


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

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Abstract

Aims Limited data are available on clinical characteristics and prognosis of heart failure (HF) in black African populations especially with respect to current classifications and HF management guidelines.

Methods and results In this post hoc analysis, African patients admitted with acute HF and enrolled in the THESUS-HF registry in one of 12 hospitals in 9 countries were classified as having preserved left ventricular ejection fraction (LVEF) (HFpEF), mid-range LVEF (HFmrEF), and reduced LVEF (HFrEF) based on echocardiography performed close to the time of admission. Sociodemographic and clinical characteristics, management, and 60 and 180 day outcomes were compared between the groups. Of 888 patients with LVEF available, there were 472 (53.2%) with HFrEF, 174 (19.6%) with HFmrEF, and 243 (27.3%) with HFpEF. History of atrial fibrillation was higher in patients with HFmrEF (28.5%) than in patients with HFrEF (14.5%). Patients with HFrEF had a larger mean LV systolic diameter (54.1 ± 9.67 mm) than patients with HFmrEF (42.9 ± 8.47 mm), who had a larger mean LV diameter than patients with HFpEF (32.6 ± 8.64 mm); a similar pattern with LV diastolic diameter was observed. The mean posterior diastolic wall thickness (10.2 ± 2.94 mm) was lower in patients with HFrEF than in those with HFmrEF (11.1 ± 2.59 mm) and HFpEF (11.2 ± 2.90 mm). Patients with HFpEF were less likely to use angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, and aldosterone inhibitors, and more likely to use beta-blockers than those with HFrEF at either admission or discharge/Day 7. Death or readmission rates through Day 60 and 180 day death rates did not differ significantly among the groups; unadjusted hazard ratios relative to patients with HFrEF were 1.32 [95% confidence interval (CI) 0.84–2.08] and 1.24 (95% CI 0.82–1.89) for 60 day death or readmission and 0.92 (95% CI 0.59–1.43) and 0.78 (95% CI 0.51–1.20) for 180 day death in patients with HFmrEF and HFpEF, respectively.

Conclusions Classification by LVEF according to European Society of Cardiology guidelines revealed some differences in clinical presentation but similar mortality and rehospitalization rates across all EF groups in Africans admitted for HF.

Keywords Heart failure; Black Africans; Ejection fraction; Management; Outcome; Sub-Saharan Africa

Received: 21 March 2020; Revised: 29 May 2020; Accepted: 29 June 2020

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Introduction

Heart failure (HF) is a global challenge of the 21st century. It is a complex clinical syndrome characterized by the reduced ability of the heart to pump and/or fill with blood. Large epidemiological studies have shown that left ventricular ejection fraction (LVEF) is a predictive marker of adverse outcomes even in the absence of symptomatic HF.¹ In 2013, the American Heart Association/American College of Cardiology Foundation (ACCF/AHA) guidelines first classified HF into three subtypes, namely, HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), and HF with mid-range ejection fraction (HFmrEF), according to the LVEF measurement at diagnosis, natriuretic peptide levels, and the presence of structural heart disease and diastolic dysfunction.² In 2016, the European Society of Cardiology (ESC) also specified three subgroups of HF based on LVEF.³ Notably, the strong rationale for these classifications as well as guidelines for the global management of HF derived from large epidemiological studies was conducted in western countries over the past four decades.^{4–6} While 17% of the world's population live in Africa,⁷ and despite HF being a major burden in this region with existing data suggesting differences in HF aetiologies, therapies, and outcomes,^{8,9} very little information has been published on these HF patients phenotype, particularly with regard to the echocardiographic subtypes. The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF) is the largest documented study of HF in the region. Publications^{8,10,11} from THESUS-HF data have been largely cited by the scientific community owing to its rigorous methodology and internal and external validity including over nine participating countries making it a unique evidence resource in the region.

The need for further post hoc analysis on THESUS-HF data to provide insight on subtypes of HF cannot be overemphasized. While HF in Africa is managed per ACCF/AHA or ESC guidelines, to date, there are no data on HF in black Africans based on the current classification of HF.

This report aimed to determine the differences in clinical presentation, management, and outcome in black Africans with HF based on their LVEF using the 2016 ESC guidelines.³

Methods

THESUS-HF was a prospective, multicentre, international observational survey conducted in 12 hospitals from 9 countries in the southern, eastern, central, and western regions of sub-Saharan Africa (SSA). Centres were selected for participation if they had a physician trained in clinical cardiology and echocardiography. The methodology of the study has been described in detail elsewhere.¹⁰ In brief, from

July 2007 to June 2010, all patients were recruited during admission for acute HF (AHF) and were followed for 6 months. Patients admitted with dyspnoea and diagnosed with AHF based on symptoms and signs (including dyspnoea, orthopnoea, dyspnoea on exercise, rales, oedema, jugular venous pulse, and oxygen saturation), and who provided written informed consent, were enrolled into the study. A detailed systematic transthoracic echocardiography assessment of left ventricular function, valvular structure, and function, as well as regional wall motion abnormalities, was performed by trained physicians. All measurements were undertaken according to the American Society of Echocardiography guidelines.¹² The most likely aetiology of HF was provided by the attending physician, based on the 2012 ESC guidelines.¹³ LVEF was assessed using the conventional apical two-chamber and four-chamber views and the modified Simpson's method. In this post hoc analysis, patients were classified according to the terminology of the 2016 ESC guidelines for the diagnosis and treatment of AHF and chronic HF³ as HFpEF (LVEF \geq 50%), HFmrEF (LVEF 40–49%), and HFrEF (LVEF $<$ 40%). Information on readmissions and death, with respective reasons and cause, was collected over the 6 month follow-up. Outcomes of interest were readmission or death within 60 days and death within 180 days. Detailed data collected on standardized case report forms at admission included medical history, medication use, laboratory values, and physical examination with symptoms and signs of HF. Human immunodeficiency virus testing was performed as clinically indicated. Patients were followed by either clinic visit or telephone contact over 6 months for the occurrence of readmissions and death.

Written informed consent was obtained from each subject before enrolment into the study. Approval was obtained from the ethics committee of each participating institution, and the study conformed to the principles of the Declaration of Helsinki.

Statistical analysis

Eight hundred and eighty-eight participants were included in this post hoc analysis. Results are presented as counts and percentages for categorical variables and means, standard deviation, median, and 25th to 75th percentiles for continuous variables. Comparison between participants with HFrEF, HFmrEF, and HFpEF for demographics, baseline clinical characteristics, medical history, echocardiographic parameters, and baseline medication use was tested using χ^2 tests for qualitative variables, Kruskal–Wallis test for ordinal variables, and one-way ANOVA for quantitative variables. No continuous variable was found to have a highly skewed distribution, which would have required ANOVA based on log-transformed values.

