ESC HEART FAILURE
ESC Heart Failure 2023; **10**: 1580–1596
Published online 19 March 2023 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14332

REVIEW

Heart failure with reduced ejection fraction and atrial fibrillation: a Sub-Saharan African perspective

Nonkanyiso Mboweni[1,2], Muzi Maseko[1] and Nqoba Tsabedze[2]*

[1]*School of Physiology, University of the Witwatersrand, Johannesburg, South Africa; and* [2]*Department of Internal Medicine, Division of Cardiology, Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand, GautengJohannesburg, South Africa*

Abstract

Cardiovascular diseases are a well-established cause of death in high-income countries. In the last 20 years, Sub-Saharan Africa (SSA) has seen one of the sharpest increases in cardiovascular disease-related mortality, superseding that of infectious diseases, including HIV/AIDS, in South Africa. This increase is evidenced by a growing burden of heart failure and atrial fibrillation (AF) risk factors. AF is a common comorbidity of heart failure with reduced ejection fraction (HFrEF), which predisposes to an increased risk of stroke, rehospitalizations, and mortality compared with patients in sinus rhythm. AF had the largest relative increase in cardiovascular disease burden between 1990 and 2010 in SSA and the second highest (106.4%) increase in disability-adjusted life-years (DALY) between 1990 and 2017. Over the last decade, significant advancements in the management of both HFrEF and AF have emerged. However, managing HFrEF/AF remains a clinical challenge for physicians, compounded by the suboptimal efficacy of guideline-mandated pharmacotherapy in this group of patients. There may be an essential role for racial differences and genetic influence on therapeutic outcomes of HFrEF/AF patients, further complicating our overall understanding of the disease and its pathophysiology. In SSA, the lack of accurate and up-to-date epidemiological data on this subgroup of patients presents a challenge in our quest to prevent and reduce adverse outcomes. This narrative review provides a contemporary overview of the epidemiology of HFrEF/AF in SSA. We highlight important differences in the demographic and aetiological profile and the management of this subpopulation, emphasizing what is currently known and, more importantly, what is still unknown about HFrEF/AF in SSA.

Keywords Atrial fibrillation; Heart failure with reduced ejection fraction (HFrEF); Sub-Saharan Africa

Received: 23 June 2022; Revised: 6 January 2023; Accepted: 7 February 2023
**Correspondence to: Nqoba Tsabedze, Department of Internal Medicine, Division of Cardiology, Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand, Johannesburg, Gauteng, South Africa. Tel: +27 722722420. Email: nqoba.tsabedze@wits.ac.za*

Introduction

Heart failure (HF) is a well-recognized public health concern in high-income countries (HICs). In the last two decades, HF has emerged as a major public health problem in Sub-Saharan Africa (SSA) owing to the effects of westernization and a subsequent epidemiological transition from infectious to non-communicable disease patterns.[1] This epidemiological transition is evidenced by an increasing prevalence of traditional risk factors for cardiovascular diseases (CVDs) such as obesity, sedentary lifestyle, diabetes mellitus, and hypertension.[2] HF as a clinical syndrome is associated with increased morbidity and mortality.[3] The aetiological profile of HF in SSA differs greatly from that of HICs, with the majority of causes of HF being non-ischaemic in nature.[1,4–7] Many HF-related hospitalizations impose a major burden on the global economy, particularly those of SSA's low-middle-income countries (LMICs).[8]

Atrial fibrillation (AF) is a common comorbidity of HF and is characterized by rapid and haphazard electrical activity in the atria marked by an irregular heart beat and absent p-waves on an electrocardiogram (ECG).[9,10] The aetiological spectrum of HF in SSA is broad. This has an impact on the relative AF prevalence across the HF spectrum in SSA. Rheumatic heart disease (RHD) is a common risk factor for AF in SSA, with a prevalence ranging from 10% to 46%.[11–14] However, recent studies are beginning to demonstrate an increase in non-valvular AF in this setting with RHD not so prevalent

anymore in some regions.[11,15–17] A few studies have demonstrated heart failure with preserved ejection fraction (HFpEF) and heart failure with mid-range ejection fraction (HFmrEF) to have a higher AF prevalence than heart failure with reduced ejection fraction (HFrEF).[6,18] However, in patients with longstanding HF, the prevalence of HFrEF/AF becomes more apparent.[16] Interesting insights from the multinational THESUS-HF registry reported a significantly higher prevalence of AF in HFmrEF (28.5%) compared with that of HFpEF (21.3%) and HFrEF (14.5%).[19]

Data from SSA suggest that AF is a major decompensating factor among HF patients in SSA.[6,15,16,19–22] A Tanzanian study found a survival rate of 63% [vs. 96% ($P < 0.001$)] in HF/AF patients.[21] Similarly, AF was found to be a significant predictor of death in one of the largest HF outcomes studies ($n = 1488$) undertaken in Ghana.[6] However, AF was not significantly associated with all-cause death in HFmrEF or HFpEF patients, unlike HFrEF.[6] Similarly, data from the THESUS-HF registry revealed that in the setting of HF, 6 month mortality was substantially greater in individuals with valvular AF compared with non-valvular AF.[15]

AF predisposes individuals to a five-fold greater stroke risk and an increased rehospitalization risk.[26,27] Across the global population, 1 to 2 in 10 individuals with any cardiomyopathy, excluding post-partum cardiomyopathy, will develop AF.[28] Furthermore, HF/AF patients, in SSA, are at a 1.3- to 3.4-fold risk of death compared with HF patients without AF.[21,29] This is particularly concerning given the significant morbidity and mortality associated with AF. AF is common in both HFpEF and HFrEF but portends a higher risk of mortality in patients with HFrEF.[6,30,31] A recent study demonstrated that HFrEF/AF patients had a greater 1 year mortality rate (36.5%) than patients with HFmrEF/AF (27.7%) and HFpEF/AF (27.7%).[7,31]

Over the last decade, significant advancements in the management of both HFrEF and AF have emerged. However, managing HFrEF with co-existing AF remains a clinical challenge for physicians, compounded by the suboptimal efficacy of guideline-mandated pharmacotherapy in this group of patients. Furthermore, there may be an important role for racial differences and genetic influence on therapeutic outcomes of HFrEF/AF patients, further complicating our overall understanding of the disease and its pathophysiology. In SSA, the lack of accurate and up-to-date epidemiological data on this subgroup of patients presents a challenge in our quest to prevent and reduce adverse outcomes.

This narrative review provides a contemporary overview of the epidemiology on HFrEF/AF in SSA. We further highlight important differences in this subpopulation's demographic and aetiological profile and, more importantly, what is still unknown about HFrEF/AF in SSA. With emerging data from HIC studies advocating for a timely aggressive rhythm control strategy in this cohort of patients, we were compelled to bring SSA to the conversation. We aim to raise awareness about the growing burden of HFrEF/AF and provide a summary of new approaches to managing HFrEF/AF.

Methods

We searched PubMed/MEDLINE, EMBASE, and Scopus from inception to September 2022, without language restriction, to identify all published studies providing data on the prevalence, epidemiology, and outcomes of HFrEF and concomitant AF in Sub-Saharan African populations. Countries below the equator were considered SSA. Although this review aims to focus on the co-occurrence of HFrEF/AF, due to the lack of data, we independently screened AF and HF population studies to identify data on the relevant subgroup of interest (HFrEF/AF). These studies are summarized in *Table 1*.

The following keywords were used in the search strategy: 'heart failure', 'atrial fibrillation', and the name of all the SSA countries. We included all cross-sectional and cohort studies. The following definition of HF was employed: patients with signs and symptoms of HF as well as an echocardiographic diagnosis. We excluded studies where the study does not report on AF's impact on outcomes, AF populations where HF population is heterogenous with HFpEF/HFmrEF predominance, and HF studies where HFrEF is a minority. A narrative review approach was adopted to enable a broad discussion on various aspects of HFrEF/AF.

PubMed search strategy

Search: heart failure atrial fibrillation Africa

('heart failure'[MeSH Terms] OR ('heart'[All Fields] AND 'failure'[All Fields]) OR 'heart failure'[All Fields]) AND ('atrial fibrillation'[MeSH Terms] OR ('atrial'[All Fields] AND 'fibrillation'[All Fields]) OR 'atrial fibrillation'[All Fields]) AND ('Africa'[MeSH Terms] OR 'Africa'[All Fields] OR 'Africa s'[All Fields] OR 'Africa's'[All Fields])

Translations

heart failure: 'heart failure'[MeSH Terms] OR ('heart'[All Fields] AND 'failure'[All Fields]) OR 'heart failure'[All Fields] atrial fibrillation: 'atrial fibrillation'[MeSH Terms] OR ('atrial'[All Fields] AND 'fibrillation'[All Fields]) OR 'atrial fibrillation'[All Fields] africa: 'Africa'[MeSH Terms] OR 'Africa'[All Fields] OR 'Africa's'[All Fields] OR 'Africa'[All Fields].

A PRISMA flow diagram is shown in *Appendix S1*.

Epidemiology

CVDs are a well-established cause of death in HICs. In the last 20 years, SSA has seen one of the sharpest increases in

Table 1 Studies reporting on the impact of atrial fibrillation on HF across Sub-Saharan Africa

Author	Sample size (*n*)	Country	Heart failure phenotype	Heart failure diagnosis	Study population	Mean age	Study design	Outcome	AF prevalence	Impact of AF on study outcome
Makubi (2014)[a,21]	427	Tanzania	ADHF LVEF = 41 (12)	Framingham criteria[23]	HF population	55	Prospective observational study	All-cause mortality	15.7%	The survival rate was significantly lower in patients with atrial fibrillation compared with those without 63% vs. 96% ($P < 0.001$).
Ogah (2014)[24]	262	Nigeria	ADHF LVEF = 39.7 (18)	Framingham criteria[23]	HF population	56.1	Prospective observational study	Hospital readmission	12.6%	The frequency of atrial fibrillation was higher in readmitted patients. This was not significant.
Malamba-Lez (2018)[a,25]	231	Democratic Republic of Congo	ADHF LVEF = 29 (15)	Framingham criteria[23]	HF population	56	Retrospective analysis	In-hospital mortality rate	20%	AF was significantly associated with in-hospital mortality rate ($P = 0.02$).
Mandi (2019)[a,16]	107	Burkina Faso	HF/AF (93.1%)	Framingham criteria[23]	AF population	66.6	Prospective observational study	All-cause mortality Rehospitalization Ischaemic stroke	HFrEF/AF: 59% HFmrEF/AF: 8.9% HFpEF/AF: 31.9%	Very high overall long-term mortality (40.59%). Patients with AF and idiopathic dilated cardiomyopathy were at higher risk of death than other patients (log-rank test = 11.88, $P < 0.001$).

Abbreviations: ADHF, acute decompensated heart failure; AF, atrial fibrillation; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.
[a]Studies where AF had a significant impact on study outcome.

