Heart failure update

This report is based on the recording of the MERCK Medical Summit 2020 – Heart Failure

Learning objectives

You will learn:

- The typical symptoms and criteria for classification of heart failure
- A recommended algorithm for investigating heart failure
- The importance of heart rate in the development of heart failure
- The role of beta blockers and other therapies in the treatment of heart failure.

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Click here – you need to watch the video in order to complete the CPD questionnaire.

Introduction

Heart failure (HF) occurs in 1 - 2% of the adult population in developed countries. In South Africa, heart failure is a significant problem, particularly because it is commonly related to hypertension. Preventing and treating hypertension effectively is vital to efforts to reduce heart failure prevalence (Table 1).[1]

Despite improvement in the treatment of heart failure over the past 20 years, many people die in hospital, many people die within a year of first admission, and the majority die within five years. In fact, if comparing the risk of dying of heart failure with that of cancer, heart failure mortality rates are higher. This condition demands careful consideration, prevention, and treatment.

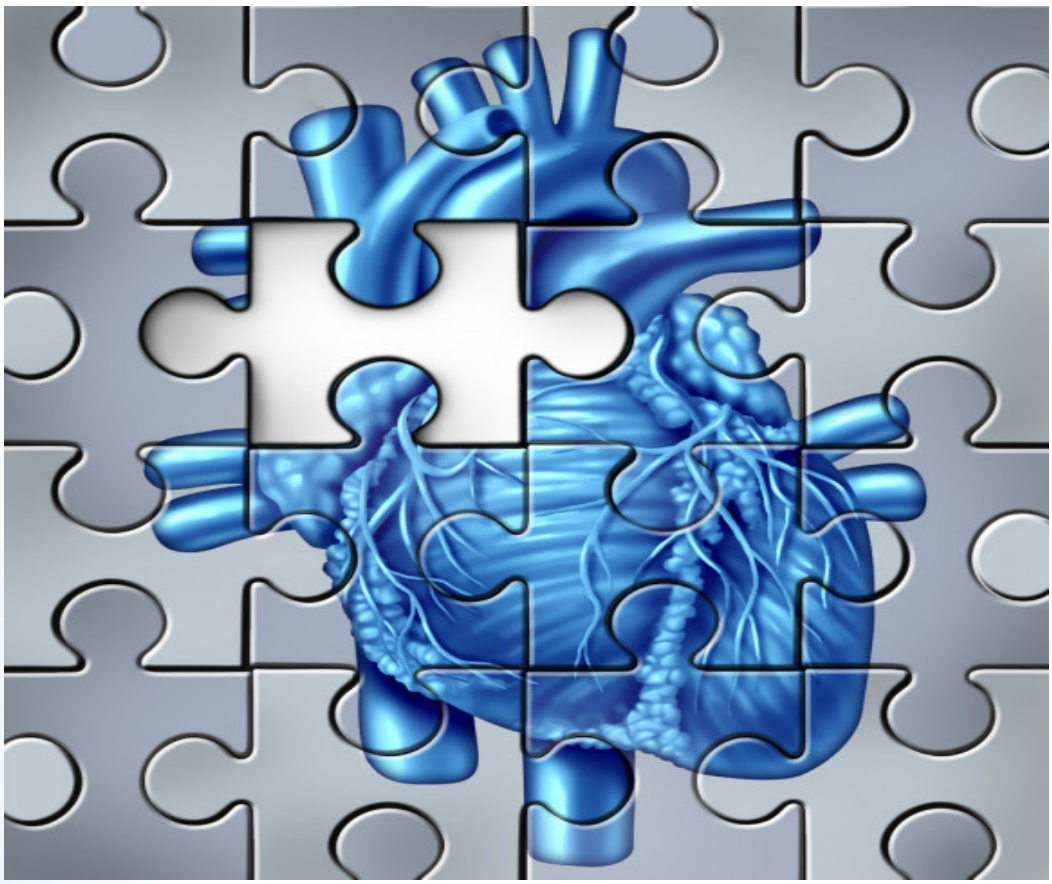

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Table 1. Prevalence of heart failure
Overall prevalence
• 1 - 2% of the adult population in developed countries
Prevalence among people >70 years of age[1]
• Rising to ≥10% • The lifetime risk of HF at age 55 years is 33% for men and 28% for women[1] • The proportion of patients with HFpEF ranges from 22% to 73%*[1] • The characteristics of patients with HFmrEF are between those with HFrEF and HFpEF[1]
* Depending on the definition applied, the clinical setting, age, and sex of the studied population, previous myocardial infarction, and the year of publication

