Introduction

Heart failure is a heterogeneous progressive syndrome of symptoms and signs, a culmination of structural and/or functional abnormalities of the heart. There is an elevated intracardiac pressure or reduced cardiac output at rest or during exercise. An echocardiogram evaluation is almost essential to diagnose heart failure with reduced ejection fraction (HFrEF) i.e. left ventricular ejection fraction (LVEF) ≤ 40%, or heart failure with preserved ejection fraction (HFpEF) i.e. LVEF ≥ 50%; and also to evaluate the structure of the heart itself, the pericardium and the structure and function of the valves. Biomarkers such as elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) are increasingly used to evaluate global function as stretching of the myocardium due to the elevated intracardiac pressure is responsible for their elevation. The 2017 American guidelines of heart failure recommend that in patients presenting with dyspnoea, measurement of NT-proBNP is useful to support a diagnosis of heart failure.

Guideline-directed medical therapy (GDMT) of HFrEF

The management of chronic heart failure with reduced ejection fraction is based on many well conducted randomised clinical trials which have shown significant reduction of mortality and hospitalisations. The clinical strategy of inhibiting the neurohormonal stimulation, as seen in HFrEF, by either an angiotensin converting enzyme (ACE)-inhibitor or angiotensin receptor II blocker (ARB) plus one of three beta blockers, plus a mineralocorticoid receptor antagonist (MRA) in selected patients, and an angiotensin receptor nephrilysin inhibitor (ARNI) such as sacubitril/valsartan, is recommended for all patients with symptomatic heart failure. This so-called triple therapy – RAAS-blocker (ACE or ARB) plus beta-blocker plus an MRA – is the backbone of evidence-based and guideline-directed medical therapy of HFrEF.

Class 1 recommendations from the guidelines include the following: Examples of the dose of some drugs commonly used for HFrEF are also shown here:

Diuretics

Diuretics, especially loop diuretics, can reduce fluid overload with relief of dyspnoea and peripheral oedema. They can also reduce hospitalisations.

Renin-angiotensin aldosterone system (RAAS)-blockers

All patients with current or prior symptoms should be given either ACE-inhibitors or ARBs for those intolerant to ACE-inhibitors. ARNIs have also received a Class 1 recommendation by these guidelines as a replacement for ACE-inhibitors and ARBs in symptomatic patients.

- ACE-inhibitors: e.g. enalapril: starting dose 6.25 mg b.d. with maximum dose 10–20 mg b.d. and a dose of 16.6 mg achieved in the clinical trials.
- ARB: e.g. candesartan: starting dose 4–8 mg once daily with maximum dose 32 mg once daily and a dose of 24 mg once daily achieved in clinical trials;
- e.g. valsartan: starting dose 20–40 mg b.d. with maximum dose 160 mg b.d. and a dose of 254 mg once daily achieved in clinical trial.
- ARNI: e.g. sacubitril/valsartan: starting dose 50 mg b.d. with maximum dose 200 mg b.d.

Beta blockers

All patients should receive one of three beta blockers that have been shown to reduce mortality: carvedilol, bisoprolol or metoprolol. These beta blockers are added to RAAS blockers.

E.g. carvedilol: starting dose 3.125 mg b.d. with maximum dose 50 mg b.d. and a dose of 37 mg once daily achieved in clinical trials.

Mineralocorticoid receptor antagonists (MRA) such as the commonly used spironolactone, should be added as the third drug, especially if there is a history of prior hospitalisation for heart failure, elevated NT-proBNP, post myocardial infarction with signs of heart failure with reduced ejection fraction below 40%, or diabetes mellitus.

E.g. spironolactone: starting dose 12.5–25 mg once daily with maximum dose 25 mg once or twice daily and achieved dose in clinical trials 25 mg once daily.

