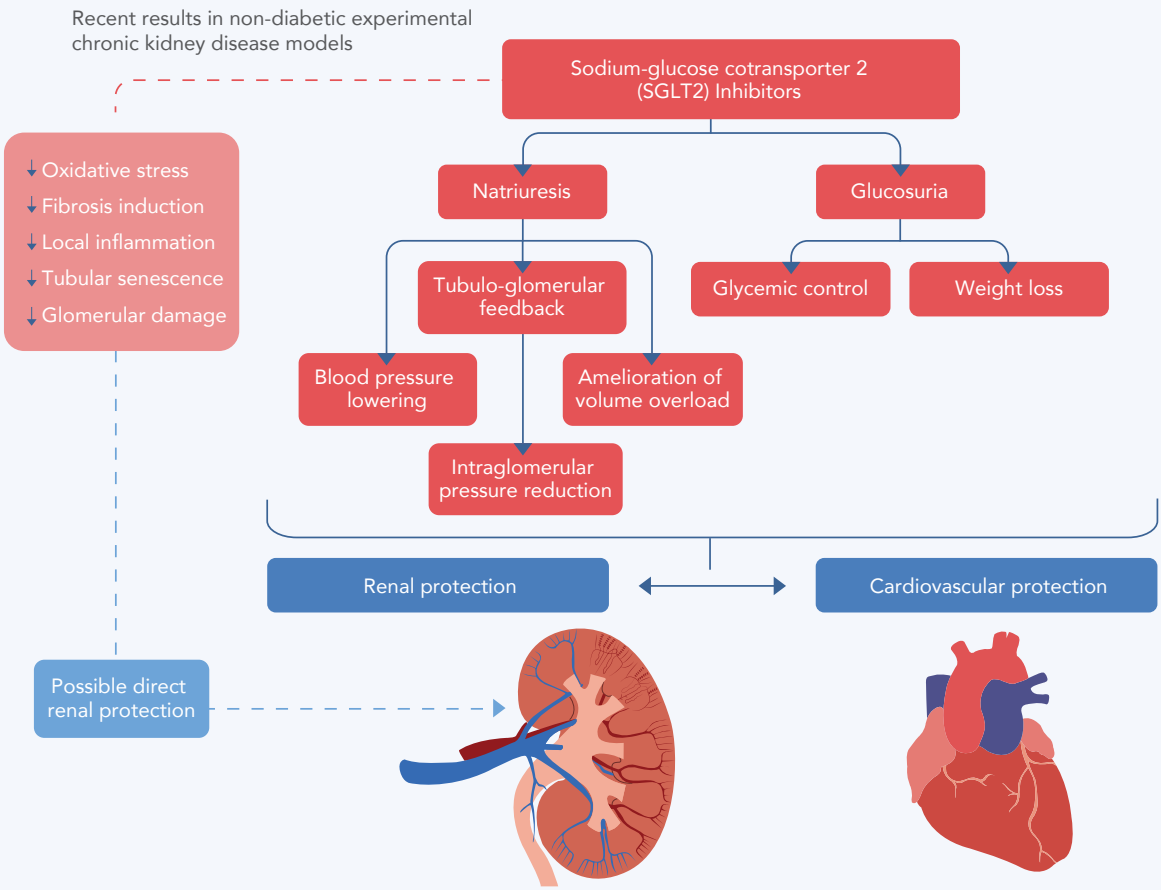
SGLT2i and progression of kidney disease	
1.	Metabolic decrease in:
a.	HbA1c
b.	Blood pressure
c.	Body weight
2.	Reduction in blood pressure and vascular stiffness
3.	Restoration of the tubuloglomerular feedback
4.	Reduction in workload regarding ATP production
5.	Anti-inflammatory and antifibrotic effects, reduction in oxidative stress
6.	Reduction in uric acid

Interaction between heart and kidney	
1.	Prevention of progress of disease in one organ may prevent deterioration of the other

CaMKII = Ca/calmodulin dependent kinase; EPO = erythropoietin; HbA1c = glycated hemoglobin Alc; LDL-C = low-density lipoprotein cholesterol; NAFLD = nonalcoholic fatty liver disease; RAAS = renin-angiotensin-aldosterone system; SGLT2i = sodium glucose cotransporter inhibitor.

