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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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Aims Rheumatic heart disease (RHD) accounts for over a million premature deaths annually; however, there is little contemporary information on presentation, complications, and treatment.

Methods and results This prospective registry enrolled 3343 patients (median age 28 years, 66.2% female) presenting with RHD at 25 hospitals in 12 African countries, India, and Yemen between January 2010 and November 2012. The majority (63.9%) had moderate-to-severe multivalvular disease complicated by congestive heart failure (33.4%), pulmonary hypertension (28.8%), atrial fibrillation (AF) (21.8%), stroke (7.1%), infective endocarditis (4%), and major bleeding (2.7%).

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One-quarter of adults and 5.3% of children had decreased left ventricular (LV) systolic function; 23% of adults and 14.1% of children had dilated LVs. Fifty-five percent ($n = 1761$) of patients were on secondary antibiotic prophylaxis. Oral anti-coagulants were prescribed in 69.5% ($n = 946$) of patients with mechanical valves ($n = 501$), AF ($n = 397$), and high-risk mitral stenosis in sinus rhythm ($n = 48$). However, only 28.3% ($n = 269$) had a therapeutic international normalized ratio. Among 1825 women of childbearing age (12–51 years), only 3.6% ($n = 65$) were on contraception. The utilization of valvuloplasty and valve surgery was higher in upper-middle compared with lower-income countries.

Conclusion Rheumatic heart disease patients were young, predominantly female, and had high prevalence of major cardiovascular complications. There is suboptimal utilization of secondary antibiotic prophylaxis, oral anti-coagulation, and contraception, and variations in the use of percutaneous and surgical interventions by country income level.

Keywords Rheumatic heart disease • Atrial fibrillation • Congestive heart failure • Stroke • Infective endocarditis • Valvuloplasty • Valve surgery

Introduction

Rheumatic heart disease (RHD) is one of the leading non-communicable diseases in low- and middle-income countries and accounts for up to 1.4 million deaths per year.[1,2] Patients with RHD also suffer from complications related to atrial fibrillation (AF), infective endocarditis, and during pregnancy.[3–5] Despite the magnitude of the problem, there are few systematically collected contemporary data on disease characteristics, treatments, complications, and long-term outcomes in patients with RHD.[6] The proposal of the World Health Organization to reduce mortality from RHD and other NCDs by 25% by the year 2025 requires an understanding of the contemporary characteristics and the use of proven interventions in patients living in endemic countries.[7]

Much of the morbidity and mortality due to RHD can be prevented by existing therapies.[8,9] There is good evidence to suggest that secondary prophylaxis with long-acting penicillin reduces the recurrence of episodes of acute rheumatic fever.[10] Oral anti-coagulants (OACs) in patients with rheumatic AF can reduce thromboembolic complications, and percutaneous or surgical interventions can improve symptoms and prevent congestive heart failure (CHF).[11,12] However, several older reports from developing countries have documented inadequate adherence to secondary prophylaxis and poor control of OAC therapy,[13–15] and it is not known whether this has changed in recent times. In addition, rates of the use of percutaneous and surgical interventions in developing countries may be limited by the shortage of health facilities and trained staff.[16]

The Global Rheumatic Heart Disease Registry (the REMEDY study) was designed to assemble a contemporary cohort of RHD patients from developing countries to document patient characteristics and treatment patterns with particular reference to valvular involvement, the prevalence of adverse cardiac events and the use of key treatments.[17]

Methods

Study design

The Global Rheumatic Heart Disease Registry is a multi-centre, international hospital-based prospective registry of patients with RHD which is conducted in two phases: a pilot phase which will be followed by a full study. The baseline characteristics of patients enrolled in the pilot phase are reported here. Enrolled patients underwent assessment and treatment according to standard practices followed at each participating site. Patients were enrolled from 25 sites in 12 African countries, Yemen, and India. Countries were grouped into three income categories (2011 World Bank definitions): low-income countries (Ethiopia, Kenya, Malawi, Rwanda, Uganda, and Zambia), lower-middle-income countries (Egypt, India, Mozambique, Nigeria, Sudan, and Yemen), and upper-middle-income countries (Namibia and South Africa).[18] This study was approved by local ethics committees and written informed consent was obtained from the subjects (adults $\geq$ 18 years) or their guardians (children $<$ 18 years).

