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)

BACKGROUND: There are few contemporary data on the mortality and morbidity associated with rheumatic heart disease or information on their predictors. We report the 2-year follow-up of individuals with rheumatic heart disease from 14 low- and middle-income countries in Africa and Asia.

METHODS: Between January 2010 and November 2012, we enrolled 3343 patients from 25 centers in 14 countries and followed them for 2 years to assess mortality, congestive heart failure, stroke or transient ischemic attack, recurrent acute rheumatic fever, and infective endocarditis.

RESULTS: Vital status at 24 months was known for 2960 (88.5%) patients. Two-thirds were female. Although patients were young (median age, 28 years; interquartile range, 18–40), the 2-year case fatality rate was high (500 deaths, 16.9%). Mortality rate was 116.3/1000 patient-years in the first year and 65.4/1000 patient-years in the second year. Median age at death was 28.7 years. Independent predictors of death were severe valve disease (hazard ratio [HR], 2.36; 95% confidence interval [CI], 1.80–3.11), congestive heart failure (HR, 2.16; 95% CI, 1.70–2.72), New York Heart Association functional class III/IV (HR, 1.67; 95% CI, 1.32–2.10), atrial fibrillation (HR, 1.40; 95% CI, 1.10–1.78), and older age (HR, 1.02; 95% CI, 1.01–1.02 per year increase) at enrollment. Postprimary education (HR, 0.67; 95% CI, 0.54–0.85) and female sex (HR, 0.65; 95% CI, 0.52–0.80) were associated with lower risk of death. Two hundred and four (6.9%) patients had new congestive heart failure (incidence, 38.42/1000 patient-years), 46 (1.6%) had a stroke or transient ischemic attack (8.45/1000 patient-years), 19 (0.6%) had recurrent acute rheumatic fever (3.49/1000 patient-years), and 20 (0.7%) had infective endocarditis (3.65/1000 patient-years). Previous stroke and older age were independent predictors of stroke/transient ischemic attack or systemic embolism. Patients from low- and lower-middle–income countries had significantly higher age- and sex-adjusted mortality than patients from upper-middle–income countries. Valve surgery was significantly more common in upper-middle–income than in lower-middle– or low-income countries.

CONCLUSIONS: Patients with clinical rheumatic heart disease have high mortality and morbidity despite being young; those from low- and lower-middle–income countries had a poorer prognosis associated with advanced disease and low education. Programs focused on early detection and the treatment of clinical rheumatic heart disease are required to improve outcomes.

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Sources of Funding, see page 1463

Key Words: developing countries ■ heart valves ■ morbidity ■ mortality ■ patient outcome assessment ■ rheumatic heart disease

Clinical Perspective

What Is New?

- To our knowledge, this is the first prospective multicenter study of mortality and morbidity in rheumatic heart disease (RHD) patients from low- and middle-income countries.
- Clinical RHD was associated with high mortality at a median age of 28.7 years. Complications such as congestive heart failure and stroke affect one-fifth of patients over 2 years.
- Mortality was higher in low-income and low-middle–income in comparison with upper-middle–income countries. Apart from age and sex, the independent risk factors for mortality (ie, severe valve disease, congestive heart failure, dyspnea, atrial fibrillation, and low education) were modifiable.

What Are the Clinical Implications?

- Clinical guidelines recommend the use of percutaneous or surgical valve interventions for RHD with congestive heart failure; however, these interventions are not available to the majority of affected patients.
- Strategies to make proven percutaneous and surgical valve interventions more accessible are needed to improve the outcome of patients with RHD living in low- and middle-income countries.
- Patients with RHD seeking tertiary care present with advanced disease, and the markers of severity are the greatest determinants of poor outcome.
- Additional research to identify symptomatic patients with early RHD in the whole population (in addition to screening studies of asymptomatic schoolchildren) is required in this field.

Rheumatic heart disease (RHD) is a major public health problem in low- and middle-income countries (LMICs).[1] According to the most recent estimates, there are nearly 33 million people with RHD globally, contributing to ≈275 000 deaths every year.[2] However, there are sparse data on RHD demographics, morbidity and mortality, and information on factors that affect outcomes from the countries most affected by the disease.[3] In most high-income countries, RHD ceased to be a public health problem several decades ago. Prospective studies describing outcomes and progression of RHD from these countries are >50 years old. Therefore, the results from high-income countries may not be applicable to patients in LMICs.[4,5] Most previous studies were performed before the availability of echocardiography, penicillin prophylaxis, drugs for heart failure, or surgical and percutaneous valve interventions became part of standard care. Therefore, the findings of previous studies may not be applicable to contemporary patient populations. Furthermore, much of the currently available prospective data are from small pockets of highly susceptible indigenous groups in New Zealand and Australia,[6–8] among whom the incidence of acute rheumatic fever (ARF) and RHD-related morbidity and mortality are unusually high.[7] Therefore, these data have limited generalizability.

