

## International Collaborative Partnership for the Study of Atrial Fibrillation (INTERAF): Rationale, Design, and Initial Descriptives

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Atrial fibrillation (AF) is a global problem with a significant impact on health outcomes, affecting up to 1% to 2% of the global adult population, and is projected to increase in both developed and developing countries over the coming decades.<sup>1</sup> AF is associated with higher mortality and morbidity, as well as decreased quality of life, and increases the risk of thromboembolic events (including stroke), heart failure (HF), myocardial infarction, dementia, and chronic kidney disease. The mainstays of AF treatment are arrhythmia management (with pharmacologic or mechanical rate or rhythm control) and prevention of thromboembolism.<sup>2</sup> The field of AF treatment is dynamic, with the recent development of new procedures to restore sinus rhythm (catheter and surgical ablation) and new treatments to reduce

thromboembolism (target-specific oral anticoagulants and catheter-based exclusion of the left atrial appendage). However, there is significant global variation in use of these therapies, particularly in developing countries, and the global implementation, diffusion, and anticipated real-world effectiveness of these technologies is uncertain.<sup>3</sup> Therefore, a better understanding of global AF treatments, barriers and facilitators to its optimal use, and its subsequent outcomes is needed.

As AF incidence and its arsenal of treatments continue to expand globally, the longitudinal and comprehensive nature of clinical registries can provide important insights into the clinical management of AF. Registries are observational databases of clinical conditions and/or therapies in which there are no mandated approaches to therapy and relatively few inclusion or exclusion criteria.<sup>4</sup> In addition, registries can continuously collect longitudinal data on their target population, which allows them to monitor current and emerging clinical practices over time and associate them with clinical outcomes. Accordingly, current AF management practices and their associated outcomes can be measured, benchmarked to current best practices and clinical practice guidelines, and compared across different countries, populations, and health-care systems. As novel AF treatments emerge, their dissemination globally and effect on outcomes, both intended and unintended, can be assessed.

Currently, multiple AF databases and registries spanning a variety of countries, patients, treatments, and outcomes exist.<sup>5</sup> However, coordination among these data sources is minimal. In addition, the variations in patient enrollment, data definitions, and characterization of AF therapies in each of the registries prevent effective comparison between registries and limit their ability to track changes over time. Finally, many of the current registries are sponsored by pharmaceutical or device companies, which can limit their focus on those patients and treatments associated with their products.

The potential value of coordinating these disparate registry efforts is significant. More accurate and complete

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assessment of the treatment and outcomes of AF in various countries and populations around the world could occur. As the arsenal of AF treatments continues to expand, such a registry would allow for comparative effectiveness studies between treatments. Additionally, a global registry would allow for understanding of the impact of treatments in various patient populations and within the context of their local healthcare environments. Large registries could also utilize their size to detect infrequent, but important, safety signals of both AF and its treatment. Thus, the insights from such a registry effort could allow for richer insights into AF and sharing of best practices for its management. In addition, these insights could inform ongoing research efforts, supporting a “learning healthcare system” iterative cycle of knowledge generation from clinical practice insights.<sup>6</sup>

To respond to this need, we present the International Collaborative Partnership for the Study of Atrial Fibrillation (INTERAF). This worldwide partnership, with initial participants from the United States, Europe, China, Brazil, South Korea, Taiwan, Singapore, Japan, and the Balkan countries, provides a common platform for investigators and countries to study AF populations, treatments, and outcomes. In order to allow for the integration of registries from a wide variety of countries, INTERAF utilizes a distributed data and analytic platform, rather than a single, combined registry structure. The INTERAF leadership provides general data requirements, standards, and governance policies for existing and future country- and region-specific registries. This design allows for easier integration of pre-existing registries and greater

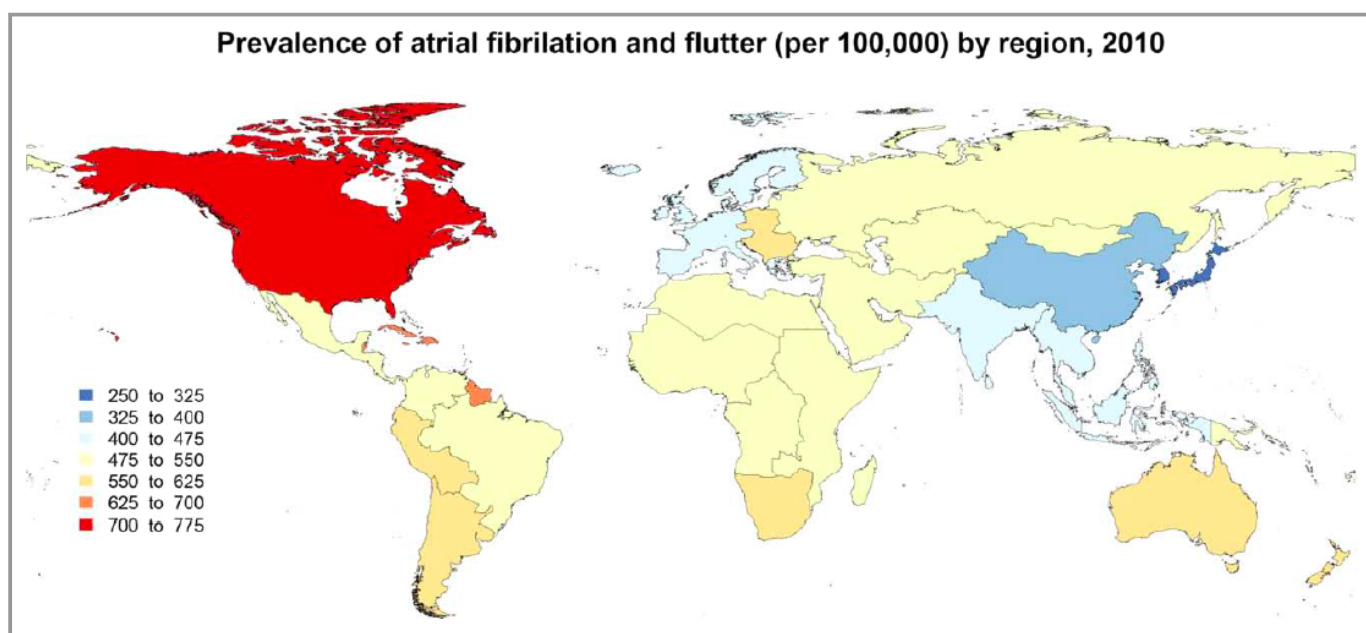
flexibility in data collection, which can lower barriers to participation, allow for an expansive view of global AF treatment and outcome patterns, and support country-specific and international efforts to optimize the care for the large and growing population of AF patients.