Definition of heart failure

Heart failure is actually very difficult to define, but descriptively it is an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolising tissues, despite normal filling pressures or only at the expense of increased filling pressures.[2] This is not a clinical definition.

Typical symptoms include breathlessness, ankle swelling, and fatigue. Typical signs of heart failure that include fluid retention are pulmonary congestion, elevated jugular venous pressure, pulmonary crackles, and peripheral oedema, which often resolve quite quickly on diuretic therapy.[3] However, diuretic therapy does not lead to long-term prevention of death from heart failure.

Heart failure classification

There are three types of heart failure: heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), and an intermediate group with moderately reduced ejection fraction (HFmrEF) of 40 - 49%. This review does not include a focus on HFpEF, but it is important to note that it is associated with elevated levels of natriuretic peptides.

The most common heart failure presentation is HFrEF, with elevated natriuretic peptides. HRmrEF lies in the middle of the spectrum, with new data from the European Society of Cardiology (ESC) suggesting an important role for beta blockers in this group of patients. There are four grades of heart failure: those at risk, those with structural heart disease without symptoms, those with structural heart disease with prior or current heart failure (graded I to IV), and those patients with refractory heart failure who remain symptomatic at rest despite optimal treatment (Table 2).[4]

Table 2. ACCF/AHA stages of heart failure classification[4]
Comparison of ACCF/AHA stages of HF classification and NYHA functional classification[3]

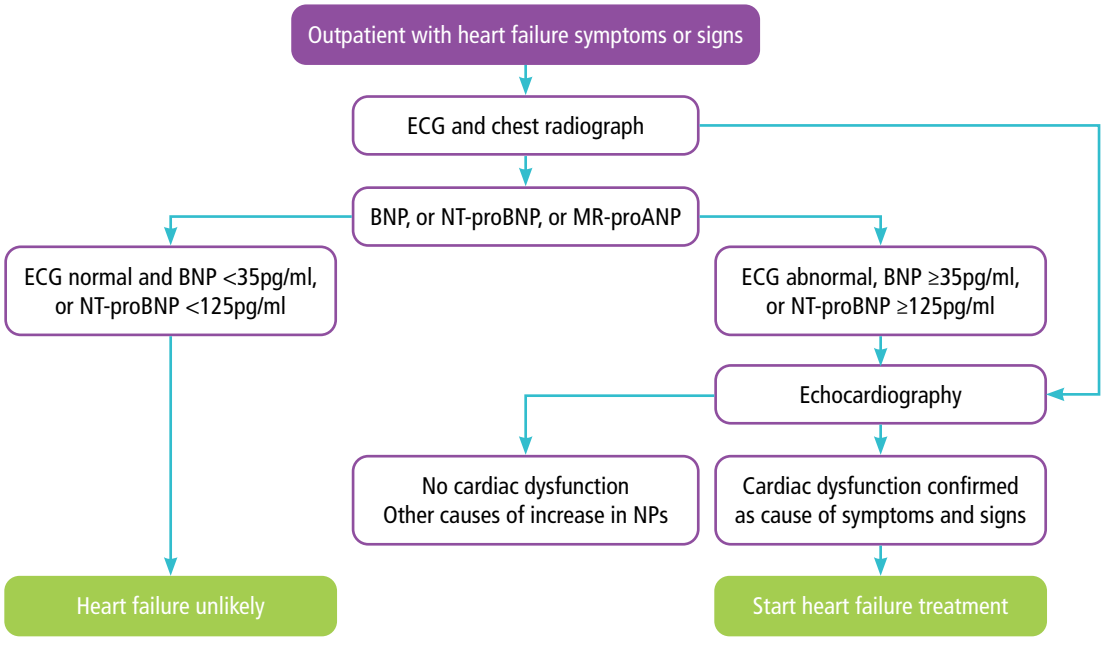
ACCF/AHA stages of HF	NYHA functional classification
A At high risk for HF but without structural heart disease	None
B Structural heart disease but without signs or symptoms of HF	I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF

C Structural heart disease with prior or current symptoms of HF	I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
	II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF
	III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF
	IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest
D Refractory HF requiring specialised interventions	IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

ACCF: American College of Cardiology Foundation; AHA: American Heart Association; HF: heart failure; NYHA: New York Heart Association

Investigating heart failure

When heart failure is suspected, brain natriuretic peptide (BNP) must be tested as it is a very good exclusion test for heart failure if levels are normal. Usually, the electrocardiogram (ECG) will show left ventricular hypertrophy (LVH) or evidence of myocardial ischaemia. The chest X-ray usually shows cardiac enlargement with upper lobe venous diversion, pulmonary congestion or a right sided pleural effusion. Cardiac dysfunction is then confirmed by echocardiogram; BNP or proBNP should also be elevated. If there is no cardiac dysfunction on echocardiogram, consider other reasons for the raised BNP levels. If the BNP is very low or normal and the ECG is normal, the patient is very unlikely to have heart failure. BNP can be falsely positive and elevated in several clinical conditions (Figure 1).[5] Remember, heart failure is not a diagnosis and that there is a cause that must be identified: is it hypertensive heart disease or pulmonary? Is it valvular heart disease, particularly in Africa, and is it due to infectious disease such as rheumatic fever?



BNP: brain natriuretic peptide; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; MR-proANP: mid-regional pro-atrial natriuretic peptide; ECG: electrocardiogram; NPs: natriuretic peptides

Figure 1. Algorithm for the diagnosis of heart failure[5]

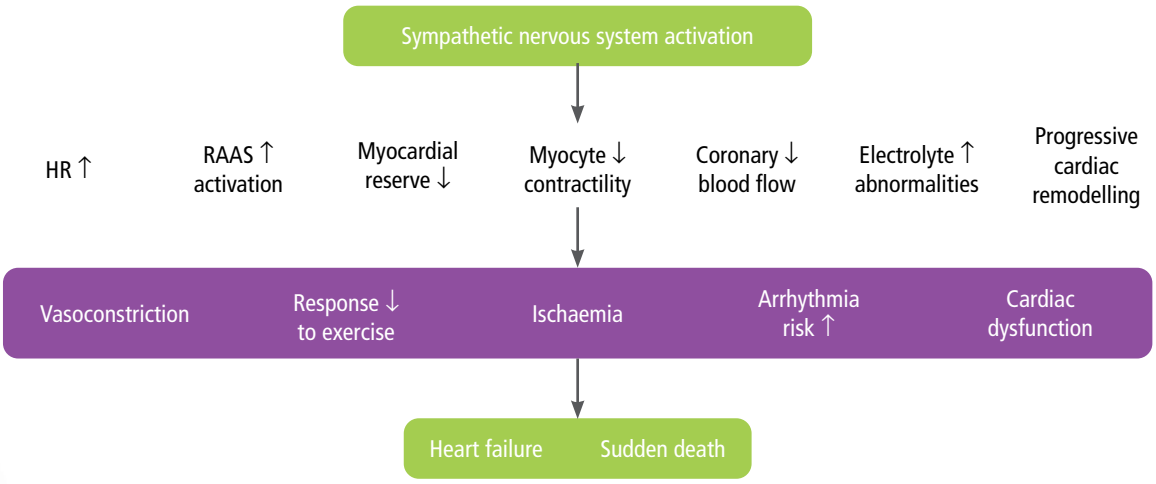
Management of heart failure

Initial targets for heart failure drug intervention were aimed to improve the pump with digoxin, and reduce congestion with diuretics. More recently, targets for drug intervention include decreased stroke volume and neurohormonal response activation of both of the renin angiotensin aldosterone system (RAAS) and the sympathetic nervous system, resulting in vasoconstriction, sodium and fluid retention, further worsening and remodelling of ventricular function, and further heart failure.