Adapted from Zelniker and Braunwald, 2020

Why are cardiologists interested in diabetic medications? (continued)



Adapted from Zelniker and Braunwald, 2020

Figure 1. SGLT2i cardiorenal protection mechanistic overview

The next frontier – anticancer agents?

Observational studies have suggested that SGLT2i may potentially offer protection against cardiotoxic chemotherapy. Preclinical studies have also demonstrated cardioprotective and anticancer effects of SGLT2 inhibitors.

While it is too early for these findings to influence clinical practice, future research into the benefits of SGLT2 inhibitors looks promising.

Stay tuned.

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What's new in heart failure with reduced ejection fraction (HFrEF)?

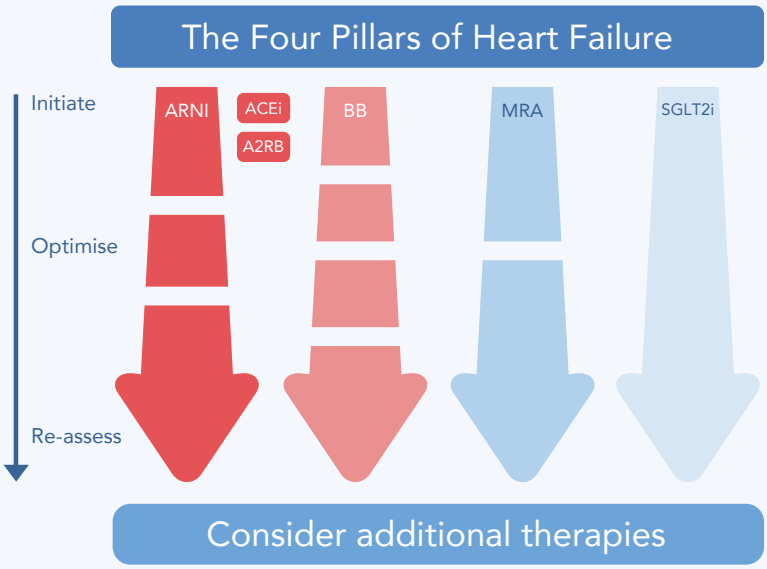
A/Prof Martin Brown

Specialising in advanced heart failure, pulmonary hypertension, and transplant cardiology.

Heart failure with reduced ejection fraction affects over 500,000 Australians per year - 2.1% of the population, resulting in 1.1 million days of inpatient hospital stays and A$3.1 billion in healthcare costs annually. It has a high 1-year readmission rate at 32% and mortality rate at 8%.[1] There are several new pharmacological treatments available beyond angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (A2RB), and beta-blockers (BB), which can further reduce heart failure readmissions and mortality. This article provides a brief overview of those treatments and their use.

Four Pillars of heart failure therapy

Guidelines now recommend four standard therapies for patients with HFrEF and left ventricular ejection fraction (LVEF) below 40%. Traditionally, we used ACEi or A2RB and BB. Now, recommendations are for the continued use of these agents or switching ACEi/A2RB to the combination of angiotensin receptor blocker (Valsartan®) and neprilysin inhibitor (Sacubitril®), known as ARNI (Entresto®). It is also recommended to add a mineralocorticoid receptor antagonist (MRA – spironolactone or eplerenone) and a sodium-glucose cotransporter-2 inhibitor (SGLT-2i – dapagliflozin or empagliflozin). Ideally, all these agents should be started at a low dose early and up-titrated every 2–4 weeks for outpatients (quicker for inpatients).[2]



