GLOBAL VOICES - SCIENCE

Outcomes and care quality metrics for people living with rheumatic heart disease and atrial fibrillation in Uganda

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BACKGROUND Atrial fibrillation (AF) is a common complication of rheumatic heart disease (RHD) and is challenging to treat in lower-resourced settings in which RHD remains endemic.

OBJECTIVE We characterized demographics, treatment outcomes, and factors leading to care retention for participants with RHD and AF in Uganda.

METHODS We conducted a retrospective analysis of the Uganda national RHD registry between June 2009 and May 2018. Participants with AF or atrial flutter were included. Demographics, survival, and care metrics were compared with participants without AF. Multivariable logistic regression was used to identify factors associated with retention in care among participants with AF.

RESULTS A total of 1530 participants with RHD were analyzed and 293 (19%) had AF. The median age was 24 (interquartile range 14–38) years. Mortality was similar in both groups (adjusted hazard ratio 1.183, $P = .77$) over a median follow-up of 203 (interquartile range 98–275) days. A total of 79% of AF participants were prescribed anticoagulation, and 43% were aware of their target international normalized ratio. Retention in care was higher in participants with AF (18% vs 12%, $P < .01$). Factors associated with decreased retention in care include New York Heart Association functional class III/IV (adjusted odds ratio [OR] 0.48, 95% confidence interval [CI] 0.30–0.76) and distance to nearest health center (adjusted OR 0.94, 95% CI 0.90–0.99). Anticoagulation prescription was associated with enhanced care retention (adjusted OR 1.86, 95% CI 1.24–2.79).

CONCLUSION Participants with RHD and AF in Uganda do not experience higher mortality than those without AF. Anticoagulation prescription rates are high. Although retention in care is poor among RHD participants, those with concurrent AF are more likely to be retained.

KEYWORDS Atrial fibrillation; Rheumatic heart disease; Outcomes; Retention in care; Global health

(Heart Rhythm O^2 2024;5:201–208)

Introduction

Rheumatic heart disease (RHD) is a leading cause of morbidity and mortality in lower-resourced settings and contributes substantially to early mortality in the most disadvantaged populations globally.[1,2] Atrial fibrillation (AF) is the most common arrhythmia in RHD, owing to resultant atrial remodeling and dysfunction, and it affects approximately 1 in 3 patients with RHD.[3,4] AF is associated with major adverse cardiovascular events including stroke and thromboembolic disorders.[5–8] Despite this, patients with RHD have been systematically excluded from AF trials. Current AF guidelines largely pertain to those with nonvalvular AF.[9–11] The Investigation of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies (the INVICTUS trial) remains the only large, randomized trial to inform anticoagulation strategy in those with RHD and AF.[12] Other studies have elucidated potential AF rate and rhythm management strategies specific to those with

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2666-5018/

https://doi.org/10.1016/j.hroo.2024.02.002

KEY FINDINGS

- Our study demonstrates that, in Uganda, people with rheumatic heart disease (RHD) and atrial fibrillation (AF) do not have higher mortality compared with people with RHD who do not have AF.
- People with AF were more likely to be retained in RHD care than were those without AF. Retention in care has been previously shown to be associated with increased survival.
- Among people with AF, being prescribed anticoagulation was strongly associated with enhanced retention in RHD care.

RHD.[13–19] Nonetheless, there remains a paucity of data to guide management of AF in patients with RHD within their respective local contexts. National and regional health metrics are essential in guiding implementation strategies and policy interventions to improve health outcomes.

To address this issue, we aimed to describe the epidemiologic and clinical profile of patients with AF in the Uganda national RHD registry. We further evaluated whether AF affects mortality in this population. Given the significant comorbidities of RHD and AF, understanding retention in clinical care was of importance in this study. The RHD treatment cascade has been previously described and seeks to define outcomes along critical aspects of RHD care.[20–23] This framework is adopted from that used in HIV care.[24] Further, retention in care has been associated with improved survival among those in Uganda living with RHD.[23] As such, we additionally evaluated the effect AF had on retention in care in this cohort.

