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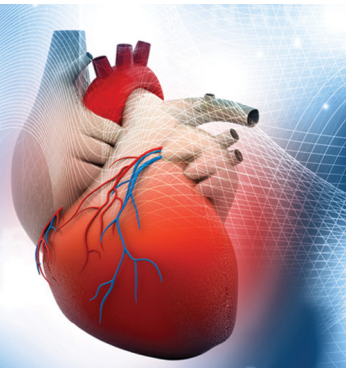
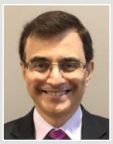
SPEAKER SERIES

How to welcome the fantastic four



Making Education Easy 2023

About the speaker



Professor Andrew Sindone
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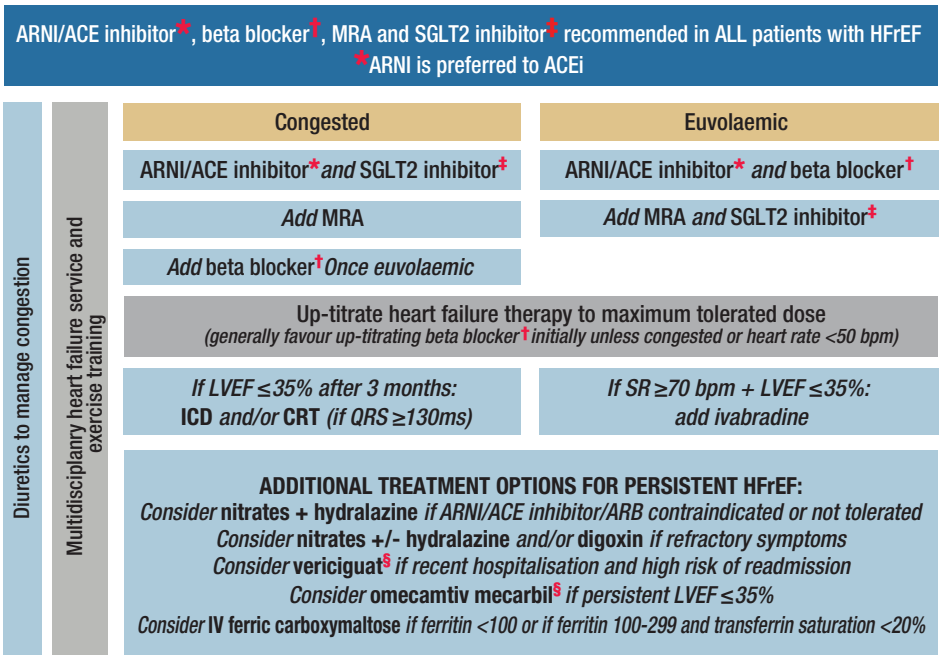
Andrew Sindone is a practicing cardiologist with private practice in Ryde and Westmead and is the Director of the Heart Failure Unit and Department of Cardiac Rehabilitation at Concord Hospital and Head of Department of Cardiology at Ryde Hospital, Sydney, NSW. He has a long history of cardiovascular research having presented over one hundred research papers both nationally and internationally. He has been principal investigator in more than 45 international multicentre clinical trials and is an advisor to the NSW Ministry of Health, as well as being co-author of the Australian Guidelines for the Management of Chronic Heart Failure.

This publication summarises a Novartis-sponsored breakfast symposium presentation by Professor Andrew Sindone, held in June 2023, in Auckland at the Cardiac Society of Australia and New Zealand Annual Scientific Meeting. In this symposium, Professor Sindone provided a summary of international heart failure guidelines for starting the four pillars of heart failure therapy – angiotensin receptor/neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRA) and sodium-glucose cotransporter-2 (SGLT2) inhibitors – and rapidly up-titrating these agents. He provided a brief overview of why use of the 'fantastic four' is important in heart failure and how to implement such therapy. The complete CSANZ symposium presentation video can also be viewed here.

In 2013, there were three main pillars of heart failure therapy, the angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), the beta blockers, and the MRAs. Now, in 2023, there are four main pillars of heart failure therapy, the ARNIs, the beta-blockers, MRAs and the SGLT2 inhibitors. So how do we use the 'fantastic four', how do we manage them and how do we introduce them? The European guidelines lack detail on how to introduce these agents, so Professor Sindone and colleagues developed guidelines for when to introduce each pillar based on whether patients are congested or euvolaemic (**Figure 1**).[1,2] Additionally, these guidelines highlight the importance of multidisciplinary care for all patients and point out that diuretics should be used only to manage congestion.



The key overarching theme is to commence all patients on the four destination therapies of ARNI/ACE inhibitor*, beta blocker†, MRA and SGLT2 inhibitor‡ as soon as clinically possible, given their early morbidity and mortality benefit. *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 (carvedilol, bisoprolol, metoprolol succinate or nebivolol). ‡ Use SGLT2 inhibitor with outcome trial proven HFrEF efficacy (dapagliflozin or empagliflozin). § Unavailable in New Zealand.

