Design and rationale of Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation: A global registry program on long-term oral antithrombotic treatment in patients with atrial fibrillation

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Background Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting 1% to 2% of the population and raising the risk of stroke 5-fold. Until recently, the only treatment choices for stroke prevention in patients with AF have been vitamin K antagonists (VKA) or antiplatelet drugs. With approval of novel oral anticoagulants (NOACs) antithrombotic treatment, patterns are changing. The Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation is designed to investigate patient characteristics influencing choice of antithrombotic treatment of stroke prevention in patients with nonvalvular AF and to collect data on outcomes of antithrombotic therapy in clinical practice.

Methods The GLORIA-AF is a large, international, observational registry involving patients with newly diagnosed nonvalvular AF at risk for stroke, enrolling up to 56,000 patients in nearly 50 countries. We will collect and analyze data from routine care using an inception cohort design. Phase I includes patients before approval of NOACs. Phase II, beginning early after approval of dabigatran, monitors dabigatran safety and addresses potential channeling across treatment options based on propensity scoring to assess comparability of baseline characteristics of patients treated with dabigatran or VKA. Phase III entails analysis of large treatment groups, adjusting for differences in propensity score, to provide information about the relative effectiveness and safety of NOACs and VKA in routine clinical care.

Conclusions Novel features of this registry program will add data from clinical practice to those from randomized trials to expand knowledge of antithrombotic treatment in patients with AF. (Am Heart J 2014;167:329-34.)

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, increasing in incidence and prevalence.[1] Rising with age,[2,3] the lifetime risk of developing AF is approximately 25% for persons age >40 years.[4]

Ischemic stroke and systemic embolism are major causes of morbidity and mortality in patients with AF who have a 5-fold higher risk of stroke than those without AF. Up to 15% of all strokes are attributable to AF, and strokes in patients with AF have worse outcomes and higher mortality rates than those in patients without AF.[5]

Until recently, the only treatment choices for stroke prevention in patients with AF were vitamin K antagonists (VKAs eg, warfarin) or antiplatelet agents such as clopidogrel or aspirin. The latter are minimally effective and not much safer than warfarin in terms of major bleeding, especially in the elderly.[6] In contrast, adjusted dose VKA therapy reduces the risk of stroke by

Figure 1
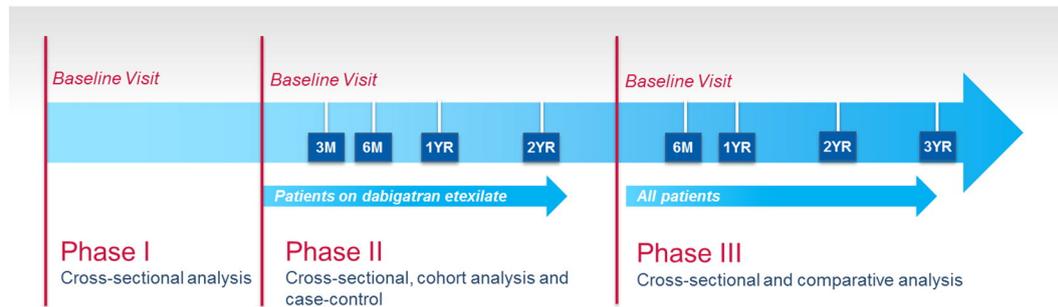
Design of the GLORIA-AF registry program.

approximately 64% and mortality by 26% compared with placebo.[7] There are significant limitations to VKA therapy, however, including a narrow therapeutic margin, unpredictable dose-response, numerous drug-drug and drug-food interactions, and slow onset and offset of action. With the approval of novel oral anticoagulants (NOACs) for stroke prevention in patients with nonvalvular AF, antithrombotic treatment patterns are changing around the world.

In 2010, the first NOAC for stroke prevention in patients with AF, dabigatran etexilate (hereinafter dabigatran), was approved by the US Food & Drug Administration and is now available in >80 countries. Dabigatran is a direct thrombin inhibitor with rapid onset and offset of action, limited drug-drug interactions, and no significant drug-food interactions. It can be administered without routine anticoagulation monitoring.[8,9] Other NOACs are the factor Xa inhibitors, rivaroxaban (first approved in 2011), apixaban (first approved in 2012), and edoxaban (not currently approved for clinical use).[10-13]