The rationale, design, and objectives of the REMEDY study have been described previously.[17]

We enrolled patients regardless of age with a primary diagnosis of symptomatic RHD from outpatient clinics, emergency departments, or inpatient facilities, based on clinical and echocardiographic criteria.[19] Patients with asymptomatic disease diagnosed through community screening were not included. The AHA/ACC guidelines were used for assessment of severity of valve lesions, left ventricular (LV) systolic dysfunction (i.e. left ventricular ejection fraction, LVEF $<$ 54% in children and adults), and LV dilatation (i.e. LV end diastolic dimension $<$ 50 mm in children and $<$ 55 mm in adults).[11] Adherence to penicillin prophylaxis was calculated based on percentage of prescriptions received over the 12 months preceding enrolment. Patients were excluded from the study if the primary diagnosis of valvular disease was not RHD.

Data collection

Demographic data, clinical findings, and details of electrocardiographic and echocardiographic findings were recorded on case report forms at research sites and transmitted to the University of Cape Town Department of Medicine Project Coordinating Office. These were relayed to the Population Health Research Institute at Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada for further data checks and data storage.

Statistical considerations

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 unpaired *t*-test was used to determine group differences for continuous variables. Linear regression was utilized to explore relationships between variables. Test results were adjusted by age and by

specifying study centres as clusters. Statistical analyses were performed using STATA 11 (StataCorp, College Station, TX, USA).

Results

Clinical characteristics

A total of 3343 participants with RHD were enrolled between January 2010 and November 2012 (Supplementary material online, *Table S1*). Patients with RHD were young (median age 28 years), mainly female (66.2%), and largely unemployed (75.3%) (*Table 1* and *Figure 1*). There were greater proportions of women in childbearing age in low-income (86.5%) and lower-middle-income countries (90.3%) compared with upper-middle-income countries (66.9%) ($P < 0.01$).

Atrial fibrillation was documented in 586/2688 (21.8%) of patients with electrocardiograms performed at enrolment to the study (*Table 2*). There were substantial variations in clinical features and the use of percutaneous and surgical interventions between the different country income groups (*Table 2*). Stroke, peripheral embolism, and the composite outcome of cardiovascular complications (i.e. stroke, systemic embolism, bleeding, or infective endocarditis) were reported more frequently in patients living in upper-middle-income countries (14.5, 2.2, and 22.2%, respectively) compared with those from lower-middle-income (3,8, 0.2, and 10.1%, respectively) and low-income countries (5.2, 0.3, and 8.7%, respectively) ($P < 0.02$). The proportion of children with decreased LVEF was lower in upper-middle-income countries than in lower-middle- and low-income countries ($P < 0.01$). The use of valve replacement/repair and valvuloplasty positively correlated with rising country income level ($P \leq 0.03$) (*Table 2* and *Figure 2*).

Pattern and severity of native valve disease

Figure 3 demonstrates the pattern of valve disease by age group in patients without percutaneous or surgical intervention. Children in the first decade of life presented predominantly with pure mitral regurgitation, with mixed mitral and mixed aortic valve disease emerging as a dominant mitral valve lesion from the second decade of life. The frequency of pure mitral stenosis, isolated aortic valve disease (i.e. aortic stenosis or aortic regurgitation) and mixed aortic valve disease without mitral disease was low in early life, and increased with age.

The majority of cases of mitral stenosis (1119/1535, 72.9%), mitral regurgitation (1479/2464, 60.4%), pulmonary stenosis (19/32, 59.4%), tricuspid stenosis (58/107, 54.2%), and aortic stenosis (187/302, 61.9%) had moderate-to-severe disease, whereas the majority of cases of aortic regurgitation (922/1671, 55.2%) were mild. Patients with native valve disease had a dilated left ventricle (LV) in 23% ($n = 581$) of adults and 16.4% ($n = 413$) of children, and a decreased ejection fraction in 18.3% ($n = 460$) of adults and 5.6% ($n = 140$) of children. There was a gradient as patients increased in age for dilated LV ($P < 0.0001$) and falling LVEF ($P < 0.0001$), which suggest disease progression.