CVD-related mortality, superseding that of infectious diseases and malignant neoplasms, combined in South Africa.[29,49] This increase is evidenced by a growing burden of HF and AF risk factors. CVD-related deaths accounted for 17.7% of the total causes of death in South Africa, and among these were cerebrovascular diseases (5.1%), heart disease (5.1%), hypertensive heart disease (4.5%), and ischaemic heart disease (3.0%).[49] Furthermore, it is worth noting that in 2017, diabetes, an independent risk factor for HFrEF and AF, was the second highest cause of death (5.9% of total deaths) in South Africa.[49] The co-occurrence of HF and AF, in HICs, is reported in more than 40% of HF patients.[50,51] According to the few studies that have been conducted in SSA, the prevalence of AF in HF has been reported to range between 12.5% and 62.6%, with South Africa (56%) and Ivory Coast (62.6%) showing the highest prevalence[11,21,22,24,52-54] (*Table 1*). This wide range reflects SSA's dearth of robust datasets. There are a number of possible explanations for this, including varying (outdated) definitions of HF and AF, and a paucity of research studies employing recent definitions and diagnostic criteria. Additionally, it is possible that estimated HFrEF/AF incidence and prevalence underestimate the true burden in SSA due to under-reporting, insufficient AF screening, limited access to healthcare facilities, and geographical disparity in published data.

In SSA, the age and risk factor profile for AF differ compared with HIC, where most cases are recorded in the 8th decade of life.[11,17,18,55] In SSA, AF presents throughout the lifespan, with most patients presenting before age 50.[11] On average, a South African cohort from the large Heart of Soweto Study was 8 years younger than AF patients in Cameroonian and Burkina Faso populations.[16,17] Despite differences in the mean age of onset across SSA, it appears that the young age of onset is widespread.[11,15,18,55–57]

It is worth noting that AF appears to be more common among females than in males.[11,15,17,18,54,55] In the Heart of Soweto Study, women were more likely to be obese than their male counterparts (73% vs. 40%). The independent risk of developing AF with an increasing body mass index (BMI) is well documented in the literature. The study authors hypothesize that the preponderance of AF in women may be explained by the pattern of obesity in the cohort rather than gender per se. Other studies in SSA found a female predilection for AF, especially after excluding women with peripartum cardiomyopathy.[15,54]

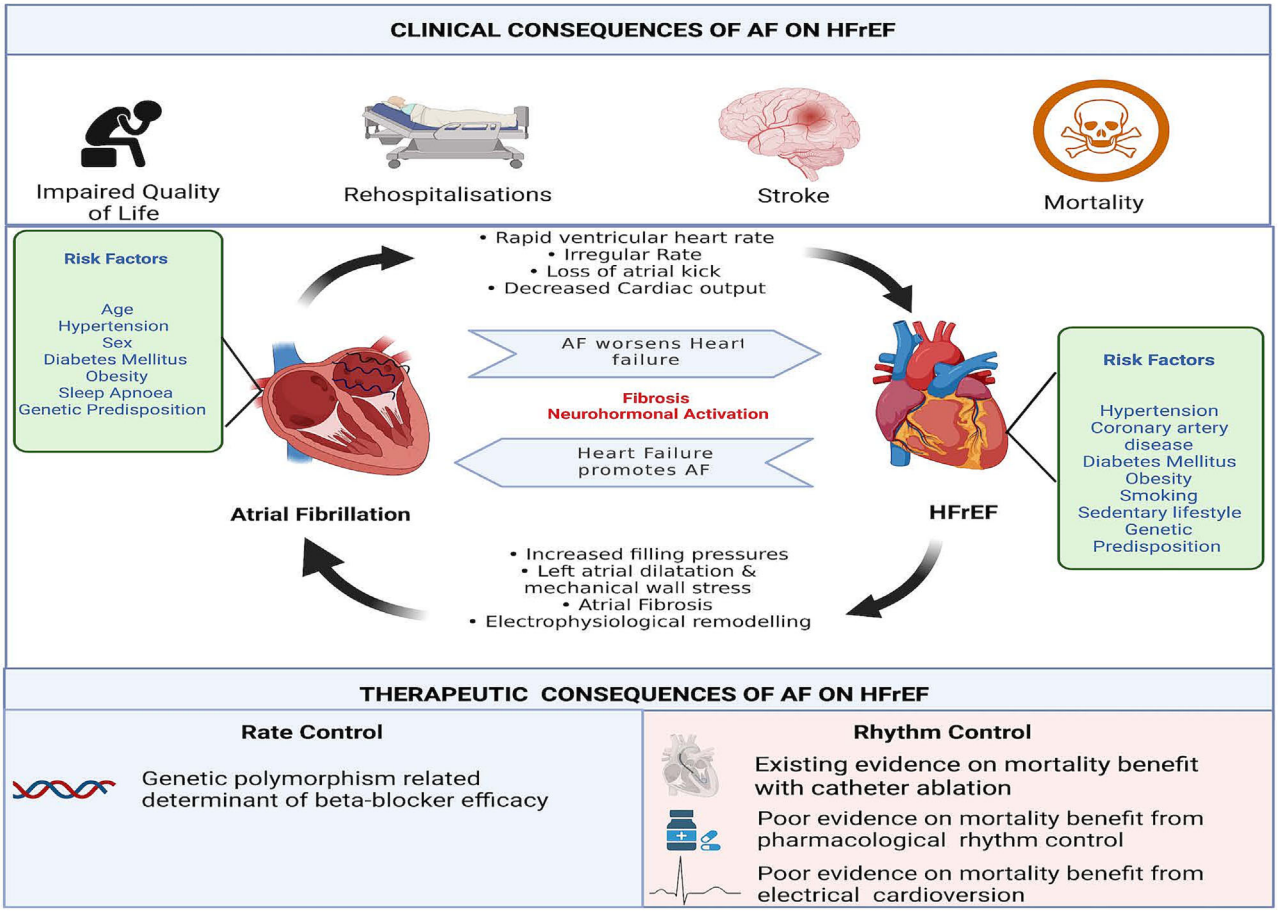
Significant sex-based differences persist against the backdrop of a heterogeneous aetiological HF spectrum. Women with non-valvular AF in South Africa are more likely to have hypertensive heart disease and less likely to have dilated cardiomyopathy. Men, on the other hand, frequently presented with left ventricular systolic dysfunction and larger cardiac dimensions.[11,15]

AF had the largest relative increase in CVD burden between 1990 and 2010 in SSA and the second highest

(106.4%) increase in disability-adjusted life-years (DALY) after peripheral vascular disease between 1990 and 2017.[58,59] This increase was observed despite a decrease in RHD over the prescribed time period, suggesting that factors beyond RHD are likely to contribute to the rise in AF in SSA. Consistent with other systematic reviews, stroke emerged as the leading cause of CVD burden in SSA.[58] Given the established relationship between AF and stroke, it is worth speculating that the former could contribute to the latter's rise.

Independent risk factors for both AF and HFrEF are advanced age, hypertension, diabetes mellitus, and coronary artery disease (*Figure 1*). Hypertension, obstructive sleep apnoea (OSA), diabetes mellitus, and obesity are among some of the strongest predictors of AF in HIC.[60,61] In SSA, hypertension is a common risk factor across all countries, whereas RHD varies by country. For example, RHD was one of the least significant risk factors for AF in Kenya, whereas hypertension, HF, and diabetes mellitus were the most prevalent predictors.[53] Coronary artery disease remains uncommon; however, emerging data and an increase in atherosclerosis risk factors across SSA suggest that this may not remain at low prevalence rates indefinitely.[21] Contemporary epidemiological studies hypothesize that the burden of AF in SSA will be double that of HIC by 2060.[2,27,62] The rising burden of HFrEF, AF, and co-existing CVDs, many of which are risk factors for AF, is confirmed by the upward trend in HFrEF/AF-related hospitalizations in SSA.[2,3,63] Characterizing the clinical profile of these patients in SSA is critical as it has therapeutic, socioeconomic, and policy implications. Such data may be used to advance strategies to mitigate modifiable risk factors. Reducing healthcare utilization by preventing AF recurrence and decreasing the AF burden has been shown to be extremely beneficial in HIC economies.[64,65] A study conducted by Pathak *et al*. demonstrated that aggressive management of risk factors like OSA, weight, hypertension, and diabetes significantly reduced the AF burden after catheter ablation.[64,65] This study highlights optimal modifiable risk factor management's potential benefits for upstream non-invasive therapy. Whether the same benefits are observed in the setting of HFrEF is unclear.

Figure 1 The effects of atrial fibrillation (AF) on heart failure with reduced ejection fraction (HFrEF). AF significantly impairs the quality of life and increases the risk of stroke, rehospitalization, and mortality in patients with HFrEF. AF is both a cause and a result of HFrEF with both entities sharing independent risk factors. Genetic polymorphisms in the beta-adrenergic receptor may modulate beta-blocker efficacy in patients with HFrEF/AF.



Pathophysiology

AF is caused by HFrEF, a process facilitated by adverse structural and electrical remodelling of the atria (*Figure 1*).[10,66] Moreover, AF aggravates HF, eliciting an increase in HF symptoms, hospitalizations, and mortality (*Figure 1*).[67] AF is both a cause and a result of HFrEF, and in clinical practice, the index diagnosis of both conditions is not uncommon, making a causal link unclear.[68] A subgroup analysis of the temporal associations of AF and HF, from the Framingham Heart Study, found that AF occurring after HFrEF confers a worse prognosis than AF that occurs before HF.[30] Depending on whether AF or HF is the underlying condition, patient groups differ significantly in terms of outcomes and the required therapeutic approach. In SSA, there are currently no data on what proportion of HFrEF/AF patients are atrial tachycardia-induced HFrEF vs. AF secondary to HFrEF.

Most published literature on the pathophysiological mechanisms of HF/AF is based on HFrEF/AF in animal models. Left atrial enlargement and dysfunction have been implicated in the bidirectional relationship between HFrEF and AF (*Figure 1*). AF promotes HF through a persistently increased ventricular rate, sympathetic dysregulation, and loss of atrial contraction mediated by calcium 2^{+} mishandling (*Figure 1*).[69] As a result, gross morphological and functional changes such as reduced systolic function, cardiac chamber dilatation, and greater wall tension result. In a matter of weeks, the full HF phenotype with reduced ejection fraction is established.[68] This is commonly referred to as tachyarrhythmia-induced HF.

