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## Outcomes registry for better informed treatment of atrial fibrillation II: Rationale and design of the ORBIT-AF II registry

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### Abstract

**Background**—Recent clinical trials have demonstrated the safety and efficacy of several non-vitamin K oral anticoagulants (NOACs) for the treatment of atrial fibrillation (AF). However, there are limited data on their use and outcomes in routine clinical practice, particularly among patients newly diagnosed as having AF and patients with AF recently transitioned to a NOAC.

**Methods/Design**—ORBIT-AF II is a multicenter, national registry of patients with AF that is enrolling up to 15,000 newly diagnosed patients with AF and/or those with AF recently transitioned to a NOAC from 300 US outpatient practices. These patients will be followed for up to 2 years, including clinical status, outcomes (major adverse cardiovascular events, bleeding), and management of anticoagulation surrounding bleeding events. In addition, detailed data regarding the use of these agents in and around cardiac procedures, their complications, and management of such complications will be collected.

**Conclusions**—The ORBIT-AF II registry will provide valuable insights into the safety and effectiveness of NOACs used in AF in community practice settings.

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Atrial fibrillation (AF) represents the most common dysrhythmia worldwide and leads to significant morbidity, mortality, and cost.<sup>1</sup> It is a major risk factor for stroke, and patients with AF who experience stroke experience worse survival and disability compared with stroke patients without AF.<sup>2</sup> The use of warfarin for the prevention of stroke in patients with AF was a landmark public health advancement, decreasing all-cause mortality in clinical trials by 26%.<sup>3-5</sup> Annual rates of stroke in this population can be reduced from 5%-10% to less than 2%, depending on underlying risk.<sup>4</sup> Although warfarin has been used for oral anticoagulation for more than 50 years, it has significant shortcomings including the need for routine monitoring and numerous drug and food interactions.

In October 2010, dabigatran etexilate (a direct thrombin inhibitor) became the first oral alternative to warfarin for the prevention of stroke or systemic embolism in patients with nonvalvular AF. Subsequently, several additional agents have been approved or are in late-stage development (eg, oral factor Xa inhibitors rivaroxaban, apixaban, and edoxaban) as alternatives for anticoagulation in these patients. Each of these agents has been proven to be equivalent to or better than warfarin with regard to prevention of stroke or systemic embolism and risk of bleeding.<sup>6-10</sup>

The ORBIT-AF I registry<sup>11</sup> described the use, effectiveness, and outcomes of oral anticoagulation in more than 10,000 all-comer patients with AF treated at a diverse collection of electrophysiologists, cardiologists, and generalists from across the United States between June 2010 and August 2011. To date, this long-term follow-up registry has provided important insights into risk stratification, treatment, and outcomes of these patients.<sup>12-17</sup> However, most patients and data in ORBIT-AF I involve anticoagulation with warfarin; that registry largely predated the development of non-vitamin K oral anticoagulants (<10% of patients in ORBIT-AF I were treated with such drugs).

Moving forward, the proliferation of alternatives to warfarin has generated significant interest in the utilization, management, and outcomes associated with non-vitamin K oral anticoagulants in clinical practice, outside clinical trials. Specifically, dosing, temporary interruptions, perioperative management, and management of bleeding are major considerations urgently requiring evidence-based approaches. Therefore, in an effort to address these knowledge gaps, phase II of ORBIT-AF was designed (ORBIT-AF II).

## Registry objectives

The objectives of the ORBIT-AF II registry are as follows: (1) to evaluate the safety of non-vitamin K oral anticoagulants, including factor Xa inhibitors and direct thrombin inhibitors, in outpatients with AF; (2) to evaluate clinical outcomes in patients with AF treated with non-vitamin K oral anticoagulants; (3) to describe the management of patients with AF undergoing cardiac procedures and their outcomes; (4) to describe AF patient characteristics, with specific attention to the use of non-vitamin K oral anticoagulants and high-risk subgroups, such as those with chronic kidney disease, acute coronary syndromes,

or risk factors for stroke or bleeding; and (5) to describe patterns of switching and discontinuation among anticoagulant strategies in patients with AF.

