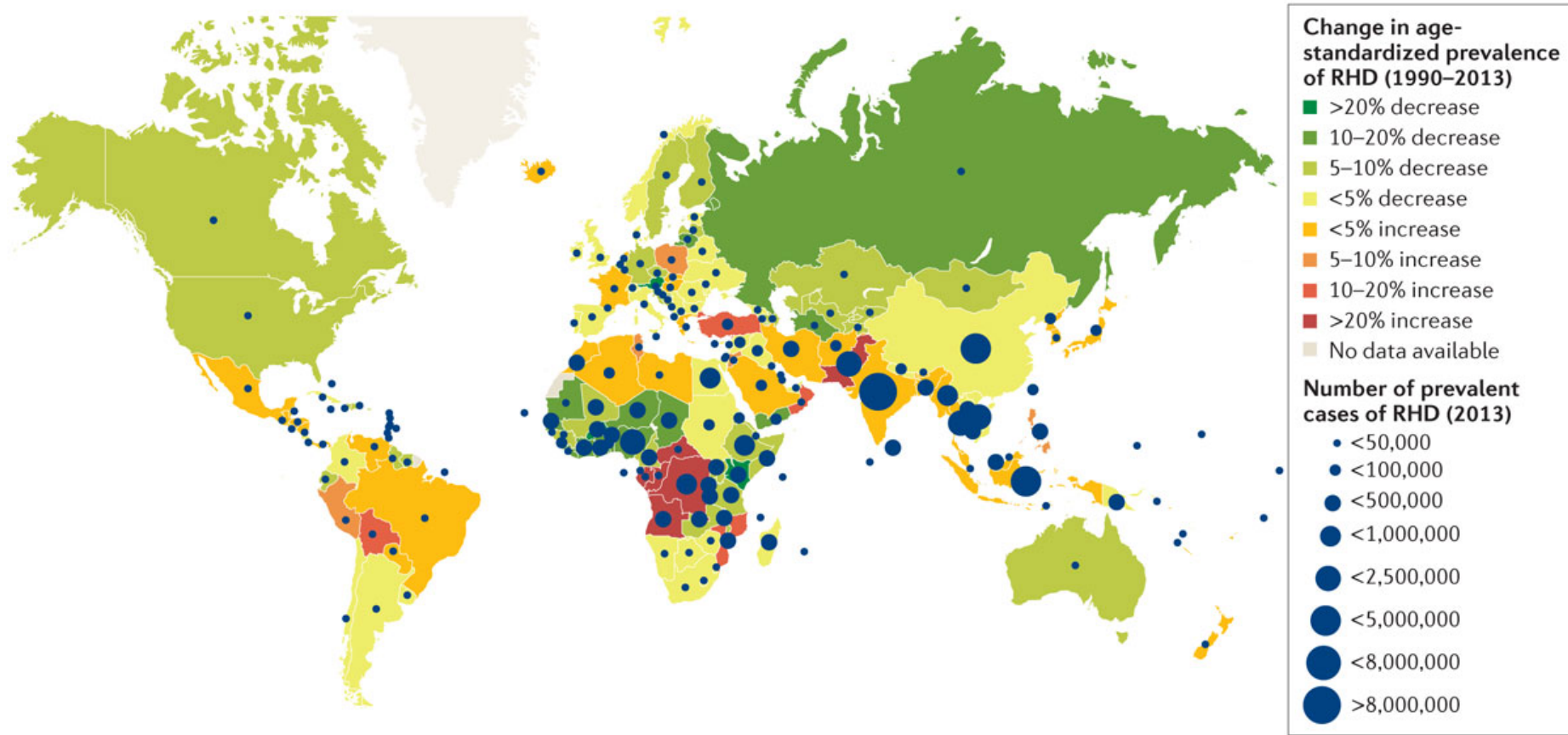




Clinical Outcomes of 3343 Children and Adults with Rheumatic Heart Disease from 14 Developing Countries: 2-Year Follow-up of the Global Rheumatic Heart Disease Registry (REMEDY)