In the setting of HFrEF, AF results from dysfunctional calcium handling in the atria secondary to atrial dilatation.[10] The increase in left ventricular end-diastolic pressure results in elevated left atrial pressure. The elevated atrial pressure increases atrial mechanical wall stress, which subsequently alters calcium handling within the atria.[70] Atrial mechanical stress constitutes stretch and shear stress resulting from increased intra-atrial volume and pressure, respectively.[71] Underlying these pathophysiological mechanisms of HFrEF are processes of inflammation and fibrosis (*Figure 1*). These pathophysiological mechanisms ultimately cause structural and electrophysiological remodelling of the atria, which sets the milieu for spontaneous depolarization, and hence arrhythmogenicity at the site of the pulmonary vein confluence with the left atria.[72] These changes in left atrial structure and function have important prognostic implications in HFrEF, independent of recognized parameters such as left ventricular ejection fraction (LVEF).[73]

In patients with ventricular dysfunction, left atrial contraction has an essential compensatory role to play in augmenting ejection force and stroke volume by increasing end-diastolic volume and pressure.[74] In the setting of AF, the atrial contraction component is lost and replaced by the ineffective quivering of the atria compounded by rapid ventricular activation and shortened diastolic filling time.[74] This results in a 20–30% reduction in cardiac output.[74] This loss in cardiac output is particularly notable in the elderly population as they are highly dependent on the atrial pump function. Consequently, recurrent and worsened HF symptoms and syncopal episodes are observed.[67,74] Therefore, restoration of atrial contraction can significantly stabilize the haemodynamics and symptoms in patients with AF and concomitant HFrEF.

Management of heart failure with reduced ejection fraction/atrial fibrillation

Irrespective of the temporal association of AF and HFrEF, managing both conditions concomitantly is a clinical challenge as these patients do not respond optimally to HFrEF pharmacological mortality-benefitting therapy. Optimal management of HFrEF constitutes a combination of neurohormonal antagonists such as angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), or a neprilysin inhibitor [angiotensin receptor neprilysin inhibitor (ARNI)], as well as mineralocorticoid receptor antagonists and beta-blockers.[75] These therapies have all been shown to provide significant mortality benefits and reduce rehospitalizations.[76–78] With AF in the picture, this regimen includes a rate and rhythm control strategy and stroke prevention with oral anticoagulants (OAC).[9] Following data from the PARADIGM-HF trial, the 2021 ESC Guidelines for diagnosing and treating acute and chronic HF now recommend using sacubitril/valsartan, an ARB and neprilysin inhibitor (ARNI), as first-line therapy in symptomatic HFrEF patients.[75] There is evidence that sacubitril/valsartan could lessen the AF burden in HFrEF/AF patients with non-permanent AF.[79] Human and animal model studies support this conclusion, implying that ARNIs may exert antiarrhythmic effects indirectly by preserving left atrial function and modulating atrial fibrosis in pressure-loaded subjects.[80] However, this antiarrhythmic effect was not observed in PARADIGM-HF and a recent meta-analysis. Rather, the incidence of de novo AF remained the same in the ARNI and enalapril arms.[81,82] A sub-study analysis found that although HFrEF/AF patients do benefit from reduced mortality, the advantage is not as great as seen in sinus rhythm patients.[83] A prospective randomized control trial (RCT) is necessary to verify or refute these findings.

More recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors, which are glucose-lowering agents, have evolved as HF therapy. They have recently been included as part of first-line HFrEF therapy for their significant cardiovascular death reduction, regardless of baseline HF medication use or diabetic status.[84] Data from the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) revealed dapagliflozin demonstrated a significant reduction in

cardiovascular deaths and HF events in patients with symptomatic HFrEF.[84] The study comprised a small number of Black participants (5.1%) and did not include any patients from SSA. The reported prevalence of AF in this cohort was 38.6%.[84] Dapagliflozin may also reduce the incidence of AF, regardless of whether patients have a history of AF or pre-existing CVD or HF, according to new findings from a sub-analysis of the DECLARE-TIMI trial.[85]

Most landmark HFrEF and AF RCTs enrolled <10% of Black patients and even lesser Africans. Therefore, caution should be exercised when generalizing findings from data in HICs. It is also worth noting that most African Americans are of West African ancestral descent and are not representative of the entire African population.[86] Even among Africans, there is a large degree of genetic and risk factor heterogeneity; thus, extrapolations from these large RCTs to Sub-Saharan Africans cannot be made definitively.

Rate control

Autonomic dysregulation is a hallmark of HF, independent of aetiology. The imbalance between the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) not only is reactive to HF, to try and maintain homeostasis acutely, but also contributes to the progression of chronic HFrEF.[87] These complex interactions' net effects are excessive SNS stimulation and a corresponding decrease in PNS tone.[87] Chronic SNS stimulation promotes myriad biological changes that lead to cardiac dysfunction. Among these changes are myocyte death and necrosis, desensitization of beta-adrenergic signalling, myocardial hypertrophy, and fibrosis. Beyond that, chronic SNS stimulation results in increased end-diastolic volume, left ventricular afterload, contractility, and heart rate.[88] Therefore, it seems implicit that the benefit of beta-blockade in HFrEF would translate into improved morbidity and mortality benefit. This mortality benefit was demonstrated in landmark trials for bisoprolol, carvedilol, and metoprolol; and was among the highest for these agents.[89–91]

Beta-blockers and ACE-I/ARBs are used as first-line therapy to manage stable patients with HFrEF. Similarly, beta-blocker monotherapy is often the first-line rate-controlling agent used for the symptomatic management of patients with lone AF.[9,92] Unlike sinus rhythm, slower heart rates are not associated with improved survival HFrEF/AF (*Table 2*).[44,45,93] Carvedilol in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, bisoprolol in Cardiac Insufficiency Bisoprolol Study (CIBIS)-II, and metoprolol succinate in the Metoprolol Controlled-Release Randomized Intervention Trial in Heart Failure (MERIT-HF) all showed a significant reduction in mortality, of 34–35%, when compared to placebo.[89–91] On the other hand, Bucindolol in the Beta-Blocker Evaluation of Survival Trial (BEST) showed a non-significant 13% risk reduction in mortality compared to placebo.[94] These findings suggest differences in outcomes by geographic region and race. Trials CIBIS-II, CORPENICUS, and MERIT-HF were conducted outside of the United States, and BEST recruited patients in the United States and Canada. Twenty-four per cent of patients in BEST were African American and demonstrated no mortality benefit from bucindolol [hazard ratio (HR) 1.17, P = 0.27], whereas non-Black patients did benefit [HR 0.82; confidence interval (CI): 0.70 to 0.96; P = 0.01].[94] Investigators of The Multicenter Oral Carvedilol in Heart Failure Assessment (MOCHA) trial reported a dose-dependent increase in LVEF and decreased mortality and rate of hospitalization in patients with HFrEF.[95] In another study, by McAlister *et al*., a reduction in heart rate was significantly associated with mortality benefit, but this was not dose dependent.[96] The SHIFT trial evaluated the efficacy of ivabradine in HFrEF patients with a heart rate of ≥70 b.p.m. Ivabradine is a sinus node (I_f – *Channel*) inhibitor and hence does not work via the beta-adrenoreceptor. Ivabradine demonstrated a significant reduction in HF events but not in cardiovascular-related deaths.[97] These findings highlight the importance of heart rate reduction for improving clinical outcomes in HFrEF. There were no study participants from SSA in these trials.

A large meta-analysis done by Kotecha *et al*. concluded that beta-blockers do not provide any mortality benefit and reduction in hospitalizations in patients with HFrEF/AF.[45] The study analysed 10 landmark trials with a cumulative sample size of n = 18 254 and an HFrEF/AF prevalence of 17% (n = 3066). The prevalence reported by Kotecha and colleagues is relatively low compared with what other studies have reported. This could be attributable to the fact that AF was documented only based on a single baseline ECG, predisposing potential misclassification errors in establishing a diagnosis of AF, especially for non-permanent AF.[45] All-cause mortality, cardiovascular death, and cardiovascular and HF-related hospitalizations were major outcomes. Patients with HFrEF/AF had no significant reduction in all primary and clinical composite outcomes compared to placebo.[45] However, this retrospective meta-analysis used relatively old trials and only 1 out of 10 trials differentiated between AF and atrial flutter. All other trials included in the analyses classified AF as both atrial flutter and fibrillation.[45] Suppose beta-blockers do not provide mortality benefits. In that case, it is unclear why the positive effects of beta-blockers, particularly on myocardial remodelling, do not correspond to prognostic benefits in patients with AF. This is an anomaly that requires further investigation.

On the contrary, more recent studies are at variance with the findings by Kotecha *et al*., reporting a 25–29% reduction in mortality with the use of beta-blockers[46–48] (*Table 2*). Cadrin-Tourigny and colleagues are commended for their thorough attempt to characterize AF in their cohort. In their study, AF was characterized according to baseline rhythm

Table 2 Studies on the outcomes of rate and rhythm control strategies in heart failure with reduced ejection fraction/atrial fibrillation

Intervention	Trial name/study type	Sample size	Study population	Effect in HFrEF/SR	Effect in HFrEF/AF	Reference
Antiarrhythmic drug therapy (dofetilide) vs. placebo	DIAMOND-CHF	*N* = 1518	• Patients with new or worsening HFrEF • NYHA class III or IV or paroxysmal nocturnal dyspnoea • Danish population	-	No effect on mortality.	Torp-Pedersen *et al.* (1999)[32]
Antiarrhythmic drug therapy vs. pharmacological rate control therapy	AF-CHF	*N* = 1376	• LVEF ≤ 35% • NYHA class II to IV • Canadian, North and South American, European, and Israeli population	-	HR 1.06 (0.86–1.30) in the rhythm control group. There was no difference with respect to primary (death from cardiovascular causes) and secondary outcomes.	Roy *et al.* (2008)[33]
Catheter ablation (PVI) vs. AV node ablation and with biventricular pacing (CRT)	PABA-CHF	*N* = 82	• Symptomatic, AAD-resistant AF • LVEF < 40% • NYHA class II to IV	-	Catheter ablation was superior with respect to LVEF, exercise capacity, and symptoms.	Khan *et al.* (2008)[34]
Catheter ablation vs. pharmacological rate control		*N* = 41	• Persistent AF • LVEF < 40% • NYHA class II to IV		No difference in MRI measured LVEF.	MacDonald *et al.* (2011)[35]
Catheter ablation vs. pharmacological rate control therapy	ARC-HF	*N* = 52	• Persistent AF • LVEF < 35% • NYHA class II to IV • British population	-	Catheter ablation was superior with respect to exercise capacity. Catheter ablation showed a non-significant trend towards LVEF improvement [mean difference, +5.6% (95% CI, −0.1 to +11.3); *P* = 0.055].	Jones *et al.* (2013)[36]
Catheter ablation vs. pharmacological rate control therapy	CAMTAF	*N* = 50	• Persistent AF • NYHA class II to IV • LVEF < 50%	-	Catheter ablation was superior with respect to LVEF. Catheter ablation was superior with respect to exercise capacity, BNP quality of life, and symptoms compared with rate control.	Hunter *et al.* (2014)[37]
Catheter ablation vs. amiodarone	AATAC	*N* = 203	• Persistent AF • LVEF ≤ 40% • NYHA class II or III • Dual-chamber ICD or CRT	-	Catheter ablation was superior with respect to freedom from AF.	Di Biase *et al.* (2016)[38]
Catheter ablation vs. rate control	CAMERA-MRI	*N* = 68	• Persistent AF • LVEF ≤ 45%		Catheter ablation was superior with respect to LVEF.	Prabhu *et al.* (2017)[39]
Catheter ablation vs. basic medical therapy	CASTLE-AF	*N* = 363	• Symptomatic, AAD-resistant AF • LVEF < 35%	-	Catheter ablation was superior with respect to composite primary endpoint	Marrouche *et al.* (2018)[40]