Before approval, dabigatran was evaluated in the REVOLUTION Program, which comprised >38,000 patients and demonstrated both efficacy and safety in controlled trials. After approval, additional data collection from a large number of patients is essential to characterize the broad spectrum of comorbidities and concurrent medication use and understand treatment patterns and responses outside the context of clinical trials. These data from clinical practice provide long-term safety and effectiveness information in heterogeneous populations and raise the level of evidence upon which to base treatment recommendations.[14] Existing administrative data sets, such as those based on insurance claims data or electronic medical records, are increasingly used to conduct such research.[15] Among the disadvantages of that approach is that important baseline information (eg, smoking and alcohol use) may be missing, inconsistently collected, or inaccurate. Furthermore, concurrent use of over-the-counter medications such as aspirin may not be documented comprehensively. To avoid these limita-

tions, data can be collected prospectively in patients managed in the course of routine care.

The Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) is designed to provide information on a population with recently diagnosed AF to address questions of safety and effectiveness. The intent is to collect accurate, pertinent information, control for confounding factors, and avoid selection bias.

The study aims and objectives are as follows: (1) to characterize patients newly diagnosed with nonvalvular AF at risk for stroke in various regions of the world, (2) to describe current patterns of antithrombotic treatment, and (3) to collect data on the effectiveness and safety of NOACs compared with VKA during routine patient care.

Methods
Design

A registry is an organized data collection system that uses epidemiological study methods for collecting data to evaluate prespecified outcomes for a population defined by a particular disease, condition, or exposure, thus serving ≥1 predetermined scientific, clinical, or policy purposes.[16] Within a registry, various epidemiological study designs can be applied, for example, cohort, case-control, or cross-sectional designs.

The GLORIA-AF registry program combines these different approaches across 3 phases (Figure 1). In each phase, patients with newly diagnosed AF will be enrolled, and clinical characteristics and treatment strategies will be recorded.

Phase I, conducted before approval of dabigatran, uses a cross-sectional approach, with no data collected beyond the initial visit. Because dabigatran was the first NOAC to be tested in a Phase III study, patients using this NOAC will be followed up during Phase II, commencing once dabigatran is approved in a participating country, with collection of data on the baseline characteristics of all patients, irrespective of the anticoagulant prescribed, and follow-up of all patients initiating dabigatran >2 years. This allows for case-control analyses of risk factors for various outcomes, in addition to assessing safety. Phase III will

Figure 2
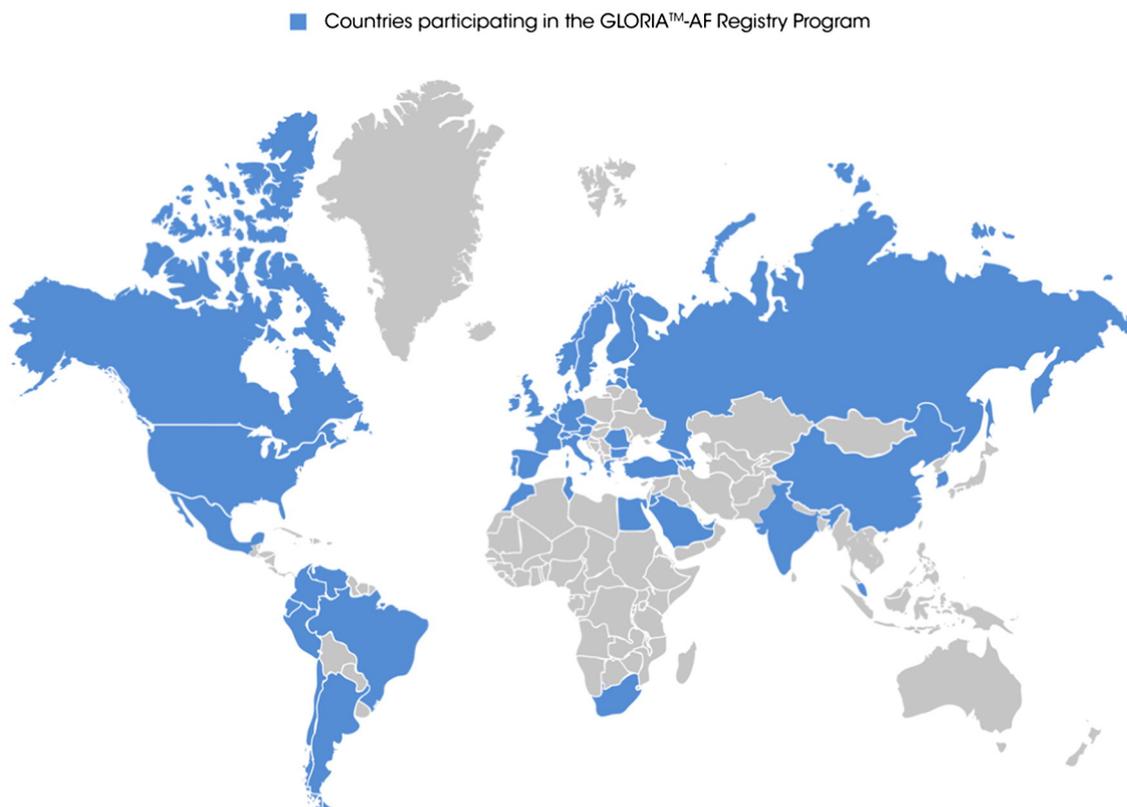
Countries participating in the GLORIA-AF registry program.

