ONLINE FIRST

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

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Background: Acute heart failure (AHF) in sub-Saharan Africa has not been well characterized. Therefore, we sought to describe the characteristics, treatment, and outcomes of patients admitted with AHF in sub-Saharan Africa.

Methods: The Sub-Saharan Africa Survey of Heart Failure (THESUS–HF) was a prospective, multicenter, observational survey of patients with AHF admitted to 12 university hospitals in 9 countries. Among patients presenting with AHF, we determined the causes, treatment, and outcomes during 6 months of follow-up.

Results: From July 1, 2007, to June 30, 2010, we enrolled 1006 patients presenting with AHF. Mean (SD) age was 52.3 (18.3) years, 511 (50.8%) were women, and the predominant race was black African (984 of 999 [98.5%]). Mean (SD) left ventricular ejection fraction was 39.5% (16.5%). Heart failure was most commonly due to hypertension (n=453 [45.4%]) and rheumatic heart disease (n=143 [14.3%]). Ischemic heart disease (n=77 [7.7%]) was not a common cause of AHF. Concurrent renal dysfunction (estimated glomerular filtration rate, <30 mL/min/173 m^2), diabetes mellitus, anemia (hemoglobin level, <10 g/dL), and atrial fibrillation were found in 73 (7.7%), 114 (11.4%), 147 (15.2%), and 184 cases (18.3%), respectively; 65 of 500 patients undergoing testing (13.0%) were seropositive for the human immunodeficiency virus. The median hospital stay was 7 days (interquartile range, 5-10), with an in-hospital mortality of 4.2%. Estimated 180-day mortality was 17.8% (95% CI, 15.4%-20.6%). Most patients were treated with renin-angiotensin system blockers but not β-blockers at discharge. Hydralazine hydrochloride and nitrates were rarely used.

Conclusions: In African patients, AHF has a predominantly nonischemic cause, most commonly hypertension. The condition occurs in middle-aged adults, equally in men and women, and is associated with high mortality. The outcome is similar to that observed in non-African AHF registries, suggesting that AHF has a dire prognosis globally, regardless of the cause.

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HEART FAILURE (HF) AND especially acute HF (AHF) are important causes of morbidity and mortality in the developed world. The high rate of rehospitalization, the unproductive years of life, and the price of treatment constitute an important economic burden. Little is known about acute and chronic HF in sub-Saharan Africa.[1] Recent studies[2-5] suggested that the main underlying causes of HF are different in Africa, including some conditions that are almost unique, such as endomyocardial fibrosis and tuberculous pericarditis,[6,7] as well as a high prevalence of peripartum cardiomyopathy and idiopathic dilated cardiomyopathy.[8] At the same time, with a nonuniform epidemiologic transition to a more Western way of living, prevalences of hypertension, obesity, and diabetes are increasing, particularly in urban centers, with a possible effect on the etiology of HF.[9]

See Invited Commentary

The Sub-Saharan Africa Survey of Heart Failure (THESUS–HF) was initiated to determine the causes and treatment of AHF and morbidity and mortality among those with the disease in the African subcontinent.

METHODS

STUDY DESIGN AND CLINICAL SETTING

We conducted THESUS–HF as a prospective, multicenter, international observational survey in 12 cardiology centers from 9 countries in the southern, eastern, central, and western regions of sub-Saharan Africa. The countries and centers were selected on the basis of availability of a physician trained in clinical cardiology and echocardiography who had previously participated in research projects. Ethiopia, Kenya, and Senegal joined the study late, resulting in a shorter enrollment period.

INCLUSION AND EXCLUSION CRITERIA

Patients older than 12 years admitted with dyspnea as the main complaint and diagnosed with AHF based on symptoms and signs that were confirmed by echocardiography (de novo or decompensation of previously diagnosed HF) were enrolled in the present study. Exclusion criteria were acute ST-elevation myocardial infarction, severe known renal failure (patients undergoing dialysis or with a creatinine level of >4 mg/dL) (to convert to micromoles per liter, multiply by 88.4), nephrotic syndrome, hepatic failure, or another cause of hypoalbuminemia. Written informed consent was obtained from each subject who was enrolled into the study. Ethical approval was obtained from the ethical review board of the participating institutions, and the study conformed to the principles outlined in the Declaration of Helsinki.

DATA COLLECTION AND CASE DEFINITION

A comprehensive range of clinical data was collected on a standardized case report form. A detailed echocardiographic assessment of ventricular function, valvular structure and function, and regional wall abnormalities was performed. All echocardiographic procedures were undertaken by trained physicians, and measurements were made according to the American Society of Echocardiography Guidelines.[10] Electrocardiograms were read centrally by a cardiologist at Momentum Research, Inc, using standard reference ranges.[11] Laboratory evaluations provided by the local institution and intravenous and oral medications were recorded at admission and on days 1, 2, and 7 (or at discharge if earlier). Symptoms and signs of HF, vital signs, and laboratory test data (when indicated) were collected at baseline and through day 7 (or at discharge if earlier). The probable primary cause of HF was based on the European Society of Cardiology guidelines[12] and as recently applied in the chronic HF cohort of the Heart of Soweto Study.[13] Ischemic causes were determined on the basis of accepted criteria, such as history, or results of noninvasive (eg, electrocardiography, stress test) or invasive tests when available. Testing for human immunodeficiency virus infection was only performed when clinical findings raised suspicion and after patient consent was obtained.