(*Continues*)

Table 2 (continued)

Intervention	Trial name/study type	Sample size	Study population	Effect in HFrEF/SR	Effect in HFrEF/AF	Reference
			• NYHA class II or III • Dual-chamber ICD or CRT with home monitoring		(death or hospitalization for worsening heart failure).	
Catheter ablation vs. basic medical therapy	AMICA	*N* = 140	• Persistent AF • LVEF ≤ 35% • German, Hungarian, and Spanish participants		Catheter ablation was not superior to BMT with respect to LVEF.	Kuck *et al*. (2019)[41]
AV node ablation + CRT vs. rate control	APAF-CRT	*N* = 102	• Permanent AF • N arrow QRS (≤110 ms) • ≥1 HF hospitalization in previous year		AV node ablation was superior with respect to composite outcome (death caused by HF, HF hospitalization, or worsening HF).	Brignole *et al*. (2018)[42]
Catheter ablation vs. medical rate or rhythm control	CABANA	*N* = 2204	• ≥2 paroxysmal or 1 persistent AF episodes in the last 6 months • Age ≥ 65 years • Age < 65 years + ≥1 risk factor for stroke		Catheter ablation did not reduce composite primary endpoint.	Packer *et al*. (2019)[43]
Rate control	Meta-analysis	*N* = 8680	• HFrEF/SR vs. HFrEF/AF	HR 0.63 (0.54–0.73)	HR 0.86 (0.66–1.13) (No mortality benefit)	Rienstra *et al*. (2013)[44]
Rate control	Meta-analysis	*N* = 18 254	• HFrEF/SR vs. HFrEF/AF	HR 0.73 (0.67–0.80)	HR 0.97 (0.83–1.14) (No mortality benefit)	Kotecha *et al*. (2014)[45]
Rate control	HF registry	*N* = 18 858	• HFrEF/SR vs. HFrEF/AF • Swedish participants	HR 0.77 (0.63–0.94)	HR 0.71 (0.61–0.84) (29% reduction in mortality)	Li *et al*. (2015)[46]
Rate control	AF registry	*N* = 39 741	• HFrEF/AF • Danish population	-	HR 0.75 (0.71–0.79) (25% reduction in mortality)	Nielsen *et al*. (2016)[47]
Rate control	AF-CHF sub-analysis, propensity score matching	*N* = 1376	• HFrEF/AF • North, South American and Israeli population	-	HR 0.72 (0.55–0.95) (28% reduction in mortality)	Cadrin-Tourigny *et al*. (2017)[48]

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; AV, atrioventricular; BMT, bone marrow transplantation; CI, confidence interval; CRT, cardiac resynchronization therapy; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NYHA, New York Heart Association; RCT, randomized control trial; SR, sinus rhythm.

and pattern, with an ECG taken in each participant every 4 months.[48] Furthermore, findings from a large-scale (n = 18 858) prospective study conducted in Sweden demonstrated that a heart rate > 100 b.p.m. was associated with an increase in mortality.[46] These contrasting findings further highlight geographical and possible genetic and environmental factors that may influence the outcomes of beta-blocker therapy in HFrEF/AF.

Although there is no consensus on the therapeutic benefit of beta-blockers in patients with HFrEF/AF, their use did not predispose patients to death and hospital admissions, proving their use to be at least safe.[45] Using beta-blockers in HFrEF reduced the incidence of AF in sinus rhythm patients. This finding may be clinically relevant and an important component of the benefit seen in sinus rhythm.

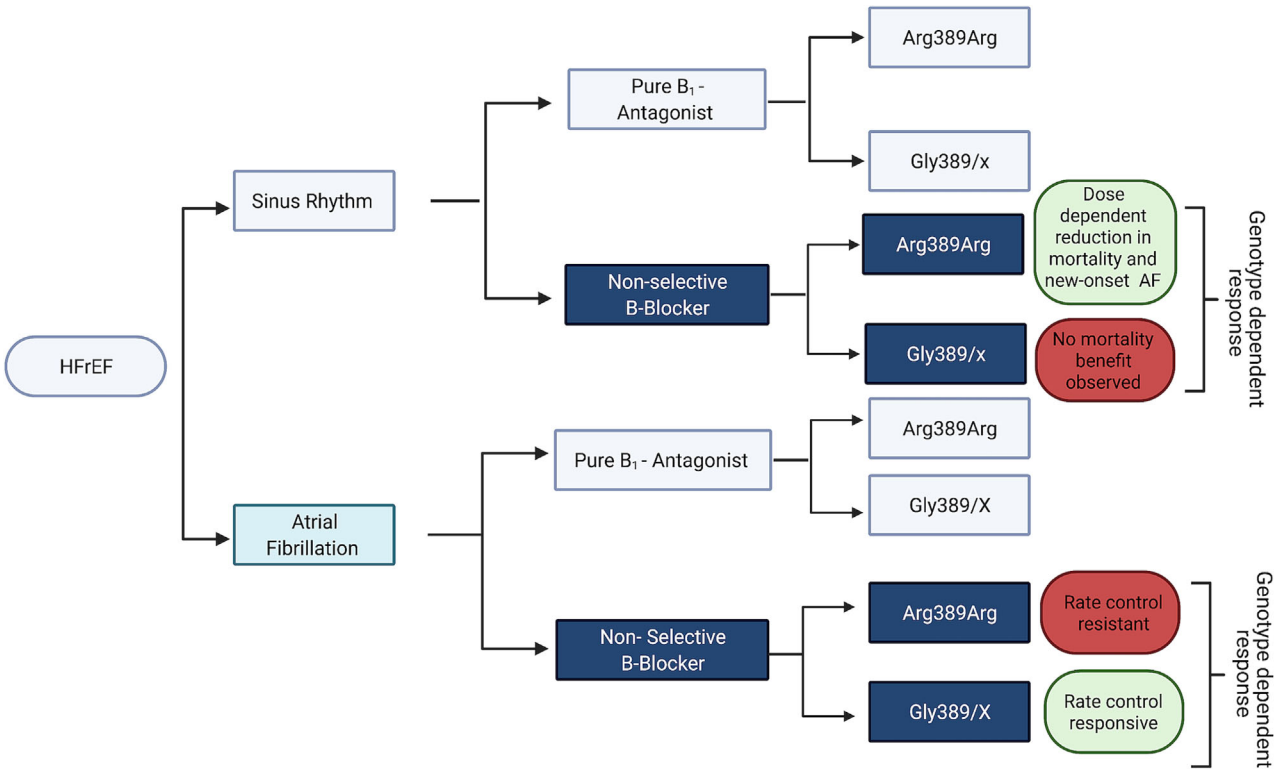
Arg389Gly polymorphism

Given the heterogeneity of HF and the burden of idiopathic dilated cardiomyopathy in SSA, strides have been made to investigate HF's genetic undertones.[4,98] Of note, the role of the β1-adrenoceptor (ADRB1) polymorphisms has been extensively elucidated in hypertension and HF in the broader population context.[4,99] Only recently, the response to rate control has been considered genotype dependent.[100] However, no studies have been done in our setting in this regard.

Data show that adverse drug responses, including failure to respond, may be attributable to polymorphisms in the ADRB1 gene. Identifying patients on this basis may be helpful in managing patients with HFrEF and HFrEF/AF. It has been hypothesized that the arginine389glycine (Arg389Gly) polymorphism modulates such differential responses to beta-blockers in HFrEF patients from HIC.[101–103] These effects were also recently shown to be dose dependent in specific subgroups (*Figure 2*). Its significance in SSA HFrEF and HFrEF/AF patients remains undetermined but demonstrates the importance of precision-based medicine and its potential therapeutic utility in our setting.

The ADRB1 is a G-protein coupled receptor (GPCR) expressed on cell surfaces. It is activated by catecholamine binding, which leads to increased intracellular cyclic-adenosine monophosphate (cAMP) activity and a resultant increase in inotropic and chronotropic effects on the

Figure 2 Genotype-dependent efficacy of beta-blockers in heart failure with reduced ejection fraction/atrial fibrillation (HFrEF/AF). Grey: HFrEF pathways where the efficacy of beta-blockers are genotype independent. Navy blue: HFrEF pathways where the efficacy of beta-blockers are genotype dependent. In sinus rhythm patients, there is dose-dependent mortality benefit and reduction in new-onset AF in patients with the gain of function Arg389Arg variant. In patients with HFrEF/AF, the Arg389Arg variant was unresponsive to the rate-lowering effects of non-selective beta-blockers.



myocardium.[104–106] Data from *in vitro* studies show that Gly389 is a 'loss of function variant' with less constitutive activity and a low affinity for norepinephrine. When bound to an agonist, the receptor elicits reduced cAMP production, thereby attenuating the cAMP-dependent beta-adrenergic signal transduction cascade.[107,108] The gain of function, Arg389, mutant, on the other hand, has a higher affinity for norepinephrine and thus a higher potential for signal transduction.[109,110] This receptor variant is also said to be more constitutively active (i.e. transducing signal/active in the absence of bound ligand).[110]

Heart failure with reduced ejection fraction and ADRB1 genotype

Available data from the BEST trial show a dose-dependent decrease in all-cause mortality and HF hospitalization in a select group of HFrEF patients treated with low-dose bucindolol, a non-selective beta-blocker, compared to placebo.[102] Patients on low-dose bucindolol (0–25 mg daily) with the homozygous Arg389 variant had a significantly greater event rate, when corrected for common risk factors, compared to placebo (P = 0.006). When up-titrated to a high dose of bucindolol (>25 mg daily), Arg389 homozygotes had a 60% reduction in all-cause mortality (P = 0.0002).[103] This benefit was not observed in patients carrying the Gly389 allele.[102] Another sub-study of the BEST trial showed that HFrEF patients with the Arg389Arg genotype had a 74% reduction in new-onset AF when treated with bucindolol [HR 0.26 (95% CI: 0.12–0.57)] and no effect observed in the Gly389 patients[111] (*Figure 2*). These findings support a pharmacogenetic role for the polymorphism in managing HFrEF patients, directly impacting clinical outcomes. The effects of high-dose bucindolol in HFrEF/AF are proposed to be a function of selective inverse agonism, which attenuates the receptor's constitutive activity, bucindolol's sympatholytic properties, which impact the gain of function mutant receptor, and/or its norepinephrine-lowering properties impacting the high-affinity ADRB1 Arg389 receptors.[112,113]