Methods

Data source

Data from the Uganda National RHD Registry were utilized for this analysis. This registry was established as a centralized database for individuals living in Uganda diagnosed with RHD clinically or by echocardiogram.[25] The registry was initially based at the Uganda Heart Institute, a quasi-independent clinical and research facility affiliated with the Mulago National Referral Hospital in Kampala. The registry has since expanded to include 4 regional referral centers in Lubowa, Mbarara, Gulu, and Lira. All people living with RHD at 1 of the 5 centers participating in the registry are invited to enroll.[21] Informed written consent was obtained from all participants at least 18 years of age, parental consent for all participants under 18 years of age, and assent for participants 8–17 years of age.

The initiative was 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.

Study population

We performed a retrospective cohort analysis which spanned from June 16, 2009, to May 16, 2018. The cutoff of 2018 was used to avoid confounding introduced by enrollment of participants in the INVICTUS trial, a randomized clinical trial that evaluated the usage of rivaroxaban instead of warfarin in the RHD population.[12] Participation in this trial led to substantial changes in AF management (including deviation from usual standards of care central to the study hypothesis) including increased international normalized ratio (INR) monitoring at the Uganda Heart Institute.

We included all participants in the registry who had a diagnosis of clinical RHD (RHD detected by echocardiogram in the presence of symptoms). We excluded those with latent RHD detected through screening because these participants were followed closely in research studies during the time period of our study, and their outcomes do not reflect routine clinical care. The primary predictor variable of interest for our analysis was a diagnosis of AF or flutter at baseline. We defined the presence of AF or atrial flutter as a clinical history in the medical record or de novo detection on intake electrocardiogram. We included a diagnosis of atrial flutter in the analysis because its management is nearly identical to that of AF in Uganda due to lack of a reliable procedural arrhythmia ablation infrastructure.

The research reported in this article adhered to human subjects research guidelines as outlined in the Declaration of Helsinki. The Uganda RHD Registry is reviewed and approved by the Makerere University School of Medicine and the Uganda National Council for Science and Technology. All adult participants provided written informed consent, and written parental consent was obtained for participants <18 years of age.

Covariates

Covariates of interest included self-reported demographics (age, clinic site, highest level of education, employment status, number of household occupants, and distance to nearest health center) and chart medical history (decompensated heart failure, prior stroke or transient ischemic attack, endocarditis, HIV status, valve replacement or repair, hypertension, diabetes, coronary artery disease, and prior significant bleeding). New York Heart Association (NYHA) functional class and medical treatment information (benzathine penicillin G and warfarin prescriptions) were by self-report and chart review. Most participants underwent 2-dimensional echocardiography at the baseline clinic visit. Echocardiographic parameters, abnormalities, and their severity were graded according to the American Society of Echocardiography guidelines.[26]

Mortality was documented during hospital admission when participants died of RHD complications. Nurses also obtained vital status information in person or by phone and regularly contacted participants and/or family when they were lost to follow-up. We also periodically captured data regarding participants' statuses along the RHD treatment cascade, which is a previously defined quality-of-care