## Design

The ORBIT-AF II registry will be a prospective, observational study of outpatients with AF, followed up every 6 months to 2 years. By design, it will have a specific and unique focus on enrollment of patients with new-onset AF and those newly transitioned to non-vitamin K oral anticoagulants.

## Site selection

Sites around the United States will be invited to participate, with particular attention to geographic and provider characteristics. Adaptive site enrollment will be used to ensure geographic heterogeneity, as well as diversity across practice type (eg, academic and private clinic) and provider type (primary care physician, neurologist, cardiologist, electrophysiologist). Approximately 300 sites will be activated to participate.

## Patient enrollment criteria

The primary inclusion criteria will be age  $\geq$  21 years and with electrocardiographically confirmed AF (eg, by electrocardiogram, Holter monitoring, implanted device, etc) (Table I). In an effort to recruit patients on or eligible for non-vitamin K oral anticoagulants, the registry will include only patients who either (a) have a new diagnosis of AF within the previous 6 months or (b) have started taking a non-vitamin K oral anticoagulant for AF (dabigatran, rivaroxaban, apixaban, or any oral agent subsequently approved) within the previous 3 months (Figure). Patients can be enrolled from both inpatient and outpatient settings and are expected to be followed up clinically at least every 6 months.

Principle exclusion criteria will be AF due to a reversible cause (eg, thyroid disease and pulmonary embolism), including postoperative AF, life expectancy less than 6 months, participation in ORBIT-AF I, or current enrollment in a clinical trial of an anticoagulant for AF. Patients with atrial flutter only will be excluded. Patients with both valvular and nonvalvular AF are eligible, and the use of warfarin is not an exclusion criterion.

## Sample size and anticoagulation strategy

The target enrollment for ORBIT-AF II will be up to 15,000 patients from the 300 clinical sites. This will allow for balanced sampling across anticoagulant strategies, including each non-vitamin K agent, as well as warfarin or none (for patients with new-onset AF). In addition, we will use an adaptive design to allow for serial assessments of prevalent anticoagulation strategies. Thus, enrollment of patients receiving a specific agent may be capped to prevent any single drug or strategy from predominating in the registry.

## Data collection

Primary data collection will be derived from the patient's medical record, with input from the treating provider where needed. All data will be entered into a Web-based case report form, enabled with dynamic data checking for patient eligibility, validity, expected data

ranges, and mandatory fields. Data entry will occur at 6-month intervals, regardless of patient clinic follow-up. All incident events and therapeutic changes will be entered at each collection interval (Table II).

Baseline data will include patient demographics, medical history, cardiovascular history, details of AF history and therapies, vital signs, laboratory measurements, electrocardiographic data, cardiac imaging parameters, details of medical management, and any contraindications to anticoagulation. At follow-up, major incident events and procedures (see “Outcomes,” below), as well as subsequent vital signs, laboratory studies, imaging parameters, and medication changes will be recorded. In-depth data regarding antithrombotic therapies, dosing, discontinuations, and reasons for discontinuations will be included in follow-up medication data. For patients on warfarin, international normalized ratio values will be recorded.

## Outcomes

The primary safety outcome will be incidence of major bleeding during 2 years of follow-up, collected every 6 months, and defined by the International Society of Thrombosis and Haemostasis criteria; these include bleeding events meeting at least 1 of the following criteria<sup>18</sup>:

1. Fall in hemoglobin  $\geq 2$  g/dL
2. Transfusion of  $\geq 2$  units of packed red blood cells or whole blood
3. Any bleeding in a critical site (intracranial, intraspinal, intraocular, intra-articular, pericardial, retroperitoneal, or intramuscular with compartment syndrome)
4. Any fatal bleeding

Additional, unique, detailed data on management of bleeding events will be collected. This will include the use of any blood products or transfusions, potential reversal agents, and necessity for invasive management of bleeding events.

