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Mazurek, M.; Huisman, M.V.; Lip, G.Y.H.

REVIEW

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Registries in Atrial Fibrillation: From Trials to Real-Life Clinical Practice

Michał Mazurek, MD, PhD,[a,b] Menno V. Huisman, MD, PhD,[c] Gregory Y.H. Lip, MD[a,d]

[a]University of Birmingham, Institute of Cardiovascular Sciences, City Hospital, United Kingdom; [b]Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Silesian Medical University, Silesian Centre for Heart Diseases, Zabrze, Poland; [c]Department of Medicine-Thrombosis and Hemostasis, Leiden University Medical Center, The Netherlands; [d]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Denmark.

ABSTRACT

BACKGROUND: Recent improvements in atrial fibrillation diagnosis and management have prompted the initiation of various registries, predominantly to assess adherence to new guidelines but also to address the pending questions of safety and effectiveness of newly introduced management options in "real-world" clinical practice settings. In this review, we appraise antithrombotic treatment patterns for stroke prevention in atrial fibrillation registries.

METHODS: We searched PubMed, Science Direct, and the Cochrane databases for registries focusing on stroke thromboprophylaxis in atrial fibrillation.

RESULTS: Registry data show that over the last decade, the proportion of patients receiving oral anticoagulation has increased (from ~67% to >80%), whereas the proportion of those treated with aspirin only or untreated has diminished. Vitamin K antagonists are being replaced gradually by non−vitamin K antagonist oral anticoagulants as the more prevalent option. Regional and country differences in anticoagulation are evident, with its highest uptake in Europe (90.2%) and lowest in Asia (57.4%). Moreover, oral anticoagulation is given to approximately 50% of patients with no stroke risk factors, whereas more than one third of high-risk subjects are not anticoagulated but often prescribed antiplatelet therapy alone or untreated. Guideline-nonadherent thromboprophylaxis results in an increase in all-cause mortality and thromboembolism.

CONCLUSIONS: Registry data show that despite an increase in anticoagulation rates over the last decade, management gaps in stroke prevention are still evident with approximately one third of patients not treated in line with the guidelines. Mortality rates of atrial fibrillation patients remain relatively high, mostly because of the comorbid disease.

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KEYWORDS: Antithrombotic treatment; Atrial fibrillation; Registry; Stroke prevention

Over the last decade, our knowledge of atrial fibrillation has substantially improved, mainly because of better understanding of the epidemiology and pathophysiology of stroke and thromboembolism. As a consequence, new risk factors for stroke have been identified, and our procedure for assessment of patients at risk has changed; formerly, there was a tenacious search for patients at high thromboembolic risk, whereas now there is an effort to identify those individuals who have a truly low risk of stroke and do not need any antithrombotic treatment, so that stroke prevention can be focused on those with ≥1 stroke risk factors.[1-6] These changes coincided with the introduction of non−vitamin K antagonist oral anticoagulants (NOACs), which offer greater efficacy, safety, and

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Requests for reprints should be addressed to Gregory Y.H. Lip, MD, PhD, University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, UK.

E-mail address: g.y.h.lip@bham.ac.uk

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convenience compared with the vitamin K antagonists (eg, warfarin).[7-10]

Several national and worldwide registries were initiated recently, predominantly to assess whether daily clinical practice is in accord with atrial fibrillation guidelines and to collect data on treatment with new drugs. The design and methodology of those registries vary substantially and have evolved over the last decade. This review provides an overview of past and current atrial fibrillation registries with respect to treatment patterns for stroke prophylaxis and aims to inform clinicians on the interpretation of results and limitations that may be inherent in different registry designs.

CLINICAL SIGNIFICANCE

- There is a wide variety of registries on atrial fibrillation with evident differences in design and methodology.
- Registry data demonstrate that despite gradual improvement in anticoagulation rates worldwide, there are apparent regional differences and gaps in stroke prevention, with approximately one third of patients with atrial fibrillation not treated in accordance with guidelines.
- Remote mortality of patients with atrial fibrillation is relatively high, whereas guideline-adherent antithrombotic therapy significantly reduces thromboembolism and improves survival.

MATERIALS AND METHODS

We searched PubMed, Science Direct, and the Cochrane Library databases for studies that reported on atrial fibrillation and stroke thromboprophylaxis. Multiple queries using the following keywords were performed on July 1, 2016: ("atrial fibrillation" AND "registry") AND ("stroke prevention" OR "antithrombotic treatment" OR "oral anticoagulation"). We screened titles and abstracts for relevance to the topic. Articles of selected titles and abstracts were then reviewed for inclusion.

