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Mortality and Morbidity in Adults With Rheumatic Heart Disease

Ganesan Karthikeyan, DM; Mpiko Ntsekhe, PhD; Shofiqul Islam, PhD; Sumathy Rangarajan, MSc; Alvaro Avezum, PhD; Alexander Benz, MD; Tantchou Tchoumi Jacques Cabral, PhD; Ma Changsheng, MD; Philly Chillo, MD; J. Antonio Gonzalez-Hermosillo, MD; Bernard Gitura, MMed; Albertino Damasceno, PhD; Antonio Miguel L. Dans, MD; Kairat Davletov, MD; Alaa Elghamrawy, MD; Ahmed ElSayed, MD; Golden Tafadzwa Fana, MMed; Lillian Gondwe, MBBS; Abraham Haileamlak, MD; Azhar Mahmood Kayani, MD; Peter Lwabi, MMed; Fathi Maklady, MD; Onkabetse Julia Molefe-Baikai, MMed; John Musuku, MMed; Okechukwu Samuel Ogah, PhD; Maria Paniagua, MD; Emmanuel Rusingiza, MD; Sanjib Kumar Sharma, DM; Liesl Zuhlke, PhD; Stuart Connolly, MD; Salim Yusuf, DPhil; for the INVICTUS Investigators

IMPORTANCE Rheumatic heart disease (RHD) remains a public health issue in low- and middle-income countries (LMICs). However, there are few large studies enrolling individuals from multiple endemic countries.

OBJECTIVE To assess the risk and predictors of major patient-important clinical outcomes in patients with clinical RHD.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, hospital-based, prospective observational study including 138 sites in 24 RHD-endemic LMICs.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality. Secondary outcomes were cause-specific mortality, heart failure (HF) hospitalization, stroke, recurrent rheumatic fever, and infective endocarditis. This study analyzed event rates by World Bank country income groups and determined the predictors of mortality using multivariable Cox models.

RESULTS Between August 2016 and May 2022, a total of 13 696 patients were enrolled. The mean age was 43.2 years and 72% were women. Data on vital status were available for 12 967 participants (94.7%) at the end of follow-up. Over a median duration of 3.2 years (41 478 patient-years), 1943 patients died (15% overall; 4.7% per patient-year). Most deaths were due to vascular causes (1312 [67.5%]), mainly HF or sudden cardiac death. The number of patients undergoing valve surgery (604 [4.4%]) and HF hospitalization (2% per year) was low. Strokes were infrequent (0.6% per year) and recurrent rheumatic fever was rare. Markers of severe valve disease, such as congestive HF (HR, 1.58 [95% CI, 1.50-1.87]; $P < .001$), pulmonary hypertension (HR, 1.52 [95% CI, 1.37-1.69]; $P < .001$), and atrial fibrillation (HR, 1.30 [95% CI, 1.15-1.46]; $P < .001$) were associated with increased mortality. Treatment with surgery (HR, 0.23 [95% CI, 0.12-0.44]; $P < .001$) or valvuloplasty (HR, 0.24 [95% CI, 0.06-0.95]; $P = .042$) were associated with lower mortality. Higher country income level was associated with lower mortality after adjustment for patient-level factors.

CONCLUSIONS AND RELEVANCE Mortality in RHD is high and is correlated with the severity of valve disease. Valve surgery and valvuloplasty were associated with substantially lower mortality. Study findings suggest a greater need to improve access to surgical and interventional care, in addition to the current approaches focused on antibiotic prophylaxis and anticoagulation.

Supplemental content

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The INVICTUS Investigators are listed in Supplement 2.

Corresponding Author: Ganesan Karthikeyan, MD, DM, Department of Cardiology, Cardiothoracic Sciences Centre, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India (karthik2010@gmail.com).

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Rheumatic heart disease (RHD) causes more than 300 000 deaths annually, mainly in low- and middle-income countries (LMICs).[1] In 2018, the member states of the World Health Organization adopted a global resolution on rheumatic fever and rheumatic heart disease, calling for high-quality data that would improve understanding of disease epidemiology to help in the effort to reduce morbidity and mortality due to the disease.[2] However, there are no globally representative data on contemporary populations living with RHD. Most studies on RHD enrolled a small number of patients, were retrospective, or restricted to small geographical regions or high-risk ethnic groups.[3,4] The only prospective study enrolled patients mainly from low-income African countries and had high rates of loss to follow-up (>10% over 2 years).[5] Moreover, data on use of heart failure (HF) medications, as well as utilization and effectiveness of surgery and catheter interventions during the study, were not systematically collected.[5] Because HF due to structural valve disease is the primary cause of morbidity and mortality in patients with RHD,[5,6] such data are needed to guide policy and practice in LMICs.

Investigation of Rheumatic Atrial Fibrillation Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies (INVICTUS) is an international, collaborative research effort focused on patients with RHD enrolled from all regions of the world where RHD is endemic.[7] The program consisted of a randomized trial of stroke prevention in RHD-associated atrial fibrillation (AF) and a large prospective registry.[6,7] This study presents the results of all patients included in the program. The principal objective of the program was to describe the incidence and predictors of patient-important clinical outcomes among patients with RHD across a range of country income levels.

