

# 2020 Heart Failure Society of South Africa perspective on the 2016 European Society of Cardiology Chronic Heart Failure Guidelines

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Heart failure with a reduced ejection fraction (HFrEF) is a condition frequently encountered by healthcare professionals and, in order to achieve the best outcomes for patients, needs to be managed optimally. This guideline document is based on the European Society of Cardiology Guidelines for the treatment of acute and chronic heart failure published in 2016, and summarises what is considered the best current management of patients with the condition.

It provides information on the definition, diagnosis and epidemiology of HFrEF in the African context. The best evidence-based treatments for HFrEF are discussed, including established therapies (beta-blockers, ACE-i/ARBs, mineralocorticoid receptor antagonists (MRAs), diuretics) that form the cornerstone of heart failure management as well as therapies that have only recently entered clinical use (angiotensin receptor-neprilysin inhibitor (ARNI), sodium/glucose cotransporter-2 (SGLT2) inhibitors).

Guidance is offered in terms of more invasive therapies (revascularisation, implantable cardioverter defibrillators (ICDs) and cardiac resynchronisation therapy (CRT) by implantation of a biventricular pacemaker with (CRT-D) or without (CRT-P) an ICD, left ventricular assist device (LVAD) use and heart transplantation) in order to ensure efficient use of these expensive treatment modalities in a resource-limited environment.

Furthermore, additional therapies (digoxin, hydralazine and nitrates, ivabradine, iron supplementation) are discussed and advice is provided on general preventive strategies (vaccinations).

Sections to discuss conditions that are particularly prevalent in sub-Saharan Africa (HIV-associated cardiomyopathy (CMO), peripartum CMO, rheumatic heart disease, atrial fibrillation) have been added to further improve clinical care for these commonly encountered disease processes.

**You are encouraged to read the complete 2016 ESC Heart Failure guideline:** Ponikowski P, Voors AA, Anker SD, et al.; on behalf of the European Society of Cardiology. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;37:2129-2200.

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## 1. Background

The South African Heart Association (SA Heart) is an affiliate of the European Society of Cardiology (ESC). SA Heart endorses ESC treatment guidelines, with adjustments to suit local circumstances. The Heart Failure Society of South Africa (HeFSSA) Committee – a special interest group of SA Heart – compiled this guidance based on the 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure.<sup>[1]</sup> The Heart Failure Guideline Writing Committee consists of specialist cardiologists with an interest in heart failure management. The committee members work in various regions of the country and in various settings, and as such represent the healthcare providers of most patients with heart failure needing

therapy in SA. It is noted that no members of the public, patients with heart failure or non-cardiologist clinicians were consulted for input on the guidelines. The Writing Committee acknowledges that this should be addressed in the writing process of subsequent iterations of the Heart Failure Guidelines.

The Guidelines Committee based most of its recommendations on the 2016 ESC Chronic Heart Failure Guidelines.<sup>[1]</sup> The ESC Guidelines follow a rigorous scientific and evidence-based process to make recommendations on management, and indicate the strength of the scientific evidence available to support these. The committee holds that this process was rigorous enough for the document to serve as the basis for the updated SA Heart Failure Guidelines.

Where necessary, the guidelines have been adapted to suit local circumstances based on additional clinical trials or clinical studies that apply specifically to the management of conditions seen more frequently in sub-Saharan Africa (sSA). In drafting these guidelines, the Guidelines Committee considered potential resource constraints when making recommendations on resource-intensive interventions.

There were circumstances where committee members did not reach unanimous agreement on specific recommendations. All management issues were discussed comprehensively, and these guidelines were finalised and accepted only after a majority consensus was reached. All authors contributed to the writing of these guidelines and agree that the final document is applicable and represents optimal and cost-effective heart failure management in our SA context.

Guidelines summarise and evaluate all available evidence on a specific topic, with the goal of assisting healthcare professionals in selecting the best management strategies for an individual patient with a specific condition, considering the impact on outcome as well as the risk:benefit ratio of diagnostic or therapeutic approaches. Guidelines and recommendations should help health professionals to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s), in consultation with the patient and caregiver(s), as appropriate. Table 1 contains the abbreviations used in the text.

## 2. Objectives

The primary objectives of these guidelines are to summarise optimal treatment of patients with heart failure with a reduced ejection fraction (HFrEF), based on the 2016 ESC Guidelines for Acute and Chronic Heart Failure, and to highlight changes to the diagnosis and treatment of chronic heart failure that are relevant to sSA. The guidelines are aimed at all medical professionals (including heart failure nurses, general practitioners, surgeons, specialist physicians and cardiologists) who manage adult patients with heart failure. HeFSSA plans to review the current guidelines at 2 - 3-year intervals to ensure that they remain up to date with the ongoing advances in therapies for heart failure patients. Indeed, there have been a number of important developments since the previous HeFSSA guidelines were published in 2013.<sup>[2]</sup> These new developments have already had an impact on the management of heart failure in SA.

Guideline-based heart failure therapy has significantly improved management of patients with HFrEF. This document provides clear recommendations for the evidence-based treatment of such patients. Our recommendations, we believe, tempered by the clinical assessment of the treating physician and consideration of local circumstances, will result in optimal individualised therapy for our patients. A compromise between comprehensiveness and readability needed to be reached, and therefore not all aspects of heart failure care could be covered in this document.

## 3. Methodology

### 3.1 Grading the level of evidence

Most national guideline recommendations either follow the appraisal system used by the American Heart Association (AHA), or the definitions of levels of evidence used by the ESC (Tables 2 and 3). The validity of both instruments is well established.

### 3.2 Guideline development process

The guideline was compiled by the Heart Failure Guideline Writing Committee of HeFSSA. The group consists of independent academic

**Table 1. Abbreviations**

ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACE-I	Angiotensin-converting enzyme inhibitor
AF	Atrial fibrillation
AFL	Atrial flutter
AHA	American Heart Association
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
ART	Antiretroviral therapy
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ASD	Atrial septal defect
BB	Beta blocker
BNP	Brain natriuretic peptide
CAD	Coronary artery disease
CVD	Cardiovascular disease
CMO	Cardiomyopathy
CMR	Cardiovascular magnetic resonance
CRT	Cardiac resynchronisation therapy
CRT-D	Cardiac resynchronisation therapy with a defibrillator
CRT-P	Cardiac resynchronisation therapy with a pacemaker
DCM	Dilated cardiomyopathy
DOAC	Direct oral anticoagulant
ECG	Electrocardiogram
EF	Ejection fraction
EMF	Endomyocardial fibrosis
ESC	European Society of Cardiology
HCM	Hypertrophic cardiomyopathy
HeFSSA	Heart Failure Society of South Africa
HES	Hypereosinophilic syndrome
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
ICD	Implantable cardioverter-defibrillator
IDA	Iron deficiency anaemia
IHD	Ischaemic heart disease
LBBB	Left bundle branch block
LOE	Level of evidence
LV	Left ventricle/ventricular
MRA	Mineralocorticoid receptor antagonist
NNT	Numbers needed to treat
NSAID	Non-steroidal anti-inflammatory drug
OMT	Optimal medical therapy
PCI	Percutaneous coronary intervention
RAAS	Renin-angiotensin-aldosterone system
RAS	Renin-angiotensin system
RHD	Rheumatic heart disease
RV	Right ventricle/ventricular
SA Heart	South African Heart Association
SCD	Sudden cardiac death
sSA	Sub-Saharan Africa
TSAT	Transferrin saturation
VSD	Ventricular septal defect

and private cardiologists and physicians who represent carers in the public, private and non-governmental organisation sectors.

A broader heart failure working group provided input into the guidelines. Possible conflicts of interest have been declared. A national consensus meeting was held on 14 October 2017. The purpose of the meeting was to discuss the provisional draft of the guidelines and to obtain broad input and consensus on the guidelines from all relevant role players involved in the management and planning of heart failure management, from different regions and levels of care in the country. The draft document was extensively edited by JH and NABN to include inputs and comments from the consensus meeting and individual members, as well as the comments of the reviewers following a peer-review process. The final version reflects a broad agreement on appropriate, evidence-based standards for management of heart failure in our unique and challenging healthcare environment.

#### 4. Definition of heart failure

Heart failure is a clinical syndrome of effort intolerance related to an abnormality of cardiac function, characterised by typical symptoms of shortness of breath, fatigue and leg swelling. These symptoms may be accompanied by signs of congestion, which include peripheral oedema, elevated jugular venous pressure and pulmonary crepitations. Heart failure is associated with structural and functional abnormalities of the left ventricle (LV), leading to either systolic or diastolic dysfunction or a combination thereof, which is usually accompanied by neurohormonal adaptations in the renin-angiotensin-aldosterone system (RAAS) and the autonomic nervous system. These neurohormonal adaptations may be protective initially but are maladaptive in the long term, and contribute to the ongoing pathophysiology of heart failure.<sup>[3]</sup>

A key limitation of the current definition of heart failure is that it is restricted to stages of the condition in which clinical manifestations are apparent. However, even before symptoms become manifest, many patients already have evidence of structural and functional abnormalities in the LV, which may be precursors to heart failure.<sup>[1]</sup> Early recognition of these subclinical precursors is important because they often portend poor outcomes in heart failure patients,<sup>[4]</sup> and commencement of therapy at the precursor stage may reduce mortality in patients with asymptomatic systolic LV dysfunction.<sup>[5]</sup>

While heart failure usually reflects structural and functional abnormalities of the LV myocardium, abnormalities of the valves, pericardium, endocardium, heart rhythm and conduction can also cause heart failure. Identification of the exact underlying problem is crucial for therapeutic reasons, as the precise pathology determines the specific treatment used (e.g. pharmacotherapy, devices and transplantation for myocardial disease; percutaneous interventions and coronary artery bypass grafting (CABG) for coronary artery disease (CAD); valve repair or replacement for valvular heart disease; and specific drug therapies and ablation for arrhythmias and tachycardiomyopathy).