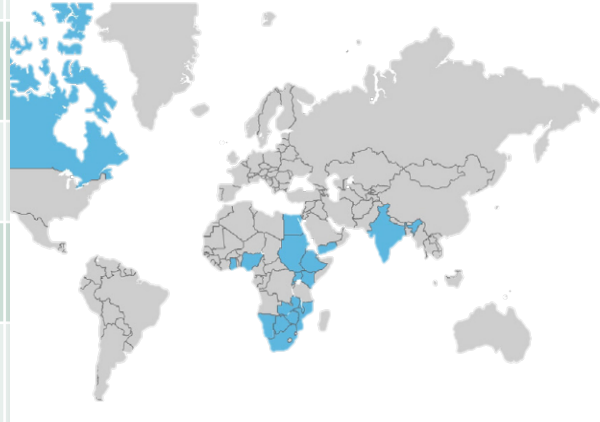
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Koon Teo, PhD Salim Yusuf, D Phil Bongani Mayosi, D Phil
for
the REMEDY investigators





Nature Reviews | Disease Primers



Low income countries (n 1110, 33.2%)	Lower middle income countries (n 1370, 41%)	Upper middle income countries (n 863, 25.8%)
Ethiopia (n 400)	Egypt (n 286)	Namibia (n 266)
Kenya (n 316)	India (n 293)	South Africa (n 654)
Malawi (n 37)	Mozambique (n 41)	
Rwanda (n 5)	Nigeria (n 199)	
Uganda (n 311)	Sudan (n 175)	
Zambia (n 116)	Yemen (n 301)	



Rationale and design of a Global Rheumatic Heart Disease Registry: The REMEDY study

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Background Rheumatic heart disease (RHD) is the principal cause of valvular heart disease–related mortality and morbidity in low- and middle-income countries. The disease predominantly affects children and young adults. It is estimated that RHD may potentially be responsible for 1.4 million deaths annually worldwide and 7.5% of all strokes occurring in developing countries. Despite the staggering global burden, there are no contemporary data documenting the presentation, clinical course, complications, and treatment practices among patients with RHD.

Methods The REMEDY study is a prospective, international, multicenter, hospital-based registry planned in 2 phases: the vanguard phase involving centers in Africa and India will enrol 3,000 participants with RHD over a 1-year period. We will document clinical and echocardiographic characteristics of patients at presentation. Over a 2-year follow-up, we will document disease progression and treatment practices with particular reference to adherence to secondary prophylaxis and oral anticoagulation regimens. With 3,000 patients, we will be able to reliably determine the incidence of all-cause mortality, worsening heart failure requiring hospitalization, systemic embolism (including stroke), and major bleeding individually among all participants. We will identify barriers to care in a subgroup of 500 patients.

Conclusion The REMEDY study will provide comprehensive, contemporary data on patients with RHD and will help in the development of strategies to prevent and manage RHD and its complications. (*Am Heart J* 2012;163:535-540.e1.)



Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study)

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Methods I

- Prospective registry over 24 months
- Baseline and follow-up assessments
 - Baseline: clinical characteristics, pharmacological treatments, and use of percutaneous and surgical interventions
- Follow-up completed in November 2014
 - Adverse cardiovascular events
 - Death, Atrial fibrillation(AF), Bleeding, Congestive Heart Failure, Hospitalisation, Pregnancy, Thrombosis, Stroke, Systemic Embolism, Infective Endocarditis, Surgery/valvuloplasty

Participants	3 343
Age, median [IQR]	28 [18-40]
Females, n (%)	2 211 (66.2)
Women in childbearing age (12-51) , n (%)	1 825 (54.6)
Unemployed adults, n (%)	1 815 (75.3)



Conclusions I

- There are gaps in the implementation of medical and surgical interventions of proven effectiveness for RHD in low and middle income countries.
- These include:
 - Suboptimal use of penicillin for secondary prophylaxis.
 - Inadequate monitoring and control of oral anticoagulant therapy.
 - Extremely limited use of contraception in women with RHD.
 - Disparities in the use of percutaneous and surgical interventions between countries of different income groups.
- Our data reflects that access to evidence-based interventions for RHD are inadequate among the poorest.



