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Heart failure: what a GP needs to know in 2020

Making Education Easy 2020

About the speaker

Professor Richard Troughton

Richard Troughton is a Cardiologist at Christchurch Hospital and the Christchurch Heart Institute, and a Professor of Medicine at the University of Otago, Christchurch.

Abbreviations used in this review
ACE = angiotensin converting enzyme
ARB = angiotensin receptor blocker
ARNI = angiotensin receptor neprilysin inhibitor
BNP = B-type natriuretic peptide
ECG = electrocardiogram
eGFR = estimated glomerular filtration rate
NT-proBNP = N-terminal pro-BNP
MRA = mineralocorticoid receptor antagonist
NYHA = New York Heart Association
SGLT2 = sodium-glucose cotransporter 2

The 11th Annual South GP CME Meeting took place using an online format in August 2020. Professor Richard Troughton from Christchurch Hospital and the Christchurch Heart Institute spoke at a breakfast symposium sponsored by Novartis (NZ) Ltd. Professor Troughton provided an overview of heart failure, focusing on what GPs need to know to provide gold standard treatment. He also reviewed evidence for the use of sacubitril/valsartan (Entresto®) in heart failure patients with reduced ejection fraction, an important treatment advance for this condition. This review summarises key points of Professor Troughton's presentation.

Trends in heart failure

Heart failure is a highly prevalent condition. From middle age onwards, adults have an approximately 20% chance of developing heart failure during their lifetime.[1] For Māori and Pasifika populations, heart failure tends to develop at a younger age, which has a heavy personal and societal impact.

Hypertension is the most important risk factor for the development of heart failure, accounting for up to 60% of the attributable risk in women and in the order of 40% in men.[1] Myocardial infarction is another important risk factor, especially for men in whom it contributes 34% of the risk for heart failure.[1] Optimal management of hypertension and prevention of vascular events can substantially reduce the risk of heart failure.

While symptoms may be similar, the pathophysiology of heart failure patients with preserved vs reduced left ventricular ejection fraction is quite different. In patients with preserved ejection fraction, vascular and ventricular stiffness and loss of diastolic reserve are key contributors to cardiac dysfunction. Patients with reduced ejection fraction have diminished pump function and show systolic impairment on echocardiogram.

Heart failure with preserved ejection fraction is more common in older age and in women, while heart failure with reduced ejection fraction is more common in men, reflecting higher rates of myocardial infarction.[2] Ejection fraction is an important predictor of mortality risk, with both all-cause death and cardiovascular death rates rising steeply at ejection fractions <40%.[2] The risk of dying from heart failure with reduced ejection fraction is ≥30% over 3 years, while the risk of dying from heart failure with preserved ejection fraction is substantially lower, although the latter still causes significant morbidity.[2]

Heart failure mortality statistics

- 50% of all heart failure patients will die within 5 years[3-5]
- 42% of NYHA class III and IV treated patients will die within 3 years[6]
- 34% of NYHA class I and II treated patients with die within 3 years[6]
- Patients with mild symptoms are still at risk of hospitalisation and death.[7]

Diagnosis of heart failure

Heart failure is primarily a clinical diagnosis. Initial assessment should include collecting clinical history, undertaking a physical examination, and performing an ECG (see **Table 1**).[7]

Clinical history	
• History of coronary artery disease (myocardial infarction, revascularisation)	• Exposure to cardiotoxic drug/radiation
• History of arterial hypertension	• Use of diuretics
	• Orthopnoea/paroxysmal nocturnal dyspnoea
Physical examination	
• Rales	• Jugular venous dilatation
• Bilateral ankle oedema	• Laterally displaced/broadened apical beat
• Heart murmur	
ECG	
• Any abnormality	

Table 1. Assessment of heart failure probability.[7]

If clinical features suggestive of heart failure are present, guidelines now recommend measurement of natriuretic peptides to aid in diagnosis, either BNP or NT-proBNP.[7-9] BNP is secreted primarily from cardiac myocytes. Pressure or volume loading of the heart will lead to secretion.[10] Normal or low natriuretic peptide levels accurately rule out heart failure. If levels are elevated (BNP ≥35 pg/ml or NT-proBNP ≥125 pg/ml in community settings), heart failure is likely and an echocardiogram should be undertaken if this has not previously been done.

Measurement of BNP/NT-proBNP levels

- Guideline-endorsed for diagnosis and monitoring of heart failure
- Low levels **rule out** heart failure
- High levels indicate heart failure is likely (or functionally important heart disease)
- Levels fall with effective heart failure treatment
- Persisting high levels are associated with high mortality and hospitalisation risk.

