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

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Background Rheumatic heart disease (RHD) is a neglected disease affecting 33 million people, mainly in low and middle income countries. Yet very few large trials or registries have been conducted in this population. The INVICTUS program of research in RHD consists of a randomized-controlled trial (RCT) of 4500 patients comparing rivaroxaban with vitamin K antagonists (VKA) in patients with RHD and atrial fibrillation (AF), a registry of 17,000 patients to document the contemporary clinical course of patients with RHD, including a focused sub-study on pregnant women with RHD within the registry. This paper describes the rationale, design, organization and baseline characteristics of the RCT and a summary of the design of the registry and its sub-study. Patients with RHD and AF are considered to be at high risk of embolic strokes, and oral anticoagulation with VKAs is recommended for stroke prevention. But the quality of anticoagulation with VKA is poor in developing countries. A drug which does not require monitoring, and which is safe and effective for preventing stroke in patients with valvular AF, would fulfill a major unmet need.

Methods The INVestIgation of rheumatiC AF Treatment Using VKAs, rivaroxaban or aspirin Studies (INVICTUS-VKA) trial is an international, multicentre, randomized, open-label, parallel group trial, testing whether rivaroxaban 20 mg given once daily is non-inferior (or superior) to VKA in patients with RHD, AF, and an elevated risk of stroke (mitral stenosis with valve area ≤ 2 cm^2, left atrial spontaneous echo-contrast or thrombus, or a CHA$_2$DS$_2$VASc score ≥ 2). The primary efficacy outcome is a composite of stroke or systemic embolism and the primary safety outcome is the occurrence of major bleeding. The trial has enrolled 4565 patients from 138 sites in 23 countries from Africa, Asia and South America. The Registry plans to enroll an

additional 17,000 patients with RHD and document their treatments, and their clinical course for at least 2 years. The pregnancy sub-study will document the clinical course of pregnant women with RHD.

Conclusion INVICTUS is the largest program of clinical research focused on a neglected cardiovascular disease and will provide new information on the clinical course of patients with RHD, and approaches to anticoagulation in those with concomitant AF. (Am Heart J 2020;225:69-77.)

Acute rheumatic fever and its sequela, rheumatic heart disease (RHD), is a major public health problem in low and middle income countries (LMICs).[1,2] Patients with RHD are at a high risk of death, heart failure, stroke and infective endocarditis.[3] However, little research funding is devoted to RHD compared to other neglected diseases. [4] The INVICTUS program is a multinational, collaborative research effort which aims to fill knowledge gaps in three critical areas: (1) The clinical course of RHD in a population of patients drawn from all the endemic regions of the world. This will enable us to study variations in clinical course, treatment practices and outcomes over a range of country income levels and baseline clinical characteristics. (2) The safety and efficacy of the direct oral anticoagulant (DOAC) rivaroxaban compared to vitamin K antagonists (VKA) for stroke prevention in RHD and atrial fibrillation (AF). (3) The effect of RHD on pregnancy outcomes, and also the effect of pregnancy on the clinical course of RHD. This manuscript describes the rationale and design of the INVestIgation of rheumatiC AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies, comparing rivaroxaban with VKA (INVICTUS-VKA) trial, and highlights salient aspects of the Registry.

Stroke prevention in rheumatic atrial fibrillation

Atrial fibrillation confers a 5-fold increased risk of stroke,[5] and is the primary cause identified in about 15% of all strokes.[6] Over the last 3 decades, a number of randomized trials have established the efficacy and safety of anticoagulation in reducing stroke risk in AF both with vitamin K antagonists (VKA),[7] and more recently, with the direct oral anticoagulants (DOAC).[8] But all these studies excluded patients with significant valve disease, particularly those with RHD and significant mitral stenosis (MS), who have been considered to be at the highest risk of stroke.[9,10] Therefore, current guidelines recommend the use of VKAs for stroke prevention in RHD and AF, based on the results of retrospective studies and expert clinical opinion, and do not recommend the use of DOACs.[10-12] However, only a minority of patients requiring anticoagulants actually receive VKAs,[13] and the quality of anticoagulation among those who do so is poor.[14] This may be because,

regular INR monitoring is often not readily available in LMICs. A simple-to-use drug that has no need for monitoring, and is safe and effective, would fulfill a critical and unmet need of patients with rheumatic valvular AF living in the developing world. Rivaroxaban is a DOAC with proven efficacy in stroke prevention in AF.[15] We hypothesized that rivaroxaban would be non-inferior (or superior) to VKAs for stroke prevention in patients with RHD and AF.