Key Points

Questions What is the risk of major clinical outcomes in patients with rheumatic heart disease (RHD) and what are the risk predictors in endemic countries?

Findings In this prospective observational study including 13 696 patients enrolled from 24 low- and middle-income countries, nearly 15% of patients died at 3 years, mostly due to heart failure or sudden death. Corrective valve surgery or valvuloplasty was independently associated with a reduced risk of death. However, although most patients were symptomatic, only about 5% underwent valve surgery in 3 years.

Meaning Improved availability and access to surgical and interventional care for patients with RHD in endemic countries are needed.

Methods

Study Design

The design of the research program has been published previously.[7] The study was designed, conducted, and analyzed by investigators affiliated with the Population Health Research Institute at Hamilton, Canada, and was supported through an unrestricted grant from Bayer AG. The study adhered to the STROBE reporting guidelines for cohort studies.

Patient Enrollment and Follow-Up

Consenting adult patients with clinically detected RHD confirmed via echocardiography were consecutively enrolled at participating sites in 24 LMICs. Patients who had AF and a high risk of stroke (based on the presence of mitral stenosis with a valve area ≤2 cm^2 or a CHA_2DS_2-VASc score of ≥2 [based on the presence of congestive HF, hypertension, diabetes, a history of stroke, transient ischemic attack {TIA} or systemic embolism, and vascular disease]) were enrolled in the randomized trial of stroke prevention.[6] All other patients were enrolled in the INVICTUS registry. Patients younger than 18 years were not enrolled. There were no other exclusion criteria. The study protocol was approved by institutional ethics committees at all participating sites and the relevant national regulatory authorities. Written informed consent was obtained from all participants.

Baseline data were collected using standardized case record forms. Ethnicity data were collected because RHD tends to be more prevalent in certain ethnic groups. Ethnicity was self-reported based on prespecified categories. Patients were followed up at 6-month intervals either during in-person visits (trial participants) or by telephone. All patients were evaluated in person at 1-year intervals. Information regarding medication use, performance of interventions or surgical valve procedures, and clinical outcomes were collected at all visits.

Study Outcomes

The primary outcome for this analysis was all-cause mortality. Cause of death was centrally adjudicated for the trial participants. For other patients, the study relied on the cause of death information provided by site investigators. Deaths were categorized as due to vascular or nonvascular causes. Vascular deaths included those due to HF, cardiogenic shock, sudden death, stroke, myocardial infarction, or major bleeding. Deaths were classified as due to unknown causes when the available information was insufficient to identify a cause with certainty. Stroke was defined as any focal neurologic deficit lasting 24 hours with or without brain imaging suggestive of a primary ischemic or hemorrhagic origin leading to tissue infarction. Secondary outcomes were hospitalization for HF, stroke/TIA, infective endocarditis, and recurrence of acute rheumatic fever. For patients with mechanical heart valves, information on admissions for heart valve thrombosis was collected. Cardiovascular outcomes for individuals who became pregnant during the study are included in this analysis and not shown separately. Peripartum maternal and fetal outcomes for pregnant individuals will be reported in a subsequent report.

Statistical Analysis

Clinical and sociodemographic characteristics and outcomes were stratified by country income level using the most recent World Bank classification (low, lower-middle-, and upper-middle-income groups). Event rates are presented as percent per patient-year. Determinants of mortality were identified

using Cox regression with time zero set as the date of enrollment. Patient-level predictors of mortality were first identified by including the following variables in the model (model 1): age, female sex, atrial fibrillation, hypertension, diabetes, former or current smoking, prior stroke or TIA, coronary artery disease, congestive HF, New York Heart Association class, moderate or severe mitral stenosis, mitral regurgitation, aortic stenosis, aortic regurgitation, tricuspid regurgitation, involvement of more than 1 valve, pulmonary hypertension, left ventricular dysfunction, right ventricular dilatation and/or dysfunction, prior balloon valvuloplasty, and prior valve surgery. In addition, the study adjusted for the effect of oral anticoagulation (vitamin K antagonists and rivaroxaban) on mortality in the model. Next, the influence of balloon mitral valvuloplasty and valve surgery performed during follow-up on the incidence of the primary outcome was assessed by considering them as time-varying covariates (model 2). The date of the follow-up visit was used to approximate the time of procedure in this analysis. Finally, any interaction of patient-level predictors with country income level was explored. For this analysis, the patients' country of origin was considered as having a random effect and the patient-level variables and country income group as having fixed effects in a Cox frailty model (model 3). The proportionality assumption of the Cox models was assessed using the log of the negative log survival vs log of time plot for each covariate under consideration. The effect of secondary antibiotic prophylaxis on mortality was explored separately in patients aged 40 years or younger using the same models as described above. The strength of association of individual variables with mortality was quantified using hazard ratios and their 95% CIs. The widths of the 95% CIs have not been adjusted for multiplicity. All analyses were performed using SAS version 9.4 (SAS Institute).