Professor Troughton acknowledged that accessing echocardiography in primary care can be difficult. It is, however, the single most important diagnostic test for heart failure. Echocardiography has become increasingly sophisticated, allowing phenotyping and prognostic assessment of heart failure, as well as the ability to identify additional prognostic markers.

Echocardiography measures

- The single most important diagnostic test for heart failure
- Key indices in suspected heart failure:
  - Left ventricular ejection fraction
  - Presence of left ventricular hypertrophy (increased mass or wall thickness)
  - Left ventricular diastolic dysfunction (elevated filling pressures)
  - Left atrial dilatation
  - More than moderate valve disease
  - Elevated right heart pressures (right ventricular systolic pressure >30 mm Hg).

Treatment of heart failure with reduced ejection fraction

The cornerstone of treatment for heart failure with reduced ejection fraction has been the combination of an ACE inhibitor (or ARB) with a β-blocker and MRA.[7-9] Use of this combination leads to a >50% reduction in mortality.[7,11] For patients who are still symptomatic, guidelines now recommend switching the ACE inhibitor/ARB to an ARNI.[7,8]

ARNIs are an important step forward in the treatment of heart failure with reduced ejection fraction. These agents restore the neurohormonal imbalance that occurs in heart failure, during which the vasoconstrictor system such as renin, angiotensin II, aldosterone, and norepinephrine dominates and leads to adverse cardiovascular remodelling and worsening of heart failure.[12] The vasoconstrictor system has historically been the target of successful heart failure therapies.[12] The ARNI class is the first to augment the beneficial activities of vasodilator systems such as the natriuretic peptides and adrenomedullin.

Sacubitril/valsartan is the first ARNI to become available, and was registered for use in New Zealand in November 2016.[13] Sacubitril/valsartan combines the ARB valsartan with the neprilysin inhibitor sacubitril into a single agent.[13] Neprilysin is an endopeptidase widely present in the kidneys, heart, brain, gut and lungs.[14] It inhibits the breakdown of key vasodilatory peptides, including the natriuretic peptides and adrenomedullin.[14] It also inhibits breakdown of angiotensin II, which is why an ARB must be given in combination with a neprilysin inhibitor.[14]

Pharmacodynamic effects of sacubitril/valsartan

- On the renin angiotensin system:
  - Reduces vasoconstriction, blood pressure, sympathetic tone, aldosterone levels, and ventricular hypertrophy
- On the natriuretic peptide system:
  - Enhances vasodilation and natriuresis/diuresis
  - Reduces blood pressure, sympathetic tone, and aldosterone levels.[13]

Efficacy of sacubitril/valsartan: the PARADIGM-HF trial

PARADIGM-HF, published in 2014, was a randomised controlled trial comparing sacubitril/valsartan with enalapril in 8442 patients with heart failure and reduced ejection fraction.[15] Key inclusion criteria for the trial were:

- NYHA class II-IV heart failure
- Left ventricular ejection fraction ≤ 40% (later revised to ≤35%)
- BNP levels ≥ 150 pg/ml or NT-proBNP levels ≥600 pg/ml
- Receiving an ACE inhibitor or ARB, at a dose equivalent to enalapril 10 mg/day for 4 weeks
- Guideline-recommended use of a β-blocker and MRA
- Systolic blood pressure ≥95 mm Hg, eGFR ≥30 mg/min/1.73 m^2 and potassium ≤5.4 mEq/L.[15]

Patients in the trial entered a single-blind run-in period prior to randomisation, during which they received enalapril 10 mg twice daily for 2 weeks, followed by sacubitril/valsartan 100 mg (49 mg/51 mg) twice daily for 1-2 weeks and then sacubitril/valsartan 200 mg (97 mg/103 mg) twice daily for 2-4 weeks.[15] Patients who tolerated enalapril and sacubitril/valsartan during the run-in period were eligible to be randomised to double-blind treatment with sacubitril/valsartan 200 mg (97 mg/103 mg) twice daily or enalapril 10 mg twice daily.[15]

Results of the PARADIGM-HF trial demonstrated a clinically and statistically significant reduction in the primary composite endpoint of cardiovascular death or heart failure hospitalisation with sacubitril/valsartan compared with enalapril (hazard ratio 0.80; 95% CI 0.73-0.87; p<0.001).[15] The risk of all-cause mortality was also significantly reduced with sacubitril/valsartan vs enalapril.[15]