Heart failure with reduced ejection fraction/atrial fibrillation and genotype

In Arg389 homozygous HFrEF/AF patients, bucindolol demonstrated a borderline significant reduction in all-cause mortality/HF hospitalization and cardiovascular mortality/cardiovascular hospitalization.[102] A pharmacogenetic sub-study of the prospective, double-blind, randomized CIBIS-ELD (Cardiac Insufficiency Bisoprolol Study in Elderly study) trial (n = 528) demonstrated that the heart rate-lowering effects of carvedilol, a non-selective beta-blocker, in patients with HFrEF/AF were also dependent on the Arg389Gly polymorphism[53,61] (*Figure 2*). The CIBIS-ELD trial assessed bisoprolol's and carvedilol's tolerability and feasibility in South-Eastern European patients with HFrEF/AF and HFrEF alone (sinus rhythm).[114] Carvedilol appeared to have a smaller heart rate-lowering effect in HFrEF/AF patients than in sinus rhythm.[100] Patients with HFrEF/AF who possessed the 'gain of function' homozygous Arg389 allele were resistant to rate control using carvedilol vs. patients with a Gly389 allele over a ~12 week period of dose up-titration (maximum daily dose = 50 mg)[100] (*Figure 2*). There was 12 b.p.m. difference between homozygous Arg389 HFrEF/AF patients compared with those with the 'loss of function' variant. This genotype-dependent effect was only observed during the chronic phase of treatment with carvedilol in HFrEF/AF patients.[100] Unlike the BEST trial, this study is limited by its lack of outcomes data, and therefore, findings cannot be used to infer prognosis.

It is unclear what the underlying molecular mechanisms explaining the interactions between the genotype, beta-blocker administered, dose, and heart rhythm are. However, some authors have attempted to hypothesize/attribute carvedilol's effect to its high binding affinity as an inverse agonist and suggest that it could modulate the phenotype of the atrioventricular (AV) node and/or atrial myocardium in Arg389 homozygotes.[100] Carvedilol's binding to the ADRB1 has negative intrinsic activity by way of decreasing cAMP-dependent signalling pathways and activating arrestin-dependent, cAMP-independent, pathways, for example, the activation of epidermal growth factor receptors. Epidermal growth factor has been shown to confer cardioprotection against the deleterious effects of catecholamines in murine models.[115] The authors hypothesize that the cAMP-independent effects may be modulated by the Arg389Gly polymorphism.[100]

The frequency distribution of the Arg389Gly genetic variants differs significantly between European and non-European populations.[116] There is a paucity of data on this polymorphism in SSA. Despite compelling evidence to support differential therapeutic outcomes based on geographical region and genotype, little is known about the clinical relevance of this polymorphism and which genetic variant is dominant in our setting. To date, only one study has looked for this polymorphism in an African population and employed very stringent selection criteria excluding patients on beta-blocker therapy and patients with arrhythmias.[98]

Rhythm control

Rhythm control has been and will remain a cornerstone of treatment in patients with AF. Rhythm control is accomplished by antiarrhythmic drugs (AADs), electrical cardioversion, or catheter ablation (cryoablation or radiofrequency). Depending on the approach used, the advantages of rhythm management include increased quality of life, decreased rehospitalizations, and, more recently, a reduction in mortality (*Table 2*).[40]

Compared with pharmacological rate control, AADs had no clear advantage with regard to mortality, rehospitalization, and stroke reduction in patients with AF (*Table 2*). This is largely driven by the adverse effects of AADs, which marred the survival benefit.[117] There has been a shift in the therapeutic paradigm of AF from a 'one size fits all' approach to a recent, AF-classification (temporal heterogeneity classification) and symptom-based approach. Despite their lack of superiority to rate control, the use of AADs to restore sinus rhythm is indicated in symptomatic AF patients.[9] Patients with HFrEF/AF of SSA origin are non-existent in large clinical trials evaluating the efficacy and safety of AADs. Thus, findings from these data cannot be easily generalized to an SSA context. However, anecdotal evidence suggests similar trends to those observed in studies conducted in HICs.

The use of AADs in patients with HF and concomitant AF can be especially challenging because of their suboptimal efficacy and dangerous side effects profile.[118] Amiodarone and dofetilide are the only two antiarrhythmics that have demonstrated safety in patients with HFrEF but are not without side effects.[32,33] The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial and the Danish Investigators of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure (DIAMOND-CHF) trial cast scepticism on the mortality benefit of sinus-rhythm maintenance vs. rate control in patients with co-existing HFrEF and AF.[32,33] The AAD of choice was predominantly amiodarone and exclusively dofetilide in the AF-CHF and DIAMOND-CHF trials, respectively. These trials concluded that neither drug was associated with lower mortality in patients with co-existing AF and HF despite lowering the AF burden. Dofetilide had a greater rate of reduction in AF burden (81%); however, it is not available in SSA. Amiodarone has been documented to facilitate successful electro-cardioversion in patients with persistent AF regardless of their ejection fraction and is currently the most widely used AAD in SSA.[119,120]

Results from the South African (SAFIR-RSA) survey demonstrated that the majority (74%) of patients were on rate control therapy, in the form of beta-blockers, and the remainder rhythm control therapy primarily with class III agents. In the SAFIR-RSA survey, hospitalizations for HF occurred more frequently in patients on AADs.[120] The study participants were not stratified according to HF modality. Thus, it is impossible to extrapolate what proportion of these HF admissions were attributable to HFrEF/AF patients. It is also unclear whether these HF-related hospitalizations result from the AADs or the AF itself. Furthermore, this study was done in the South African private-health sector, not representative of the overall SSA population.

It is widely known that AF in the setting of HFrEF is a marker of poorer outcomes.[83] Furthermore, data from the GENETIC-AF study have shown that longer durations of AF and HF attenuate treatment efficacy.[121] Similarly, rhythm control improved outcomes in HFrEF/AF when initiated within 1 year of AF diagnosis.[122] Hence, there is a lot of debate around early and aggressive rhythm control of these patients in order to improve outcomes. In recognition of this, recent National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand's Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation (2018) and the ESC 2020 guidelines recommend catheter ablation for HFrEF/AF as first-line therapy.[75,123,124] This is in contrast to previous guidelines that recommended catheter ablation for AF patients refractory to AADs.

The potential benefit of catheter ablation in patients with HFrEF/AF has not been fully elucidated until recently.[40] Several observational studies have illustrated that catheter ablation improves the quality of life, functional class, rehospitalizations, and LVEF by 8.5%.[125–128] However, this improvement in LVEF initially did not translate into any mortality benefits.[127] Results from the CASTLE-AF trial and a meta-analysis by Alturki *et al*. (2019) have shown that catheter ablation, as an aggressive rhythm control strategy, does indeed offer mortality benefit in AF patients with co-existing HFrEF compared to the standard pharmacotherapy (rate control or rhythm control) (*Table 2*).[40,129] A significant reduction in cardiovascular-related deaths drove this mortality benefit. The investigators of CASTLE-AF did not mandate a specific strategy for the reason that previous studies show neither rate control nor rhythm control are superior to one another.[40]

The benefit of catheter ablation in this cohort of interest may not be homogenous and there may be underlying genetic and racial determinants of procedural success. A small study demonstrated that the PITX2 single nucleotide polymorphism, known to predispose to AF, predicts AF recurrence in European patients undergoing catheter ablation.[130,131] However, the same association was not observed in Korean patients.[132] These findings warrant large cross-population studies investigating the genetic determinants of AF and the response to therapeutic interventions across different populations, inclusive of SSA.

Four in five AF patients in SSA are managed via a rate control strategy and/or via pharmacological rhythm control/AADs.[28,133] This demonstrates that evidenced-based AF rhythm control strategies with catheter ablation are not widely available in SSA. It is unlikely that catheter ablation will soon become routine practice in SSA, attributable to a lack of infrastructure and various barriers to access. South Africa is one of the very few countries in SSA performing catheter ablation with a slowly growing repository of data with a preponderance to the private sector. Awareness and understanding of AF's prognostic effect on HFrEF in SSA is critical. We do not want SSA to remain behind in the diaspora, as successful management of HFrEF/AF in our young cohort will be time dependent. The aforementioned warrants more inter-Africa initiatives/collaborations to conduct large-scale studies across SSA.

Conclusions

The future risk of CVDs, predominantly driven by the rising prevalence of cardiovascular risk factors, is a growing public health concern in SSA. The incidence of previously rare forms of CVD, such as coronary artery disease, will increase, in concert with historically prevalent forms of disease, such as RHD, that are yet to be optimally eradicated. In SSA, where infrastructure and resources remain a major barrier to definitive treatment of both HFrEF and AF, the success of strategies designed to curtail the evolving and increasing burden of HFrEF/AF will be dependent upon accurate and up-to-date epidemiological data and well-defined RCTs evaluating the efficiency and efficacy of pharmacological and non-pharmacological interventions.

There are evident huge gaps in the SSA diaspora as it pertains to HFrEF/AF. There seems to be a slowly growing knowledge base in specific geographical locations in SSA like South Africa, Botswana, Ghana, and Nigeria. However, these data do not reflect SSA's overall status quo and demographics. There also exists wide heterogeneity across studies conducted in SSA with regard to the diagnosis of HF, and few studies report on the modalities of HF. To date, there is not a single systematic review published on HFrEF/AF in SSA, and most extrapolations about this subpopulation are made from HF or AF studies. Contrary to extensive data available in HIC on the types of AF prevalent among HFrEF patients, very little is known in our setting. Prioritized research areas to address knowledge gaps should encompass the following: pathophysiology, risk factor profiles and clinical phenotypes of HFrEF/AF, genetic predictors of disease onset, response to therapy, and factors influencing therapeutic outcomes in SSA.

Acknowledgements

The authors thank Dr Dineo Mpanya for her expertise and assistance in writing the manuscript. Mpanya provided technical editing, language editing, and help in reviewing the manuscript for grammar and syntax.

Conflict of interest

None declared.

Funding

The work reported herein was made possible through funding by the South African Medical Research Council (SAMRC) through its Division of Research Capacity Development under the SAMRC Institutional Clinician Researcher Programme. The content hereof is the sole responsibility of the authors and does not necessarily represent the official views of the SAMRC.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Supporting Information.