#### 5. Classification of heart failure

Heart failure may be classified, historically, as left-sided or right-sided, based on the predominant symptoms. The symptoms of left-sided heart failure have included shortness of breath and the classical signs of crackles or rales on auscultation. Features of right-sided heart failure have included an elevated jugular venous pressure (JVP), ascites, an enlarged and tender liver as well as lower limb oedema. Heart failure may also be classified as compensated or decompensated, based on the presence of features of congestion. Heart failure may be acute or chronic, based on the time course of symptoms and disease onset. High-output heart failure refers to heart failure patients presenting with warm extremities, pulmonary congestion, tachycardia and a wide pulse pressure. Underlying conditions include anaemia, thyrotoxicosis, beri beri, liver failure and skeletal conditions such as Paget's disease.

Based on disease severity, the symptoms of heart failure may be classified according to the New York Heart Association (NYHA) functional class (Table 4). There are several stages in the evolution of heart failure, as outlined by the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (Table 5).

Heart failure may be caused by a variety of disorders, including diseases affecting the pericardium, myocardium, endocardium, cardiac valves, vasculature or metabolism. Pathophysiologically, heart failure may be due to either systolic or diastolic dysfunction. Systolic and diastolic dysfunction each may be due to a variety of aetiologies. Effective management is often dependent upon establishing the correct aetiological diagnosis. HFrEF (HFrEF – left ventricular ejection fraction (LVEF)  $\leq 40\%$ ) is also known as systolic heart failure or heart failure due to systolic dysfunction. Common

**Table 2. Levels of evidence (LOE)**

LOE	Definition
A	Data derived from multiple randomised clinical trials or meta-analyses
B	Data derived from a single randomised clinical trial or large non-randomised clinical studies
C	Consensus of expert opinion and/or evidence from small studies, retrospective studies or registries

**Table 3. Classes of recommendation**

Class	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial/useful/effective	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion in favour of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy less well established by evidence/opinion	May be considered
Class III	Evidence and/or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended

causes of HFrEF include CAD, idiopathic dilated cardiomyopathy (DCM), hypertension and valvular disease. Heart failure with preserved EF (HFpEF) – LVEF  $\geq 50\%$  is also known as diastolic heart failure. HFpEF may be induced by many of the same conditions that lead to systolic dysfunction. Common causes of HFpEF include hypertension, CAD, diabetes, hypertrophic cardiomyopathy (HCM) and restrictive cardiomyopathy. However, many patients with symptoms suggestive of heart failure who have a preserved EF may not have diastolic dysfunction, and other aetiologies may account for the symptoms, including obesity, lung disease or occult coronary ischaemia.

## 6. Comorbidities in heart failure

Comorbidities are of prime importance in heart failure (see Table 6). They may affect the efficacy of heart failure therapies (e.g. it may not be possible to use RAAS inhibitors in some patients with renal impairment). Further, drugs used to treat comorbidities may cause worsening of heart failure (e.g. non-steroidal anti-inflammatory drugs (NSAIDs) given for arthritis, anti-cancer drugs). The comprehensive management of comorbidities is a key component of holistic care for patients with heart failure. This guidance identifies where the presence of heart failure should change the way a comorbidity would normally be treated.

## 7. Heart failure in SA

Heart failure is the dominant form of CVD in sSA, including SA.<sup>[6]</sup> The main causes of heart failure in the region include hypertension, cardiomyopathy, rheumatic heart disease (RHD) and ischaemic heart disease. Heart failure in SA is different from in high-income countries because of certain features: (i) it affects predominantly younger patients; (ii) the causes are largely non-ischaemic; and (iii) there is a substantial contribution from infective causes. As a result of the impact on young, economically active individuals, heart failure in SA and other sSA countries has a disproportional impact on already fragile economies.

### 7.1 Epidemiology of heart failure in SA

There is a paucity of published data on the epidemiology of heart failure in SA. To the best of our knowledge, there are no population-based studies or studies that have evaluated the incidence of heart failure in the country. Almost all studies are hospital-based.<sup>[6]</sup> In SA, heart failure is predominantly a disease of the adult, occurring between the third and fifth decades of life, with a varying sex predilection across different studies.<sup>[7]</sup>

The largest contemporaneous study of confirmed cases of heart failure in SA, the Heart of Soweto study ( $N=4\,162$ ),<sup>[8]</sup> included

**Table 4. Classification of heart failure severity using the NYHA functional class**

Class	Description
I	Patients with heart disease without resulting limitation of physical activity. Ordinary physical activity does not cause heart failure symptoms such as fatigue or breathlessness.
II	Patients with heart disease resulting in slight limitation of physical activity. Symptoms of heart failure develop with ordinary activity but there are no symptoms when at rest.
III	Patients with heart disease resulting in marked limitation of physical activity. Symptoms of heart failure develop with less than ordinary physical activity but there are no symptoms at rest.
IV	Patients with heart disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure may occur even at rest.

NYHA = New York Heart Association.

**Table 5. Stages in the development of heart failure (AHA/ACC staging)**

Stage	Description
A	At high risk for heart failure but without structural heart disease or symptoms of heart failure.
B	Structural heart disease but without signs or symptoms of heart failure. This stage includes patients in NYHA functional class I with no prior or current symptoms or signs of heart failure.
C	Structural heart disease with prior or current symptoms of heart failure. This stage includes patients in any NYHA functional class (including NYHA class I with prior symptoms).
D	Refractory heart failure requiring specialised interventions. This stage includes patients in NYHA functional class IV with refractory heart failure.

AHA = American Heart Association; ACC = American College of Cardiology; NYHA = New York Heart Association.

**Table 6. Importance of comorbidities in heart failure**

- Interfere with the diagnostic process of heart failure (e.g. COPD as a potentially confounding cause of dyspnoea).
- Aggravate heart failure symptoms and further impair quality of life.
- Contribute to the burden of hospitalisations and mortality as the main cause of readmissions at 1 and 3 months.
- Affect the use of treatments for heart failure (e.g. RAAS inhibitors are contra-indicated in some patients with renal dysfunction, or beta-blockers are relatively contra-indicated in asthma).
- Evidence base for heart failure treatment is more limited as there are few studies on managing heart failure in the presence of comorbidities.
- Drugs used to treat comorbidities may cause worsening heart failure (e.g. NSAIDs given for arthritis, some anti-cancer drugs).
- Interaction between drugs used to treat heart failure and those used to treat occurrence of side-effects (e.g. beta-blockers for HFrEF and beta-agonists for COPD and asthma).

COPD = chronic obstructive pulmonary disease; RAAS = renin-angiotensin-aldosterone system; NSAIDs = non-steroidal anti-inflammatory drugs; HFrEF = heart failure with a reduced ejection fraction.

1 593 newly diagnosed and 2 569 previously diagnosed (and under treatment) cases who attended the cardiology unit at the Chris Hani Baragwanath Hospital in Soweto, SA. It was found that 59% of those affected were women, with females being slightly younger than males (mean age 53 v. 55 years, respectively); 25% of those studied were <40 years old and 85% were black Africans.

**7.2 Causes of heart failure in SA**

Recent publications report that the main causes of heart failure in SA are hypertension, DCM, RHD, HIV-associated heart disease, CAD and tuberculous pericarditis.<sup>[6]</sup> Table 7 provides a comprehensive list of the causes of heart failure. In the Heart of Soweto study,<sup>[8]</sup> the

four most common causes of heart failure – accounting for >90% of cases – were hypertension, DCM, valvular heart disease/dysfunction and CAD, in order of frequency. A recent publication from Cape Town reported on 119 admissions for acute heart failure at Groote Schuur Hospital and found that 58% were female, with a mean age of 50 years; 70% were hypertensive and 37% were diabetic. The top five causes of heart failure were DCM, CAD, RHD, cor pulmonale and hypertension.<sup>[9]</sup>

Similarly, the THESUS-HF study<sup>[10]</sup> found that causes of heart failure in SA and other countries in sSA were hypertension, idiopathic DCM, valvular heart disease (particularly related to RHD), ischaemic LV dysfunction and HIV-associated cardiomyopathy, with endocrine/

**Table 7. Aetiologies of heart failure**

**Diseased myocardium**

Ischaemic heart disease	Myocardial scar Myocardial stunning/hibernation Epicardial coronary artery disease Abnormal coronary microcirculation Endothelial dysfunction	
Toxic damage	Recreational substance abuse Heavy metals Medications	Alcohol, cocaine, amphetamines, anabolic steroids Copper, iron, lead, cobalt Cytostatic drugs (e.g. anthracyclines), immunomodulating drugs (e.g. trastuzumab, cetucimab), antidepressants, antiarrhythmics, NSAIDs, anaesthetics
Immune-mediated and inflammatory damage	Radiation Related to infection Not related to infection	Lymphocytic/giant cell myocarditis, autoimmune diseases (e.g. Graves' disease, connective tissue disorders), hypersensitivity and eosinophilic myocarditis (Churg-Strauss)
Infiltration	Related to malignancy Not related to malignancy	Direct infiltration, metastases Amyloidosis, sarcoidosis, haemochromatosis, glycogen storage diseases, lysosomal storage diseases
Metabolic derangements	Hormonal  Nutritional	Thyroid/parathyroid diseases, acromegaly, growth hormone deficiency, hypercortisolaemia, Conn's disease, Addison's disease, metabolic syndrome, diabetes, pheochromocytoma, pathologies related to pregnancy/peripartum Deficiencies in thiamine, L-carnitine, selenium, iron, phosphates, calcium, obesity, complex malnutrition (e. g. eating disorders, HIV)
Genetic abnormalities	Diverse forms	HCM, DCM, ARVC, LV-non-compaction, restrictive CMO, muscular dystrophies, laminopathies