The associations between LVEF and clinical outcomes were examined. Length of initial hospital stay was compared between groups using *t*-test. A logistic regression model was used for the comparison between groups on in-hospital mortality with the odds ratio, 95% confidence interval (CI), and Wald χ^2 *P*-value presented. For time-to-event outcomes, Kaplan–Meier estimates are presented with the log-rank test used for comparison between groups (HFrEF, HFmrEF, and HFpEF); hazard ratios and 95% CIs from Cox regression models are also given. Adjusted hazard ratios are also presented for the outcomes of death or readmission to Day 60 and all-cause death to Day 180 adjusting for predictors known to be associated with each of these outcomes.¹¹ These predictors include history of hyperlipidaemia, malignancy, and cor pulmonale and baseline rales, ejection fraction, blood urea nitrogen, and systolic blood pressure for death or readmission to Day 60 and history of malignancy, cor pulmonale, and HIV, gender, smoking status, and baseline values for systolic blood pressure, creatinine, haemoglobin, heart rate, orthopnoea, rales, and oedema for death to Day 180. To account for missing predictors in the adjusted analyses, multiple imputation methods were used to impute missing values. Seven imputation datasets were used with parameter estimates averaged across these datasets using

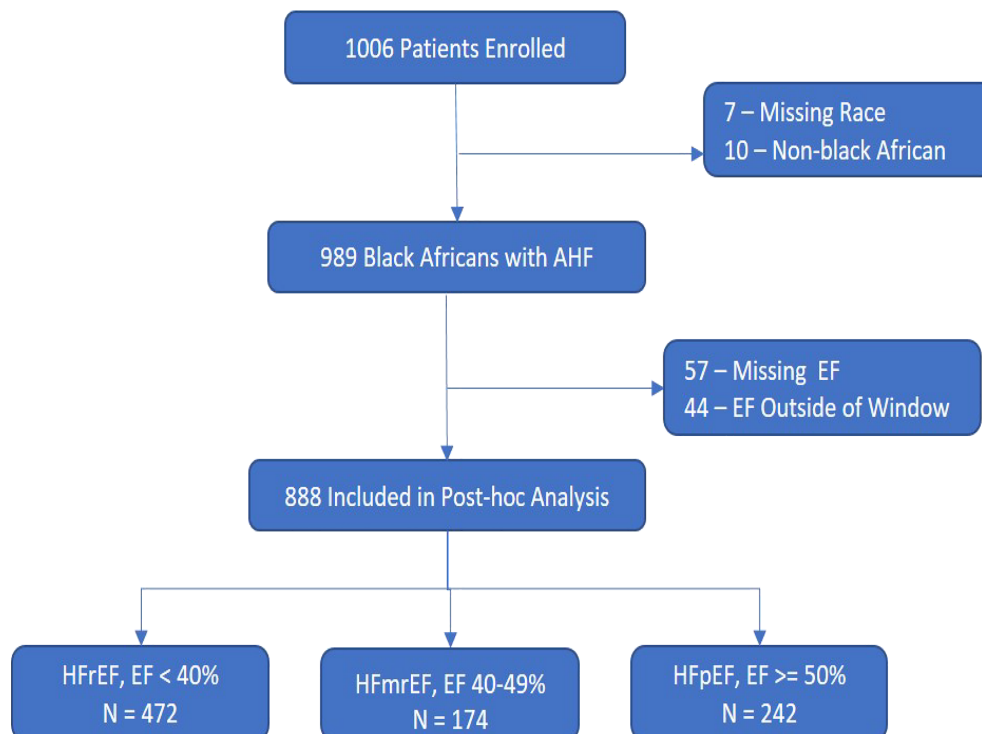
Rubin's algorithm (SAS PROC MIANALYZE). Plots of Kaplan–Meier curves for time to all-cause death and/or HF readmission according to the EF (HFrEF, HFmrEF, and HFpEF) are shown. Data were analysed with the use of SAS software version 9.4 (SAS Institute, Cary, NC, USA). A *P*-value <0.05 was considered statistically significant.

Results

Participants

A total of 1006 patients with AHF from 9 countries in Africa were enrolled in the THESUS-HF cohort study. Of these, 989 (98.3%) were black Africans. We excluded 101 patients for missing ejection fraction (57 cases) and patients whose ejection fraction was measured more than 4 months before or 2 months after admission (44). The median time of the echocardiogram from admission was 1.0 (interquartile range 0.0–2.0) day. Of the 888 patients with AHF included in this post hoc analysis, 472 (53.2%) had an ejection fraction <40%, 174 (19.6%) had an EF 40–49%, and 242 (27.3%) had an EF \geq 50% (Figure 1).

Figure 1 Study flow chart. AHF, acute heart failure; EF, ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



Comparison of sociodemographic and risk factor profile by ejection fraction group

There were 438 (49.4%) male patients, and the mean age was 52.5 (18.19) years. The sociodemographic and risk factors profile are shown in *Table 1*. There were more males in patients with HFrEF (53.4%) and more females in patients with HFpEF (58.1%). History of cor pulmonale was more prevalent in patients with HFpEF (12.4%) and HFmrEF (9.2%) than in patients with HFrEF (3.6%). History of atrial fibrillation was higher in patients with HFmrEF (28.5%) than in patients with HFrEF (14.5%). As previously reported, the most common aetiology in this patient population was hypertensive cardiomyopathy.¹⁰

Comparison of clinical presentation and echocardiographic characteristics by ejection fraction group

The clinical presentation is shown in *Table 2*. Patients with HFrEF had a lower mean systolic blood pressure (125.8 ± 30.82 mmHg) than those with HFmrEF (133.1 ± 34.84 mmHg) or HFpEF (137.3 ± 36.38 mmHg). The mean heart rate was higher in those with HFrEF (106.0 ± 19.63 b.p.m.) than in patients with HFpEF (101.1 ± 22.72 b.p.m.). Patients with HFrEF were more likely to have 3+ oedema than those with HFmrEF and HFpEF ($P = 0.013$). The echocardiographic characteristics are shown in *Table 3*. Patients with HFrEF had a larger mean LV systolic diameter (54.1 ± 9.67 mm) than patients with HFmrEF (42.9 ± 8.47 mm), who had a larger mean LV diameter than patients with HFpEF (32.6 ± 8.64 mm); a similar pattern with LV diastolic diameter was observed. The mean posterior diastolic wall thickness (10.2 ± 2.94 mm) was lower in patients with HFrEF than in those with HFmrEF (11.1 ± 2.59 mm) and HFpEF (11.2 ± 2.90 mm). The transmitral inflow velocities were lowest in patients with HFrEF.

Comparison of management and outcome by ejection fraction group

The treatment of AHF is shown in *Table 4*. There were significant differences in the prescription of HF medicines across LVEF groups. Patients with HFpEF were less likely prescribed angiotensin-converting enzyme inhibitor/angiotensin receptor blockers and aldosterone inhibitors than those with HFrEF. Patients with HFpEF were more likely prescribed beta-blockers than those with HFrEF.