Methods

The INVICTUS-VKA trial is an investigator-initiated, international, multicentre, randomized trial testing the hypothesis that rivaroxaban 20 mg given once daily is non-inferior (and potentially superior) to VKA in preventing stroke or systemic embolism in patients with rheumatic AF and an elevated risk of stroke. The trial is open-label with blinded outcome assessment. The trial was approved by the institutional review boards and ethics committees at all the participating sites and relevant regulatory authorities. Written informed consent was obtained from all participants prior to randomization. The trial has enrolled 4565 patients from 138 sites in 23 countries. The first patient was randomized in August 2016, and enrolment was completed by September 2019. Follow-up will be completed in late 2021.

Participants

Patients over the age of 18 years with echocardiographically proven RHD and current or past AF, or atrial flutter were eligible. In addition, patients needed to be at a higher risk of stroke based on the presence of at least one of the following: CHA_2DS_2VASc score $\geq$ 2, mitral stenosis with mitral valve area (MVA) ≤ 2 cm^2, or the presence of left atrial spontaneous echo contrast or thrombus. Key exclusion criteria were the presence of a mechanical heart valve, or likelihood of receiving one within the next 6 months, the need for dual antiplatelet therapy or treatment with combined inhibitors of CYP3A4 and p-glycoprotein, or the presence of severe renal insufficiency (eGFR <15 mL/min). Women of child bearing potential were excluded if they were pregnant, or were not using an effective form of contraception. The eligibility criteria are detailed in Table I in the appendix.