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begin after data from Phase II indicate that characteristics of patients receiving dabigatran treatment are roughly comparable with those given VKA treatment. At that point, the degree of channeling (see below) would be considered addressable through mainstream analytic methods to produce valid results from comparative analysis.

To assess comparability of patients prescribed dabigatran or VKA, propensity scores for receiving dabigatran rather than VKA will be calculated from the cross-sectional assessments in Phase II. The propensity score describes the probability that a patient receives dabigatran rather than VKA based on baseline clinical characteristics. New drugs may be preferentially prescribed to patients who differ in prognosis from the overall patient population, biasing comparisons (this is termed "channeling bias").[17] Prescribing patterns may change rapidly after a drug is first marketed but gradually stabilize as physicians become accustomed to the new therapy. These changes should be reflected in changing propensity score results over time and will be monitored in Phase II of the program. Phase III will be initiated when the dabigatran- and VKA-treated patients in Phase II have sufficiently overlapping ranges of respective propensity score distributions. During Phase III, patients will be followed up for 3 years to evaluate the effectiveness and safety of NOACs compared with VKA. Given sufficient overlap of propensity scores between

cohorts, it should be possible to control for potential measured confounders.

Study population and setting

We intend to enroll in the multinational, multicenter, prospective, noninterventional GLORIA-AF registry program up to 56,000 patients in nearly 50 countries (Figure 2) grouped into 5 regions: Asia, Europe, North America, Latin America, and Africa/Middle East.

Patients age ≥18 years with newly diagnosed (<3 months before the baseline visit) nonvalvular AF at risk for stroke (CHA_2DS_2VASc score >1) will be included. To reduce selection bias on the site level, GLORIA-AF will include up to 2,200 sites and include a broad cross-section of patients treated within the different health care settings of each participating country, for example, general practices, specialist offices, community hospitals, university hospitals, outpatient care centers, anticoagulation clinics, etc. To avoid selection bias on the patient level, physicians are encouraged to consecutively enroll unselected, consenting patients meeting the inclusion criteria.

Patients will be excluded if they have (1) mechanical heart valves or valve disease expected to require valve replacement, (2) received >60 days of VKA treatment in their lifetime for any indication, (3) AF with a generally reversible cause, (4) expected

Table. Data collection overview

Baseline visit	Follow-up visits

•Date of diagnosis of nonvalvular AF
•Inclusion/exclusion criteria
 	
•Demographic data, including date of birth, gender, weight, height, ethnicity
•Blood pressure, heart rate, and serum creatinine (if available)
•Information regarding AF
  ○Symptomatic, minimally symptomatic, asymptomatic
  ○Type (paroxysmal, persistent, permanent)
  ○Previous cardioversion, ablation, pacemaker, implantation, use of
  left atrial appendage occlusion device and/or left atrial procedures
•Antithrombotic treatment
•Medical history
•Selected concomitant treatments
	•Concomitant diseases (current, any change)
	•Antithrombotic treatment (current, any change, including
	  compliance, reason for changes, and interruptions)
	•Selected concomitant treatment (current, any change)
	•Outcome events
	•Adverse events
	•Vital status

life expectancy <1 year at the time of enrollment as assessed by the investigator, or (5) a medical condition other than AF for which chronic use of VKAs is indicated.

Study timelines and enrollment

Phase I of the program commenced enrollment in May 2011, and the last patient was enrolled in January 2013. A total of 1,063 patients were enrolled in the first phase. Phase II initiated enrollment in North America in November 2011 and as of October 2013 is ongoing with 6,939 patients entered in 5 regions. Phase III will commence when the first region has met established criteria for transition from Phase II and is expected by early 2014.