Major outcomes of death or readmission through Days 60 and 180 are shown in *Table 5* and *Figure 2*. There was no statistically significant difference in the outcomes across the EF groups (all $P > 0.05$), even after covariate adjustment. Death or readmission rates through Day 60 and 180 day death rates

did not differ significantly among the groups; unadjusted hazard ratios relative to patients with HFrEF were 1.32 (95% CI 0.84–2.08) and 1.24 (95% CI 0.82–1.89) for 60 day death or readmission and 0.92 (95% CI 0.59–1.43) and 0.78 (95% CI 0.51–1.20) for 180 day death in patients with HFmrEF and HFpEF, respectively.

Discussion

The current post hoc analysis of the THESUS-HF registry describes the characteristics and outcomes of patients admitted for AHF in SSA according to the current guidelines of HF definition and classification.

In 2016, a new version of the ESC guidelines for the management of AHF and chronic HF was released. The guideline introduced a new category of HF–HFmrEF.³ The guideline also updated recommendations about the diagnosis and treatment of HF.

To the best of our knowledge, no major registries of HF patients have been published in SSA after publication of the 2016 ESC guidelines especially regarding HFmrEF prevalence, characteristics, treatment, and outcome. Thus, there is a gap in evidence for patients with HFmrEF in SSA. The THESUS-HF registry, the largest registry to date on HF in SSA, was published in 2012,¹⁰ and since then, none of the secondary papers has focused on echocardiographic subtypes of HF. In this post hoc analysis to compare the clinical characteristics, treatment, and outcome across the LVEF categories (HFrEF, HFmrEF, and HFpEF) based on the 2016 ESC guidelines, we reclassified participants in the THESUS-HF registry into these three categories. More than half of participants (53%) had HFrEF while 20% were ascribed to HFmrEF. To our knowledge, this is one of the rare descriptions of HFmrEF in SSA. Our prevalence of HFmrEF was in accordance with the 17–20% reported in other registries and cohort studies in the majority of high-income countries^{14–16} but lower than the 10% reported by Nelson *et al.* in Denmark. That Nelson *et al.* included all acute cases of dyspnoea and classified severe valve disease before other echocardiographic subtypes of HF may account for the lower prevalence of HFmrEF in their study. Thus, HFmrEF is common in clinical practice with a prevalence that might be similar in high-income and low-income countries. When compared with previous LVEF classification, the prevalence of participants with HFrEF was similar.¹⁷ Reports from registries and cohort studies have shown HFrEF to be the most prevalent category of HF.^{14,18} HFmrEF is an intermediate between HFrEF and HFpEF. Data from registries and cohort studies are inconsistent as to whether clinical characteristics in HFmrEF might be similar to those in HFrEF or HFpEF or intermediate.^{17–21} In the THESUS-HF registry, patients with HFmrEF were similar to those with HFrEF and HFpEF with respect to some

Table 1 Comparison of sociodemographic and risk factor profile by ejection fraction group

Parameter	Observed n (% missing)	Statistic	HFREF (N = 472)	HFmEF (N = 174)	HFpEF (N = 242)	P-value ^a	Total (N = 888)
Age (years)	880 (0.9%)	Mean (SD) Median (Q1, Q3)	51.4 (17.49) 53.0 (39.0, 65.0)	54.6 (18.01) 57.0 (41.0, 69.0)	53.2 (19.52) 56.5 (39.0, 70.0)	0.11	52.5 (18.19) 55.0 (40.0, 67.0)
Male sex	887 (0.1%)	n (%)	252 (53.4%)	85 (48.9%)*	101 (41.9%)*	0.015	438 (49.4%)
Hx of atrial fibrillation prior to admission	881 (0.8%)	n (%)	68 (14.5%)	49 (28.5%)*	51 (21.3%)	0.0002	168 (19.1%)
# AHF admission in prior 12 months	820 (7.7%)	Mean (SD) Median (Q1, Q3)	0.4 (0.76) 0	0.3 (0.63) 0	0.4 (0.80) 0	0.64	0.4 (0.75) 0.0 (0.0, 0.0)
Hx hyperlipidaemia	870 (2.0%)	n (%)	33 (7.2%)	20 (11.7%)	23 (9.7%)	0.17	76 (8.7%)
Hx of smoking	884 (0.5%)	n (%)	46 (9.8%)	14 (8.1%)	17 (7.1%)	0.46	77 (8.7%)
Hx hypertension	884 (0.5%)	n (%)	259 (55.2%)	105 (60.3%)	138 (57.3%)	0.50	502 (56.8%)
Hx of diabetes	886 (0.2%)	n (%)	52 (11.1%)	18 (10.3%)	26 (10.7%)	0.97	96 (10.8%)
Hx of malignancy	885 (0.3%)	n (%)	10 (2.1%)	0	3 (1.2%)*	0.13	13 (1.5%)
Hx of cor pulmonale	882 (0.7%)	n (%)	17 (3.6%)	16 (9.2%)*	30 (12.4%)*	<0.0001	63 (7.1%)
Hx of myocardial infarction	854 (3.8%)	n (%)	16 (3.5%)	8 (4.9%)*	7 (3.0%)*	0.60	31 (3.6%)
Valvular disease	883 (0.6%)	n (%)	93 (19.8%)	69 (40.1%)*	89 (36.9%)*	<0.0001	251 (28.4%)
Mitral stenosis	883 (0.6%)	n (%)	13 (2.8%)	19 (11.0%)*	22 (9.1%)*	<0.0001	54 (6.1%)
Mitral regurgitation	883 (0.6%)	n (%)	69 (14.7%)	49 (28.5%)*	65 (27.0%)*	<0.0001	183 (20.7%)
Aortic stenosis	883 (0.6%)	n (%)	9 (1.9%)	7 (4.1%)*	9 (3.7%)*	0.21	25 (2.8%)
Aortic regurgitation	883 (0.6%)	n (%)	25 (5.3%)	22 (12.8%)*	26 (10.8%)*	0.0024	73 (8.3%)
Other	883 (0.6%)	n (%)	41 (8.7%)	19 (11.0%)*	37 (15.4%)*	0.028	97 (11.0%)
Heart failure aetiology	865 (2.6%)	n (%)	199 (42.7%)	75 (43.9%)	86 (37.7%)		360 (41.6%)
Hypertensive cardiomyopathy		n (%)	103 (22.1%)	16 (9.4%)*	2 (0.9%)*		121 (14.0%)
Idiopathic dilated cardiomyopathy		n (%)	34 (7.3%)	41 (24.0%)	54 (23.7%)		129 (14.9%)
Rheumatic heart disease		n (%)	37 (7.9%)	15 (8.8%)	10 (4.4%)		62 (7.2%)
Ischaemic heart disease		n (%)	55 (11.8%)	3 (1.8%)*	2 (0.9%)*		60 (6.9%)
Peripartum cardiomyopathy		n (%)	10 (2.1%)	13 (7.6%)	35 (15.4%)		58 (6.7%)
Other		n (%)	18 (3.9%)	4 (2.3%)*	23 (10.1%)		45 (5.2%)
Pericardial effusion/tamponade		n (%)	10 (2.1%)	2 (1.2%)*	8 (3.5%)*		20 (2.3%)
HIV cardiomyopathy		n (%)	0	2 (1.2%)*	8 (3.5%)*		10 (1.2%)
Endomyocardial fibroelastosis		n (%)	0	0	0		0
Body mass index	863 (2.8%)	Mean (SD) Median (Q1, Q3)	24.6 (5.52) 23.7 (20.8, 27.8)	25.2 (5.80) 24.2 (21.3, 28.1)	24.7 (6.10) 23.9 (20.4, 28.1)	0.51	24.8 (5.74) 23.9 (20.8, 27.9)

AHF, acute heart failure; HFmEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation.