Subjects underwent evaluation for symptoms and signs of HF and laboratory testing (when indicated) at the 1- and 6-month follow-ups. Information on readmissions and death, with respective reasons and cause, was collected through the 6-month follow-up. We initiated telephone contact with patients who could not attend additional clinic visits because they moved to a different location or to another province. Patients who could not be contacted were censored at the last available contact.

To better understand the changes in the pattern of AHF in Africa, the present cohort was classified as having endemic causes (group 1; ie, rheumatic heart disease, the cardiomyopathies, and infective causes, such as pericarditis and human immunodeficiency virus–associated cardiomyopathy), and emerging causes (group 2; ie, hypertension and ischemic heart disease).[14-17]

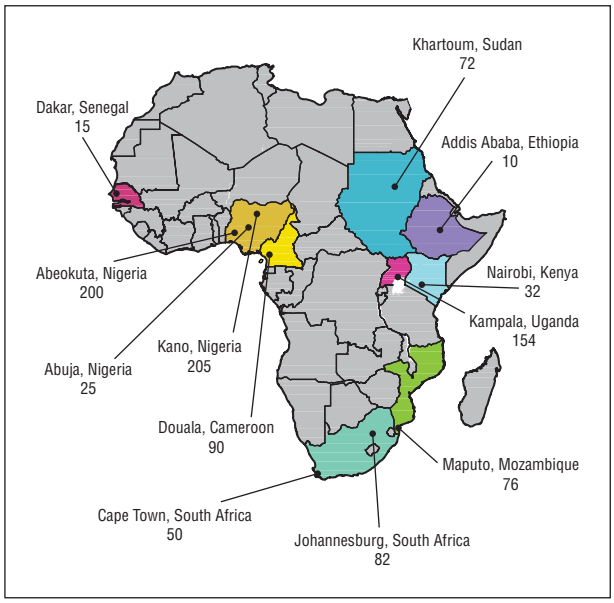

Figure 1. Patients included in the Sub-Saharan Africa Survey of Heart Failure per country. Case report forms were available for 1006 of 1011 patients.

STATISTICAL ANALYSES

All data were processed at Momentum Research, Inc. Data were verified and analyzed using commercially available software (SAS, version 9.2; SAS Institute, Inc). Continuous data were presented as mean (SD) or median (interquartile range, ie, 25th and 75th percentiles). Continuous variables were compared using 2-tailed, 2-sample *t* tests and categorical variables using χ^2 tests. Sex-adjusted differences between patients with emerging and endemic causes were estimated using weighted least squares regression for dichotomous characteristics and ordinary linear regression for continuous characteristics. Kaplan-Meier estimates of mortality and readmission rates were provided. The time to the first event was considered; times for patients without the event of interest were censored at the earlier of the last date the patient was known to be alive or the period of interest.

RESULTS

BASELINE PATIENT CHARACTERISTICS ON ADMISSION

From July 1, 2007, to June 30, 2010, 1011 patients were enrolled in the study, for whom 1006 case report forms were received (**Figure 1**).

Table 1 shows the demographic and clinical presentation on admission for the entire cohort and compares men with women (50.8% of the cohort). Electrocardiographic strips were available for 814 patients. The most frequent arrhythmia was atrial fibrillation, which was found in 147 of 806 patients (18.2%). The most frequent conduction abnormality was left anterior hemiblock, present in 143 of 804 patients (17.8%). Complete left

Table 1. Demographic and Clinical Presentation[a]