**Abnormal loading conditions**

Hypertension		
Valve and myocardium structural defects	Acquired Congenital	e.g. ASD, VSD
Pericardial and endomyocardial pathologies	Pericardial Endomyocardial	Constrictive pericarditis or pericardial effusion HES, EMF, endomyocardial fibroelastosis
High output states		Severe anaemia, sepsis, thyrotoxicosis, pregnancy, Paget's disease, AV fistula
Volume overload		Renal failure, iatrogenic fluid overload

**Arrhythmias**

Tachyarrhythmias		Atrial/ventricular tachyarrhythmias
Bradyarrhythmias		Sinus node dysfunction, conduction disorders

ESC = European Society of Cardiology; HCM = hypertrophic cardiomyopathy; DCM = idiopathic dilated cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; LV = left ventricular; CMO = cardiomyopathy; ASD = atrial septal defect; VSD = ventricular septal defect; HES = hyper-eosinophilic syndrome; EMF = endomyocardial fibrosis; AV = arteriovenous. \*Adapted from the 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure.<sup>[1]</sup>

metabolic causes also accounting for a smaller proportion of HFrEF. SA centres contributed cases to the Inter-CHF study,<sup>[11]</sup> comprising 5 813 heart failure patients from 108 centres in 16 countries in Africa, Asia, the Middle East and South America. The mean age of all patients was 59 years, with 39% female, 31% from rural settings and 26% with HFpEF. African heart failure patients in the Inter-CHF study were young (mean age 53 years), and most likely not to have formal education (43%) and lack health insurance (66%). Causes of heart failure were hypertension (35%), CAD (20%), DCM (15%) and RHD (7%).<sup>[11]</sup>

**7.3 Prognosis of heart failure in SA**

Despite improved heart failure treatment with contemporary medical therapy and device implantation, the prognosis of patients with HFrEF has remained poor. Data from studies in high-income nations show that 20% of patients will die within 1 year of diagnosis, and the 5-year mortality is consistently reported to be ~50%.<sup>[12]</sup> One-year mortality for patients with HFrEF in Africa is reported to be 34%.<sup>[13]</sup> In SA, the in-hospital mortality of heart failure is 8.4%, and the case fatality rate at 6 months was 26%.<sup>[9]</sup> Apart from highlighting the clear need for new and improved remedies for HFrEF, this observation also emphasises the importance of optimal usage of currently available therapies.

**8. What is new in the ESC 2016 Heart Failure Guidelines?**

This section highlights the updates made to this guideline document, with particular emphasis on the principal changes between the 2012 and 2016 ESC Guidelines on Chronic Heart Failure. The principal changes relate to:

- A. New definition of ejection fraction (EF) with clear diagnostic criteria, as outlined in Table 8.
- B. Indications for the use of valsartan/sacubitril compound as the first-in-class angiotensin receptor-nepriylsin inhibitor (ARNI).
- C. Modified indications for cardiac resynchronisation therapy (CRT).
- D. The use of SGLT-2 inhibitors in the treatment of HFrEF.
- E. Peripartum cardiomyopathy (PPCMO).
- F. HIV-associated cardiovascular disease (CVD).

In addition, data regarding the use of implantable cardioverter-defibrillators (ICDs), as well as the use of iron supplementation in patients with heart failure, have been published since the release of the 2016 ESC Heart Failure Guidelines. This will be discussed in the relevant sections of this document. An algorithm summarising the management of HFrEF is presented in Fig. 1.

**8.1 Definition and diagnosis of heart failure**

Heart failure is a clinical syndrome consisting of typical symptoms and signs, caused by a structural and/or functional cardiac abnormality. The assessment of patients with suspected heart failure therefore includes a detailed history and a thorough physical examination, as well as an electrocardiogram (ECG). If these are all completely normal, heart failure is unlikely, and an alternative diagnosis should be considered. If the diagnosis of heart failure remains uncertain, measurement of natriuretic peptide can be helpful, particularly if the natriuretic peptides measured are not elevated (brain natriuretic peptide (BNP) <35 pg/mL or N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) <125 pg/mL). This test has an excellent negative predictive value. It must be noted that while there are different cut-off levels in the setting of chronic and acute heart failure, as well as according to gender and age, there is no difference in patients with HFrEF and HFpEF. Echocardiography is needed to measure LV function and possibly determine aetiology in the appropriate clinical setting.

The latest ESC Guidelines have added a new category of heart failure – heart failure with mid-range ejection fraction (HFmrEF) – and a clear EF cut-off for HFpEF. Patients who have HFmrEF fall into a grey area, with limited data to guide management. It is possible that these patients represent an early or mild form of LV systolic dysfunction, and it is likely that they would benefit from established therapies used in HFrEF, which should, therefore, be considered in such patients. Patients may also start out with HFrEF and experience partial recovery of LV function with LVEF measurements in the mid-range category – continued therapy for HFrEF is recommended in these patients.

Once the diagnosis of HFrEF is confirmed, treatment should be initiated as soon as possible and further investigations should be performed to rule out reversible causes of LV dysfunction. These include: hypertension; valvular heart disease; tachycardia-induced cardiomyopathy; ischaemic heart disease (IHD); alcohol abuse; chemotherapy; peripartum cardiomyopathy; and metabolic causes such as haemochromatosis and thiamine deficiency.

**8.2 Cardiovascular magnetic resonance imaging in heart failure**

Cardiovascular magnetic resonance (CMR) imaging is an accurate tool for assessing a patient’s ventricular volumes, as well as EF, and is useful to establish heart failure aetiology. It can distinguish an ischaemic from a non-ischaemic cause, and provides further diagnostic value in myocarditis, infiltrative disorders (sarcoidosis, amyloidosis) and rarer entities such as non-compaction or haemochromatosis. Indications for CMR imaging are shown in Table 9.<sup>[14-16]</sup>

**Table 8. Revised definition and classification of heart failure**

Type of heart failure		
HFrEF	HFmrEF	HFpEF
<b>Symptoms and signs</b>	<b>Symptoms and signs</b>	<b>Symptoms and signs</b>
LVEF <40%	LVEF 40 - 49%	LVEF >50%
	1. Elevated levels of natriuretic peptide (NT-proBNP >125 pg/mL or BNP >35 pg/mL)	Elevated levels of natriuretic peptide (NT-proBNP >125 pg/mL or BNP >35 pg/mL)
	2. At least one additional criterion: <ul style="list-style-type: none"> <li>i. Relevant structural heart disease (LVH and/or LAE)</li> <li>ii. Diastolic dysfunction</li> </ul>	At least one additional criterion: <ul style="list-style-type: none"> <li>i. Relevant structural heart disease (LVH and/or LAE)</li> <li>ii. Diastolic dysfunction</li> </ul>

HFrEF = heart failure with a reduced ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; BNP = brain natriuretic peptide; LVH = left ventricular hypertrophy; LAE = left atrial enlargement.

