Markers of Atherosclerosis, Clinical Characteristics, and Treatment Patterns in Heart Failure

A Case-Control Study of Middle-Aged Adult Heart Failure Patients in Rural Kenya

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Background: Although risk factors for heart failure are increasingly common worldwide, the contribution of atherosclerosis to heart failure in sub-Saharan Africa is largely unknown.

Objective: This study assessed the association between atherosclerotic risk factors and heart failure in a developing country.

Methods: We performed a case-control study of heart failure in rural Kenya. We assessed the risk factors for heart failure by using international criteria based on electrocardiogram (ECG), echocardiogram, physical examination findings, and laboratory testing. Atherosclerotic risk factors were determined by ECG, echocardiogram, ankle-brachial index (ABI), and lipid testing. We described the relationship of wall motion abnormalities on echocardiogram, ABI <0.9, and ischemic pattern on ECG with the presence of heart failure with multivariable logistic regression adjusting for age and sex and using adjusted odds ratios (AORs) and 95% confidence intervals (CIs).

Results: There were 125 cases and 191 controls (n = 316); 49% were male. The mean age was 60 (SD = 13) years. Most patients had hypertension (53%), and 16% had human immunodeficiency virus infection. Lipids were in the normal range for all. Cases were older than controls (62 years vs. 58 years, respectively). The most common abnormality associated with heart failure was dilated cardiomyopathy. Ischemic heart failure was the second most common cause in men. Cases were more likely to have an ABI <0.9 (46% vs. 31%; AOR: 1.99; 95% CI: 1.19 to 3.32), ischemia or infarct on ECG (68% vs. 43%; AOR: 3.01; 95% CI: 1.43 to 6.34), and wall motion abnormalities on echocardiogram (54% vs. 15%; AOR: 7.00; 95% CI: 3.95 to 12.39).

Conclusions: Ischemic heart failure is more common in Kenya than previously recognized. Noninvasive markers of atherosclerosis are routinely found among patients with heart failure. Treatment and prevention of heart failure in sub-Saharan Africa must consider many causes including those related to atherosclerosis.

In 2010, more than 41 million people had heart failure (HF) worldwide, a 14% increase from 1990 [1]. In the United States, there are more than 3 million physician visits and 1 million hospital discharges yearly for HF [2]. Readmission rates after hospitalization for HF are >50% 6 months after discharge, and 5-year mortality rates are 40% to 65% in the United States and Europe [3–5]. The economic impacts of HF in the United States are astonishing, with costs in 2010 topping $39.2 billion [6]. Corresponding data from sub-Saharan Africa (SSA) are not available because of challenges in disease classification [7] and a lack of population-based studies [8].

Coronary atherosclerosis is the most common cause of HF in high-income settings [9]. However, ischemic heart disease (IHD) and atherosclerosis have historically accounted for <2% of the burden of HF in SSA [10]. Much of the research showing a low prevalence of IHD in SSA, however, relied on a patient's report or electrocardiogram (ECG) alone [11,12]. Atherosclerotic cardiovascular diseases are becoming more common among patients in SSA with HF, according to some studies using contemporary diagnostic techniques in SSA [13,14], but not all [15,16]. Epidemiological and clinical data about the causes of HF from most countries in SSA remain unavailable, in part because of the generally low cardiovascular research productivity from the region [10,17].

To address this unmet need, we designed this study to 1) assess the major abnormalities associated with HF by using clinical, laboratory, and echocardiographic parameters; 2) describe treatment patterns for HF; and 3) assess the association between atherosclerotic risk factors and HF in western Kenya. Kenya (population 43.2 million in 2012)

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is a middle-income country that is marked by a double burden of communicable and noncommunicable diseases [18] and is underrepresented in publications from SSA on HF epidemiology [8]. Findings from an economically developing country in the midst of an epidemiological transition may have local and worldwide relevance for similarly situated countries.

METHODS

Study design

We performed a case-control study to identify associations of markers of atherosclerosis with HF at a national referral hospital in western Kenya. Our methodological approach has 3 main components:

1. A description of the primary probable etiology of HF adjudicated using clinical, physical examination, and radiographic criteria according to society guidelines.
2. A determination of the distribution of risk factors (both atherosclerotic and nonatherosclerotic) for HF in cases and controls.
3. Regression modeling to determine the extent to which atherosclerotic risk factors were associated with higher or lower odds of having HF.

Setting

One of the 11 U.S. National Heart, Lung and Blood Institute Centers of Excellence [19] is in western Kenya, where Moi University School of Medicine has a 22-year relationship with a consortium of U.S. medical schools. This collaboration, the Academic Model Providing Access to Healthcare (AMPATH) [20,21], partners with Moi Teaching and Referral Hospital (Kenya's second national referral hospital, with 750 beds, and serving a catchment area of 13 million people [Fig. 1]) and Moi University School of Medicine. This study was conducted at Moi Teaching and Referral Hospital between June 2010 and December 2012 in the city of Eldoret, Kenya.