It is really important to note that the higher the heart rate is in heart failure, the worse the outcome

Historically, it was absolutely contraindicated to prescribe beta blockers to a patient with heart failure, even an angiotensin-converting enzyme (ACE)-inhibitor was considered to be contraindicated. An evidence base on the use of these drugs indicates that sympathetic nervous system activation has numerous effects including increased heart rate, activated RAAS, reduced coronary blood flow, electrolyte abnormalities, remodelling, and cytokine activation leading to vasoconstriction, ischaemia, arrhythmia, cardiac dysfunction, and further heart failure and sudden death.[6]

There is a whole cardiovascular continuum where heart rate may be critically important as a marker of sympathetic overactivity, which may have played a role in the development of cardiac instability and cardiac complications (Figure 2).[6] It is really important to note that the higher the heart rate is in heart failure, the worse the outcome. Heart rate is the probability marker of the severity of heart failure. In certain heart failure trials, there is actually a suggested linear relationship between reaching a target heart rate, reduction in heart rate, and mortality. With respect to reducing heart rate, the dihydropyridine calcium channel blockers (CCBs), verapamil and diltiazem, are absolutely contraindicated and are unsafe in HFrEF. Beta blockers, particularly bisoprolol and carvedilol, are recommended. Ivabradine, an I*f* channel inhibitor, may have a specific role in a small subset of patients with heart failure.



HR: heart rate; RAAS: renin angiotensin aldosterone system

Figure 2. Chronically increased sympathetic activity (sympathetic overdrive) leads to multiple responses that contribute to heart failure and sudden death[6]

The role of beta blockers

The beta blocker studies were brought to clinical practice by Swedish investigators in the CIBIS II study[7] of beta blocker therapy which demonstrated that, as compared to placebo, bisoprolol reduced mortality by a striking 34% (Figure 3).[7] More importantly, not only were survival rates higher but sudden death, hospital admissions, and hospital admissions for worsening heart failure were also reduced. There was no signal for lack of tolerability.

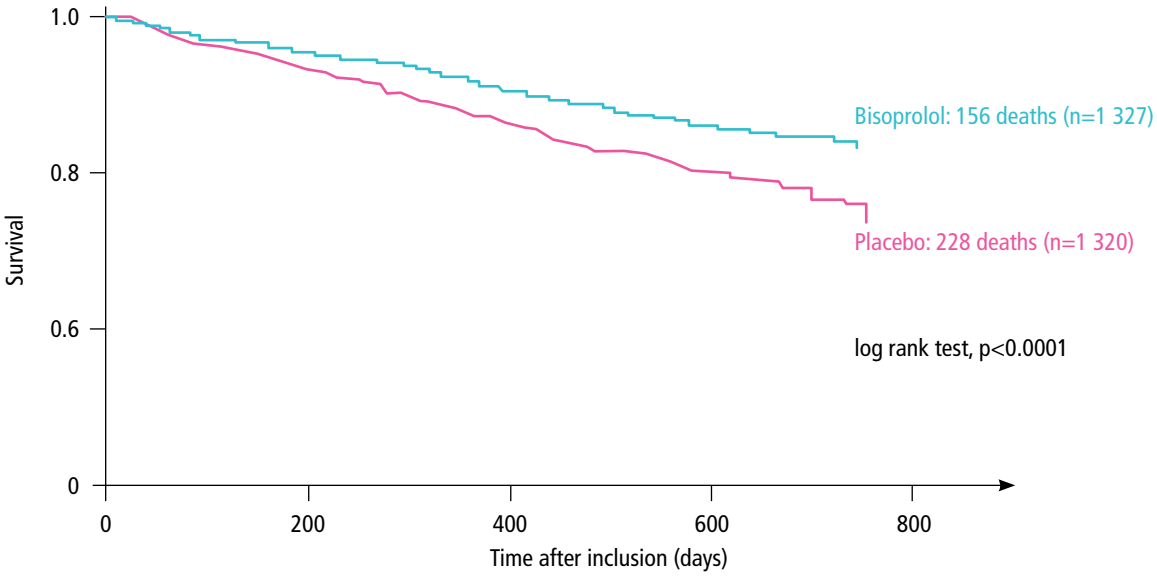


Figure 3. CIBIS II survival[7]