Methods II

- Incidence rate
- Univariable comparisons
- Multivariable Cox regression models
- A priori models for death, CCF and Stroke/thromboembolism
- Total follow-up time:
 - 5232.09 person-years
- Total lost to follow-up:
 - 383 (11.4%)
- Follow-up methods:
 - Clinical visit: 52%
 - Telephonic, third party or via hospital records: 19.7%
 - Died: 16.9%



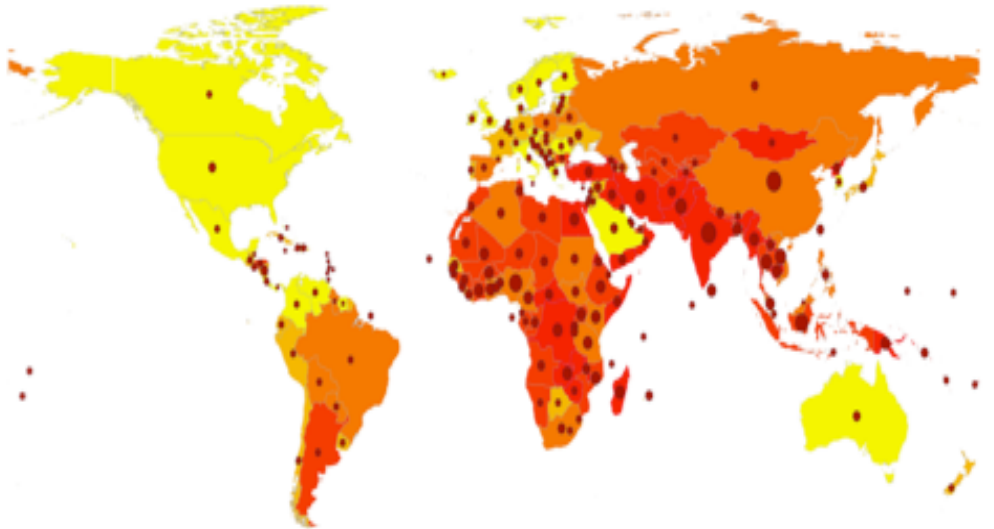
Mortality

Number of prevalent cases of RHD (2013)

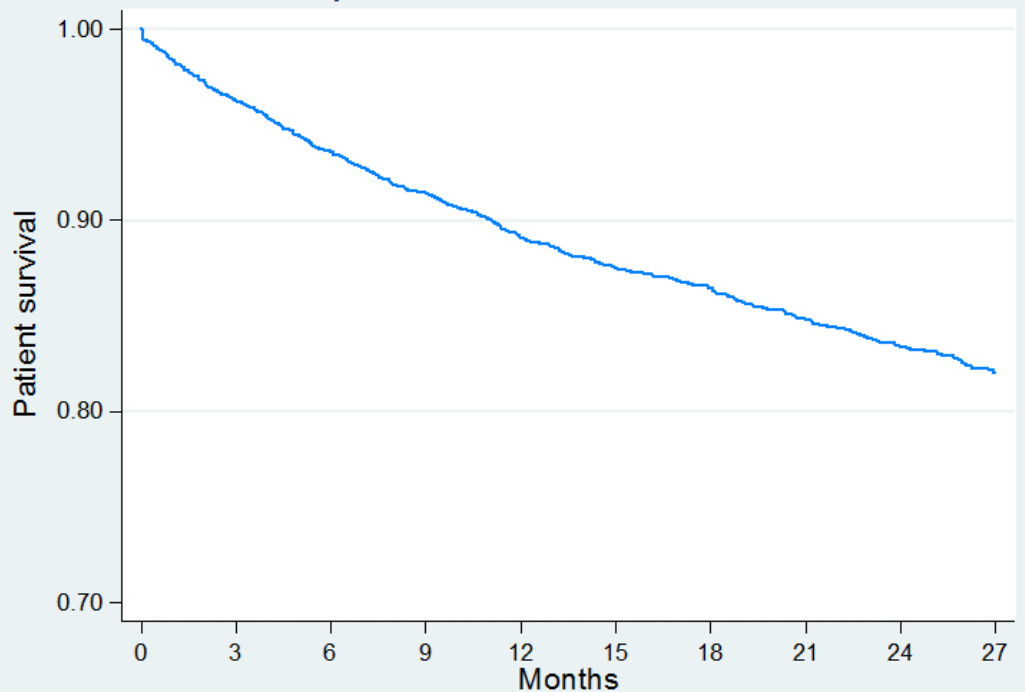
- < 50
- 50 to 10,000
- 10,000 to 100,000
- 100,000 to 500,000
- 500,000 to 1 million
- 1 million to 2.5 million
- 2.5 million to 5 million
- > 5 million