Results

Study Participants

Between August 2016 and May 2022, a total of 13 696 patients with RHD were enrolled from 138 sites in 24 countries. More than 8400 patients (62%) were from low-middle-income countries and 2769 (20%) were from low-income countries (LICs). The remaining patients were from upper-middle-income countries (UMICs). Mean age of patients overall was 43 years and women predominated (72%). Asian patients constituted about 35% of the enrolled participants and 30% were of Black African ethnicity. Most patients (85%) had moderate or severe disease involving the mitral valve and 25.9% had significant disease involving at least 2 valves. Significant aortic stenosis was uncommon (<2.5%). Nearly 40% had pulmonary arterial hypertension and 32% had tricuspid regurgitation. Additionally, 32.7% of patients were in AF at enrollment and 27% had clinical HF. Most patients (76%) were receiving diuretics. Overall, 41.3% of patients were receiving secondary antibiotic prophylaxis. Of these, 73.3% received injection of benzathine penicillin and most of the remaining patients received oral penicillin V (eTable 1 in Supplement 1).

There were significant differences in baseline characteristics between patients from different country income groups (**Table 1**). Patients in LICs were, on average, 10 years younger than those in low-middle–income countries, who were in turn 10 years younger than those from UMICs. The prevalence of AF was highest in UMICs (36% vs 26% in LICs). The frequency of moderate or severe mitral and aortic regurgitation decreased progressively with higher income status. Significant aortic stenosis was more common in higher-income countries. Diuretic use and secondary antibiotic prophylaxis were more frequent in lower-income countries. Patients in UMICs were most likely to have had either a valve intervention or valve surgery in the past (Table 1). The prevalence of risk factors for atherosclerosis progressively increased with country income status. Patients in low-middle- and upper-middle-income countries were more likely to smoke and have hypertension, diabetes, coronary artery disease, or prior stroke.

Mortality

Patients were followed up for a median duration of 3.2 years (41 478 patient-years). Data on vital status were available for 12 967 participants (94.7%). Overall, 1943 patients (14.2%) died over the period of follow-up (4.7% per patient-year). Of the patients who died, 1312 of the deaths (67.5%) were vascular, most of which (1165 of 1312 [88.8%]) were due to cardiac causes (**Table 2**). Death from HF and sudden cardiac death accounted for most deaths (77%) due to vascular causes.

Valve Surgery, Valvuloplasty, and Clinical Outcomes

Over the duration of the study, 604 patients (4.4%) underwent valve surgery and 227 (1.7%) underwent valvuloplasty. Nearly one-fifth of patients were hospitalized at least once (2510 [18.3%]). Of these, 392 patients (15.6%) were hospitalized twice and 207 (8.2%) had 3 or more hospitalizations. Most hospitalizations (1969 [78.4%]) were for cardiovascular causes, and HF was the most frequent cause (Table 2). Of the hospitalizations, 23.5% were for valve surgery. Strokes were infrequent (0.6% per year) and caused less than 1% of all deaths (74 deaths [0.5%]). Infective endocarditis and recurrence of rheumatic fever were rare (Table 2).

Determinants of Mortality

Patient-level factors that were independently associated with increased mortality were those related to the severity of valve disease (**Figure 1**). The strongest predictors were the presence of HF (HR, 1.68 [95% CI, 1.50-1.87]; $P < .001$) and pulmonary arterial hypertension at baseline (HR, 1.52 [95% CI, 1.37-1.69]; $P < .001$). No differences in the risk of death were observed between patients with significant disease involving the mitral or aortic valves or the presence of multivalve involvement (eTables 2-4 in Supplement 1). The presence of coronary artery disease, prior stroke, diabetes, and current or former smoking were independently associated with mortality (Figure 1). Older age was associated with a small but statistically significant higher risk of mortality (HR, 1.07 [95% CI, 1.03-1.11]; $P < .001$).

A history of valve surgery (HR, 0.23 [95% CI, 0.12-0.44]; $P < .001$) or valvuloplasty (HR, 0.24 [95% CI, 0.06-0.95];