Contemporary data on penicillin prophylaxis, anticoagulants, recurrent ARF, morbidity and mortality, and their determinants among RHD patients are needed to inform patient management, develop healthcare policy, and guide resource allocation for control of RHD in LMICs. Suboptimal use of inexpensive interventions such as secondary penicillin prophylaxis and oral anticoagulation is well recognized,[9,10] and contemporary data are needed to document the impact of their underuse on important clinical outcomes. In addition, there is limited information on the determinants of disease progression and clinical outcomes in contemporary patients with RHD living in LMICs.[7] The REMEDY study (Global Rheumatic Heart Disease Registry) was designed to help fill this knowledge gap.[3] We have previously reported the baseline characteristics of the 3343 patients recruited from 14 LMICs in REMEDY.[9] This report describes the major clinical outcomes at 2 years of follow-up among these patients.

METHODS

Study Design and Setting

The design of the REMEDY study has been published previously.[3] In brief, REMEDY is a prospective, multicenter, international, hospital-based registry of patients with symptomatic RHD. We enrolled patients with a clinical and echocardiographic diagnosis of RHD, who were seen in outpatient clinics, emergency departments, or inpatient facilities of 25 participating hospitals in 14 countries (12 African countries, Yemen, and India).[11] We did not include asymptomatic patients in whom RHD was detected solely by clinical or echocardiographic screening. The study was approved by the institutional review board at each site, and the subjects gave informed consent.

Follow-Up and Outcomes

Clinical, demographic, and echocardiographic data were collected at baseline, and patients were followed up annually for 2 years. At each visit, patients were assessed for the occurrence of adverse outcomes, use of secondary antibiotic prophylaxis and oral anticoagulation medication, and need for valve intervention or surgery. The principal outcomes of interest were death, congestive heart failure (CHF), stroke or transient ischemic attack (TIA), recurrence of acute rheumatic fever (ARF), and infective endocarditis (IE). Other outcomes that were monitored included non–central nervous system systemic embolism, major bleeding, atrial fibrillation or flutter (AF), prosthetic heart valve thrombosis, and use of percutaneous or surgical valve procedures.

CHF was diagnosed if any 2 of the following 3 criteria were present: (1) symptoms (dyspnea on exertion or at rest, orthopnea, nocturnal paroxysmal dyspnea, or ankle edema) or signs (rales, increased jugular venous pressure, or ankle edema) of

CHF; (2) radiological signs of pulmonary congestion; and (3) treatment with diuretics. Stroke was diagnosed on the basis of physician-confirmed sudden onset of neurological deficit consistent with ischemia/infarction of a vascular territory, lasting ≥24 hours, with or without neuroimaging evidence. A similar deficit lasting <24 hours was recorded as a TIA. A systemic embolic episode was diagnosed clinically in a patient with loss of arterial pulse and evidence of end-organ ischemia (eg, ischemic limb pain or gangrene). We used the World Health Organization criteria for diagnosing recurrence of ARF[11] and the modified Duke criteria for diagnosing IE during follow-up.[12] We determined the severity of valve lesions based on American College of Cardiology/American Heart Association recommendations.[13] The definitions of all outcome measures have been reported previously.[3]

Statistical Analysis

Continuous variables were expressed as means with standard deviations or as medians with interquartile ranges as appropriate, and categorical variables as frequencies and percentages. Comparisons between categorical variables were assessed for statistical significance using the χ^2 test and the Fisher exact test where cells had a value of <5; the unpaired *t* test was used to determine group differences for continuous variables. Linear regression was used to explore relationships between variables. Test results were adjusted by age and by specifying study centers as clusters.[9]

We anticipated that mortality among patients with RHD would be ≈3.3% per year based on a community-based study in India.[14] We expected that with 3000 patients followed up for 2 years, we would be able to determine the rates of the principal outcomes of interest (ie, death, CHF, and stroke) individually, with 95% confidence and a precision of ±1%.

