# Supplementary Appendix

Supplement to: Connolly SJ, Karthikeyan G, Ntsekhe M, et al. Rivaroxaban in rheumatic heart disease–associated atrial fibrillation. N Engl J Med. DOI: 10.1056/NEJMoa2209051

This appendix has been provided by the authors to give readers additional information about the work.

Rivaroxaban in Rheumatic Heart Disease Associated Atrial Fibrillation – Supplementary Appendix

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*National Leader

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|---|---|
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| **Brazil** | Instituto Dante Pazzanese de Cardiologia |
| | Instituto do Coração - HCFMUSP |
| | Fundação Faculdade de Medicina de São José do Rio Preto |
| | Nucleo de Estudios Clinicos - Universidade Federal do Triângulo Mineiro |
| | Instituto de Pesquisa Clínica de Campinas |
| | Instituto de Cardiologia do Rio Grande do Sul |
| | Clínica Procardio Ltda. |
| | Via Médica Centro Clínico / Barroso e Sebba Ltda |
| | LOEMA - Instituto de Pesquisa Clínica & Consultores Ltda |
| | Santa Casa de Misericórdia de Votuporanga |
| | Eurolatino Pesquisas Médicas Ltda |
| | Cardresearch - Cardiologia Assistencial e de Pesquisa |
| | Hospital das Clínicas da Universidade Federal de Uberlândia |
| | Hospital Carlos Fernando Malzoni |
| **Cameroon** | St. Elizabeth Catholic General Hospital, Cardiac Centre |
| | Hopital Central Yaounde |
| | Douala General Hospital |
| | Clinique Coeur Et Vie |
| **China** | Beijing Anzhen Hospital |
| | Liangxiang Hospital |
| | Affiliated Zhongshan Hospital of Dalian University |
| | Guangshan County People's Hospital |
| | Jixi People's Hospital |
| | Tonghua Central Hospital |
| | Jianshi County People's Hospital |
| | Luoyang Central's Hospital affiliated to Zhengzhou University |
| | Ningxia Peple's Hospital |
| | Anyue County People's Hospital |
| | Suiping Renan Hospital |
| | Tieli People's Hospital |
| | Zhengzhou 9th People's Hospital |
| | Zhengzhou No.7 People's Hospital |
| | Zhongmou County People's Hospital |
| | The First Affiliated Hospital of Dalian Medical University |
| | Pi County People's hospital |
| | Dancheng County People's Hospital |
| | Ninghai People's Hospital |
| | The First Affiliated Hospital/School of Clinical Medicine of Guangdong Pharmaceutical University |

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| | Suqian Peaple's Hospital of Nanjing Drum-Tower Hospital Group |
| | Wendeng Central Hospital |
| **Egypt** | Assuit General Hospital |
| | Benha University Cardiology Department, Benha |
| | Specialized Medical Hospital - Mansoura |
| | Sohag University, Sohag |
| | Suez Canal University Hospital |
| | Zagazig University Hospital |
| | El Minia University Hospital |
| | Ain shams university hospital |
| | Alexandria University Hospital |
| | Kasr El Einy Hospital (Cairo University) |
| | Mehallah Rheumatic Heart Center |
| | Fayoum General Hospital |
| | Beni Suef University Hospital |
| **Ethiopia** | Jimma University Hospital |
| | College of Health Sciences, Addis Ababa University, Black Lion Hospital |
| | Mekelle University |
| | Hawassa University Referral Hospital |
| **India** | All India Institute of Medical Sciences |
| | Govind Ballabh Pant Hospital (GIPMER) |
| | Dr. Ram Manohar Lohia Hospital @ PGIMER |
| | Sanjay Gandhi Post Graduate Institute of Medical Sciences |
| | King George's Medical College |
| | SMS Medical College |
| | Sri Jayadev Institute of Cardiovascular Sciences and Research |
| **Kazakhstan** | Kazakh National Medical Institute, |
| **Kenya** | Kenyatta National Hospital |
| | Moi Teaching and Referral Hospital |
| | Karen Hospital |
| **Malawi** | Kamuzu Central Hospital |
| | Mzuzu Central Hospital |
| | Queen Elizabeth Central Hospital |
| **Mexico** | Instituto Nacional de Cardiología Ignacio Chavez |
| | Hospital General Dr. Jorge Soberon Acevedo.Secretaria de Salud del Estado de Guerrero |
| | Hospital Angeles León |
| | Hospital Bernardette |
| | Centro para el Desarrollo de la Medicina y Asistencia Especializada S.C. |
| | Centro de Estudios Clínicos de Querétaro S.C. |
| | Instituto de Investigación del Hospital Cardiológica Aguascalientes |