Landmark studies have shown that ACE-inhibitors also reduce all-cause mortality but the evidence indicates, very importantly, that there should be no delay in starting beta blockers at a very low dose in patients with heart failure. Firstly, achieve control of oedema with diuretics, so that the patient becomes less symptomatic, and then initiate 1.25mg bisoprolol, a low-dose ACE-inhibitor, and then slowly titrate-up based on tolerability and signs and symptoms. This is generally in the hands of the cardiologist, but the patient will be followed up in the long term by primary care practitioners.

Mechanism of beta blocker benefits

The range of effects of beta blockers in heart failure include reduction of sympathetic tone, reduction of sudden death, antiarrhythmic activity, upregulation of β-1 receptors, modification of remodelling, and antagonism of stimulatory autoantibodies. This reduces heart rate, inhibits the renin-angiotensin system and catecholamine-induced necrosis and apoptosis, and restores calcium release/cardiac ryanodine receptor function (Figure 4).[8-11]

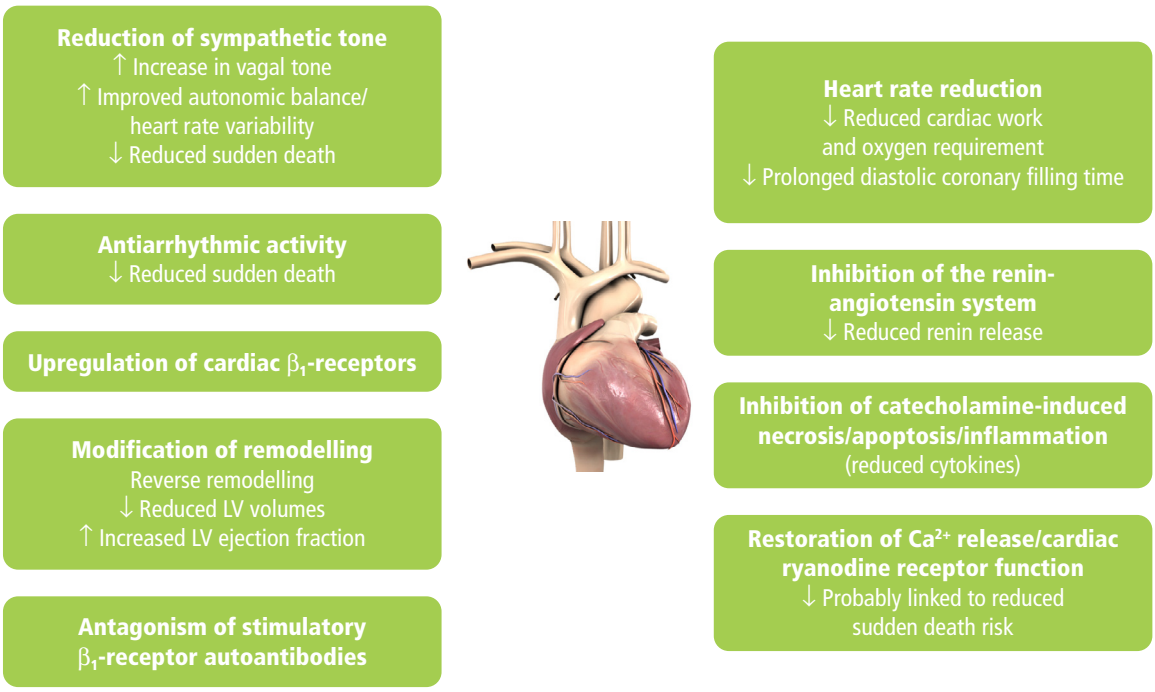


Figure 4. Mechanisms of benefit of beta-blockers in heart failure[8-11]

Other heart failure drugs

Spironolactone is also used to treat heart failure, the pivotal Randomized Aldactone Evaluation Study (RALES) demonstrated an increase in heart failure survival in patients with HFrEF. There is a need to watch kidney function and particularly potassium levels when spironolactone is given to patients with heart failure.

