ORIGINAL RESEARCH

Outcomes and Care Quality Metrics for Women of Reproductive Age Living With Rheumatic Heart Disease in Uganda

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BACKGROUND: Rheumatic heart disease disproportionately affects women of reproductive age, as it increases the risk of cardiovascular complications and death during pregnancy and childbirth. In sub-Saharan Africa, clinical outcomes and adherence to guideline-based therapies are not well characterized for this population.

METHODS AND RESULTS: In a retrospective cohort study of the Uganda rheumatic heart disease registry between June 2009 and May 2018, we used multivariable regression and Cox proportional hazards models to compare comorbidities, mortality, anticoagulation use, and treatment cascade metrics among women versus men aged 15 to 44 with clinical rheumatic heart disease. We included 575 women and 252 men with a median age of 27 years. Twenty percent had New York Heart Association Class III-IV heart failure. Among patients who had an indication for anticoagulation, women were less likely than men to receive a prescription of warfarin (66% versus 81%; adjusted odds ratio, 0.37; 95% CI, 0.14–0.96). Retention in care (defined as a clinic visit within the preceding year) was poor among both sexes in this age group (27% for men, 24% for women), but penicillin adherence rates were high among those retained (89% for men, 92% for women). Mortality was higher in men than women (26% versus 19% over a median follow-up of 2.7 years; adjusted hazard ratio, 1.66; 95% CI, 1.18–2.33).

CONCLUSIONS: Compared with men, women of reproductive age with rheumatic heart disease in Uganda have lower rates of appropriate anticoagulant prescription but also lower mortality rates. Retention in care is poor among both men and women in this age range, representing a key target for improvement.

Key Words: anticoagulation ■ epidemiology ■ outcomes research ■ quality of care ■ rheumatic heart disease ■ valvular heart disease ■ women's health

Cardiovascular disorders are already the leading cause of mortality in low- and middle-income countries (LMICs), yet they are underrecognized and poorly understood in these settings.[1–4] Rheumatic heart disease (RHD), which has largely been eliminated in wealthy nations, remains a major contributor to the noncommunicable disease burden in LMICs, affecting 33 million people worldwide and killing ≈320 000 each year.[5,6] In sub-Saharan Africa, RHD is estimated to be responsible for up to 32% of heart failure cases.[4,7] Progression of the disease can be prevented but requires prophylactic benzathine penicillin G administered by intramuscular injection at health centers.[3,8–11] Furthermore, treatment of RHD's myriad complications, including valve failure, atrial fibrillation, and stroke, often necessitate complex surgeries or lifelong anticoagulation, both of which are difficult to deliver in low-resource countries.[3,9,10]

Women of childbearing age are an especially vulnerable group of patients with RHD, as the disease increases their risk of complications and death during pregnancy.[8,9,12–18] Furthermore, the anticoagulant

CLINICAL PERSPECTIVE

What Is New?

- This study represents one of the first investigations of the quality of care and outcomes of women of reproductive age living with rheumatic heart disease in sub-Saharan Africa.
- A key finding of this work was that female rheumatic heart disease patients of reproductive age with an indication for anticoagulation were less likely than men to be prescribed warfarin in Uganda.

What Are the Clinical Implications?

- Retention in clinical care following rheumatic heart disease diagnosis was poor among both women and men of reproductive age, making it a key target for quality improvement.

Nonstandard Abbreviations and Acronyms

HR	hazard ratio
IQR	interquartile range
LMIC	low- and middle-income country
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
OR	odds ratio
RHD	rheumatic heart disease
TIA	transient ischemic attack
UHI	Uganda Heart Institute

medication warfarin (used to prevent stroke and thromboembolism in patients with RHD with atrial fibrillation, severe mitral stenosis, or prior mechanical valve surgery) is a potential teratogen that raises the risk of miscarriage and maternal hemorrhage if used improperly.[5,10,19–24] Unfortunately, the epidemiologic profile of this population is poorly described in sub-Saharan Africa. The REMEDY (Global Rheumatic Heart Disease Registry) RHD registry broadly examined those living with RHD in 14 LMICs in Africa and Asia and found that although 40.7% of the study patient population had an indication for warfarin, only 3.6% of female participants of reproductive age were on contraceptives.[5,25] It is unclear if this gap in appropriate care extends to other RHD therapies, and its cause was not explored.

To further investigate the impact of RHD on women of reproductive age, our group recently completed a qualitative study in Uganda of this population.[26,27] We found that young women living with RHD in the country experience significant stigma attributable to beliefs that they have limited childbearing potential from their condition. Many were assumed by friends and family to have HIV because they were observed to be taking lifelong medications for their heart disorders. Furthermore, their precarious financial situations from the cost of the illness left many dependent on others to fill their prescriptions. To extend these findings, we examined data from the Uganda national RHD registry in this current study to explore whether women of childbearing age had different medication prescription and adherence patterns compared with men and, if so, whether there were impacts on their health outcomes such as mortality. In addition, we sought to identify differences in the disease treatment cascade—an established care quality metric used in other chronic diseases like HIV.[28–31]

METHODS

Data Source

The Ugandan national healthcare cardiac system is composed of national- and district-level health centers. National-level health institutions are referral centers including national referral hospitals such as Mulago Hospital in Kampala (of which the Uganda Heart Institute [UHI] is a semi-autonomous tertiary cardiology referral center), and below them, regional referral centers. At the lower district level, there is a vertical network of village, parish, subcounty, county, and district clinics and hospitals from which complex cases are referred to regional and national centers. Beginning in 2013, regional referral centers at Lubowa, Mbarara, Gulu, and Lira were designated RHD centers of excellence in the model of existing regional centers of excellence for HIV care.[27] They are able to provide at least 1 physician champion, 1 to 2 specialized nurses, an ultrasonography machine, and wireless mobile Internet access and airtime with the aim of catering to the specialized needs of RHD patients including echocardiography and penicillin prophylaxis administration. Vertical referrals and follow-up site are at the discretion of the encounter provider, though most RHD patients tend to be retained at the level of a regional center of excellence with complex cases (eg, those requiring catheterization) referred up to the national center of excellence at the UHI.[27,32]