| | |
|---|---|
| **Mozambique** | Maputo Central Hospital |
| | Instituto Nacional de Saude & Universidade Eduardo Mondlane |
| **Nepal** | BP Koirala Institute of Health Sciences |
| | Sahid Gangalal Heart Center |
| | Manipal College of Medical Sciences |
| | Nobel medical college and teaching hospital pvt ltd |
| | Gautam Buddha Community Heart Hospital |
| | College of Medical Sciences |
| | Chitwan Medical College |
| | Bheri Zonal Hospital |
| | Manmohan Cardiothoracic Vascular and Trasplant Center, IOM, TU |
| **Nigeria** | Ladoke Akintola University of Technology Teaching Hospital |
| | Federal Medical Center |
| | Aminu Kano University Teaching Hospital, Kano |
| | Jos University Teaching Hospital |
| | College of Medicine, University of Ibadan |
| | Department of Medicine, Delta State University Teaching Hospital |
| | Department of Medicine, Lagos University Teaching Hospital |
| | Ahmadu Bello University Teaching Hospital |
| | University of Nigeria Teaching Hospital |
| **Pakistan** | Lady Reading Hospital |
| | Isra University Hospital |
| | Rawalpindi Institute of Cardiology |
| | Punjab Institute of Cardiology |
| **Paraguay** | Hospital Regional de Ciudad Del Este |
| | Clinical Hospital |
| | Hospital Nacional Itaugua |
| | Barrio Obrero Hospital |
| | Instituto Nacional de Cardiología |
| **Philippines** | Philippines General Hospital |
| | Philippine Heart Center |
| | Quirino Memorial Medical Center |
| | Palawan Medical City |
| **Rwanda** | University of Rwanda, Kigali University Teaching Hospital |
| **South Africa** | University of Cape Town |
| | Nelson Mandela Academic Hospital |
| | Sefako Makgatho Health Sciences University |
| | University of Limpopo |
| | Charlotte Maxeke Academic Hospital |
| | Cardiology Research Universitas private hospital |
| | Port Elizabeth Hospital Complex |

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|---|---|
| | Chris Hani Baragwanath Hospital |
| **Sudan** | Alshaab Teaching Hospital |
| | Alobeid Teaching Hospital |
| | Ahmed Gasim Hospital |
| | Digna Prince Hospital |
| | Sudan Heart Center |
| | Ahmed Gasim Pediatric Hospital |
| | Medani Heart Centre |
| | Atbara Teaching Hospital |
| **Tanzania** | Muhimbili University of Health and Allied Sciences |
| | Mbeya Zonal Referral Hospital |
| **Uganda** | Uganda Heart Institute |
| **Zambia** | University Teaching Hospital (UTH) |
| **Zimbabwe** | University of Zimbabwe, Parirenyatwa Hospital |
| | Harare Hospital |
| | Mpilo Hospital, National University Science & Technology |