The incidence rates of the principal outcomes were calculated as number of events per 1000 patient-years of follow-up, and countries were stratified by the 2011 World Bank country income groups (low income, lower-middle income, and upper-middle income groups).[15] We used the Stata stptime command to calculate incidence rates, which allowed for variable follow-up time for each patient and provided the 95% confidence intervals for the estimate. The Stata sts list command was used to determine the risks of the adverse events at interval time points. For mortality, CHF, stroke, and thromboembolism, we computed Kaplan-Meier survival probabilities and determined predictors of death, CHF, and a composite outcome of death or CHF by using a Cox multivariable regression model. Comparisons between unadjusted events and baseline variables were cross-tabulated and assessed for statistical significance by using the χ^2 test, unpaired *t* test, or univariate linear regression.

The variables included in the multivariable model were decided a priori based on prior information relating them to prognosis. They were: age, sex, the presence of AF, New York Heart Association functional class, CHF at enrollment, previous heart valve surgery or intervention, a history of stroke or IE, severe disease (severe valve disease of at least 1 affected valve), multivalve involvement, and use of secondary penicillin prophylaxis. We also determined the association of nonadherence with secondary prophylaxis with the occurrence of episodes of ARF, CHF, and death.

Among patients with an accepted indication for oral anticoagulation, we determined the association of adherence to vitamin K antagonists (VKAs) with the occurrence of stroke/TIA or other systemic embolism, and death. We computed hazard ratios (HRs) and their 95% confidence intervals (CIs). A *P* value of ≤0.05 was considered statistically significant. All analyses were performed using Stata version 14 (StataCorp LP).

RESULTS

Between January 2010 and November 2012, 3343 patients were enrolled at 25 participating sites. One-third of the patients were from low-income countries, 41% were from LMICs, and one-quarter were from upper-middle–income countries. The baseline characteristics of enrolled patients are summarized in Table 1.[9] In brief, patients were relatively young (median age, 28 years) and predominantly female (66.2%). Over one-quarter of patients were <18 years of age (921 patients, 27.9%). Mixed mitral and aortic valve disease was the most common pattern of valve involvement, with the exception of children <10 years of age, in whom isolated mitral regurgitation was the predominant lesion. One-fifth of the patients were in AF. A substantial proportion had clinical signs of CHF (13.2%) or poor functional class (New York Heart Association class III/IV) at presentation (24.2%), particularly in low-income countires and LMICs. The use of secondary penicillin prophylaxis was suboptimal and oral anticoagulation was low.[9]

Vital status at 24 months was known for 2960 (88.5%) patients. At 2 years, 55% of patients completed a follow-up visit, 20% were interviewed by telephone, and, in the remaining, follow-up information was obtained through relatives or the patient's physician. Patients were followed up for a median of 24 months (interquartile range, 22.9–26.6).

Mortality

Five hundred patients (16.9%) died (Table 2, Figure 1). The median age at the time of death was 28.7 (interquartile range, 17.4–46.6) years. The majority of deaths (n=323, 64.6%) occurred within 12 months of enrollment. The mortality rate was 116.3/1000 patient-years in the first year and 65.4/1000 patient-years in the second year. There were 7 risk factors at enrollment that were independently associated with mortality (Table 3). Severe valve disease (HR, 2.36; 95% CI, 1.80–3.11), CHF (HR, 2.16; 95% CI, 1.70–2.72), AF (HR, 1.40; 95% CI, 1.10–1.78), and poor New York Heart Association functional class (ie, III or IV) (HR, 1.67; 95% CI, 1.32–2.10) were the strongest independent predictors of mortality. There was also a significant increase in mortality with increasing age, with adults having a 50% higher risk of death than those <18 years of age (HR, 1.50; 95% CI, 1.11–1.95). Education beyond primary school was as-

Table 1. Baseline Characteristics of the 3343 Children and Adults With Rheumatic Heart Disease, by Country Income Group

	Low-Income Countries (n=1110)	Lower-Middle-Income Countries (n=1370)	Upper-Middle-Income Countries (n=863)	*P* Value
Age, median (IQR), y	24 (15–34)	28 (18–38)	39 (22–52)	0.51
Women, n (%)*	728 (65. 8)	867 (63.0)	616 (71.3)	0.33
Schooling below or at primary school, n (%)†	312 (44.7)	632 (62.3)	242 (35)	0.23
Atrial fibrillation, n (%)‡	163 (18.2)	241 (22.6)	182 (27.5)	<0.0001
Severe disease, n (%)§	682 (61.4)	684 (49.9)	343 (39.8)	<0.001
Multivalve disease, n (%)	719 (64.8)	825 (60.2)	470 (54.7)	<0.001
Congestive heart failure at enrollment, n (%)‖	173 (15.9)	165 (12.2)	102 (11.9)	0.010
New York Heart Association functional class III/IV, n (%)#	306 (27.6)	384 (29.1)	119 (13.9)	0.24
Prior infective endocarditis, n (%)**	25 (2.3)	59 (4.4)	49 (5.7)	<0.001
Prior stroke or systemic embolism, n (%)††	58 (5.2)	52 (3.8)	125 (14.5)	<0.001
Secondary prophylaxis, n (%)‡‡	716 (69.8)	794 (59.7)	251 (29.3)	<0.001