A2RB	Beta-Blocker
Valsartan 80-320mg	Carvedilol 12.5-50mg bd
Candesartan 4-32mg	Metoprolol succinate 23.75-195mg
Losartan 25-100mg	Bisoprolol 2.5-10mg
	Nebivolol 2.5mg-10mg
MRA	**SGLT-2**
Spironolactone 12.5-50mg daily	Dapagliflozin 10mg daily
Eplerenone 12.5-50mg daily	Empagliflozin 10mg daily

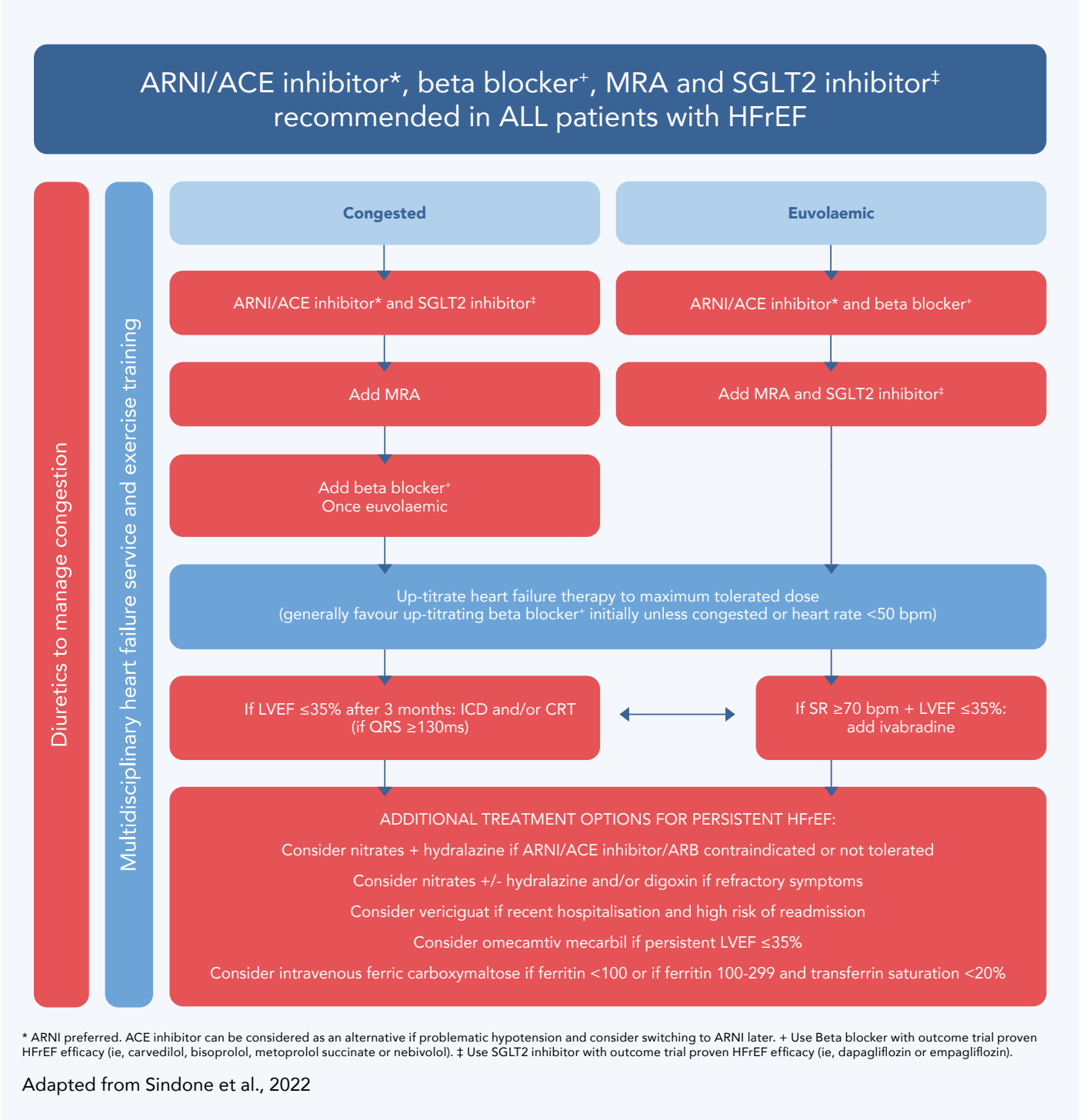
Adapted from Straw, McGinlay and Witte, 2021

Figure 1. Initiation and optimisation of the Four Pillars of Heart failure.