Data collection and follow-up

The GLORIA-AF includes follow-up periods in Phase II (when dabigatran is available for prescription) as well as in Phase III when other NOACs (rivaroxaban or apixaban) are available as well. Data collection at baseline and during the follow-up visits is described in Table.

In addition, clinical and laboratory components of various risk score measures for stroke and bleeding are collected, when these are assessed in the course of routine care.

The dabigatran cohort will be followed up for 2 years in Phase II, with visits scheduled around 3, 6, 12, and 24 months. The comparative effectiveness and safety study (Phase III) will be conducted for 3 years, with visits expected around 6, 12, 24, and 36 months.

To reduce potential bias related to data collection, we will use standardized data collection tools. Because patients may not recall specific events accurately when visits are separated by long intervals, specific questions related to compliance will be limited to abbreviated time intervals before each visit.

Outcomes of major interest

The following clinical outcomes will be recorded during follow-up: stroke (hemorrhagic, ischemic, uncertain type), transient ischemic attack, systemic embolism, pulmonary embolism, myocardial infarction, bleeding, and death (all-cause, nonvascular, vascular). In addition, a composite end point of stroke, systemic embolism, myocardial infarction, life-threatening bleeding and vascular death and a vascular composite end point of stroke, systemic embolism, myocardial infarction, and vascular death will be analyzed. Prescription patterns, persistence, and adherence will also be assessed.

Data management

All clinical data will be accumulated using a web-based Electronic Data Capture System (Cambridge, MA) that ensures confidentiality. Local site staff will enter and edit data over a secure network while a complete electronic audit trail is maintained. A comprehensive plan has been developed to monitor the quality of data entered into the electronic database during the course of the program, with multiple edit checks, data quality review, and on-site monitoring and audits.

Statistical analysis

Demographic and baseline characteristics (including stroke/bleeding risk scores [CHADS$_2$, CHA$_2$DS$_2$VASc, and HAS-BLED]) will be described for all eligible patients by antithrombotic treatment at the baseline visit. Antithrombotic treatment (eg, none, VKA, aspirin, clopidogrel, dabigatran, etc) will be described overall and summarized by region. Incidence rates and cumulative risks over time since initiation for important outcome events will be calculated with 95% CI for the respective antithrombotic treatments overall as well as for relevant subgroups. Propensity Scoring (PS) techniques will be used to assess the broad comparability of the treatment groups (dabigatran vs VKA). As described above, the PS estimates the probability of prescribing dabigatran rather than VKA based on patient characteristics. The decision to begin Phase III will be based on the overlap of the PS, as measured by the proportion of patients in the region of overlap of the PS. Analysis of comparative effectiveness in Phase III will be based on multivariable Cox regression models that include the propensity score and other analyses such as those that are stratified by the PS.

Study size

The width of CI used to describe patient characteristics and incidence rates for outcome events were calculated based on the expected enrollment in the 3 phases to illustrate the expected precision overall and within subgroups based on the method described by Hahn and Meeker,[18] for example, for an

outcome event that will be observed with an event rate of 1 per 100 patient years (eg, stroke), the 2-sided 95% CI for the population incidence rate per 100 patient years will be 0.83 to 1.19 for a patient cohort of 8,000 patients in Phase II (assuming a total treatment discontinuation and lost to follow-up rate of 25% per year and a 2-year follow-up). For Phase III, subgroups that initially consist of ≥6,000 patients will be sufficient to reach estimates of incidence that have approximately the same precision as described above for 8,000 patients in Phase II, given longer follow-up (3 years).

Administrative structure

The academic steering committee (SC) designed and provided scientific oversight of all phases of the program. It comprises experts in cardiology, vascular medicine, neurology, and epidemiology with 2 cochairs as well as nonvoting representatives of the sponsor (Boehringer Ingelheim GmbH). Study conduct is overseen by the operations committee, consisting of the chair, cochair, and epidemiologist of the SC and representatives of the sponsor. The operations committee oversees the execution of the registry and, in conjunction with the SC, facilitates publications.

The GLORIA-AF registry is sponsored by Boehringer Ingelheim GmbH. 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.