Table 1 Baseline demographics and clinical and echocardiographic characteristics

	Atrial fibrillation			No atrial fibrillation		
	Male (n = 77)	Female (n = 216)	Total (n = 293)	Male (n = 380)	Female (n = 854)	Total (n = 1234)
Demographic characteristics						
Age, y	30 (21–41)	44 (29–54)	39 (26–52)	17 (12–28)	23 (13–36)	20 (13–33)
Clinic site						
Uganda Heart Institute	69 (89.6)	185 (85.6)	254 (86.7)	310 (81.6)	725 (84.9)	1035 (83.9)
Mbarara	1 (1.3)	11 (5.1)	12 (4.1)	15 (3.9)	27 (3.2)	42 (3.4)
Lubowa	1 (1.3)	3 (1.4)	4 (1.4)	6 (1.6)	15 (1.8)	21 (1.7)
Gulu	2 (2.6)	9 (4.2)	11 (3.8)	37 (9.7)	61 (7.1)	98 (7.9)
Lira	4 (5.2)	8 (3.7)	12 (4.1)	9 (2.4)	22 (2.6)	31 (2.5)
Highest education level						
None	3 (3.9)	35 (16.2)	38 (13.0)	22 (5.8)	52 (6.1)	74 (6.0)
Primary	35 (45.5)	109 (50.5)	144 (49.1)	178 (46.8)	390 (45.7)	568 (46.0)
Secondary	23 (29.9)	51 (23.6)	74 (25.3)	95 (25.0)	231 (27.0)	326 (26.4)
Trace/vocational	4 (5.2)	1 (0.5)	5 (1.7)	16 (4.2)	28 (3.3)	44 (3.6)
College/university	9 (11.7)	16 (7.4)	25 (8.5)	40 (10.5)	99 (11.6)	139 (11.3)
Not applicable (participant is a child)	2 (2.6)	1 (0.5)	3 (1.0)	23 (6.1)	45 (5.3)	68 (5.5)
Employed	56 (72.7)	178 (82.4)	234 (79.9)	292 (76.8)	658 (77.0)	950 (77.0)
Household occupants	5 (4–8)	5 (4–8)	5 (4–8)	6 (4–8)	6 (4–8)	6 (4–8)
Nearest health center, km	3 (2–6)	3 (2–6)	3 (2–6)	3 (1–5)	2 (1–5)	3 (1–5)
Clinical characteristics						
History of decompensated heart failure	21 (27.3)	80 (37.0)	101 (34.5)	84 (22.1)	197 (23.1)	281 (22.8)
Initial NYHA functional class						
I	15 (19.5)	20 (9.3)	35 (11.9)	66 (17.4)	163 (19.1)	229 (18.6)
II	37 (48.1)	107 (49.5)	144 (49.1)	173 (45.5)	415 (48.6)	588 (47.6)
III	10 (13.0)	42 (19.4)	52 (17.7)	52 (13.7)	120 (14.1)	172 (13.9)
IV	7 (9.1)	21 (9.7)	28 (9.6)	25 (6.6)	41 (4.8)	66 (5.3)
Prior stroke/transient ischemic attack	4 (5.2)	23 (10.6)	27 (9.2)	7 (1.8)	27 (3.2)	34 (2.8)
History of endocarditis	0 (0.0)	3 (1.4)	3 (1.0)	7 (1.8)	8 (0.9)	15 (1.2)
Valve replacement	4 (5.2)	13 (6.0)	17 (5.8)	18 (4.7)	30 (3.5)	48 (3.9)
Valve repair	3 (3.9)	3 (1.4)	6 (2.0)	9 (2.4)	10 (1.2)	19 (1.5)
HIV positive	1 (1.3)	11 (5.1)	12 (4.1)	8 (2.1)	44 (5.2)	52 (4.2)
Hypertension	2 (2.6)	19 (8.8)	21 (7.2)	15 (3.9)	43 (5.0)	58 (4.7)
Diabetes mellitus	0 (0.0)	1 (0.5)	1 (0.3)	2 (0.5)	6 (0.7)	8 (0.6)
Coronary artery disease	0 (0.0)	2 (0.9)	2 (0.7)	2 (0.5)	2 (0.2)	4 (0.3)
History of significant bleeding	3 (3.9)	3 (1.4)	6 (2.0)	0 (0.0)	4 (0.5)	4 (0.3)
Echocardiographic findings						
Left ventricular ejection fraction <55%	28 (0.4)	69 (0.3)	97 (0.3)	84 (0.2)	148 (0.2)	232 (0.2)
Aortic stenosis						
Mild	5 (6.5)	2 (0.9)	7 (2.4)	12 (3.2)	28 (3.3)	40 (3.2)
Moderate	0 (0.0)	2 (0.9)	2 (0.7)	9 (2.4)	13 (1.5)	22 (1.8)
Severe	0 (0.0)	3 (1.4)	3 (1.0)	9 (2.4)	5 (0.6)	14 (1.1)
Aortic regurgitation						
Mild	26 (33.8)	56 (25.9)	82 (28.0)	83 (21.8)	221 (25.9)	304 (24.6)
Moderate	11 (14.3)	15 (6.9)	26 (8.9)	51 (13.4)	115 (13.5)	166 (13.5)
Severe	5 (6.5)	7 (3.2)	12 (4.1)	51 (13.4)	66 (7.7)	117 (9.5)
Mitral stenosis						
Mild	9 (11.7)	18 (8.3)	27 (9.2)	23 (6.1)	60 (7.0)	83 (6.7)
Moderate	9 (11.7)	43 (19.9)	52 (17.7)	17 (4.5)	87 (10.2)	104 (8.4)
Severe	26 (33.8)	60 (27.8)	86 (29.4)	47 (12.4)	119 (13.9)	166 (13.5)
Mitral regurgitation						
Mild	11 (14.3)	36 (16.7)	47 (16.0)	83 (21.8)	159 (18.6)	242 (19.6)
Moderate	21 (27.3)	48 (22.2)	69 (23.5)	73 (19.2)	160 (18.7)	233 (18.9)
Severe	31 (40.3)	95 (44.0)	126 (43.0)	150 (39.5)	387 (45.3)	537 (43.5)
Tricuspid regurgitation						
Mild	34 (44.2)	61 (28.2)	95 (32.4)	120 (31.6)	250 (29.3)	370 (30.0)
Moderate	9 (11.7)	49 (22.7)	58 (19.8)	47 (12.4)	138 (16.2)	185 (15.0)
Severe	16 (20.8)	53 (24.5)	69 (23.5)	32 (8.4)	103 (12.1)	135 (10.9)

