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)

Liesl Zühlke, PhD Ganesan Karthikeyan, DM Mark E. Engel, PhD Koon Teo, PhD Salim Yusuf, D Phil Bongani Mayosi, D Phil

for the REMEDY investigators
<table>
<thead>
<tr>
<th>Low income countries</th>
<th>Lower middle income countries</th>
<th>Upper middle income countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n 1110, 33.2%)</td>
<td>(n 1370, 41%)</td>
<td>(n 863, 25.8%)</td>
</tr>
<tr>
<td>Ethiopia (n 400)</td>
<td>Egypt (n 286)</td>
<td>Namibia (n 266)</td>
</tr>
<tr>
<td>Kenya (n 316)</td>
<td>India (n 293)</td>
<td>South Africa (n 654)</td>
</tr>
<tr>
<td>Malawi (n 37)</td>
<td>Mozambique (n 41)</td>
<td></td>
</tr>
<tr>
<td>Rwanda (n 5)</td>
<td>Nigeria (n 199)</td>
<td></td>
</tr>
<tr>
<td>Uganda (n 311)</td>
<td>Sudan (n 175)</td>
<td></td>
</tr>
<tr>
<td>Zambia (n 116)</td>
<td>Yemen (n 301)</td>
<td></td>
</tr>
</tbody>
</table>
Rationale and design of a Global Rheumatic Heart Disease Registry: The REMEDY study

Ganeesan Karthikeyan, DM, Liisi Zühlke, MBChB, MPH, Mark Engel, MPH, Sumathy Rangarajan, MSc, Salim Yusuf, DPh, Koon Teo, PhD, and Bongani M. Mayosi, DPhil. New Delhi, India; Cape Town, South Africa; and Ontario, Canada.

Background Rheumatic heart disease (RHD) is the principal cause of valvular heart disease-related morbidity and mortality 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 75% 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 India and Africa 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;163:533-540.e1)
Methods

- 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

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Participants</td>
<td>3,343</td>
</tr>
<tr>
<td>Age, median [IQR]</td>
<td>28 [18-40]</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>2,211 (66.2)</td>
</tr>
<tr>
<td>Women in childbearing age (12-51), n (%)</td>
<td>1,825 (54.6)</td>
</tr>
<tr>
<td>Unemployed adults, n (%)</td>
<td>1,815 (75.3)</td>
</tr>
</tbody>
</table>
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
Deaths

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

- Upper middle income countries
- Lower middle income countries
- Low income countries

Hazard ratio

- 0.5
- 1.0
- 2.0

- 0.001
- <0.001

Years

Patient survival

Low-income countries
Low-middle-income countries
Upper-middle-income countries

ESC CONGRESS ROME 2016 #esccongress

www.escardio.org/ESC2016
<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.01 - 1.02</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.65</td>
<td>0.52 - 0.80</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Education beyond primary school</td>
<td>0.67</td>
<td>0.54 - 0.85</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.40</td>
<td>1.10 - 1.78</td>
<td>0.008</td>
</tr>
<tr>
<td>Severe disease</td>
<td>2.36</td>
<td>1.80 - 3.11</td>
<td>0.01</td>
</tr>
<tr>
<td>Congestive heart failure at enrolment</td>
<td>2.16</td>
<td>1.70 - 2.72</td>
<td>0.001</td>
</tr>
<tr>
<td>New York Heart Association functional class III/IV</td>
<td>1.67</td>
<td>1.32 - 2.1</td>
<td>0.001</td>
</tr>
<tr>
<td>On secondary antibiotic prophylaxis at enrolment</td>
<td>0.86</td>
<td>0.70 - 1.07</td>
<td>0.165</td>
</tr>
</tbody>
</table>
Adverse events
<table>
<thead>
<tr>
<th>Condition</th>
<th>Low income (N=956)</th>
<th>Lower-middle income (N=1158)</th>
<th>Upper-middle income (N=838)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>200 (20.8)</td>
<td>195 (16.8)</td>
<td>105 (12.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>87 (9.0)</td>
<td>66 (5.7)</td>
<td>51 (6.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>28 (2.9)</td>
<td>14 (1.2)</td>
<td>14 (1.7)</td>
<td>0.013</td>
</tr>
<tr>
<td>Stroke or transient ischaemic attack, n (%)</td>
<td>14 (1.5)</td>
<td>12 (1.0)</td>
<td>20 (2.4)</td>
<td>0.053</td>
</tr>
</tbody>
</table>
**Multivariate Hazard ratios - composite of CHF and Death**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled in CHF</td>
<td>2.11</td>
<td>1.67-2.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA III&amp;IV</td>
<td>1.76</td>
<td>1.42-2.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe Valve disease</td>
<td>2.15</td>
<td>1.68-2.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>0.81</td>
<td>0.65-0.99</td>
<td>0.04</td>
</tr>
<tr>
<td>Higher than primary education</td>
<td>0.70</td>
<td>0.57-0.87</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Surgery and valvuloplasty