Participants

All patients ≥40 years old who were being seen in the inpatient wards, medical outpatient clinic, and cardiology outpatient clinics were eligible for enrollment. Cases constituted patients with a known or presumed diagnosis of HF on the basis of on a modified version of the Framingham HF criteria that uses clinical, physical examination, and radiographic parameters [22]. Controls constituted patients from the same clinical areas who had shortness of breath but no known HF. Symptomatic controls were selected to achieve similarities in location of enrollment, health care seeking behavior, and acuity of illness between groups. Patients were enrolled consecutively and were not matched. Patients were excluded if they were human immunodeficiency virus (HIV) seropositive with a CD4 count level ever <100 cells/ml, if they were within 6 months post-partum, if they were within 3 months of major trauma, or if they were known to have a history of malignant disease.

Variables

Enrollment and data collection. The following data were prospectively obtained from each patient: self-reported medical history; socioeconomic status (SES); occupation; residence; alcohol consumption; tobacco use; self-reported history of malaria, tuberculosis, and other recurrent infections; medication use; New York Heart Association functional class; cardiac symptoms and signs; family cardiovascular disease history; and physical activity. Heavy or hazardous alcohol drinkers were identified using

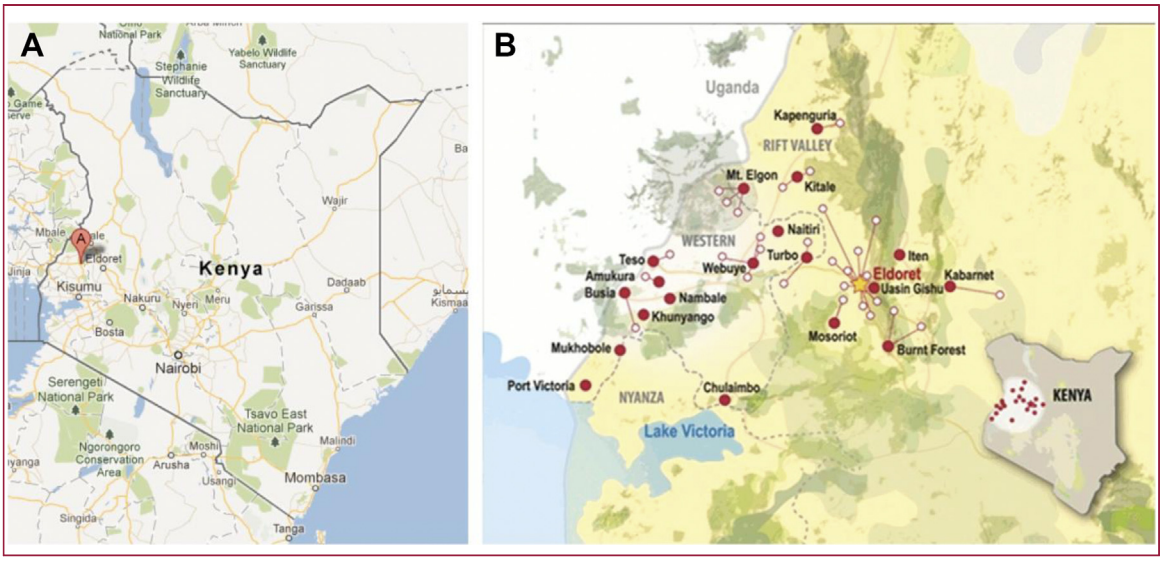

FIGURE 1. Map of the study catchment area. (A) Kenya. (B) Academic Model Providing Access to Healthcare (AMPATH) catchment area in western Kenya. This study was carried out in Eldoret, Kenya (red type).

the Alcohol Use Disorders Identification Test (AUDIT-C) screening tool [23]. SES was measured by an unweighted summary variable accounting for ownership of 5 items (automobile, flushing toilet, television, electricity, and refrigerator) [24].

Clinical evaluation. All patients underwent a thorough cardiopulmonary examination by a physician. Blood pressure was measured in the right arm after the patient had been seated for 10 minutes. Three readings were obtained, each 2 minutes apart. Doppler ultrasound was used to measure ankle systolic blood pressure bilaterally with an HP Sonos 2500 (Philips Healthcare, Bothell, WA, USA) device using a linear phased array probe. The ankle-brachial index (ABI) was calculated by dividing the highest of the ankle blood pressures by the ipsilateral brachial blood pressure [25]. An ABI <0.9 increases the risk for coronary heart disease 2- to 4-fold [26].

Electrocardiogram and echocardiogram. A 12-lead resting ECG was recorded for each patient. Echocardiograms were performed by a trained sonographer using a standardized acquisition protocol on a Philips CX-50 machine (Philips Healthcare). Images were digitally archived for analysis in the Duke Echocardiography Core Laboratory (Durham, NC, USA), which has reported high standards of measurability and reproducibility [27]. All echocardiograms were reviewed by 1 physician or sonographer and approved by 1 physician overreader.

Echocardiograms included a thorough assessment of left ventricular diameters, wall thicknesses, volumes, ejection fraction, diastolic function, valvular disease, rheumatic heart disease, and right-sided heart function using American Society of Echocardiography, European Association of Echocardiography, and World Heart Federation guidelines [28–33]. Left ventricular volumes and ejection fraction were measured using the biplane Simpson's volumetric method combining apical 4-chamber and 2-chamber views. When images were inadequate for definition of the left ventricular endocardial border, visual ejection fraction was used instead. Using a 17-segment wall motion scoring system, a wall motion score index (WMSI) was calculated according to American Society of Echocardiography guidelines [33]. Greater scores indicate more wall motion abnormalities. The echocardiographic assessment also evaluated the presence and type of congenital heart disease, pericardial effusion size, and the presence of stranding within the effusion and cardiac masses or thrombi.