The use of secondary prophylaxis

Overall, secondary penicillin prophylaxis was prescribed in 54.8% (1761/3213) of patients. Intramuscular penicillin was the commonest mode of administration, used by 1926 (89.5%) of patients with data ($n = 2153$); the remainder (227, 10.5%) were either on oral penicillin or erythromycin. The use of secondary prophylaxis differed by country income group (*Figure 4*). Whereas oral and parenteral antibiotics were used in almost equal proportions in upper-middle-income countries, nearly all participants in low- and lower-middle-income countries received intramuscular penicillin. Overall, adherence to intramuscular penicillin and oral antibiotic prophylaxis was similar (i.e. 78.6 $\pm$ 32.3 and 78.0 $\pm$ 32.9%, respectively). However, adherence was higher in children compared with adults, for both intramuscular penicillin (81.8 $\pm$ 30.8 vs. 76.9 $\pm$ 33.1%, $P < 0.001$) and oral antibiotics (83.1 $\pm$ 24.9 vs. 75.0 $\pm$ 36.6%; $P < 0.001$), respectively. Post-surgery patients were less likely to be on secondary prophylaxis compared with those awaiting surgery (31.1 compared with 61.5%, $P < 0{\cdot}001$). Patients on a 2-weekly intramuscular regime showed lower levels of adherence (68·4%) than those on either a 3-weekly (76.0%) or 4-weekly regimen (82.8%) ($P < 0.05$).

The use of oral anti-coagulants and other medications

There were 1362 (40.7%) patients with indications for OACs in RHD (*Table 3*).[11] Oral anti-coagulants were prescribed in 69.5% (946) of such patients; the use of OACs was high in patients with mechanical heart valves (91.6%) and AF (68.6%), but low in those with mitral stenosis in sinus rhythm with either dilated left atrium or left atrial thrombus (20.3%). Of the patients on OACs for the recognized indications, 12.2% (115) had had no international normalized ratio (INR) monitoring, whereas 34.1% (323) had only one to three INR tests in the 6 months preceding enrolment. The INR at enrolment was subtherapeutic in 32.7% (309), therapeutic in 28.3% (268), and above the therapeutic range in 17.7% (167) (no INR testing on the remainder of 21.4% (202)). Sixty percent of participants were unaware of the therapeutic range of INR values.

There was a high use of additional medication: 67.8% (2239/3296) of patients were on diuretics, 39.3% (1296/3296) on β-blockers, 34.7% (1144/3298) on digoxin, and 1.6% (52/3279) on other anti-arrhythmic drugs. Of those tested for human immune deficiency virus (HIV) infection (1180, 35.3%), 56 (4.7%) were HIV positive; the remainder (2163, 64.7%) were either unaware of their HIV status or declined to provide the information. In 1825, women of childbearing age (12–51 years), only 3.6% (65) were on contraceptive medication. A total of 73 women (3·6%) were pregnant at the time of enrolment, the youngest 14 years, and the oldest 51 years of age. In total, 15 (20.6%) pregnant women were on warfarin.

Discussion

This study has five main findings. First, the patients with RHD from low- and middle-income countries were young (median age 28 years), largely female (66.2%), and had a high unemployment rate (75.3%). Second, the majority had moderate-to-severe valvular heart disease that was associated with pulmonary hypertension and up to a quarter of patients had LV dysfunction. Third, there was an inadequate use of secondary antibiotic prophylaxis in developing countries, with lack of preventive treatment in nearly half of

Table 1 Demographic characteristics of 3343 children and adults with rheumatic heart disease