What's new in heart failure with reduced ejection fraction (HFrEF)? (continued)

Guidelines

The Cardiac Society of Australia and New Zealand (CSANZ) updated their guideline - directed algorithm in 2022 which outlines treatment commencement dependent on whether the patient is congested (fluid overloaded) or euvolaemic.[3]



* ARNI preferred. ACE inhibitor can be considered as an alternative if problematic hypotension and consider switching to ARNI later. + Use Beta blocker with outcome trial proven HFrEF efficacy (ie, carvedilol, bisoprolol, metoprolol succinate or nebivolol). ‡ Use SGLT2 inhibitor with outcome trial proven HFrEF efficacy (ie, dapagliflozin or empagliflozin).

Adapted from Sindone et al., 2022

Figure 2. Consensus statement on the current pharmacological prevention and management of heart failure.[3]

New Treatments

Entresto

The ARNI combination (Entresto®) was shown in the PARADIGM study of 8,442 patients with LVEF <40% and predominantly NYHA class II symptoms, to reduce the composite endpoint of heart failure hospitalisation (HFH) and cardiovascular death (CVD) by 20% when compared to ACEi (Enalapril®).[4]

SGLT-2 inhibitor

The two trials of SGLT-2i versus placebo, dapagliflozin (DAPA-HF) and empagliflozin (EMPEROR-Reduced), in a combined 8,474 patients with LVEF <40% and predominantly NYHA class II symptoms, when added to standard therapy, had similar results showing a reduction in HFH and CVD by 26% and 25% respectively.[5,6]

Omecamtiv mecarbil

Omecamtiv mecarbil is a myosin activator or "myotrope" which facilitates a 6-fold increase in binding of myosin heads to actin filaments, resulting in a greater "power stroke" or myocardial contractility. The Galactic HF study (2021) had 8,256 patients with LVEF <35% and predominantly NYHA class II-III, showed an 8% reduction in the combined endpoint of HFH, death, and urgent medical visits when added to standard therapy.[7] This is not currently available on the PBS in Australia.

Vericiguat

Vericiguat is an oral soluble guanylate cyclase stimulator which increases cyclic GMP and thus increases vascular dilation via the nitric oxide pathway. In the Victoria Study (2020) of 5,050 patients with LVEF <45%, NYHA class II-III, and recent decompensated heart failure, it showed a 10% reduction in CV death or HFH on top of standard therapy.[8]

This is currently available on the PBS for patients with LVEF <40% despite OMT, recent hospitalisation for heart failure or IV diuretics, and SBP >100 mmHg with NYHA II-IV.

What's new in heart failure with reduced ejection fraction (HFrEF)? (continued)

Conclusion

HFrEF is a common disease with high readmission and mortality rates. Using the "four Pillars" of heart failure therapy (ACEi/A2RB/ARNI, BB, MRA, and SGLT-2i) results in improved outcomes. The combination of ARNI, BB, MRA, and SGLT-2i together results in a 30% risk reduction versus ACEi and BB alone, with a 6.3-year gain in life expectancy for patients >55 years of age. The addition of vericiguat or omecamtiv results in a small but significant further benefit; however, only vericiguat is currently available in Australia.