Table 1. Key Baseline Characteristics by Country Income Group

Characteristic[a]	Overall (N = 13 696)	LICs[b] (n = 2769)	LMICs[b] (n = 8453)	UMICs[b] (n = 2474)
Age, mean (SD), y	43.2 (16.9)	33.1 (16.3)	43.9 (15.9)	52.3 (14.9)
Females	9882 (72.2)	1943 (70.2)	6066 (71.8)	1873 (75.7)
Males	3814 (27.8)	826 (29.8)	2387 (28.2)	601 (24.3)
Current atrial fibrillation	4482 (32.7)	719 (26.0)	2874 (34.0)	889 (35.9)
Valve lesions and medication use[c]				
Moderate to severe mitral regurgitation	5892 (43.0)	1249 (45.1)	3723 (44.0)	920 (37.2)
Moderate to severe aortic regurgitation	2283 (16.7)	546 (19.7)	1367 (16.2)	370 (15.0)
Moderate to severe aortic stenosis	331 (2.4)	29 (1.1)	206 (2.4)	96 (3.9)
Pulmonary hypertension[d]	5301 (38.7)	1087 (39.2)	3411 (40.4)	803 (32.5)
Diuretic use	10 362 (75.7)	2182 (78.8)	6626 (78.4)	1554 (62.8)
Secondary antibiotic prophylaxis	5655 (41.3)	1748 (63.1)	3522 (41.7)	385 (15.6)
Prior valve interventions or surgery				
Any valve intervention or surgery	2850 (20.8)	378 (13.7)	1348 (16.0)	1124 (45.4)
Valve surgery	1859 (13.6)	308 (11.1)	582 (6.9)	969 (39.2)
Mitral valvuloplasty	1105 (8.1)	80 (2.9)	788 (9.3)	237 (9.6)
Concomitant disease and risk factors				
Hypertension	2490 (18.2)	222 (8.0)	1223 (14.5)	1045 (42.2)
Current or former smoking	1299 (9.5)	103 (3.7)	587 (6.9)	609 (24.6)
Diabetes	633 (4.6)	48 (1.7)	347 (4.1)	238 (9.6)
Prior stroke/TIA/systemic embolism	1201 (8.8)	167 (6.0)	568 (6.7)	466 (18.8)
Coronary artery disease	145 (1.1)	18 (0.7)	46 (0.5)	81 (3.3)

Abbreviations: GNI, gross national income; LICs, low-income countries; LMICs, lower-middle–income countries; TIA, transient ischemic attack; UMICs, upper-middle–income countries.

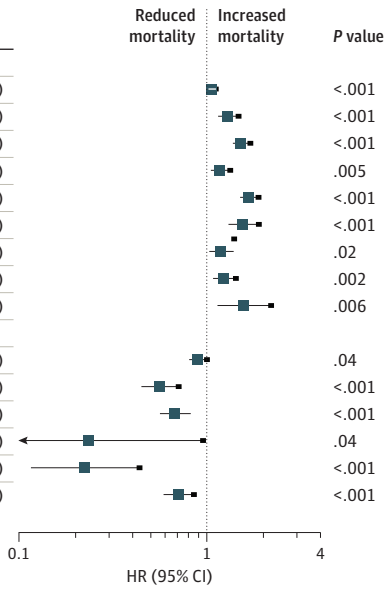
[a] All listed characteristics significantly differed between country income groups; *P* value for trend <.001.

[b] All values are No. (%) unless otherwise indicated; LICs (GNI per capita, $1025 or less) include Ethiopia, Malawi, Mozambique, Nepal, Rwanda, Tanzania, and Uganda; LMICs (GNI per capita, $1026-$3995) include Cameroon, Egypt, India, Kenya, Nigeria, Pakistan, Philippines, Sudan, Zambia, and Zimbabwe; and UMICs (GNI per capita, $3996-$12 375) include Botswana, Brazil, China, Kazakhstan, Mexico, Paraguay, and South Africa (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups).

[c] Severity of valve lesions was assessed using standard criteria (Nishimura et al).

[d] Pulmonary arterial hypertension was diagnosed in the presence of clinical evidence (a loud pulmonary component of the second heart sound and/or a parasternal heave), with or without a tricuspid valve regurgitant jet velocity >2.8 m/s on transthoracic echocardiography.

Figure 1. Determinants of Mortality in Rheumatic Heart Disease



Determinants of mortality	HR (95% CI)	*P* value
Factors associated with increased mortality		
Age (per 10-y increase)	1.07 (1.03-1.11)	<.001
Atrial fibrillation	1.30 (1.15-1.46)	<.001
Pulmonary hypertension	1.52 (1.37-1.69)	<.001
Left ventricular dysfunction	1.18 (1.05-1.32)	.005
Congestive heart failure	1.68 (1.50-1.87)	<.001
Diabetes	1.56 (1.30-1.87)	<.001
Current or former smoking	1.20 (1.03-1.39)	.02
Prior stroke/TIA/systemic embolism	1.24 (1.08-1.42)	.002
Coronary artery disease	1.57 (1.14-2.18)	.006
Factors associated with reduced mortality		
Female sex	0.90 (0.81-1.00)	.04
Prior valvuloplasty	0.56 (0.45-0.70)	<.001
Prior valve surgery	0.68 (0.57-0.82)	<.001
Valvuloplasty during follow-up	0.24 (0.06-0.95)	.04
Valve surgery during follow-up	0.23 (0.12-0.44)	<.001
Secondary prophylaxis[a]	0.71 (0.59-0.85)	<.001

Variables associated with increased mortality after adjustment for baseline variables include the performance of valvuloplasty or surgery during follow-up and country income group. HRs are based on mutually adjusted multivariable Cox regression model. HR indicates hazard ratio; TIA, transient ischemic attack.