All RHD patients in clinical care at the UHI (the national referral center) or one of 4 other regional centers of excellence (Lubowa, Mbarara, Gulu, and Lira) are approached to enroll in the Uganda national RHD registry.[27] Additional subjects are enrolled through echocardiographic screening studies of children and a limited number of adults diagnosed with latent RHD using World Heart Federation criteria.[33] The registry includes individuals from a wide variety of socioeconomic groups

and tribal affiliations. Data collection for the Uganda RHD registry began in 2011, and the registry was expanded to an online RedCap platform in 2013. Written informed consent is obtained from all participants (with both parental informed consent and patient consent for subjects <18 years of age), and the registry is approved by the Institutional Review Boards of University Hospitals Cleveland Medical Center, Makerere University School of Medicine, and the Uganda National Council for Science and Technology. Baseline echocardiograms are performed on all amenable subjects. The primary investigators have full access to all the data in the study and take responsibility for its integrity and the data analysis. The Uganda RHD registry data set used to perform this analysis is available from the corresponding author upon reasonable request.

Study Population

We included all women in the cohort who met the World Health Organization definition of reproductive age[34] (15–44 years) with a diagnosis of clinical RHD (ie, those with signs/symptoms of the disease) dating from June 16, 2009, to May 16, 2018.[35] Individuals with latent or borderline latent RHD (silent disease) were excluded because of a lack of consistent screening strategies in Uganda. For the comparative portions of the analysis, all male patients with clinical RHD of the same age range in the registry were included.

Predictors and Covariates

Variables of interest captured in the analysis included self-reported demographics (age, sex, clinic site, occupation, educational status [less than secondary school versus secondary or higher]); distance from nearest health center; baseline medical history by chart review (eg, diabetes mellitus, HIV status, prior stroke, prior decompensated heart failure, atrial fibrillation, thromboembolism, prior major bleeding, infective endocarditis); functional class (New York Heart Association [NYHA] heart failure class); history of heart valve replacement or repair; and medical treatment information (eg, benzathine penicillin G and warfarin prescriptions by self-report and chart review). Indications for anticoagulation are documented by the local treating physician and include atrial fibrillation/flutter, history of embolic stroke, left atrial thrombus on echo, deep vein thrombosis or pulmonary embolism (PE), mechanical heart valve, or other (eg, severe mitral stenosis). Echocardiograms (eg, aortic valve pathology, mitral valve pathology, left ventricular ejection fraction, from in-clinic 2-dimensional echocardiography) are available for most patients at the baseline visit. Mortality was often documented in the hospital when patients died of RHD complications. In addition, study nurses obtain vital status information in person or by phone and routinely contact subjects and/

or family when they are lost to follow-up. When possible, a cause of death is documented; however, death certificates are not routinely available for these patients. Our registry also contains data regarding the RHD treatment cascade, a quality-of-care metric that our group has previously defined and described.[36] Briefly, the steps of the cascade are (1) alive (no documentation of death); (2) retained in care (seen in clinic within 365 days of their last clinic visit); (3) prescribed penicillin; and (4) optimally adherent to ≥80% of their prescribed penicillin doses. Cards that document date and nurse signature for all benzathine penicillin G injections are carried by RHD patients in the registry for this purpose.

Statistical Analysis

Baseline clinical characteristics were described using counts, medians, and interquartile ranges for continuous variables. Binary/categorical variables were reported as frequencies and percentages. Binary variables in 2 groups were compared using the chi-square test, while continuous variables were compared using the Wilcoxon rank-sum test. Crude descriptive data on cause of death were presented as frequencies and percentages. We then constructed multivariable-adjusted binary logistic regression models to determine if women differed from men in the likelihood of warfarin prescription. For model selection, we initially forced age and sex into the model. Next, other sociodemographic and clinical covariates were chosen a priori by clinical likelihood and incorporated into the final model by automated forward selection process with retention for those with $P<0.1$.[37] Area under the receiver operating characteristic curve was assessed for each final model, and the Hosmer-Lemeshow goodness-of-fit test was used to evaluate the findings. A similar multivariable logistic regression approach was used to assess retention in care among women. Survival for men and women were visualized using Kaplan–Meier curves and compared as hazard ratios using a multivariable Cox proportional hazards model adjusted for the following a priori covariates likely to affect outcomes in this population: age, educational status, employment status, household crowding (defined as total household occupants >7 people), history of valve surgery, and poor NYHA class. Harrell's C-index was calculated to evaluate goodness of fit for this model. Statistical analyses were performed using the Stata 12 software package (StataCorp, College Station, TX). $P<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

There were 575 women and 252 men in the registry who met our inclusion criteria. Table 1 shows the baseline