Crude incidence rates of interventions

* \( p < 0.0001 \)
** \( p < 0.0001 \)
Comparison of baseline characteristics of patients lost to follow-up compared to those whose vital status was known at the end of the study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vital status known</th>
<th>Lost to follow-up</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2960 (88.5)</td>
<td>383 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Age (med, IQR)</td>
<td>28 (18-41)</td>
<td>26 (17-36)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Low-income countries</td>
<td>964 (32.6)</td>
<td>146 (38.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Upper-middle income countries</td>
<td>838 (28.3)</td>
<td>25 (6.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Severe involvement</td>
<td>1470 (49.6)</td>
<td>239 (62.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous intervention or surgery</td>
<td>2212 (74.9)</td>
<td>339 (34.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NYHA III&amp;IV</td>
<td>679 (23.3)</td>
<td>130 (34.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Higher education</td>
<td>1328 (44.6)</td>
<td>96 (24.6)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
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
Acknowledgements and thanks
Principal investigators and data managers
Prof Bongani Mayosi
Prof Ganesan Karthikeyan
Prof Mark Engel

Patients and staff
Steering committee

Funders
Cannectin
Novartis
World Heart Federation
PASCAR
Medical Research Council
Population Health Research Institute
Prof S Yusuf, Dr Koon Teo, Pam Mackie,
Sumathy Rangarajan
Shofique Islam, Katya Mauff
and Kathryn Manning

Participating hospitals, centres and clinics
Local funders
Egypt
Prof. Azza Abul-Fadl
Prof. Sahar Shaker Sheta

Ethiopia
Prof. Abraham Haileamlak
Wandimu Daniel
Dr Araya Gidey Desta
Dr Bekele Alemayehu Shasso
Dr Dufera Mekonnen Begna

India
Prof. Ganesan Karthikeyan
Dr Jitender Sharma
Dr Gaurav Purohit

Kenya
Prof. Stephen Ogendo
Dr Bernard Gitura
Dr Christine Yuko Jowi

Malawi
Dr. Neil Kennedy

Mozambique
Prof. Albertino Damasceno
Dr. Ana Olga Mocumbi
Neusa Jessen

Nigeria
Dr. Moshood Adeoye
Prof. Fidelia Bode-Thomas
Dr. Okechukwu Ogah
Dr Taiwo Olunuga
Dr. Dike Ojji
Prof. Mahmoud Sani
Ganiyu Amusa
Ludu Audu
Charity Durojaiye-Amodu
Ngozi Elekwa
Olukemi Ige
Ogechi Maduka
Oludolapo Marcaulay
Shamsudeen Mohammed
Halim Odiachi
Basil Okeahialam
Christopher Yilgwan

Uganda
Dr. Charles Mondo
Dr Emmy Okello
Dr Peter Lwabi

Sudan
Prof. Ahmed El-Sayed
Huda H. M. Elhassan
Tagwa Elshir
Huda Hamid
Ahmed S. Ibrahim

Yemen
Prof. Mohammed Al-Kebsi

Zambia
Dr John Musuku

PHRI
Sumathy Rangarajan
Pam Mackie
Shofiquel Islam
Dr Koon Teo
Dr Salim Yusuf

Namibia
Dr Christopher Hugo-Hamman
Dr Henning du Toit
Dr Masomi Kaaya
Dr Liina Sikwaya
Dr Andreas Wilberg

CT and Coordination Office
Veronica Francis
Dylan Barth
Prof Patrick Commerford
Felicia Gill
Dr John Lawrenson
Carolise Lemmer
Nonkululeko Koyana
Dr Wendy Matthiessen
Alet Meiring
Peggy Mgwai
Lwazi Mhlanti
Alice Ngcolomba
Simpwe Nkepu
Prof Mpiko Ntsekhe
Janine Saaiman
Unita September
Dr Kathie Walker
Marnie van de Wall

Department of Statistics
Katya Mauff

Department of Medicine
Kathryn Manning