Table I. Baseline characteristics of enrolled patients

Characteristics	Overall (n = 4565)	Low-income countries (n = 1400)	Lower-middle-income countries (n = 2323)	Upper-middle-income countries (n = 842)
Age, years (median, IQR)	50 (40, 61)	46 (36, 56)	49 (40, 59)	60 (51, 67)
Female sex, n (%)	3296 (72.2%)	1031 (73.6%)	1646 (70.9%)	619 (73.5%)
Ethnicity, n (%)				
South Asian	791 (17.3%)	40 (2.9%)	742 (31.9%)	9 (1.1%)
Chinese	233 (5.1%)	3 (0.2%)	0 (0.0%)	230 (27.3%)
Other Asian	802 (17.6%)	720 (51.4%)	82 (3.5%)	0 (0.0%)
Arab	779 (17.1%)	0 (0.0%)	779 (33.5%)	0 (0.0%)
Black African	1155 (25.3%)	362 (25.9%)	588 (25.3%)	205 (24.3%)
Latin American (Latino)	346 (7.6%)	0 (0.0%)	0 (0.0%)	346 (41.1%)
Other	459 (10.1%)	275 (19.6%)	132 (5.7%)	52 (6.2%)
BMI, kg/m^2 (median, IQR)	24 (20, 28)	21 (19, 24)	25 (21, 29)	26 (22, 29)
Blood pressure, mm Hg- (median, IQR)				
Systolic	111 (101, 125)	110 (100, 120)	111 (102, 126)	120 (110, 130)
Diastolic	73 (70, 80)	70 (65, 80)	75 (70, 81)	74 (69, 81)
Previous Medication use, n (%)				
Rheumatic fever prophylaxis	1446 (31.7%)	609 (43.5%)	744 (32.0%)	93 (11.0%)
β-Blocker	3300 (72.3%)	983 (70.2%)	1768 (76.1%)	549 (65.2%)
ACE inhibitor or ARB	1302 (28.5%)	357 (25.5%)	553 (23.8%)	392 (46.6%)
Digoxin	1932 (42.3%)	655 (46.8%)	1015 (43.7%)	262 (31.1%)
Calcium-channel blocker	259 (5.7%)	55 (3.9%)	150 (6.5%)	54 (6.4%)
Diuretic	3849 (84.3%)	1287 (91.9%)	1990 (85.7%)	572 (67.9%)
HIV/AIDS treatment	59 (1.3%)	25 (1.8%)	11 (0.5%)	23 (2.7%)
CHA2DS2-VASc Score (mean ± SD)	1.9 ± 1.4	1.7 ± 1.2	1.8 ± 1.4	2.7 ± 1.4
Score, n (%)				
0	533 (11.7%)	161 (11.5%)	347 (14.9%)	25 (3.0%)
1	1449 (31.8%)	490 (35.0%)	840 (36.2%)	119 (14.1%)
2	1285 (28.2%)	466 (33.3%)	551 (23.7%)	268 (31.8%)
3	663 (14.5%)	172 (12.3%)	289 (12.4%)	202 (24.0%)
4	399 (8.7%)	77 (5.5%)	192 (8.3%)	130 (15.4%)
5	161 (3.5%)	23 (1.6%)	70 (3.0%)	68 (8.1%)
6	59 (1.3%)	7 (0.5%)	29 (1.2%)	23 (2.7%)
>6	14 (0.3%)	3 (0.2%)	4 (0.2%)	7 (0.8%)
Co-existing Condition, n (%)				
Previous stroke	503 (11.0%)	140 (10.0%)	220 (9.5%)	143 (17.0%)
Previous TIA	147 (3.2%)	15 (1.1%)	66 (2.8%)	66 (7.8%)
Previous systemic embolism	49 (1.1%)	15 (1.1%)	16 (0.7%)	18 (2.1%)
Congestive heart failure	1766 (38.7%)	625 (44.6%)	747 (32.2%)	394 (46.8%)
Hypertension	1071 (23.5%)	197 (14.1%)	483 (20.8%)	391 (46.4%)
Diabetes	290 (6.4%)	32 (2.3%)	169 (7.3%)	89 (10.6%)
Previous Myocardial infarction	15 (0.3%)	2 (0.1%)	6 (0.3%)	7 (0.8%)
Creatinine clearance, ml/min (median, IQR)	77 (59, 98)	72 (55, 93)	81 (62, 101)	74 (57, 94)
Mitral valve stenosis-present, n (%)	**3844 (84.2%)**	**1189 (84.9%)**	**1937 (83.4%)**	**718 (85.3%)**
– Present, valve area <1.0 cm^2	1063 (27.9%)	449 (37.8%)	465 (24.1%)	149 (21.4%)
– Present, valve area 1.0 to <1.5 cm^2	1546 (40.5%)	432 (36.3%)	805 (41.7%)	309 (44.4%)
– Present, Valve area 1.5 to <=2.0 cm^2	1104 (28.9%)	294 (24.7%)	598 (31.0%)	212 (30.5%)
– Present, valve area >2.0 cm^2	103 (2.7%)	14 (1.2%)	63 (3.3%)	26 (3.7%)
Left atrial spontaneous echo contrast, n (%)	531 (11.6%)	222 (15.9%)	239 (10.3%)	70 (8.3%)
Left atrial thrombus on echo, n (%)	306 (6.7%)	115 (8.2%)	140 (6.0%)	51 (6.1%)

IQR indicates interquartile range.
Country Income grouped by reference found at https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Low-Income ($1025 or less) countries include Ethiopia, Malawi, Mozambique, Nepal, Rwanda, Tanzania, Uganda; Lower-Middle-Income ($1026–$3995) countries include Cameroon, Egypt, India, Kenya, Nigeria, Pakistan, Philippines, Sudan, Zambia, Zimbabwe; Upper-Middle-Income ($3996–$12,375) countries include Botswana, Brazil, China, Kazakhstan, Mexico, Paraguay, South Africa.

Randomization, treatment and follow-up

Within each site, patients were randomized, to receive either rivaroxaban or VKA in a 1:1 ratio, using a central, web-based randomization system. Patients allocated to rivaroxaban receive 20 mg of the drug once a day.

Patients with a creatinine clearance <50 mL/min receive 15 mg rivaroxaban per day. Patients assigned to VKA receive any of the locally approved VKAs with dose adjustment to maintain INR in the range of 2–3. The trial schematic is shown in Figure 1.