Table 1. Baseline Demographic, Clinical, Echocardiographic Characteristics

	Women	Men	*P* Value
Demographic characteristics			
Total number	575	252	…
Age (IQR), y	27 (20–35)	25 (19–32)	0.05
Clinic site, n (%)			
Uganda Heart Institute	508 (88.7)	212 (84.1)	0.29
Mbarara	15 (2.6)	12 (4.8)	
Lubowa	12 (2.1)	6 (2.4)	
Gulu	23 (4.0)	16 (6.4)	
Other	15 (2.6)	6 (2.4)	
Highest education level, n (%)			
None	35 (6.2)	14 (5.7)	0.32
Primary	213 (37.5)	92 (37.4)	
Secondary	193 (34.0)	80 (32.5)	
Trade/Vocational	22 (3.9)	16 (6.5)	
College/University	101 (17.8)	39 (15.9)	
Not applicable (patient is a child)	4 (0.7)	5 (2.0)	
Employed	160 (28.1)	71 (28.6)	0.88
Household occupants, n (IQR)	6 (4–8)	5 (3–8)	0.07
Nearest health center, km (IQR)	2 (1–5)	2 (1–5)	0.13
Comorbidities and complications, n (%)			
History of decompensated heart failure, n (%)	147 (25.8)	58 (23.1)	0.27
Initial NYHA class, n (%)			
Class I	113 (22.1)	51 (23.3)	0.47
Class II	286 (56.0)	115 (52.5)	
Class III	81 (15.9)	33 (15.1)	
Class IV	31 (6.1)	20 (9.1)	
Prior stroke/transient ischemic attack, n (%)	25 (4.4)	7 (2.8)	0.27
History of endocarditis, n (%)	5 (0.9)	4 (1.6)	0.36
Valve replacement, n (%)	31 (5.5)	18 (7.3)	0.33
Valve repair, n (%)	6 (1.1)	7 (2.8)	0.07
HIV positive, n (%)	38 (6.6)	8 (3.2)	0.05
Hypertension, n (%)	31 (5.5)	12 (4.8)	0.70
Diabetes mellitus, n (%)	3 (0.5)	2 (0.8)	0.64
Coronary artery disease, n (%)	3 (0.5)	1 (0.4)	0.81
History of significant bleeding, n (%)	20 (3.5)	14 (5.6)	0.17
Echocardiographic findings, n (%)			
Left ventricular ejection fraction <55%, n (%)	122 (22.1)	71 (29.6)	0.03
Aortic stenosis, n (%)	33 (6.1)	30 (12.4)	<0.01
Mild	23 (4.1)	12 (5.0)	
Moderate	5 (0.9)	8 (3.3)	
Severe	5 (0.9)	10 (4.1)	
Aortic regurgitation, n (%)	244 (43.7)	134 (55.4)	<0.01
Mild	134 (24.0)	60 (24.8)	
Moderate	82 (14.7)	38 (15.7)	
Severe	28 (5.0)	36 (14.9)	

(Continued)

Table 1. Continued

	Women	Men	P Value
Mitral stenosis, n (%)	248 (44.3)	82 (34.5)	0.04
Mild	47 (8.4)	18 (7.6)	
Moderate	82 (14.6)	20 (8.4)	
Severe	119 (21.3)	44 (18.5)	
Mitral regurgitation, n (%)	450 (80.7)	192 (80.4)	0.29
Mild	120 (21.5)	57 (23.9)	
Moderate	129 (23.1)	57 (23.9)	
Severe	201 (36.0)	78 (32.6)	
Tricuspid regurgitation, n (%)	319 (57.2)	136 (56.9)	0.01
Mild	148 (26.5)	83 (34.7)	
Moderate	91 (16.3)	27 (11.3)	
Severe	80 (14.3)	26 (10.9)	

IQR indicates interquartile range; and NYHA, New York Heart Association.

characteristics of the cohort at the time of their enrollment into the registry. Women in this age range were slightly older than men (median [interquartile range], 27 (20–35) versus 25 (19–32) years; P=0.05). The majority of women were seen at the Uganda Heart Institute in Kampala (89%). Less than half of women had only primary school or no formal schooling. Twenty-eight percent of women or their primary caregivers were employed, and median household size was 6 people. Most subjects lived relatively close to a health center of some type (regardless of RHD prophylaxis administration capacity), with a median distance of 2 km.

Clinical Profile and Comorbidities
Table 1 also describes the complications and clinical comorbidities of the population at the time of registry enrollment. These were generally similar among men and women; however, women had statistically borderline lower rates of prior valve repair (1.1 versus 2.8%; P=0.07) and higher rates of HIV infection (6.6 versus 3.2%; P=0.05) compared with men. Regarding RHD complications among women, 26% had experienced decompensated congestive heart failure, with 22% having an initial NYHA class of III or IV. Four percent had previously suffered a stroke or transient ischemic attack. Only 1% had experienced endocarditis, and 7% had undergone valve surgery (either replacement or repair). Traditional atherosclerotic vascular disease or risk factors were uncommon: 6% had hypertension, and 1% had diabetes mellitus and coronary artery disease, respectively.

Echocardiographic Findings
Nearly all (97%, n=560) patients in our cohort had an echocardiogram performed at the time of enrollment into the registry. Among women, there was considerable burden of advanced disease findings, including decreased left ventricular ejection fraction (<55%) in 22%, 21% with severe mitral stenosis, and 36% with severe mitral regurgitation. Compared with male members of the registry within the same range, women had a lower proportion with reduced left ventricular ejection fraction and aortic valve disease but a higher proportion with mitral stenosis.

Anticoagulation Therapy
Twenty-two percent (n=129) of the women of our cohort had a documented reason for receiving anticoagulation therapy (Table 2). Primary indications for anticoagulant therapy were atrial fibrillation/flutter (64%), history of embolic stroke (9%), and mechanical heart valve (12%). Of those with an indication, only 66% were prescribed warfarin. When compared with men, a higher proportion of women had a history of embolic stroke as an indication (9% women versus 3% men) and a lower proportion had a mechanical heart valve indication (12% versus 18%); however, these differences were not statistically significant (P>0.15).