Laboratory analysis. Blood was collected by venipuncture for analysis and storage. The following serum tests were performed in the accredited AMPATH Reference Laboratory in Eldoret, Kenya: C-reactive protein (CRP), total cholesterol, low-density lipoprotein, high-density lipoprotein (HDL), triglycerides, apolipoprotein A1 (apo A1), apolipoprotein B (apo B), lipoprotein a, hemoglobin A1c, creatinine, blood urea nitrogen, hemoglobin, complete blood count, rapid HIV-1 antibody testing and enzyme-linked immunosorbent assay if positive, and CD4 count. Higher lipid values are associated with greater risk for atherosclerosis, with the exception of HDL, which generally shows the inverse relationship. Clinically relevant values for serum lipids were determined on the basis of recent guidelines [34]. Cutoff values were used for CRP (>75th percentile) and apo B (>0.9 g/l) because these levels predict ischemic cardiovascular events [35,36]. The presence of metabolic syndrome was determined by applying International Diabetes Federation criteria [37].

Statistical analysis

Enrollment of at least 50 cases and 148 controls was defined a priori to achieve at least 90% power to detect a statistically significant difference in the proportions of cases versus controls with regional wall motion abnormalities. We based the calculation on a 3:1 sampling ratio of controls to cases and a 1-sided test with a type-1 error rate of 0.05. It was assumed that the prevalence of regional wall motion abnormalities would be 10% in the control group and between 25% and 35% among the cases, on the basis of previous estimates [38,39].

Primary probable etiologies of HF were assessed by examining associations between various abnormalities and HF, by using clinical, echocardiographic, and ECG criteria and presented as a proportion of all cases (Table 1). These criteria incorporate European Society of Cardiology guidelines and HF registry protocols from SSA [13,14,40]. Medical history, SES, physical findings, laboratory results, and markers of atherosclerosis were compared between cases and controls. Markers of atherosclerosis were defined a priori as follows: WMSI >1.8; ABI <0.9; and ischemic changes on ECG [41,42]. Using the case status as the outcome and controls as the reference group, multivariable logistic regression analyses were used to examine the extent to which each HF risk factor and each demographic and clinical measurement were associated with higher or lower odds of HF diagnosis. Except for age and sex analyses, all models were adjusted for age and sex. The linearity assumption between the log-odds of HF and the continuous exposures was confirmed using generalized additive models. Results are reported using adjusted odds ratios (AORs) for each measurement and 95% confidence intervals (CIs).

Separate analyses were used to examine the distribution of demographic and clinical risk factors for HF by sex, by using only data for the HF cases. Because these measurements were of 3 data types (continuous, binary, or ordinal), 3 types of analyses were required to explore sex as an independent predictor of each risk. Linear regression was used for continuous data, proportional odds logistic regression was used for ordinal outcomes, and logistic regression was used for binomial outcomes. Fisher exact test was used for categorical outcomes with a small number of observations. All models (excluding Fisher exact test) were also adjusted for age as a linear term.

TABLE 1. Criteria for primary probable cause of heart failure

Study Definition	Criteria
LV systolic dysfunction	LVEF ≤45%
LV diastolic dysfunction	On the basis of mitral valve inflow velocities, left atrial size, and mitral annulus tissue Doppler velocities according to recommendations from the American Society of Echocardiography
Idiopathic dilated cardiomyopathy	(1) LVEF ≤45% and LV end-diastolic dimension >55 mm (2) Absence of myocardial ischemic or infarct pattern on ECG
Ischemic cardiomyopathy	(1) LVEF ≤45% (2) WMSI ≥1.8 or myocardial ischemic or infarct pattern on ECG
Hypertensive HF	(1) LVEF ≤45% or LV septal wall dimension >1.3 cm or diastolic dysfunction grade ≥2 (2) Systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg
HFpEF	(1) LVEF >50% (2) Diastolic dysfunction grade ≥2
Valvular HF	(1) LVEF ≤45% (2) Presence of rheumatic or degenerative valvular disease
Right-sided HF	(1) LVEF >40% (2) Elevated jugular venous pressure or maximum inferior vena cava size >2.1 cm or <50% reduction in inferior vena cava size with inspiration (3) Greater than moderate tricuspid regurgitation or peak pulmonary arterial pressure >35 mm Hg or signs of venous congestions (4) Absence of rheumatic heart disease (5) Diastolic dysfunction grade <3
Hypertrophic cardiomyopathy	(1) LV septal or posterior wall dimension >1.5 cm (2) Diastolic dysfunction grade ≥2 or moderate or severe mitral regurgitation or aortic outflow gradient ≥30 mm Hg
Endomyocardial fibrosis	(1) LVEF ≤45% (2) Typical intraventricular thrombus or endomyocardial thickening present
HIV-associated HF	(1) LVEF ≤45% (2) HIV positivity (3) Absence of other identifiable cause
Other causes	HF secondary to congenital heart defects, endocrine disorders, and pericardial disease

ECG, electrocardiogram; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HIV, human immunodeficiency virus; LV, left ventricular; LVEF, left ventricular ejection fraction; WMSI, wall motion score index.

Ethical considerations

All participants provided written informed consent, and the study conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the Institutional Research and Ethics Committee of Moi University College of Health Sciences (Eldoret, Kenya), the Institutional Review Boards of Duke University (Durham, NC, USA) and Brown University (Providence, RI, USA), and the National Heart, Lung, and Blood Institute (Bethesda, MD, USA).