(*Continued*)

Table 1 (*Continued*)

	Atrial fibrillation			No atrial fibrillation		
	Male (n = 77)	Female (n = 216)	Total (n = 293)	Male (n = 380)	Female (n = 854)	Total (n = 1234)
Mixed moderate-to-severe valvular disease						
Mitral stenosis and mitral regurgitation	27 (35.1)	60 (27.8)	87 (29.7)	90 (23.7)	209 (24.5)	299 (24.2)
Mitral stenosis and aortic stenosis	11 (14.3)	21 (9.7)	32 (10.9)	31 (8.2)	79 (9.3)	110 (8.9)
Mitral stenosis and aortic regurgitation	22 (28.6)	43 (19.9)	65 (22.2)	72 (18.9)	190 (22.2)	262 (21.2)
Mitral regurgitation and aortic stenosis	13 (16.9)	39 (18.1)	52 (17.7)	93 (24.5)	178 (20.8)	271 (22.0)
Mitral regurgitation and aortic regurgitation	26 (33.8)	56 (25.9)	82 (28.0)	136 (35.8)	297 (34.8)	433 (35.1)
Aortic stenosis and aortic regurgitation	15 (19.5)	16 (7.4)	31 (10.6)	60 (15.8)	133 (15.6)	193 (15.6)

Values are median (interquartile range) or n (%).
NYHA = New York Heart Association.

metric.[20] The progression of the cascade is as follows: (1) alive (no documentation of mortality), (2) retained in care (participant seen in clinic within 365 days of their immediately previous clinic visit), (3) prescribed penicillin prophylaxis, and (4) adherent to at least 80% of their prescribed penicillin doses. RHD participants in the registry carry physical treatment log cards, which document dates and nurse signature for all benzathine penicillin G injections.

Statistical analysis

Baseline characteristics were described utilizing counts, medians, and interquartile ranges for continuous variables. Categorical variables were reported as frequencies and percentages. The chi-square test was used to compare rates of anticoagulation prescription between men and women with AF. Time to death was described by AF status using Kaplan-Meier curves. Differences between curves were described using the log-rank test. Hazard ratios (HRs) for mortality (with 95% confidence intervals [CIs]) were estimated using multivariable Cox proportional hazards models. The variables (AF, participant age, number of household occupants, history of valve surgery, NYHA functional class III or IV, distance to nearest health center) were chosen a priori given their biologic plausibility in the natural history of RHD and AF. Univariate and multivariable logistic regressions were used to assess whether prespecified variables (age, sex, nearest health center, prescribed anticoagulation, NYHA functional class III or IV) were associated with retention in care. Statistical analyses were conducted using Stata version 14.2 (StataCorp). A P value of $<.05$ was considered statistically significant.