^aP-value from ANOVA (F-test) for continuous variables or from χ^2 test for categorical variables.

*P < 0.05 vs. HFREF (adjusted P-value using Bonferroni step-down).

**P < 0.05 vs. HFmEF (adjusted P-value using Bonferroni step-down).

Table 2 Comparison of clinical presentation

Parameter	Observed n (% missing)	Statistic	HFrEF (N = 472)	HFmrEF (N = 174)	HFpEF (N = 242)	P-value ^a	Total (N = 888)
NYHA class 1 month prior to admission	574 (35.4%)						
I		n (%)	46 (15.6%)	18 (16.1%)	41 (24.6%)*	0.11	105 (18.3%)
II		n (%)	137 (46.4%)	54 (48.2%)	73 (43.7%)		264 (46.0%)
III		n (%)	94 (31.9%)	36 (32.1%)	50 (29.9%)		180 (31.4%)
IV		n (%)	18 (6.1%)	4 (3.6%)*	3 (1.8%)		25 (4.4%)
Systolic BP (mmHg)	878 (1.1%)	Mean (SD)	125.8 (30.82)	133.1 (34.84)*	137.3 (36.38)*	<0.0001	130.4 (33.56)
		Median (Q1, Q3)	120.0 (102.0, 143.0)	130.0 (108.0, 153.0)	130.0 (110.0, 160.0)		128.0 (107.0, 150.0)
Diastolic BP (mmHg)	877 (1.2%)	Mean (SD)	84.0 (20.47)	83.6 (20.45)	85.5 (22.08)	0.57	84.3 (20.91)
		Median (Q1, Q3)	80.0 (70.0, 100.0)	81.5 (70.0, 100.0)	80.0 (70.0, 100.0)		80.0 (70.0, 100.0)
Heart rate (b.p.m.)	882 (0.7%)	Mean (SD)	106.0 (19.63)	103.1 (23.97)	101.1 (22.72)*	0.011	104.1 (21.49)
		Median (Q1, Q3)	108.0 (92.0, 120.0)	100.0 (88.0, 120.0)	100.0 (86.0, 113.0)		104.0 (90.0, 116.0)
Peripheral oedema	875 (1.5%)	Mean (SD)	2.0 (1.01)	1.7 (1.03)*	1.7 (1.09)*	0.0008	1.8 (1.04)
0		n (%)	58 (12.5%)	31 (17.9%)	47 (19.7%)	0.013	136 (15.5%)
1		n (%)	70 (15.1%)	33 (19.1%)	47 (19.7%)		150 (17.1%)
2		n (%)	168 (36.3%)	67 (38.7%)	77 (32.2%)		312 (35.7%)
3+		n (%)	167 (36.1%)	42 (24.3%)	68 (28.5%)		277 (31.7%)
Rales	797 (10.2%)	Mean (SD)	1.7 (0.86)	1.7 (0.88)	1.6 (1.00)	0.15	1.7 (0.91)
0		n (%)	44 (10.1%)	18 (12.5%)	44 (20.3%)	0.013	106 (13.3%)
1		n (%)	111 (25.5%)	28 (19.4%)	43 (19.8%)		182 (22.8%)
2		n (%)	208 (47.7%)	75 (52.1%)	92 (42.4%)		375 (47.1%)
3		n (%)	73 (16.7%)	23 (16.0%)	38 (17.5%)		134 (16.8%)
Creatinine (mg/dL)	848 (4.5%)	Mean (SD)	1.4 (1.00)	1.4 (0.99)	1.3 (1.07)	0.80	1.4 (1.02)
		Median (Q1, Q3)	1.1 (0.9, 1.5)	1.2 (0.9, 1.6)	1.0 (0.8, 1.5)		1.1 (0.9, 1.5)
BUN (mg/dL)	846 (4.7%)	Mean (SD)	34.5 (29.55)	36.8 (29.53)	36.0 (38.41)	0.69	35.4 (32.18)
		Median (Q1, Q3)	27.4 (17.6, 40.6)	28.0 (18.0, 42.0)	25.8 (15.0, 45.0)		27.6 (17.0, 42.0)

BP, blood pressure; b.p.m., beats per minute; BUN, blood urea nitrogen; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; Q1, 25th percentile; Q3, 75th percentile; Q3, 75th percentile; SD, standard deviation.
^aP-value from ANOVA (F-test) for continuous variables or from χ^2 test for categorical variables.
^{*}P < 0.05 vs. HFpEF (adjusted P-value using Bonferroni step-down).
^{**}P < 0.05 vs. HFmrEF (adjusted P-value using Bonferroni step-down).