# Chronic heart failure: Diagnosis and treatment algorithm 2020<sup>\*†</sup>

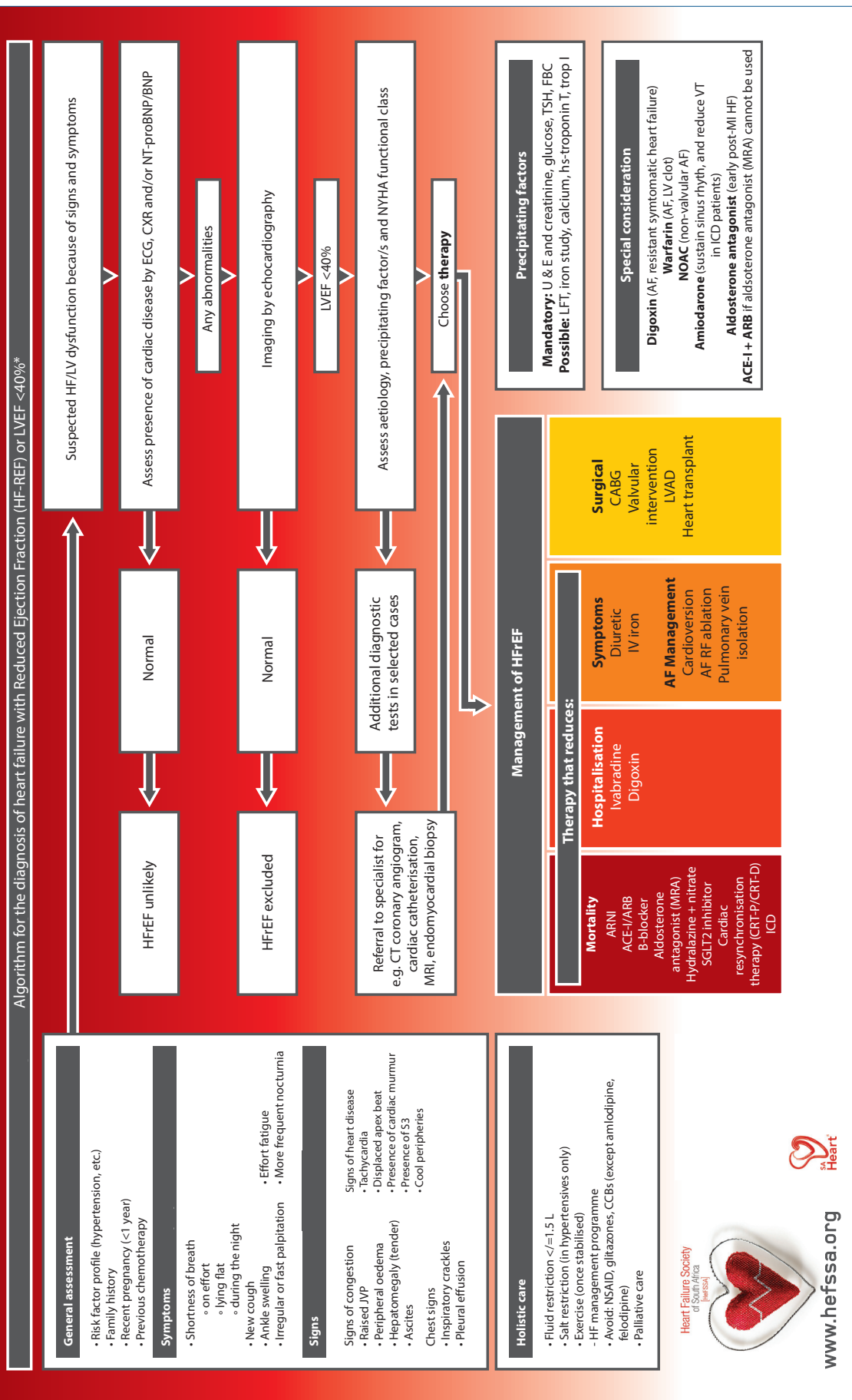


Fig. 1. Algorithm for the diagnosis of heart failure with reduced ejection fraction (HF-REF) or LVEF <40%. LVEF = left ventricular ejection fraction; LV = left ventricular; ECG = electrocardiography; CXR = chest X-ray; NT-proBNP = N-terminal pro-B-type natriuretic peptide; BNP = brain natriuretic peptide; JVP = jugular venous pressure; S3 = third heart sound; CT = computed tomography; MRI = magnetic resonance imaging; NYHA = New York Heart Association; NSAID = non-steroidal anti-inflammatory drug; CCBs = calcium-channel blockers; U & E = urea and electrolytes; TSH = thyroid-stimulating hormone; FBC = full blood count; LFT = liver function tests; hs-troponin T = high-sensitivity troponin T; trop I = troponin I; ARNI = angiotensin receptor-neprilysin inhibitor; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; B-blocker = beta blocker; MRA = mineralocorticoid receptor antagonists; SGLT2 = sodium/glucose transporter-2; CRT-P = cardiac resynchronisation therapy by implantation of a biventricular pacemaker without an ICD; CRT-D = cardiac resynchronisation therapy by implantation of a biventricular pacemaker with an ICD; ICD = implantable cardioverter defibrillator; IV = intravenous; CABG = coronary artery bypass graft; LVAD = left ventricular assist device; AF = atrial fibrillation; NOAC = non-vitamin K antagonist oral anti-coagulants; VT = ventricular tachycardia; MI = myocardial infarction.)  
<sup>†</sup>Patients with heart failure with mid-range ejection fraction (HFmrEF; EF 40 - 49%) can be treated similarly.  
<sup>\*</sup>Adapted from European Society of Cardiology (ESC) heart failure 2016 guidelines.<sup>[1]</sup>



### 8.3 Heart failure therapy

The combination of beta-blockers (BBs),<sup>[17-19]</sup> renin-angiotensin system (RAS) antagonists, angiotensin-converting enzyme (ACE)-inhibitors (ACE-Is)/angiotensin receptor blockers (ARBs)<sup>[20,21]</sup> and mineralocorticoid antagonists (MRAs)<sup>[22,23]</sup> remains the cornerstone of therapy in all symptomatic patients with HFrEF. Their use is supported by excellent clinical data and they have established beneficial prognostic impact with associated symptomatic benefit. The estimated number needed to treat for all-cause mortality over 5 years is listed in Table 10. These combined therapies should therefore be introduced as soon as possible and become a routine part of management, particularly if diuretic therapy for heart failure symptoms is contemplated. The drugs must be started at low dosages and progressively titrated to target level dosages (with incremental increases every 2 - 3 weeks), as used in the clinical trials. The starting and target level dosages of the various drugs proven in HFrEF are shown in Table 10. During this period, patients should be monitored closely, with particular emphasis on heart failure symptoms, side-effects, heart rate and blood pressure, as well as renal function and potassium levels. **ESC recommendation Class I; LOE A.**

#### 8.3.1 Angiotensin receptor-neprilysin inhibitor (ARNI)

Valsartan/sacubitril is a first-in-class molecule that combines moieties of valsartan and sacubitril in one molecule. Sacubitril is a neprilysin inhibitor. It prevents neprilysin from breaking down natriuretic peptides and bradykinin, as well as other vasoactive substances such as adrenomedullin, substance P and calcitonin gene-related peptide.

The combination of valsartan and sacubitril was evaluated in the PARADIGM-HF study, which compared valsartan/sacubitril with enalapril (10 mg twice daily) in patients with HFrEF on background optimal medical therapy (OMT) in an outpatient setting. The trial was stopped early because of clear benefit in the treatment arm. The valsartan/sacubitril combination was superior to enalapril in terms of all-cause mortality, cardiovascular mortality and fewer hospitalisations for worsening heart failure.<sup>[24]</sup> The number needed to treat (NNT) over the duration of the trial (27 months) to prevent one primary outcome event was 21. The NNT to reduce 1 death from any cause was 35, and to prevent 1 cardiovascular death was 32.

There was no signal that valsartan/sacubitril was less safe than enalapril. Angioedema was rare, and occurred in 0.4% of the treatment arm, as opposed to in 0.2% of the enalapril arm. This difference was not statistically significant.

The 2016 ESC Heart Failure Guidelines have issued a Class I, LOE B recommendation for the use of valsartan/sacubitril as *'a replacement for an ACE-I/ARB, to further reduce the risk of heart failure hospitalisation and death in ambulatory patients with HFrEF who remain symptomatic, despite optimal treatment with an ACE-I, a beta-blocker and an MRA.'* The recommendation is strictly in line with the way valsartan/sacubitril was studied in the PARADIGM-HF trial and the ESC furthermore recommends establishing patients on ACE-I, BB and MRA therapy for at least 30 days before considering switching to the ARNI in patients who have ongoing symptoms.

Valsartan/sacubitril was initiated at a dose of 100 mg twice per day and, if tolerated, the dose was increased to the target dose of 200 mg twice per day after 2 weeks of therapy. Although not used in the trial, a lower dose of 50 mg twice per day can be used in patients where there is concern that a higher dose may not be tolerated. Importantly, as with ACE-Is or ARBs, renal function, potassium levels and blood pressure should be monitored closely when using this class of drug. Hypotensive patients with a systolic blood pressure of less than 90 mmHg are particularly prone to the hypotensive effect of the drug

(and these patients were excluded from the PARADIGM trial).<sup>[24]</sup> Lastly, when switching patients from an ACE-I based regimen to the ARNI, it is important to stop the ACE-I for 36 hours prior to starting the ARNI to allow adequate clearance of the ACE-I, as there is a risk of developing angioedema when taking an ACE-I in combination with a neprilysin inhibitor.

We support the view that, although there are no data to support ARNI initiation in ACE-I naive patients, given the substantial mortality benefit of the ARNI, there should be a low threshold to switch patients with HFrEF from an ACE-I to an ARNI early, and initiation of an ARNI in a treatment-naive patient would not be unreasonable.<sup>[25,26]</sup> This is in agreement with a recent focused update of the ACC/AHA/HFSA **Heart Failure Guidelines, which have given a Class I recommendation (LOE B - R) for starting a patient with HFrEF on an ARNI *ab initio*.**<sup>[27]</sup>

#### 8.3.2 Diuretics

Diuretics have never been shown to have prognostic benefits, but clearly provide substantial symptomatic relief from symptoms of congestion and fluid overload. They should be used in appropriate dosages. Patients with a reduced glomerular filtration rate may require high dosages, or more frequent administration, to achieve the desired diuretic effect. A thiazide diuretic may be added to a loop diuretic in resistant patients (e. g. 25 mg hydrochlorothiazide or 5 mg metozalone 1 hour prior to the morning dose of furosemide, 2 - 3 times per week). These agents act synergistically and often improve the diuretic effect in this group of patients.

The dose of diuretic is dynamic and should be carefully adjusted according to the needs of the patient. As the doses of other heart failure therapies are increased, in particular ACE-Is/ARBs, the diuretic requirements often decrease and, to avoid over-diuresis and associated postural hypotension, the diuretic dose should concomitantly be reduced. Many patients can be taught to adjust their diuretic dose themselves, based on symptoms and changes in body weight.

Patients receiving diuretics, especially a thiazide/loop diuretic combination, may experience large electrolyte shifts, and potassium and sodium as well as urea and creatinine need to be monitored closely. The loop diuretics available in SA are furosemide, torasemide and bumetanide. Although they have varying potencies, their efficacies are equivalent. **ESC recommendation Class I; LOE B.**

#### 8.3.3 Ivabradine

Ivabradine only slows the heart rate in patients with sinus rhythm, with few additional physiological effects. It was evaluated in the SHIFT trial as add-on therapy to optimal heart failure therapy (BB, ACE-I and MRA).<sup>[28]</sup> Mortality from heart failure and hospitalisation for worsening heart failure were reduced, with most benefit seen in patients with a resting heart rate persistently above 70 bpm.