Legend

A2RB = Angiotensin II receptor blockers
ACE = Angiotensin-converting enzyme
ACEi = Angiotensin converting enzyme inhibitors
ARNI = Angiotensin receptor neprilysin inhibitor
BB = Beta-blockers
CRT = Cardiac resynchronisation therapy
CSANZ = Cardiac Society of Australia and New Zealand
CVD = Cardiovascular death
HFrEF = Heart failure with reduced ejection fraction
HFH = Heart failure hospitalisation
ICD = Implantable cardioverter defibrillator
LVEF = Left ventricular ejection fraction
MRA = Mineralocorticoid receptor antagonist
NYHA = New York heart association
OMT = Optimal medical therapy
PBS = Pharmaceutical benefits scheme
SBP = Systolic blood pressure
SGLT-2i = Sodium-glucose cotransporter-2 inhibitor
SR = Sinus rhythm

References: 1. Chen, D.L. et al. 2017 'Snapshot of Heart Failure in Australia'. **2.** Straw, S., McGinlay, M. and Witte, K.K. (2021) 'Four pillars of heart failure: contemporary pharmacological therapy for heart failure with reduced ejection fraction', Open Heart, 8(1), p. e001585. Available at: https://doi.org/10.1136/openhrt-2021-001585. **3.** Sindone, A.P. et al. (2022) 'Consensus statement on the current pharmacological prevention and management of heart failure', The Medical Journal of Australia, 217(4), pp. 212–217. Available at: https://doi.org/10.5694/mja2.51656. **4.** McMurray John J.V. et al. (2014) 'Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure', New England Journal of Medicine, 371(11), pp. 993–1004. Available at: https://doi.org/10.1056/NEJMoa1409077. **5.** McMurray John J.V. et al. (2019) 'Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction', New England Journal of Medicine, 381(21), pp. 1995–2008. Available at: https://doi.org/10.1056/NEJMoa1911303. **6.** Packer Milton et al. (2020) 'Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure', New England Journal of Medicine, 383(15), pp. 1413–1424. Available at: https://doi.org/10.1056/NEJMoa2022190. **7.** Teerlink John R. et al. (2021) 'Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure', New England Journal of Medicine, 384(2), pp. 105–116. Available at: https://doi.org/10.1056/NEJMoa2025797. **8.** Armstrong Paul W. et al. (2020) 'Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction', New England Journal of Medicine, 382(20), pp. 1883–1893. Available at: https://doi.org/10.1056/NEJMoa1915928. **9.** A Systematic Review and Network Meta-Analysis of Pharmacological Treatment of Heart Failure With Reduced Ejection Fraction (no date). Available at: https://doi.org/10.1016/j.jchf.2021.09.004.

Educational activities

Dr Fiona Foo

Specialising in general and interventional cardiology with an interest in heart disease affecting women and sports cardiology.

On Demand: Cases in chronic plaque psoriasis – improving outcomes in moderate disease

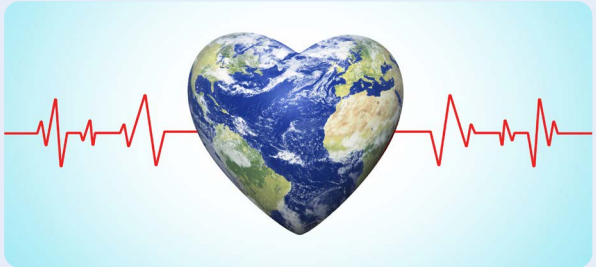
This webinar focuses on optimising the management of chronic plaque psoriasis as a systemic disease. Join Dr Fiona Foo and a panel of multidisciplinary experts as they present and discuss real-world clinical cases.

Click here to visit our website to access the webinar.

Clinical Takeaway Podcasts

Climate change and cardiovascular disease – part 1

Dr Fiona Foo explores how global warming increases the risk of cardiovascular disease, stroke and cardiac arrest. She identifies vulnerable populations and provides essential guidance to improve overall health.



Click here to visit our website to access the webinar.

Air pollution and cardiovascular disease – part 2

Dr Fiona Foo highlights the importance of educating patients about the health impacts of climate change, and the practical ways to reduce both personal and workplace carbon footprints.

Click here to visit our website to access the webinar.