Table 3 Comparison of echocardiographic evaluations

Parameter	Observed n (% missing)	Statistic	HFpEF (N = 472)	HFmrEF (N = 174)	HFpEF (N = 242)	P-value ^a	Total (N = 888)
Heart rate (b.p.m.)	690 (22.3%)	Mean (SD) Median (Q1, Q3)	96.1 (15.21) 96.0 (86.5, 104.0)	92.9 (20.20) 94.0 (81.5, 102.0)	92.7 (20.37) 90.0 (82.0, 104.0)	0.057	94.5 (17.87) 94.0 (84.0, 104.0)
Dimensions and LV function							
LV systole diameter (mm)	879 (1.0%)	Mean (SD)	54.1 (9.67)	42.9 (8.47)*	32.6 (8.64)**	<0.0001	46.0 (13.05)
LV diastole diameter (mm)	882 (0.7%)	Median (Q1, Q3)	54.0 (48.6, 60.0)	44.0 (37.0, 48.0)	32.0 (26.0, 38.0)	<0.0001	47.0 (37.0, 55.0)
IV septum (diastole) (mm)	863 (2.8%)	Mean (SD)	63.1 (9.60)	55.9 (10.16)*	49.1 (10.47)**	<0.0001	57.9 (11.62)
Posterior wall (diastole) (mm)	840 (5.4%)	Median (Q1, Q3)	63.0 (57.1, 68.0)	57.0 (50.0, 62.0)	49.0 (41.8, 56.0)	<0.0001	58.1 (50.0, 65.0)
Diastolic function		Mean (SD)	10.6 (3.15)	11.9 (3.03)	12.1 (3.45)	<0.0001	11.2 (3.29)
Left atrial diameter (mm)	845 (4.8%)	Median (Q1, Q3)	10.0 (8.7, 12.4)	11.7 (10.0, 14.0)	12.0 (9.0, 14.0)	<0.0001	11.0 (9.0, 13.0)
Left atrial area (mm ²)	475 (46.5%)	Mean (SD)	10.2 (2.94)	11.1 (2.59)	11.2 (2.90)	<0.0001	10.7 (2.90)
Mitral E wave (cm/s)	731 (17.7%)	Median (Q1, Q3)	10.0 (8.0, 12.0)	11.0 (9.4, 13.0)	11.0 (9.0, 13.0)	0.89	10.0 (9.0, 12.9)
E wave deceleration time (ms)	699 (21.3%)	Mean (SD)	47.3 (7.58)	47.0 (9.60)	47.0 (11.35)	0.54	47.2 (9.15)
Mitral A wave (cm/s)	606 (31.8%)	Median (Q1, Q3)	47.0 (42.0, 52.0)	46.5 (41.0, 53.0)	46.0 (38.4, 54.0)	0.031	47.0 (41.0, 53.0)
Mitral A wave duration time (ms)	483 (45.6%)	Mean (SD)	2759.4 (712.87)	2793.9 (995.43)	2867.9 (1190.44)	<0.0001	2800.6 (942.68)
		Median (Q1, Q3)	2620.0 (2285.0, 3200.0)	2750.0 (2115.0, 3404.5)	2685.0 (2030.0, 3410.0)	<0.0001	2657.0 (2200.0, 3300.0)
		Mean (SD)	47.6 (41.54)	54.3 (54.06)	58.3 (56.69)	<0.0001	51.8 (48.75)
		Median (Q1, Q3)	41.3 (8.7, 81.0)	36.7 (10.1, 83.0)	45.8 (10.6, 90.5)	<0.0001	44.0 (9.4, 83.0)
		Mean (SD)	127.1 (67.63)	168.0 (114.92)	171.0 (88.73)	<0.0001	146.5 (86.28)
		Median (Q1, Q3)	120.0 (96.0, 142.0)	146.5 (120.0, 192.0)	160.0 (120.0, 210.0)	<0.0001	130.0 (100.0, 170.0)
		Mean (SD)	29.0 (27.31)	43.4 (37.40)	42.5 (38.62)	<0.0001	35.2 (33.30)
		Median (Q1, Q3)	22.0 (5.0, 46.0)	32.0 (7.6, 67.0)	36.5 (6.9, 69.0)	<0.0001	26.9 (5.9, 55.0)
		Mean (SD)	117.0 (39.61)	131.0 (37.66)	141.4 (56.69)	<0.0001	126.2 (45.89)
		Median (Q1, Q3)	114.0 (94.0, 140.0)	127.0 (110.0, 156.0)	137.0 (107.0, 161.0)	<0.0001	121.0 (100.0, 150.0)

HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; LV, left ventricle; Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation.

^aP-value from ANOVA (F-test) for continuous variables or from χ^2 test for categorical variables.

*P < 0.05 vs. HFpEF (adjusted P-value using Bonferroni step-down).

**P < 0.05 vs. HFmrEF (adjusted P-value using Bonferroni step-down).

Table 4 Comparison of oral medication use at admission and discharge/Day 7

Parameter	Observed <i>n</i> (% missing)	Statistic	HFrEF (<i>N</i> = 472)	HFmrEF (<i>N</i> = 174)	HFpEF (<i>N</i> = 242)	<i>P</i> -value ^a	Total (<i>N</i> = 888)
Admission							
ACEi/ARBs	879 (1.0%)	<i>n</i> (%)	372 (79.5%)	125 (72.7%)	163 (68.2%)*	0.0033	660 (75.1%)
Loop diuretics	863 (2.8%)	<i>n</i> (%)	59 (12.9%)	22 (13.0%)	42 (17.7%)*	0.20	123 (14.3%)
Beta-blockers	874 (1.6%)	<i>n</i> (%)	64 (13.8%)	34 (19.9%)	50 (21.0%)*	0.028	148 (16.9%)
Digoxin	873 (1.7%)	<i>n</i> (%)	240 (51.9%)	83 (48.3%)	79 (33.1%)*,**	<0.0001	402 (46.0%)
Hydralazine	866 (2.5%)	<i>n</i> (%)	2 (0.4%)	2 (1.2%)	5 (2.1%)	0.12	9 (1.0%)
Nitrates	875 (1.5%)	<i>n</i> (%)	23 (5.0%)	11 (6.4%)	11 (4.6%)	0.69	45 (5.1%)
Aldosterone inhibitors	878 (1.1%)	<i>n</i> (%)	351 (75.5%)	113 (65.3%)*	145 (60.4%)*	<0.0001	609 (69.4%)
Statins	866 (2.5%)		40 (8.8%)	16 (9.4%)	27 (11.3%)	0.57	83 (9.6%)
Aspirin	876 (1.4%)	<i>n</i> (%)	176 (38.1%)	62 (35.8%)	83 (34.4%)	0.62	321 (36.6%)
Anticoagulants	877 (1.2%)	<i>n</i> (%)	164 (35.3%)	69 (39.9%)	70 (29.2%)	0.068	303 (34.5%)
Discharge or Day7							
ACEi/ARBs	861 (3.0%)	<i>n</i> (%)	397 (86.5%)	136 (81.0%)	177 (75.6%)*	0.0015	710 (82.5%)
Loop diuretics	855 (3.7%)	<i>n</i> (%)	368 (80.3%)	133 (79.6%)	169 (73.5%)*	0.11	670 (78.4%)
Beta-blockers	853 (3.9%)	<i>n</i> (%)	115 (25.2%)	52 (31.0%)	78 (34.2%)*	0.037	245 (28.7%)
Digoxin	853 (3.9%)	<i>n</i> (%)	318 (69.6%)	109 (65.7%)	108 (47.0%)*,**	<0.0001	535 (62.7%)
Hydralazine	845 (4.8%)	<i>n</i> (%)	10 (2.2%)	5 (3.0%)	4 (1.7%)*	0.70	19 (2.2%)
Nitrates	858 (3.4%)	<i>n</i> (%)	38 (8.3%)	18 (10.7%)	10 (4.3%)*	0.050	66 (7.7%)
Aldosterone inhibitors	861 (3.0%)	<i>n</i> (%)	369 (80.4%)	126 (74.1%)	156 (67.2%)*	0.0006	651 (75.6%)
Statins	850 (4.3%)	<i>n</i> (%)	56 (12.5%)	27 (16.1%)	38 (16.3%)*	0.30	121 (14.2%)
Aspirin	860 (3.2%)	<i>n</i> (%)	289 (63.4%)	91 (53.5%)*	114 (48.7%)*	0.0006	494 (57.4%)
Anticoagulants	860 (3.2%)	<i>n</i> (%)	83 (18.1%)	37 (21.9%)	45 (19.3%)	0.57	165 (19.2%)

ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

^a*P*-value from ANOVA (*F*-test) for continuous variables or from χ^2 test for categorical variables.