Ivabradine should therefore be started in patients with HFrEF who remain symptomatic, with a heart rate above 70 bpm, despite being on maximally tolerated BB, ACE-I/ARB and MRA. It should be noted that ivabradine has no effect in patients with atrial fibrillation (AF) and should therefore not be administered to these patients. **ESC recommendation Class IIa; LOE B.**

#### 8.3.4 Hydralazine and nitrates

The combination of nitrates and hydralazine is under-used, despite reports of beneficial effects on both hospitalisation for heart failure, and mortality in black African patients.<sup>[29]</sup> This therapy can be used in patients who are unable to tolerate a RAAS inhibitor, or who remain symptomatic despite receiving therapy with a BB, RAAS inhibitor and MRA.



The recommended dose is 25 mg hydralazine 3 times per day, increased to 75 mg 3 times per day, and 10 mg isosorbide dinitrate 3 times per day, increased to 40 mg 3 times per day, in the absence of hypotension. If an isosorbide mononitrate formulation is used, the dose is 10 mg twice per day, increased to 40 mg twice per day. **ESC recommendation Class IIa; LOE B.**

### 8.3.5 Digoxin

The primary role of digoxin is in treating HFrEF with concomitant AF and patients who have refractory heart failure. The comments that follow relate to HFrEF and sinus rhythm. There has only been one randomised controlled clinical trial that has evaluated digoxin in patients with HFrEF. It failed to show any mortality benefit, but reduced hospitalisation for acute heart failure exacerbations.<sup>[30]</sup> Digoxin has a low therapeutic index and a high potential for toxicity, particularly in the elderly, in patients with impaired renal function, in the presence of hypokalaemia and in patients with low body mass.

Digoxin use has persisted, and it is still used in 30 - 50% of patients in heart failure trials. In our opinion, it remains useful for patients who have not responded to optimal anti-failure therapy, including ivabradine, hydralazine and nitrates, as well as device therapy. The recommended dose is 0.125 mg daily, and the blood drug level should be monitored closely with the aim of keeping the digoxin level in the range of 0.5 - 0.9 ng/mL. **ESC recommendation Class IIb; LOE B.**

### 8.3.6 Sodium/glucose cotransporter-2 inhibitors

Heart failure and diabetes often coexist, and either condition worsens the clinical outcome of the other. Sodium/glucose cotransporter-2 (SGLT2) inhibitors have been developed for use in the management of diabetes. These agents prevent the reabsorption of glucose in the proximal tubule in the kidney. This results in glycosuria and caloric loss, which can lead to osmotic diuresis and weight loss. Empagliflozin, dapagliflozin and canagliflozin have all been evaluated in patients with type 2 diabetes, and have shown variable benefit in terms of cardiovascular outcomes.

Empagliflozin was evaluated in the EMPA-REG OUTCOME trial.<sup>[31]</sup> There was significant reduction in cardiovascular mortality and heart failure hospitalisation, as well as all-cause mortality in diabetic patients receiving empagliflozin. The dose of empagliflozin used in the trial was 10 or 25 mg, with similar outcomes for either dosing regimen.<sup>[31]</sup>

Dapagliflozin was studied in diabetic patients in the DECLARE-TIMI 58 trial.<sup>[32]</sup> Dapagliflozin did not reduce the overall rate of major adverse cardiovascular events, but there was a significantly lower rate of heart failure hospitalisation in the treatment arm.

In the CANVAS trial,<sup>[33]</sup> canagliflozin also reduced heart failure hospitalisation and was found to possibly confer benefit in terms of reduction of cardiovascular death. However, it was also associated with an increased risk of limb amputations.

In all three trials there was an increased risk of diabetic ketoacidosis, although the absolute risk was still very small. Genitourinary fungal infections were increased, but most of these were minor and easily treated.

Dapagliflozin was evaluated in both diabetic and non-diabetic patients in the DAPA-HF trial (55% of the patients enrolled in the study did not have diabetes). In this trial, HFrEF patients were randomised to standard HFrEF therapy or HFrEF with 10 mg dapagliflozin daily. Over 2 years there was a relative risk reduction of 26% in the treatment arm with an NNT of 21 over 2 years to prevent one primary endpoint (cardiovascular death,

HF hospitalisation, urgent HF visit). All-cause mortality was a secondary endpoint, and revealed a relative risk reduction of 17%. Only a small proportion of patients (~10%) were on an ARNI, but this did not affect the magnitude of the benefit. The drug was well tolerated, and treatment discontinuation rates were low. The dose of dapagliflozin used was 10 mg daily.<sup>[34]</sup>

It is not clear whether the benefit of the SGLT2 inhibitors in heart failure patients without diabetes is a class effect or limited to dapagliflozin specifically. At this stage a strong recommendation can only be made for the addition of dapagliflozin to standard HFrEF therapy to achieve the best outcomes.

### 8.3.7 Implantable percutaneous device therapy

Cardiac resynchronisation therapy (CRT) can be achieved by implantation of a biventricular pacemaker with (CRT-D) or without (CRT-P) the additional functionality of an internal cardioverter-defibrillator (ICD). Furthermore, some patients do not qualify for CRT, but will benefit from ICD implantation only, to reduce the risk of sudden cardiac death (SCD).

The criteria for CRT in heart failure have been simplified, and now include a broader group of patients who could potentially derive benefit from biventricular pacing. CRT therapy is recommended in all patients with HFrEF with an EF of <35% who remain persistently symptomatic, despite OMT for heart failure and a QRS complex broader than 130 ms on resting ECG. The magnitude of the therapeutic benefit is greatest in patients in sinus rhythm with left bundle branch block (LBBB) morphology, a QRS duration >150 ms, with progressively less benefit as QRS duration becomes relatively shorter and the QRS morphology moves away from LBBB. The NNT over 5 years for all-cause mortality is 14. This should be taken into consideration when individualising the decision to implant these expensive devices. Patients with atrial fibrillation may need atrioventricular node ablation after CRT device implantation to ensure 100% pacing.

Most patients who qualify for CRT would also meet the criteria for ICD implantation (see below), and the use of a combination device to achieve CRT-D should be strongly considered. There has not been a trial that compares CRT-D with CRT-P, and the decision as to which device to implant should, in this regard, be individualised, with careful consideration of the patient's own wishes and expected survival.

To prevent SCD secondary to malignant tachyarrhythmias, the implantation of an ICD is recommended in patients with HFrEF who remain symptomatic, despite being on established OMT for more than 3 months. An ICD should be considered only in patients with a reasonable functional status and an expected survival substantially longer than 1 year. If the LV dysfunction (EF <35%) is due to IHD, implantation should be delayed for 40 days after an acute myocardial infarction to allow for recovery of LV dysfunction after the acute ischaemic event, and the need for an ICD should then be re-evaluated.

In the 2016 ESC Heart Failure Guidelines, the recommendations for ICD implantation apply to patients with HFrEF, regardless of whether the LV dysfunction is secondary to IHD or due to an underlying idiopathic DCM.

The risks of ICD implantation include procedure-related complications and device infection, as well as inappropriate shocks. **ESC recommendation Class I; LOE A.**

### 8.3.8 Revascularisation in heart failure

CABG surgery had, up until publication of the STICH Extension Study,<sup>[35]</sup> disappointingly failed to reduce mortality in patients with ischaemic LV dysfunction. The STICH Extension Study is the long-term follow-up of the STICH trial,<sup>[36]</sup> which evaluated CABG against medical therapy and demonstrated benefit in the group that had

**Table 9. Indications for cardiovascular magnetic resonance imaging**

Common indications	Contraindications
Accurate assessment of LV function	<b>Absolute</b> Non-MR compatible implantable devices Severe claustrophobia
Cardiac function and anatomy for device implantation	
Myocardial viability	<b>Relative</b> Dysrhythmia affecting ECG gating Severe renal impairment (risk of nephrogenic systemic fibrosis)
Detection of intraventricular thrombus	
Myocarditis	
Myocardial inflammation/oedema	
Interstitial fibrosis (dilated and infiltrative/restrictive cardiomyopathies)	
Congenital heart disease	
RV quantification	
Evaluation for ARVC	
Post OHT cardiac surveillance	
Constrictive pericarditis	
Quantification of valvular function	
Aortic and vascular assessments	
Iron overload quantification	

LV = left ventricular; MR = magnetic resonance; ECG = electrocardiogram; RV = right ventricular; ARVC = arrhythmogenic right ventricular cardiomyopathy; OHT = orthotopic heart transplantation.

**Table 10. Recommended doses for heart failure therapies**

	Starting dose	Target dose	Estimated NNT for all-cause mortality
ACE-I			18 over 30 months
Enalapril	2.5 mg BD	10 - 20 mg BD	
Lisinopril	2.5 mg OD	20 mg OD	
Ramipril	2.5 mg OD	10 mg OD	
Beta-blockers			8 over 30 months
Bisoprolol	1.25 mg OD	10 mg OD	
Carvedilol	3.125 mg BD	25 - 50 mg BD	
ARBs			24 over 30 months
Candesartan	4 mg OD	32 mg OD	
Valsartan	40 mg BD	160 mg BD	
Losartan	50 mg OD	150 mg OD	
MRAs			15 over 30 months
Eplerenone	25 mg OD	25 - 50 mg OD	
Spironolactone	25 mg OD	25 - 50 mg OD	
ARNI			35 over 27 months
Valsartan/sacubitril*	100 mg BD	200 mg BD	
If-channel blocker			Not applicable
Ivabradine	5 mg BD	7.5 mg BD	
Digitalis compounds			Not applicable
Digoxin	0.125 mg OD	Adjust according to levels <sup>†</sup>	
Vasodilators			25 over 10 months
Hydralazine	25 mg TD	75 mg TD	
Isosorbide dinitrate	10 mg TD	40 mg TD	
Isosorbide mononitrate	10 mg BD	40 mg BD	
SGLT2-inhibitor			43 over 18 months
Dapagliflozin	10 mg OD	10 mg OD	

NNT = number needed to treat; ACE-I = angiotensin-converting enzyme inhibitor; BD = twice per day; OD = once daily; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist; ARNI = angiotensin receptor-neprilysin inhibitor; TD = three times per day; SGLT2 = sodium/glucose cotransporter-2.