Characteristic	All (N=1006)	Men (n=494)	Women (n=511)	*P* Value
Age, y				
Mean (SD)	52.3 (18.3)	54.0 (16.9)	50.7 (19.5)	.005
Median (IQR)	55.0 (39.0-67.0)	55.0 (43.0-67.0)	53.0 (33.0-67.0)	
Black African, No. (%)	984 (98.5)	486 (98.8)	497 (98.2)	.47
Atrial fibrillation, No. (%)	184 (18.3)	77 (15.7)	107 (21.1)	.03
No. of AHF admissions in last 12 mo				
Mean (SD)	0.37 (0.78)	0.41 (0.77)	0.34 (0.78)	.15
Median (IQR)	0 (0-0)	0 (0-1)	0 (0-0)	
Hyperlipidemia, No. (%)[b]	90 (9.2)	52 (10.8)	38 (7.6)	.09
History of smoking, No. (%)	98 (9.8)	85 (17.3)	13 (2.6)	<.001
History of hypertension, No. (%)	556 (55.5)	296 (60.0)	259 (51.0)	.004
History of diabetes mellitus, No. (%)	114 (11.4)	58 (11.8)	56 (11.0)	.68
Body mass index[c]				
Mean (SD)	25.2 (9.0)	24.7 (4.9)	25.7 (11.6)	.08
Median (IQR)	24.0 (20.9-28.1)	24.0 (21.2-27.6)	23.9 (20.5-28.6)	
Systolic blood pressure, mm Hg				
Mean (SD)	130.4 (33.5)	132.4 (33.7)	128.4 (33.3)	.06
Median (IQR)	126.5 (106.0-150.0)	130.0 (110.0-151.0)	120.0 (102.0-150.0)	
Diastolic blood pressure, mm Hg				
Mean (SD)	84.3 (20.9)	85.5 (21.2)	83.2 (20.7)	.08
Median (IQR)	80.0 (70.0-100.0)	82.0 (70.0-100.0)	80.0 (70.0-96.0)	
Heart rate, bpm				
Mean (SD)	103.7 (21.6)	101.6 (21.4)	105.7 (21.6)	.003
Median (IQR)	104.0 (90.0-116.0)	100.0 (88.0-112.0)	108.0 (90.0-120.0)	
LVEF, %				
Mean (SD)	39.5 (16.5)	37.8 (16.2)	41.1 (16.6)	.002
Median (IQR)	38.0 (27.0-50.0)	37.0 (25.0-112.0)	40.0 (28.4-53.0)	
Creatinine level, mg/dL				
Mean (SD)	1.44 (1.19)	1.57 (1.21)	1.30 (1.16)	<.001
Median (IQR)	1.12 (0.89-1.50)	1.23 (0.96-1.65)	1.01 (0.80-1.33)	
SUN level, mg/dL				
Mean (SD)	35.6 (34.1)	41.1 (38.9)	30.2 (27.7)	<.001
Median (IQR)	26.6 (16.5-42.0)	30.5 (20.0-49.0)	23.2 (14.3-34.5)	
Sodium level, mEq/L				
Mean (SD)	135.1 (6.6)	134.9 (6.5)	135.3 (6.8)	.33
Median (IQR)	135.8 (131.0-139.1)	135.0 (131.0-139.0)	146.0 (131.4-140.0)	
Glucose level, mg/dL				
Mean (SD)	109.7 (49.7)	109.7 (44.0)	109.5 (54.9)	.94
Median (IQR)	93.7 (84.0-117.0)	97.2 (84.6-122.0)	93.0 (82.8-111.6)	
eGFR, mL/min/1.73 m^2				
Mean (SD)	83.3 (48.0)	85.3 (51.4)	81.4 (44.4)	.20
Median (IQR)	76.7 (54.0-103.5)	79.6 (55.5-106.2)	74.7 (52.6-101.3)	
Renal dysfunction, No. (%)[d]	73 (7.7)	35 (7.5)	38 (7.8)	.83
Hemoglobin level, g/dL				
Mean (SD)	12.2 (2.6)	12.6 (2.6)	11.8 (2.5)	<.001
Median (IQR)	12.3 (10.7-13.7)	13.0 (11.0-14.5)	11.8 (10.5-13.1)	
Anemia, No. (%)[e]	147 (15.2)	68 (14.3)	79 (16.1)	.43
Total WBC count, No./μL				
Mean (SD)	7699 (4092)	7484 (3505)	7914 (4581)	.10
Median (IQR)	6800 (5200-8980)	6700 (5200-8900)	6900 (5200-9000)	
Lymphocyte count, %				
Mean (SD)	30.3 (13.4)	29.8 (12.9)	30.9 (13.8)	.25
Median (IQR)	30.0 (20.0-39.6)	30.0 (20.0-39.0)	30.5 (20.3-40.0)	

(continued)

and right bundle branch blocks were seen in 62 of 803 (7.7%) and 39 of 803 patients (4.9%), respectively.

CAUSES OF HF

Figure 2 shows the causes of HF in the entire study cohort. In some patients, more than 1 cause was identified. **Table 2** shows the characteristics by endemic vs emerging HF causes and interaction of those causes with sex. **Figure 3** shows the different causes of AHF by country.

THERAPIES FOR HF

The most commonly administered intravenous medication at admission was furosemide in 927 of 998 patients (92.9%), with use decreasing to only 215 of 938 pa-

Table 1. Demographic and Clinical Presentation[a] (continued)

Characteristic	All (N=1006)	Men (n=494)	Women (n=511)	*P* Value
Cholesterol level, mg/dL				
Mean (SD)	157.6 (54.2)	160.0 (59.0)	155.2 (49.1)	.26
Median (IQR)	152.1 (124.0-187.0)	156.0 (124.8-187.2)	152.1 (120.9-183.3)	
Triglyceride level, mg/dL				
Mean (SD)	106.2 (53.9)	109.8 (56.7)	102.7 (50.9)	.09
Median (IQR)	97.9 (71.2-124.6)	97.9 (73.5-125.0)	95.5 (71.2-124.6)	
CK level, U/L				
Mean (SD)	232.2 (447.7)	259.4 (412.6)	210.8 (473.9)	.40
Median (IQR)	88.0 (55.0-171.0)	110.0 (62.5-251.6)	83.0 (48.9-139.0)	
CK-MB fraction, U/L				
Mean (SD)	37.4 (76.0)	39.1 (83.9)	35.9 (68.6)	.78
Median (IQR)	19.0 (13.0-32.0)	19.0 (14.0-31.0)	20.0 (12.0-32.5)	
Seropositive for HIV, No./No. undergoing testing (%)	65/500 (13.0)	30/240 (12.5)	35/260 (13.5)	.75[f]

Abbreviations: AHF, acute heart failure; CK, creatine kinase; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; IQR, interquartile range; LVEF, left ventricular ejection fraction; SUN, serum urea nitrogen; WBC, white blood cell.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; CK to microkatals per liter, multiply by 0.0167; creatinine to micromoles per liter, multiply by 88.4; glucose to millimoles per liter, multiply by 0.0555; hemoglobin to grams per liter, multiply by 10.0; lymphocyte fraction to a proportion of 1, multiply by 0.01; sodium to millimoles per liter, multiply by 1; SUN to millimoles per liter, multiply by 0.357; triglycerides to millimoles per liter, multiply by 0.0113; WBC count to cells $\times 10^9$ per liter, multiply by 0.001.