The PARADIGM trial compared sacubitril, an angiotensin receptor neprilysin inhibitor (ARNI) that is a combination of an angiotensin receptor blocker (ARB) and a neprilysin inhibitor, against the standard treatment of enalapril. Sacubitril reduced cumulative primary endpoints of deaths from cardiovascular disease, hospitalisations for heart failure, and death from any cause. This is an important advance in the treatment of heart failure.[12]

The current standard of treatment of heart failure is ARNI therapy. However, as cost is a factor, many patients remain on enalapril. Beta blockers are absolutely mandatory. Mineralocorticoid receptor antagonist (MRA) therapy is used in selected patients especially in those not responding to the above three treatments. Potassium and kidney function need to be monitored.

The therapeutic approach for patients with HFrEF is to start with an ACE-inhibitor and a beta blocker at low dose, up-titrate until asymptomatic; add a MRA if the patient is still symptomatic and consider switching to an ARNI. Cardiac resynchronisation therapy (CRT) can be considered in patients if they have long QRS duration on ECG. If the heart rate remains high despite beta blockers, consider ivabradine (Table 3).

Table 3. Current standard of care with medication for HFrEF

- ARNI
- Beta blockers
- MRAs
- Digoxin, hydralazine/nitrate, and ivabradine in selected patients.

There are two new studies in heart failure. The EMPEROR-reduced trial of cardiovascular and renal outcomes with the sodium-glucose co-transporter-2 (SGLT-2) inhibitor, empagliflozin, in heart failure, was a double-blind, placebo-controlled study of nearly 4 000 patients with HFrEF randomised to either empagliflozin or placebo while receiving optimal background heart failure treatment. Of importance, hospitalisations, deaths, and cardiovascular deaths from heart failure were significantly reduced in patients both with and without diabetes. SGLT-2 inhibitors are diabetic drugs, but we now understand that they also work in patients with heart failure with and without diabetes. Also, very important, the composite renal outcomes were better with empagliflozin in patients with heart failure.

Beta blockers and heart rate

A meta-analysis of individual covariates of heart rate indicated that reduction in heart rate is really a very important issue; getting the heart rate down and titrating the beta blocker to control the heart rate and heart failure is extremely important (Figure 5).[13]

A heart rate between 55 and 65 bpm could be considered a pragmatic treatment goal in elderly CHF patients

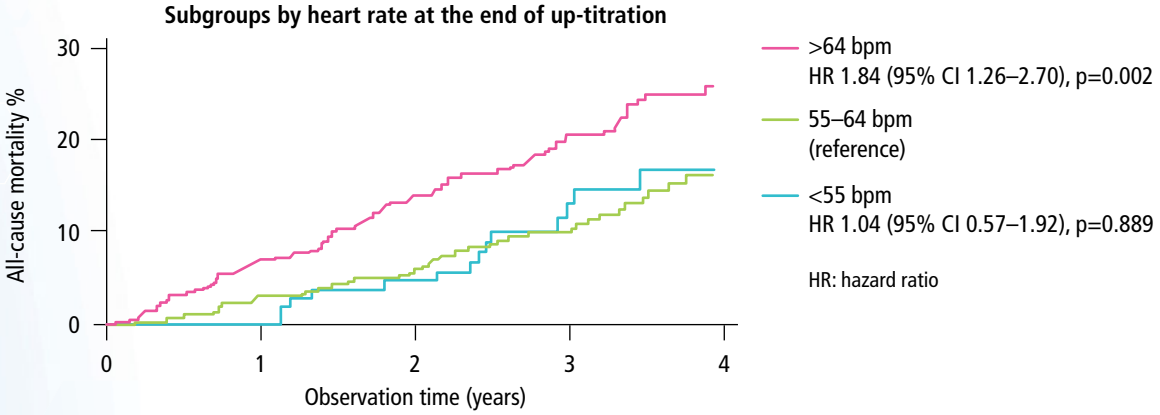


Figure 5. Heart rate range 55-64 bpm showed lowest mortality and treatment-related adverse events[13]