\*Valsartan/sacubitril may be started at a dose of 50 mg BD and titrated upwards in patients where there is concern regarding hypotension.

<sup>†</sup>See section 8.3.5.

received revascularisation. At 10-year follow-up, the CABG group had a median survival of 1.44 years longer than the control group. The NNT to prevent 1 death was 14, and the NNT to prevent 1 CV death was 11.<sup>[35]</sup> The benefit was primarily restricted to the group of patients who were <65 years of age, irrespective of myocardial viability.

If feasible, revascularisation should be performed in patients with ischaemic LV dysfunction. Although percutaneous intervention (PCI) is less invasive and could conceivably have similar effects to surgical revascularisation, there are no current data available to support this mode of revascularisation. PCI is currently being

evaluated in randomised clinical trials in this patient population. ESC recommendation Class I; LOE A.

### 8.4. Additional heart failure therapies

#### 8.4.1 Iron supplementation

Symptomatic patients with HFrEF, on OMT, should have their haemoglobin and full iron studies (serum iron, transferrin saturation and ferritin levels) assessed. If anaemic and/or iron deficient, a reversible cause should be identified and treated. An absolute iron deficiency is present when the serum ferritin is <100 ug/L, and a relative iron deficiency when the serum ferritin is between 100 - 299 ug/L and transferrin saturation (TSAT) <20%. Considering the costs involved, the recommendation of the HeFSSA is as follows. It is reasonable to attempt an oral course of iron therapy initially (relatively low cost and ease of administration) and to assess the response after 16 weeks of therapy. It is important to note that there are limited data on the effectiveness of oral iron therapy in patients with HFrEF and IDA. Advice to patients should include taking iron therapy on an empty stomach (as gastric acidity is crucial for effective absorption of iron), to avoid concomitant use of antacids, dairy products, tea and coffee, and to co-administer oral supplementation with vitamin C or lemon juice. Gastric side-effects limit oral supplementation tolerance. Enteric-coated iron supplements have fewer side-effects.

It is further suggested that IV iron supplementation should be administered to HFrEF patients who are persistently iron deficient and symptomatic (NYHA FC II - IV). While the available evidence suggests that IV iron replacement provides symptomatic and functional benefits

in HFrEF, further studies are awaited before a clear, stronger mandate for IV iron supplementation in HFrEF and ID can be made. The effect in patients with preserved LVEF remains unknown. The regimens of IV iron and doses used are shown in Table 11. ESC recommendation Class II; LOE A.

#### 8.4.2 Vaccinations

Annual influenza vaccinations by the end of February each year, as well as pneumococcal vaccinations, are strongly recommended.<sup>[37,38]</sup> ESC recommendation Class I; LOE A.

#### 8.4.3 Left ventricular assist devices

Patients with end-stage heart failure who are on the waiting list for transplantation have a long waiting time and, often, poor quality of life. Recent evidence suggests improved survival of patients on the transplant waiting list if they receive a left ventricular assist device (LVAD).<sup>[39]</sup> An LVAD should, therefore, be considered in patients with end-stage HFrEF, despite OMT (including medical treatment, as well as devices), in order to improve symptoms and reduce hospitalisation and premature death, as a bridge to transplantation.

In patients with end-stage HFrEF who are not transplant candidates, an LVAD can also be considered to improve outcomes (destination therapy).

Lastly, an LVAD is indicated to bridge patients to recovery if they have fulminant acute heart failure that is likely to be reversible (e.g. acute myocarditis, peripartum cardiomyopathy).

LVAD insertion has significant potential problems: bleeding,

**Table 11. Regimens of IV iron used in the clinical trials**

Ferric carboxymaltose (FCM) (Ferinject): 500 - 1 000 mg single dose, followed by a ferritin/TSAT at 1 - 3 months, then FCM 500 mg to maintain ferritin/TSAT on target. Check Hb/iron studies 1 - 2 times per year. FCM can be administered over 15 minutes, with minimal risk of adverse effects.
Ferric hydroxide surface (Venofer): 200 mg weekly until repletion.
Ferric gluconate (Ferrlecit): 125 - 250 mg per IV dose
Ferric hydroxide dextran (Cosmofer): 20 mg/kg over 4 - 6 hours (maximum daily dose 1 000 mg).

IV = intravenous; TSAT = transferrin saturation; Hb = haemoglobin.

**Table 12. Indications for heart transplantation**

Absolute	Haemodynamic compromise due to heart failure <ul style="list-style-type: none"> <li>• Refractory cardiogenic shock</li> <li>• Documented dependence on IV inotropic support to maintain adequate organ perfusion</li> <li>• VO<sub>2</sub> max &lt;10 mL/kg/min</li> <li>• Severe symptoms of ischaemia that consistently limit routine physical activity where revascularisation is not possible</li> <li>• Recurrent symptomatic ventricular arrhythmias refractory to all treatment modalities</li> </ul>
Relative	Peak VO <sub>2</sub> 11 - 14 mL/kg/min (or 55% predicted) and major limitation of the patient's daily activities Recurrent unstable ischaemia not amenable to other interventions Recurrent instability of fluid balance/renal function not due to patient non-adherence with medical regimen

IV = intravenous; VO<sub>2</sub> max = peak oxygen consumption.

**Table 13. Haemodynamic criteria for evaluation of candidates for transplantation**

PAH and elevated PVR are relative contraindications to heart transplantation particularly when the PVR is >4 Woods units, or the transpulmonary gradient is >16 - 20 mmHg
If the PAH is >60 mmHg (systolic) the risk of right heart failure and early death is increased
If the PVR can be reduced to <2.5 Woods units with a vasodilator but the systolic BP falls below 85 mmHg in the process, the patient is also at high risk of right heart failure and mortality after transplantation

PAH = pulmonary artery hypertension; PVR = pulmonary vascular resistance.

thromboembolism, infection and device failure are not uncommon. Additionally, LVAD therapy is very expensive. Potential patients must therefore be carefully assessed by a heart team to determine whether they are candidates for this type of complex intervention.<sup>[40]</sup>  
**ESC recommendation Class IIa; LOE B to C.**

#### 8.4.4 Heart transplantation

Heart transplantation is indicated in end-stage heart failure. It remains an underused treatment, due to lack of appropriate referral for qualifying candidates and an ongoing lack of suitable donor hearts. Indications for transplantation are shown in Table 12. Table 13 portrays the haemodynamic criteria for evaluation of candidates for transplantation.

Although randomised controlled trials have never been conducted for transplantation in heart failure, there is a consensus that transplantation – provided that proper selection criteria are applied – significantly increases survival, exercise capacity, quality of life and return to work, compared with conventional medical and device treatment. While an active infection remains a relative contraindication to heart transplantation, patients with HIV, hepatitis, Chagas disease and tuberculosis can be considered as suitable candidates, provided certain strict management principles are adhered to by the treatment teams. In patients with cancer requiring heart transplantation, a close collaboration with oncology specialists should occur to stratify each patient as to their risk of tumour recurrence.

#### 8.5 Management of atrial fibrillation/atrial flutter in patients with HFrEF

Atrial fibrillation (AF) and atrial flutter (AFL) occur frequently in patients with heart failure, irrespective of LVEF. These supraventricular arrhythmias increase the risk of thromboembolic events, and may contribute to worsening of symptoms by impairing cardiac function. In some cases of HFrEF, AF/AFL may be primarily responsible for the underlying LV dysfunction (tachycardia-induced cardiomyopathy). Numerous factors must be considered when deciding on management of patients with these arrhythmias. Therapy therefore needs to be carefully individualised for the patient to provide optimal treatment.

The principles of therapy are as follows and, unless otherwise indicated, apply equally to patients with AF or AFL:

- Potentially correctable causes (hyperthyroidism, electrolyte disorders) and precipitating factors (recent surgery, infections, alcohol excess) should be identified and managed accordingly.
- The need for anticoagulation should be assessed using the CHADS-VASC score (most patients with HFrEF will need an anticoagulant). For patients with non-valvular AF, a direct oral anticoagulant (DOAC) is the preferred anticoagulant. Only warfarin should be used in patients with mechanical heart valves. In patients with severe renal dysfunction, the benefits of anticoagulation need to be cautiously weighed against the considerable risk of bleeding, particularly if patients are on dialysis – in these cases, warfarin is also the only currently available option.
- Urgent electrical conversion is recommended if AF contributes to the patient's haemodynamic compromise.
- A rate control strategy is a reasonable option for most patients with AF with the aim of reducing the resting heart rate to <100 bpm. BB are first-line treatment in NYHA I - III patients with euolemic state. In those with marked congestion or haemodynamic instability, digoxin or amiodarone should be used to control the rate until such time that the patient is stable enough for BB to be introduced. Atrioventricular node ablation

with CRT implantation is a useful option for patients where medical therapy fails to control the heart rate.