Key outcomes of the PARADIGM-HF trial

- Sacubitril/valsartan was more effective than enalapril in reducing:
  - Cardiovascular death and heart failure hospitalisation
  - Cardiovascular death - *by an incremental 20%*
  - Heart failure hospitalisation - *by an incremental 21%*
  - All-cause mortality - *by an incremental 16%*
  - Symptoms and physical limitations.[15]
- Sacubitril/valsartan was better tolerated than enalapril:
  - Less likely to cause cough, hyperkalaemia, or renal impairment
  - Less likely to be discontinued due to an adverse event
  - More hypotension, but no increase in discontinuations
  - Not more likely to cause serious angioedema.[15]

The positive outcomes of the PARADIGM-HF trial led to updates in European and American guidelines for the management of heart failure.[7,9] In 2018, the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand also published updated guidelines, recommending that patients with heart failure and ejection fraction ≤40% despite optimal treatment with an ACE inhibitor or ARB are switched to an ARNI.[8]

Reimbursement of sacubitril/valsartan

Sacubitril/valsartan has been reimbursed by PHARMAC since October 2018 with the following special authority criteria:

- Patients must have NYHA/WHO functional class II, III or IV heart failure
- Patients must have documented left ventricular ejection fraction ≤35%
- Patients must be receiving concomitant optimal standard chronic heart failure treatments.[16]

Initial applications and renewals can be made by any relevant practitioner.[16] Due to the angiotensin II receptor blocking activity of sacubitril/valsartan, it should not be co-administered with an ACE inhibitor or an ARB.[13]

A recent change to the special authority criteria for sacubitril/valsartan because of COVID-19 restrictions* means new applications do not require an echocardiogram if this is not reasonably practical, thereby simplifying access.[16] However, the treating practitioner must believe that the patient would benefit from treatment with sacubitril/valsartan.[16]

*Since the Annual South GP CME Meeting took place, this change has been made permanent.

Local experience with sacubitril/valsartan

Professor Troughton has found the special authority process for sacubitril/valsartan to be straightforward. He emphasised that patients must be withdrawn from treatment with an ACE inhibitor or ARB before starting on sacubitril/valsartan. He has found the drug to be well tolerated, with a few instances of hypotension that can be managed using gradual dose titration. Patients have shown symptom improvement, and often have a reduced need for loop diuretics. In summary, Professor Troughton's experience with sacubitril/valsartan has been very positive and replicates what has been reported in the literature.

Efficacy of SGLT2 inhibitors: the DAPA-HF trial

SGLT2 inhibitors were initially developed for the treatment of diabetes, but have also proven to be a powerful treatment for heart failure. These agents inhibit proximal tubular glucose reabsorption, cause diuresis and natriuresis, lower blood pressure and reduce bodyweight.

The recently published DAPA-HF trial investigated the efficacy of the SGLT2 inhibitor dapagliflozin when added to standard of care in 4744 patients with heart failure and reduced ejection fraction.[17] Key inclusion criteria of the randomised, placebo-controlled trial were:

- NYHA class II-IV heart failure
- Left ventricular ejection fraction ≤40%
- NT-proBNP levels ≥600 pg/ml
- Standard heart failure device therapy and standard drug therapy, including an ARB, ACE inhibitor or ARNI, plus a β-blocker
- Systolic blood pressure ≥95 mm Hg and eGFR ≥30 mg/min/1.73 m^2.[17]

Results of the DAPA-HF trial demonstrated a clinically and statistically significant reduction in the primary composite endpoint of worsening heart failure or cardiovascular death with dapagliflozin compared with placebo (hazard ratio 0.74; 95% CI 0.65-0.85; p=0.00001).[17] In a post-hoc subgroup analysis, the benefit of dapagliflozin was similar in patients who received treatment with sacubitril/valsartan and those who did not receive such treatment.[17]

Cumulative impact of treatments

Evidence suggests that an SGLT2 inhibitor used in combination with an ARNI provides additional value in patients with heart failure and reduced ejection fraction, and that an ARNI provides additional value over an ACE inhibitor or ARB. The 2-year mortality rate in these patients can be reduced from 35% with no treatment to:

- 27% with the use of an ACE inhibitor or ARB
- 18% with the addition of a β-blocker
- 13% with the addition of an MRA
- 10.9% with use of an ARNI in place of an ACE inhibitor or ARB
- 9.1% with the addition of an SGLT2 inhibitor.[18]

SGLT2 inhibitors are not yet reimbursed by PHARMAC, but patients are able to self-fund treatment with these agents.