RESULTS

Clinical and demographic characteristics

Of the 5,562 individuals we screened, 316 participants—125 (40%) cases and 191 (60%) controls—were included for analysis (Fig. 2). Participants were enrolled from the inpatient setting (41%), outpatient clinics (34%), or the casualty department (24%). Mean ± SD age of cases and controls were 61 ± 13 and 58 ± 12 years, respectively (Table 2). About half of the participants were male. Most participants were of low SES, and 41% were farmers. Atrial fibrillation was more common among cases (18%) versus controls (5%, $p < 0.01$), but asthma was significantly more common among controls (22%) than cases (12%) ($p < 0.05$). A greater percentage of cases (22%) than controls (10%) had chronic kidney disease ($p < 0.01$), defined as an estimated glomerular filtration rate <60 ml/min. There were no significant differences in blood pressure, hemoglobin, HIV seropositivity, or heavy alcohol use.

Etiologies of heart failure

Eight primary probable etiologies of HF were identified. Among the 125 cases, 120 had echocardiograms completed, and an etiology of HF could be assigned in 118. Among those 118 patients, the most common etiologies of HF were dilated cardiomyopathy (19.5%), IHD (17.8%), valvular heart disease (17.8%), hypertension (11.9%), HF with preserved ejection fraction (HFpEF, 9.3%), right-

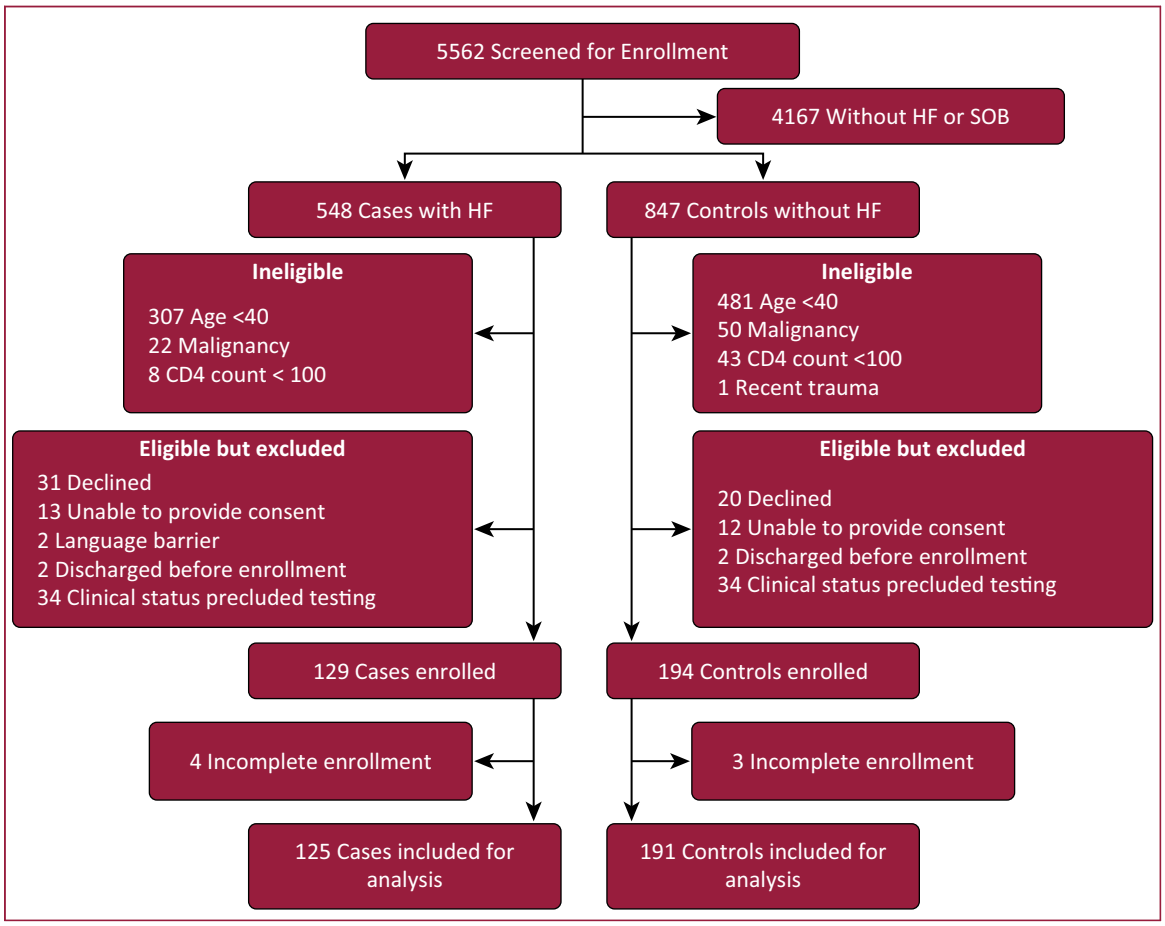

FIGURE 2. Screening and enrollment diagram. HF, heart failure; SOB, shortness of breath.

sided HF (8.5%), and HIV-associated HF (8.5%). Thyroid disease (2.5%) and pericardial disease (1.7%) accounted for a small portion of cases. One case of HF secondary to hypertrophic cardiomyopathy and 2 cases of HF of unknown etiology were noted.