Figure 1
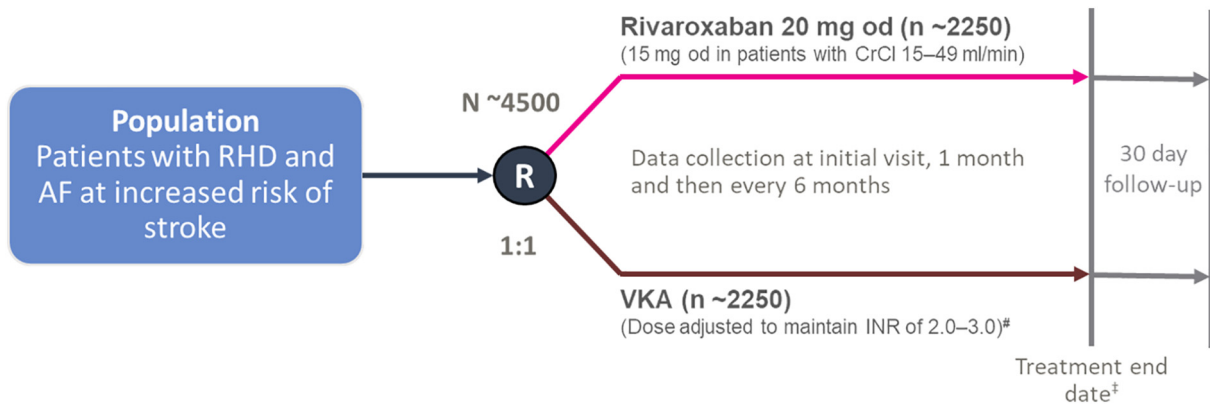
Overview of the INVICTUS-VKA trial.

Rivaroxaban (Xarelto, Bayer AG, Leverkusen, Germany) is provided as 20 and 15 mg tablets by the manufacturer. Patients allocated to VKA receive locally available preparations. Study treatment was initiated on the day of randomization in VKA-naïve patients. Among patients on non-study VKA, the timing of initiation of rivaroxaban was determined by the most recent INR value (obtained at least within 2 weeks) prior to randomization. After randomization, in patients on study VKA, a validated algorithm (see appendix) is being used to guide dose changes. Broadly, the algorithm recommends a VKA dose change of no more than 10% of the previous weekly dose. Training sessions on using the algorithm have been conducted during investigator meetings. Consistency with the algorithm and the proportion of INRs in therapeutic range are tracked for each site, and regular feedback is provided to the site investigators and national leaders. Participants are followed up 1 month after randomization, and thereafter at 6

monthly intervals. The follow-up and evaluation schedule is detailed in Table II in the appendix.

Study outcomes

The primary efficacy outcome for the trial is a composite of stroke or systemic embolism. Stroke is 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. Transient ischemic attacks with positive neuroimaging will be considered a stroke. Systemic embolism is defined as abrupt vascular insufficiency associated with clinical and radiological evidence of arterial occlusion in the absence of other likely mechanisms.

The key secondary efficacy outcomes are the occurrence of myocardial infarction or vascular death. Vascular death includes death due to stroke, myocardial infarction, heart failure or cardiogenic shock, sudden death or any

Table II. Comparison of key baseline characteristics between patients with valvular heart disease recruited in the four large DOAC trials, and patients enrolled in INVICTUS-VKA.

Characteristics	DOAC trials*	INVICTUS-VKA
Valve disease	Mild to moderate valve disease, mostly of non-rheumatic origin. A small number of patients with mild rheumatic mitral stenosis	Over 80% of patients had rheumatic mitral stenosis with valve area ≤ 2.0 cm^2. No restriction enrolment of patients with severe regurgitation
Average age (y)	69–75	50
Female gender (%)	39–42	72
CHA$_2$DS$_2$VASc score (mean)	2–3.5	1.9
History of stroke or systemic embolism (%)	20–48	12
Hypertension (%)	85–93	23
Diabetes mellitus (%)	23–40	6
History of myocardial infarction (%)	17–40	<0.5
Heart failure (%)	40–74	39

* Data pertaining to the 4 DOAC (direct acting oral anticoagulants) trials[18,22-24] were abstracted from Pan KL et al.[17] The majority of patients enrolled in the DOAC trials were from developed countries where rheumatic heart disease is not endemic.

other death due to cardiovascular causes. Death due to hemorrhage is also considered a vascular death.