Supplementary Figure S1: CONSORT Flow Diagram

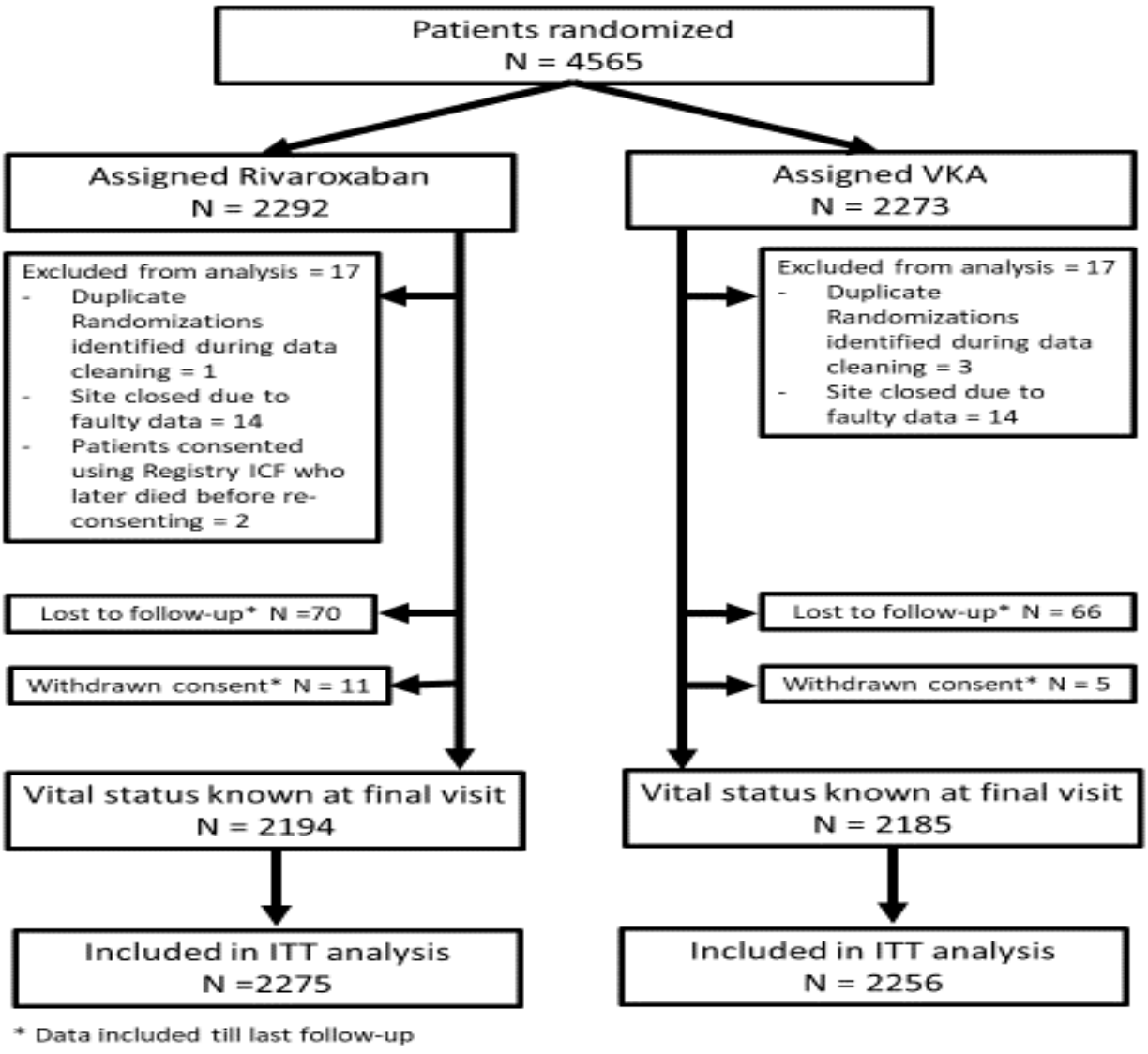

Table S1 Patient ethnicity

| | Overall | | Rivaroxaban | | VKA | |
|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** |
| Patients randomized | 4531 | | 2275 | | 2256 | |
| Ethnicity** | | | | | | |
| South Asian | 791 | 17.5 | 395 | 17.4 | 396 | 17.6 |
| Chinese | 232 | 5.1 | 119 | 5.2 | 113 | 5.0 |
| Japanese | 7 | 0.2 | 2 | 0.1 | 5 | 0.2 |
| Malays | 25 | 0.6 | 14 | 0.6 | 11 | 0.5 |
| Other Asian | 800 | 17.7 | 398 | 17.5 | 402 | 17.8 |
| Persian | 3 | 0.1 | 2 | 0.1 | 1 | 0.0 |
| Arab | 778 | 17.2 | 390 | 17.1 | 388 | 17.2 |
| Black African | 1125 | 24.8 | 561 | 24.7 | 564 | 25.0 |
| Colored African | 140 | 3.1 | 72 | 3.2 | 68 | 3.0 |
| European | 44 | 1.0 | 20 | 0.9 | 24 | 1.1 |
| Native North/South American or Australian | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Latin American (Latino) | 346 | 7.6 | 181 | 8.0 | 165 | 7.3 |
| Bantu/Semi Bantu | 134 | 3.0 | 69 | 3.0 | 65 | 2.9 |
| Hemitic/Semi Hemitic | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Nilotic/Hausa | 29 | 0.6 | 12 | 0.5 | 17 | 0.8 |
| Pygmie | 1 | 0.0 | 1 | 0.0 | 0 | 0.0 |
| Swahili | 68 | 1.5 | 35 | 1.5 | 33 | 1.5 |
| Other | 8 | 0.2 | 4 | 0.2 | 4 | 0.2 |

Table S2. Study drug compliance at end of study

| | Overall | | Rivaroxaban | | VKA | |