IQR indicates interquartile range.
§Severe disease includes all patients with severe disease involving at least 1 valve.
Baseline data were available for *3340, †3317, ‡2624, ‖3320, #3287, **3320, ††3325, and ‡‡3213 participants.

sociated with a 33% lower risk of death (HR, 0.67; 95% CI, 0.54–0.85). Mortality was also lower among female patients (HR, 0.65; 95% CI, 0.52–0.80).

CHF and Valve Procedures

One-third of the patients (1110, 33.4%) had a history of CHF at the time of enrollment. New CHF occurred in 204 patients (6.9%) over the follow-up period (38.42/1000 patient-years; Table 4). Most of the variables that were associated with death were also independently associated with the occurrence of CHF or the composite of death or CHF (online-only Data Supplement Table I). Secondary prophylaxis and education were significantly protective for the combined outcome of death or CHF.

Two hundred and twenty-three patients (6.7%) underwent valve surgery and 57 (1.7%) underwent percutaneous intervention.

Stroke and Thromboembolism

Overall, 46 (1.7%) patients had a stroke or TIA (8.45/1000 patient-years; Table 4) and 3 patients had a non–central nervous system systemic embolism. Patients who were in AF at enrollment were twice as likely to have a stroke as those who were in sinus rhythm (2.4% versus 1.2%,

Table 2. Clinical Outcomes at 2 Years of Follow-Up in 2960 Children and Adults With Rheumatic Heart Disease

	Low-Income Countries (n=964)	Lower-Middle-Income Countries (n=1158)	Upper-Middle-Income Countries (n=838)	*P* Value
Death, n (%)	200 (20.8)	195 (16.8)	105 (12.5)	<0.001
Congestive heart failure, n (%)	87 (9.0)	66 (5.7)	51 (6.1)	0.006
Stroke or transient ischemic attack, n (%)	14 (1.5)	12 (1.0)	20 (2.4)	0.053
Recurrence of acute rheumatic fever, n (%)	4 (0.4)	11 (1.0)	4 (0.5)	0.244
Infective endocarditis, n (%)	1 (0.1)	13 (1.1)	6 (0.7)	0.18
Atrial fibrillation	28 (2.9)	14 (1.2)	14 (1.7)	0.013
Prosthetic valve thrombosis	0 (0)	2 (0.1)	7 (1.0)	0.003
Surgery	30 (3.1)	84 (7.3)	109 (13.0)	<0.001
Death, congestive heart failure, or acute rheumatic fever, n (%)	251 (26.0)	228 (19.7)	143 (17.1)	<0.001
Death, stroke, systemic embolism, or major bleeding, n (%)	209 (21.7)	203 (17.5)	129 (15.4)	0.002