The primary effectiveness end point will be stroke or systemic embolism, which will be the only end point adjudicated by review of primary documentation. Additional outcomes will be captured, including transient ischemic attack, myocardial infarction, incident heart failure, cause-specific hospitalization, and cause-specific mortality. Specific design elements of the ORBIT-AF II case report form may also allow for longer-term follow-up and outcomes derived from administrative datasets, without the compromise of Health Insurance Portability and Accountability Act-protected (HIPAA-protected) information. These methods have been previously described and validated.<sup>19,20</sup>

## Cardiac procedures

The management of non-vitamin K oral anticoagulants in the setting of trauma and/or invasive procedures (elective, urgent, or emergent) has become an area of great concern for patients and providers. These agents offer the benefits and the risks of being quick-acting, with half-lives that are relatively short compared with warfarin. Furthermore, there are few known reversible agents or antidotes, although several compounds including synthetics,

biologics, and blood products have been tried or are in development.<sup>21-23</sup> There is an unmet need for more information regarding outcomes following interruption of these agents, necessity of bridging therapies, and implications for bleeding management.

Therefore, an area of particular focus in the registry will be the management of these patients in and around cardiac procedures. Specific, additional data on (1) cardioversion, (2) electrophysiology procedures, (3) cardiac catheterization, and (4) cardiac surgery will be collected and will focus on risk of the procedure and provide granular detail on management of antithrombotic medications before, during, and after the procedure. In addition, data on complications and management of such events will be collected. This will include management and outcomes of bleeding complications, including blood product administration, reversal strategies, and the necessity of more aggressive management for bleeding. These data are unique to ORBIT-AF II, whereas ORBIT-AF I and other comparable registries have focused primarily on broader treatment strategies and outcomes.

### Statistical analyses

Statistical considerations will vary according to specific analyses performed. However, there will be several important considerations common to all analyses from ORBIT-AF II.

Principally, a variety of adjustment methodologies will be considered when attempting to compare patients; these may include simple multivariable adjustment, propensity scoring (matched or unmatched), inverse probability weighting, or other methods. Variables with <15% missing will routinely be imputed, using methods specific to individual analyses.<sup>24-26</sup> Furthermore, within-site clustering of similar patients will need to be addressed in many analyses.

Of note, the registry is not designed or powered to address questions of direct comparative effectiveness *between* non-vitamin K anticoagulants. Although analyses may be stratified by anticoagulant strategy, such treatments are not randomized, and it would not be possible to adjust for all confounding.<sup>27</sup> Thus, any conclusions of relative effectiveness between agents could be misleading.

## Registry organization

### Oversight and leadership

The protocol of the ORBIT-AF II registry has been approved by the Duke University Institutional Review Board. In addition, enrollment centers will obtain site-specific institutional review board approval pursuant to local regulations. All patients will be required to sign written, informed consent prior to collection of any study data. The ORBIT-AF II registry is led by independent executive and steering committees comprising electrophysiologists, cardiologists, anticoagulation specialists, and outcomes researchers. The Duke Clinical Research Institute will serve as the coordinating center, and the academic leadership will have full access to all of the primary data.

### Study sponsorship

The ORBIT-AF II registry is sponsored by Janssen Scientific Affairs, LLC, Raritan, NJ. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

### Timeline

Patient enrollment and data collection began in spring 2013. It is anticipated that enrollment will continue through the end of 2015. Follow-up will continue until all patients have 2-year data.

### Reporting of potential severe adverse events

The ORBIT-AF II registry will provide postmarketing approval surveillance data regarding the safety of non-vitamin K oral anticoagulants. As such, all sites will be educated as to the importance and recognition of potential severe adverse events. Those events *potentially* related to rivaroxaban will be reported to the sponsor (which is responsible for marketing and approval of rivaroxaban in the United States); such events will be investigated, and the sponsor will be subsequently responsible for reporting of such events to regulatory authorities. Potential events related to all agents other than rivaroxaban (including nonanticoagulants) will be reported pursuant to local regulations and consistent with good clinical practice (ie, via the Food and Drug Administration's MedWatch Safety Reporting Program: <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>).