**P* < 0.05 vs. HFrEF (adjusted *P*-value using Bonferroni step-down).

***P* < 0.05 vs. HFmrEF (adjusted *P*-value using Bonferroni step-down).

characteristics and intermediate between HFrEF and HFpEF with respect to others. But patients with HFmrEF and HFpEF were more likely to have atrial fibrillation, and patients with HFpEF had the highest prevalence of cor pulmonale. Several studies from high-income countries have reported that the clinical characteristics of HFmrEF patients are generally intermediate between HFrEF and HFpEF.¹⁴ Hypertension that is the most common cause of HF in SSA was higher in HFmrEF, though not significant. On the contrary, it was most frequently associated with HFpEF in some studies from high-income countries.^{15,17} Our patients with HFpEF were more often female, a finding that is in accordance with some studies from high-income countries.^{15,17} Clinical presentation with respect to symptoms and signs was similar among groups, except for participants with HFpEF who had a higher mean systolic blood pressure and a lower heart rate. Also, HFrEF patients had more severe oedema compared with the other HF categories. A recent study in Europe did not show any differences in signs and symptoms between the three categories of HF.¹⁷ When comparing echocardiographic parameters, patients with HFrEF had larger heart chambers and lower wall thicknesses than those with HFmrEF and HFpEF. This was a similar finding in other studies.¹⁷

In our study, there was no significant age difference between the three categories of HF. This is in contrast with some studies that reported a significantly older age in HFmrEF compared with HFrEF.¹⁷ Generally, HF occurs at a younger age in SSA compared with high-income countries.

The mean age of HFmrEF in this study was 54.6 years, lower than reported in developed countries.^{14,22} In this report, the mean ages across all EF categories were lower than the mean age across corresponding EF categories in high-income countries.¹⁴ This may reflect differences in HF aetiologies between low-income and high-income countries.

In the current analysis, patients with HFrEF were more likely prescribed inhibitors of the renin-angiotensin system and mineralocorticoid receptor antagonists (MRAs) compared with patients with HFmrEF and HFpEF. This is not surprising as several studies have shown that patients with HFrEF are more likely to be prescribed guideline-directed medical treatment.¹⁵ MRAs were commonly prescribed in the THESUS-HF registry. The impact of MRA on outcome in HFmrEF is less well known. A recent study showed that the MRA spironolactone was independently associated with a significant reduction in mortality and HF rehospitalization in HFmrEF.²² Although patients with HFpEF in our study had lower heart rates, they were more likely to be prescribed beta-blockers. This finding is in contrast with the guideline suggested treatment for patients with HF where the use of beta-blockers is mandated in patients with HFrEF regardless of their EF. Finally, many more patients in the current registry regardless of EF were prescribed digoxin.

Patients with HFmrEF had a non-significant longer mean hospitalization duration compared with HFrEF and HFpEF. A total of 4% of the participants experienced the endpoint of death on initial hospitalization without any significant

Table 5 Comparison of clinical outcomes

Parameter	Observed n (% missing)	Statistic	HFrEF (N = 472)	HFmrEF (N = 174)	HFpEF (N = 242)	P-value ^a	Total (N = 888)
Length of initial hospital stay (days)	764 (14.0%)	Mean (SD) Median (Q1, Q3)	9.7 (9.74) 8.0 (6.0, 11.0)	10.1 (13.36) 8.0 (6.0, 10.0)	8.3 (6.90) 7.0 (5.0, 10.0)	0.14	9.4 (9.93) 8.0 (6.0, 10.0)
Initial hospitalization mortality		n (%)	13 (2.8%)	10 (5.7%)	13 (5.4%)	0.11	36 (4.1%)
Readmission to Day 60		n (KM%)	34 (8.7%)	14 (9.9%)	17 (9.0%)	0.93	65 (9.0%)
Death to Day 60		n (KM%)	42 (10.2%)	18 (11.3%)	23 (10.7%)	0.83	83 (10.5%)
Death or readmission to Day 60							
Unadjusted		n (KM%)	58 (14.1%)	28 (17.8%)	35 (16.6%)	0.39	121 (15.5%)
Covariate-adjusted ^b , complete cases ^c		HR (95% CI) ^a	[REF]	1.32 (0.84, 2.08)	1.24 (0.82, 1.89)	0.40	
		N	406	136	204		
Covariate-adjusted ^b , multiply imputed		HR (95% CI) ^a	[REF]	1.06 (0.62, 1.80)	1.07 (0.65, 1.76)	0.96	
		N	472	174	242		
Death to Day 180		HR (95% CI) ^a	[REF]	1.29 (0.82, 2.03)	1.35 (0.87, 2.08)	0.33	
Unadjusted		n (KM%)	76 (19.6%)	26 (17.0%)	30 (14.5%)	0.52	132 (17.7%)
Covariate-adjusted ^d , complete cases ^c		HR (95% CI) ^a	[REF]	0.92 (0.59, 1.43)	0.78 (0.51, 1.20)	0.53	
		N	440	163	220		
Covariate-adjusted ^b , multiply imputed		HR (95% CI) ^a	[REF]	0.94 (0.58, 1.51)	0.90 (0.57, 1.44)	0.90	
		N	472	174	242		
		HR (95% CI) ^a	[REF]	0.94 (0.59, 1.52)	0.90 (0.57, 1.43)	0.91	

HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation.

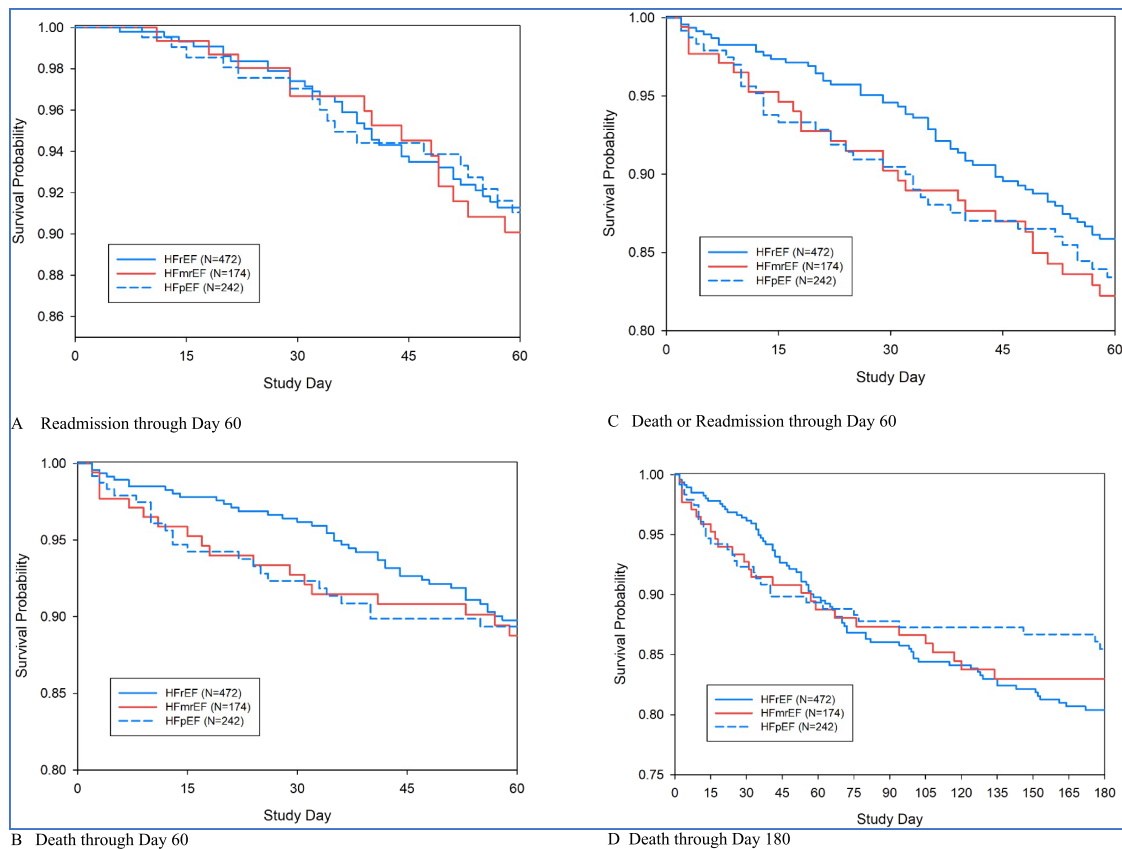
^aP-value from ANOVA (F-test) for continuous variables, log-rank test for time-to-event outcomes or from χ^2 test for categorical variables; hazard ratios (HRs), and associated confidence intervals (CIs) and P-values from Cox regression.