[a] HR for secondary prophylaxis estimated from the fully adjusted model but restricted to those aged 40 years or younger.

P = .042) was associated with a lower risk of death. Further, the performance of valve surgery or valvuloplasty during follow-up was independently associated with lower mortality (Figure 1). Women had a small but significantly lower risk of death. Among patients aged 40 years or younger, the use of secondary antibiotic prophylaxis was independently associated with lower mortality (HR, 0.71 [95% CI, 0.59-0.85]; P < .001) (Figure 1; eTable 5 in Supplement 1).

Differences in Outcomes by Country Income Group

Low country income status was associated with higher crude and adjusted mortality compared with both lower-middle- and upper-middle-income status. The differences in mortality persisted after adjustment for valve surgery and mitral valvuloplasty performed during follow-up (**Figure 2**; eFigure 1 in Supplement 1). Hospitalizations for HF were similar for LICs and UMICs and lowest among patients in LMICs (**Table 3**). However, the rate of hospitalization for HF was lower than the corresponding mortality rate for all patients irrespective of country income status (Table 3). The crude mortality rate after HF hospitalization was high, with more than one-third (UMICs, 31.3%; LMICs, 43.7%; LICs, 41.2%) of patients dying within 30 days. The 30-day mortality rates were significantly higher for both LICs and LMICs compared with UMICs (Table 3).

More patients in UMICs underwent valve surgery (179 [7.2%]) than in LMICs (334 [4%]; P < .0001) and LICs (91 [3.3%]; P < .001). The crude 30-day mortality rate following admissions for valve surgery was about 10% and was similar across country income groups. Patients in UMICs had the highest risk of stroke (120 [1.6%] per year) compared with both LMICs (137 [0.5%] per year; P < .001), and LICs (63 [0.8%] per year; P < .001).

Table 2. Major Clinical Outcomes

Outcome	N = 13 696	
	No. of events, No./total No. (%)	Rate (n = 41 478 patient-years), % per year
Primary outcome		
All-cause death	1943 (14.2)	4.7
Vascular death	1312 (9.6)	3.2
HF	667 (4.9)	1.6
Sudden cardiac death	352 (2.6)	0.9
Stroke or systemic embolism	79 (0.6)	0.2
Myocardial infarction	26 (0.2)	0.1
Major bleeding[a]	42 (0.3)	0.1
Nonvascular death	233 (1.7)	0.6
Death due to unknown causes	398 (2.9)	1.0
Secondary outcomes		
Hospitalization	2510 (18.3)	6.7
HF hospitalization	805 (5.9)	2.0
Other cardiac causes	854 (6.2)	2.1
Nonfatal stroke or TIA	246 (1.8)	0.6
Nonfatal major bleeding	85 (0.6)	0.2
Infective endocarditis	30 (0.2)	0.07
Rheumatic fever recurrence	10 (0.07)	0.02

Abbreviations: HF, heart failure; TIA, transient ischemic attack.

[a] As defined by the International Society on Thrombosis and Hemostasis.

Discussion

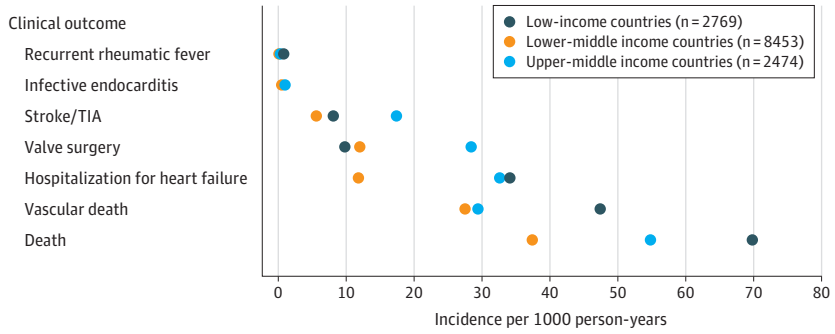
This research program is the largest global cohort of contemporary patients with clinically significant RHD. Several key findings emerged from this analysis. First, mortality among patients with clinically significant RHD remains high, particularly among those in LICs, and is correlated with the severity of valve disease at diagnosis. Second, most of the mortality from RHD is due to HF or sudden cardiac death. Third, there is a strong, independent, inverse association between the utilization of valve surgery and mitral valvuloplasty and mortality. Fourth, the incidence of stroke is low and complications such as infective endocarditis and the recurrence of acute rheumatic fever are rare.

The overall mortality rate was nearly 5% per year and as high as 7% per year in LICs. This is in line with previous data from the REMEDY registry, which largely comprised patients from low-income African countries (mortality of 8.5% per year).[5] The high mortality is despite the fact that patients with RHD are, on average, more than 20 years younger (mean age, 43 years) than those with chronic HF due to other causes (mean age, about 65 years).[8,9] Measures of severity of valve disease, such as left ventricular dysfunction, pulmonary hypertension, and HF, were associated with a higher risk of death, independent of the specific valve lesion or number of valves involved. Patients in UMICs tended to have a lower prevalence of severe regurgitant lesions, pulmonary hypertension, and diuretic use. This may indicate that patients in UMICs are diagnosed earlier in the course of disease. However, these patients were older and had a greater burden of coronary artery disease and risk factors for atherosclerosis, perhaps increasing the risk of non-RHD-related mortality. This may be 1 potential explanation for why mortality in these patients was not the lowest among the 3 income groups.