[a] Data are computed from nonmissing values, the number of which may vary from variable to variable. The sex of 1 patient was not reported.

[b] Indicates cholesterol level of more than 200 mg/dL, low-density lipoprotein level of at least 130 mg/dL, or high-density lipoprotein level of less than 30 mg/dL.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Indicates eGFR of less than 30 mL/min/1.73 m^2.

[e] Indicates hemoglobin level of less than 10 g/dL.

[f] Calculated as comparison of seropositivity for HIV test with negative/unknown results.

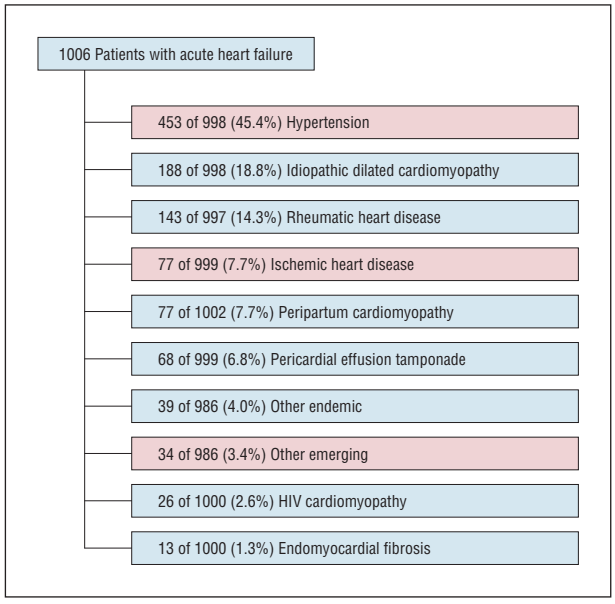

Figure 2. Causes of acute heart failure in the study cohort. Blue indicates earlier stages of epidemiologic transition (endemic causes); pink, later stages of epidemiologic transition (emerging causes); and HIV, human immunodeficiency virus.

tients (22.9%) at day 7 or discharge. The next commonly administered parenteral drugs on admission were digoxin in 13.7% and nitrates in 7.9%. Parenteral inotropes (ie, dopamine hydrochloride and dobutamine hydrochloride) were used in 5.0% and 5.1%, respectively, on admission. Mechanical ventilation was rarely used (0.6%). **Figure 4** shows prescribed oral medications on admission and follow-up.

PATIENTS' FOLLOW-UP AND OUTCOMES

Of 1006 patients, 1-month follow-up assessments were completed for 578 (57.5%) and 6-month assessments for 461 (45.8%). A total of 159 of 1006 patients (15.8%) died without completing a 6-month assessment; an additional 316 (31.4%) had a last date known alive provided and were included in the analysis. The remaining 70 patients (7.0%) were lost to follow-up. Reasons for loss to follow-up were provided for 35 of these patients and included lack of telephone contact (2.3%), financial constraints (0.3%), unwillingness to come for follow-up (0.3%), lack of transportation to the site (<0.1%), and others, for example, transfer of care to other facilities (0.5%). **Table 3** reports the main clinical outcomes observed in the study. The rate of death or readmission at 60 days was 15.4% (**Figure 5**A), and the estimated 6-month mortality rate was 17.8% (Figure 5B). Mortality rates were similar among countries, except that a somewhat lower rate was reported in the Ugandan center (6.3%).

COMMENT

To our knowledge, our data represent Africa's first and largest multinational prospective registry of AHF. This registry reveals a few unique characteristics of AHF in sub-Saharan Africa.

One of the most striking features of this cohort of African patients with AHF is the relative youth of the patients affected (median age, 55 years). In industrialized countries, AHF is a disease of the elderly, with a mean

Table 2. Sociodemographic and Risk Factor Profile of HF Patients According to Endemic vs Emerging Causes