RHD Age-standardised death rate per 100,000 people (2010)

- 0 - 1.99
- 2 - 2.99
- 3 - 4.99
- 5 - 7.99
- > 8



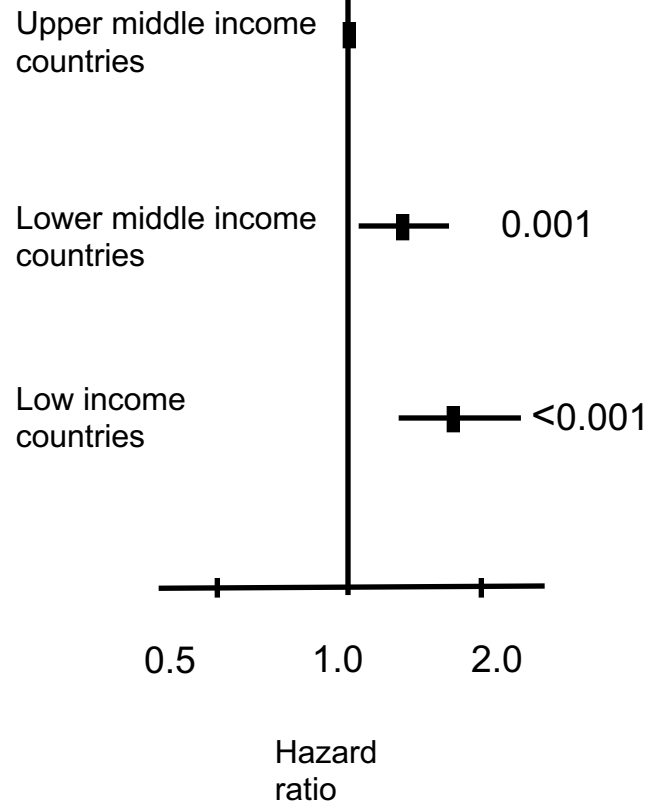
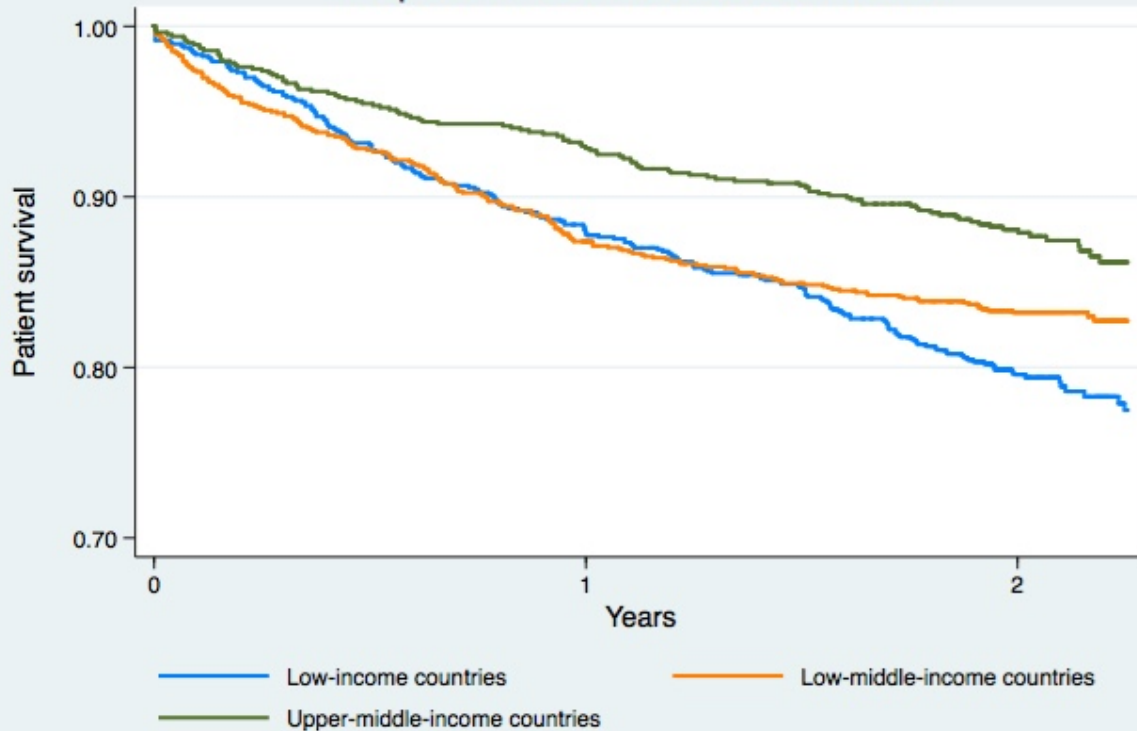
Kaplan-Meier survival estimate