### Initial ORBIT-AF II patient recruitment

Characteristics of the initial 1,000 patients enrolled in ORBIT-AF II, compared with other contemporary AF registries, as well as controlled trials, are shown in Table III. This population is very similar to ORBIT-AF, phase I: 40% of the patients are women, and cardiovascular disease and risk factors are common. Consistently, patients studied are in their 70s and at significant risk for stroke or systemic embolism (as assessed by CHADS<sub>2</sub> scores).

### Discussion

The ORBIT-AF II study will function as a postmarket surveillance study after the transition from clinical practice with a single available anticoagulant (ie, warfarin) to the era of widely available non-vitamin K, or target-specific, oral anticoagulants. This transition follows on the recent completion of several "mega-trials" of both direct thrombin and factor Xa inhibitors.<sup>6-10</sup> These large, phase III trials were conducted to demonstrate safety and efficacy in specific populations, with a major objective being market approval by the Food and Drug Administration. Thus, they could not address myriad issues in the clinical implementation of the drugs, including transitions between therapies, perioperative management, and treatment of bleeding in patients receiving non-vitamin K oral anticoagulants. The ORBIT-AF II study will collect detailed data on patients experiencing these events and, importantly, their outcomes. Subsequent analyses of these data can help guide clinicians through many everyday management decisions where clinical trials cannot.



The ORBIT-AF I registry served as a primary observational cohort of more than 10,000 outpatients with AF, predominantly managed with vitamin K antagonism for stroke prevention. It has provided valuable data on the contemporary management of such patients, including rhythm strategies, symptom management, and anticoagulation, in the United States.<sup>12-15,17</sup> However, the timing of enrollment in ORBIT-AF I precluded in-depth study of patients managed with each of the non-vitamin K oral anticoagulants. Furthermore, detailed data regarding periprocedural management and management of bleeding complications were not the focus of ORBIT-AF I. Whereas ORBIT-AF I provided novel data on contemporary, overall management, and outcomes in US patients with AF, ORBIT-AF II will provide complimentary, detailed insights regarding management of anticoagulants around specific clinical scenarios.

This will contrast with the methods previously used to assess postmarketing use of these drugs. Such studies have so far been limited to (1) post hoc analyses of the randomized trials,<sup>28,29</sup> (2) experiences within a single or few centers,<sup>30,31</sup> or (3) international and/or administrative claims data.<sup>32,33</sup> Although each method has strengths, there are inherent limitations that we hope to address in ORBIT-AF II. These include the following: the availability of data from community, “real-world” use of these drugs; broad enrollment across practice centers around the United States; and detailed data on medical diagnoses, medication use, dose, discontinuation, reasons for medication changes, periprocedural data, clinical outcomes, and management of adverse events.

A key feature of ORBIT-AF II is the careful attention to periprocedural management and transitions among stroke prevention strategies. Detailed data surrounding many of the most common cardiovascular procedures, including drug management, complications, and management of bleeding, will provide valuable insights for providers—implementation of these drugs can be relatively straightforward in the most stable patients. It is during these transitions and interventions where providers are challenged as to the best management for their patients, and up to now, data have been lacking.

However, ORBIT-AF II will also extend data from ORBITAF I—the culmination will be a cohort of approximately 25,000 outpatients with AF with long-term follow-up. It will be, by far, the largest detailed observational cohort of patients with AF in the United States, powered to explore a variety of outcomes, including ischemic, hemorrhagic, and mortality. This will have important implications for the assessment of rare events and outcomes, as well as continued refinement of risk stratification tools that are broadly applicable.

Additional observational studies of patients with AF are enrolling in the United States and around the world. Contemporary international cohorts have shown limited data on non-vitamin K oral anticoagulants, may focus on a single agent, and/or include minority representation of US patients.<sup>34,35</sup> Others will have a specific focus on quality of care and implementation of guidelines, such as the American Heart Association’s expansion of “Get With The Guidelines” to patients with AF (GWTG-AFIB). Although GWTG-AFIB will generate feedback on short-term quality metrics among hospitalized patients to ensure that specific, previously identified best practices are followed, the ORBIT-AF program will

identify broad patterns of treatment and outcomes longitudinally to help better inform what those best practices should be.