In this report, we present the current knowledge and gaps in global AF management and outcomes, and discuss how INTERAF can fill these gaps. We also outline the organizing principles and structure of the INTERAF partnership, and introduce its initial research agenda and future directions. Finally, we provide initial descriptive data of the participating registries and their AF populations.

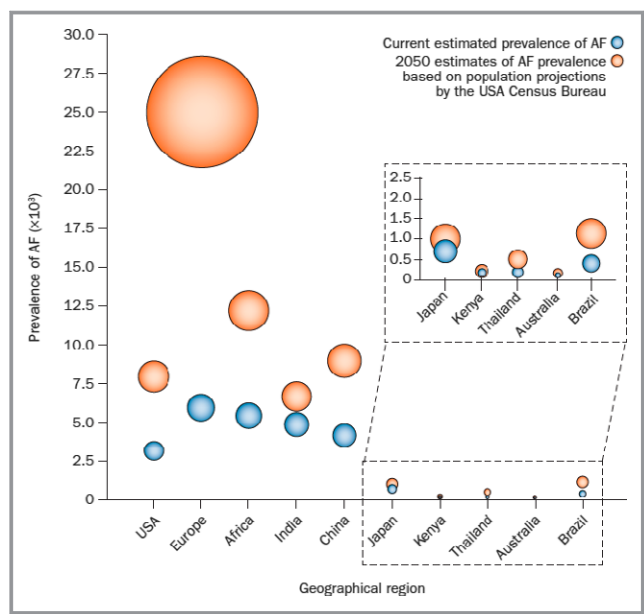
## Global AF Prevalence and Projections for Growth

AF is a global problem, with projections for significant growth in the coming years. Although comprehensive data are lacking, the 2010 Global Burden of Disease study provides some insights, suggesting that the total number of AF patients is  $\approx$ 33 million, with an age-adjusted prevalence of 596 per 100 000 men and 373 per 100 000 women, with significant regional variation (Figure 1).<sup>1,7</sup>

Over the coming years, AF prevalence is expected to grow significantly. Current census projections for 2050 suggest that the number of Americans, Europeans, and Japanese with AF will increase by 2- to 3-fold.<sup>1</sup> In addition, the number of people in the developing world who are older than 60 years, where AF incidence is concentrated, is projected to double by 2050 (Figure 2).<sup>1</sup>



**Figure 1.** International age-adjusted AF prevalence rates (per 100 000 population) in the 21 Global Burden of Disease regions, 2010. Figure reproduced from Chugh et al<sup>7</sup> with permission from Wolters Kluwer Health, Inc. AF indicates atrial fibrillation.



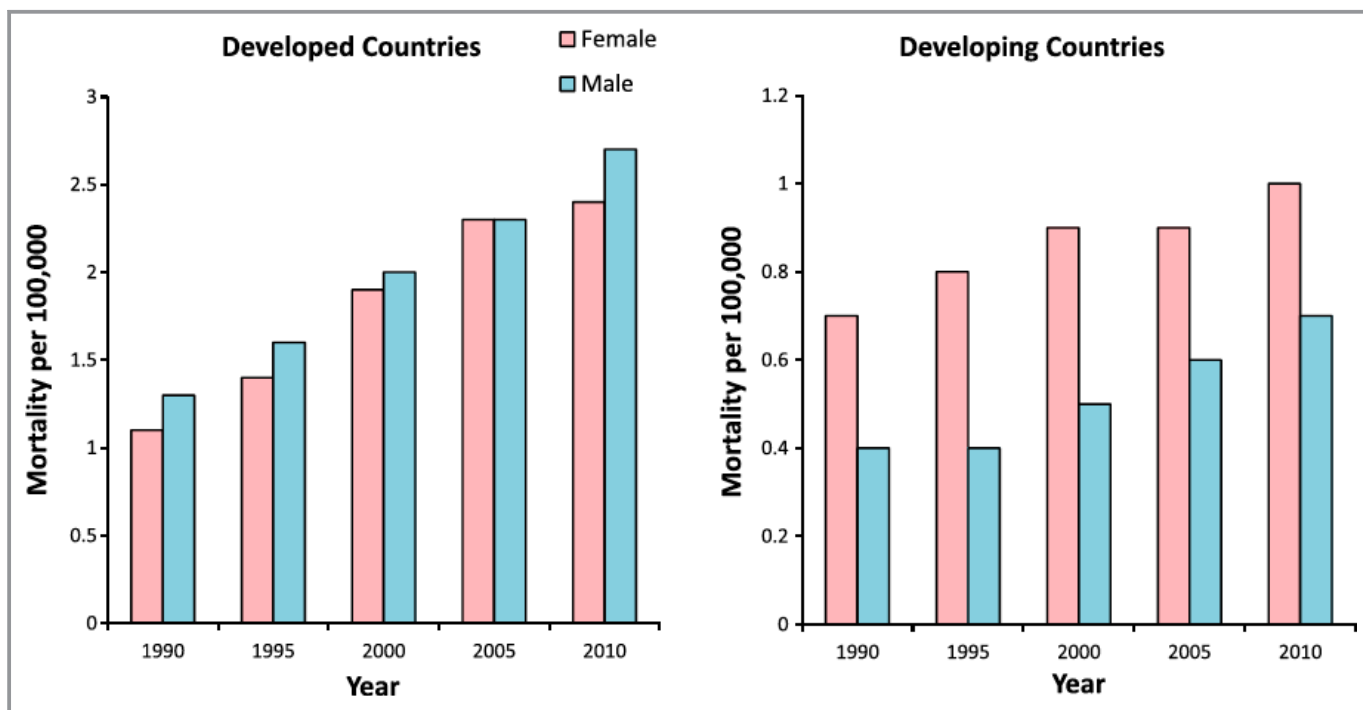
**Figure 2.** Global AF prevalence and projected increases. Figure reproduced from Rahman et al<sup>1</sup> with permission from Nature Publishing Group. AF indicates atrial fibrillation.