Results

Baseline characteristics

Table 1 outlines the baseline clinical characteristics of participants who met our inclusion criteria at the time of their enrollment into the registry. There were 1530 total participants included in the analysis. A total of 293 participants were in the AF category vs 1234 who were not. Of those in the AF category, 259 (88%) had AF, while 34 (12%) had atrial flutter. Among those in the AF group, the diagnosis was made by electrocardiogram alone in 194, by history alone in 5, and by combination of electrocardiogram and history in 94. The mean ventricular rate of the AF group was 100 ± 28 beats/min, compared with 91 ± 40 beats/min in the non-AF group. The median age of AF participants was 39 compared with 20 for those without AF. More than 8 in 10 (84%) participants received RHD care at the Uganda Heart Institute and lived within a median of 3 km from a health center. The highest level of education for almost half of all participants (47%) was primary school and most participants reported being employed (78%). The median household size was 6 occupants.

Clinical profile and comorbidities

Additionally, Table 1 compares prevalent clinical characteristics among participants at the time of registry enrollment. At time of initial enrollment into the cohort, 27% of participants with AF had advanced NYHA functional class III or IV functional class and 9.2% reported a history of stroke. This is compared with 19% NYHA functional class III or IV prevalence and 2.8% prevalent stroke for those without AF. A total of 4.2% of all participants had HIV. Traditional atherosclerotic cardiovascular disease risk factors were uncommon, as only 5.2% had hypertension and <1.0% had diabetes.

Echocardiographic features

Less than 1% of participants had left ventricular ejection fraction <55%. Severe mitral stenosis and severe tricuspid regurgitation were present in 29% and 24% of those with AF, respectively. This compares with 14% with severe mitral stenosis and 11% with severe tricuspid regurgitation in those without AF. A total of 43% of participants with AF had severe mitral regurgitation, compared with 44% in those without AF. About 30% of participants with AF had mixed moderate-to-

Table 2 Anticoagulation prescription prevalence among cohort participants with atrial fibrillation

	Men	Women	*P* value	Total
Prescribed anticoagulation	61 (79.2)	171 (79.2)	.992	232 (79.2)
Prescribed aspirin without anticoagulation	13 (16.9)	46 (21.3)	.407	59 (20.1)
Prescribed anticoagulation with aspirin	0 (0.0)	0 (0.0)	N/A	0 (0.0)
Aware of target INR	34 (44.2)	90 (41.7)	.069	124 (42.3)

Values are n (%).
INR = international normalized ratio; N/A = not applicable

severe mitral stenosis and mitral regurgitation, compared to 24% in those without AF.

Anticoagulation therapy

Four (79%) of 5 participants with AF reported being prescribed anticoagulation (warfarin), while 20% reported being prescribed aspirin alone, as shown in Table 2. The mean dose of warfarin was 4.8 ± 0.6 mg. Less than half of participants with AF (42%) were aware of their INR targets. Among men and women with AF, there was no difference in reported aspirin or anticoagulation prescription rates. There was also no difference in awareness of INR targets between men and women with AF.

Mortality

The median follow-up period of the study was 203 (interquartile range 98–275) days. A total of 40 participants died during the study time frame. The cause of death could not be routinely ascertained due to paucity of death certificate data. Kaplan-Meier analysis did not demonstrate a difference in mortality among participants with AF and participants without AF ($P = .55$) (Figure 1). After adjusting for participant, age, number of household occupants, history of valve surgery, severity of heart failure, and distance of place of residence from a health center, AF was not associated with excess early mortality by the Cox proportional hazards model (adjusted HR 1.18, 95% CI 0.39–3.59) (Table 3). Male sex was associated with reduced mortality among those living with RHD and AF (adjusted HR 0.28, 95% CI 0.11–0.71).

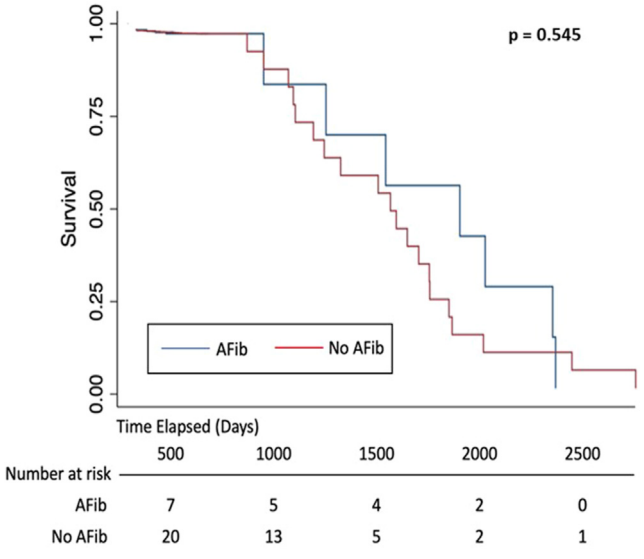

Figure 1 Kaplan-Meier survival curve among participants with and without atrial fibrillation (AFib).