	Low-income countries	Lower-middle-income countries	Upper-middle-income countries	P	Total
Participants, *n* (%)	1110 (33.2)	1370 (41.0)	863 (25.8)		3343
Age, median (IQR)[a]	24 (15–34)	28 (18–38)	39 (22–52)	0.4	28 (18–40)
Women, *n* (%)[b]	728 (65.8)	867 (63)	616 (71.3)	0.33	2211 (66.2)
Women in childbearing age, *n* (%)[c]	630 (86.5)	783 (90.3)	412 (66.9)	<0.01	1825 (82.5)
Children, *n* (%)[d]	405 (36.6)	349 (25.5)	167 (19.4)	0.54	921 (27.6)
Adults with no formal schooling, *n* (%)[e]	66 (9.5)	354 (34.9)	38 (5.5)	<0.01	458 (19.1)
Completed primary level schooling	246 (35.2)	278 (27.4)	204 (29.6)	0.48	728 (30.3)
Completed secondary level schooling	373 (53.4)	372 (36.7)	436 (63.3)	0.03	1181 (49.2)
Completed tertiary level education	13 (1.98)	10 (1.0)	11 (1.6)	0.5	34 (1.4)
Unemployed adults, *n* (%)[f,g]	529 (75.4)	766 (75.1)	520 (75.5)	0.98	1815 (75.3)

[a]Data are available for 3339 participants.
[b]Data are available for 3340 participants.
[c]Defined as between the ages of 12 and 51.
[d]Children are defined as younger than 19 years of age.
[e]Data are available for 3317 participants.
[f]Data are available for 2411 participants.
[g]Adults are 19 years or older.

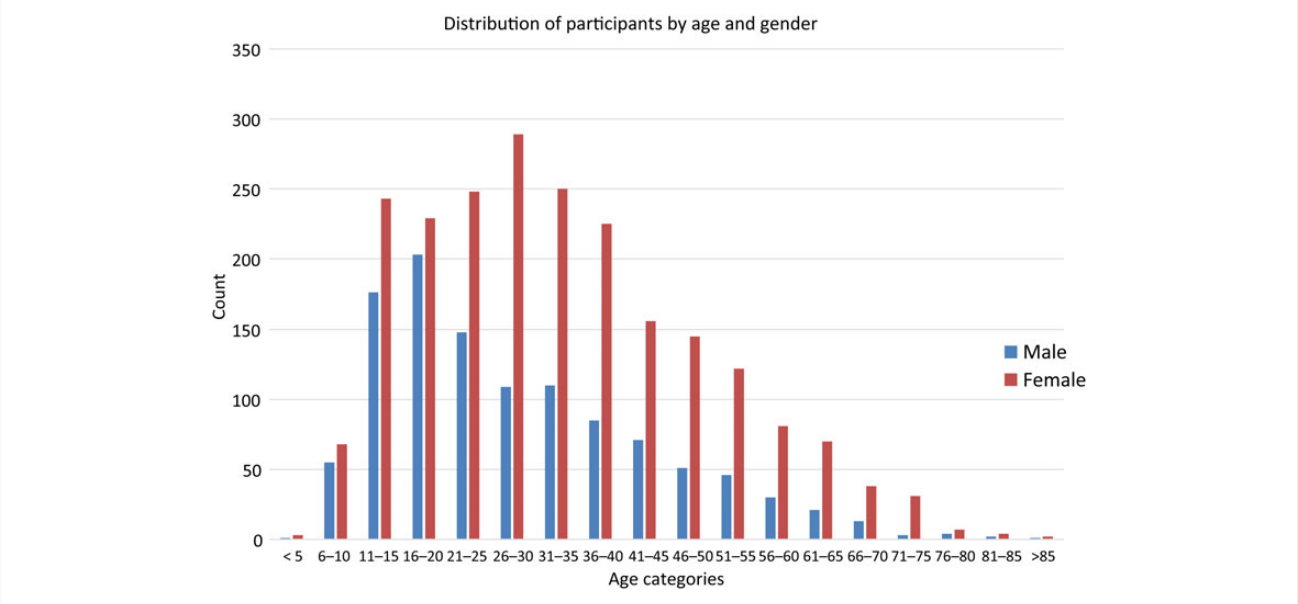

Figure 1 Age and gender distribution of 3339 children and adults with rheumatic heart disease.

patients. Fourth, whilst the overall use of OACs in patients with appropriate indications was relatively high (69.5%), it was low in patients with mitral stenosis in sinus rhythm at high risk for cardiac embolism. The quality of anti-coagulation control at study enrolment was poor, with only a quarter of patients having INRs in the therapeutic range. Finally, there were variations between low-, lower-middle- and upper-middle-income countries in the ascertainment and prevalence of cardiovascular complications, and the use of percutaneous and surgical interventions for RHD.