Deaths

n	500 (16.9%)
Median age at death (IQR)	28.6 (17.4-46.6)
Rate per 1000 patient-years (95% CI)	
First year	116.3 (104.3-129.8)
Subsequent period	65.4 (56.4-75.8)

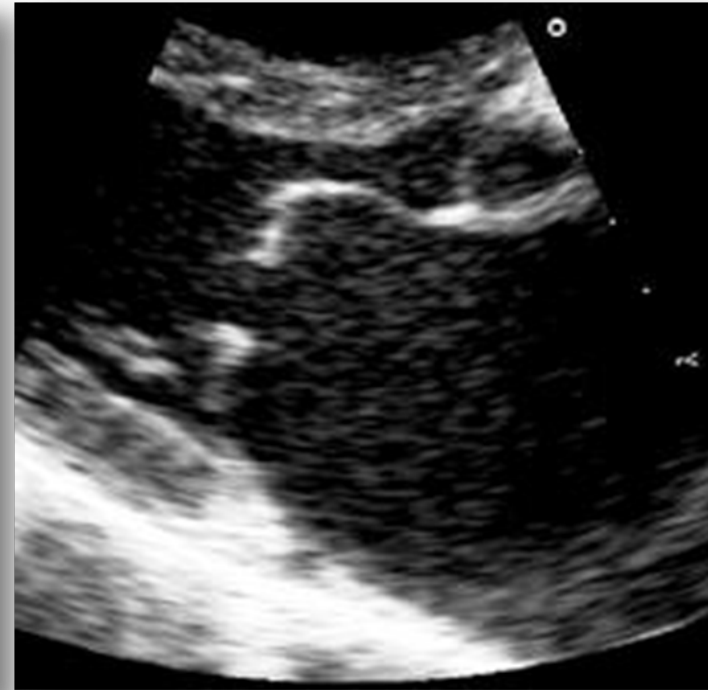
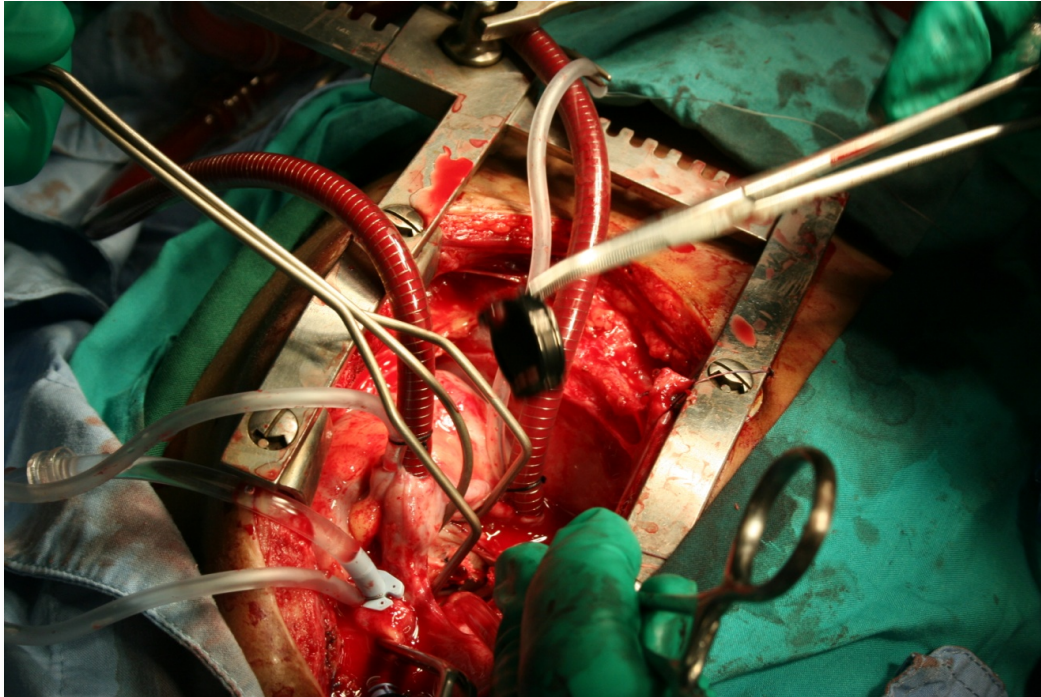
Kaplan-Meier survival estimates