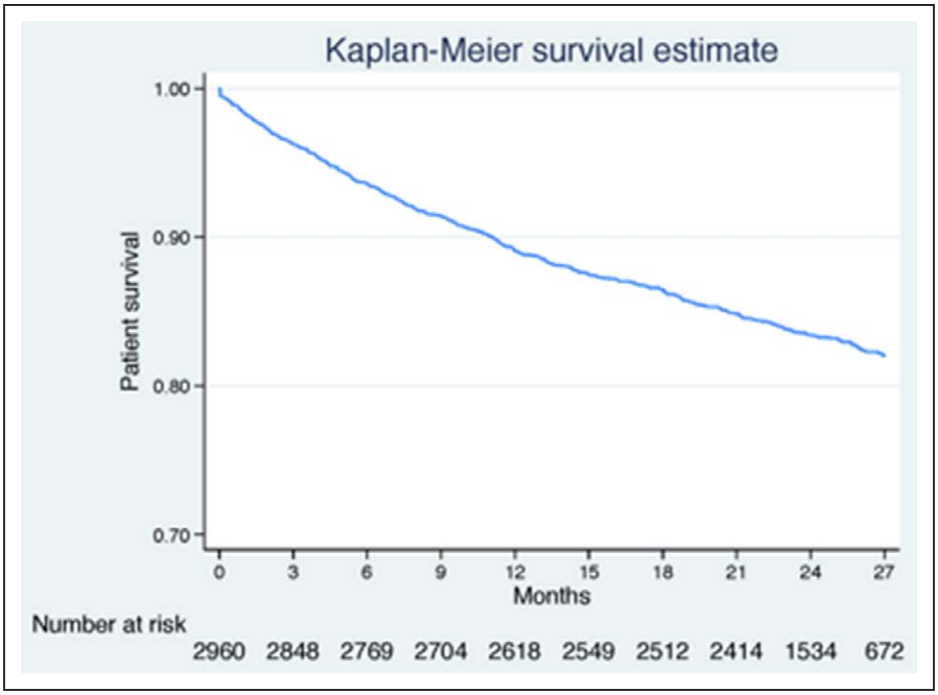

Figure 1. Kaplan-Meier estimates of time to death (in months) in the overall group.

P=0.04). Stroke also occurred more commonly among patients with prosthetic heart valves than in those with native valves (2.6% versus 1.1%, *P*=0.01). However, after adjustment for other variables, previous stroke (HR, 2.71; 95% CI, 1.18–6.39) and older age remained the only significant predictors of stroke, TIA, or systemic embolism. Prosthetic heart valve thrombosis occurred in 9 of 547 patients (1.64%) with mechanical valves. There were 588 patients with prosthetic valves, 547 of whom had mechanical valves.

At baseline, there were 1362 (40.7%) patients with indications for oral anticoagulation.[9] VKAs were prescribed in

Table 3. Predictors of Mortality in 2960 Children and Adults With Rheumatic Heart Disease Followed Up Over 2 Years

Baseline Variable	Hazard Ratio*	95% Confidence Interval	*P* Value
Age†	1.02	1.01–1.02	<0.0001
Female sex	0.65	0.52–0.80	<0.0001
Education beyond primary school	0.67	0.54–0.85	0.001
Atrial fibrillation	1.40	1.10–1.78	0.008
Severe disease‡	2.36	1.80–3.11	<0.01
Multivalve disease	0.97	0.75–1.25	0.852
Congestive heart failure at enrollment	2.16	1.70–2.72	<0.001
New York Heart Association functional class III/IV	1.67	1. 32–2.10	<0.001
Prior valve intervention or surgery	0.78	0. 57–1.07	0.14
Prior infective endocarditis	1.30	0.84–2.14	0.22
Prior stroke	1.19	0. 78–1.77	0.39
On secondary antibiotic prophylaxis at enrollment	0.86	0. 70–1.09	0.17

*Hazard ratios were calculated by using only the overall a priori model with only the following variables: age, sex, presence of atrial fibrillation, New York Heart Association functional class, congestive heart failure at enrollment, previous heart valve surgery or intervention, a history of stroke or infective endocarditis, severe disease (severe valve disease of at least 1 affected valve), multivalve involvement, and use of secondary penicillin prophylaxis.

†Hazard ratio was 1.16 (1.11–1.25) when age was categorized as <18 years, and 10-year increments thereafter.

‡Severe disease refers to patients with severe disease involving at least 1 valve.

Table 4. Incidence of Morbid Outcomes in 2960 Children and Adults With Rheumatic Heart Disease Followed Up Over 2 Years

Outcome	Number of Events Over 27 mo	Patient-Years	Incidence Rate per 1000	95% Confidence Interval
Congestive cardiac failure	204	5309.1	38.42	33.50–44.10
Stroke or transient ischemic attack	46	5440.8	8.45	6.33–11.29
Acute rheumatic fever	19	5444.9	3.49	2.23–5.47
Infective endocarditis	20	5473.8	3.65	2.36–5.66
Atrial fibrillation	56	5431.1	10.30	7.94–13.40
Major bleeding	23	5455.5	3.51	2.80–6.34
Prosthetic valve thrombosis	9	5478.9	1.64	0.85–3.16
Valvuloplasty	57	5403.8	8.83	8.14–13.67
Surgery	223	5187.7	42.99	37.70–49.01

69.5% (946) of such patients. VKA use was high in patients with mechanical heart valves (91.6%) and AF (68.6%), but low in those with mitral stenosis in sinus rhythm (20.3%) with other markers of high embolic risk (such as dilated left atrium or left atrial thrombus). Among patients prescribed VKAs, just over a quarter (27.4%) had an international normalized ratio (INR) in the therapeutic range.