Figure 3 shows the distribution of HF etiology as a function of sex. Dilated cardiomyopathy and IHD were the most common causes of HF among men, whereas hypertension and valvular heart disease (mostly rheumatic) were most common among women. IHD occurred in only 10% of women. Right-sided HF, HFpEF, and hypertensive heart disease were more common among women than men. HIV-associated HF was equally common among men and women.

Figure 4 shows the distribution of etiologies of HF according to age category (<60 or ≥60 years). Among older patients, dilated cardiomyopathy, IHD, and hypertension were the main probable etiologies of HF. For younger patients, valvular heart disease was the most common etiology.

Atherosclerotic risk factors among cases and controls

The risk factor profile among cases and controls is shown in Table 3. A history of treatment for hypertension was more common among cases than controls (odds ratio (OR): 2.55; 95% CI: 1.57 to 4.14). Of the clinical history-based risk factors, there were no statistically significant differences in diabetes, smoking history, family history of early myocardial infarction, or reported physical activity. Of the physically measured risk factors, more cases (46%) than controls (31%) had an ABI <0.9 ($p < 0.01$).

Analysis of laboratory-based markers revealed that the 75th percentile for CRP was approximately 30 mg/l, and the groups did not differ significantly in the odds of exceeding this cutoff. Levels of low-density lipoprotein, apo A1, total cholesterol, and triglycerides were in the normal or low range in both groups; however, cases had lower values of these markers. Lipoprotein (a) levels were not statistically significant different between groups. There was no difference in the proportion of cases and controls with apo B ≥0.9 g/l. HDL levels were significantly lower among cases versus controls (OR: 0.67; 95% CI: 0.6 to 0.8), and cases more often met criteria for the metabolic syndrome (OR: 1.66; 95% CI: 1.04 to 2.65), thus indicating greater cardiovascular risk.

Table 4 shows the associations of markers of atherosclerosis with HF. A WMSI >1.8 (OR: 7.00; 95% CI: 3.95 to

TABLE 2. General characteristics of heart failure cases and controls

	Total (n = 316)	Case (n = 125)	Control (n = 191)
Age, yrs	60 ± 13	61 ± 13	58 ± 12*
Male	49	49	49
Socioeconomic status category			
0	53	52	53
1	21	18	23
2	15	14	15
3	7	8	6
4	3	6	2
5	1	2	1
Farmer	41	42	39
Urban residence	25	25	25
Past medical history			
Stroke	4	5	4
Thyroid disease	2	3	1
Asthma	18	12	22*
Angina	38	45	34
Atrial fibrillation	10	18	5†
Tuberculosis	15	12	17
Malaria	93	93	94
NYHA functional class			
1	12	11	12
2	37	28	43
3	34	41	29
4	18	20	16
Heart rate, beats/min	86 ± 20	87 ± 22	85 ± 18
Systolic BP, mm Hg	129 ± 29	130 ± 27	129 ± 30
Diastolic BP, mm Hg	79 ± 17	81 ± 18	78 ± 15
Peripheral edema	48	69	34†
S3 gallop	25	45	12†
eGFR <60 ml/min/1.73m^2	15	22	10†
Hemoglobin, g/dl	13.4 ± 3	13.3 ± 3	13.5 ± 3
HIV positive	16	14	17
Heavy alcohol intake	16	16	16

Continuous variables presented as mean ± SD; others are %. All comparisons adjust for age and sex.
BP, blood pressure; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; other abbreviations as in Table 1.
*$p < 0.05$.
†$p < 0.01$.

12.39), a low ABI (OR: 1.99; 95% CI: 1.19 to 3.32), and an ischemic or infarct pattern on ECG (OR: 2.68; 95% CI: 1.53 to 4.68) were all significantly more common among cases versus controls ($p < 0.01$ for all). Cases were also more likely to have 1, 2, or all 3 of these markers present. There were no significant differences in results when analyses were adjusted for glomerular filtration rate (data not shown).

Electrocardiographic, echocardiographic, and treatment parameters

Table 5 shows selected ECG, echocardiographic, clinical, and medication use features according to the main causes of HF. Rhythm and conduction system disturbances were most common among cases with dilated cardiomyopathy or valvular heart disease. The average resting heart rate for HF cases was generally >75 beats/min. With the exception of cases with HFpEF, most patients presented with advanced New York Heart Association functional class symptoms. Most patients with HF reported taking diuretic medications, and a wide range (29% to 70%) reported taking angiotensin-converting enzyme inhibitor medications. Less than half of patients with HF reported taking beta-blockers, and ≤20% were taking angiotensin receptor blockers. Antiplatelet medications were used by only 30% of patients with ischemic HF.

DISCUSSION

This study of HF in SSA is unique for a number of reasons. Our study reports probable etiologies of HF in rural Kenya

and specifically includes a variety of modalities to assess communicable and noncommunicable etiologies. In addition, we use a case-control design to compare associations between atherosclerotic risk factors and HF. Combining ECG, ABI, and regional wall motion abnormalities on echocardiogram, we specifically assessed the contribution of atherosclerosis to HF in a rural community in western Kenya.