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
Congestive heart failure at enrolment	2.16	1.70 - 2.72	0.001
New York Heart Association functional class III/IV	1.67	1.32 - 2.1	0.001
On secondary antibiotic prophylaxis at enrolment	0.86	0.70 - 1.07	0.165



Adverse events

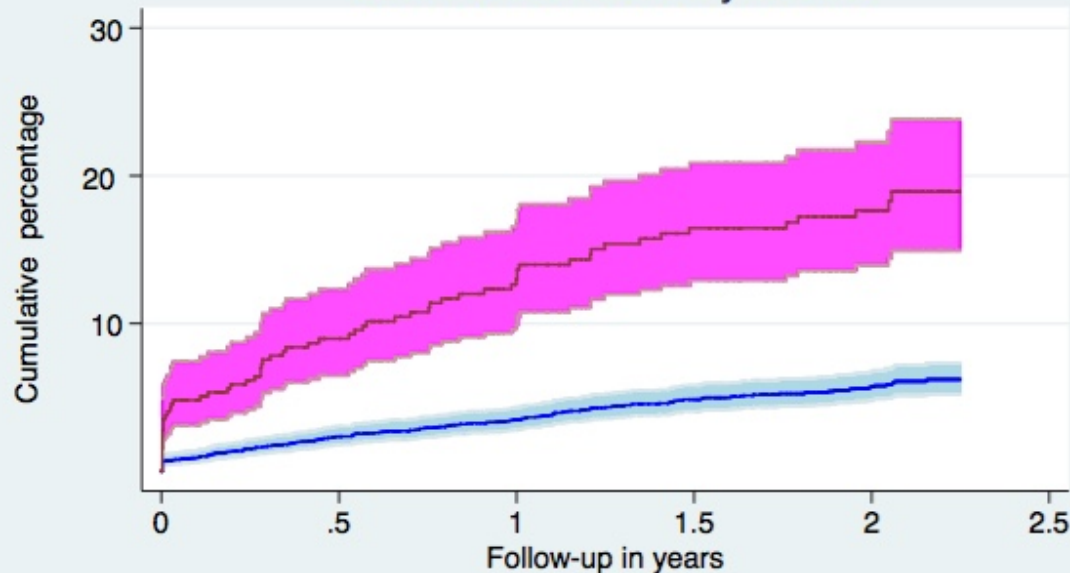


Low income countries (N=956)	Lower-middle income countries (N=1158)	Upper-middle income countries (N=838)	p
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Death, n (%)	200 (20.8)	195 (16.8)	105 (12.5)	<0.001
Congestive heart failure, n (%)	87 (9.0)	66 (5.7)	51 (6.1)	0.006
Atrial fibrillation, n (%)	28 (2.9)	14 (1.2)	14 (1.7)	0.013
Stroke or transient ischaemic attack, n (%)	14 (1.5)	12 (1.0)	20 (2.4)	0.053



Cumulative mortality curve



Number at risk		0	0.5	1	1.5	2	2.5
Enrolment in cardiac failure	396	311	262	232	162	0	0
No cardiac failure	2544	2385	2267	2169	1505	0	0