### Associations Between AF and Mortality, Morbidity, and Quality of Life

AF is associated with increased mortality. As AF prevalence and average lifespan increases over time, this burden will

likely increase as well. In adjusted analyses from the Framingham Heart Study in the United States, AF was associated with a 50% higher risk of death among men (odds ratio 1.5, 95% CI 1.2–1.8) and a 90% higher risk of death among women (odds ratio 1.9, 95% CI 1.5–2.2).<sup>8</sup> Globally, the age-adjusted mortality rate, per 100 000 individuals, from AF in 2010 was 1.6 (95% CI 1–2.4) among men and 1.7 (95% CI 1.4–2.2) among women, representing a 2-fold increase since the previous survey conducted in 1990.<sup>7</sup> Perhaps surprisingly, AF mortality rates in the developed world were 3 to 4 times higher than the developing world (Figure 3).

AF is also associated with significant morbidity. One of the most devastating consequences of AF is arterial thromboembolism. AF is associated with a 4 to 5 times higher risk of stroke, even after accounting for standard stroke risk factors (eg, hypertension, congestive HF, etc).<sup>9,10</sup> However, this risk of thromboembolism and its subsequent outcomes vary significantly among ethnic groups and geographies. For example, Americans of either Hispanic ethnicity or African-American race appear to have higher stroke risks, despite a lower prevalence of AF relative to white individuals.<sup>8,11</sup> Asians with AF may have particularly high risks for stroke, potentially due to variations in both anticoagulant prescribing practices and variable genetic-based responses to anticoagulation with warfarin.<sup>12–15</sup> Similar variation in thromboembolism risk and outcomes may also occur in other regions, but comprehensive global assessments of thromboembolism outcomes, particularly in developing countries, are lacking.



**Figure 3.** Mortality associated with atrial fibrillation (AF) stratified by sex and type of region (developed vs developing). Figure reproduced from Chugh et al<sup>7</sup> with permission from Wolters Kluwer Health, Inc.

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AF is also associated with other causes of morbidity, including coronary artery disease, dementia, chronic kidney disease, and HF. Coronary artery disease has been associated with AF across a wide variety of ethnicities and countries.<sup>3,10,16–18</sup> A US-based study found that AF was associated with a 70% increased risk of incident myocardial infarction (hazard ratio, 1.96; 95% CI, 1.52, 2.52), with higher risks in women and blacks.<sup>19</sup> AF has also been associated with cognitive decline and dementia. A meta-analysis of 21 studies found decreased cognitive scores associated with AF in different populations.<sup>11</sup> In Brazil, AF patients were 2.8 times more likely to have dementia, relative to those without AF.<sup>14</sup> AF also is associated with chronic kidney disease. A US-based study noted that the development of new-onset AF in chronic kidney disease patients was associated with a 1.7 times increased risk of developing end-stage renal disease, relative to those without AF.<sup>15</sup> Similarly, a Japanese study found the incidence of kidney dysfunction was 18.2 per 1000 person-years in AF patients, compared to 6.8 per 1000 person-years in patients without AF.<sup>20</sup> Finally, HF among AF patients is common, occurring in  $\approx$ 40% of patients, and associated with increased morbidity and mortality.<sup>12</sup> These associations between AF and HF in the developed world have also been demonstrated in the developing world. In particular, African studies have documented a 10% to 20% prevalence of AF among patients admitted to hospitals with HF.<sup>13</sup>

These associations between AF, mortality, and morbidity impair overall quality of life. This effect can be estimated by a disability-adjusted life years calculation, which adds up the years lost due to the condition with the years lived with the condition, weighted for its impact on quality of life.<sup>9</sup> As illustrated in Figure 4, AF-associated DALYs have consistently increased over the past 2 decades and continued increases are projected for the coming year.<sup>7</sup>

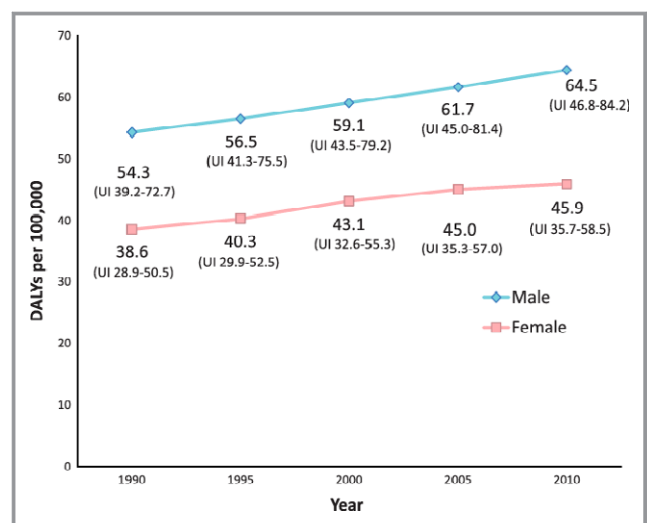
Although these data underscore the impact that AF has on mortality, morbidity, and quality of life, a full assessment of its worldwide impact is lacking. The INTERAF initiative can address these gaps, and uncover additional insights into the impact of AF globally.

## Global Trends and Differences in AF Treatments

There are notable variations in AF treatment and outcomes between different patient and country populations. Some of this variation is due to the availability of medications and interventions that, in turn, are dependent on resource availability and differences in healthcare systems (eg, national healthcare systems, private health insurance, or a mixture of both). In general, AF treatments are directed towards symptom reduction, typically via heart rate or rhythm control, and the

prevention of complications, such as arterial thromboembolism. Rate and/or rhythm-control treatments include heart rate controlling medications, antiarrhythmic medications, electrical cardioversion, or AF ablation. Thromboembolism prevention treatments include antithrombotic medications and mechanical left atrial appendage occlusion devices.

The use of rate and rhythm-control treatments varies globally, both in the developed and developing world. In the Euro Heart Survey, 65% of AF patients received rate-control medication, 40% received antiarrhythmic medication, and 12% received neither.<sup>21</sup> In contrast, a German AF registry—the Central Registry of German Competence Network on Atrial Fibrillation (AFNET)—demonstrated that only 21.3% of patients received antiarrhythmic medication, but 53.4% received electrical or pharmacologic cardioversion and 5% underwent AF ablation.<sup>22</sup> Chinese data demonstrated variable use of rate-control treatments, partly dependent on the AF phenotype.<sup>23,24</sup> Among those with paroxysmal AF, 44% of patients received rate-control treatment, compared to 83% of patients with permanent AF. These differences likely result from a variety of factors, including availability of more advanced and technically complex treatments, such as AF ablation.<sup>25</sup> In the developing world, rate-control treatments, particularly digoxin, dominate the use of antiarrhythmic medications, given their low cost and wide availability. For example, recent surveys of AF treatments in Cameroon found that 83% of patients were being treated with rate-control medications, with over 60% receiving digoxin.<sup>26</sup> Similarly, over 50% of Kenyan patients on rate-control therapy were receiving digoxin.<sup>27</sup> However, better characterization of rate-control



**Figure 4.** Disability-adjusted life years (DALYs) related to AF. Estimated global age-adjusted DALYs (per 100 000) related to atrial fibrillation: 1990 to 2010. UI indicates uncertainty index. Figure reproduced from Chugh et al<sup>7</sup> with permission from Wolters Kluwer Health, Inc.



treatments, especially in developing countries, is needed. In addition, as newer technologies such as AF ablation gain traction in these countries, registries will be needed to guide their safe and effective deployment.