When examining patients with an indication for anticoagulation, we found that women were less likely than men to receive a warfarin prescription in the final multivariable model (odds ratio [OR], 0.37; 95% CI, 0.14–0.96; P=0.04; Table 3). Conversely, there was a statistically borderline trend toward increased odds of prescription of aspirin in women over men (OR, 2.50; P=0.07). The models were adjusted for age, educational status, and poor NYHA functional class (NYHA Class III or IV). The models had a C-statistic of 0.71 (Hosmer-Lemeshow P=0.40) and 0.74 (P=0.11), respectively. In analyses restricted to women, high educational status (secondary school or higher) was found to be a significant predictor of likelihood of receiving a warfarin prescription (OR, 2.90; P=0.02; Table S1).

Table 2. Anticoagulant-Indicated Population

	Patients With Documented Requirements for Anticoagulation		
	Women, n=129 (22% of Total Cohort), n (%)	Men, n=59 (23% of Total Cohort), n (%)	*P* Value
Atrial fibrillation (% of patients of that sex with oral anticoagulant indication)	82 (63.6)	39 (63.9)	0.96
History of embolic stroke	11 (8.5)	2 (3.3)	0.18
Left atrial thrombosis on echo	1 (0.8)	1 (1.6)	0.59
Deep vein thrombosis /pulmonary embolism	1 (0.8)	0	0.49
Mechanical heart valve	15 (11.6)	11 (18)	0.23
Other	15 (11.6)	5 (8.2)	0.47

Number of patients in the cohort who had indications for guideline-based anticoagulation, subdivided into the specific indication by sex.

RHD Treatment Cascade

All patients in the cohort met criteria for lifelong benzathine penicillin prophylaxis as recommended by current national guidelines for anyone with symptomatic RHD. Women did not differ from men in the likelihood of receiving a prescription for penicillin (OR, 1.44; *P*=0.32; Table 3). Our model was adjusted for age, educational status, employment status, and poor NYHA functional class.

When looking at steps of the treatment cascade by sex, there were no major differences between men and women. Both groups, however, showed the greatest dropout at the retention in care stage (Figure 1), with only 24% to 27% of living patients retained in care following RHD diagnosis. Over 90% of patients who were retained were prescribed penicillin and were adherent to it, respectively. Prescription rates and adherence rates were relatively high for both men and women.

As retention in care was the treatment cascade step with the greatest dropoff, we next explored predictors of retention among women of reproductive age. We found that younger age and closer distance to nearest health center were significantly associated with retention in care (Table 4). Poor NYHA class was also associated with lower likelihood of retention (OR, 0.30; *P*=0.01) Interestingly, patients with an indication for anticoagulation were more likely to be retained in care (OR, 4.30; *P*=0.03). Receiving care in Kampala at the UHI (compared with regional centers) was associated with a decreased likelihood of retention (OR,

0.20; *P*<0.01). The model had a C-statistic of 0.74 and Hosmer-Lemeshow *P*=0.19).

Mortality

Thirty-two percent (n=186) of women in the registry died during the follow-up period (Table S2). Median (interquartile range) follow-up was 2.7 (1.0–4.3) years. Cause of death included a large percentage of unknown cause, sudden death, or death at home (49%). An additional 35% of the cohort had heart failure or cardiogenic shock listed as the cause of death. Interestingly, Kaplan–Meier analysis revealed higher all-cause mortality in men than women in our cohort (log rank test *P*=0.003; Figure 2). In a Cox proportional hazards model adjusted for age (Table 5), educational status, employment status, household crowding, history of valve surgery, and poor NYHA class, male sex was associated with a higher likelihood of death (adjusted hazard ratio, 1.66; *P*<0.01). Harell's C for the model was 0.65.

DISCUSSION

Our present study is among the first to specifically describe both the epidemiologic profile and quality of care for women of childbearing age living with RHD in sub-Saharan Africa. We have shown that rates of appropriate anticoagulation use are low, putting women at increased risk of thromboembolic complications of

Table 3. Prescriptions of Medications by Sex (Among Those With Indication)

Medication	Women, n (%)	Men, n (%)	Odds Ratio (Women Relative to Men)	95% CI	*P* Value
Warfarin	85 (65.9)	48 (81.4)	0.37*	0.14–0.96	0.04
Aspirin	39 (30.2)	11 (18.6)	2.43*	0.93–6.36	0.07
Penicillin	550 (95.7)	237 (94.0)	1.44†	0.71–2.94	0.32

Presented as number and percentage of those who received a prescription for a medication among those with an indication for treatment. Odds ratios have been adjusted for the demographic and clinical covariates.

*Adjusted for age, educational status, poor New York Heart Association functional class.

†Adjusted for age, educational status, employment status, poor New York Heart Association functional class.
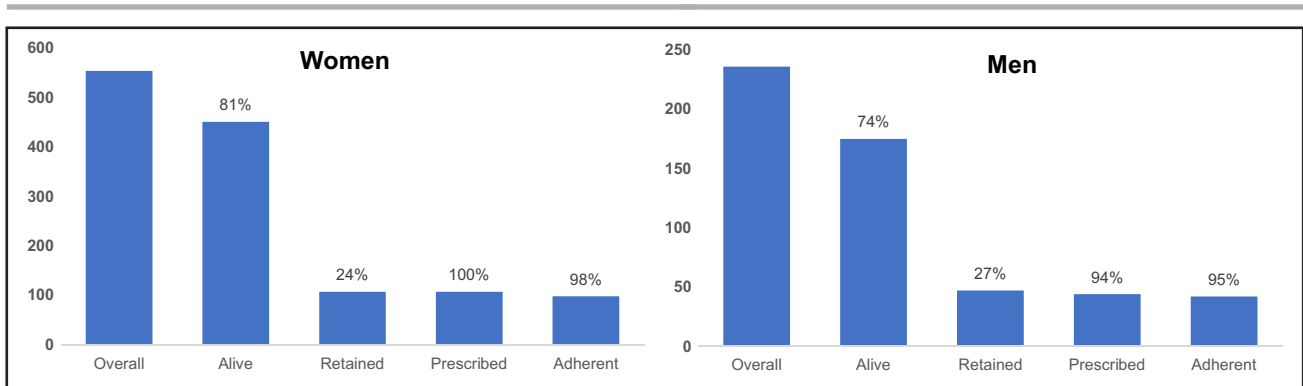
Figure 1. Treatment cascade for women and men with rheumatic heart disease aged 15 to 44.
The vertical axis on the right indicates the number of patients in each outcome category of the cascade. Listed percentage values indicate the percentage of patients as a proportion of the parent (prior) category.