Among patients with native valves and AF or those with mitral stenosis and concomitant high-risk features, the likelihood of having a stroke was lower among patients who had an INR in the therapeutic range (ie, 2–3) at baseline (1.4% versus 4.3%, *P*=0.031). For patients with mechanical valves (n=547), the risk of stroke was not statistically different between those with an INR in the therapeutic range or otherwise (3.0 versus 3.6%, *P*=0.69). There were 23 major bleeding events (0.8%) in all. The incidence of bleeding did not differ significantly by INR at baseline.

ARF, IE, and Secondary Prophylaxis

Nineteen patients (0.6%) had recurrent ARF, and 20 (0.7%) had IE (Table 4). At enrollment, just over half the patients (1761, 54.8%) were on secondary prophylaxis, and, of these, 78% were adherent to therapy (ie, had received ≥80% of the prescribed number of doses in the preceding 12 months).[9] Patients who were prescribed secondary prophylaxis were less likely to have ARF, new onset of CHF, or die at 2 years (16.2% versus 20.7% *P*=0.001). However, this association did not remain statistically significant after adjustment for other prognostic variables.

Country Income Group

Patients from upper-middle–income countries were older, and more often had a history of complications attributable to valve disease (such as stroke or IE), or were in CHF at baseline (Table 1).[9] A larger proportion of patients from upper-middle–income countries had valve surgery or intervention before entry into the study. Consequently, the risk of valve-related and anticoagulation-related problems (such as stroke) were significantly higher among patients who had prior valve surgery or intervention. However, they were significantly less likely to die at the end of 2 years than patients from low-income and LMIC countries (12.7% upper-middle–income countries, 14.2% LMIC, and 18.0% low-income countries, respectively; *P*=0.001) (Figure 2). The hazard for mortality remained higher for low-income (HR, 1.95; 95% CI, 1.51–2.50) and LMICs (HR, 1.51; 95% CI, 1.17–1.92), in comparison with upper-middle–income countries, after adjustment for patient age and sex. Adjustment for all other prognostic variables resulted in the attenuation of risk for low-income countries (HR, 1.53; 95% CI, 1.12–2.14), and LMICs (HR, 1.34; 95% CI, 1.02–1.87).

DISCUSSION

In this contemporary registry, the rates of death, CHF, and stroke were high among patients with clinical RHD

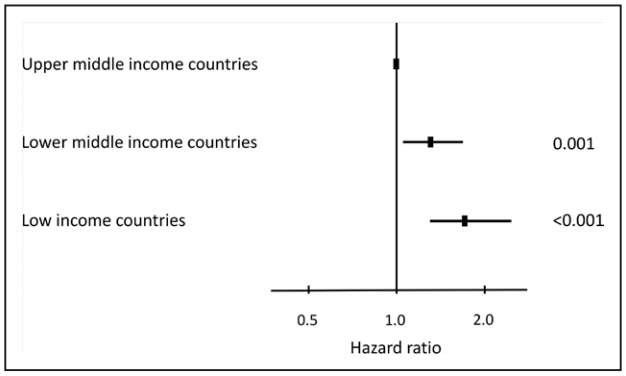

Figure 2. Risk of age- and sex-adjusted mortality by country income group.
Mortality was higher in low-income countries (HR, 1.95; 95% CI, 1.51–2.50, *P*<0.001) and low- and middle-income countries (HR, 1.51; 95% CI, 1.17–1.92, *P*=0.001). CI indicates confidence interval; and HR, hazard ratio.

living in LMICs despite their relatively young age (mean, 28 years). Nearly one-fifth of patients developed one of these complications over 2 years. This was largely attributable to advanced disease at the time of presentation. Mortality was significantly higher among patients living in low-income countries and among the less educated. The use of secondary antibiotic prophylaxis was suboptimal. Oral anticoagulation was underused, and the quality of oral anticoagulation was poor, contributing to an increased risk of stroke. These indicate that patients with RHD are managed suboptimally despite the availability of simple and effective preventive and management strategies.

There are few contemporary prospective studies reporting on mortality among patients with echocardiographically confirmed RHD. In a small community-based cohort of 257 patients with RHD who were followed up for 12 years, Kumar and colleagues[14] reported a death rate of 32.5/1000 patient-years. In a report from a register from the Northern Territory of Australia, Lawrence and colleagues showed a survival of 96.1% at 5 years, and 88.4% at 10 years.[7] The mortality rates reported in these studies are those of unselected patients with ARF and RHD recruited from the community, and it is not surprising that the rates are substantially lower than those from our estimates. Moreover, nearly all patients were on secondary prophylaxis and had access to high-quality care through outreach services by expert clinicians.[7] By contrast, Gunther and colleagues[16] reported a very high mortality rate of 125.3/1000 person-years in a small cohort of 47 patients in a community from Ethiopia, but there was an excessively high loss to follow-up rate of 44%.