PURPOSE AND DESIGN OF VARIOUS OBSERVATIONAL STUDIES

There is considerable variety in registry design (**Tables 1-3**). National registries (eg, Swedish and Danish National Patient Registries) are "real-time" databases of the whole country population, where every patient is enrolled, every prescribed drug is recorded, follow-up of patients is counted in years, and vital status along with cause of death can be routinely verified.[11-13] There are also international registries sponsored by learned societies, such as the EURObservational Research Programme Atrial Fibrillation General Pilot Registry (EORP-AF), which was initiated by the European Society of Cardiology (ESC), but its long-term extension to non-ESC countries continues by open collaboration, as part of the INTER-AF program.[14] Moreover, there are academic-led registries from one single city or defined region, such as Fushimi AF (**Table 1**).[15,16]

In addition to large government-sponsored databases, there are also several large, international, industry-sponsored or funded registries (**Table 2**), such as the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) and the Global Anticoagulant Registry in the FIELD − Atrial Fibrillation (GARFIELD-AF).[17,18] Some registries enroll only outpatients, such as Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), J-RHYTHM, or PINNACLE-AF (the American College of Cardiology Practice Innovation and Clinical Excellence Program), whereas others include only inpatients, for example, the Get With the Guidelines-AFIB (GWTG-AFIB) Registry.[19-22] Some of the registries are actually linked to specific programs to improve atrial fibrillation management. For example, the GWTG-AFIB is a US nationwide quality improvement program that is intended not only to gather data but also to provide a wide spectrum of health care sites with support to improve guideline adherence, arrhythmia management, and treatment outcomes.[22] There are also registries that record only baseline cross-sectional data,[23,24] although most have follow-up analyses. Registries have varying strategies to ensure data quality with some implementing rigorous standards, such as onsite monitoring, extensive edit checks, frequent manual data reviews, and periodic quality review of aggregate data. Others may not include such checks or make no mention of whether such standards were implemented; thus, the measures taken to ensure data integrity should be considered when interpreting data.

EURO HEART SURVEY: EXAMPLE OF AN "Early" NONINDUSTRY-SPONSORED REGISTRY

Until 2005 there were no large-scale European studies that prospectively collected data on atrial fibrillation epidemiology, management, and outcomes. The Euro Heart Survey (EHS) on Atrial Fibrillation was the first to verify routine clinical practice against the 2001 atrial fibrillation guidelines.[25-27]

The registry enrolled 5333 inpatients and outpatients from 35 countries and reported oral anticoagulation at 67%, with only 7% of patients not receiving any antithrombotic treatment. This was one of the highest oral anticoagulation rates that were reported from a daily clinical practice in Europe.[25,28,29] Nevertheless, a discordance between guidelines and clinical practice was noted because 49% of ineligible patients received oral anticoagulation, whereas 33% with an indication for anticoagulation were not treated as such.[25]

Furthermore, prescription of oral anticoagulation was only marginally guided by available stroke risk stratification schemes.[26] Of note, the well-known risk factors for stroke