RHD. This may be balanced by other factors, however, such that overall mortality for women of childbearing age with RHD is lower than that for men of the same age range. Further studies should continue to evaluate the burden of poor pregnancy-related outcomes for women with RHD in sub-Saharan Africa and the role that specific medical treatments and engagement in care play in determining these outcomes. In addition, we found that rates of retention in RHD care were low, although levels were similar among women and men.

Similar to other sub-Saharan African cohorts of RHD, our patients come from relatively low socioeconomic status (44% primary or no education, 28% employed), but most live relatively close to a health center (median distance 2 km). For comparison, the 2016 Demographic and Health Survey of Uganda found that 19% of women aged 6 and older in the country have not had formal education, while 73% of women age 15 to 49 were employed.[38] The registry had very high representation from the UHI, since it is known as the national referral center for RHD care. However, after a national effort to decentralize RHD care began in 2013, a greater proportion of patients have been able to receive primary RHD care at a regional center rather than having to travel far

distances to the capital city. Interestingly, we found that subjects with a primary clinic site of the UHI had a lower likelihood of retention to care, suggesting decentralization may improve follow-up. RHD patients in Uganda present clinically with advanced disease. The subjects in our cohort had high rates of heart failure (26%) and decreased functional status (22% were Class III or IV), representing greater disease progression at the examined age than in other high-income nation cohorts.[6]

A high proportion of women in this study had indications for anticoagulation, but rates of warfarin prescription were suboptimal. Female sex was strongly associated with lower odds of warfarin prescription, confirming our qualitative findings in our prior analysis.[26] In that study, subjects described fear of gynecologic complications (particularly a myth of uterine fibroid development from warfarin), stigmatization of chronic medication use, and fear that anticoagulants would harm the fetus as barriers to their use. Low-molecular-weight heparin is an alternative therapy with a lower associated risk of fetal embryopathy, but it is expensive and not readily available in LMICs.[10] The trend toward increased aspirin use in women suggests that women are taking antiplatelet therapy in lieu of anticoagulation; however, aspirin has been shown to be far inferior to

Table 4. Association of Variables with Retention in Care Among Women

	Unadjusted		Multivariable*	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age (per y)	0.97 (0.94–0.99)	0.01	0.96 (0.93–0.99)	0.02
Nearest Health Center (per km)	0.92 (0.86–0.98)	0.02	0.91 (0.84–0.99)	0.03
Clinic Site (UHI)	0.15 (0.08–0.27)	<0.01	0.23 (0.10–0.52)	<0.01
Poor NYHA class (Class III or IV)	0.36 (0.16–0.82)	0.02	0.30 (0.11–0.74)	0.01
Anticoagulation indication	1.64 (0.97–2.75)	0.06	4.30 (1.18–15.48)	0.03

Associations of demographic and clinical variables with retention in care, restricted to women. The results of univariable and multivariable logistic regressions are provided. OR indicates odds ratio; NYHA, New York Heart Association; and UHI, Uganda Heart Institute.
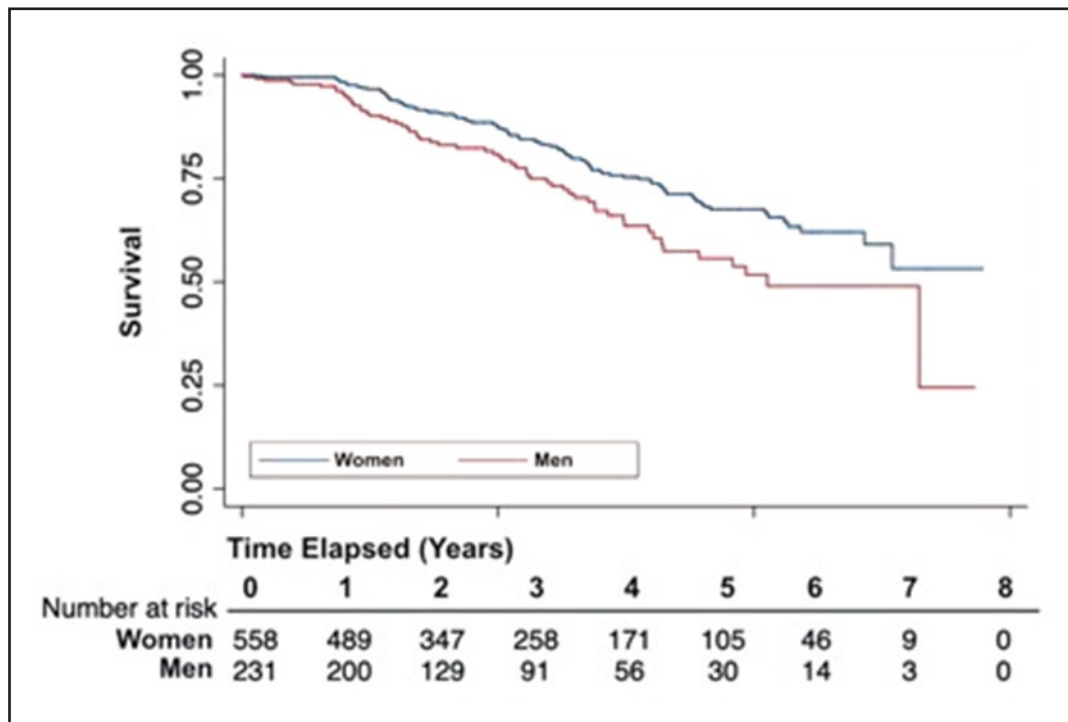*Adjusted for age, clinic site, nearest health center, poor NYHA functional class, and requirement of anticoagulation.