Thromboembolic events related to AF are significantly reduced with the use of anticoagulation therapies. However, large variations occur in its provision and effect among various populations. For example, despite the recommendation that patients at moderate to high risk for thromboembolism receive anticoagulation, large numbers of patients, across multiple countries, do not.<sup>3,21,28</sup> Furthermore, even among those patients receiving anticoagulation with warfarin, its use is often suboptimal, with several studies demonstrating significant rates of subtherapeutic warfarin levels globally, particularly in developing countries.<sup>29,30</sup> Finally, certain populations appear to have higher risks of significant bleeding with anticoagulation, thus diminishing its benefit. In particular, Asian, Hispanic, and black populations all appear to have higher rates of intracranial hemorrhage on oral anticoagulation (OAC), relative to white populations.<sup>31,32</sup>

In recent years, 2 new modalities for thromboembolism prevention have emerged: direct oral anticoagulants (DOACs) and left atrial appendage occlusion devices. There is a need to understand how these new therapies will diffuse into global practice, and their impact on both thromboembolic event prevention and bleeding outcomes. DOACs have similar or better efficacy than warfarin, and have a dose-dependent, predictable anticoagulant effect, thus enabling fixed dosing that does not require laboratory monitoring of anticoagulation intensity. In addition, DOACs have a favorable safety profile, particularly for intracranial hemorrhage. All of these characteristics are potentially attractive to regions with relatively underdeveloped healthcare systems. However, DOACs are more expensive than warfarin and, with the exception of dabigatran, cannot be easily reversed.<sup>33</sup> These factors may limit their dissemination to the developing world. Left atrial appendage occlusion devices are an option for those patients who have absolute contraindications to OAC or completely refuse OAC, and appear to have similar efficacy to OAC in thromboembolism prevention.<sup>34</sup> However, the safety of left atrial appendage occlusion device implantation is largely operator dependent, with better outcomes in those who perform a high number of procedures. Thus, technical complexity, as well as cost, will likely slow its dissemination to the developing world. Registries to monitor its dissemination and safety of these new therapies are needed.<sup>35</sup>

## The International Collaborative Partnership for the Study of Atrial Fibrillation (INTERAF)

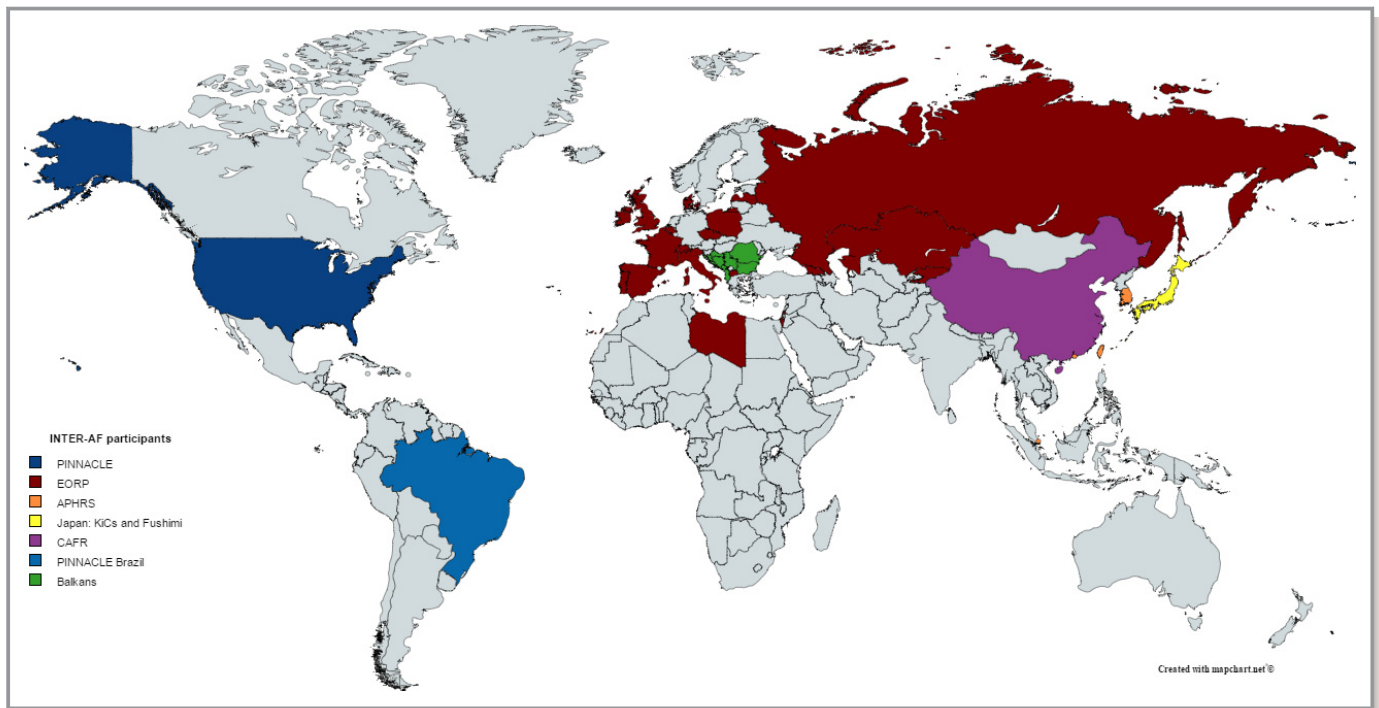
In response to this need for a more coordinated approach to AF registries, the International Collaborative Partnership for

the Study of Atrial Fibrillation (INTERAF) was established. Organized by an international group of AF and clinical registry experts, INTERAF is a collaborative, international consortium of AF registries to characterize worldwide AF care and establish a foundation for ongoing efforts to optimize AF care. The goals of INTERAF are 4-fold:

1. Build the foundation for a sustained international collaboration to identify and address meaningful questions related to AF management and improve AF patient outcomes.
2. Explore ways to harmonize existing and future AF registries in order to compare AF care across countries, identify gaps, and to influence and change global practice to close those gaps.
3. Prioritize research projects focused on international quality improvement.
4. Develop a roadmap for global AF quality improvement and educational initiatives, informed by best practices.