Rheumatic heart disease is a chronic disease of the young that accounts for the greatest cardiovascular related loss of disability-adjusted life years in children.[20] Whilst female predominance is well recognized,[9] the prominence of women in the reproductive age has major implications for the reproductive health of patients living in developing countries.[21] Rheumatic heart disease increases the risk of pregnancy and is one of the major non-obstetric causes of maternal death in Africa.[3,22] The extremely low rate of the use of contraception in this cohort is alarming, and reflects the poor

Table 2 Clinical characteristics of 3343 children and adults with rheumatic heart disease

	Low-income countries (*N* 1110) *N* (%)	Lower-middle-income countries (*N* 1370) *N* (%)	Upper-middle-income countries (*N* 863) *N* (%)	*P*
New York Heart Association Functional Class III & IV	306 (27.6)	384 (29.1)	119 (13.9)	0.24
Medical history				
Acute rheumatic fever	247 (22.3)	593 (44.3)	500 (59.0)	0.06
Congestive heart failure	476 (43.0)	285 (21.0)	349 (40.6)	0.06
Pulmonary hypertension	329 (29.9)	465 (34.2)	163 (19)	0.5
Stroke	58 (5.2)	52 (3.8)	125 (14.5)	<0.01
Infective endocarditis	25 (2.3)	59 (4.36)	49 (5.7)	0.1
Major Bleeding	21 (1.9)	38 (2.8)	30 (3.5)	0.61
Peripheral embolism	3 (0.3)	3 (0.2)	19 (2.2)	<0.001
Cardiovascular complications[a]	96 (8.7)	137 (10.1)	191 (22.2)	0.02
Atrial fibrillation	163 (17.9)	241 (22.0)	182 (22.7)	0.49
Echocardiography				
Decreased LVEF in adults	223 (20.6)	262 (19.8)	176 (22.2)	0.58
Decreased LVEF in children	67 (6.2)	83 (6.3)	18 (2.3)	<0.01
Dilated LVEDD in adults	260 (23.9)	302 (22.7)	180 (22.3)	0.81
Dilated LVEDD in children	191 (17.6)	177 (13.3)	86 (10.7)	0.3
Left atrial thrombus	19 (1.8)	18 (1.4)	7 (0.8)	0.6
Surgery				
Valve replacement or repair	81 (11.3)	199 (27.8)	435 (60.8)	<0.01
Mechanical valve only	55 (93.2)	136 (86.6)	349 (93.8)	0.31
Bio-prosthetic valve only	4 (6.8)	18 (11.5)	19 (5.1)	
Mechanical and biological prostheses	0 (0)	3 (1.9)	4 (1.1)	
Percutaneous valvuloplasty	12 (1.1)	54 (4.0)	69 (8.0)	0.03

LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic dimension.
[a]Cardiovascular complications include any of the following events: stroke, infective endocarditis, major bleeding, or peripheral embolism.

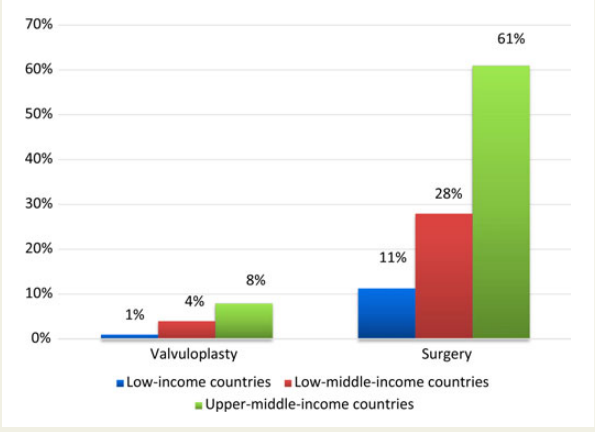

Figure 2 Utilization of valve surgery and valvuloplasty in children and adults from low-income, lower-middle-income, and upper-middle-income countries.

provision of family planning and pre-pregnancy advice for women with heart disease in many regions of the world.[21,23] We found that 20.6% of women who were pregnant were on warfarin despite the known teratogenicity of the agent. This calls for safer alternatives in these women.