Our findings demonstrate that contemporary probable etiologies of HF in Kenya are myriad. Although dilated cardiomyopathy remains the most common form of HF in this patient population, an ischemic etiology is nearly as common. Markers of atherosclerosis appear to exist commonly among patients with HF in rural Kenya, in contrast to earlier reports [10,43]. Our findings challenge prevailing assumptions about the paucity of atherosclerotic disease among patients with HF and provide much needed data on HF in patients from rural SSA. These data have important clinical and public health implications for Kenya and other populations in low- and middle-income countries in the midst of the epidemiological transition.

Most data from SSA on HF epidemiology demonstrate that patients are, on average, 10 to 15 years younger than patients with HF in high-income countries. In the largest HF registries from SSA, the average age of participants was 52 to 57 years; in high-income countries, HF is mostly a disease of septuagenarians [13–16,44]. This difference likely relates to the lower life expectancy in SSA. Rheumatic heart disease, a common cause of HF in SSA, also manifests earlier in life. However, it is also clear that, in SSA, IHD appears earlier than in developed countries [45]. Thus, many forms of HF are present simultaneously in SSA. The earlier age of presentation with HF has tremendous human and economic implications for the workforce, productivity losses, and caregivers [46].

Noncommunicable conditions are the most common causes of HF worldwide [47]. A systematic review supports our finding that the contemporary causes of HF in SSA are myriad and include both endemic and emerging causes [8]. In low- and middle-income countries, hypertension accounts for 45% (range 15% to 80%) of cases, whereas cardiomyopathies and valvular heart disease account for 24% (range 14% to 40%) and 18% (range 4% to 53%), respectively. IHD accounts for 8% of cases (range 1% to 48%) [8]. Dilated cardiomyopathy was the most common form of HF in the current study, consistent with the bulk of the literature on HF from SSA [43].

Treatment patterns in patients with HF are poor. In the present study, only 55% of patients with dilated cardiomyopathy were taking angiotensin-converting enzyme inhibitor medications, 45% were taking beta-blockers, and 23% were taking digoxin. This mirrors findings from THESUS-HF (the Sub-Saharan Africa Survey of Heart Failure), showing equally poor use of guideline-directed medical therapy (GDMT) [14], and it may be related to provider- or patient-level factors. Given the mortality gains from GDMT [48], it is imperative that implementation and

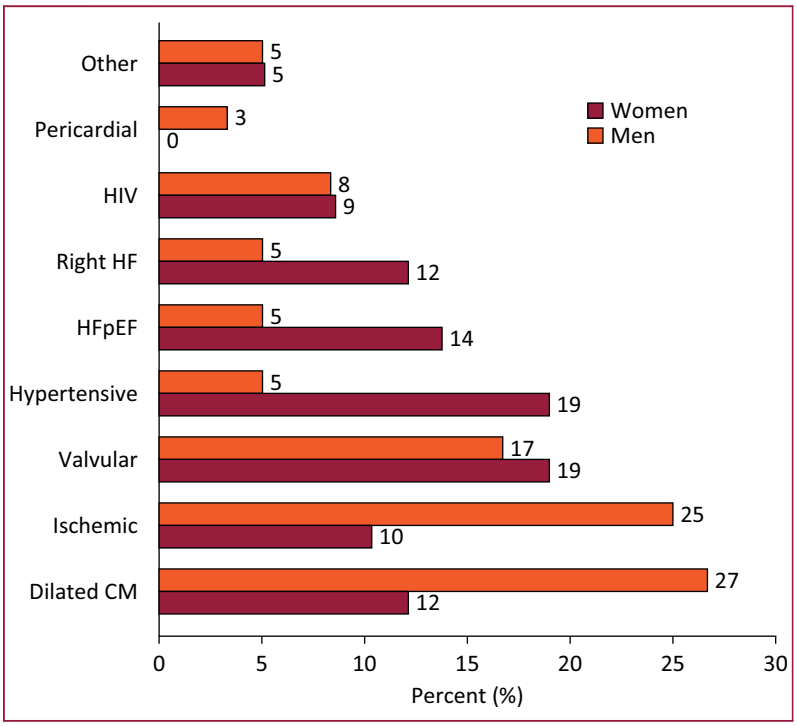

FIGURE 3. Percentage of causes of heart failure (HF) (n = 118) in western Kenya by sex. CM, cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; HIV, human immunodeficiency virus.