Table 1 Nonindustry-Sponsored Registries

Registry	Size (n)	Start Date	Inclusion Criteria	Follow-Up	Design	Country	Comment
EHS on AF[25-28,30-32]	5333	2003	AF confirmed by ECG within 1 y before diagnosis, inpatients/outpatients	1 y	Prospective observational	35 European countries	First large prospective registry assessing AF management against 2001 ACC/AHA/ESC guidelines; AF undertreatment results in a 2-fold increase in thromboembolism; need for simple stroke/bleeding risk scale
ESC EORP AF Pilot[14,38,40-42]	3119	2012	AF confirmed by ECG within 1 y before diagnosis, inpatients/outpatients	1 y	Prospective, consecutive, observational	9 EU countries	Nonadherence to 2012 ESC AF guidelines increases mortality; antithrombotic overtreatment of low risk patients (with CHA_2DS_2-VASc = 0) and undertreatment of high-risk patients (one third on antiplatelet therapy)
PINNACLE-AF (National Cardiovascular Data Registry)[21,43-45]	>121,000	2008	AF, outpatients	Ongoing	National prospective, office-based, cardiac quality-improvement registry	US	Antithrombotic overtreatment of low-risk patients with AF; undertreatment of patients with paroxysmal AF with moderate- to high-risk scores
GWTG-AFIB (National Cardiovascular Data Registry)[22,68,74,75]	>5 million patients	2013	AF, inpatients	Ongoing	Part of the national prospective, cardiac quality improvement program	US	Large data registry; support for healthcare providers and patients; antithrombotic undertreatment of patients with AF and stroke
GWTG-ACTION Registry (National Cardiovascular Data Registry)[76]	4959	2007	Acute myocardial infarction and AF	2 y	National prospective, cardiac quality improvement program	US	Triple therapy (DAPT plus warfarin) vs DAPT in patients with AF after acute myocardial infarction increases major bleeding with no difference in composite myocardial infarction, death, or stroke
J-RHYTHM[20,55-57,77,78]	7937	2009	AF, outpatients	2 y	National, prospective, observational	Japan	OAC in subtherapeutic doses; narrow INR values (1.6 and 2.59); female gender not an independent risk factor for stroke
Fushimi[15,16,69-71,79]	3304	2011	AF, inpatients/outpatients	2 y	Community-based survey of consecutive patients with AF	Japan, Kyoto	Kyoto region registry; high representation of private clinics of general practitioners; overall OAC rate at 53.1% and therapeutic INR at 54.4% resulting in similar outcomes between OAC and non-OAC users.
Nationwide Danish AF cohort[11,13]		1996	AF, inpatients/outpatients	Ongoing	National Patient Register; consecutive patients with AF	Denmark	Extensive data on all hospital admissions in Denmark since 1977. Civil registration system holds information on vital status of all citizens.
Nationwide Swedish AF cohort[12]		2005	AF, inpatients/outpatients	Ongoing	National Patient Register; retrospective, unselected patients with AF	Sweden	Extensive national data for all patients since 1997
Nationwide Taiwan AF cohort[50,80]		1999	AF, inpatients/outpatients	Ongoing	National Patient Register; retrospective, unselected AF	Taiwan	Extensive national data for all patients since 1996

ACC = American College of Cardiology; AF = atrial fibrillation; AHA = American Heart Association; CHA_2DS_2-VASc = congestive heart disease, hypertension, age ≥75 years [doubled], diabetes, stroke/TIA [transient ischemic attack]/systemic thromboembolism [doubled], vascular disease, age ≥65 years, sex category [female]; DAPT = dual antiplatelet therapy; ECG = electrocardiogram; ESC = European Society of Cardiology; EHS = Euro Heart Survey; EORP AF = EURObservational Research Programme Atrial Fibrillation General Pilot Registry; EU = European Union; GWTG = Get With the Guidelines; INR = international normalized ratio; OAC = oral anticoagulation.

Table 2 Pharma Industry-Sponsored or Funded Registries

Registry	Size (n)	Start Date	Inclusion Criteria	Follow-Up	Design	Country	Comment
RealiseAF Survey[23,24]	10,523	2009	AF confirmed by ECG within 1 y before diagnosis	Cross-sectional observation only	Cross-sectional observational survey; participating physicians randomly selected from physician list forms	831 sites in 26 countries and 4 continents	Great regional differences in OAC uptake; overuse or underuse of antithrombotics in approximately 50% of patients
GLORIA-AF[17,58,59]	56,000	2011	New AF diagnosis - within 3 mo, CHA_2DS_2-VASc $\geq$1	3 y in phase III	Prospective, inception cohort design, 3 phases: 1. Pre-NOAC 2. With NOAC 3. Propensity comparison of patients on VKA vs NOAC	5 regions, >1000 sites in 50 countries	Strong design through increased comparability and minimized bias; high representativeness; 27,000 patients to date; broad physician representation; more than one fifth of patients in North America and one third in Asia undertreated or not treated with OAC
GARFIELD-AF[18,60-62]	57,000	2009	New AF diagnosis - within 6 wk, at least 1 risk factor by physician assessment	Minimum 2 y, up to 8 y	Parallel enrollment of 5 prospective cohorts of unselected, consecutive patients with 1 retrospective validation cohort; 5 overlapping phases	1048 sites in 32 countries	>49,000 patients enrolled; C1-4 complete C5 since August 2015 CHA_2DS_2-VASc 3.2; broad spectrum of care settings; overtreatment of low-risk patients and undertreatment of high-risk patients; one half of patients at moderate to high stroke risk not treated with OAC because of physician decision
PREFER-AF[63,65,81,82]	7243	2012	History of AF within the preceding 12 mo, inpatients/outpatients	1 y	Prospective	461 sites in 7 West and South Europe countries	AF management against 2010 guidelines; valvular AF not excluded; tendency toward a higher use of OAC in patients with higher stroke risk scores; substantial regional differences in OAC uptake
ORBIT-AF I[19,64,66,83-85]	10,126	2009	Incident + prevalent AF, outpatients	3 y	Prospective, ambulatory-based	184 US outpatient practices	$CHADS_2$ score 2.3; valvular AF not excluded; includes cost and quality of life assessment; broad spectrum of health care providers; higher use of OAC in patients with higher stroke risk scores; discrepancy in OAC prescription among different care providers
ORBIT-AF II[86]	15,000	2013	New AF diagnosis (within 6 mo) or initiation or transitioned to NOACs within the last 3 mo	2 y	Prospective, ambulatory based	300 US outpatient practices	Main focus on safety and effectiveness of NOACs (dosing, temporary interruptions, perioperative, and bleeding management) used in community practice settings