- AF ablation should be considered to restore sinus rhythm in patients with HFrEF. The CASTLE-AF<sup>[41]</sup> trial showed a 38% relative risk reduction of the primary outcome (all-cause mortality and worsening heart failure admissions) in patients who underwent pulmonary vein isolation compared with the group of patients undergoing conventional standard of care treatment.
- In patients with AFL, rate control is often very difficult, and there is a very high recurrence rate of the arrhythmia after electrical cardioversion. These patients should therefore be referred for atrial flutter ablation.
- Dronedarone, calcium channel blockers (verapamil/diltiazem) and class I antiarrhythmic agents should be avoided in patients with symptomatic heart failure and LV systolic dysfunction because of an increased risk of premature death.

**ESC recommendation Class I to II; LOE A to C.**

### 9. Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCMO) deserves specific attention in the African context. It occurs in about 1 in 1 000 women in SA, and has a high 1-year mortality of up to 28%.<sup>[42]</sup> The management of PPCMO is challenging. Pre-delivery, the effects of medication on the fetus must be considered. After delivery, standard recommendations for treatment of HFrEF should be followed.<sup>[43]</sup> Studies suggest that the detrimental effect of a 16 kDa cleavage product of prolactin plays a key role in the development of PPCMO.<sup>[44]</sup> It is hypothesised that prolactin suppression with bromocriptine in the postpartum period is beneficial in patients with PPCMO.<sup>[45]</sup> Despite limited data from 2 clinical studies,<sup>[46,47]</sup> we would recommend the addition of bromocriptine at a dose of 2.5 mg 2 times/day for 2 weeks, followed by 2.5 mg daily for a further 4 weeks. This is particularly important in women presenting with a NYHA FC III - IV and/or EF <35%. Concomitant anticoagulation with warfarin should be considered as patients on bromocriptine are hypercoagulable in the peripartum period.<sup>[43]</sup>

PPCMO patients have a high risk of re-emergence of LV dysfunction, leading to poor outcome in the peripartum period of subsequent pregnancies. This applies particularly to those patients whose LV function has not recovered prior to getting pregnant again. Therefore, in general, unless LV size and ejection fraction return to normal, PPCMO patients should be advised to avoid pregnancies, and appropriate contraception should be prescribed. Hormonal contraceptive medication can interact with heart failure medication, and an intrauterine contraceptive device is therefore recommended.<sup>[48]</sup>

**ESC recommendation Class II; LOE B.**

### 10. HIV-associated CVD

HIV-associated CVD involves every aspect of the cardiovascular axis, and commonly affects all layers of the heart, including the myocardium, valves, pericardium and coronary, pulmonary, cerebrovascular, and peripheral vasculature.<sup>[49]</sup> The incidence of HIV-related heart failure is on the increase, and current evidence suggests that diastolic, rather than systolic, dysfunction is the predominant form of heart failure in the era of antiretroviral therapy (ART).<sup>[50]</sup> The pathophysiology of heart failure in HIV-infected persons is multifactorial and intimately related to the presence of traditional risk factors for CAD, myocardial inflammation, myocardial fibrosis, pericardial disease, impaired vascular compliance, myocardial steatosis, and pulmonary vascular and renal disease.<sup>[49,51,52]</sup>

There is a paucity of data on optimal management of HIV-associated heart failure, and data are extrapolated from studies conducted on

HIV-uninfected persons. ART has significantly altered the natural history of HIV infection, lengthened survival, improved the quality of life of HIV-infected patients and changed the natural history of HIV-associated cardiovascular disease.<sup>[53]</sup> ART use has also been linked to lipid and metabolic abnormalities associated with an increased risk of both peripheral and CADs, which may contribute to the development of heart failure.<sup>[50]</sup>

Several observations have been made about HIV-associated cardiovascular disease in SA. The first relates to unexpectedly low rates of cardiac events and mortality in patients receiving ART, particularly in view of the prior evidence that HIV increased the risk of CVD and the assumption that, since ART was allowing HIV-infected persons to survive longer, there would be a proportionate increase in HIV-associated CVD. Second, although HIV does increase the risk of atherosclerotic cardiovascular complications, a significant proportion of the risk is attributable to conventional or traditional modifiable risk factors. Third, the increasingly earlier introduction and increased uptake of ART appear to have significantly reduced the risks of HIV-associated cardiomyopathy, pericardial disease and possibly HIV-associated pulmonary hypertension. Fourth, the phenotype of heart muscle disease has shifted from systolic dysfunction associated with opportunistic infections to diastolic dysfunction associated with inflammation and fibrosis. Finally, in sSA, where the burden of HIV infection is highest, the anticipated pandemic of HIV-associated CVD has not materialised, which may be related to insufficient research and technology focusing on these specific questions.<sup>[50,54]</sup>

## 11. Rheumatic heart disease

Rheumatic heart disease (RHD) deserves special attention because of its significant contribution to the heart failure burden in SA. An estimated 33 million people globally are living with RHD.<sup>[55]</sup> It accounts for 350 000 deaths per year, and the majority of these occur in low- and middle-income countries (including SA), with >80% of those affected living in sSA.<sup>[55]</sup> The overall crude incidence of symptomatic RHD in SA is 24.7 per 100 000 population per annum among adults, while the prevalence of asymptomatic echocardiographic RHD in schoolchildren is 20.2 cases per 1 000 children.<sup>[56]</sup> The 60-day mortality after admission with heart failure due to RHD was 24.8%, and the 180-day mortality was 35.4%. Postoperative mortality at 30 days was 2%, while post-surgical survival was >75% at 5 years and >70% at 10 years. The cause-specific mortality rate per 100 000 population decreased from 1.27 in 1997 to 0.7 in 2012.<sup>[56]</sup>

Although much has been achieved over the last 2 decades in terms of improved understanding of the high burden and poor outcomes associated with RHD in SA, minimal progress has been made in terms of further reducing its incidence. Of great concern is that the availability of penicillin in many primary healthcare centres in the country is quite variable due to drug shortages. RHD outcomes in Africa are very poor,<sup>[57]</sup> and life-changing and life-saving surgery is not available to all patients.

## 12. Conclusion

Heart failure is a common disease with a poor prognosis. Rapid diagnostic assessment and aggressive implementation of optimal guideline-mandated therapies are essential to improve outcomes in patients with HFrEF.

The guidelines have been extensively revised, and recommendations regarding the latest therapeutic options have been added. Major updates from the 2013 edition of the guidelines include:

1. the use of cardiac MRI in the diagnosis of HFrEF aetiology
2. the beneficial role of ARNIs, SGLT2 inhibitors and parenteral iron therapy

3. ICD use for primary prevention of SCD
4. management of atrial fibrillation in patients with HFrEF
5. revascularisation for patients with ischaemic LV dysfunction
6. additional information on conditions commonly encountered in sSA – HIV-associated CVD, PPCMO and RHD.

This perspective, taken in conjunction with the 2016 ESC Heart Failure Guidelines, provides the practising clinician with the necessary tools to optimally meet the great need to manage patients with this condition on our continent.

**Disclaimer.** These guidelines do not override the health professional's responsibility to make appropriate decisions according to the circumstances of the patient. It is also the health professional's responsibility to verify the locally approved indications for the devices mentioned.