RHD treatment cascade

Figure 2 highlights features of the RHD treatment cascade among those with and without AF. The cohort demonstrated overall low retention in care, with only 13% reporting being seen in clinic within the last year. However, once retained in care, the drop-off in the cascade appeared to be less severe, with 77% of the retained group reporting adherence to penicillin therapy. Compared with those without AF, those with AF were statistically more likely to be retained in care (18% vs 12%, $P = .005$) and prescribed penicillin (15% vs 11%, $P = .029$). Among those with AF receiving anticoagulation, there was a trend toward higher retention in care, and penicillin prescription and adherence (19%, 17%, and 15%, respectively), compared with those with AF not receiving anticoagulation (13%, 10%, and 8.2%, respectively).

Univariable and multivariable logistic regression was used to evaluate factors associated with retention in care among participants with AF (Table 4). Following adjustment, poor NYHA functional class (III or IV) (adjusted odds ratio [OR] 0.46, 95% CI 0.22–0.99), greater distance to a health center (adjusted OR 0.91, 95% CI 0.83–0.99), and male sex (adjusted OR 0.54, 95% CI 0.34–0.84) were associated with reduced retention in care. Being prescribed anticoagulation was the only variable associated with enhanced retention in care (adjusted OR 1.86, 95% CI 1.24–2.80).

Table 3 Multivariable Cox proportional hazards of overall early mortality

Variable	HR	95% CI	*P* value
Atrial fibrillation	1.183	(0.389–3.594)	.767
Male participant	0.280	(0.111–0.707)	.007
Age (per year)	1.013	(0.984–1.044)	.382
Household >7 occupants	1.474	(0.583–3.724)	.412
History of valve surgery	0.210	(0.022–1.997)	.174
Poor NYHA functional class (III or IV)	0.964	(0.396–2.352)	.937
Nearest health center (per km)	1.004	(0.960–1.051)	.849

CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association.