The initial partners of INTERAF include representatives from the United States, Europe, China, Brazil, South Korea, Taiwan, Singapore, Japan, and the Balkan countries (Figure 5). Each of the partners oversees country- or region-specific AF registries, and can thus inform efforts to unify their respective registries. In addition, the countries represent a variety of patient populations and healthcare systems, which can inform the technical challenges inherent in creating a unified, global AF registry. Table 1 lists the participating registries and their various characteristics.

A challenge for all clinical registries, particularly those that are global in scope, is organizing data collection and analytic efforts to gain meaningful insights. Simply establishing a single registry that collects the same data elements in every participating country is not feasible, given the enormous costs and logistical difficulties associated with such an effort. Instead, INTERAF will be organized as a distributed research network, similar to the National Heart, Lung, and Blood Institute–supported Cardiovascular Research Network and the Patient-Centered Outcomes Research Institute (PCORI)–supported PCORnet.<sup>36,37</sup> A distributed research network allows for data collection and local analyses to be conducted within each participating partner's infrastructure. These data are then aggregated and analyzed across partner registries. This distributed structure thus avoids the difficulties with data security, patient privacy, and governance inherent in a single registry structure. At the same time, the structure allows for greater size and power of the overall registry, an ability to assess and compare partner practice patterns, greater diversity in studied patient populations, and an opportunity to assess the heterogeneity of treatment effect in various real-world settings. It also lowers barriers to participation in INTERAF and engages with local AF experts to best identify partner-specific characteristics and challenges in AF management for analysis.



**Figure 5.** Initial INTERAF partners, by country. APHRS indicates Asia-Pacific Heart Rhythm Society; CAFR, Chinese Atrial Fibrillation Registry; EORP, EURObservational Research Programme, INTERAF, International Collaborative Partnership for the Study of Atrial Fibrillation; KiCs, Keio Interhospital Cardiovascular Studies; PINNACLE, Practice Innovation and Clinical Excellence.

In order to effectively manage this distributed research network, a governance structure will be established to determine the minimal data elements and standards needed for partner participation in INTERAF and the technical specifications necessary to integrate registries. Examples of necessary data elements include patient and clinical demographics, AF phenotype (eg, paroxysmal, persistent, permanent) characteristics, relevant clinical comorbidities, stroke and bleeding risk scores, AF therapies (eg, rate control, rhythm control, anticoagulation), and relevant concurrent medications. In addition, efforts to link to other longitudinal outcomes data will occur to help in understanding the impact of AF on mortality, quality of life, healthcare utilization, and costs. Once the individual registry analyses are completed, a dedicated analytic center will utilize informatics tools to merge individual analyses into an aggregated result.

Ensuring effective data harmonization and quality across the partner registries will require significant and ongoing effort. Participating registries in INTERAF will have differences in data elements and enrollment criteria (Table 1), which will require coordination in order to allow for inter-registry comparisons. For example, the Chinese Atrial Fibrillation Registry (CAFR) is largely an AF ablation registry, the European EurObservational Research Programme (EORP) AF registry enrolls all ambulatory AF patients seen by European cardiologists, and the US Practice Innovation and Clinical Excellence (PINNACLE) registry enrolls all AF patients seen in

participating cardiovascular practices. As such, an initial task of the INTERAF consortium is to harmonize the data elements between these registries.

Finally, the success of INTERAF will hinge on effective leadership to organize and accommodate the variety of research, organizational, and cultural needs anticipated in a global partnership. In addition, effective ethical and regulatory oversight will be critical, especially in light of the different countries, healthcare systems, and research standards expected to participate in INTERAF. For example, institutional review board and data privacy standards for each participating registry will be obtained and unified across participants to ensure that appropriate patient protection and privacy occurs.

Once these analytic and organizational priorities are established, then inter-registries research into AF characteristics, treatments, and outcomes can begin. Table 2 lists the following areas that the INTERAF partners have identified as priorities for inter-registry research. These priority areas for research were generated from INTERAF partner meetings, after discussion on important areas of focus regarding global AF care.

## Patient Descriptives

The patient characteristics of the initial AF registries participating in the INTERAF partnership are listed in Table 3 and include all patient information collected through the end of

**Table 1.** Characteristics of the Current INTERAF Registries, as of December 31, 2015

	United States NCDR PINNACLE AF Registry	European Society of Cardiology EURObservational Research Program (EORP) AF General Registry	Chinese AF Registry (CAFR)	Brazil PINNACLE AF Registry	Asia Pacific Heart Rhythm Society	Japanese Fushimi AF Registry	Japanese Keio Internospital Cardiovascular Studies (KICS) AF Registry	Balkan AF Registry
Patient setting	Outpatients	Outpatients	Inpatients and outpatients	Inpatients and outpatients	Inpatients and outpatients	Inpatients and outpatients	Outpatients	Inpatients and outpatients
Geographic location	United States	Albania, Belgium, Czech Republic, Denmark, France, Georgia, Ireland, Israel, Italy, Kyrgyzstan, Kazakhstan, Latvia, Libya, Macedonia, Malta, Poland, Portugal, Romania, Russia, Serbia, Spain, Switzerland, UK	China	Brazil	Hong Kong, South Korea, Singapore, Japan, Taiwan	Japan	Japan	Albania, Bosnia & Herzegovina, Bulgaria, Croatia, Montenegro, Romania and Serbia
Number of patients, providers, and healthcare settings	927 511 patients at 1400 practice locations	10 000 patients (Target enrollment: 23 000 patients)	15 000 patients at 31 hospitals (Target enrollment: 20 000 patients)	Target enrollment 10 000 patients (to begin enrolling in late 2015)	Target enrollment 5000 patients with at least 5 centers in each country (to begin enrolling in early 2016)	4426 patients at 79 participating institutions (2 cardiovascular centers, 10 rehab hospitals, 67 private clinics)	1284 patients at 10 cardiovascular centers	2712 patients in 49 centers (university and non-university hospitals and health centers)
Registry dates of collection	2008–present	2014–2016	2011–present	2015–2017	2016–2017	2011–present	2012–present	December 2015–February 2015
Data collection method	Automated EHR data collection	Paper-based case report form	EHR and paper data collection	EHR and paper data collection	EHR and paper data collection	EHR and paper data collection	EHR and paper data collection	Electronic case report form, backed up with paper data source
Data elements and quality	Complete data on comorbidities, vital signs, and labs; partial data on event history, events between visits; CHADS2 and CHA2DS2-VASc score calculation	Complete data on comorbidities, medications, vital signs, CHADS2 and CHA2DS2-VASc score data on events at 1 year	Data elements similar to US PINNACLE	Data elements similar to US PINNACLE	Complete data on comorbidities, medications, vital signs, CHADS2 and CHA2DS2-VASc score calculations; partial data on events at 1 year	Complete data on comorbidities, medications, vital signs, CHADS2 and CHA2DS2-VASc score calculations	Complete data on comorbidities, medications, vital signs, CHADS2 score, treatment strategy, and baseline DoL data; partial data embolic events, bleeding events, and QoL at 1 and 2 years	Complete data on patient characteristics, presentation, healthcare setting, AF management strategies, and diagnostic procedures
Availability and characteristics of longitudinal data	Linked to longitudinal US Medicare claims data	Annual follow-up assessment over 3 years	Longitudinal follow-up assessment every 6 months	Planned longitudinal follow-up assessment	Annual follow-up over 2 years	Annual follow-up assessment	Annual follow-up over 2 years	None