Treatment of heart failure with preserved ejection fraction

Most established treatments for heart failure with reduced ejection fraction have not shown a benefit in those with preserved ejection fraction. However, if ejection fraction continuum is considered, patients with an ejection fraction ≤55% may benefit. The CHARM-Programme found that the ARB candesartan reduced cardiovascular death or heart failure hospitalisation up to an ejection fraction of approximately 55%.[19] Furthermore, the TOPCAT study showed a benefit of the MRA spironolactone on heart failure outcomes up to an ejection fraction of 55%.[20]

Heart failure with preserved ejection fraction differs in some aspects of pathophysiology from heart failure with reduced ejection fraction. There tends to be less neurohumoral activation, which may explain why neurohormonal antagonists are not as effective. There are multiple phenotypes in heart failure with preserved ejection fraction, that may show differences in key factors such as degree of diastolic dysfunction, systolic dysfunction, abnormal vasodilation and endothelial dysfunction, right ventricular dysfunction, and chronotropic incompetence with autonomic imbalance. Heart failure with preserved ejection fraction is also commonly associated with comorbidities such as atrial fibrillation, lung disease, obesity, ageing and deconditioning.

A recently published analysis highlighted three distinct clinical phenotypes among patients enrolled in the TOPCAT study:

- Phenotype 1: younger patients, normal left ventricular geometry, low arterial stiffness
- Phenotype 2: older patients, concentric left ventricular remodelling, large-artery stiffening, left atrial enlargement, atrial fibrillation
- Phenotype 3: patients with obesity, diabetes, tumour necrosis factor-α-mediated inflammation, liver and renal injury/dysfunction, high renin levels.[21]

Phenotype 3 patients were at the highest risk of adverse heart failure outcomes, and showed the most benefit from spironolactone.[21]

Key management strategies for heart failure with preserved ejection fraction

- Treat congestion with a loop diuretic (use lowest feasible dose)
- Manage comorbidities (atrial fibrillation, hypertension, ischaemic heart disease, diabetes)
- Consider an ACE inhibitor or ARB, especially for patients with ejection fraction ≤55%
- Consider spironolactone for patients with ejection fraction ≤55%.

Comorbidities in patients with heart failure

Community-based population studies have shown that patients with heart failure (both men and women) have a median of four comorbidities.[2] Approximately 30-40% have iron deficiency,[22] and intravenous iron can be beneficial for these patients in terms of symptomatic status and functional performance.[23]

Diabetes is another common comorbidity, and it is likely that SGLT2 inhibitors will play an important role in the management of heart failure and diabetes. Up to 40-50% of patients will have atrial fibrillation, and attention to anticoagulation and rate control is important for these patients.[24] Obstructive sleep apnoea is another common comorbidity to be aware of. Use of CPAP in these patients can improve symptoms of heart failure.[25]

TAKE-HOME POINTS

- Heart failure with preserved ejection fraction and heart failure with reduced ejection fraction are common conditions with similar symptoms and clinical features but different underlying pathophysiologies
- Measurement of BNP levels and echocardiography are key tools for diagnosis of heart failure
- Effective treatments are available for heart failure with reduced ejection fraction:
  - Those in NYHA class II-IV despite optimal standard treatment are eligible for sacubitril/valsartan
- Treatment of heart failure with preserved ejection fraction is more challenging:
  - Consider an ACE inhibitor/ARB and spironolactone for those with ejection fraction ≤55%.

Questions and answers

How can we differentiate between heart failure with preserved ejection fraction and heart failure with reduced ejection fraction without an echocardiogram?

It is very difficult to differentiate accurately based on clinical features alone - echocardiography is the key to diagnosis.

How much does a private echocardiogram cost?

This will vary from centre to centre, but the average cost would be between $400-500.

How do you a transition a patient receiving a high dose of diuretics (spironolactone and furosemide) and an ACE inhibitor to sacubitril/valsartan?

The ACE inhibitor should be stopped at least 36 hours before starting sacubitril/valsartan, to allow for adequate washout. Professor Troughton's approach has been to start with the lower dose of sacubitril/valsartan and up-titrate to the target dose. This allows time to adjust the diuretic dose according to volume status, and to monitor blood pressure. Practice nurses can be useful for carrying out blood pressure checks and measuring bodyweight during this time.

Is sacubitril/valsartan only for heart failure patients with reduced ejection fraction?

Sacubitril/valsartan is only approved for the treatment of patients with reduced ejection fraction. The PARAGON-HF trial found that there does appear to be a benefit of sacubitril/valsartan in patients with an ejection fraction 45-57%, and also in women, but more data is needed.[26] At present, there is no ejection fraction restriction for PHARMAC reimbursement of sacubitril/valsartan.

For patients requiring anticoagulation who are in renal failure, should you choose warfarin or dabigatran?

The risk of bleeding complications with the novel oral anticoagulants, including dabigatran, rises substantially in patients with an eGFR <30 mg/min/1.73 m^2, and particularly in those with an eGFR <15 mg/min/1.73 m^2. In these patients, warfarin should be used if anticoagulation is needed.

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