Despite the extent and severity of valve disease at baseline, few patients underwent valve surgery or mitral valvuloplasty during follow-up. Unlike in patients with HF due to reduced ejection fraction in whom medical treatment improves survival, surgery and balloon valvuloplasty are the only options that can potentially improve outcomes in patients with RHD. The substantially lower risk of death associated with the performance of valve surgery or interventions lends support to this argument. We also observed that nearly one-fifth of the variation in the use of valve surgery and 28% of the variation in the use of mitral valvuloplasty was attributable to country income status, partly explaining the higher mortality associated with low-income status. These findings are in alignment with published data highlighting the limited access to surgical and catheter-based interventions in lower-income countries, resulting in patients not receiving necessary and timely life-saving treatment.[10]

Access to hospitalization for acute decompensation of HF or other cardiac causes may be limited in LMICs. The study found that the annual rate of hospitalization for HF was just

Figure 2. Incidence of Clinical Outcomes by Country Income Group



Crude incidence rate of clinical outcomes during follow-up. TIA indicates transient ischemic attack.

Table 3. Rates and Outcomes of Heart Failure Hospitalization by Country Income Group

	LICs (n = 2769)	LMICs (n = 8453)	UMICs (n = 2474)
Annualized rate of mortality per patient-year, %	7.0	3.7	5.5
Annualized rate of hospitalization for all causes per patient-year, %	7.9	4.5	13.7
Ratio of hospitalization/death	1.1	1.2	2.5
Annualized rate of hospitalization for HF per patient-year, %	3.4	1.2	3.3
Ratio of HF hospitalization/death	0.5	0.3	0.6
In-hospital mortality after hospitalization for HF, No. (%)	99 (37.8)	108 (36.0)	64 (26.3)
30-d mortality after hospitalization for HF, No. (%)[a]	108 (41.2)	131 (43.7)	76 (31.3)

Abbreviations: HF, heart failure; LICs, low-income countries; LMICs, lower-middle–income countries; UMICs, upper-middle–income countries.

[a] LICs vs UMICs, $P = .02$; LMICs vs UMICs, $P = .003$.

half the annual rate of mortality. Hospitalizations due to any cause were also less frequent in relation to mortality. These data suggest limited access compared with high-income countries, where hospitalizations for HF occur twice as frequently as death and the rates of hospitalization for any cause are 4 to 5 times the mortality rates.[9] Further, even among those hospitalized for HF, the in-hospital and 30-day mortality rates were high, with more than one-third of patients dying at 30 days. The 30-day mortality rate was higher for both LICs and LMICs compared with UMICs, explaining some of the difference in mortality associated with country income status.

This study found that the use of secondary penicillin prophylaxis was associated with reduced mortality among patients aged 40 years or younger. However, on exploratory analyses, this lower risk appeared to extend to patients of all ages, including those aged 60 years or older (eTable 7 in Supplement 1). There is no plausible biological mechanism by which older individuals may benefit from antibiotic prophylaxis. Population-level data indicate that acute rheumatic fever is extremely unlikely beyond age 30 years[11] and, expectedly, was rare in study patients (a total of 10 events). Moreover, although a reduction in the risk of echocardiographic progression has been observed in patients with subclinical RHD (with trivial or mild valve lesions[12]), such effects have not been consistently observed among those with clinically significant valve disease.[3,5] In patients who already have severe valve disease, the hemodynamic consequences of the structural valve lesions likely have a far greater impact on clinical outcomes than any putative effect of secondary prophylaxis. On the other hand, benzathine penicillin injections (the most common form of prophylaxis) are administered by health care professionals at 3- to 4-week intervals, and secondary prophylaxis may simply be a proxy for increased frequency of health care contact, which may then translate to better outcomes.

Taken together, the data indicate that prioritizing tertiary care (focusing mainly on outpatient and inpatient management of HF) and surgical and interventional services for patients with clinical RHD are likely to improve outcomes. A number of modeling studies suggest that scaling up tertiary care may reduce RHD-related deaths. Coates and colleagues showed that scaling up tertiary care to improve coverage from the present 5% to 25% of the eligible population (together with secondary prophylaxis) may reduce age-standardized mortality due to RHD in African Union countries by 30.7% over 10 years.[13] They estimated that this would result in a net benefit of USD $2.8 billion over this period.[13] Likewise, an analysis from India showed that a strategy of improving coverage for tertiary care (and secondary prophylaxis) would be cost-effective, with an incremental cost of just USD $30 per quality-adjusted life-year gained.[14] The authors also indicated that this strategy would have favorable distributional effects by conferring greater benefit on people in the poorest income groups and reducing out-of-pocket spending.[14] From the perspective of LICs with little or no surgical infrastructure, another model-based analysis suggested that referral of patients to an LMIC (such as India) for surgery may be a more cost-effective option than developing in-country infrastructure.[15] Some of these intervention bundles included secondary prophylaxis despite the lack of strong evidence and also assumed an unrealistically large reduction in the risk of disease progression from its use.[16] Nevertheless, population-level interventions should probably include secondary prophylaxis to cover younger