## Limitations

The ORBIT-AF II registry is designed as a large, prospective, observational, clinical study in an effort to address specific questions regarding the care of patients with AF in community practice. However, there are specific limitations inherent in such methods. Primarily, there is no random assignment of patients to any treatments, and thus, comparisons among groups will be limited by residual and unmeasured bias. They could provide descriptive and hypotheses-generating observations. Second, data will be dependent on the quality of medical record abstraction. Lastly, the recruitment of sites prescribing non-vitamin K oral anticoagulants may represent unique providers (eg, “early-adopters”), difficult to extrapolate to a broader population of AF providers.

## Conclusions

The ORBIT-AF II registry will fill a significant gap in the dynamic landscape of AF care and research. It will provide unique and necessary data on the management and outcomes of outpatients treated with emerging therapies and, combined with ORBIT-AF I, will yield the largest, contemporary longitudinal cohort of patients with AF in the United States.

## Appendix

### Disclosures

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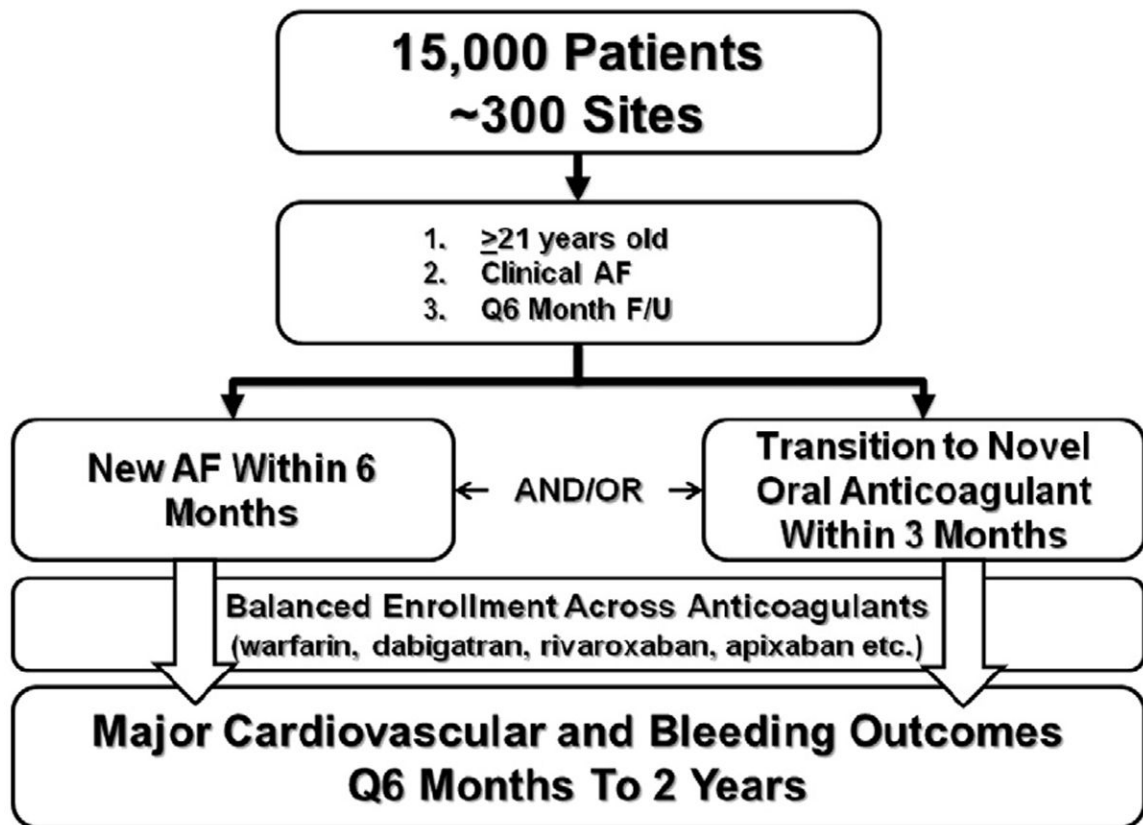
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**Figure.**  
Design schematic of the ORBIT-AF II registry.