The primary safety outcome is major bleeding according to the International Society on Thrombosis and Hemostasis (ISTH) criteria, and the secondary safety outcome is the time to occurrence of life-threatening or clinically relevant, non-major bleeding. (Appendix Table 3) The primary outcome events and bleeding events will undergo blinded, independent adjudication by an expert committee.

Sample size considerations

An annual stroke rate of 2% is expected in the VKA arm, and the non-inferiority margin was 1.46, the upper bound of the 95% confidence interval of the relative risk (warfarin vs. control) derived from a meta-analysis of trials of VKAs against control in patients with AF.[7] The margin of 1.46 would guarantee that at least 50% of the benefit of VKAs over control for reduction of stroke or systemic embolism would be preserved. Assuming 10% non-compliance to rivaroxaban in the first year with additional non-compliance of 5% per year thereafter, enrolment of at least 4500 patients will provide 88% power to conclude that rivaroxaban is non-inferior to VKAs for the primary outcome. These assumptions allow for the occurrence of 251 primary outcome events during the course of the study. If non-inferiority is established, then testing for superiority of rivaroxaban over VKA will be undertaken without statistical penalty.

Analysis plan

Survival curves will be estimated for the primary outcomes using the Kaplan–Meier method and compared using the log-rank test. The primary analysis will be the time to a confirmed primary outcome event (time to first event in a composite outcome) using a stratified Cox proportional hazards model. From the Cox regression model, we will report hazard ratios and 95% confidence intervals. Statistical significance will be claimed if the p value is less than 0.05 for the primary outcome for treatment comparison. All primary analyses will be based on the intention-to-treat principle. Secondary analyses examining on-treatment effects will include all patients who received at least one dose of study medication, and will include all events up until 5 days after permanent discontinuation of study medication, or final follow up visit whichever is earlier. The main sub-groups of interest will be patients with mitral stenosis compared to those without, male versus female, by age group, body weight, renal function, and by the time in therapeutic range.

Two formal interim analyses of efficacy will be performed after 50% and 75% of expected events have occurred. The independent Data and Safety Monitoring Board (DSMB) will use a modified Haybittle-Peto approach to evaluate the possibility of greater than expected efficacy, and will consider early trial termination for benefits of rivaroxaban over VKA that consistently exceed 4 standard deviations in the first analysis, and 3 standard deviations in the second analysis. Recommendations to terminate the study will be based on the totality of information on efficacy and safety.

INVICTUS registry and pregnancy sub-study

The INVICTUS Registry is an extension of the REMEDY Registry, which enrolled 3343 RHD patients mainly from Africa and India.[14,16] The INVICTUS Registry proposes to enroll an additional 17,000 patients with RHD, for a total of 20,000 patients. The design of the INVICTUS Registry is similar to REMEDY.[16] All patients with RHD will be eligible for enrolment. The large number of patients from all the RHD endemic regions of the world will allow us to identify differences in clinical course and outcomes by country income status and clinical characteristics. The Registry will also be able to determine the rates of occurrence of infrequent events such as infective endocarditis and recurrent rheumatic fever. The INVICTUS pregnancy sub-study aims to enroll 500 pregnant patients with RHD during the course of the registry. The objectives of this sub-study are to describe maternal and fetal outcomes among women with RHD, particularly those from LMICs. The sub-study will also allow us to determine the effects of pregnancy on hemodynamics and disease progression.

Trial organization and management

The INVICTUS-VKA trial and Registry are both investigator-initiated and funded through a grant from Bayer AG, Germany. The trial and the registry are centrally coordinated from the Project Office at the Population Health Research Institute (PHRI) at McMaster University, Canada, working closely with the National Project Offices within each country. The Steering Committee (composed of National Leaders, PIs and Co-PIs) makes all major decisions regarding study design and implementation. A subset of the Steering Committee, the Operations Committee, is responsible for addressing operational matters that arise between the Steering Committee meetings. (See appendix for study organization) Within each country, the national project office team meets regularly, as appropriate.