New individual data meta-analysis from the recent ESC congress looked at patients in heart failure, with or without atrial fibrillation (AF), who received beta blockers. They evaluated age, gender, renal dysfunction, heart rate, and ejection fraction, in order to decide which patients with HFrEF are improved by beta blocker therapy. Included patients were either in sinus rhythm or with AF. These two cohorts were relatively well matched for blood pressure, the vast majority were on an ACE-inhibitor or ARB and diuretic therapy, and not many were using aldosterone antagonists. What was really important was that those in sinus rhythm receiving a beta blocker had a 27% reduction of all-cause mortality. However, in the presence of AF, there was no reduction in mortality, and this is yet to be explained. However, beta blockers still remain an important drug to control heart rate in patients with AF in heart failure, because heart rate that remains elevated in AF may lead to tachycardia-induced cardiomyopathy. With respect to baseline heart rate and treatment, the ESC review showed that in patients with a heart rate <70 bpm there was a 28% risk reduction using beta blockers; with a heart rate of 70-90 bpm there was an 18% risk reduction, and a 29% risk reduction for a heart rate >90 bpm. Even starting with lower heart rate, there was still benefit in sinus rhythm.

There is no conclusive evidence-based treatment for patients with HFmrEF and HFpEF. In sub-analysis of studies of patients with HFmrEF, there was benefit on all-cause mortality and cardiovascular death, while patients with HFpEF gained no benefit on long term outcomes.

In older patients and women, often precluded from evidence-based therapy studies for heart failure, the ESC review found that even at age 75 years, there was a significant absolute risk reduction with a number needed to treat (NNT) of 23. Women had the same benefit from treatment of heart failure as men, a 5.1% absolute risk reduction.

Th BB-meta-HF 10-year study looked at landmark randomised clinical trials of heart failure and found that beta blockers appeared not to reduce mortality in HFrEF with AF, but was safe. This lack of efficacy may relate to lack of a distinct relationship with heart rate. There is a substantial reduction in mortality with beta blockers in patients with sinus rhythm irrespective of race, age, gender, and if LVEF <40% or 40 – 49%. Concomitant renal dysfunction has a major impact on prognosis, but beta blockers remain effective in eGFR <30ml/min/1.73m^2 (Table 4).[14]

Table 4. BB-meta-HF 10-year study summary

BB-meta-HF:	Global partnership that over a ten-year period has harmonised individual patient data from landmark double-blind RCTs in heart failure to answer key clinical questions about prognosis and the efficacy and safety of beta-blockers.
Findings	
1.	Beta-blockers do not reduce mortality in HFrEF plus AF, but are safe
2.	Lack of efficacy may relate to the distinct relationships with heart rate
3.	Substantial reduction in mortality with betablockers in patients with sinus rhythm, irrespective of heart rate, age, gender and if LVEF <40% of 40-49%
4.	Concomitant renal dysfunction has a major impact on prognosis; in sinus rhythm, betablockers remain effective down to an eGFR of 30ml/min/1.73m^2
Discontinuation due to an adverse event: Beta-blockers 14.7%, Placebo 15.5%	

Conclusion

Despite advances in heart failure treatment, beta blockers are essential lifesaving treatment and must be optimally dosed based on heart rate and symptoms. In addition, the heart rate needs to be targeted. Sacubitril, if affordable, is starting to replace ACE-inhibitors and ARBs in heart failure treatment. There is also data in both diabetics and non-diabetics that SGLT-2 inhibitors are an additional treatment for heart failure and they also appear to protect kidney function, a major issue in heart failure.

Key learnings

- Heart failure mortality rates are higher than that of cancer
- There are three types of heart failure: HFrEF, HFpEF, and HFmrEF
- Suspected heart failure is investigated through BNP testing, ECG, and chest X-ray; cardiac dysfunction can be confirmed by echocardiogram
- Beta blockers are essential lifesaving treatment and must be optimally dosed based on heart rate and symptoms.

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