|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** |
| Patients randomized | 4531 | | 2275 | | 2256 | |
| | | | | | | |
| ON study drug at the time of final visit | 3871 | 85.43 | 1753 | 77.05 | 2118 | 93.88 |
| Never interrupted | 3107 | 68.57 | 1345 | 59.12 | 1762 | 78.10 |
| Restarted after interruption | 764 | 16.86 | 408 | 17.93 | 356 | 15.78 |
| | | | | | | |
| OFF study drug at the time of final visit | 660 | 14.57 | 522 | 22.95 | 138 | 6.12 |
| Never started | 12 | 0.26 | 9 | 0.40 | 3 | 0.13 |
| Permanently discontinued | 648 | 14.30 | 513 | 22.55 | 135 | 5.98 |
| Reasons for permanent discontinuation* | | | | | | |
| Outcome event | 59 | 9.10 | 44 | 8.58 | 15 | 11.11 |
| Serious adverse event | 13 | 2.01 | 8 | 1.56 | 5 | 3.70 |
| Non-serious adverse event | 27 | 4.17 | 18 | 3.51 | 9 | 6.67 |
| Hospitalization | 60 | 9.26 | 37 | 7.21 | 23 | 17.04 |
| Participant decision | 156 | 24.07 | 125 | 24.37 | 31 | 22.96 |
| Pregnancy | 8 | 1.23 | 5 | 0.97 | 3 | 2.22 |
| Poor/Non-compliance | 58 | 8.95 | 44 | 8.58 | 14 | 10.37 |
| COVID | 6 | 0.93 | 5 | 0.97 | 1 | 0.74 |
| Valve surgery- crossover | 173 | 26.70 | 161 | 31.38 | 12 | 8.89 |
| Cross-over (other) | 6 | 0.93 | 6 | 1.17 | 0 | 0.00 |
| Physician decision | 14 | 2.16 | 10 | 1.95 | 4 | 2.96 |
| Travel difficulty/regional insecurity | 8 | 1.23 | 7 | 1.36 | 1 | 0.74 |
| Other | 59 | 9.10 | 42 | 8.19 | 17 | 12.59 |