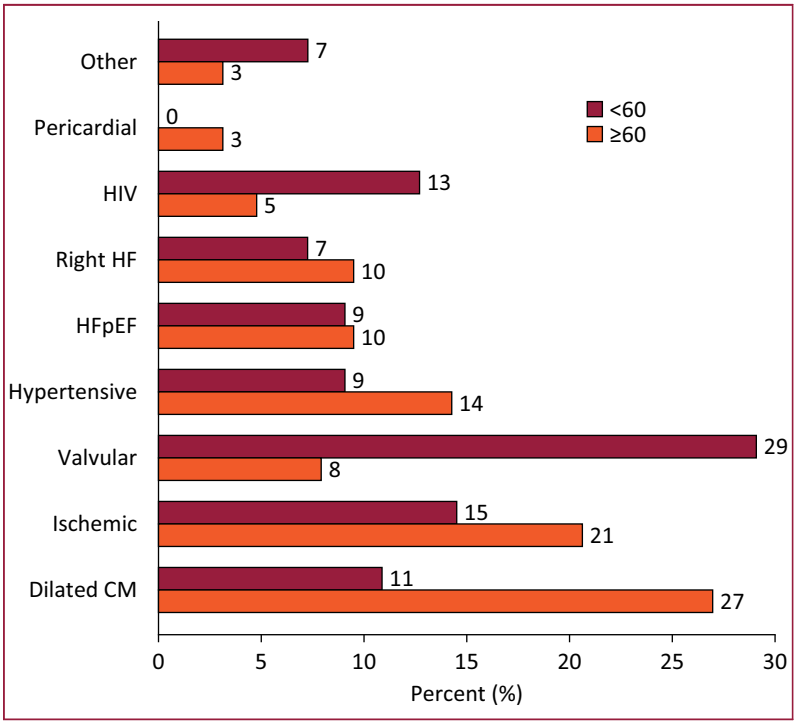

FIGURE 4. Percentage of causes of heart failure (HF) (n = 118) in western Kenya by age category. Abbreviations as in Figure 3.

TABLE 3. Clinical, physical, and laboratory-based cardiovascular risk factors among cases and controls

Risk Factor	Total (n = 316)	Case (n = 125)	Control (n = 191)	Odds Ratio* (95% CI)
Clinical risk factors				
Past medical history				
Treatment for hypertension	53	68	44†	2.55 (1.57–4.14)†
Diabetes	11	11	11	0.98 (0.47–2.04)
Current/former smoker	37	39	35	1.18 (0.71–1.99)
Family history of early MI	6	6	6	0.88 (0.27–2.82)
Physically active	32	27	35	0.80 (0.48–1.35)
Physically measured risk factors				
Overweight/obese‡	34	38	32	1.39 (0.85–2.27)
Waist-hip ratio	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.06 (0.76–1.49)
Ankle brachial index <0.9	37	46	31	1.99 (1.19–3.32)†
Laboratory-based risk factors				
C-reactive protein >75th percentile§	24	22	25	0.88 (0.50–1.56)
LDL, mg/dl	99 ± 49	91 ± 45	104 ± 50	0.94 (0.9–1.0)‖
HDL, mg/dl	36 ± 16	32 ± 14	39 ± 17	0.67 (0.6–0.8)†
Apolipoprotein A1, g/l	1.2 ± 0.4	1.1 ± 0.3	1.3 ± 0.4	0.18 (0.09–0.35)†
Apolipoprotein B ≥0.9, g/l	32	28	34	0.79 (0.47–1.33)
Lp(a), g/l	0.60 ± 0.6	0.53 ± 0.5	0.64 ± 0.6	0.69 (0.43–1.10)
Total cholesterol, mg/dl	164 ± 57	152 ± 56	173 ± 56	0.93 (0.89–0.97)†
Triglycerides, mg/dl	131 ± 68	115 ± 47	141 ± 77	0.94 (0.9–0.98)‖
Metabolic syndrome	42	50	38	1.66 (1.04–2.65)‖
Hemoglobin A1c, %	6.4 ± 1.4	6.4 ± 1.2	6.4 ± 1.4	0.99 (0.83–1.18)

Values are % or mean ± SD, unless otherwise indicated. Overweight/obesity defined as body mass index ≥25 kg/m^2. Waist-hip ratio calculated as waist circumference/hip circumference.

CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); MI, myocardial infarction; OR, odds ratio.

*OR for LDL, HDL, total cholesterol, and triglycerides is per 10 units higher. OR for sedentary time is per 1 hour longer. OR for waist-hip ratio is per 0.1 unit higher. All models adjusted for age and sex.

†$p < 0.01$.

‡Defined as body mass index ≥25 kg/m^2.

§Log-transformed; 75th percentile corresponds to 30 mg/l.

‖$p < 0.05$.

TABLE 4. Markers of atherosclerosis among congestive heart failure cases and controls*

Marker	Total (n = 316)	Case (n = 125)	Control (n = 191)	Odds Ratio (95% CI)
WMSI >1.8†	31	54	15	7.00 (3.95–12.39)‡
Ankle-brachial index <0.9§	37	46	31	1.99 (1.19–3.32)‡
Ischemic/infarct pattern on ECG‖	24	35	17	2.68 (1.53–4.68)‡
Total number of markers¶				
0	36	13	53	Reference
1	39	42	37	4.65 (2.26–9.56)‡
2	21	36	10	15.06 (6.35–35.68)‡
3	4	9	1	61.01 (6.96–535.21)‡

Values are % unless otherwise noted.

ECG, electrocardiogram; other abbreviations as in Tables 1 and 3.

*Adjusted for age and sex.

†N = 290.

‡$p < 0.01$.

§N = 270.

‖N = 292.

¶N = 246.