The pattern of rheumatic valve involvement that is characterized by pure mitral regurgitation in the first two decades of life is similar to what has been observed previously.[24–27] This study additionally found that the patients had moderate-to-severe rheumatic valve disease that was associated with pulmonary hypertension and LV dysfunction in substantial proportions of cases. The enrolment of severe cases probably reflects the referral patterns to the participating sites which served as tertiary centres in their countries. These patients are at high risk of developing CHF and infective endocarditis and will require surgical intervention. In the Heart of Soweto study of 344 new cases of RHD seen at a tertiary centre, 22% required valve replacement/repair within a year, and 26% developed infective endocarditis within 30 months.[24]

While the effectiveness of control programmes of RHD through secondary prevention in the form of regular long-acting intramuscular benzathine penicillin injections is proven,[28] implementation is difficult and extremely variable both within and between countries.[29] Low uptake has been highlighted in numerous countries.[13,14,30,31] The WHO recommends the life-long use of antibiotic prophylaxis to prevent rheumatic fever in patients with moderate-to-severe RHD,

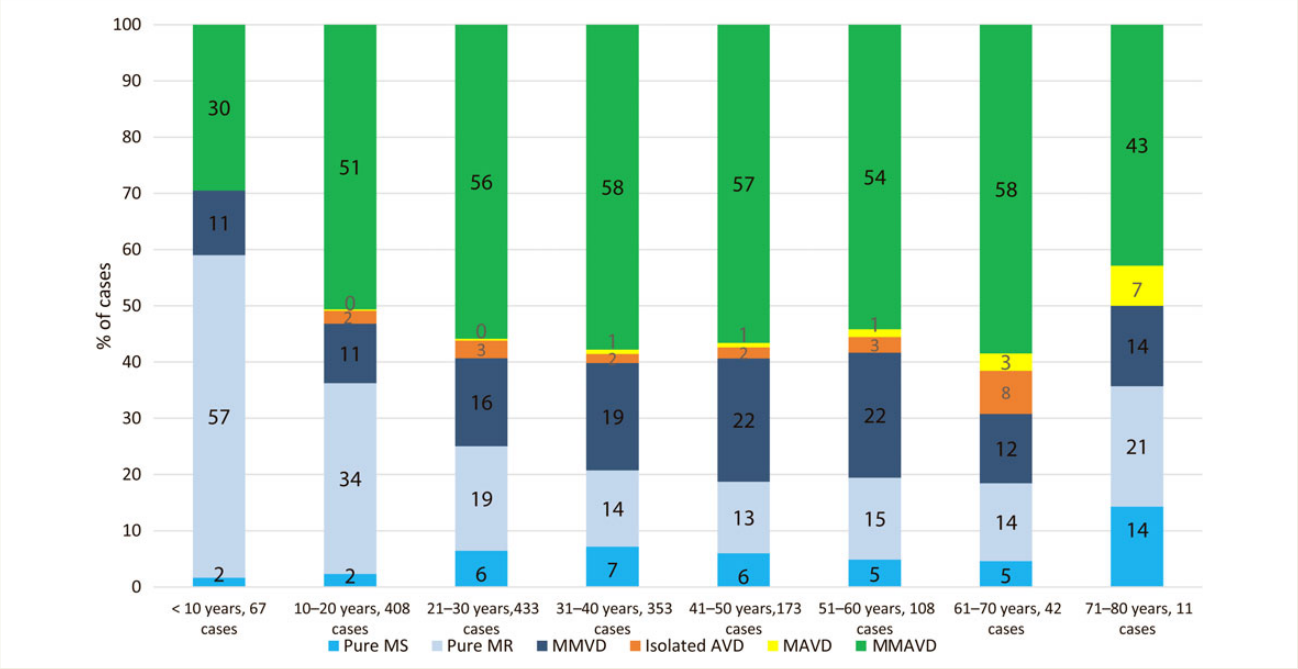

Figure 3 The pattern of native rheumatic valve disease in 2475 children and adults with no percutaneous or surgical interventions. AVD, aortic valve disease; MAVD, mixed aortic valve disease; MMAVD, mixed aortic and mitral valve disease; MMVD, mixed mitral valve disease; MR, mitral regurgitation; MS, mitral stenosis.