Figure 1. Heart failure with reduced ejection fraction management algorithm, with one of several possible d rug initiation regimens based on presence or absence of clinical congestion.[1]

Abbreviations used in this review
ACC = American College of Cardiology
ACE = angiotensin-converting enzyme
ACEI = angiotensin-converting enzyme inhibitors
ACEI/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker
AHA = American Heart Association
ARB = angiotensin receptor blockers
ARNI = angiotensin receptor/neprilysin inhibitors
BB = beta-blockers
CI = confidence interval
COR = class of recommendation
CRT = cardiac resynchronisation therapy
CV = cardiovascular
ESC = European Society of Cardiology
GDMT = guideline-directed medical therapy
HF = heart failure
HFrEF = heart failure with reduced ejection fraction
HFSA = Heart Failure Society of America
HR = hazard ratio
ICD = implantable cardioverter defibrillator
LVEF = left ventricular ejection fraction
MRA = mineralocorticoid receptor antagonists
SGLT2 = sodium–glucose cotransporter 2
SGLT2I = sodium-glucose cotransporter-2 inhibitors
SR = sinus rhythm

What is the evidence for the fantastic four?

The PARADIGM-HF trial demonstrated that, compared with the ACE inhibitor enalapril (n=4212), Entresto®, which is a fixed-dose combination of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan, (n=4187) was associated with about a 20% reduction in the primary endpoint of cardiovascular death or heart failure hospitalization, with a 21% reduction in heart failure hospitalisation and a 16% reduction in death.[3] Moreover, compared with placebo, several studies, going back over 20 years, have demonstrated that the beta-blockers are associated with about a 35% reduction in mortality on top of standard therapy.[4-7] MRAs have also been shown, in studies dating back to the 1990s, to be associated with substantial risk reductions for mortality, compared with placebo, with a 30% risk reduction with spironolactone in severe heart failure with reduced ejection fraction,[8] a 15% risk reduction for eplerenone post-myocardial infarction[9] and a 22% risk reduction for eplerenone in mild to moderate heart failure.[10]

Then there are the SGLT2 inhibitors, which were found to lead to a 35% reduction in heart failure hospitalisation in patients with type 2 diabetes,[11] with consistent results subsequently obtained in patients with heart failure alone.[12] Similar findings were obtained in the DAPA HF trial, which demonstrated a 26% relative risk reduction in the composite endpoint of worsening heart failure or cardiovascular death with dapagliflozin.[13] Importantly, this risk reduction was seen in both patients with and patients without diabetes; these are not diabetes medications, they are heart failure medications that have a side effect of lowering glucose.

Drugs that reduce mortality in heart failure

The ACE inhibitors can be considered as the original first-line agents in the treatment of heart failure, consistently demonstrating about a 20% reduction in overall mortality in mild, moderate and severe heart failure.[14-18] The ARBs are not as good as the ACE inhibitors, as demonstrated by several studies, and clearly shown by the results of a network meta-analysis looking at the relative risk reduction for all-cause mortality of the various drug classes for use in heart failure, in almost 100,000 patients (**Figure 2**).[19]

In this meta-analysis, there was an approximately 25% relative risk reduction for all-cause mortality with the ARNIs, 24% with the MRAs, 22% with the beta-blockers, 12% with the SGLT2 inhibitors, and 11% with the ACE inhibitors, but only about a 5% reduction in all-cause mortality with the ARBs. This shows the hierarchy of benefit – with the first four categories being the fantastic four.

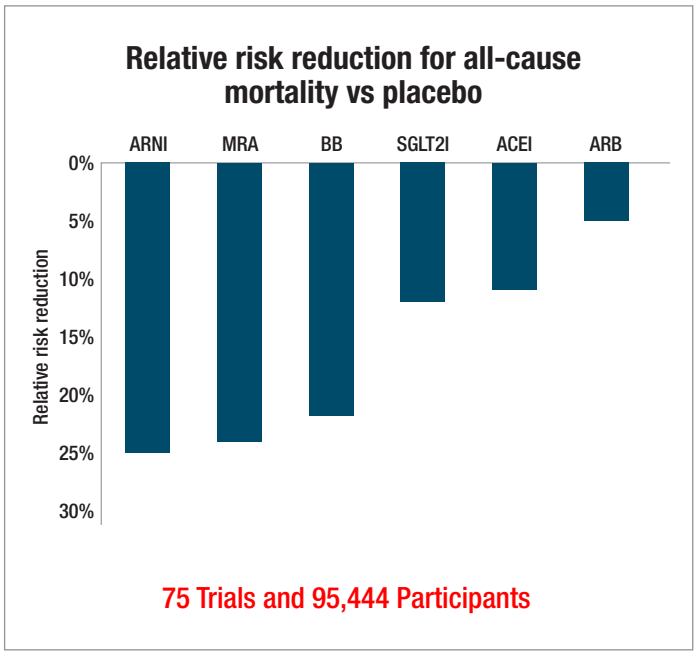


Figure 2. Network meta-analysis of randomized controlled trials in heart failure with reduced ejection fraction.[19]