AF = atrial fibrillation; CHA_2DS_2-VASc = congestive heart disease, hypertension, age $\geq$75 years [doubled], diabetes, stroke/TIA [transient ischemic attack]/systemic thromboembolism [doubled], vascular disease, age $\geq$65 years, sex category [female]; ECG = electrocardiogram; GARFIELD-AF = Global Anticoagulant Registry in the FIELD — Atrial Fibrillation; GLORIA-AF = Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation; NOAC = non—vitamin K oral antagonist; OAC = oral anticoagulation; ORBIT-AF II = Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II.

Table 3 Comparison of Registries Supported by Pharma Industry

	GLORIA-AF (Phase II, n = 10,871)[59]	GARFIELD (Cohort 1, n = 10,614)[60,61]	PREFER-AF (n = 7243)[63]	ORBIT-AF I (n = 10,097)[66]	ORBIT-AF II (n = 1011)[86]
Site	International including United States	International excluding United States	International excluding United States	United States only	United States only
Setting	Inpatients/outpatients (broad spectrum of settings)	Inpatients/outpatients	Inpatients/outpatients	Outpatients only	Outpatients only (academic and private clinics)
Physicians	Cardiologists/neurologists/internists/geriatricians/GPs;92% of patients enrolled by cardiologists	Cardiologists/neurologists/internists/geriatricians/GPs;59% of patients enrolled by cardiologists	Cardiologists/other specialists; 89% patients enrolled by cardiologists	Internists, primary care physicians, cardiologists, and electrophysiologists;80.5% of patients enrolled by cardiologists/electrophysiologists	Primary care physicians, neurologists, cardiologists, electrophysiologists
Definition of AF	New-onset AF <3 mo before baseline visit	New-onset AF <6 wk before baseline visit; ≥6 mo but ≤24 mo for validation group (5000 patients) only in cohort 1	New-onset AF + all AF episodes <12 mo before baseline visit; AF diagnosed by an implanted pacemaker or defibrillator allowed	Incident or prevalent AF	New-onset AF <6 mo before baseline visit
New-onset AF	100%	30%	N/A	4.7%	76%
History of anticoagulant therapy	Patients excluded with a history of VKA therapy >60 d	Patients included regardless of prior or current VKA use	Patients included regardless of prior or current VKA use	Patients included regardless of prior or current VKA use	Previous VKA treatment allowed; initiation or transition to NOAC <3 mo
Stroke risk scales	CHA_2DS_2-VASc ≥1 needed for inclusion	≥1 stroke risk factor by the physician discretion; $CHADS_2$/CHA_2DS_2-VASc scales not needed for inclusion	$CHADS_2$/CHA_2DS_2-VASc scales not needed for inclusion	$CHADS_2$/CHA_2DS_2VASc scales not needed for inclusion	CHADS2/CHA2DS2VASc scales not needed for inclusion
Mean $CHADS_2$ score	1.9	1.9	N/A	2.3	2.0
Mean CHA_2DS_2-VASc score	3.2	3.2	3.4	3.9	N/A
Enrollment timeframes with respect to NOAC approval dates	Sites selected only once NOACs available	Enrollment in time intervals irrespective of marketing authorization	Enrollment irrespective of marketing authorization	Enrollment irrespective of marketing authorization	Enrollment after NOACs approval
Overall OAC uptake	80%	62%	82%	76%	86%
Overall OAC uptake by drug type	32.3% VKA 47.7% NOACs	58% VKA 4% NOACs	76% VKA 6% NOACs	71% VKA 5% NOACs	22% VKA 64% NOACs