^bAdjusted for rates, cor pulmonale, blood urea nitrogen, and systolic blood pressure.

^cComplete cases are subjects with non-missing values for all the covariates.

^dAdjusted for oedema, creatinine, cor pulmonale, and systolic blood pressure.

Figure 2 Kaplan–Meier plots by ejection fraction groups. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrfEF, heart failure with reduced ejection fraction.



difference between groups of HFrfEF, HFmrEF, and HFpEF although it was higher in patients with HFrfEF. During the follow-up period of 6 months, there was no statistically significant difference in the short-term outcomes between the groups of HFrfEF, HFmrEF, and HFpEF. This was in accordance with findings by some authors in high-income countries.^{17,23} Previous studies in patients with stable, chronic HF have described an association between outcome and LVEF.^{17,23}

Strengths and limitations

Prospective clinical cohort studies in the African setting are challenging with a lot of pitfalls including lack of infrastructure, limited funding and resources, and high rates of loss to follow-up, but it is the only way to characterize real-world African patients who may present with features that are not similar to what has been described in high-income countries. Our results are of relevance and generate data to describe the new phenotype, HFmrEF, in SSA, which deserves further investigation and may be of clinical importance.

The advantages of the present study include that all HF cases were rigorously diagnosed and followed up in a large hospital-based registry with multiple centres in Africa. All AHF cases underwent a systematic and comprehensive echocardiogram evaluation by certified cardiologists. Although this was a post hoc analysis of the THESUS-HF registry and HFmrEF was not predefined, the comprehensive cardiologist echocardiographic evaluation of our population permitted the assessment of criteria of diastolic function to diagnose HFpEF rather than relying only on the incomplete criterion 'lack of an echocardiogram showing a low LVEF'.

Some limitations are noteworthy. First, natriuretic peptides were not available for confirmation of HF in several centres and should be acknowledged as a limitation. A second limitation is that the EF was assessed once close to admission and not longitudinally throughout follow-up, and hence, changes in EF during follow-up were not captured in the current analysis. Finally, the data presented are a post hoc analysis of the THESUS-HF registry, which enrolled patients between 2007 and 2010 and may not be entirely representative of current African patients with HF.

Conclusions

Our study showed that the proportions of HF_rEF, HF_mrEF, and HF_pEF occurrences among SSA hospitalized HF patients were 53.2%, 19.6%, and 27.3%, respectively. The clinical characteristics and the medication prescription of these patients were slightly different, with the new phenotype of HF_mrEF sharing intermediate characteristics with HF_rEF and HF_pEF. Despite the differences in clinical characteristics between patients with AHF in SSA and other regions of the world, the current analysis suggests that similarly to data from other regions, there was no difference in short-term outcomes of patients admitted with AHF by admission EF.

Acknowledgement

The authors thank all the physicians, nurses, and patients who participated in the registry.

Conflict of interest

Drs Cotter and Davison report grants from Abbott Laboratories, Amgen Inc., Celyad, Cirus Therapeutics Inc., Sanofi, Roche Diagnostics Inc., Trevena Inc., Ventrix, and Windtree Therapeutics, Inc. None reported for all other authors.

References

- 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**: 977–982.
- Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR. ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. *Circulation* 2013 2013; **128**.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. ESC Scientific Document Group. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016 2016; **37**: 2129–2200m.
- Zannad F, Briançon S, Juilliere Y, Mertes PM, Villemot JP, Alla F, Virion JM. Incidence, clinical and etiologic features, and outcomes of advanced chronic heart failure: the EPICAL study. *J Am Coll Cardiol* 1999; **33**: 734–742.
- Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, Dietz R, Gavazzi A, van Gilst W, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, Widimsky J, Freemantle N, Eastaugh J, Mason J, Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. *Eur Heart J* 2003; **24**: 464–474.
- Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE™): opportunities to improve care of patients hospitalized with acute decompensated heart failure. *Rev Cardiovasc Med* 2003; **4**.
- Population of Africa (2020) - Worldometer [Internet]. [cited 2020 Feb 21]. Available from: <https://www.worldometers.info/world-population/africa-population/>
- Sani MU, Cotter G, Davison BA, Mayosi BM, Damasceno A, Edwards C, Ogah OS, Mondo C, Dzudie A, Ojji DB, Kouam Kouam C, Suliman A, Yonga G, Abdou Ba S, Maru F, Alemayehu B, Sliwa K. Symptoms and signs of heart failure at admission and discharge and outcomes in the Sub-Saharan Acute Heart Failure (THESUS-HF) registry. *J Card Fail* 2017; **23**: 739–742.
- Dokainish H, Teo K, Zhu J, Roy A, AlHabib KF, ElSayed A, Palileo-Villaneuva L, Lopez-Jaramillo P, Karaye K, Yusoff K, Orlandini A. 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**: e665–e672.
- 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: results of the sub-Saharan Africa survey of heart failure. *Arch Intern Med* 2012; **172**: 1386–1394.
- Sliwa K, Davison BA, Mayosi BM, Damasceno A, Sani M, Ogah OS, Mondo C, Ojji D, Dzudie A, Kouam Kouam C, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Cotter G. Readmission and death after an acute heart failure event: predictors and outcomes in sub-Saharan Africa: results from the THESUS-HF registry. *Eur Heart J* 2013; **34**: 3151–3159.
- Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2010; **23**: 685–713.
- McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitzer J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart. *Eur Heart J* 2012; **33**: 1787–1847.
- Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, Swedberg K, Yusuf S, Granger CB, Pfeffer MA, McMurray JJV, Solomon SD. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail* 2018; **20**: 1230–1239.
- Gu J, Yin ZF, Zhang HL, Fan YQ, Zhang JF, Wang CQ. Characteristics and outcomes of transitions among heart failure categories: a prospective observational cohort study. *ESC Hear Fail* 2020; **7**: 616–625.
- Nauta JF, Hummel YM, van Melle JP, van der Meer P, Lam CSP, Ponikowski