How to use the fantastic four in heart failure

The currently available strategy, utilising the fantastic four, is associated with substantial improvements in patient outcome compared with the approach available ten years ago, as demonstrated in **Figure 3**, with substantial reductions in cardiovascular death, heart failure hospitalization and in all-cause mortality.[20] In a patient diagnosed with heart failure at age 55, the fantastic four provide about an additional 6.3 years of life, compared with ACEi/ARB plus a beta blocker.

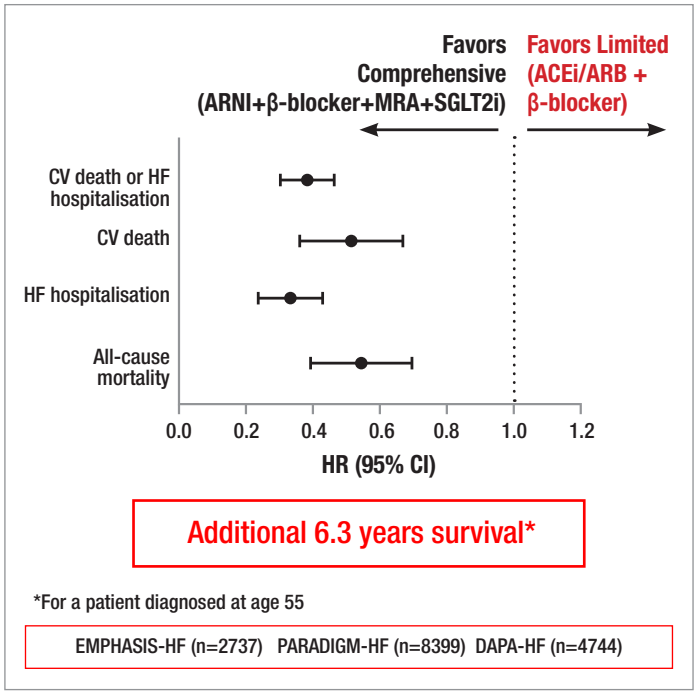


Figure 3. Estimating the impact of comprehensive therapy (ARNI + beta blocker + MRA + SGLT2i) compared with limited therapy (ACEi/ARB + beta blocker) for heart failure with reduced ejection fraction.[20]

However, a concerted effort is now needed, using multidisciplinary therapy, to ensure that patients actually receive this treatment, to improve post-hospitalisation heart failure outcomes in both Australia and New Zealand. Data from New Zealand and Australia show that fewer than one in five patients survive up to ten years after a heart failure hospitalisation, with 7.3 years of life expectancy lost due to heart failure on average compared with the general population.[21] Importantly, the incidence rate of death is highest in the first three months after hospitalisation.

In Australia, each hospitalisation for heart failure has a high rate of readmission and death and is associated with substantial healthcare costs.[22] A patient hospitalised with heart failure has an estimated all-cause readmission rate at 30 days of 20% and of 56% at one year, with corresponding all-cause mortality rates of 8% and 25%.[22] As the population ages there will be an increasing number of people with heart failure, with an estimated three quarters of a million people with heart failure in Australia by 2030.[23]

In-hospital initiation of guideline-directed medical therapy is imperative

While it is clear what should be happening, in terms of guideline-directed medical therapy for patients hospitalised with heart failure, the real-world situation is disappointing. In a study looking at guideline-directed medical therapy globally and in the Western Pacific Region, the proportion of patients with heart failure with reduced ejection fraction who were discharged on guideline-directed medical therapy varied by region, with a substantial portion of patients discharged without receiving such therapy, and considerably more patients failing to receive such therapy at six months post-discharge (**Table 1**).

Table 1. Medications at discharge and at six months post-discharge in patients following hospitalisation for heart failure.[24]

	Global		Western Pacific region	
Medication	At discharge	At 6 month follow up	At discharge	At 6 month follow up
ACEI/ARB	70%	59%	73%	55%
BB	76%	67%	71%	57%
MRA	59%	43%	71%	50%
1 year mortality	20%		17%	
HF hospitalisation	22%		20%	

Heart failure is a chronic progressive disease and early intervention is critical. Optimising in-hospital initiation of guideline-directed medical therapy may offer opportunities to improve the long-term survival of heart failure patients.[25] Initiating such treatment in hospital is crucial, this is the time where there is the greatest chance to make a difference to patient outcomes. This time is the most important opportunity to optimise therapy because hospitalisation for acute decompensated heart failure is a critical point in the disease trajectory, it is the turning point.