Discussion

The GLORIA-AF will be 1 of the largest AF-registry programs of its type, with an innovative design intended to minimize bias and be highly efficient. Its purpose is to collect long-term effectiveness and safety data on NOACs and VKA for stroke prevention in patients with non-valvular AF and those receiving no antithrombotic therapy. The results will inform future treatment decisions and enhance understanding of public health aspects of this highly prevalent condition.

Observational studies are an effective tool to observe the course of illness and evaluate treatment effectiveness and safety. Such studies can disclose variations in outcomes and provide insights into factors that affect survival that might not be apparent in more selected populations enrolled in randomized trials. This type of information is particularly pertinent to new therapies, such as the NOACs. Large observational studies based on prospectively collected data to assess rare events take years to generate results. Without the benefit of randomization, the design and analysis of such studies are challenging.

The GLORIA-AF registry program is based on a new user design, that is, only newly diagnosed patients are enrolled. There are several reasons why it is preferable to enroll only new users. First, if the risk of treatment-related outcomes is higher when treatment is initiated, such effects could be missed if studying patients who have begun treatment earlier. Second, characteristics of prevalent patients at study start might well be affected

by disease duration or caused by previous treatments. Adjustment for such covariates on the causal pathway introduces bias. Third, channeling bias or preferential prescribing, affects comparisons across heterogeneous prevalent and incident patient groups; thus, a new drug could be prescribed primarily to patients who were not experiencing improvement on the previous treatment, were not adherent, or who suffered adverse effects. This group would be at higher risk than those who remained on the initial treatment.[17] For these reasons, GLORIA-AF includes only newly diagnosed patients.

Several registries addressing management and outcomes of patients with AF, such as the Euro Heart Survey[19] or RECORD-AF[20] focused on characteristics, risk factors, and treatment but were limited by relatively small sizes and short periods of follow-up. Few attempts have been made to compare major adverse events across treatments outside the framework of randomized trials. The Euro Heart Survey reported all-cause mortality and a combined end point of mortality, thromboembolism, and major bleeding during 1 year of follow-up and found no important effect of oral anticoagulant or antiplatelet treatment on those outcomes.[21] A comparative assessment of treatment outcomes was not the primary aim of the study. The GLORIA-AF is designed to overcome these limitations by virtue of its scope and length of follow-up. It also uses a novel-phased design approach, undertaking final analyses only when there is rough comparability between treatment groups as indicated by the overlap in PS distributions.

Currently, 2 other large registries focusing on AF patients and antithrombotic treatment are ongoing. The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation is a multicenter prospective registry of patients with incident or prevalent AF intended to analyze treatment patterns and outcomes in the United States. Approximately 10,000 patients will be enrolled. Predefined outcomes include stroke or systemic embolism, major adverse cardiac events, all-cause mortality, and major bleeding.[22] The Global Anticoagulant Registry in the Field, an industry-initiated registry including patients with incident AF, aims to recruit >50,000 patients with newly diagnosed nonvalvular AF and ≥1 additional risk factor for stroke. Five sequential prospective cohorts are enrolled for treatment comparisons, with each subsequent cohort initiated once recruitment of the preceding cohort has been completed.[23] The first cohort of patients, recruited mainly in Europe and the Asia-Pacific region, consists of prospectively enrolled patients with newly diagnosed non-valvular AF and retrospectively enrolled patients with prevalent AF[24]; hence, results for this cohort represent a combination of incident and prevalent AF patients.

Strengths

The novel 3-phase design of GLORIA-AF allows for early analysis and reporting of useful information. The results will serve as a cornerstone in the active surveillance of

experience with NOACs in clinical practice. Based on newly diagnosed patients (incident cohort), the phased design allows periodic assessment of potential channeling and start of Phase III when rough comparability is reached, as measured by PS overlap between treatment groups. This ensures that data analysis is undertaken early enough to ensure efficient use of the available information but not until roughly comparable cohorts are available.

Limitations

Beyond time and cost, there are other limitations of this global observational registry program. Bias and confounding cannot be entirely eliminated, and some channeling bias and residual confounding will persist. Second, outcome events will not be adjudicated. Third, data quality can vary across the diverse sites, especially when some have limited research experience. Despite these limitations, the novel features of this registry program promise to expand knowledge about the NOACs compared with VKA across a wide variety of patient care settings.

Conclusion

The GLORIA-AF registry program will provide valuable data from antithrombotic management for patients with newly diagnosed nonvalvular AF in clinical practice around the world. The novel design of the GLORIA-AF registry program will expand knowledge of the NOACs compared with VKA in patients with AF in clinical practice.

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