TABLE 5. Selected electrocardiographic, echocardiographic, clinical, and medication use patterns in heart failure according to cause (n = 118)

	DCM (n = 23)	Ischemic (n = 21)	Valvular (n = 21)	HTN (n = 14)	HFpEF (n = 11)	Right-Sided HF (n = 10)	HIV (n = 10)	Other* (n = 8)
Atrial fibrillation	19	14	47	0	0	22	0	0
LBBB	22	5	0	7	0	10	0	12
Heart rate, bpm	99 ± 26	87 ± 21	84 ± 18	75 ± 19	83 ± 23	75 ± 17	96 ± 18	78 ± 14
LVEF, %	23 ± 10	23 ± 10	45 ± 15	37 ± 17	61 ± 13	50 ± 8	37 ± 14	44 ± 18
LVIDs, cm	5.5 ± 0.8	5.1 ± 0.9	3.7 ± 1.0	4.0 ± 1.0	2.7 ± 0.7	2.9 ± 0.8	4.1 ± 1.4	4.0 ± 0.8
LVIDd, cm	6.1 ± 0.8	5.6 ± 0.9	4.9 ± 1.2	5.0 ± 0.6	4.1 ± 0.7	3.8 ± 0.9	5.1 ± 1.1	5.1 ± 0.3
IVSd, cm	1.0 ± 0.2	1.0 ± 0.3	1.2 ± 0.4	1.3 ± 0.2	1.2 ± 0.2	1.3 ± 0.4	1.0 ± 0.2	1.3 ± 0.6
LA volume, cm^3	11 ± 6	9 ± 4	15 ± 11	8 ± 3	6 ± 3	7 ± 4	8 ± 4	9 ± 3
RVSP, mmHg	50 ± 12	43 ± 15	54 ± 17	53 ± 28	38 ± 16	75 ± 28	48 ± 14	63 ± 13
Smoking	43	43	52	14	45	30	40	38
Angina	35	38	57	50	45	70	30	50
NYHA ≥3	68	67	67	69	27	56	60	50
Ankle brachial index	0.89 ± 0.1	0.90 ± 0.2	0.89 ± 0.2	0.91 ± 0.2	0.81 ± 0.2	1.0 ± 0.1	1.0 ± 0.2	1.0 ± 0.3
Heavy/hazardous drinking	13	24	24	7	27	0	10	25
Medication use								
Diuretic	86	85	76	100	82	90	67	100
Digoxin	23	11	43	23	9	30	29	14
ACEI	55	65	29	62	55	70	50	43
ARB	9	11	5	15	18	20	12	0
Beta-blocker	45	42	14	31	18	40	25	25
Antiplatelet	27	30	43	15	27	10	12	14

Values are % or mean ± SD.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DCM, dilated cardiomyopathy; HTN, hypertension; IVSd, interventricular septum dimension in diastole; LA, left atrial; LBBB, left bundle branch block; LVIDd, left ventricular internal dimension during diastole; LVIDs, left ventricular internal dimension in systole; RVSP, right ventricular systolic pressure; other abbreviations as in Tables 1 and 2.

*Other includes hypertrophic cardiomyopathy, pericardial disease, thyroid disease, and unknown etiology.

monitoring of GDMT for patients with HF in SSA be prioritized.

Our methods are notable for a novel approach to identifying markers of atherosclerosis. To determine the extent to which atherosclerosis and ischemia contributed to HF, we used a combination of widely available, noninvasive techniques. We chose this approach on the basis of limitations in access to a broad range of investigative tools and the "erroneously reinforced beliefs that IHD only affects the wealthy and the elderly" in SSA [12]. The ABI, ECG, and echocardiogram have a modest to strong correlation with significant coronary artery disease or previous myocardial infarction [41,42]. Using this scheme, we identified that markers of atherosclerosis are more common in patients with HF in this region than previously described [8,10]. Lower HDL, in a clinically meaningful range, and a greater proportion of patients with metabolic syndrome also signal a greater risk for cardiovascular disease [49]. There was a relative paucity of traditional cardiovascular risk factors other than hypertension. It is possible that participants underreported behavioral factors. These factors notwithstanding, this study is one of the first in a rural community in SSA to employ specific investigations for markers of atherosclerosis. THESUS-HF demonstrated that IHD was the most common cause of HF in urban Kenya [14], and other studies from the region support the notion of an increasing burden of IHD and its associated risk factors [12,50]. These findings underscore the need to develop more accessible tools to diagnose IHD and for clinicians and policy makers to consider varied causes of HF in urban and rural settings.

Strengths and limitations

The strengths of this study include a uniform definition of HF applied to case and control patients who were prospectively identified, a sample size chosen on the basis of power calculations, and the use of an independent echocardiography core laboratory to analyze images blinded to the clinical information. There are some limitations to our study. We restricted our sample to participants ≥40 years old to understand causes of HF in middle-aged adults, but as a result, we may have underrepresented causes of HF that are more common in a younger population. Congenital and rheumatic heart diseases, for example, are more likely in younger age groups. Our study was based at a referral hospital and therefore may not completely represent the community epidemiologically. Behavior data

elements were self-reported, and participants may have misreported them. Finally, without advanced imaging or functional studies, we were not able to diagnose ischemic HF definitively. The absence of sensitive measures may have resulted in underestimations of coronary atherosclerosis. In most of SSA, however, access to invasive imaging techniques is limited. Each of the 3 markers we used (ABI, WMSI, ECG) correlates with coronary atherosclerosis; however, the positive predictive value of this combination for significant coronary atherosclerosis is unknown in SSA.

CONCLUSIONS

Contemporary etiologies of HF in SSA seem myriad and include communicable and noncommunicable diseases. The use of GDMT for patients with HF in SSA is poor, and strategies to improve its use for HF in SSA are warranted. Markers of atherosclerosis are more common among patients with HF than among patients without HF. Atherosclerosis is also an African disease and commonly manifests as HF, as it does elsewhere. Inattention to atherosclerosis in SSA risks ignoring an important and common contributor to the cardiovascular disease burden and a missed opportunity for disease prevention.

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