Several of the factors that we found to be strongly associated with mortality and other major adverse outcomes are potentially amenable to intervention. The majority of our patients had moderate to severe disease and nearly one-third were in New York Heart Association class III/IV at enrollment,[9] and the severity of valve disease was the strongest predictor of mortality. Although most of these patients were likely to require intervention, only 10.3% (n=175) of those with severe valve disease had surgery or percutaneous intervention. In a study of newly diagnosed RHD with a similar profile, seen at a well-equipped tertiary care center in South Africa, 22% of patients underwent surgery at 30 months of follow-up.[17] Timely surgery or percutaneous intervention may improve outcomes in patients with severe disease.[13,18] However, facilities for cardiac surgery are scarce in poor countries and waiting periods are long.[19,20] Gaps in the use of effective therapies may be attributable to difficulties in access to care, and may explain some of the observed differences in mortality between middle-income and low-income countries (Figure 2). Strategies to provide high-quality tertiary care for patients with RHD have been proposed in Africa.[21]

Despite a substantial proportion of patients being in AF, oral anticoagulation was used in only 70% of these individuals. Even among patients with mechanical valves, ≈9% of patients were not on any oral anticoagulation. Among those on VKAs, INR monitoring was infrequent and less than one-third of patients were in the therapeutic range. It is predictable that patients with INRs outside the therapeutic range had a 3-fold higher risk of stroke. Underuse of oral anticoagulation is widespread,[22] but the level of INR control is poorer in developing countries. In a worldwide registry of AF, the time in therapeutic range for patients from Africa, China, and India was <40%.[23] This may be because of poor awareness by both physicians and patients on their importance, poor patient education, and limited access to INR testing.[24,25] Strategies targeting these factors are needed to improve clinical outcomes with oral anticoagulation. Although self-monitoring using point-of-care devices may be theoretically appealing, they are currently not affordable for the majority of patients in Africa and Asia.[26,27] Moreover, it is unknown if patients in LMICs can effectively self-monitor and adjust their VKA doses. Perhaps novel approaches need to be tested, such as the recruitment of educated and motivated individuals from the community (eg, local school teachers), as useful surrogate healthcare providers to perform home monitoring.[14] Although newer oral anticoagulants overcome the need for monitoring, their efficacy and safety in RHD is unknown, and they are at present unaffordable to the majority of patients living in poor countries. However, it is possible that in the future these drugs may become more affordable and widely used (as has happened with antiretroviral therapy for HIV), and, therefore, trials evaluating these agents in RHD are needed.[9,28]

Although there was a significant association of nonuse of secondary prophylaxis with the occurrence of ARF, CHF, or death, this was attenuated after adjustment for other prognostic variables. However, in the fully adjusted Cox regression analysis, there was a significant association of secondary prophylaxis with education and death or CHF. The effect of secondary prophylaxis on the occurrence of CHF or death is likely to be greatest among patients in the early stages of disease. Patients in poor countries are likely to have experienced substantial valve damage from multiple, unrecognized episodes of ARF before they first come to clinical attention, at which point the hemodynamic consequences of severe valve disease may be the overwhelming determinants of prognosis.[29] A similar lack of impact of secondary prophylaxis on mortality was observed in the Australian Northern Territory register that relied on clinical diagnosis of RHD at the point of entry.[7] These findings highlight the need for studying the efficacy of earlier institution of secondary prophylaxis in patients detected through screening programs,[30,31] combined with approaches to prevent the first episode of ARF.[29] In patients with ad-

vanced disease, given its documented effect of reducing recurrences of ARF, secondary prophylaxis should continue to be administered in addition to definitive therapy for valve disease.[32]

Education beyond primary school was associated with a significant reduction in mortality. Patient education is an indicator of socioeconomic status in resource-poor countries. A multinational retrospective study of African patients with RHD showed that the ratio of patients with severe disease to any RHD valvular lesion was higher in countries with the lowest gross domestic product.[33] This observation is consistent with the mortality gradient observed with respect to the country income group in this study. These findings point to the inextricable link between socioeconomic development and RHD, and emphasize the need for overall societal development as a key prerequisite for RHD control.[34]