Study progress. Between August 2016 and September 2019, 4565 patients were enrolled from 138 sites in 23 countries. (Figure 2) About 43% of the recruited patients were from Africa, 40% from Asia, and 8% from S America. Patients were predominantly female with an average age of 50 years. About 80% of recruited patients had rheumatic MS with a valve area ≤ 2.0 cm^2. Nearly half the patients had a CHA$_2$DS$_2$VASc score< 2. (Table I) Patients from higher income countries tended to be older, have a higher CHA$_2$DS$_2$VASc score, and were also

Figure 2
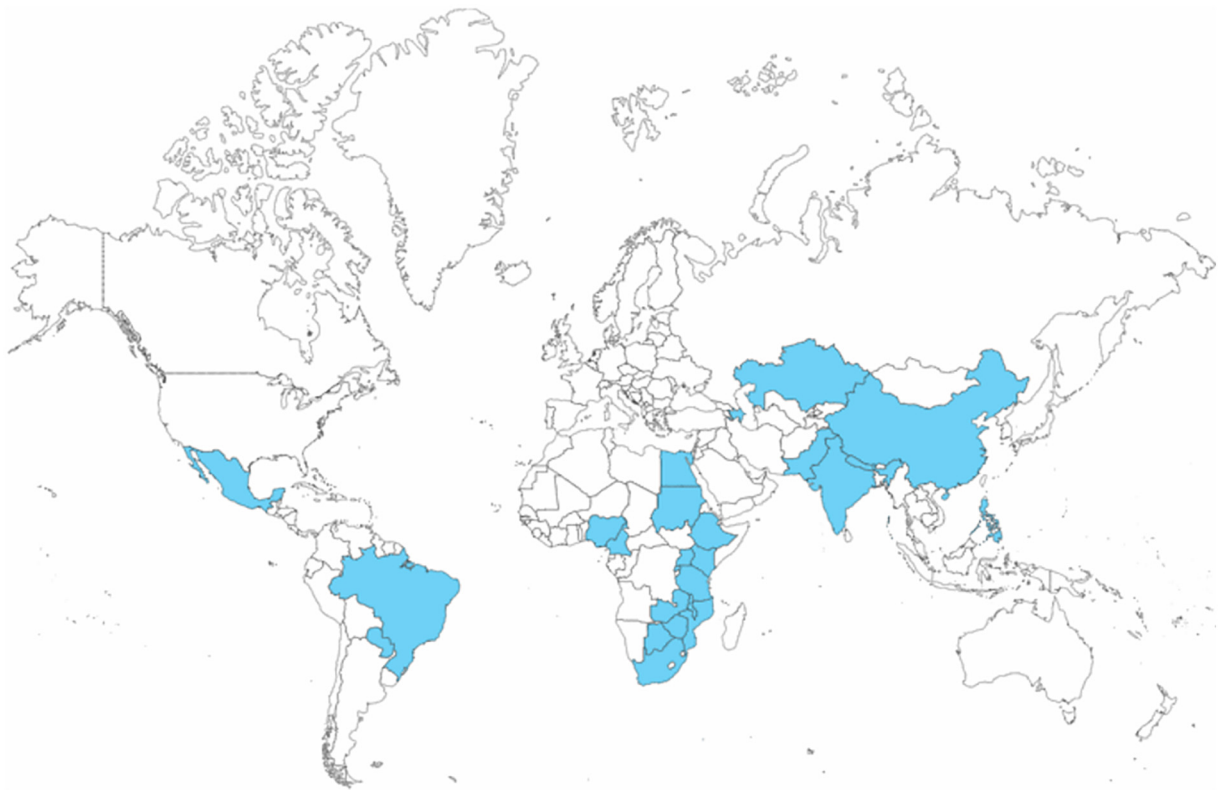
Countries participating in the INVICTUS trial. The participating countries are listed in the footnote to Table I and in the appendix.

more likely to be hypertensive, diabetic, or to have suffered a previous stroke or systemic embolism. (Table I) Only about 53% of patients were on oral anticoagulation at the time of enrolment, and the proportion of INR values in therapeutic range (between 2 and 3) was 33%.