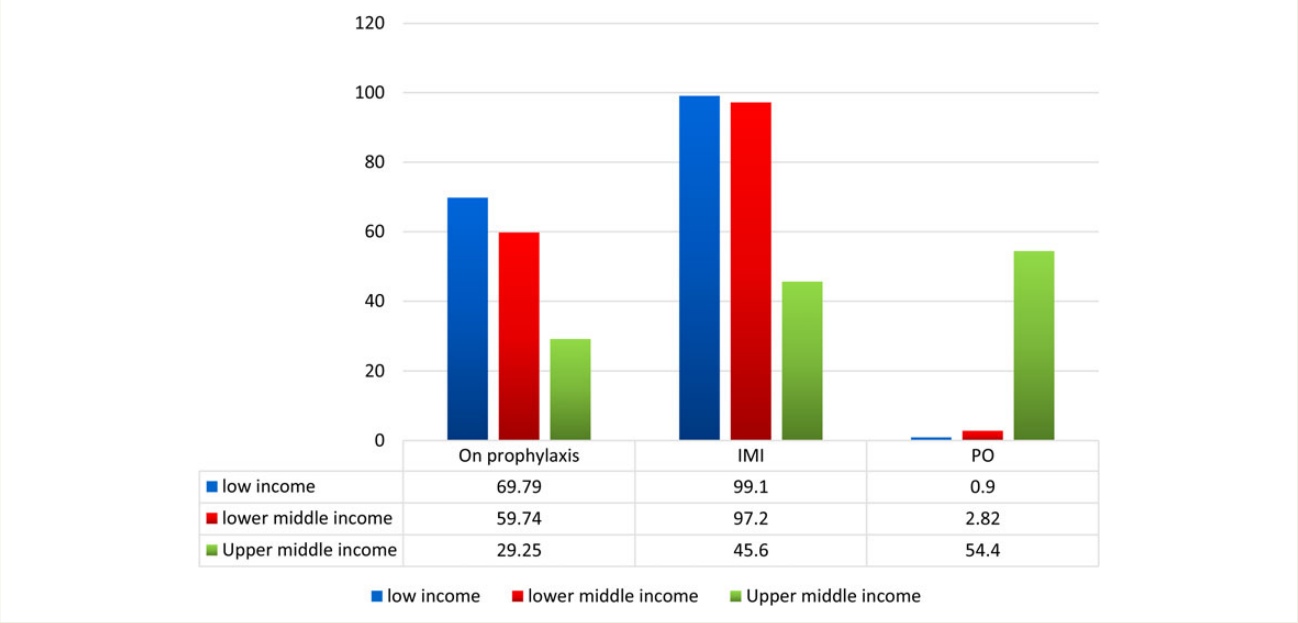

Figure 4 Adherence to secondary prophylaxis with penicillin in low-income, low-middle-income, and upper-middle-income countries.

such as those enrolled in this study.[32] However, nearly half of participants in this study were not on antibiotic prophylaxis at the time of enrolment. Thus, there is a need to identify barriers and enhance the delivery of secondary prophylaxis for RHD within the framework of care for chronic diseases in low- and middle-income countries.[33]

Oral anti-coagulants are recommended in RHD patients with mechanical heart valves, valvular heart disease associated with AF, or patients in sinus rhythm with mitral stenosis associated with a high-risk factor such as previous stroke, left atrial thrombus, or dilated left atrium.[11] In the present study, OACs were prescribed in 70% of

Table 3 Use of anti-thrombotic medication and quality of anti-coagulation in patients with an indication for oral anti-coagulant therapy