*- % are based on permanent discontinuation

Table S3 Reasons for permanent discontinuation of rivaroxaban

| | **Received non-study VKA after rivaroxaban discontinuation** | | | |
|---|---|---|---|---|
| | **Yes** | | **No** | |
| | **N** | **(%)** | **N** | **(%)** |
| Total permanently discontinued | 338 | | 175 | |
| Reasons for permanent discontinuation | | | | |
| Outcome event | 18 | 5.33 | 26 | 14.86 |
| Serious adverse event | 5 | 1.48 | 3 | 1.71 |
| Non-serious adverse event | 13 | 3.85 | 5 | 2.86 |
| Hospitalization | 13 | 3.85 | 24 | 13.71 |
| Participant decision | 87 | 25.74 | 38 | 21.71 |
| Pregnancy | 2 | 0.59 | 3 | 1.71 |
| Poor/Non-compliance | 14 | 4.14 | 30 | 17.14 |
| COVID | 5 | 1.48 | 0 | 0.00 |
| Valve surgery - crossover | 146 | 43.20 | 15 | 8.57 |
| Cross-over (other) | 6 | 1.78 | 0 | 0.00 |
| Physician decision | 8 | 2.37 | 2 | 1.14 |
| Travel difficulty/regional insecurity | 6 | 1.78 | 1 | 0.57 |
| Other | 15 | 4.44 | 27 | 15.43 |

Table S4. Restricted Mean Survival Time analysis on the primary outcome - Competing risk analysis

| | | | | | Rivaroxaban vs. VKA | | |
|---|---|---|---|---|---|---|---|
| | **N** | **Number of events (including the competing events)** | **Number of competing events** | **RMST in days** | **RMST in days** | | |
| | | | | | **Difference (days)** | **95% CI** | **P value*** |
| Rivaroxaban | 2275 | 560 | 42 | 1554 | -76 | (-118 to -34) | <0.001 |
| VKA | 2256 | 446 | 34 | 1629 | . | | |
| Total | 4531 | 1006 | 76 | . | . | | |

Restricted mean survival time (RMST) at the end of the study

* -P value for testing the homogeneity of two or more cumulative incidence function using Gray's test (Gray 1988)

Gray, R. J. (1988). A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *Annals of Statistics* 16:1141-1154

Table S5: International Society of Thrombosis and Hemostasis (ISTH) definition of major bleeding in non-surgical patients

| |
|---|
| Fatal bleeding |
| and/or |
| Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome |
| and/or |
| Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells |

Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients *J Thromb Haemost* 2005: **3** (4): 692–4. doi:10.1111/j.1538-7836.2005.01204.x. PMID 15842354.

**Representativeness of study participants**

| Category | Considerations |
|---|---|
| Disease under investigation | Patients with rheumatic heart disease (RHD) with atrial fibrillation (AF). |
| Sex and gender | Patients with RHD are more often female. In recent studies, 65-75% of enrolled patients were female.[1] |
| Age | Patients with RHD who develop AF, tend to be older than those without AF,[2] but are about 2 decades younger than patients with non-valvular AF.[3] |
| Race or ethnic groups | Some ethnic groups (Black Africans, South Asians, and indigenous people in high income countries such as Australia and New Zealand) are overrepresented in cohorts of RHD. This is believed to be because of environmental factors such as overcrowding and poverty that is more prevalent among these groups. |
| Geography | Rheumatic heart disease is largely restricted to low and lower middle income countries in Africa, Asia and Latin America. |
| Other considerations | Because patients with RHD and AF are younger, they have fewer conventional atherosclerotic stroke risk factors, and lower $CHA_2DS_2VASc$ scores, than patients with non-valvular AF enrolled in stroke-prevention trials.[3] |
| Overall representativeness of this trial | The patients in this trial demonstrated the expected magnitude of female preponderance (72%) seen in typical RHD populations. We did not collect data on gender in this study. As expected, patients were younger (average age 50 years), had lower $CHA_2DS_2VASc$ scores (15% with a score ≥2), and a lower stroke-risk, compared to patients with non-valvular AF enrolled in recent trials.[2] The prevalence of hypertension (25%), diabetes (6.4%) and coronary artery disease (1.1%) were also low. The majority of patients included in this trial were from Africa (43%), Asia (40%), and Latin America (8%). Patients were enrolled from the RHD endemic regions of the world, and this ethnic mix is representative of the geographic distribution of the disease. |

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3. Karthikeyan G, Connolly SJ, Ntsekhe M, et al. 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.