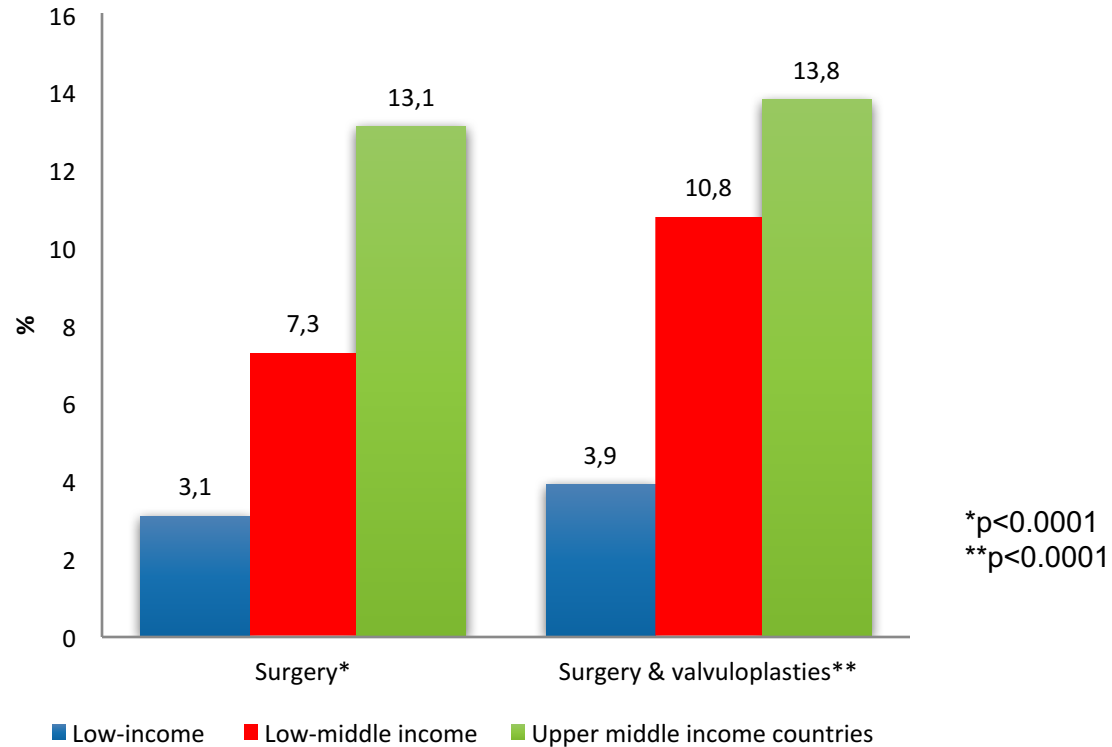
■	95% CI	■	95% CI
—	not in Cardiac Failure at enrolment	—	Enrolled in Cardiac Failure

Multivariate Hazard ratios- composite of CHF and Death

n	204
Enrolled in CHF	2.11 (1.67-2.75) P<0.001
NYHA III&IV	1.76 (1.42-2.17) P<0.001
Severe Valve disease	2.15 (1.68-2.75) P<0.001
Secondary prophylaxis	0.81 (0.65-0.99) P=0.04
Higher than primary education	0.70 (0.57-0.87) P=0.001

Surgery and valvuloplasty

Crude incidence rates of interventions



Comparison of baseline characteristics of patients lost to follow-up compared to those whose vital status was known at the end of the study

	Vital status known	Lost to follow-up	p
	2960 (88.5)	383 (11.5)	
Age (med, IQR)	28 (18-41)	26 (17-36)	0.0016
Low-income countries	964 (32.6)	146 (38.1)	
Upper-middle income countries	838 (28.3)	25 (6.5)	<0.0001
Severe involvement	1470 (49.6)	239 (62.4)	<0.0001
Previous intervention or surgery	2212 (74.9)	339 (34.6)	<0.0001
NYHA III&IV	679 (23.3)	130 (34.6)	<0.0001
Higher education	1328 (44.6)	96 (24.6)	<0.0001



Conclusions

- This contemporary registry indicates unequivocally that the rates of death, CHF and stroke are high amongst symptomatic patients living in RHD in LMICs despite their relatively low age.
- Nearly 20% developed one of these complications over two years.
- Mortality was significantly higher in patients living in low-income countries and amongst the less educated.
- Better access to high-quality tertiary care services and optimising the use of proven interventions are likely to improve outcomes.
- More research is needed to devise effective ways of improving access to essential care amongst patients with RHD in LMICs.



Global Rheumatic Heart Disease Registry

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