In patients who have not previously received optimal guideline-directed medical therapy for heart failure, in-hospital initiation of treatment is associated with substantial improvements in outcomes;[26] if such therapy is not initiated at this time, then more than 75% of the time these therapies are not initiated over the next 12 months.[27] Moreover, patients who initiate therapy in hospital are more likely to continue on such treatment, at least in part because patients are more likely to consider such therapy to be important.[28] The importance of in-hospital initiation of this therapy is supported by both the European and American guidelines for heart failure (**Table 2**).[2, 29]

However, evidence suggests that many patients are discharged from hospital without receiving optimal therapy, with one such study, using data from the Get with the Guidelines Heart Failure Registry in the United States, finding that 91% of eligible patients were discharged without receiving the ARNI sacubitril/valsartan.[30] This is a missed opportunity, as patients discharged without receiving such treatment, will likely never receive this during follow up. Professor Sindone puts this largely down to clinical inertia.

The second important facet of the guidelines is the recommendation for early follow-up after hospital discharge (**Table 2**).[2, 29] If patients are seen early, the clinician can assess if they are still congested, if they are too dry, whether treatment been initiated too rapidly, they can check if the patient is hypotensive, they can determine if there is something else going on, for example, do they have a respiratory tract infection? Additionally, once the patient is out of hospital and resuming normal activities, their blood pressure may go up, and they may require further up-titration of their ARNI treatment, up-titration of their beta blocker and perhaps down-titration of diuretics.

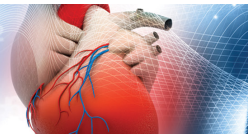
The STRONG-HF study looked at usual care versus high-intensity care (up-titration of treatments to 100% of recommended doses within 2 weeks of discharge and four scheduled outpatient visits over 2 months after discharge).[31] Notably, the study was terminated prematurely due to the superior efficacy of this high-intensity care vs usual care, with a reduction in patient symptoms, improved quality of life and reduced risk of 180-day all-cause death or heart failure readmission.

Table 2. Recommendations for management of patients after heart failure hospitalisation.

2021 ESC Guidelines[2]	COR	2022 AHA/ACC/HFSA Guidelines[29]	COR
It is recommended that patients hospitalised for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment	I	For patients hospitalised with HF, therapy with diuretics and other guideline-directed medications should be titrated with a goal to resolve clinical evidence of congestion to reduce symptoms and rehospitalisation	I
It is recommended that evidence-based oral medical treatment be administered before discharge	I	In patients with HRfEF, GMDT should be initiated during hospitalization after clinical stability is achieved	I
An early follow-up visit is recommended at 1-2 weeks after discharge to assess signs of congestion, drug tolerance, and to start and/or up-titrate evidence-based therapy	I	In patients being discharged after hospitalisation for worsening HF, an early follow-up, generally within 7 days of hospital discharge, is reasonable to optimise care and reduce rehospitalisation	2a

Recognise the four main therapies with a class 1 recommendation in heart failure with reduced ejection fraction[1]

- ARNI + beta-blocker + MRA + SGLT2I are recommended for all HFrEF patients.
- ARNI + beta-blocker + MRA + SGLT2I is estimated to provide 6.3 additional years of survival for a 55 year old or 1.4 additional years for an 80 year old, compared to ACEI/ARB + beta-blocker.
- All patients with HFrEF should be commenced on comprehensive therapy (*Comprehensive therapy includes an ARNI/ACE inhibitor, β-blocker, MRA and SGLT2i) as soon as clinically possible to reduce morbidity and mortality.
- HF therapies should be up-titrated to the maximum tolerated dose.
- ARNI or ACEI (ARNI preferred) is recommended in HFrEF (including newly diagnosed HF).
- ARNI is recommended as a replacement for ACEI or ARB in patients with HFrEF despite receiving ACEI (or ARB) and a beta-blocker.



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INITIAL APPLICATION
Applications from any relevant practitioner. Approvals valid for 12 months.

Prerequisites (tick boxes where appropriate)

☐ Patient has heart failure

and

☐ Patient is in NYHA/WHO functional class II

or

☐ Patient is in NYHA/WHO functional class III

or

☐ Patient is in NYHA/WHO functional class IV

and

☐ Patient has a documented left ventricular ejection fraction (LVEF) of less than or equal to 35%

or

☐ An ECHO is not reasonably practical, and in the opinion of the treating practitioner the patient would benefit from treatment

and

☐ Patient is receiving concomitant optimal standard chronic heart failure treatments

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