Characteristic[a]	All Patients (N=1006)	Endemic Causes (n=473)		Emerging Causes (n=506)		Sex-Adjusted Difference[b]	
		Men (n=197)	Women (n=276)	Men (n=287)	Women (n=219)	Difference (95% CI)	*P* Value
Sociodemographic Profile							
Age, y							
Mean (SD)	52.3 (18.3)	46.8 (18.2)	41.0 (18.3)	59.0 (13.7)	62.6 (13.6)	17.0 (15.0 to 19.1)	<.001
Median (IQR)	55.0 (39.0-67.0)	46.0 (34.0-59.0)	36.0 (25.0-54.0)	60.0 (50.0-69.0)	64.0 (55.0-73.0)		
Risk factor profile, No./No. not missing (%)							
Total cholesterol level >193 mg/dL	112/649 (17.3)	16/129 (12.4)	21/190 (11.1)	44/185 (23.8)	30/128 (23.4)	11.9 (5.9 to 17.9)	<.001
History of smoking	98/1001 (9.8)	34/197 (17.3)	6/276 (2.2)	50/285 (17.5)	7/218 (3.2)	0.9 (–1.8 to 3.6)	.50
Hypertension	555/1001 (55.4)	43/197 (21.8)	60/274 (21.9)	247/286 (86.4)	189/219 (86.3)	64.5 (59.6 to 69.3)	<.001
Type 2 diabetes mellitus	114/1003 (11.4)	14/197 (7.1)	17/276 (6.2)	43/285 (15.1)	37/219 (16.9)	9.3 (5.3 to 13.3)	<.001
BMI >30	158/969 (16.3)	14/188 (7.4)	41/269 (15.2)	43/278 (15.5)	52/210 (24.8)	8.6 (4.1 to 13.1)	<.001
Clinical Presentation							
NYHA, No./No. not missing (%)							
II	303/706 (42.9)	60/141 (42.6)	97/200 (48.5)	72/200 (36.0)	67/147 (45.6)		
III	216/706 (30.6)	46/141 (32.6)	49/200 (24.5)	69/200 (34.5)	47/147 (32.0)		
IV	28/706 (4.0)	4/141 (2.8)	8/200 (4.0)	13/200 (6.5)	2/147 (1.4)		
Systolic blood pressure, mm Hg							
Mean (SD)	130.4 (33.5)	116.1 (28.5)	115.7 (24.3)	143.8 (32.3)	143.8 (36.4)	27.9 (24.0 to 31.8)	<.001
Median (IQR)	127 (106 to 150)	110.0 (100.0 to 130.0)	110.0 (100.0 to 130.0)	140.0 (120.0 to 160.0)	140.0 (120.0 to 160.0)		
Diastolic blood pressure, mm Hg							
Mean (SD)	84.3 (20.9)	76.5 (19.5)	77.1 (17.0)	92.0 (19.8)	90.9 (22.4)	14.6 (12.1 to 17.1)	<.001
Median (IQR)	80 (70 to 100)	73.0 (65.0 to 89.0)	75.0 (67.0 to 90.0)	90.0 (80.0 to 100.0)	90.0 (79.0 to 100.0)		
Heart rate, bpm							
Mean (SD)	103.7 (21.6)	103.8 (24.3)	109.1 (22.4)	100.2 (19.3)	101.7 (20.0)	–5.5 (–8.3 to –2.8)	<.001
Median (IQR)	104 (90 to 116)	102.0 (89.0 to 116.0)	111.0 (93.0 to 122.0)	100.0 (88.0 to 112.0)	103.0 (89.0 to 112.0)		
Peripheral edema score[c]							
Mean (SD)	1.8 (1.0)	1.9 (1.0)	1.7 (1.0)	1.9 (1.1)	1.8 (1.1)	0.1 (–0.1 to 0.2)	.35
Median (IQR)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)		
Echocardiographic Evaluation							
Heart rate, bpm							
Mean (SD)	94.6 (17.9)	97.3 (18.4)	98.1 (18.9)	91.1 (17.5)	9.19 (15.9)	–6.2 (–8.7 to –3.6)	<.001
Median (IQR)	94.0 (84.0 to 104.0)	96.5 (87.5 to 105.0)	98.0 (88.0 to 110.0)	90.9 (80.0 to 102.0)	92.0 (81.0 to 101.0)		
Dimensions and LV Function							
LV systole size, mm							
Mean (SD)	46.0 (13.1)	49.3 (13.4)	45.7 (13.5)	47.3 (12.6)	42.8 (12.3)	–2.4 (–4.1 to –0.8)	.004
Median (IQR)	47.0 (37.0 to 55.0)	51.0 (39.0 to 58.8)	46.7 (36.0 to 55.0)	48.0 (39.5 to 55.0)	43.4 (33.0 to 53.0)		
LV diastole size, mm							
Mean (SD)	57.7 (11.6)	60.9 (11.5)	57.9 (11.9)	58.6 (11.3)	54.0 (10.7)	–3.1 (–4.5 to –1.6)	<.001
Median (IQR)	58.0 (50.0 to 65.0)	62.0 (54.0 to 68.0)	58.0 (50.0 to 65.0)	58.7 (53.0 to 65.0)	54.0 (46.0 to 63.0)		
Ejection fraction, %							
Mean (SD)	39.1 (16.3)	36.9 (16.4)	40.2 (17.1)	37.3 (15.4)	40.8 (15.5)	0.6 (–1.5 to 2.7)	.59
Median (IQR)	37.2 (26.0 to 50.0)	35.0 (24.0 to 49.0)	38.0 (27.0 to 53.0)	37.0 (25.0 to 47.0)	39.5 (29.4 to 50.0)		
Intraventricular septum (diastole), mm							
Mean (SD)	11.2 (3.3)	10.7 (3.1)	9.8 (3.1)	12.3 (3.1)	11.8 (3.0)	1.8 (1.4 to 2.2)	<.001
Median (IQR)	11.0 (9.0 to 13.0)	10.0 (9.0 to 12.1)	9.6 (8.0 to 11.0)	12.0 (10.0 to 14.0)	11.3 (10.0 to 13.4)		

(continued)

Table 2. Sociodemographic and Risk Factor Profile of HF Patients According to Endemic vs Emerging Causes (continued)