- P, Voors AA. What have we learned about heart failure with mid-range ejection fraction one year after its introduction? *Eur J Heart Fail* 2017; **19**: 1569–1573.
17. Rickenbacher P, Kaufmann BA, Maeder MT, Bernheim A, Goetschalckx K, Pfister O, Pfisterer M, Brunner-la Rocca HP, for the TIME-CHF Investigators. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). *Eur J Heart Fail* 2017; **19**: 1586–1596.
 18. Sartipy U, Dahlström U, Fu M, Lund LH. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Hear Fail* 2017; **5**: 565–574.
 19. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017; **19**: 1574–1585.
 20. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, Savarese G, Lam CSP, Lund LH. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur J Heart Fail* 2017; **19**: 1624–1634.
 21. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, Abe R, Oikawa T, Kasahara S, Sato M, Shiroto T, Takahashi J, Miyata S, Shimokawa H. on behalf of the CHART-2 Investigators. Characterization of heart failure patients with mid-range left ventricular ejection fraction—a report from the CHART-2 Study. *Eur J Heart Fail* 2017; **19**: 1258–1269.
 22. Enzan N, Matsushima S, Ide T, Kaku H, Higo T, Tsuchihashi-Makaya M, Tsutsui H. Spironolactone use is associated with improved outcomes in heart failure with mid-range ejection fraction. *ESC Hear Fail* 2020; **7**: 336–344.
 23. Doughty RN, Cubbon R, Ezekowitz J, Gonzalez-Juanatey J, Gorini M, Gotsman I, MAGGIC Executive Group (responsible for the oversight and overall conduct of the meta-analysis): Berry C, Doughty RN, Granger C, Køber L, Massie B, McAlister F, McMurray J, Pocock S, Poppe K, Swedberg K, Somaratne J, Whalley GA; MAGGIC Steering Group: The Steering Group included investigators from the original studies that provided individual patient data: Ahmed A, Andersson B, Bayes-Genis A, Berry C, Cowie M, Cubbon R, Doughty RN, Ezekowitz J, Gonzalez-Juanatey J, Gorini M, Gotsman I, Grigorian-Shamagian L, Guazzi M, Kearney M, Køber L, Komajda M, di Lenarda A, Lenzen M, Lucci D, Macín S, Madsen B, Maggioni A, Martínez-Sellés M, McAlister F, Oliva F, Poppe K, Rich M, Richards M, Senni M, Squire I, Taffet G, Tarantini L, Tribouilloy C, Troughton R, Tsutsui H, Whalley GA; MAGGIC Coordinating Centre: Doughty RN, Earle N, Perera K, Poppe K, Whalley GA; The University of Auckland, New Zealand MAGGIC Statistical Group: Dobson J, Pocock S, Poppe K; The MAGGIC Studies and Investigators: The following investigators kindly provided the individual patient data from their studies: AHFMS: Doughty RN, Whalley G; Andersson (two data sets): Andersson B, Hall C; BATTLESCARRED and Richards: Richards AM, Troughton R, Lainchbury J; Berry: Berry C, Hogg K, Norrie J, Stevenson K, Brett M, McMurray J; CHARM: Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray J, Michelson EL, Olofsson B, Östergren J, Yusuf S. for the CHARM Investigators and Committees; Diamond and ECHOS: Køber L, Torp-Pedersen C; DIG Trial: DIG limited access data, Ali Ahmed; Euro HF Survey: Lenzen MJ, Scholteop Reimer WJM, Boersma E, Vantrimpont PJMJ, Follath F, Swedberg K, Cleland J, Komajda M; Gotsman: Gotsman I, Zwas D, Planer D, Azaz-Livshits T, Admon D, Lotan C, Keren A; Grigorian-Shamagian: Grigorian-Shamagian L, Varela-Roman A, Mazón-Ramos P, Rigeiro-Veloso P, Bandin-Dieiguez MA, Gonzalez-Juanatey JR; Guazzi: Guazzi M, Myers J, Arena R; Heart Failure Clinic Edmonton: McAlister FA, Ezekowitz J, Armstrong PW, Cujec B, Paterson I; Hillingdon: Cowie MR, Wood DA, Coats AJS, Thompson SG, Suresh V, Poole-Wilson PA, Sutton GC; HOLA: Martínez-Sellés M, Robles JAG, Prieto L, Muñoa MD, Frades E, Díaz-Castro O, Almendral J; Italian HF Registry (IN-CHF): Tarantini L, Faggiano P, Senni M, Lucci D, Bertoli D, Porcu M, Opasich C, Tavazzi L, Maggioni AP; Kirk: Kirk V, Page 6 of 8 RN Doughty Downloaded from by guest on May 21, 2015; Bay M, Parner J, Krogsgaard K, Herzog TM, Boesgaard S, Hassager C, Nielsen OW, Aldershvile J, Nielsen H, Køber L; Macín: Macín SM, Perna ER, Cimbaro Canella JP, Alvarenga P, Pantich R, Ríos N, Farias EF, Badaracco JR; Madsen: Madsen BK, Hansen JF, Stokholm KH, Brons J, Husum D, Mortensen LS; MUSIC: Bayes-Genis A, Vazquez R, Puig T, Fernandez-Palomeque C, Bardají A, Pascual-Figal D, Ordoñez-Llanos J, Valdes M, Gabarrus A, Pavon R, Pastor L, Gonzalez-Juanatey JR, Almendral J, Fiol M, Nieto V, Macaya C, Cinca J, Bayes de Luna A; Newton: Newton JD, Blackledge HM, Squire IB; NPC I: Wright SP, Whalley GA, Doughty RN; Rich (data set 1): Kerzner R, Gage BF, Freedland KE, Rich MW; Rich (data set 2): Huynh BC, Rovner A, Freedland KE, Carney RM, Rich MW; Taffet: Taffet GE, Teasdale TA, Bleyer AJ, Kutka NJ, Luchi RJ; Tribouilloy: Tribouilloy C, Rusinaru D, Mahjoub H, Soulière V, Lévy F, Peltier M; Tsutsui: Tsutsui H, Tsuchihashi M, Takeshita A; UK Heart Study: MacCarthy PA, Kearney MT, Cubbon R, Nolan J, Lee AJ, Prescott RJ, Shah AM, Brooksby WP, Fox KAA; Varela-Roman: Varela-Roman A, Gonzalez-Juanatey JR, Basante P, Trillo R, Garcia-Seara J, Martinez-Sande JL, Gude F. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis: Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). *Eur Heart J* 2013; **33**: 1750–1757.