Our team

We have experienced cardiologists in all major sub-specialties to provide the highest quality of patient care. We also have specialists in related fields including endocrinology and respiratory medicine. Our Sydney Cardiology team includes:

Cardiology

Dr James Wong

Specialising in general cardiology, prevention of coronary artery disease and hypertension.

Dr Abhinav Luhach

Specialising in general adult cardiology, cardiac CT, and preventive cardiology.

Dr Gunjan Aggarwal

Specialising in general adult cardiology and non-invasive cardiac imaging, particularly echocardiography and cardiac CT.

Dr Andrew Terluk

Specialising in general cardiology with an interest in cardiomyopathy in the setting of cancer.

Dr Ru-Dee Ting

Specialising in general and interventional cardiology, including cardiac haemodynamic studies and complex coronary intervention.

Dr Fiona Foo

Specialising in general and interventional cardiology with an interest in heart disease affecting women and sports cardiology.

Dr Bill Petrellis

Specialising in general adult cardiology and electrophysiology, including atrial fibrillation and device implantation.

A/Prof Martin Brown

Specialising in advanced heart failure, pulmonary hypertension, and transplant cardiology.

Endocrinology

Dr Suja Padmanabhan

Specialising in diabetes and general endocrinology with a special interest in diabetes in pregnancy and women's health.

Respiratory Medicine

Dr Tracy Smith

Respiratory and sleep physician specialising in respiratory disease with a special interest in respiratory failure due to lung or heart disease.

Our services

Sydney Cardiology is a world class comprehensive cardiology service, delivered with expertise and experience. Using state of the art diagnostic equipment in all five clinic locations, Sydney Cardiology strives to provide exemplary outcomes for long term patient care.

Urgent access

We provide same-day urgent appointments and 24/7 on-call support for GPs with a dedicated phone number, **02 9966 7700**.

Non-invasive testing

Including stress-echocardiography, echocardiography, holter monitor studies, ambulatory blood pressure studies, coronary calcium score, dobutamine stress echo, electrocardiogram and event monitor recording.

Echo, ABP, and holter monitor-only referral services

We provide echo-only, ABP-only, and holter monitor-only referral services, with a summary report on any adverse findings.

Electrophysiology

Including diagnostic electrophysiology studies, ablation of cardiac arrhythmias, cardiac device implantation, pacemakers and defibrillators, and follow up of implanted cardiac devices.

Cardiac procedures

Including coronary angiography, cardiac biopsies, right heart catheterisation, transesophageal echocardiogram and coronary angioplasty.

Including renal and lower limb angioplasty, ankle brachial index and SphygmoCorR central blood pressure testing.

ECG fax service

For urgent advice, 12-lead ECGs can be faxed to our locations.

Bella Vista - Fax: 02 9672 6214

Blacktown - Fax: 02 9676 8900

Chatswood - Fax: 02 9411 1904

Parramatta - Fax: 02 9635 1247

Sydney City - Fax: 02 9422 6081

Peripheral vascular services

Including renal and lower limb angioplasty, ankle brachial index and SphygmoCorR central blood pressure testing.

In-hospital care

All patients with appropriate private health coverage undergoing hospital procedures, do not incur any out-of-pocket costs. Sydney Cardiology has access to leading private hospitals, including:

Sydney Adventist Hospital
Wahroonga

Norwest Private Hospital
Bella Vista

Macquarie University Hospital
North Ryde

Northern Beach Hospital
Frenchs Forest

Patient fees

Sydney Cardiology is a private clinic however there are no out of pocket costs for Department of Veterans Affairs patients.

Referrals

To request a referral pad, click here.

Clinic locations

All clinics have emergency appointment timeslots available for same-day referrals. Contact any of our clinics directly for more assistance.