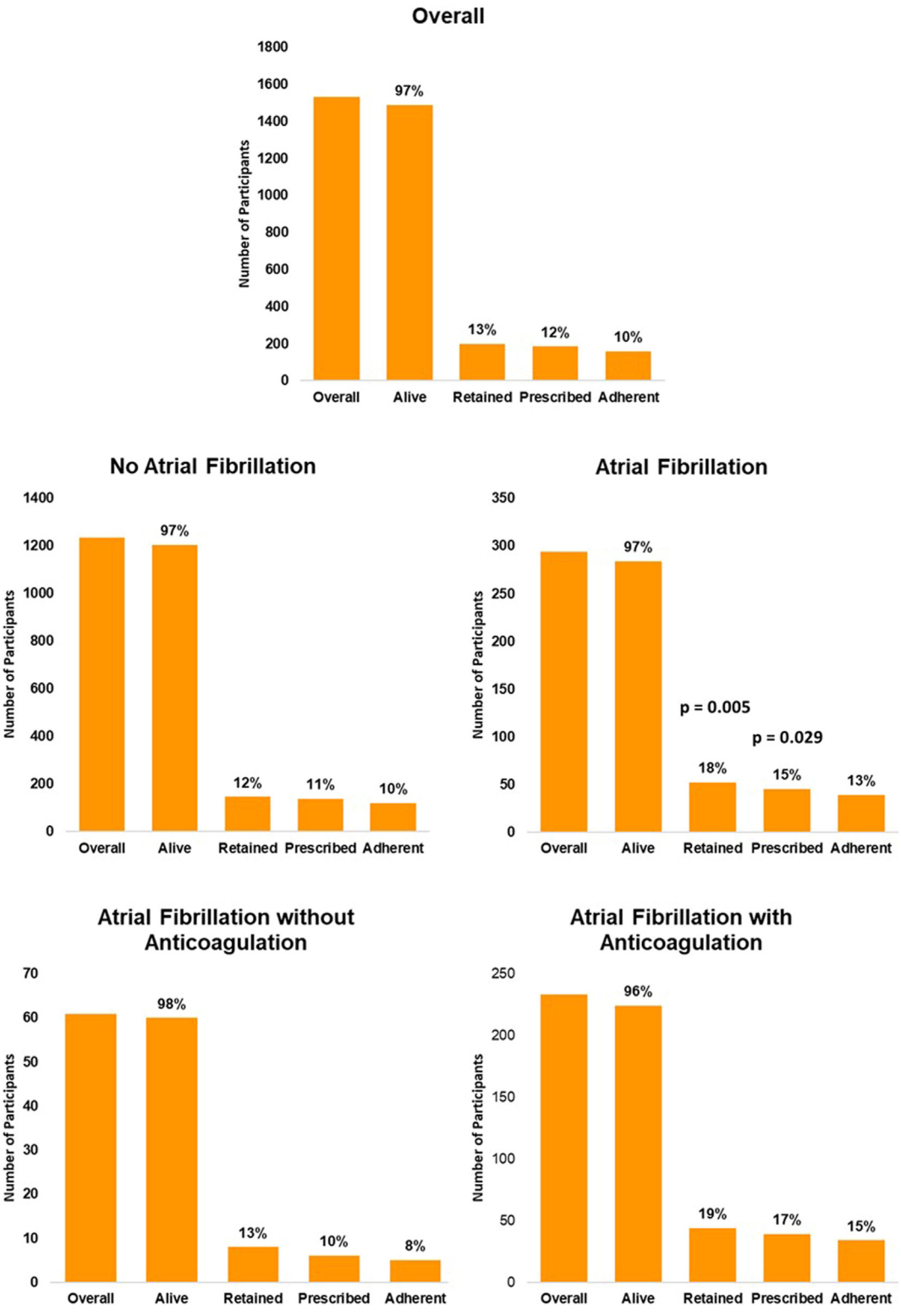

Figure 2 Rheumatic heart disease (RHD) treatment cascade among cohort participants.

Discussion

Our study is among the first to evaluate epidemiologic and clinical factors associated with RHD and AF in the sub-Saharan African context. Most participants with RHD and AF were young women with primary- or secondary-level education who lived within 3 km from a health center. Overall, many participants had significant valvular disease: 27% had moderate-to-severe mitral stenosis, 63% had moderate-to-severe mitral regurgitation, 29% had moderate-to-severe tricuspid regurgitation, and 25% had

Table 4 Logistic regression of participant characteristics vs retention in care

	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.011 (0.993–1.029)	.237	1.001 (0.989–1.012)	.932
Male	0.915 (0.477–1.755)	.789	0.536 (0.343–0.838)	.006
Nearest health center (per km)	0.912 (0.833–0.998)	.045	0.943 (0.897–0.992)	.022
Prescribed anticoagulation	1.701 (0.786–3.678)	.177	1.858 (1.236–2.792)	.003
Poor NYHA functional class (III or IV)	0.458 (0.210–0.999)	.050	0.484 (0.302–0.775)	.003

CI = confidence interval; NYHA = New York Heart Association; OR = odds ratio.

mixed moderate-to-severe mitral stenosis and mitral regurgitation. Accordingly, more than 4 in 5 of all participants had at least NYHA functional class II heart failure symptoms and with minimal traditional cardiovascular risk factors, such as hypertension or diabetes.

Among those with AF, anticoagulation prescription rates were high but not fully optimized, as only 79% were prescribed anticoagulation. Most of the remainder of participants were prescribed aspirin, which has been shown to be a suboptimal stroke prevention strategy for nonvalvular AF.[27] We did not find a significant difference in anticoagulation prescription rates between men and women in this cohort. This contrasts with prior work from our group, in which women of childbearing age (15–44 years) with any indication for anticoagulation (eg, venous thromboembolism, AF, or history of valve replacement) were found to have 63% lower anticoagulation prescription rates compared with their male peers.[22] The discrepancy between studies may be driven by differences in indications for anticoagulation or differences in age-related inclusion criteria. In our current study, among those prescribed anticoagulation, less than half were aware of their INR targets. These data suggest room for education of both participants and their prescribers as it relates to stroke prevention in RHD-associated AF.