Continued

**Table 1.** Continued

	United States NCDR PINNACLE AF Registry	European Society of Cardiology EURObservational Research Program (EORP) AF General Registry	Chinese AF Registry (CAFR)	Brazil PINNACLE AF Registry	Asia Pacific Heart Rhythm Society	Japanese Fushimi AF Registry	Japanese Keio Interhospital Cardiovascular Studies (KICS) AF Registry	Balkan AF Registry
OAC assessment and quality	Assessment of OAC use, including both VKA and DOACs	Assessment of OAC use	Assessment of OAC use, including both VKA and DOACs	Assessment of OAC use	Assessment of OAC use	Assessment of OAC use, including both VKA and DOACs	Assessment of OAC use, including both VKA and DOACs	Assessment of OAC use, including both VKA and DOACs
IRB approval*	National IRB waiver; no individual patient consent	Patients individually consented	Patients individually consented	National IRB waiver; some individual patient consent	Patients individually consented	Institutional IRB waiver; no individual patient consent	Patients individually consented	Patients individually consented
Feedback to registry participants	Feedback given to participating practices via performance reports	Feedback and some data monitoring	Feedback to hospitals twice a year	Feedback given to participating practices via performance reports	Feedback and some data monitoring	Feedback and some data monitoring	Feedback provided to participating hospitals twice a year	Regular feedback to participating sites
Participation in prospective research studies	Sites can participate in cohort studies, but consent needed	Sites can participate in cohort studies, but consent needed	Sites can participate in cohort studies, but consent needed	Sites can participate in cohort studies, but consent needed	Sites can participate in cohort studies, but consent needed	Sites can participate in cohort studies, but consent needed	Sites can participate in cohort studies, but consent needed	Sites can participate in cohort studies, but consent needed
Incentives for registry participation	Receipt of feedback reports and automatic submission to Medicare for quality bonus payments	None	CAFR funding to hospitals	Receipt of feedback reports and quality of care certification via the American College of Cardiology and São Paulo Society of Cardiology	None	None	Feedback reports and research projects	None

AF indicates atrial fibrillation; DOACs, direct oral anticoagulants; EHR, electronic health record; INTERAF, International Collaborative Partnership for the Study of Atrial Fibrillation; IRB, institutional review board; OAC, oral anticoagulant; PINNACLE, Practice Innovation and Clinical Excellence; QoL, quality of life; VKA, vitamin K antagonist.

\*An institutional waiver of consent has been obtained for collective analyses as all data are de-identified and of minimal risk to any patient.



**Table 2.** INTERAF Research Priorities

1.	Global and regional comparisons of overall age, sex, and racial/ethnic characteristics of AF populations
2.	Global and regional comparisons of AF management, including both pharmacologic and nonpharmacologic approaches to heart rate and rhythm control
3.	Global and regional comparisons of pharmacologic and nonpharmacologic approaches to thromboembolism prevention
4.	Global and regional determinants of antithrombotic therapy and effective anticoagulation control
5.	Global and regional outcomes associated with AF management practices
6.	Comparison and predictors of embolic and bleeding events associated with AF and its management
7.	Time trends in use of various treatment strategies in different healthcare systems
8.	Impact of local health systems on AF care
9.	Resource utilization for AF care
10.	Patterns of AF care as a function of national and international guideline recommendations
11.	Comparison of “real world” AF populations to those studied in AF clinical trials
12.	Global and regional predictors of high-quality AF management
13.	Quality improvement initiatives for AF care and outcomes, with a focus on those elements that can be successfully translated across countries and geographic regions

AF indicates atrial fibrillation; INTERAF, International Collaborative Partnership for the Study of Atrial Fibrillation.

2015. Of the 8 initial registries participating in the partnership, 7 had begun collecting data by the end of 2015 and the eighth, the Asia Pacific Heart Rhythm Society registry, will begin doing so in 2016. The largest patient cohort is the US-based NCDR registry, followed by the Chinese AF registry. In general, the majority of patients in all registries were older than 65 years, with the exception of the Chinese registry, which is split between those older and younger than 65. The registries were also generally balanced in patient sex, with the exception of the majority male (72%) KiCS registry in Japan. Given the preponderance of registries in the United States, northern Europe, and Asia, the majority of registry participants were either white or Asian race. Hypertension was a common comorbidity in all registries. Coronary artery disease was much more common in the US PINNACLE registry population, while HF dominated the European and Balkan registries.

The majority of patients in the registries had nonvalvular AF, with a mixture of paroxysmal and permanent AF. AF treatment consisted of a mixture of rate and rhythm control. Thromboembolism risk among registry participants was relatively high, with median CHADS2 and CHA2DS2-VASc scores indicating a moderate-to-high risk for stroke.

Strategies to reduce this risk were variable, with warfarin use more common in Europe and the Balkan countries, and DOACs more common in the Japanese KiCS and Brazilian PINNACLE registries.