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Blacktown

Suite 4,
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Blacktown NSW 2148

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Tel: 02 9422 6040 | Fax: 02 9411 1904

Parramatta

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Parramatta NSW 2150

Tel: 02 9422 6060 | Fax: 02 9635 1247

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Sydney NSW 2000

Tel: 02 9422 6080 | Fax: 02 9422 6081

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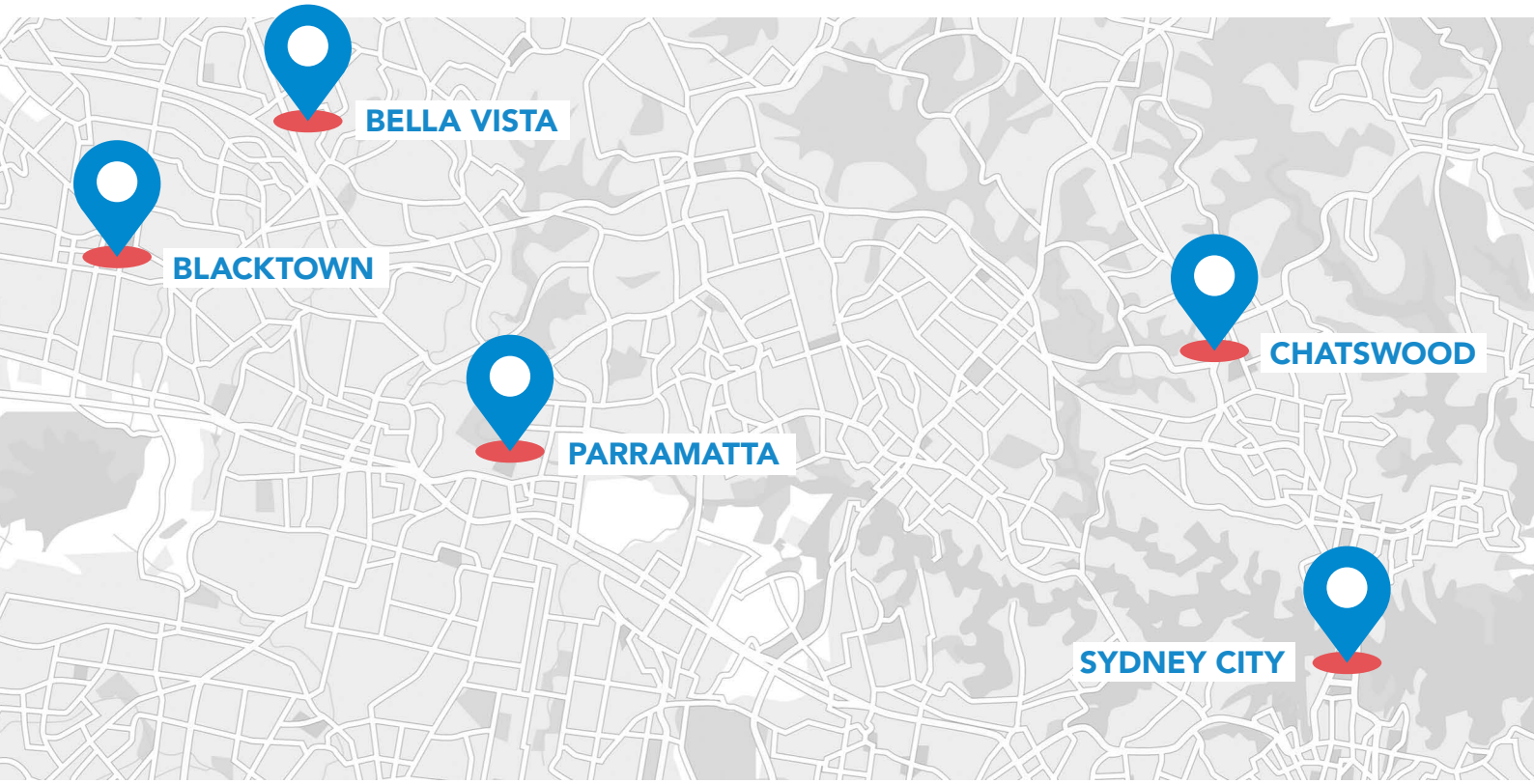
Call (02) 9966 7700 for specialist advice



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