Figure 2. Kaplan–Meier survival estimates by sex.
The vertical axis denotes the proportion of surviving individuals at each time point. Women of the cohort are represented by the blue line, while men are represented by the red line. The horizontal axis represents the number of years of follow-up, with the number of patients at risk of death listed at each time point.

therapeutic anticoagulation for prevention of thromboembolic complications for patients with atrial fibrillation or mechanical heart valves.[39–45] Not surprisingly, we found that low educational status was associated with lower odds of anticoagulant prescription.

In contrast to anticoagulation, we observed no difference between women and men in rates of benzathine penicillin prophylaxis. The lack of treatment disparity for penicillin use could be due to confidentiality

Table 5. Association of Covariates With Mortality

Variable	Hazard Ratio (95% CI)*	P Value
Male sex	1.66 (1.18–2.33)	<0.01
Age (per y)	0.98 (0.96–1.00)	0.08
Low education status	1.35 (0.96–1.89)	0.08
Employment status (employed)	0.53 (0.35–0.82)	<0.01
Household >7 occupants	0.70 (0.49–1.02)	0.06
History of valve surgery	0.39 (0.14–1.07)	0.07
Poor NYHA class (Class III or IV)	1.51 (1.07–2.14)	0.02

Multivariable Cox proportional hazards model incorporating sex, as well as other demographic and clinical characteristics, to identify factors associated with mortality. NYHA indicates New York Heart Association.
*Adjusted for age, educational status, employment status, clinical site, distance from nearest clinic, household crowding, history of valvular surgery, and poor NYHA functional status.

(the penicillin injections are given in clinic, rather than taken as pills at home or in public like warfarin), better understanding of antibiotics in LMIC settings, or low impact of penicillin on fertility/pregnancy.

In combatting cardiovascular diseases in LMICs, policymakers have sought to adapt and leverage existing tools and protocols from HIV care.[46–48] One such instrument is the Treatment Cascade model, which we first described and applied to RHD in Uganda.[36] For our present study, we explored whether the Treatment Cascade differed for women of childbearing age compared with men. Mirroring our prior study, retention in care was the cascade step with greatest dropout, but among those who were engaged in care, prescription and adherence rates were >90%. In fact, retention was worse in our current study, which may be due to exclusion of children with latent RHD who have additional mechanisms in place to ensure retention at regional centers (eg, pediatric support group in Gulu).[49] Concerningly, poor NYHA class was associated with lower likelihood of retention, suggesting that advancing disease and debility may represent barriers to obtaining care. We also expanded our initial study findings to show that patients who have an indication for anticoagulation were more likely to be retained in care, supporting the need for integrated noncommunicable disease clinics where anticoagulation monitoring can

be performed together with other chronic disease management services such as penicillin prophylaxis. Indeed, specialized programs offering decentralized or task-shifted anticoagulation management services at the community level, including those in conjunction with post–heart surgery care, have been piloted or successfully implemented elsewhere in East Africa.[50,51]

Finally, as has been observed previously in Uganda, mortality after initial presentation is high for both men and women of reproductive age.[35] Interestingly, despite lower rates of anticoagulant prescription among women, death rates were higher among men, suggesting that other forces may counter pregnancy and lower rates of anticoagulant use, which may be expected to increase mortality. Indeed, higher mortality rates among men than women have been described for other chronic diseases in LMICs, such as HIV.[52–54] It is reassuring that women of this age range are not dying at higher rates than men; however, at this time, we do not have detailed information on pregnancies during follow-up to assess rates of pregnancy-related complications. This information is being collected for future studies.

We believe that this present research is important because it contributes to a limited existing literature on the epidemiology of women living with RHD in the developing world. Our findings may also apply to premenopausal women with other types of chronic cardiovascular disease, especially those with indications for anticoagulation use. More work must be done through public destigmatization campaigns and patient education to address cardiovascular disease treatment disparities for women living in sub-Saharan Africa.

Limitations

There are several limitations to our present analysis. First, similar to all retrospective analyses of observational data, associations observed in our study cannot be considered causal and may be affected by unmeasured confounding. Second, the Uganda RHD registry has not routinely collected a detailed reproductive health history (eg, current pregnancy status, current number of children, number of pregnancies, type of delivery, warfarin use during pregnancy), which limited our ability to examine the influence of these variables on outcomes and anticoagulation use. Future prospective investigations of this population will include these variables. Third, although we have systems in place to track patients lost to follow-up, it is possible that some patients who are not retained in care have actually died, leading to misclassification and/or ascertainment bias. If that bias differentially affects women compared with men, then this may have affected our Treatment Cascade and survival analyses.

CONCLUSIONS

Ugandan women of childbearing age (15–44 years) with clinical RHD have advanced disease and high mortality. Despite a high prevalence of appropriate indications for anticoagulation, women had lower odds of warfarin prescription compared with men in the same age group. Future studies should further examine pregnancy-related outcomes among women with clinical RHD and should explore how reproductive history affects treatment decisions and care. Interventions that focus on retaining women with RHD in care may improve clinical outcomes and mortality.