Discussion

The INVICTUS program addresses several knowledge gaps in the clinical course and management of RHD. The INVICTUS-VKA trial will help determine the optimal anticoagulation strategy for stroke prevention in AF with valvular heart disease, particularly, significant mitral stenosis. The initial trials evaluating VKAs against placebo excluded patients with MS as they were presumed to be at very high risk of stroke, and it was considered unethical to randomize them. The recent trials of DOACs vs. VKAs were mostly designed as non-inferiority trials, and continued to enroll patients with non-valvular AF. The INVICTUS trial will provide new information on the efficacy of DOACs in patients with RHD, particularly those with MS.

Rivaroxaban is likely to be at least as effective in patients with AF and valve disease as it is in non-valvular AF. Data on patients with mild to moderately severe valve disease enrolled in the pivotal DOAC RCTs support this assumption.[17] However, patients with valve disease in these studies were older, had a higher burden of cardiovascular risk factors (such as hypertension, diabetes and coronary artery disease), and consequently a high risk of stroke.[18] (Table II) Patients with RHD in developing countries, on the other hand, are younger by several decades, have few risk factors for cardiovascular disease, and so may have a lower risk of stroke even in the presence of AF. (Table II) In the REMEDY study (median age 28 years), only 2.4% of patients had a stroke at 2 years of follow-up.[3] We therefore used risk markers to enroll subjects at a higher risk of stroke.

INVICTUS enrolled patients in RHD endemic countries, many with little infrastructure, experience or trained personnel for conducting clinical trials. We faced a number of operational challenges that delayed or prevented the initiation of the study in several countries. Of the 34 countries where we tried to initiate the study, 10 could not participate in the trial due to several issues including the lack of investigator experience with clinical trials, inability to obtain approval due to safety concerns

expressed by national regulatory bodies, and inability to import rivaroxaban clinical supplies. Lack of local study staff familiarity with the conduct of clinical trials, and lengthy regulatory approval processes also contributed to significant delays in initiation of the study in most countries (Figure 3).

The maintenance of therapeutic anticoagulation with VKAs (INR between 2 to 3) is an important challenge in LMICs. Data from previous observational studies from these regions indicate that INRs are in therapeutic range on the average less than 30% of the time.[13,19] Even in randomized trials with protocol driven monitoring and

dose-adjustment, the time in therapeutic range was below 50% in most developing countries.[20] The proportion of INR values in therapeutic range at the time of enrolment into INVICTUS was 33%. We employed several strategies to optimize anticoagulation quality in the VKA arm. We provided investigators with a validated algorithm (see appendix) to guide dose adjustment. Investigators and patients were reimbursed, where necessary, to ensure timely performance of INR tests. We also provided point-of-care INR measurement kits to sites where INR results could not be obtained within a reasonable period of time. We systematically recorded dosage changes

