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.³,⁸ In sub-Saharan Africa, RHD is estimated to be responsible for up to 32% of heart failure cases.³,⁷ 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 valvule 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.⁶,⁸,¹²⁻¹⁸ Furthermore, the anticoagulant
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 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 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 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 in the model of existing regional centers of excellence for HIV care.27
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 age34 (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

| Demographic 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 (%) | 35 (6.2) | 14 (5.7) | 0.32 |
| None                        | 323 (56.8) | 158 (62.7) |     |
| Primary                     | 213 (37.5) | 92 (37.4) |     |
| Secondary                   | 193 (34.0) | 80 (32.5) |     |
| 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 (%) | 147 (25.8) | 58 (23.1) | 0.27 |
| History of decompensated heart failure, 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)
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 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 | 145 (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.
Chang et al. Outcomes and Quality for Women With RHD in Uganda

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, 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.

Table 2. Anticoagulant-Indicated Population

| Medication                              | Women, n=129 (22% of Total Cohort), n (%) | Men, n=59 (23% of Total Cohort), n (%) | *P* Value |
|-----------------------------------------|-------------------------------------------|----------------------------------------|-----------|
| Atrial fibrillation                     | 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.

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.

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

| Medication | Women, n (%) | Men, n (%) | Odds Ratio (Women Relative to Men) | 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.
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. 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.

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. 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. 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
therapeutic anticoagulation for prevention of thromboembolic complications for patients with atrial fibrillation or mechanical heart valves.\textsuperscript{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 (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 combating cardiovascular diseases in LMICs, policymakers have sought to adapt and leverage existing tools and protocols from HIV care.\textsuperscript{46–48} One such instrument is the Treatment Cascade model, which we first described and applied to RHD in Uganda.\textsuperscript{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).\textsuperscript{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

### 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.

\textsuperscript{*}Adjusted for age, educational status, employment status, clinical site, distance from nearest clinic, household crowding, history of valvular surgery, and poor NYHA functional status.

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**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.
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 factors 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.

**ARTICLE INFORMATION**

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**Disclosures**

None.

**Supplementary Materials**

Tables S1–S2

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