REFERENCES

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Lond Engl*. 2017;390:1211–1259.
2. Paar JA, Berrios NM, Rose JD, Cáceres M, Peña R, Pérez W, Chen-Mok M, Jolles E, Dale JB. Prevalence of rheumatic heart disease in children and young adults in Nicaragua. *Am J Cardiol*. 2010;105:1809–1814.
3. Mocumbi AO, Sliwa K. Women's cardiovascular health in Africa. *Heart*. 2012;98:450–455.
4. Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, Dzudie A, Kouam CK, Suliman A, Schrueder N, et al. 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.
5. Zuhlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, Mauff K, Islam S, Joachim A, Daniels R, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J*. 2015;36:1115–1122.

6. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, Forouzanfar MH, Longenecker CT, Mayosi BM, Mensah GA, et al. Global, regional, and national burden of rheumatic heart disease, 1990–2015. *N Engl J Med*. 2017;377:713–722.

7. Kwan GF, Bukhman AK, Miller AC, Ngoga G, Mucumbitsi J, Bavuma C, Dusabeyezu S, Rich ML, Mutabazi F, Mutumbira C, et al. A simplified echocardiographic strategy for heart failure diagnosis and management within an integrated noncommunicable disease clinic at district hospital level for sub-Saharan Africa. *JACC Heart Fail*. 2013;1:230–236.

8. Cole TO, Adeleye JA. Rheumatic heart disease and pregnancy in Nigerian women. *Clin Cardiol*. 1982;5:280–285.

9. Sawhney H, Aggarwal N, Suri V, Vasishta K, Sharma Y, Grover A. Maternal and perinatal outcome in rheumatic heart disease. *Int J Gynecol Obstet*. 2003;80:9–14.

10. Watkins DA, Beaton AZ, Carapetis JR, Karthikeyan G, Mayosi BM, Wyber R, Yacoub MH, Zühlke LJ. Rheumatic heart disease worldwide. *J Am Coll Cardiol*. 2018;72:1397–1416.

11. Manyemba J, Mayosi BM. Penicillin for secondary prevention of rheumatic fever. *Cochrane Database Syst Rev*. 2002;CD002227.

12. Rezk M, Gamal A. Maternal and fetal outcome in women with rheumatic heart disease: a 3-year observational study. *Arch Gynecol Obstet*. 2016;294:273–278.

13. Watkins DA, Sebitloane M, Engel ME, Mayosi BM. The burden of antenatal heart disease in South Africa: a systematic review. *BMC Cardiovasc Disord*. 2012;12:23.

14. French KA, Poppas A. Rheumatic heart disease in pregnancy: global challenges and clear opportunities. *Circulation*. 2018;137:817–819.

15. Hp L, Bhandiwad A, Desai N, Kondareddy T. Maternal outcomes of rheumatic heart disease in pregnancy. *Int J Reprod Contracept Obstet Gynecol*. 2017;6:802.

16. Sartain JB, Anderson NL, Barry JJ, Boyd PT, Howat PW. Rheumatic heart disease in pregnancy: cardiac and obstetric outcomes. *Intern Med J*. 2012;42:978–984.

17. Otto H, Saether SG, Banteyrga L, Haugen BO, Skjaerpe T. High prevalence of subclinical rheumatic heart disease in pregnant women in a developing country: an echocardiographic study: high prevalence of subclinical RHD in pregnant women. *Echocardiography*. 2011;28:1049–1053.

18. Beaton A, Okello E, Scheel A, DeWyer A, Ssembatya R, Baaka O, Namisanvu H, Njeri A, Matovu A, Namagembe I, et al. Impact of heart disease on maternal, fetal and neonatal outcomes in a low-resource setting. *Heart*. 2019;105:755–760.

19. Alshawabkeh L, Economy KE, Valente AM. Anticoagulation during pregnancy. *J Am Coll Cardiol*. 2016;68:1804–1813.

20. Jeng J-S, Tang S-C, Yip P-K. Stroke in women of reproductive age: comparison between stroke related and unrelated to pregnancy. *J Neurol Sci*. 2004;221:25–29.

21. Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier L-A, Morton BC, Kells CM, Bergin ML, Kiess MC, Marcotte F, et al; Cardiac Disease in Pregnancy (CARPREG) Investigators. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation*. 2001;104:515–521.

22. Greutmann M, Pieper PG. Pregnancy in women with congenital heart disease. *Eur Heart J*. 2015;36:2491–2499.

23. Moodley J, Pattinson C, Bennun M, Cronje H, Dichabe M, Kambaran S, Mahlasela L, Makubalo L, Mangate H, Mhlanga R, et al. A review of maternal deaths in South Africa during 1998. National Committee on Confidential Enquiries into Maternal Deaths. *South Afr Med J Suid-Afr Tydskr Vir Geneeskd*. 2000;90:367–373.

24. Ginsberg JS, Greer I, Hirsh J. Use of antithrombotic agents during pregnancy. *CHEST J*. 2001;119:122S–131S.

25. Zühlke L, Karthikeyan G, Engel ME, Rangarajan S, Mackie P, Cupido-Katya Mauff B, Islam S, Daniels R, Francis V, Ogendo S, et al. Clinical outcomes in 3343 children and adults with rheumatic heart disease from 14 low- and middle-income countries: two-year follow-up of the global rheumatic heart disease registry (the REMEDY Study). *Circulation*. 2016;134:1456–1466.

26. Chang AY, Nabbaale J, Nalubwama H, Okello E, Ssinabulya I, Longenecker CT, Webel AR. Motivations of women in Uganda living with rheumatic heart disease: a mixed methods study of experiences in stigma, anticoagulation, and contraception. *PLoS One*. 2018;13:e0194030.

27. Longenecker CT, Kalra A, Okello E, Lwabi P, Omagino JO, Kityo C, Kamya MR, Webel AR, Simon DI, Salata RA, et al. A human-centered approach to CV care: infrastructure development in Uganda. *Glob Heart*. 2018;13:347–354.