Our study has several strengths. First, it is the largest prospective study of patients with RHD in LMICs allowing for precise estimates of patient-important clinical outcomes. Second, the diagnosis of RHD was confirmed by echocardiography, and disease severity and clinical outcomes were measured using prespecified, objective criteria, thereby reducing bias. Third, because we collected data from various countries in different stages of economic development, we were able to explore some of the socioeconomic factors that influence outcomes. The most important limitation of this study is that, despite extensive efforts to track patients, 11.5% of our patients were lost to follow-up. Although this proportion was lower than initially projected (20%), it reflects the challenges of conducting studies in resource-constrained settings.[16,35] Moreover, significantly greater proportions of those lost to follow-up had severe disease, were in CHF or worse functional class at enrollment, or were less educated (online-only Data Supplement Table II), and so our data may be an underestimate of the poor prognosis in this condition. This is a hospital-based registry of symptomatic patients, so our results may not apply to unselected patients in the community. Whether those who are asymptomatic when they are initially encountered will have a similar prognosis is not known.[36]

CONCLUSION

Clinical RHD is associated with high morbidity and mortality in young adults presenting to healthcare facilities. Better access to high-quality tertiary care services and optimizing the use of proven interventions such as secondary antibiotic prophylaxis and oral anticoagulation are likely to improve outcomes. Given the scarcity of high-quality data (from large international registries and randomized trials), more research is needed to devise effective ways of preventing ARF, detecting early RHD, improving access to essential care, and preventing disease progression.

ACKNOWLEDGMENTS

The authors acknowledge the substantial contribution made by the following individuals: Jitender Sharma and Gaurav Purohit (New Delhi, India); Christine Yuko Jowi (Nairobi, Kenya); Henning du Toit, Masomi Kaaya, Liina Sikwaya, and Andreas Wilberg (Windhoek, Namibia); Tanimowo Sunkanmi (Abeokuta, Nigeria); Ludu Audu, Charity Durojaiye-Amodu, Ngozi Elekwa, Ogechi Maduka, Oludolapo Marcaulay, Shamsudeen Mohammed, and Halim Odiachi (Jos, Nigeria); Dylan Barth, Patrick Commerford, Felicia Gili, Alexia Joachim, John Lawrenson, Carolise Lemmer, Nonkululeko Koyana, Kathryn Manning, Wendy Matthiassen, Alet Meiring, Peggy Mgwayi, Lwazi Mhlanti, Simpiwe Nkepu, Mpiko Ntsekhe, Janine Saaiman, Unita September, Kathie Walker, and Marnie van de Wall (Cape Town, South Africa); Priscilla Adolf, Jabulani Mbokazi, and Susan Perkins (Polokwane, South Africa); Neusa Jessen (Maputo, Mozambique); and Tagwa Eltahir (Khartoum, Sudan).

SOURCES OF FUNDING

REMEDY (Global Rheumatic Heart Disease Registry) was funded principally by the Canadian Network and Center for Trials Internationally (CANNeCTIN) program lead by the Population Health Research Institute as part of the Clinical Research Initiative of Canadian Institutes of Health Research (www.cannectin.ca/). The other sources of funding were the South African Medical Research Council, Lily and Ernst Hausmann Trust, the Else Kroner Fresenius Foundation, the University of Cape Town, the National Research Foundation of South Africa, Harold and Ethel Pupkewitz Heart Foundation (Namibia), and the World Heart Federation. The Jos site was funded by the Jos University Teaching Hospital, the Heart Aid Trust Inc., and FaithAlive Foundation. The Sudan sites had partial funding from Sheikan Insurance Company. Drs Blanche Cupido and Liesl Zühlke were funded in part by the Discovery Foundation. Dr Zühlke was also funded by a US National Institutes of Health Fogarty International Clinical Research Fellowship, Thrasher Research Fund Early Career Award, Wellcome Trust Clinical Infectious Disease Research Initiative (CIDRI) Research Officer Award, the Hamilton Naki Clinical Scholarship, and by Medtronic Foundation through support to Rheumatic Heart Disease Action. Dr Salim Yusuf is funded by the Marion Burke Chair of the Heart and Stroke Foundation of Canada. The Namibian site was supported by the Harold and Ethel Pupkewitz Heart Foundation. The funders of this study had no role in its design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the paper for publication. Several authors (Drs Mayosi, Zühlke, Karthikeyan, Yusuf, Teo, Islam, and Rangarajan) had full access to all the data in the study, and all authors had final responsibility for the decision to submit for publication.

DISCLOSURES

Dr ElSayed has received a grant from Sheikan Insurance Company to assist with data collection for this work. Other authors have no conflicts of interest to declare.

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FOOTNOTES

Received July 31, 2016; accepted September 20, 2016.

Guest Editor for this article was Patrick O'Gara, MD.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.116.024769/-/DC1.

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