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- Ponikowski P, Voors AA, Anker SD, et al.; ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129-2200. <https://doi.org/10.1093/eurheartj/ehw128>
- Mpe MT, Klug EQ, Sliwa K, Hitzeroth J, Smith DA. Heart Failure Society of South Africa (HeFSSA) perspective on the European Society of Cardiology (ESC) 2012 chronic heart failure guideline. *S Afr Med J* 2013;103(9 Suppl 2):S660-S667. <https://doi.org/10.7196/samj.7319>
- Kraus S, Ogunbanjo G, Sliwa K, Ntusi NAB. Heart failure in sub-Saharan Africa: A clinical approach. *S Afr Med J* 2016;106(11):23-31. <https://doi.org/10.7196/samj.2016.v106i11.10325>
- Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation* 2003;108(8):977-982. <https://doi.org/10.1161/01.cir.0000085166.44904.79>
- The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327(10):685-691. <https://doi.org/10.1056/nejm199209033271003>
- Ntusi NAB, Mayosi BM. Epidemiology of heart failure in sub-Saharan Africa. *Expert Rev Cardiovasc Ther* 2009;7(2):169-180. <https://doi.org/10.1586/14779072.7.2.169>
- Aghor VN, Essouma M, Ntusi NAB, Nyaga UF, Bigna JJ, Noubiap JJ. Heart failure in sub-Saharan Africa: A contemporaneous systematic review and meta-analysis. *Int J Cardiol* 2018;257:207-215. <https://doi.org/10.1016/j.ijcard.2017.12.048>
- Slwa K, Wilkinson D, Hansen C, et al. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): A cohort study. *Lancet* 2008;371(9616):915-922. [https://doi.org/10.1016/s0140-6736\(08\)60417-1](https://doi.org/10.1016/s0140-6736(08)60417-1)
- Szymanski PZ, Badri M, Mayosi BM. Clinical characteristics and causes of heart failure, adherence to treatment guidelines, and mortality of patients with acute heart failure: Experience at Groote Schuur Hospital, Cape Town, South Africa. *S Afr Med J* 2018;108(2):94-98. <https://doi.org/10.7196/samj.2017.v108i2.12519>
- Damasco A, Mayosi BM, Sani M, et al. The causes, treatment, and outcome of acute heart failure in 1 006 Africans from 9 countries. *Arch Intern Med* 2012;172(18):1386-1394. <https://doi.org/10.1001/archinternmed.2012.3310>
- Dokainish H, Teo K, Zhu J, et al.; INTER-CHF Investigators. Heart Failure in Africa, Asia, the Middle East and South America: The INTER-CHF study. *Int J Cardiol* 2016;204:133-141. <https://doi.org/10.1016/j.ijcard.2015.11.183>
- Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med* 2015;175(6):996-1004. <https://doi.org/10.1001/jamainternmed.2015.0924>
- Dokainish H, Teo K, Zhu J, et al.; INTER-CHF Investigators. Global mortality variations in patients with heart failure: Results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. *Lancet Glob Health* 2017;5(7):e665-e672. [https://doi.org/10.1016/s2214-109x\(17\)30196-1](https://doi.org/10.1016/s2214-109x(17)30196-1)
- Karamitsos TD, Francis JM, Myerson S, Selvanayagam JB, Neubauer S. The role of cardiovascular magnetic resonance imaging in heart failure. *J Am Coll Cardiol* 2009;54(15):1407-1424. <https://doi.org/10.1016/j.jacc.2009.04.094>
- Catalano O, Moro G, Mori A, et al. Cardiac magnetic resonance in stable coronary artery disease: Added prognostic value to conventional risk profiling. *Biomed Res Int* 2018;2018:2806148. <https://doi.org/10.1155/2018/2806148>
- Moosa S, Ntusi NAB. Role of cardiovascular magnetic resonance in the evaluation of cardiomyopathy. *S Afr J Radiol* 2016;20(2):1055. <https://doi.org/10.4102/sajr.v20i2.1055>
- MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353(9169):2001-2007. [https://doi.org/10.1016/s0140-6736\(99\)04440-2](https://doi.org/10.1016/s0140-6736(99)04440-2)
- CII Investigators. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. *Lancet* 1999;353(9146):9-13.
- Packer M, Bristow MR, Cohn JN, et al.; US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996;334(21):1349-1355. <https://doi.org/10.1056/nejm199605233342101>
- Flather MD, Yusuf S, Kober L, et al.; ACE-inhibitor Myocardial Infarction Collaborative Group. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: A systematic overview of data from individual patients. *Lancet* 2000;355(9215):1575-1581. [https://doi.org/10.1016/s0140-6736\(00\)02212-1](https://doi.org/10.1016/s0140-6736(00)02212-1)
- Granger CB, McMurray JJ, Yusuf S, et al.; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: The CHARM-Alternative trial. *Lancet* 2003;362(9386):772-776. [https://doi.org/10.1016/s0140-6736\(03\)14284-5](https://doi.org/10.1016/s0140-6736(03)14284-5)
- Pitt B, Zannad F, Remme WJ, et al.; Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341(10):709-717. <https://doi.org/10.1056/nejm199909023411001>
- Zannad F, McMurray JJ, Krum H, et al.; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;364(1):11-21. <https://doi.org/10.1056/nejmoa1009492>
- McMurray JJ, Packer M, Desai AS, et al.; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371(11):993-1004. <https://doi.org/10.1056/nejmoa1409077>
- Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019;380(6):539-548. <https://doi.org/10.1056/NEJMoa1812851>
- Morrow DA, Velazquez EJ, DeVore AD, et al. Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF Trial. *Circulation* 2019;139(19):2285-2288. <https://doi.org/10.1161/circulationaha.118.039331>
- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017;70(6):776-803. <https://doi.org/10.1161/cir.0000000000000509>
- Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. *Lancet* 2010;376(9744):875-885. [https://doi.org/10.1016/s0140-6736\(10\)61198-1](https://doi.org/10.1016/s0140-6736(10)61198-1)
- Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;351(20):2049-2057. <https://doi.org/10.1056/nejmoa042934>
- Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336(8):525-533. <https://doi.org/10.1056/nejm199702203360801>
- Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373(22):2117-2128. <https://doi.org/10.1056/nejmoa1504720>
- Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380(4):347-357. <https://doi.org/10.1056/nejmoa1812389>
- Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377(7):644-657. <https://doi.org/10.1056/nejmoa1611925>
- McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;381(22):1975-1984. <https://doi.org/10.1056/nejmoa1911303>
- Velazquez EJ, Lee KL, Jones RH, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med* 2016;374(16):1511-1520. <https://doi.org/10.1056/nejmoa1602001>
- Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 2011;364(17):1607-1616. <https://doi.org/10.1056/nejmoa1100356>
- Bhatt AS, DeVore AD, Hernandez AF, Mentz RJ. Can vaccinations improve heart failure outcomes? Contemporary data and future directions. *JACC Heart Failure* 2017;5(3):194-203. <https://doi.org/10.1016/j.jchf.2016.12.007>
- Mohseni H, Kiran A, Khorshidi R, Rahimi K. Influenza vaccination and risk of hospitalization in patients with heart failure: A self-controlled case series study. *Eur Heart J* 2017;38(5):326-333. <https://doi.org/10.1093/eurheartj/ehw411>
- Trivedi JR, Cheng A, Singh R, Williams ML, Slaughter MS. Survival on the heart transplant waiting list: Impact of continuous flow left ventricular assist device as bridge to transplant. *Ann Thorac Surg* 2014;98(3):830-834. <https://doi.org/10.1016/j.athoracsur.2014.05.019>
- Baras Shreibati J, Goldhaber-Fiebert JD, Banerjee D, Owens DK, Hlatky MA. Cost-effectiveness of left ventricular assist devices in ambulatory patients with advanced heart failure. *JACC Heart Failure* 2017;5(2):110-119. <https://doi.org/10.1016/j.jchf.2016.09.008>
- Marrouch NE, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. *New Engl J Med* 2018;378(5):417-427. <https://doi.org/10.1056/NEJMoa1707855>
- Sliwa K, Fetz J, Elkayam U. Peripartum cardiomyopathy. *Lancet* 2006;368(9536):687-693. [https://doi.org/10.1016/s0140-6736\(06\)69253-2](https://doi.org/10.1016/s0140-6736(06)69253-2)
- Bauersachs J, König T, van der Meer P, et al. Pathophysiology, diagnosis and management of peripartum cardiomyopathy: A position statement from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. *Eur J Heart Fail* 2019;21(7):827-843. <https://doi.org/10.1002/ehf.1493>
- Hilfiker-Kleiner D, Kaminski K, Podewski E, et al. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. *Cell* 2007;128(3):589-600. <https://doi.org/10.1016/j.cell.2006.12.036>
- Koenig T, Bauersachs J, Hilfiker-Kleiner D. Bromocriptine for the treatment of peripartum cardiomyopathy. *Card Fail Rev* 2018;4(1):46-49. <https://doi.org/10.15420/cfr.2018.4.1.46>
- Hilfiker-Kleiner D, Haghikia A, Berliner D, et al. Bromocriptine for the treatment of peripartum cardiomyopathy: A multicentre randomized study. *Eur Heart J* 2017;38(35):2671-2679. <https://doi.org/10.1093/eurheartj/ehx355>
- Sliwa K, Hilfiker-Kleiner D, Petrie MC, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: A position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. *Eur J Heart Fail* 2010;12(8):767-778. <https://doi.org/10.1093/eurjhf/hfq120>
- Hilfiker-Kleiner D, Haghikia A, Masuku D, et al. Outcome of subsequent pregnancies in patients with peripartum cardiomyopathy in relation to medical therapy. *Eur J Heart Fail* 2017;19(12):1723-1728. <https://doi.org/10.1002/ehf.808>
- Holloway CJ, Ntusi N, Suttie J, et al. Comprehensive cardiac magnetic resonance imaging and spectroscopy reveal a high burden of myocardial disease in HIV patients. *Circulation* 2013;128(8):814-822. <https://doi.org/10.1161/circulationaha.113.001719>
- Ntusi NAB, Ntsheke M. Human immunodeficiency virus-associated heart failure in sub-Saharan Africa: Evolution in the epidemiology, pathophysiology, and clinical manifestations in the antiretroviral era. *ESC Heart Failure* 2016;3(3):158-167. <https://doi.org/10.1002/ehf2.12087>
- Ntusi N, O'Dwyer E, Dorrell L, et al. HIV-1-related cardiovascular disease is associated with chronic inflammation, frequent pericardial effusions, and probable myocardial edema. *Circ Cardiovasc Imaging* 2016;9(3):e004430. <https://doi.org/10.1161/circimaging.115.004430>
- Ntusi NAB. HIV and myocarditis. *Curr Opin HIV AIDS* 2017;12(6):561-565. <https://doi.org/10.1097/coh.0000000000000416>
- Weber R, Ruppik M, Rickenbach M, et al. Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study. *HIV Med* 2013;14(4):195-207. <https://doi.org/10.1111/j.1468-1293.2012.01051.x>
- Manga P, McCutcheon K, Tsabedze N, Vachiat A, Zachariah D. HIV and nonischemic heart disease. *J Am Coll Cardiol* 2017;69(1):83-91. <https://doi.org/10.1016/j.jacc.2016.09.977>
- Watkins DA, Beaton AZ, Carapetis JR, et al. Rheumatic heart disease worldwide: JACC Scientific Expert Panel. *J Am Coll Cardiol* 2018;72(12):1397-1416. <https://doi.org/10.1016/j.jacc.2018.06.063>
- Zühlke LJ, Engel ME, Watkins D, Mayosi BM. Incidence, prevalence and outcome of rheumatic heart disease in South Africa: A systematic review of contemporary studies. *Int J Cardiol* 2015;199:375-383. <https://doi.org/10.1016/j.ijcard.2015.06.145>
- Zühlke L, Karthikeyan G, Engel ME, et al. Clinical outcomes in 3 343 children and adults with rheumatic heart disease from 14 low- and middle-income countries: 2-year follow-up of the Global Rheumatic Heart Disease Registry (the REMEDY study). *Circulation* 2016;134(19):1456-1466. <https://doi.org/10.1161/circulationaha.116.024769>