**Table I**

## Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>• Age ≥ 21 y</li> <li>• Electrocardiographically confirmed AF</li> <li>• 1 of the following:               <ul style="list-style-type: none"> <li>• New-onset AF within the previous 6 mo</li> <li>• Initiation or transition to a non-vitamin K oral anticoagulant within the previous 3 mo<sup>*</sup></li> </ul> </li> <li>• Anticipated, regular semiannual follow-up outpatient visits</li> <li>• Signed informed consent</li> </ul>	<ul style="list-style-type: none"> <li>• Anticipated life expectancy &lt;6 mo</li> <li>• Atrial flutter only without AF</li> <li>• Transient AF secondary to a reversible condition (eg, hyperthyroidism, pulmonary embolism, and postcardiothoracic surgery)</li> <li>• Participation in a randomized clinical study of any anticoagulation for AF</li> <li>• Any participation in the ORBIT-AF I registry</li> </ul>

\* Including dabigatran, rivaroxaban, and apixaban. If additional agents are approved during the study period, they will be added.

Table II

## Timeline of data collection in ORBIT-AF II

	Baseline	6 mo	12 mo	18 mo	24 mo
Demographics, medical history, AF diagnosis, provider/site information	X				
Contraindications to oral anticoagulant therapy	X				
Vital signs, laboratory data, ECG, Holter, and echo data	X	X	X	X	X
Current pharmacotherapies (including INR monitoring) and adverse events	X	X	X	X	X
Temporary and permanent discontinuation of antithrombotic therapies		X	X	X	X
Details of cardiac procedures		X	X	X	X
Outcomes		X	X	X	X

Abbreviations: ECG, Electrocardiogram; INR, international normalized ratio.

Table III

Characteristics of AF study populations

Anticoagulant(s) studied	Randomized controlled trials between non-vitamin K anticoagulants and warfarin				Contemporary observational registries				
	RE-LY <sup>6</sup> (n = 18,113) Dabigatran	ROCKET-AF <sup>9</sup> (n = 14,264) Rivaroxaban	ARISTOTLE <sup>8</sup> (n = 18,201) Apixaban	ENGAGE AF-TIMI 48 <sup>10</sup> (n = 21,105) Edoxaban	GLORIA-AF <sup>34</sup> (n = 56,000) Warfarin, dabigatran	PINNACLE <sup>36</sup> (n = 14,464) Warfarin	GARFIELD (cohort 1, n = 10,164) <sup>35</sup> warfarin, 4% non-vitamin K anticoagulant	ORBIT-AFI (n = 10,132) 72% warfarin, 4% dabigatran	ORBIT-AF II (preliminary, n = 1011) 22% warfarin, 9% dabigatran, 41% rivaroxaban, 14% apixaban
Locale	International, including the United States				International, including the United States		United States only		United States only
Patient characteristics									
Age (y)	72	73	70	72	18	67	70	73	73
Female	36%	40%	35%	38%	N/A	47%	43%	42%	44%
Heart failure	32%	62%	35%	58%	N/A	35%	21%	32%	23%
Hypertension	79%	90%	87%	94%	N/A	70%	78%	83%	83%
Diabetes	23%	40%	25%	36%	N/A	19%	22%	29%	27%
Prior stroke/TIA	20%	55%	20%	28%	N/A	3.1%	14%	15%	11%
Prior MI	17%	17%	14%	N/A	N/A	12%	10%	16%	34%
New-onset AF	N/A	1.4%	N/A	N/A	100%	N/A	30%	4.7%	76%
Mean CHADS <sub>2</sub> score	2.1	3.5	3.5	2.8	N/A	N/A	1.9	2.3	2

Abbreviations: RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thrombo-embolic Events in Atrial Fibrillation; ENGAGE AFTIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; GLORIA-AF, Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation; PINNACLE, Practice Innovation And Clinical Excellence; GARFIELD, Global Anticoagulant Registry in the FIELD; TIA, transient ischemic attack; MI, myocardial infarction; N/A, not applicable.

\* Data from GLORIA-AF are expected, based on its design.