patients with less severe disease who may benefit from it.[12] Given the resource constraints in poor countries, it may be optimal to implement these intervention bundles through existing child health or other communicable and noncommunicable disease programs, rather than creating additional vertical programs dedicated to RHD. A strategy of primary prevention, though of benefit in theory,[15] is costly, difficult to implement at scale, and has not been shown to be of benefit in randomized trials.[17] Finally, the data also suggest that the inclusion of costly interventions to reduce stroke risk (such as point-of-care devices for self-monitoring of anticoagulation and dedicated anticoagulation clinics) may not be beneficial because of the low stroke risk in this population.

Limitations

These results are based on nearly 2000 deaths observed in a large cohort from 24 countries where RHD is endemic and are therefore widely generalizable to all patients with clinically significant RHD. However, this study has limitations. First, given the observational nature of these data, the findings related to the apparent lower risk of deaths with some of the interventions need to be interpreted with caution. Second, although there was a strong inverse relationship between the performance of valve surgery or interventions and mortality, this association may not be causal. It is possible, for example, that patients at lower risk of death preferentially underwent surgery, as they were also likely to have lower perioperative mortality. This is however unlikely, as patients who underwent surgery were more likely to have severe valve disease, multiple valve involvement, pulmonary hypertension, HF, and AF at baseline compared with those who did not. Moreover, valve surgery and interventions are the standard of care for patients with structural valve disease[18] and effectively correct the hemodynamic abnormalities associated with RHD. Therefore, the observed associations are not unexpected. Further, the magnitude of risk reduction was large, and persisted after adjustment for both patient-level variables and country income.

Conclusions

Death due to clinical RHD is largely because of HF, and providing timely surgical or interventional treatment may be the best way to reduce mortality. Control programs in RHD-endemic countries should consider the provision of timely valve surgery and intervention with a goal to reduce mortality due to the disease.

ARTICLE INFORMATION

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Author Affiliations: Department of Cardiology, All India Institute of Medical Sciences, New Delhi (Karthikeyan); Translational Health Science and Technology Institute, Faridabad, India (Karthikeyan); Division of Cardiology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa (Ntsekhe); Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada (Islam, Rangarajan, Connolly, Yusuf); International Research Center, Hospital Alemão Oswaldo Cruz, São Paulo, Brazil (Avezum); Department of Cardiology, University Medical Center Mainz, Johannes Gutenberg University Mainz, Mainz, Germany (Benz); St. Elizabeth Catholic General Hospital, Shisong Cardiac Centre, Kumbo, Cameroon (Cabral); Beijing Anzhen Hospital, Beijing, China (Changsheng); Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania (Chillo); Instituto Nacional de Cardiología Ignacio Chávez, Ciudad de México, Mexico (Gonzalez-Hermosillo); Kenyatta National Teaching & Referral Hospital, Department of Cardiology, Nairobi, Kenya (Gitura); Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique (Damasceno); College of Medicine, University of Philippines, Manila (Dans); Asfendiyarov Kazakh National Medical University, Health Research Institute, Almaty, Kazakhstan (Davletov); Mehalla Heart Center, El Mahalla El Kubra, Egypt (Elghamrawy); Alzaiem Alazhari University, Khartoum, Sudan (ElSayed); University of Zimbabwe, College of Health Sciences, Harare (Fana); Kamuzu Central Hospital, Lilongwe, Malawi (Gondwe); College of Medicine and Health Sciences, University of Rwanda, Kigali (Haileamlak); Jimma University Medical Center, Jimma, Ethiopia (Haileamlak); Rawalpindi Institute of Cardiology, Rawalpindi, Punjab, Pakistan (Kayani); Uganda Heart Institute, Kampala, Uganda (Lwabi); Department of Cardiology, Suez Canal University, Ismailia, Egypt (Maklady); Princess Marina Hospital, University of Botswana, Gaborone (Molefe-Baikai); University Teaching Hospital, Lusaka, Zambia (Musuku); Cardiology Unit, Department of Medicine, University of Ibadan/University College Hospital, Ibadan, Oyo State, Nigeria (Ogah); College of Medicine Sciences, National University of Concepción, Concepción, Paraguay (Paniagua); University Teaching Hospital of Kigali, Kigali, Rwanda (Rusingiza); B.P. Koirala Institute of Health Sciences, Dharan, Nepal (Sharma); Medical Research Council of South Africa, Division of Pediatric Cardiology, Department of Pediatrics, Red Cross Children's Hospital Faculty of Health Sciences, University of Cape Town, Cape Town (Zuhlke).