Indication	Anti-thrombotic medication	*N* (%)	Details	*N* (%)[a]
Mechanical valves	Warfarin	501 (91.6)	No INR tests done in 6 months prior to enrolment	28 (5.6)
			1–3 INR tests done 6 months prior to enrolment	155 (30.9)
			Enrolment INR tests <2.5	198 (39.5)
			Enrolment INR tests in 2.5–3.5 range	168 (33.5)
			Enrolment INR tests > 3.5	72 (14.4)
	None	41 (7.5)		
	Aspirin	5 (0.9)		
	Total	547		
Atrial fibrillation	Warfarin	397 (67.8)	No INR tests done in 6 months prior to enrolment	58 (14.6)
			1–3 INR tests done 6 months prior to enrolment	147 (37.0)
			Enrolment INR tests <2.0	94 (23.7)
			Enrolment INR tests in 2.0–3.0 range	88 (22.2)
			Enrolment INR > 3.0	85 (21.4)
	None	126 (21.5)		
	Aspirin	55 (9.5)		
	Other (heparin)	8 (1.5)		
	Total	586		
Mitral stenosis in sinus rhythm and left atrial diameter ≥ 55 or left atrial thrombus	Warfarin	48 (20.3)	No INR tests done in 6 months prior to enrolment	29 (60.4)
			1–3 INR tests done 6 months prior to enrolment	21 (43.8)
			Enrolment INR tests <2.0	17 (35.4)
			Enrolment INR tests in 2.0–3.0 range	12 (25.0)
			Enrolment INR >3.0	10 (20.8)
	None	169 (71.6)		
	Aspirin	19 (8.0)		
	Total	236		

[a]The denominator is the number of patients on warfarin for each indication; INR, international normalized ratio; target range for mechanical prosthetic valves, 2.5–3.5; target range for rheumatic atrial fibrillation or mitral stenosis in sinus rhythm with high-risk features, 2.0–3.0.

patients with these indications, which is higher than the 58% use of OACs found in a world-wide registry of non-rheumatic AF.[15] International normalized ratio control was however poor, with only ~1 in 4 patients on OACs having therapeutic INR levels at the time of enrolment. Alternative strategies for improving anticoagulation in lower- and middle-income countries need to be considered, including the use of point-of-care INR testing and trials of new forms of oral anti-coagulants in RHD patients with native valves.[34–36] This study provides a basis for trials comparing different strategies for anti-coagulation in RHD patients who have been excluded in virtually all randomized controlled trials of stroke prevention.[15]

We observed variations in the ascertainment of cardiovascular complications, echocardiographic LV dysfunction and the use of percutaneous and surgical intervention by country income status. The increasing prevalence of cardiovascular sequelae with rising country income status was independent of age, suggesting more effective detection of such sequelae. The use of percutaneous and surgical interventions was extremely low in low-income countries compared with upper-middle-income countries, despite the greater prevalence of patients with RHD and LV dysfunction who require these interventions in low-income countries. These disparities in the ascertainment of cardiovascular complications and the use of effective invasive interventions probably reflect differences in access to healthcare between countries.

Limitations: We report a hospital-based registry and cannot address the burden of disease in the community. Owing to the need for availability of cardiology expertise and echocardiography facilities for the diagnosis of RHD in the study, we have enrolled cases of moderate-to-severe symptomatic RHD typically seen at referral centres. But several of our participating sites (e.g. Namibia and Zambia) were the sole (or one of few) referral centres in their respective countries, thereby providing a representative snapshot of symptomatic disease in these countries. Furthermore, past events were self- or physician reported, and were not independently verified. Similarly, adherence to secondary prophylaxis was not verified using pill counts or registers, as these were largely unavailable in the countries involved. However, INR measurements were verified from laboratory records. Finally, an additional limitation of the REMEDY baseline study is that we report observations of a cross-sectional study. The interpretation of the findings of a cross-sectional study are inherently limited. This particularly applies to comparisons across country income status as those are prone to ecological fallacy.

Conclusions

There are gaps in the implementation of medical and surgical interventions of proven effectiveness for RHD in low- and middle-income countries.[7,19] These include the suboptimal use of penicillin for

secondary prophylaxis, inadequate monitoring and control of oral anti-coagulant therapy, the dearth of reproductive services for women with RHD, and disparities in the use of percutaneous and surgical interventions between different countries.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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