Characteristic[a]	All Patients (N=1006)	Endemic Causes (n=473)		Emerging Causes (n=506)		Sex-Adjusted Difference[b]	
		Men (n=197)	Women (n=276)	Men (n=287)	Women (n=219)	Difference (95% CI)	*P* Value
Dimensions and LV Function							
Posterior wall (diastole), mm							
Mean (SD)	10.7 (2.9)	10.2 (2.9)	9.5 (2.7)	11.7 (2.7)	11.2 (2.7)	1.6 (1.2 to 2.0)	<.001
Median (IQR)	10.2 (9.0 to 12.9)	10.0 (8.0 to 12.0)	9.2 (8.0 to 11.0)	12.0 (9.9 to 13.6)	11.0 (9.4 to 13.0)		
Diastolic Function							
Left atrial anteroposterior size, mm							
Mean (SD)	47.1 (9.2)	49.1 (9.7)	47.4 (10.5)	46.9 (8.1)	45.7 (7.8)	−1.9 (−3.1 to −0.8)	.001
Median (IQR)	47.0 (41.0 to 53.0)	48.6 (43.0 to 55.0)	47.0 (41.0 to 53.0)	47.0 (42.0 to 52.0)	45.0 (40.0 to 50.9)		
Left atrial planimetry size, mm^2							
Mean (SD)	2782 (924)	3039 (1001)	2882 (1110)	2782 (770)	2532 (7808)	−306 (−465 to −147)	<.001
Median (IQR)	2635 (2200 to 3285)	2930 (2250 to 3540)	2770 (2130 to 3400)	2728 (2295 to 3200)	2478 (2100 to 2900)		
Mitral E wave, cm/s							
Mean (SD)	544.2 (500.6)	537.1 (587.0)	571.3 (585.6)	529.6 (404.7)	529.4 (449.7)	−25.8 (−97.0 to 45.4)	.48
Median (IQR)	480.0 (96.0 to 880.0)	243.0 (87.2 to 810.0)	332.0 (88.0 to 920.0)	526.0 (101.7 to 880.0)	460.0 (102.2 to 880.0)		
E-wave deceleration time, ms							
Mean (SD)	150.0 (92.1)	151.3 (146.2)	145.3 (102.9)	143.2 (54.6)	159.0 (64.4)	3.6 (−9.8 to 17.0)	.60
Median (IQR)	130.0 (100.0 to 171.0)	120.0 (92.0 to 158.0)	122.0 (100.0 to 165.0)	134.0 (106.0 to 171.0)	140.6 (120.0 to 189.0)		
Mitral A wave, m/s							
Mean (SD)	324.4 (330.2)	302.0 (289.3)	334.9 (396.1)	295.5 (274.9)	365.5 (344.9)	13.3 (−38.5 to 65.0)	.61
Median (IQR)	215.0 (53.0 to 513.0)	206.0 (52.6 to 500.0)	149.5 (44.2 to 498.0)	220.0 (59.6 to 498.0)	270.0 (69.0 to 580.0)		
Mitral A-wave duration, ms							
Mean (SD)	126.4 (45.1)	114.3 (38.1)	126.7 (57.5)	130.7 (44.1)	128.4 (34.2)	8.5 (0.6 to 16.4)	.03
Median (IQR)	123.0 (100.0 to 150.0)	20.0 (90.0 to 140.0)	118.0 (100.0 to 150.0)	130.0 (100.0 to 160.0)	128.0 (101.0 to 150.0)		

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HF, heart failure; IQR, interquartile range; LV, left ventricular; NYHA, New York Heart Association class.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

[a] Statistics are computed from nonmissing values, the number of which may vary from variable to variable. The HF causes were reported for 980 patients; sex was not reported for one of these.

[b] Calculated as the sex-adjusted difference in proportions or means between endemic and emerging causes of HF.

[c] Examined in a dependent area, including the lower extremities and sacral area, and scored as 0 (a complete absence of skin indentation with mild digital pressure in all dependent areas), 1+ (indentation of the skin that resolves in 10-15 seconds), 2+ (indentation of the skin that is easily created with limited pressure and disappears slowly [15-30 seconds or longer]), or 3+ (large areas of indentation are easily produced and slow [>30 seconds] to resolve).

age of 72 years (median age, 66-70 years)[18]; hence, the condition presents 2 decades earlier in sub-Saharan Africa. Acute HF therefore strikes patients in the prime of their lives in sub-Saharan Africa, with major economic implications because it affects the generation of breadwinners and caregivers. With respect to sex, despite the relative youth of the patients, the disease affects men and women equally, although the characteristics and causes differ by sex (Tables 1 and 2), probably contributing to slight differences in outcomes (Table 3).

Three important observations are worth noting about medical therapy for AHF (Figure 3). First, we have observed a high incidence of the use of aspirin in patients with nonischemic HF in the sub-Saharan African region. In addition, the combination of hydralazine hydrochloride and nitrates, which has been shown to be effective in patients of African descent,[19,20] is hardly ever used in the sub-Saharan region. Third, the rate of β-blocker use, even at follow-up, is relatively low. Although many patients in the present study have HF with preserved systolic function for which the use of β-blockers is less clearly indicated, the rate of β-blocker use in THESUS–HF is lower than that described in other regions.[18,21,22] These observations provide an opportunity to improve the quality of the care of patients with HF in the region. A larger randomized study investigating the combination treatment with hydralazine and nitrates vs placebo in Africans admitted with AHF will commence soon in the centers that participated in the THESUS–HF registry.