Author Contributions: Drs Karthikeyan, Connolly, and Yusuf had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Karthikeyan, Ntsekhe, Connolly, Yusuf.
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Drafting of the manuscript: Karthikeyan.
Critical review of the manuscript for important intellectual content: All authors.
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Supervision: Karthikeyan, Rangarajan, Yusuf.
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REFERENCES

1. Watkins DA, Johnson CO, Colquhoun SM, et al. Global, regional, and national burden of rheumatic heart disease, 1990-2015. *N Engl J Med*. 2017;377(8):713-722. doi:10.1056/NEJMoa1603693

2. White A. WHO resolution on rheumatic heart disease. *Eur Heart J*. 2018;39(48):4233. doi:10.1093/eurheartj/ehy764

3. Lawrence JG, Carapetis JR, Griffiths K, Edwards K, Condon JR. Acute rheumatic fever and rheumatic heart disease: incidence and progression in the Northern Territory of Australia, 1997 to 2010. *Circulation*. 2013;128(5):492-501. doi:10.1161/CIRCULATIONAHA.113.001477

4. Negi PC, Mahajan K, Kondal D, et al. Long term outcomes in patients with RF/RHD: eight-year follow-up of HP-RF/RHD (Himachal Pradesh Rheumatic Fever/Rheumatic Heart Disease) registry in a Northern Indian state. *Int J Cardiol*. 2021;343:149-155. doi:10.1016/j.ijcard.2021.09.014

5. Zühlke L, Karthikeyan G, Engel ME, et al. Clinical outcomes in 3343 children and adults with rheumatic heart disease from 14 low- and middle-income countries: two-year follow-up of the Global Rheumatic Heart Disease Registry (the REMEDY Study). *Circulation*. 2016;134(19):1456-1466. doi:10.1161/CIRCULATIONAHA.116.024769

6. Connolly SJ, Karthikeyan G, Ntsekhe M, et al; INVICTUS Investigators. Rivaroxaban in rheumatic heart disease-associated atrial fibrillation. *N Engl J Med*. 2022;387(11):978-988. doi:10.1056/NEJMoa2209051

7. Karthikeyan G, Connolly SJ, Ntsekhe M, et al; INVICTUS Investigators. The INVICTUS rheumatic heart disease research program: rationale, design and baseline characteristics of a randomized trial of rivaroxaban compared to vitamin K antagonists in rheumatic valvular disease and atrial fibrillation. *Am Heart J*. 2020;225:69-77. doi:10.1016/j.ahj.2020.03.018

8. Joseph P, Roy A, Lonn E, et al; G-CHF Investigators. Global variations in heart failure etiology, management, and outcomes. *JAMA*. 2023;329(19):1650-1661. doi:10.1001/jama.2023.5942

9. Crespo-Leiro MG, Anker SD, Maggioni AP, et al; Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail*. 2016;18(6):613-625. doi:10.1002/ejhf.566

10. Zilla P, Yacoub M, Zühlke L, et al. Global unmet needs in cardiac surgery. *Glob Heart*. 2018;13(4):293-303. doi:10.1016/j.gheart.2018.08.002

11. Kumar R, Sharma YP, Thakur JS, et al. Streptococcal pharyngitis, rheumatic fever and rheumatic heart disease: eight-year prospective surveillance in Rupnagar district of Punjab, India. *Natl Med J India*. 2014;27(2):70-75.

12. Beaton A, Okello E, Rwebembera J, et al. Secondary antibiotic prophylaxis for latent rheumatic heart disease. *N Engl J Med*. 2022;386(3):230-240. doi:10.1056/NEJMoa2102074

13. Coates MM, Sliwa K, Watkins DA, et al. An investment case for the prevention and management of rheumatic heart disease in the African Union 2021-30: a modelling study. *Lancet Glob Health*. 2021;9(7):e957-e966. doi:10.1016/S2214-109X(21)00199-6

14. Dixit J, Prinja S, Jyani G, et al. Evaluating efficiency and equity of prevention and control strategies for rheumatic fever and rheumatic heart disease in India: an extended cost-effectiveness analysis. *Lancet Glob Health*. 2023;11(3):e445-e455. doi:10.1016/S2214-109X(22)00552-6

15. Watkins D, Lubinga SJ, Mayosi B, Babigumira JB. A cost-effectiveness tool to guide the prioritization of interventions for rheumatic fever and rheumatic heart disease control in African nations. *PLoS Negl Trop Dis*. 2016;10(8):e0004860. doi:10.1371/journal.pntd.0004860

16. Karthikeyan G, Kothari SS. How should the burden of rheumatic heart disease be reduced? *Lancet Glob Health*. 2023;11(3):e316-e317. doi:10.1016/S2214-109X(23)00011-6

17. Karthikeyan G, Guilherme L. Acute rheumatic fever. *Lancet*. 2018;392(10142):161-174. doi:10.1016/S0140-6736(18)30999-1

18. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143(5):e72-e227. doi:10.1161/CIR.0000000000000923