References

1. Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, Dzudie A, Kouam CK, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Davison BA, Cotter G, Sliwa K. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. *Arch Intern Med*. 2012; **172**: 1386–1394.
2. Keates AK, Mocumbi AO, Ntsekhe M, Sliwa K, Stewart S. Cardiovascular disease in Africa: epidemiological profile and challenges. *Nat Rev Cardiol*. 2017; **14**: 273–293.
3. Stewart S, Wilkinson D, Hansen C, Vaghela V, Mvungi R, McMurray J, Sliwa K. Predominance of heart failure in the Heart of Soweto Study cohort. *Circulation*. 2008; **118**: 2360–2367.
4. Ajayi AA, Sofowora GG, Ladipo GO. Explaining heart failure hypermortality in Sub Saharan Africa: global genomic and environmental contribution review. *J Natl Med Assoc*. 2020; **112**: 141–157.
5. Sliwa K, Mayosi BM. Recent advances in the epidemiology, pathogenesis and prognosis of acute heart failure and cardiomyopathy in Africa. *Heart*. 2013; **99**: 1317–1322.
6. Bonsu KO, Owusu IK, Buabeng KO, Reidpath DD, Kadirvelu A. Clinical characteristics and prognosis of patients admitted for heart failure: a 5-year retrospective study of African patients. *Int J Cardiol*. 2017; **238**: 128–135.
7. Mandi DG, Bamouni J, Yameogo RA, Naibe DT, Kabore E, Kambire Y, et al. Spectrum of heart failure in sub-Saharan Africa: data from a tertiary hospital-based registry in the eastern center of Burkina Faso. *Pan Afr Med J*. 2020; **36**: 30.
8. Agbor VN, Essouma M, Ntusi NAB, Flore U, Joel J, Jacques J. Heart failure in sub-Saharan Africa: a contemporaneous systematic review and meta-analysis. *Int J Cardiol*. 2018; **257**: 207–215.
9. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan G-A, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau J-P, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL. ESC scientific document group, 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the

European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021; **42**: 373–498.
10. Denham NC, Pearman CM, Caldwell JL, Madders GWP, Eisner DA, Trafford AW, Dibb KM. Calcium in the pathophysiology of atrial fibrillation and heart failure. *Front Physiol*. 2018; **9**: 1380.
11. Sliwa K, Carrington MJ, Klug E, Opie L, Lee G, Ball J, Stewart S. Predisposing factors and incidence of newly diagnosed atrial fibrillation in an urban African community: insights from the Heart of Soweto Study. *Heart*. 2010; **96**: 1878–1882.
12. Okello E, Wanzhu Z, Musoke C, Twalib A, Kakande B, Lwabi P, Wilson NB, Mondo CK, Odoi-Adome R, Freers J. Cardiovascular complications in newly diagnosed rheumatic heart disease patients at Mulago Hospital, Uganda: cardiovascular topics. *Cardiovasc J Afr*. 2013; **24**: 76–79.
13. Zühlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, Mauff K, Islam S, Joachim A, Daniels R, Francis V, Ogendo S, Gitura B, Mondo C, Okello E, Lwabi P, al-Kebsi MM, Hugo-Hamman C, Sheta SS, Haileamlak A, Daniel W, Goshu DY, Abdissa SG, Desta AG, Shasho BA, Begna DM, ElSayed A, Ibrahim AS, Musuku J, Bode-Thomas F, Okeahialam BN, Ige O, Sutton C, Misra R, Abul Fadl A, Kennedy N, Damasceno A, Sani M, Ogah OS, Olunuga T, Elhassan HHM, Mocumbi AO, Adeoye AM, Mntla P, Ojji D, Mucumbitsi J, Teo K, Yusuf S, Mayosi BM. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J*. 2015; **36**: 1115–1122.
14. Yadeta D, Semeredin N, Mekonnen GE. Prevalence and predictors of atrial fibrillation and its embolic complications in patients with rheumatic heart disease at Tikur Anbessa specialized hospital, Addis Ababa, Ethiopia. *Ethiop J Health Dev*. 2019; **33**: 12–16.
15. Sani MU, Davison BA, Cotter G, Mayosi BM, Edwards C, Ogah OS, Damasceno A, Ojji DB, Dzudie A, Mondo C, Kouam CK, Suliman A, Yonga G, Abdou Ba S, Maru F, Alemayehu B, Sliwa K. Prevalence, clinical characteristics and outcomes of valvular atrial fibrillation in a cohort of African patients with acute heart failure: insights from the THESUS-HF registry. *Cardiovasc J Afr*. 2018; **29**: 139–145.
16. Mandi DG, Bamouni J, Naïbé DT, Yaméogo RA, Kaboré E, Kambiré Y, Kologo KJ, Millogo GRC, Yaméogo NV, Thiam Tall A, Zabsonré P. Epidemiology and long-term prognosis of atrial fibrillation in rural African patients. *Egypt Heart J*. 2019; **71**: 6.
17. Ntep-Gweth M, Zimmermann M, Meiltz A, Kingue S, Ndobo P, Urban P, Bloch A. Atrial fibrillation in Africa: clinical characteristics, prognosis, and adherence to guidelines in Cameroon. *Europace*. 2010; **12**: 482–487.
18. Mwita JC, Ocampo C, Molefe-Baikai OJ, Goepamang M, Botsile E, Tshikuka JG. Characteristics and 12-month outcome of patients with atrial fibrillation at a tertiary hospital in Botswana. *Cardiovasc J Afr*. 2019; **30**: 168–173.
19. Dzudie A, Hongieh Abanda M, Nkoke C, Barche B, Damasceno A, Edwards C, Davison B, Cotter G, Sliwa K, THEUS-HF investigators, Damasceno A, Sani M, Ojji D, Suliman A, Yonga G, Ogah OS, Mondo C, Dzudie A, Charles KK, Abdou Ba S, Maru F, Alemayehu B, Edwards C, Davison BA, Cotter G, Sliwa, Sliwa K. Clinical characteristics and outcomes of black African heart failure patients with preserved, mid-range, and reduced ejection fraction: a post hoc analysis of the THESUS-HF registry. *ESC Heart Fail*. 2021; **8**: 238–249.
20. Chen Y, Alphonce E, Mujuni E, Kisigo GAGA, Kingery JRJR, Makubi A, et al. Atrial fibrillation and mortality in outpatients with heart failure in Tanzania: a prospective cohort study. *BMJ Open*. 2022; **12**: 1–9.
21. Makubi A, Hage C, Lwakatare J, Kisenge P, Makani J, Ryden L, et al. Contemporary aetiology, clinical characteristics and prognosis of adults with heart failure observed in a tertiary hospital in Tanzania: the prospective Tanzania Heart Failure (TaHeF) study. *Heart*. 2014; **100**: 1235–1241.
22. Familoni OB, Olunuga TO, Olufemi BW. A clinical study of pattern and factors affecting outcome in Nigerian patients with advanced heart failure. *Cardiovasc J Afr*. 2007; **18**: 308–311.
23. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med*. 1971; **285**: 1441–1446.
24. Ogah OS, Stewart S, Falase AO, Akinyemi JO, Adegbite GD, Alabi AA, Ajani AA, Adesina JO, Durodola A, Sliwa K. Predictors of rehospitalization in patients admitted with heart failure in Abeokuta, Nigeria: data from the Abeokuta heart failure registry. *J Card Fail*. 2014; **20**: 833–840.
25. Malamba-Lez D, Ngoy-Nkulu D, Steels P, Tshala-Katumbay D, Mullens W. Heart failure etiologies and challenges to care in the developing world: an observational study in the Democratic Republic of Congo. *J Card Fail*. 2018; **24**: 854–859.
26. Dries DL, Exner DV, Gersh BJ, Hil DP, Domanski MJ, Waclawiw MA, et al. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. *Int J Cardiol*. 1998; **32**: 695–703.
27. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJL. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation*. 2014; **129**: 837–847.
28. Noubiap JJ, Bigna JJ, Agbor VN, Mbanga C, Ndoadoumgue AL, Nkeck JR, Kamguia A, Nyaga UF, Ntusi NAB. Meta-analysis of atrial fibrillation in patients with various cardiomyopathies. *Am J Cardiol*. 2019; **124**: 262–269.
29. Nyaga UF, Bigna JJ, Agbor VN, Essouma M, Ntusi NAB, Noubiap JJ. Data on the epidemiology of heart failure in Sub-Saharan Africa. *Data Brief*. 2018; **17**: 1218–1239.
30. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial fibrillation begets heart failure and vice versa. *Circulation*. 2016; **133**: 484–492.
31. Horodinschi RN, Diaconu CC. Comorbidities associated with one-year mortality in patients with atrial fibrillation and heart failure. *Healthcare*. 2021; **9**: 830.
32. Torp-Pedersen C, Møller M, Bloch-Thomsen PE, Køber L, Sandøe E, Egstrup K, Agner E, Carlsen J, Videbæk J, Marchant B, Camm AJ. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. *N Engl J Med*. 1999; **341**: 857–865.
33. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JMO, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008; **358**: 2667–2677.
34. Khan MN, Jaïs P, Cummings J, Di Biase L, Sanders P, Martin DO, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med*. 2008; **359**: 1778–1785.
35. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart*. 2011; **97**: 740–747.
36. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA, Underwood SR, Markides V, Wong T. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol*. 2013; **61**: 1894–1903.