The cause of AHF remains predominantly nonischemic, with hypertension, rheumatic heart disease, and the endemic cardiomyopathies (ie, idiopathic dilated cardiomyopathy, peripartum cardiomyopathy, and endomyocardial fibrosis) accounting for 75.5% of the cases (Figure 2 and Table 2). Although the rate of ischemic heart disease may have been underestimated owing to limited diagnostic tools, this finding is in striking contrast to reg-

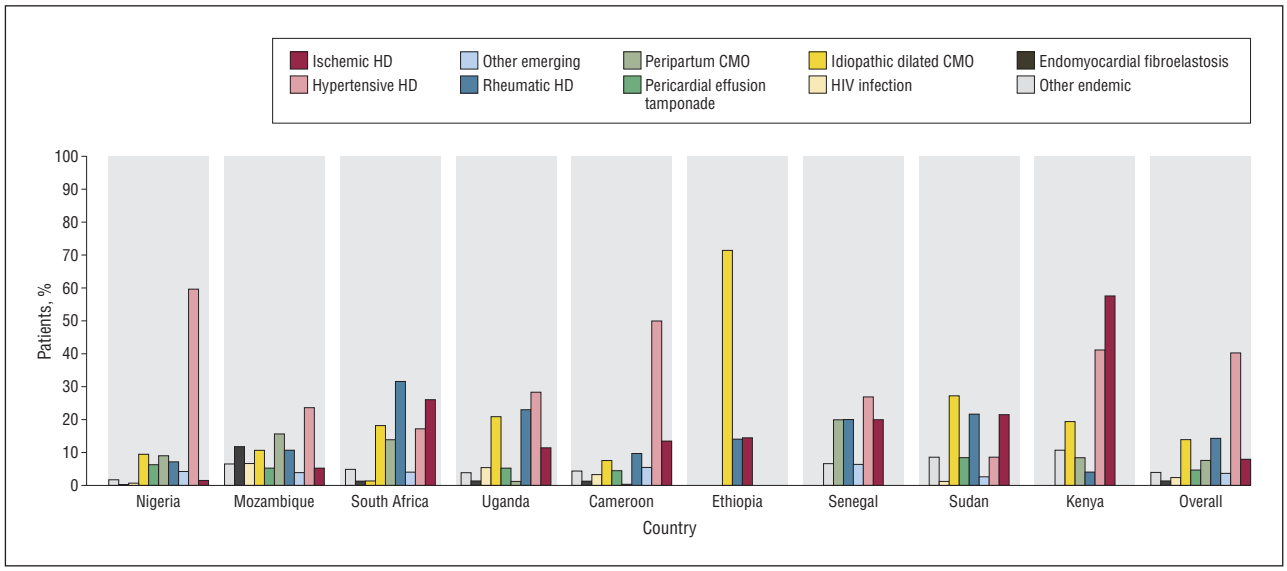

Figure 3. Primary causes of heart failure by country. CMO indicates cardiomyopathy; HD, heart disease; and HIV, human immunodeficiency virus.

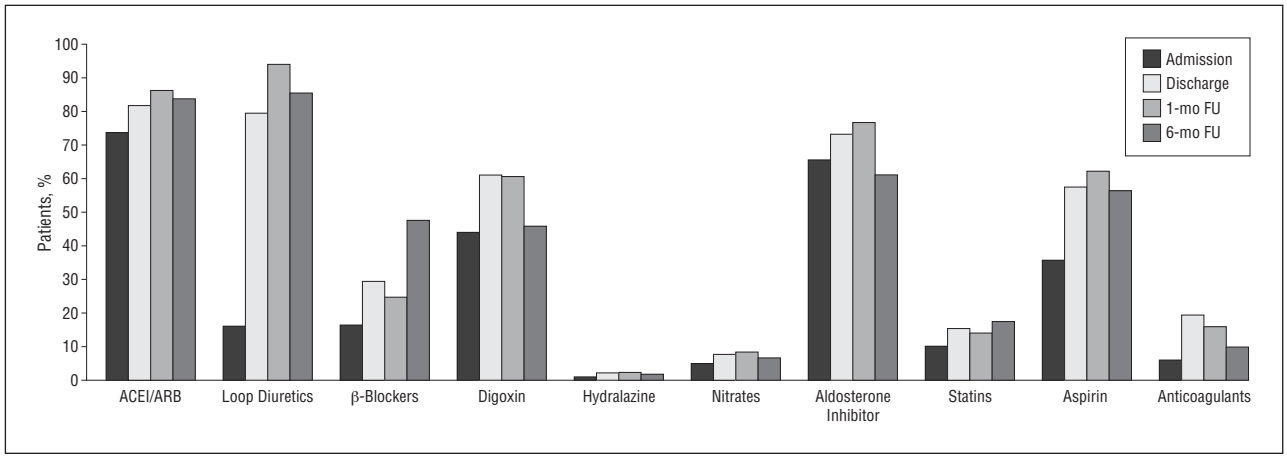

Figure 4. Prescribed oral medication. ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; FU, follow-up.

Table 3. Clinical Outcomes[a]

Outcome	Patient Groups			Causes of HF	
	All (N=1006)	Men (n=494)	Women (n=511)	Endemic (n=473)	Emerging (n=506)
Length of initial hospital stay, d					
Mean (SD)	9.2 (9.3)	9.4 (10.4)	9.1 (8.1)	9.8 (11.5)	8.7 (6.6)
Median (IQR)	7 (5-10)	7 (5-10)	8 (5-10)	8 (5-11)	7 (5-10)
Initial hospitalization mortality, No. (%)	42 (4.2)	24 (4.9)	18 (3.5)	28 (5.9)	14 (2.8)
Readmission to day 60	9.1 (7.3-11.3)	9.7 (7.2-13.1)	8.5 (6.2-11.6)	9.4 (6.8-12.8)	9.0 (6.6-12.2)
Death to day 60	10.6 (8.7-12.8)	11.0 (8.4-14.3)	10.2 (7.7-13.4)	12.5 (9.7-16.0)	9.0 (6.7-12.1)
Death or readmission to day 60	15.6 (13.3-18.1)	16.6 (13.5-20.5)	14.5 (11.6-18.2)	17.3 (14.0-21.2)	14.1 (11.2-17.8)
Death to day 180	17.8 (15.4-20.6)	18.3 (14.9-22.4)	17.4 (14.1-21.4)	20.5 (16.9-24.8)	15.5 (12.4-19.4)