## INTERAF Differences From Previous International Registries

Previously developed AF registries have mostly been derived from single nation databases, with varied areas of focus including thromboprophylaxis, rhythm control, and procedural therapies such as ablation and left atrial appendage closure.<sup>5</sup> For example, the Euro Heart Survey involved 35 countries and 3890 patients between 2003 and 2004 to evaluate management of oral anticoagulation in AF patients against European guidelines, but only involved European countries.<sup>38</sup> Two of the largest multinational registries have aimed to enroll >55 000 patients each, and include the Global Anticoagulant Registry in the Field (GARFIELD) registry evaluating 50 countries worldwide,<sup>39</sup> and the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) registry involving 62 centers globally.<sup>40</sup> The focus of both of these registries has mainly been thromboprophylaxis prescription in AF. The Real-life global survey evaluating patients with atrial fibrillation (REALISE-AF) enrolled >10 000 patients in 26 countries between 2009 and 2010,<sup>41</sup> and the Registry on Cardiac Rhythm Disorders (RECORDAF) evaluated >5000 patients from 21 countries worldwide between 2007 and 2008.<sup>42</sup> Both REALISE-AF and RECORDAF were 1-year studies that reported on rhythm-control therapies in AF patients specifically. The AF ablation Long-term Registry of EURObservational Research Programme has been enrolling patients undergoing AF ablation in 54 countries since 2010 for long-term outcomes after ablation.<sup>43</sup> The registry's main focus is procedural outcomes after AF ablation.

In contrast to these other registries, INTERAF will provide insight into international AF care across a truly global spectrum of countries, analyzing a wide variety of treatment options, with the potential to adapt to temporal changes in treatment strategies. The global spread of countries represented by INTERAF is broad, with large representation in the United States, South America, Europe, and Asia. While the GARFIELD, GLORIA-AF, and REALISE-AF registries had a similar multinational representation, INTERAF has the advantage of larger numbers of AF patients from North America and Asia, providing power for some of the largest global analyses performed regarding treatment of AF patients. As a contemporary global registry that will continue to collect data longitudinally, INTERAF will be able to capture all types of oral anticoagulation strategies (warfarin versus DOACs), and rhythm-control strategies (antiarrhythmic drug medications

**Table 3.** INTERAF Patient Characteristics by Participating Registry

Patient Characteristics	United States NCDR PINNACLE AF Registry		European Society of Cardiology EURObservational Research Program (EORP) AF General Registry		Chinese AF Registry (CAFR)		Brazil PINNACLE AF Registry		Japanese Fushimi AF Registry		Japanese KICS AF Registry		Balkan-AF Registry	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Demographics														
Age, y														
<65	240 778	24.8	1029	33.0	8678	49.7	6	23.7	779	17.6	539	42.0	883	32.6
65 to 74	313 479	32.3	1039	33.3	5077	29.1	10	38.5	1337	30.2	426	33.2	882	32.5
>75	502 917	51.9	1051	33.7	3712	21.3	10	38.5	2310	52.2	318	24.8	947	34.9
Male	547 100	56.4	1859	59.6	10 716	61.4	15	57.7	2607	58.9	926	72.1	1485	55.5
Race/ethnicity														
White	657 162	67.8	NA	NA	0	0.0	18	69.2	0	0.0	0	0.0	2494	92.0
Black/African	32 091	3.3	NA	NA	0	0.0	3	11.5	0	0.0	0	0.0	218	8.0
American Indian/Alaska Native	4591	0.5	NA	NA	0	0.0	0	0.0	0	0.0	0	0.0	NA	NA
Asian	8135	0.8	NA	NA	17 467	100.0	0	0.0	4426	100.0	1284	100.0	NA	NA
Native Hawaiian/Pacific Islander	2055	0.2	NA	NA	0	0.0	0	0.0	0	0.0	0	0.0	NA	NA
Hispanic/Latino ethnicity	22 774	2.4	NA	NA	0	0.0	5	19.2	0	0.0	0	0.0	NA	NA
South Asian (India/Pakistan/Bangladesh)	NA	NA	NA	NA	0	0.0	0	0.0	0	0.0	0	0.0	NA	NA
AF characteristics														
AF type														
Nonvalvular	961 593	99.2	1138	36.5	5766	96.4	18	69.2	4218	95.3	1278	99.5	2712	100.0
Valvular	7909	0.8	1981	63.5	216	3.6	5	19.2	208	4.7	4	0.3	0	0.0
AF duration														
First detected	47 383	4.89	945	30.3	1270	7.3	1	3.8	NA	NA	68	5.3	632	23.3
Paroxysmal	246 202	25.4	827	26.5	9768	56.3	6	23.1	1859	42.0	663	51.6	556	20.5
Persistent	48 084	5.0	811	26.0	6302	36.3	1	3.8	420	9.5	354	27.6	383	14.1
Permanent	NA	NA	540	17.3	NA	NA	14	53.8	2147	48.5	186	14.5	1088	40.1
Unknown	627 833	64.8	NA	NA	NA	NA	4	15.4	NA	NA	13	1.0	53	2.0

Continued

**Table 3.** Continued

Patient Characteristics	United States NCDR PINNACLE AF Registry		European Society of Cardiology EURObservational Research Program (EORP) AF General Registry		Chinese AF Registry (CAFR)		Brazil PINNACLE AF Registry		Japanese Fushimi AF Registry		Japanese KICS AF Registry		Balkan-AF Registry	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
AF treatment														
Rhythm control														
Antiarrhythmic drug	366 832	37.8	1123	36.0	5854	41.3	4	15.4	854	19.3	728*	56.7	889	32.8
Ablation	40 912	4.2	237	7.6	7162	41.6	0	0.0	266	6.0			95	3.5
Rate control	849 645	87.6	1213	38.9	8202	7.8	10	38.5	1987	44.9	556	43.3	1622	59.8
Stroke risk and prevention														
CHADS2 score, median (IQR)	2.0 (1.0–3.0)		2.0 (1.0–3.0)		2.0 (2.0–3.0)		3.0 (2.0–3.0)		2.0 (1.0–3.0)		1.0 (0.0–2.0)		2.0 (1.0–3.0)	
CHA2DS2-VASc score, median (IQR)	4.0 (3.5–4.5)		3.0 (2.0–4.0)		4.0 (2.0–3.0)		3.0 (2.0–3.0)		3.0 (2.0–5.0)		3.0 (2.0–4.0)		3.0 (2.0–5.0)	
OAC among those with either CHADS2s or CHA2DS2-VASc score > 1														
Warfarin	398 816	41.1	2233	71.6	5979	54.5	5	19.2	1859	43.8	220	17.1	461	20.1
Acenocoumarol	NA		NA		NA		NA		NA		NA		964	42.0
Phenprocoumon	NA		NA		NA		0	0.0	NA		NA		1	0.0
Dabigatran	81 556	8.4	212	6.8	200	93.0	6	23.1	152	3.6	161	12.5	142	6.2
Rivaroxaban	111 653	11.5	50	1.6	6	2.8	5	19.2	137	3.2	266	20.7	95	4.1
Apixaban	79 742	8.2	0	0.0	NA		2	7.7	130	3.1	256	19.9	43	1.9
Edoxaban	2 349	0.24	NA		NA		0	0.0	31	0.7	NA		0	0.0
Other	NA		NA		NA		NA		NA		6	0.5	NA	
Other medical conditions														
Coronary artery disease	479 031	49.4	1135	36.4	2647	15.2	3	11.5	646	14.6	101	7.9	821	30.3
Diabetes mellitus	245 461	25.3	643	20.6	3233	18.7	4	15.4	1005	22.7	200	15.6	668	24.6
Hypertension	770 352	79.5	2211	70.9	10 011	57.8	20	76.9	2762	62.4	713	55.5	2121	78.2
Current smoker	182 998	18.9	352	11.3	2075	12.0	2	7.7	391	8.8	217	16.9	340	12.5
Peripheral arterial disease	102 279	10.6	349	11.2	107	1.6	2	7.7	186	4.2	42	3.3	122	4.5
Prior TIA/stroke	146 132	15.1	324	10.4	2509	14.5	1	3.8	823	18.6	103	8.0	364	13.5
Congestive heart failure	276 642	28.5	1482	47.5	1397	8.1	7	26.9	1235	27.9	193	15.0	1161	42.8
Chronic kidney disease														