37. Hunter RJ, Berriman TJ, Diab MI, Kamdar MR. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol*. 2014; **7**: 31–38.
38. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. *Circulation*. 2016; **133**: 1637–1644.
39. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, et al. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. *J Am Coll Cardiol*. 2017; **70**: 1949–1961.
40. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bänsch D. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med*. 2018; **378**: 417–427.
41. Kuck KH, Merkely B, Zahn R, Arentz T, Seidl K, Schlüter M, Tilz RR, Piorkowski C, Gellér L, Kleemann T, Hindricks G. Catheter ablation versus best medical therapy in patients with persistent atrial fibrillation and congestive heart failure: the randomized AMICA trial. *Circ Arrhythm Electrophysiol*. 2019; **12**: 1–12.
42. Brignole M, Pokushalov E, Pentimalli F, Palmisano P, Chieffo E, Occhetta E, Quartieri F, Calò L, Ungar A, Mont L, APAF-CRT Investigators, Menozzi C, Alboni P, Bertero G, Klersy C, Noventa F, Brignole M, Oddone D, Donateo O, Maggi R, Croci F, Solano A, Pentimalli F, Palmisano P, Landolina M, Chieffo E, Taravelli E, Occhetta E, Quartieri F, Bottoni N, Iori M, Calò L, Sgueglia M, Pieragnoli, Giorni A, Nesti M, Giannini I, Ungar A, Padeletti L, Pokushalov E, Romanov A, Peregudov I, Vidorreda S, Nunez R, Mont L, Corbucci G, Valsecchi S, Lovecchio M. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. *Eur Heart J*. 2018; **39**: 3999–4008.
43. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, Flaker GC, Pokushalov E, Romanov A, Bunch TJ, Noelker G, Ardashev A, Revishvili A, Wilber DJ, Cappato R, Kuck KH, Hindricks G, Davies DW, Kowey PR, Naccarelli GV, Reiffel JA, Piccini JP, Silverstein AP, al-Khalidi HR, Lee KL, for the CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation. *JAMA*. 2019; **321**: 1261.
44. Rienstra M, Damman K, Mulder BA, Van Gelder IC, McMurray JJV, Van Veldhuisen DJ. Beta-blockers and outcome in heart failure and atrial fibrillation. *JACC: Heart Failure*. 2013; **1**: 21–28.
45. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder T, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD, Beta-Blockers in Heart Failure Collaborative Group. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet*. 2014; **384**: 2235–2243.
46. Li SJ, Sartipy U, Lund LH, Dahlstrom U, Adiels M, Petzold M, et al. Prognostic significance of resting heart rate and use of β-blockers in atrial fibrillation and sinus rhythm in patients with heart failure and reduced ejection fraction: findings from the Swedish Heart Failure Registry. *Circ Heart Fail*. 2015; **8**: 871–879.
47. Nielsen PB, Larsen TB, Gorst-Rasmussen A, Skjøth F, Lip GYH. β-Blockers in atrial fibrillation patients with or without heart failure: association with mortality in a nationwide cohort study. *Circ Heart Fail*. 2016; **9**: 1–9.
48. Cadrin-Tourigny J, Shohoudi A, Roy D, Talajic M, Tadros R, Mondésert B, Dyrda K, Rivard L, Andrade JG, Macle L, Guerra PG, Thibault B, Dubuc M, Khairy P. Decreased mortality with beta-blockers in patients with heart failure and coexisting atrial fibrillation: an AF-CHF substudy. *JACC Heart Fail*. 2017; **5**: 99–106.
49. Africa SS. Mortality and causes of death in South Africa: findings from death notification. *Statistical Release*. 2018; **2021**: 1–98.
50. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol*. 2003; **91**: 2–8.
51. Krijthe BP, Kunst A, Benjamin EJ, Lip GYH, Franco OH, Hofman A, Witteman JCM, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013; **34**: 2746–2751.
52. Coulibaly I, Anzouan-Kacou JB, Konin KC, Kouadio SC, Abouo-N'Dori R. Atrial fibrillation: epidemiological data from the Cardiology Institute in Abidjan, Côte d'Ivoire. *Med Trop: revue du Corps de sante colonial*. 2010; **70**: 371–374.
53. Shavadia J, Yonga G, Mwanzi S, Jinah A, Moriasi A, Otieno H. Clinical characteristics and outcomes of atrial fibrillation and flutter at the Aga Khan University Hospital. *Nairobi Cardiovasc J Africa*. 2013; **24**: 6–9.
54. Ogah OS, Davison BA, Sliwa K, Mayosi BM, Damasceno A, Sani MU, Mondo C, Dzudie A, Ojji DB, Kouam C, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Cotter G. Gender differences in clinical characteristics and outcome of acute heart failure in sub-Saharan Africa: results of the THESUS-HF study. *Clin Res Cardiol*. 2015; **104**: 481–490.
55. Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, Zhu J, Jansky P, Sigamani A, Morillo CA, Liu L, Damasceno A, Grinvalds A, Nakamya J, Reilly PA, Keltai K, van Gelder I, Yusufali AH, Watanabe E, Wallentin L, Connolly SJ, Yusuf S, RE-LY Atrial Fibrillation Registry Investigators. Variations in cause and management of atrial fibrillation in a prospective registry of 15 400 emergency department patients in 46 countries. *Circulation*. 2014; **129**: 1568–1576.
56. Stewart S, Hart CL, Hole DJ, McMurray JJV. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med*. 2002; **113**: 359–364.
57. Lugero C, Kibirige D, Kayima J, Mondo CK, Freers J. Atrial fibrillation among the black population in a Ugandan tertiary hospital. *Int J Gen Med*. 2016; **9**: 191–198.
58. Moran A, Forouzanfar M, Sampson U, Chugh S, Feigin V, Mensah G. The epidemiology of cardiovascular diseases in sub-Saharan Africa: the global burden of diseases, injuries and risk factors 2010 study. *Prog Cardiovasc Dis*. 2013; **56**: 234–239.
59. Gouda HN, Charlson F, Sorsdahl K, Ahmadzada S, Ferrari AJ, Erskine H, Leung J, Santamauro D, Lund C, Aminde LN, Mayosi BM, Kengne AP, Harris M, Achoki T, Wiysonge CS, Stein DJ, Whiteford H. Burden of non-communicable diseases in sub-Saharan Africa, 1990–2017: results from the Global Burden of Disease Study 2017. *Lancet Glob Health*. 2019; **7**: e1375–e1387.
60. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *The Lancet*. 2009; **373**: 739–745.
61. Cadby G, McArdle N, Briffa T, Hillman DR, Simpson L, Knuiman M, Hung J. Severity of OSA is an independent predictor of incident atrial fibrillation hospitalization in a large sleep-clinic cohort. *Chest*. 2015; **148**: 945–952.
62. Stambler BS, Ngunga LM. Atrial fibrillation in sub-Saharan Africa: epidemiology, unmet needs, and treatment options. *Int J Gen Med*. 2015; **8**: 231–242.
63. Agbor VN, Tianyi FL, Aminde LN, Mbanga CM, Petnga SJN, Simo LP, Dzudie A, Chobufo MD, Noubiap JJ. Burden of atrial fibrillation among

adults with heart failure in sub-Saharan Africa: a systematic review and meta-analysis. *BMJ Open*. 2022; **12**: e061618.
64. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation. *J Am Coll Cardiol*. 2014; **64**: 2222–2231.
65. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JML, Twomey D, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Impact of CARDIOrespiratory FITness on arrhythmia recurrence in obese individuals with atrial fibrillation. *J Am Coll Cardiol*. 2015; **66**: 985–996.
66. Nattel S, Harada M. Atrial remodeling and atrial fibrillation. *J Am Coll Cardiol*. 2014; **63**: 2335–2345.
67. Zafrir B, Lund LH, Laroche C, Ruschitzka F, Crespo-Leiro MG, Coats AJS, Anker SD, Filippatos G, Seferovic PM, Maggioni AP, de Mora Martin M, Polonski L, Silva-Cardoso J, Amir O, ESC-HFA HF Long-Term Registry Investigators. Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14 964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur Heart J*. 2018; **39**: 4277–4284.
68. Sossalla S, Vollmann D. Arrhythmia-induced cardiomyopathy. *Deutsches Aerzteblatt Online*. 2018; **115**: 2018.
69. Huizar JF, Ellenbogen KA, Tan AY, Kaszala K. Arrhythmia-induced cardiomyopathy. *J Am Coll Cardiol*. 2019; **73**: 2328–2344.
70. Schönleitner P, Schotten U, Antoons G. Mechanosensitivity of microdomain calcium signalling in the heart. *Prog Biophys Mol Biol*. 2017; **130**: 288–301.
71. Eckstein J, Verheule S, de Groot N, Allessie M, Schotten U. Mechanisms of perpetuation of atrial fibrillation in chronically dilated atria. *Prog Biophys Mol Biol*. 2008; **97**: 435–451.
72. Santangeli P, Zado ES, Hutchinson MD, Riley MP, Lin D, Frankel DS, Supple GE, Garcia FC, Dixit S, Callans DJ, Marchlinski FE. Prevalence and distribution of focal triggers in persistent and long-standing persistent atrial fibrillation. *Heart Rhythm*. 2016; **13**: 374–382.
73. Gan GCH, Ferkh A, Boyd A, Thomas L. Left atrial function: evaluation by strain analysis. *Cardiovasc Diagnosis Therapy*. 2018; **8**: 29–46.
74. Mehrzad R, Rajab M, Spodick D. The three integrated phases of left atrial macrophysiology and their interactions. *Int J Mol Sci*. 2014; **15**: 15146–15160.
75. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021; **42**: 3599–3726.
76. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN. 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**: 685–691.
77. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999; **341**: 709–717.
78. Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K, 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. *The Lancet*. 2003; **362**: 772–776.
79. Guerra F, Pimpini L, Flori M, Contadini D, Stronati G, Gioacchini F, et al. Sacubitril/valsartan reduces atrial fibrillation and supraventricular arrhythmias in patients with HFrEF and remote monitoring: preliminary data from the SAVE THE RHYTHM. *Eur Heart J*. 2020; **41**.
80. Suo Y, Yuan M, Li H, Zhang Y, Li Y, Fu H, Han F, Ma C, Wang Y, Bao Q, Li G. Sacubitril/valsartan improves left atrial and left atrial appendage function in patients with atrial fibrillation and in pressure overload-induced mice. *Front Pharmacol*. 2019; **10**: 1285.
81. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014; **371**: 993–1004.
82. Liu X, Liu H, Wang L, Zhang L, Xu Q. Role of sacubitril-valsartan in the prevention of atrial fibrillation occurrence in patients with heart failure: a systematic review and meta-analysis of randomized controlled trials. *PLoS ONE*. 2022; **17**: e0263131.
83. Mogensen UM, Jhund PS, Abraham WT, Desai AS, Dickstein K, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Køber L, McMurray JJV. Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2017; **70**: 2490–2500.
84. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019; **381**: 1995–2008.
85. Zelniker TA, Bonaca MP, Furtado RHM, Mosenzon O, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Budaj A, Kiss RG, Padilla F, Gause-Nilsson I, Langkilde AM, Raz I, Sabatine MS, Wiviott SD. Effect of dapagliflozin on atrial fibrillation in patients with type 2 diabetes mellitus: insights from the DECLARE-TIMI 58 trial. *Circulation*. 2020; **141**: 1227–1234.
86. Zakharia F, Basu A, Absher D, Assimes TL, Go AS, Hlatky MA, et al. Characterizing the admixed African ancestry of African Americans. *Genome Biol*. 2009; **10**: R141-R.
87. Florea VG, Cohn JN. The autonomic nervous system and heart failure. *Circ Res*. 2014; **114**: 1815–1826.
88. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. *Nat Rev Cardiol*. 2017; **14**: 30–38.
89. Investigators C-I, Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet (London, England)*. 1999; **353**: 9–13.
90. Hjalmarson Å, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, el Allaf D, Vítovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Jánosi A, Thorgeirsson G, Dunselman PHJM, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P, MERIT-HF Study Group. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure. *JAMA*. 2000; **283**: 1295.
91. Packer M, Fowler MB, Roecker EB, Coats AJS, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL. Effect of carvedilol on the morbidity of patients with severe chronic heart failure. *Circulation*. 2002; **106**: 2194–2199.
92. Gelder ICV, Rienstra M, Crijns HJGM, Olshansky B. Atrial fibrillation 2 Rate control in atrial fi brillation. *The Lancet*. 2016; **388**: 818–828.
93. Cullington D, Goode KM, Ng BE, Zhang J, Cleland JGF, Clark AL. Is heart rate important for patients with heart failure in atrial fibrillation ? *JACC Heart Fail*. 2014; **2**: 213–220.
94. Beta-Blocker Evaluation of Survival Trial I, Eichhorn EJ, Domanski MJ, Krause-Steinrauf H, Bristow MR, Lavori PW. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001; **344**: 1659–1667.
95. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation*. 1996; **94**: 2807–2816.

96. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: β-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med*. 2009; **150**: 784.
97. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *The Lancet*. 2010; **376**: 875–885.
98. Woodiwiss AJ, Badenhorst D, Sliwa K, Brooksbank R, Essop R, Sareli P, et al. Beta1- and alpha2c-adrenoreceptor variants as predictors of clinical aspects of dilated cardiomyopathy in people of African ancestry. *Cardiovasc J Afr*; **19**: 188–193.
99. Taylor MR, Sun AY, Davis G, Fiuzat M, Liggett SB, Bristow MR. Race, common genetic variation, and therapeutic response disparities in heart failure. *JACC: Heart Failure*. 2014; **2**: 561–572.
100. Rau T, Düngen H, Edelmann F, Waagstein F, Lain M, Dimkovi S, et al. Impact of the β1-adrenoceptor Arg389Gly polymorphism on heart-rate responses to Bisoprolol and carvedilol in heart-failure patients. *Clin Pharmacol Ther*. 2012; **92**: 21–28.
101. Parvez B, Chopra N, Rowan S, Vaglio JC, Muhammad R, Roden DM, Darbar D. A common β1-adrenergic receptor polymorphism predicts favorable response to rate-control therapy in atrial fibrillation. *J Am Coll Cardiol*. 2012; **59**: 49–56.
102. Kao DP, Davis G, Aleong R, Connor CMO, Fiuzat M, Carson PE, et al. Effect of bucindolol on heart failure outcomes and heart rate response in patients with reduced ejection fraction heart failure and atrial fibrillation. *Eur J Heart Fail*. 2013; **5**: 324–333.
103. Parikh KS, Fiuzat M, Davis G, Neely M, Blain-Nelson P, Whellan DJ, et al. Dose response of β-blockers in adrenergic receptor polymorphism genotypes. *Circ Genom Precis Med*. 2018; **11**: 139–148.
104. Joseph SS, Lynham JA, Grace AA, Colledge WH, Kaumann AJ. Markedly reduced effects of (−)-isoprenaline but not of (−)-CGP12177 and unchanged affinity of β-blockers at Gly389-β1-adrenoceptors compared to Arg389-β1-adrenoceptors. *Br J Pharmacol*. 2004; **142**: 51–56.
105. Madamanchi A. β-Adrenergic receptor signaling in cardiac function and heart failure. *Mcgill J Med*. 2007; **10**: 99–104.
106. Mason RP, Giles TD, Sowers JR. Evolving mechanisms of action of beta blockers: focus on nebivolol. *J Cardiovasc Pharmacol*. 2009; **54**: 123–128.
107. Sandilands AJ, O'Shaughnessy KM, Brown MJ. Greater inotropic and cyclic AMP responses evoked by noradrenaline through Arg389 β1-adrenoceptors versus Gly389 β1-adrenoceptors in isolated human atrial myocardium. *Br J Pharmacol*. 2003; **138**: 386–392.
108. Amanfu RK, Saucerman JJ. Modeling the effects of β1-adrenergic receptor blockers and polymorphisms on cardiac myocyte Ca^{2+} handling. *Mol Pharmacol*. 2014; **86**: 222–230.
109. Mason DA, Moore JD, Green SA, Liggett SB. A gain-of-function polymorphism in a G-protein coupling domain of the human β1-adrenergic receptor. *J Biol Chem*. 1999; **274**: 12670–12674.
110. Liggett SB. Pharmacogenomics of β1-adrenergic receptor polymorphisms in heart failure. *Heart Fail Clin*. 2010; **6**: 27–33.
111. Aleong RG, Sauer WH, Davis G, Murphy GA, Port JD, Anand IS, Fiuzat M, O'Connor CM, Abraham WT, Liggett SB, Bristow MR. Prevention of atrial fibrillation by bucindolol is dependent on the $beta_1$389 Arg/Gly adrenergic receptor polymorphism. *JACC Heart Fail*. 2013; **1**: 338–344.
112. Liggett SB, Mialet-Perez J, Thaneemit-Chen S, Weber SA, Greene SM, Hodne D, Nelson B, Morrison J, Domanski MJ, Wagoner LE, Abraham WT, Anderson JL, Carlquist JF, Krause-Steinrauf HJ, Lazzeroni LC, Port JD, Lavori PW, Bristow MR. A polymorphism within a conserved beta1-adrenergic receptor motif alters cardiac function and beta-blocker response in human heart failure. *Proc Natl Acad Sci*. 2006; **103**: 11288–11293.
113. O'Connor CM, Fiuzat M, Carson PE, Anand IS, Plehn JF, Gottlieb SS, et al. Combinatorial pharmacogenetic interactions of bucindolol and β1, α2C adrenergic receptor polymorphisms. *PLoS ONE*. 2012; **7**: e44324-e.
114. Inkrot S, Tahirovic E, Apostolovic S, Du H-D, Mehrhof F, Prettin C, et al. Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: the CIBIS-ELD trial. *Eur J Heart Fail*. 2011; **13**: 670–680.
115. Noma T, Lemaire A, Naga Prasad SV, Barki-Harrington L, Tilley DG, Chen J, le Corvoisier P, Violin JD, Wei H, Lefkowitz RJ, Rockman HA. β-Arrestin–mediated β1-adrenergic receptor transactivation of the EGFR confers cardioprotection. *J Clin Investig*. 2007; **117**: 2445–2458.
116. Katsarou M-S, Karathanasopoulou A, Andrianopoulou A, Desiniotis V, Tzinis E, Dimitrakis E, Lagiou M, Charmandari E, Aschner M, Tsatsakis AM, Chrousos GP, Drakoulis N. Beta 1, Beta 2 and Beta 3 adrenergic receptor gene polymorphisms in a Southeastern European population. *Front Genet*. 2018; **9**: 560.
117. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD, Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002; **347**: 1825–1833.
118. Zimetbaum P. Antiarrhythmic drug therapy for atrial fibrillation. *Circulation*. 2012; **125**: 381–389.
119. Singh SN, Tang XC, Reda D, Singh BN. Systematic electrocardioversion for atrial fibrillation and role of antiarrhythmic drugs: a substudy of the SAFE-T trial. *Heart Rhythm*. 2009; **6**: 152–155.
120. Jardine RM, Fine J, Obel IWP. A survey on the treatment of atrial fibrillation in South Africa. *S Afr Med J*. 2014; **104**: 623.
121. Piccini JP, Abraham WT, Dufton C, Carroll IA, Healey JS, van Veldhuisen DJ, et al. Bucindolol for the maintenance of sinus rhythm in a genotype-defined HF population. *JACC: Heart Failure*. 2019; **7**: 586–598.
122. Rillig A, Magnussen C, Ozga A-K, Suling A, Brandes A, Breithardt G, Camm AJ, Crijns HJGM, Eckardt L, Elvan A, Goette A, Gulizia M, Haegeli L, Heidbuchel H, Kuck KH, Ng A, Szumowski L, van Gelder I, Wegscheider K, Kirchhof P. Early rhythm control therapy in patients with atrial fibrillation and heart failure. *Circulation*. 2021; **144**: 845–858.
123. Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, Connell C, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. *Heart Lung Circ*. 2018; **27**: 1209–1266.
124. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Cosedis Nielsen J, Curtis AB, Davies DW, Day JD, d'Avila A, (Natasja) de Groot NMS, di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T, Document Reviewers, Blomström-Lundqvist C, de Paola AAV, Kistler PM, Lip GYH, Peters NS, Pisani CF, Raviele A, Saad EB, Satomi K, Stiles MK, Willems S. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace*. 2018; **20**: e1–e160.
125. Chen MS, Marrouche NF, Khaykin Y, Gillinov AM, Wazni O, Martin DO, Rossillo A, Verma A, Cummings J,

Erciyes D, Saad E, Bhargava M, Bash D, Schweikert R, Burkhardt D, Williams-Andrews M, Perez-Lugones A, Abdul-Karim A, Saliba W, Natale A. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. *J Am Coll Cardiol*. 2004; **43**: 1004–1009.

126. Anselmino M, Matta M, D'Ascenzo F, Bunch TJ, Schilling RJ, Hunter RJ, et al. Catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction. *Circ Arrhythm Electrophysiol*. 2014; **7**: 1011–1018.
127. Halabi SA, Qintar M, Hussein A, Alraies MC, Jones DG, Wong T, et al. Catheter ablation for atrial fibrillation in heart failure patients: a meta-analysis of randomized controlled trials. *JACC Clin Electrophysiol*. 2015; **1**: 200–209.
128. Ullah W, Ling L-H, Prabhu S, Lee G, Kistler P, Finlay MC, Earley MJ, Sporton S, Bashir Y, Betts TR, Rajappan K, Thomas G, Duncan E, Staniforth A, Mann I, Chow A, Lambiase P, Schilling RJ, Hunter RJ. Catheter ablation of atrial fibrillation in patients with heart failure: impact of maintaining sinus rhythm on heart failure status and long-term rates of stroke and death. *Europace*. 2016; **18**: 679–686.
129. AlTurki A, Proietti R, Dawas A, Alturki H, Huynh T, Essebag V. Catheter ablation for atrial fibrillation in heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord*. 2019; **19**: 18.
130. Shoemaker MB, Bollmann A, Lubitz SA, Ueberham L, Saini H, Montgomery J, Edwards T, Yoneda Z, Sinner MF, Arya A, Sommer P, Delaney J, Goyal SK, Saavedra P, Kanagasundram A, Whalen SP, Roden DM, Hindricks G, Ellis CR, Ellinor PT, Darbar D, Husser D. Common genetic variants and response to atrial fibrillation ablation. *Circ Arrhythm Electrophysiol*. 2015; **8**: 296–302.
131. Zhang M, Hill MC, Kadow ZA, Suh JH, Tucker NR, Hall AW, Tran TT, Swinton PS, Leach JP, Margulies KB, Ellinor PT, Li N, Martin JF. Long-range Pitx2c enhancer–promoter interactions prevent predisposition to atrial fibrillation. *Proc Natl Acad Sci*. 2019; **116**: 22692–22698.
132. Choi EK, Park JH, Lee JY, Nam CM, Hwang MK, Uhm JS, Joung B, Ko YG, Lee MH, Lubitz SA, Ellinor PT, Pak HN. Korean atrial fibrillation (AF) network: genetic variants for AF do not predict ablation success. *J Am Heart Assoc*. 2015; **4**: e002046.
133. Yuyun MF, Bonny A, Ng GA, Sliwa K, Kengne AP, Chin A, Mocumbi AO, Ngantcha M, Ajijola OA, Bukhman G. A systematic review of the spectrum of cardiac arrhythmias in sub-Saharan Africa. *Glob Heart*. 2020; **15**.