28. Hogg RS. Understanding the HIV care continuum. *Lancet HIV*. 2018;5:e269–e270.

29. Medland NA, McMahon JH, Chow EPF, Elliott JH, Hoy JF, Fairley CK. The HIV care cascade: a systematic review of data sources, methodology and comparability. *J Int AIDS Soc*. 2015;18:20634.

30. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2011;52:793–800.

31. Ali MK, Bullard KM, Gregg EW, Del Rio C. A cascade of care for diabetes in the United States: visualizing the gaps. *Ann Intern Med*. 2014;161:681–689.

32. Okello E, Longenecker CT, Scheel A, Aliku T, Rwebembera J, Mirembe G, Sable C, Lwabi P, Beaton A. Impact of regionalisation of a national rheumatic heart disease registry: the Ugandan experience. *Heart Asia*. 2018;10:e010981.

33. Reményi B, Wilson N, Steer A, Ferreira B, Kado J, Kumar K, Lawrenson J, Maguire G, Marijon E, Mirabel M, et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease–an evidence-based guideline. *Nat Rev Cardiol*. 2012;9:297–309.

34. Rutstein SO, Iqbal HS. Infecundity, Infertility, and Childlessness in Developing Countries. DHS Comparative Reports No. 9. Calverton, Maryland, USA: ORC Macro and the World Health Organization. 2004.

35. Okello E, Longenecker CT, Beaton A, Kamya MR, Lwabi P. Rheumatic heart disease in Uganda: predictors of morbidity and mortality one year after presentation. *BMC Cardiovasc Disord*. 2017;17:20.

36. Longenecker CT, Morris SR, Aliku TO, Beaton A, Costa MA, Kamya MR, Kityo C, Lwabi P, Mirembe G, Nampijja D, et al. Rheumatic heart disease treatment cascade in Uganda. *Circ Cardiovasc Qual Outcomes*. 2017;10:e004037. DOI: 10.1161/CIRCOUTCOMES.117.004037.

37. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med*. 2008;3:17.

38. Uganda Bureau of Statistics—UBOS and ICF. Uganda demographic and health survey 2016 [Internet]. 2018. Available at: http://dhsprogram.com/pubs/pdf/FR333/FR333.pdf

39. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857–867.

40. Cooper NJ, Sutton AJ, Lu G, Khunti K. Mixed comparison of stroke prevention treatments in individuals with nonrheumatic atrial fibrillation. *Arch Intern Med*. 2006;166:1269–1275.

41. McNamara RL, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. *Ann Intern Med*. 2003;139:1018–1033.

42. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: stroke prevention in atrial fibrillation II study. *Lancet Lond Engl*. 1994;343:687–691.

43. van Walraven C, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, Koudstaal PJ, Chang Y, Hellemons B. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA*. 2002;288:2441–2448.

44. Carnicelli AP, O'Gara PT, Giugliano RP. Anticoagulation after heart valve replacement or transcatheter valve implantation. *Am J Cardiol*. 2016;118:1419–1426.

45. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation*. 1994;89:635–641.

46. Ojo T, Lester L, Iwelunmor J, Gyamfi J, Obiezu-Umeh C, Onakomaiya D, Aifah A, Nagendra S, Opeyemi J, Oluwasanmi M, et al. Feasibility of integrated, multilevel care for cardiovascular diseases (CVD) and HIV in low- and middle-income countries (LMICs): a scoping review. *PLoS One*. 2019;14:e0212296.

47. Patel P, Sabin K, Godfrey-Faussett P. Approaches to improve the surveillance, monitoring, and management of noncommunicable diseases in HIV-infected persons: viewpoint. *JMIR Public Health Surveill*. 2018;4:e10989.

48. Hyle EP, Mayosi BM, Middelkoop K, Mosepele M, Martey EB, Walensky RP, Bekker L-G, Triant VA. The association between HIV and atherosclerotic cardiovascular disease in sub-Saharan Africa: a systematic review. *BMC Public Health*. 2017;17:954.

49. Scheel A, Beaton A, Okello E, Longenecker CT, Otim IO, Lwabi P, Sable C, Webel AR, Aliku T. The impact of a peer support group for children with rheumatic heart disease in Uganda. *Patient Educ Couns*. 2018;101:119–123.

50. Manji I, Pastakia SD, Do AN, Ouma MN, Schellhase E, Karwa R, Miller ML, Saina C, Akwanalo C. Performance outcomes of a pharmacist-managed anticoagulation clinic in the rural, resource-constrained setting of Eldoret, Kenya. *J Thromb Haemost*. 2011;9:2215–2220.

51. Rusingiza EK, El-Khatib Z, Hedt-Gauthier B, Ngoga G, Dusabeyezu S, Tapela N, Mutumbira C, Mutabazi F, Harelimana E, Mucumbitsi J, et al. Outcomes for patients with rheumatic heart disease after cardiac surgery followed at rural district hospitals in Rwanda. *Heart Br Card Soc*. 2018;104:1707–1713.

52. Garenne M, Lydie N. Gender and AIDS. Paper prepared for the WHO monograph on Gender Analysis of Health [Internet]. 2001. Available at: https://www.who.int/gender/documents/GenderAIDS.pdf

53. Castilho JL, Melekhin VV, Sterling TR. Sex differences in HIV outcomes in the highly active antiretroviral therapy era: a systematic review. *AIDS Res Hum Retroviruses*. 2014;30:446–456.

54. Alibhai A, Kipp W, Saunders LD, Senthilselvan A, Kaler A, Houston S, Konde-Lule J, Okech-Ojony J, Rubaale T. Gender-related mortality for HIV-infected patients on highly active antiretroviral therapy (HAART) in rural Uganda. *Int J Womens Health*. 2010;2:45–52.