Abbreviations: HF, heart failure; IQR, interquartile range.
[a]Unless otherwise indicated, data are expressed as Kaplan-Meier estimate (95% CI).

istries in Europe or the United States,[18,21,22] where ischemic heart disease (a rarity in Africa) accounts for most of the cases. However, Africa is clearly facing an additional burden because, in addition to the high prevalence of endemic diseases, we are observing a high (and probably increasing) burden of emerging diseases, such as ischemic heart disease and hypertension, in particular in some countries (Figure 3). As socioeconomic changes continue to progress across the continent, the number of AHF cases (particularly in women) caused by

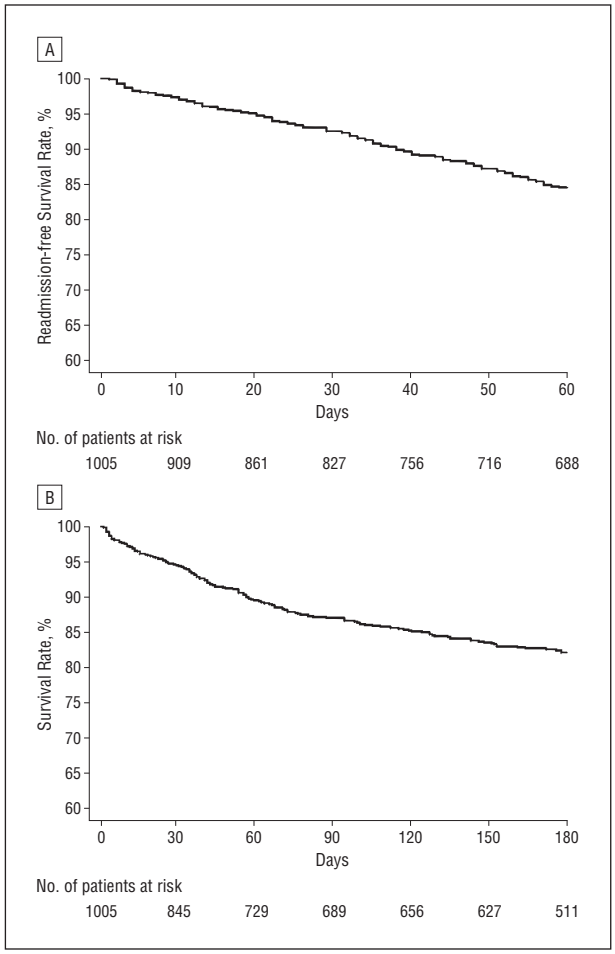

Figure 5. Kaplan-Meier estimates of study outcomes. A, Kaplan-Meier estimates of the cumulative risk for all-cause death or readmission to 60 days. B, Kaplan-Meier estimates of the cumulative risk for all-cause death to day 180.

noncommunicable forms of heart disease may further increase. Finally, human immunodeficiency virus infection, which can affect the myocardium in various ways,[23] is a common condition among patients with HF in Africa. Whether the early introduction of antiretroviral therapy in human immunodeficiency virus–seropositive patients with HF and otherwise no indication for antiretroviral therapy will change their outcome remains to be established in future studies.

Few studies of the outcome of HF in sub-Saharan Africa exist.[24] The outcome of AHF in this study, including high in-hospital and 6-month mortality rates (the latter a possible underestimation owing to higher rates of loss to follow-up) are remarkably similar to those observed in registries in Europe and the United States.[18,21,22] This finding is remarkable because this almost identical outcome was registered despite large differences in patient characteristics (eg, a 20-year difference in age) and causes of HF, suggesting that once AHF occurs, it may have a distinct course independent of patient characteristics. When we compared endemic and emerging causes, AHF due to emerging causes had a slightly better outcome, probably secondary to the better outcome of hypertensive AHF. However, these data should be confirmed in other studies.

Our study's limitations deserve mention. Loss to follow-up was higher in THESUS–HF than in studies conducted in other regions. This finding is common in the population studied owing to such factors as the opportunity to work if the patient is still healthy (in the case of migrant workers) or the need to obtain care if unhealthy. Some inhabitants of those regions have no telephone contact.

This registry has been compiled in selected centers and may represent only AHF patients seen in specialized centers. This limitation has to be seen in the context that many African countries do not train cardiologists and that access to cardiac ultrasonography is limited.

Unfortunately, there are no criterion standards for definitively categorizing HF. We applied a clinically oriented approach based on published criteria. As a clinical registry, we did not systematically validate diagnostic criteria. Owing to no access to cardiac catheterization in a number of centers, we might have missed HF due to ischemic origin.

CONCLUSIONS

Acute HF affects patients in sub-Saharan Africa at an extremely early age and is caused mostly by hypertension and primary cardiomyopathies. The disease leads to a high burden of readmission and death, similar to that observed in other countries, affecting younger patients in the prime of their life. These data challenge us to recognize and respond to HF in Africa by responding to common precursors, such as hypertension and the urgent need for culturally sensitive interventions. Dedicated awareness programs that strive to improve the pharmacological and nonpharmacological management of AHF (including better follow-up) need to be developed.

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