Consistent with our previous studies of cascade-of-care metrics, overall retention in RHD care is quite low within our cohort, with only 13% retained in care.[22,24] However, once retained, the drop-off along the cascade appears less dramatic. Those with AF were significantly more likely to be retained in care and prescribed penicillin. Being prescribed anticoagulation demonstrated a very strong association with being retained in care. This is cause for optimism, as participants requiring anticoagulation are a particularly high-risk group of RHD patients. Our findings thus also strongly support the need for integrated specialty care centers of excellence in the East African context.

Factors associated with lower retention in care were male sex, having NYHA functional class III or IV heart failure, and greater residential distance from a health center. Costs from the household perspective can play a significant role in health outcomes, particularly in nations with limited public health infrastructure.[28] We have shown that participants in the Uganda RHD registry incur significant amounts of direct medical and direct nonmedical household costs as a result of the high price of medications and transportation to RHD health facilities.[29] These data suggest a need for improved implementation strategies and policy interventions to enhance retention in care for this population. Such interventions include further decentralization of the Ugandan RHD treatment paradigm to include health centers more proximal to participants. Another possible intervention is universal health coverage reform with mechanisms to reduce or eliminate out-of-pocket household expenditure related to RHD.

Within the median study follow-up period of 203 days, there were 43 deaths, representing 2.8% of the cohort. The death rate found in our study compares with a 2-year 16.9% death incidence in a follow-up of The Global Rheumatic Heart Disease Registry (the REMEDY study).[30] Factors that inform lower death rates seen in our study include the short median follow-up period and the possibility that those who died at home may not have been fully accounted for.

We did not find an association with AF and early excess mortality. It is possible that enhanced retainment in care among those with AF may have been protective against any possible AF-associated early excess mortality. We did find that male sex was protective against mortality, although being male was associated with lower retention in care. Future studies will require longer follow-up periods to further diagnose the effect of AF on RHD within the Ugandan context.

Limitations

Our analysis of this cohort contains several important limitations. First, this was a retrospective observational design using registry data. The associations found cannot be construed as causal, and there may be further unmeasured confounding variables. Second, there is referral bias, as those in the RHD registry may be uniquely different than those who do not have the means to come to 1 of 5 regional RHD health centers. Another limitation is the relatively short-term median follow-up of 6–7 months. Further, we did not measure incident stroke in our study. Although enrolled in a registry, acquiring data on incident stroke proved challenging. Those who died at home unknowingly may have had incident stroke that was not accounted for. Even when a death certificate was available, the cause of death was not always clearly discerned. Among those who present to a hospital who may have a stroke, there may be barriers to a stroke diagnosis, including poor access to imaging modalities, such as head computed tomography and magnetic resonance imaging. Finally, our study included fewer men, which is typical of RHD epidemiology, but it limits our power to explore sex

disparities in care and outcomes. As the registry grows, it may warrant repeat of this analysis in a larger cohort with more men and longer median follow-up time.

Conclusion

Participants in the Uganda RHD registry with AF have significant symptomatic heart failure with suboptimal anticoagulation prescription rates; however, they do not appear to experience higher rates of mortality compared with those without AF. Those with AF (particularly participants who are prescribed anticoagulation) are more likely to be retained in RHD care than participants who do not have AF. This finding may, in part, explain the lack of mortality differential. Future implementation and health policy research should explore methods to enhance retention in care in this vulnerable population.

Funding Sources: The Uganda RHD Registry was established with funding from the Medtronic Foundation.

Disclosures: The authors have no conflicts to disclose.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: Informed written consent was obtained from all participants at least 18 years of age, parental consent for all participants under 18 years of age, and assent for participants 8–17 years of age.

Ethics Statement: The initiative was 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. The research reported in this article adhered to human subjects research guidelines as outlined in the Declaration of Helsinki.

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