The basis of guideline-based treatment of HFrEF is thus a combination of three drug classes: RAAS-blocker (ACE or ARB) plus beta blocker plus an MRA. International registries have demonstrated improved clinical outcomes with adherence to these GDMT.
Not recommended:
Routine anti-coagulation is not recommended but is suggested when there is an intra-cardiac blood clot and with atrial fibrillation.

Device therapy such as intra-cardiac defibrillator (ICD) and cardiac resynchronisation therapy (CRT) is recommended, and is best left for specialised opinion.

Vulnerable periods during the clinical course of HFrEF

Newly diagnosed HFrEF
It is important not to delay the initiation of evidence-based therapy as tardiness can lead to significant disease progression. Good practice is to initiate the three critical drugs at their starting doses and to increase their dose slowly every 4–8 weeks until either the maximum doses or maximum tolerated doses are reached over a period of 6–12 months.

In a meta-analysis of 70 trials, delaying evidence-based drugs by as little as one year can cause a 12% worse survival.4 With deferment of all three essential drugs the risk of death at one year was as high as 1 in 8.

British guidelines recommend that all patients presenting to general practice who have symptoms suggestive of heart failure have a NT-proBNP blood test and if the level is above 400 pg/ml, the general practitioner should immediately start treatment for heart failure and refer.

In another study, those patients not achieving recommended doses of the heart failure drugs, had a higher risk of mortality, while those achieving less than 50% of recommended doses had the worst survival.8

Management of worsening heart failure
1. All the guideline life-saving drugs: RAAS-blockers, beta blockers, MRA and ARNI have shown a reduction in mortality, a reduction in hospitalisations for heart failure and a reduction in worsening heart failure.

2. Recently other drugs have been tested in heart failure and worsening heart failure:
   (a) In the DAPA-HF trial, dapagliflozin, an SGLT-2 inhibitor, was given to heart failure patients in addition to best-practice.9 The heart failure patients consisted of type-2 diabetes mellitus as well as non-diabetic patients. The primary endpoint was a combination of worsening heart failure and cardiovascular death.

   The primary endpoint occurred in 16.3% of the dapagliflozin group compared to 21.2% in the placebo group. This showed an absolute risk reduction of 4.9% with a number-needed-to-treat (NNT) of 21 (95% CI: 15–38). This drug was also highly effective in reducing worsening heart failure with hospitalisation with a NNT of 27 (95% CI: 19–47).

   (b) In a sub-analysis of the EMPA-REG outcome trial, a second re-hospitalisation for worsening heart failure was two-fold less in those patients receiving empagliflozin, another SGLT-2 inhibitor:10

   (c) The SHIFT trial tested ivabradine, a sinoatrial-node inhibitor of the f-channel, in patients with heart failure, in sinus rhythm and with a resting pulse rate of more than 70/minute despite beta blocker therapy. Hospitalisation for worsening heart failure was significantly reduced with NNT of 20.11

   (d) The VICTORIA trial tested vericiguat, a guanylate cyclase stimulator, in heart failure patients with an ejection fraction of less than 45% on top of evidence-based treatment.12 The primary endpoint was a combination of cardiovascular death plus worsening heart failure requiring hospitalisation. The NNT was 33 over 10.8 months or calculated to be 24–28 over one year.

   (e) The current available ARNI, sacubitril/valsartan (Entresto®), was compared to the ACE-inhibitor, enalapril, in heart failure with reduced ejection fraction. The absolute risk reduction of worsening heart failure by sacubitril/valsartan was 2.8% with NNT of 36 over 2.25 years.11 It is indicated to reduce the risk of cardiovascular death and hospitalisation for these patients, usually in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARBs.

Concluding points
1. Worsening heart failure is a vulnerable period during the life-course of a patient with heart failure which can develop after a period of stability.

2. Worsening heart failure has a worse prognosis.

3. All guideline-directed medical therapy (GDMT) has shown that all the drugs used for heart failure reduce the risk of worsening heart failure.

4. The most common avoidable cause for worsening heart failure is not adhering to the guidelines and not achieving the maximum doses of the life-saving drugs.
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