Continued

**Table 3.** Continued

Patient Characteristics	United States NCDR PINNACLE AF Registry		European Society of Cardiology EURObservational Research Program (EORP) AF General Registry		Chinese AF Registry (CAFR)		Brazil PINNACLE AF Registry		Japanese Fushimi AF Registry		Japanese KICS AF Registry		Balkan-AF Registry	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
	N=969 502		N=3119		N=17 467		N=26		N=4426		N=1284		N=2712	
Stage IIIa (GFR 45–59)	1117	0.1	NA	NA	382	2.7	NA	NA	1226	27.7	315	24.5	NA	NA
Stage IIIb (GFR 30–44)	1222	0.1	NA	NA	146	1.0	NA	NA	606	13.7	169	13.2	NA	NA
Stage IV (GFR 15–29)	755	0.1	NA	NA	60	0.4	NA	NA	230	5.2	42	3.3	NA	NA
Stage V (GFR <15) or HD	297	0.0	NA	NA	32	0.2	NA	NA	124	2.8	13	1.0	NA	NA

The Brazil PINNACLE registry began enrolling patients in late 2015; The Asia Pacific HRS registry will begin enrolling patients in 2016. AF indicates atrial fibrillation; GFR, glomerular filtration rate; HD, hemodialysis; INTERAF, International Collaborative Partnership for the Study of Atrial Fibrillation; IQR, interquartile range; NA, not available/applicable; NDCR, National Cardiovascular Data Registry; PINNACLE, Practice Innovation and Clinical Excellence; OAC, oral anticoagulant; TIA, transient ischemic attack.  
\*Includes both antiarrhythmic drug and AF ablation.

and ablation) to allow for a broad spectrum of treatment analyses; most other global registries have been devised to focus only on a specific treatment protocol. Another advantage of INTERAF compared to other global registries will be planned ongoing shared data collection and analyses, which will not be limited by a specific end date, to allow for evolution of the global registry, including the countries that participate in sharing data. By using a distributive analytic method to allow for data collection and analyses, and expanding information collected to several different aspects of AF care, INTERAF would be poised to provide longitudinal information on practice patterns, and track changes over time as a comprehensive global AF registry.

### Limitations

The proposed project should be viewed in light of the following limitations. First, each of the multinational registries included in INTERAF have previously identified important covariates to prospectively collect, which may not be completely duplicative. However, we specifically have included and will analyze universally important characteristics and comorbidities that have a common interest related to AF. Although this may seem to produce a challenge with data organization, we have specifically chosen a distributed analytic method by which local analyses may be conducted by each participating registry, and then analyzed across all partner registries. Second, differences in data element definition or inclusion criteria for each country’s specific registry may lead to heterogeneity in the overall patient population studied. For example, the percentage of valvular versus nonvalvular as well as paroxysmal versus persistent AF differed across each specific registry, and AF patients from specific countries appeared to have more frequent comorbidities, potentially due to differences in data element definitions. Finally, each registry within INTERAF will have differences in the type of outcomes collected, as well as frequency and timeframe of patient follow-up. While this may limit the types of specific treatment strategies able to be compared, INTERAF will focus on those outcomes and treatment strategies that have universal availability of data across specific registries to allow for analytic integrity.

### Future Directions

The initial organization and goals of INTERAF, as outlined above, are only the beginning of efforts to better characterize and improve global AF care. Future directions for the initiative will include continued data harmonization across country partners and improvements in data collection. Moreover, attempts to validate country-specific observations, risk stratification schemes, and outcomes may be attempted, in order



to identify generalizability of previously established research findings to a multinational AF population, as has been previously performed examining acute kidney injury, bleeding, and mortality in Japanese patients undergoing percutaneous coronary intervention.<sup>44,45</sup> Another important effort will involve INTERAF expansion to include a wide variety of clinical registries and participating countries, with special emphasis on registries in the developing world, where little information about AF care and outcomes currently exists. Efforts to expand the partnership are under way, and we anticipate partners from areas such as the Middle East, Africa, Central America, and Australia.

## Conclusions

We present the INTERAF, a worldwide collaboration for observational study of AF. This project can provide a global platform for investigators and countries to study AF populations, treatments, and outcomes and support country-specific and international efforts to optimize global care for the large and growing population of AF patients. As insights from the consortium accumulate, INTERAF will develop mechanisms to understand regional variation in practice for AF management, with a particular focus on understanding those practices, which can be shared globally.

## Disclosures

None of the authors have material conflicts of interest. All of the authors participated in either the drafting or critical review of the manuscript. The International Collaborative Partnership for the Study of Atrial Fibrillation project is supported by an unrestricted award from Bristol-Myers Squibb and Pfizer, Inc. to the American College of Cardiology. The funders have no role in project governance, management, or research activities.

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**Key Words:** atrial fibrillation • clinical registries • global health • quality of care and outcomes



## **International Collaborative Partnership for the Study of Atrial Fibrillation (INTERAF): Rationale, Design, and Initial Descriptives**

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