Figure 3
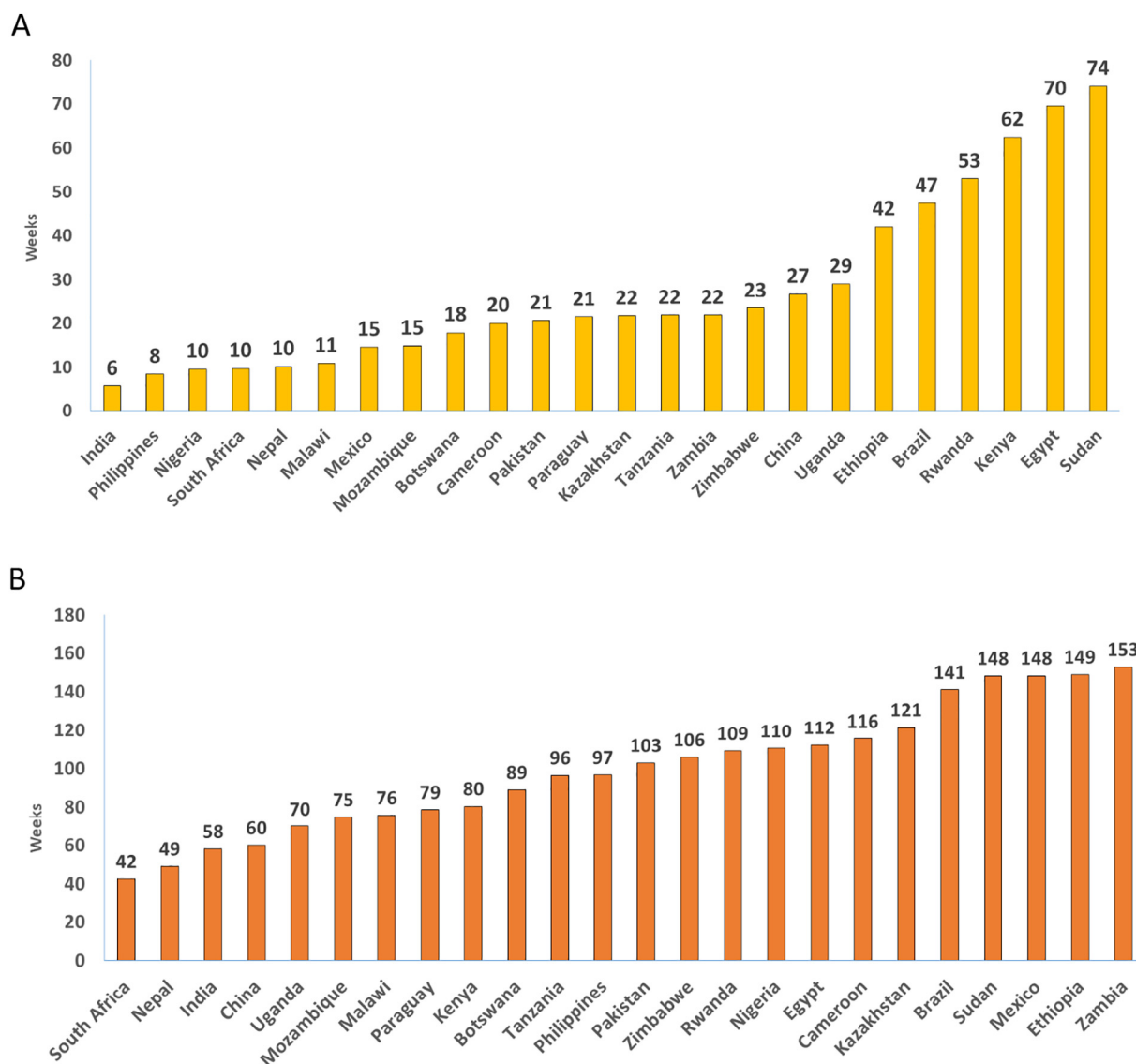
Operational delays (in weeks) in initiating the trial in participating countries. A, Time from protocol availability to submission by investigator for ethics and regulatory approvals. B, Time from protocol availability to recruitment of first patient.

made in response to INR values for all sites. Regular feedback was provided to sites regarding their adherence to the dosing algorithm, and the proportion of INR values in therapeutic range. Our goal is to maintain INR in therapeutic range at least 55% of the time, which is similar to that achieved in the rivaroxaban vs. warfarin for non-valvular AF (ROCKET-AF) trial.[15]

We have enrolled a large number of patients with RHD and significant valve disease (predominantly MS), from RHD-endemic countries from all the major regions of the world. We therefore expect that the INVICTUS trial will provide definitive and generalizable information on the safety and efficacy of rivaroxaban compared to VKA for stroke prevention in patients with rheumatic AF. Significantly, INVICTUS is by far the largest study involving patients with RHD, a disease endemic to poor countries, that receives little attention and research funding.[4] The INVICTUS program provides a practical model for conducting much needed research which addresses the needs of people in LMICs. More specifically, it may encourage researchers to undertake similar studies to evaluate interventions to reduce other patient-important outcomes in RHD such as heart failure. Such efforts will be needed to achieve the sustainable development goal of reduction in mortality due to non-communicable diseases (including RHD) by a third, by 2030.[21]

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2020.03.018.

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