Table 3 Continued

	GLORIA-AF (Phase II, n = 10,871)[59]	GARFIELD (Cohort 1, n = 10,614)[60,61]	PREFER-AF (n = 7243)[63]	ORBIT-AF I (n = 10,097)[66]	ORBIT-AF II (n = 1011)[86]
OAC uptake over time	Phase I (2011-2013) Europe 64.1% Asia 20.3% Middle East 45.0% Phase II (2011-2014) Europe 90.2% Asia 57.4% Middle East/Africa 79.8% North America 78.2% Latin America 84.9%	Cohort 1 (2009-2011) 57.5% Cohort 2 (2011-2013) 62.3% Cohort 3 (2013-2014) 67.5% Cohort 4 (2014-2015) 71% cohort 5 ongoing enrollment	N/A	N/A	N/A

AF = atrial fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/TIA [doubled]; CHA_2DS_2-VASc = congestive heart disease, hypertension, age ≥75 years [doubled], diabetes, stroke/TIA [transient ischemic attack]/systemic thromboembolism [doubled], vascular disease, age ≥65 years, sex category [female]; GARFIELD = Global Anticoagulant Registry in the FIELD; GLORIA-AF = Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation; GP = general practitioner; N/A = not available; NOAC = non–vitamin K oral antagonist; OAC = oral anticoagulation; ORBIT-AF I = Outcomes Registry for Better Informed Treatment of Atrial Fibrillation I; VKA = vitamin K antagonist.

were often not the trigger for anticoagulation, whereas other factors such as atrial fibrillation pattern (less oral anticoagulation in paroxysmal arrhythmia) or availability of an anticoagulation monitoring clinic played a more predominant role in antithrombotic treatment decision making.[26,30] Multiplicity and complexity of risk stratifications schemes along with debates at that time on the importance of various risk factors for stroke, such as hypertension or arrhythmia pattern, were some of the postulated reasons for guideline nonadherence.[26,31,32]

In 2010, 2 new scoring systems were proposed: the congestive heart disease, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/systemic thromboembolism [doubled], vascular disease, age ≥65 years, sex category [female] (CHA_2DS_2-VASc) to assess stroke risk and the hypertension, abnormal renal/liver function, stroke, bleeding, labile international normalized ratio, age >65 years, drug/alcohol intake for bleeding (HAS-BLED) risk assessment.[2,33,34] Both scales are presently recommended by European and American guidelines.[35-37]

TEN YEARS LATER: WHAT DO WE KNOW FROM ONGOING REGISTRIES TODAY?

Nonindustry-Sponsored Registries

European Perspective. In 2012, the ESC established the EORP-AF General Pilot Registry to systematically collect contemporary data on atrial fibrillation treatment by cardiologists in Europe.[14] The registry enrolled 3119 inpatients and outpatients with atrial fibrillation diagnosed within the preceding year and shortly after the first NOACs were offered. This registry showed oral anticoagulation use at 80.0% (71.6% vitamin K antagonists and 8.4% NOACs), with one third of patients receiving other antithrombotics (mostly aspirin) and 4.8% receiving no antithrombotic treatment.[38,39] Surprisingly, oral anticoagulation was used in 56.4% of patients with CHA_2DS_2-VASc = 0, whereas only 66.7% of those with CHA_2DS_2-VASc = 9 were anticoagulated.[38]

Guideline-adherent antithrombotic therapy was low at 61%, with 17.3% of patients being undertreated and 21.7% of patients being overtreated.[40] Of note, antithrombotic management that was in line with the 2012 ESC guidelines was associated with significantly better 1-year outcomes (all-cause death/thromboembolic event of 9.0%), whereas the corresponding numbers for undertreatment and overtreatment were 14.3% and 13.9%, respectively.[40]

One-year outcomes of the EHS and EORP-AF Pilot Registry were strikingly similar. Mortality rates were 5.3% versus 5.7%, respectively, and the cause of death was cardiovascular in 67% versus 70%, respectively.[41,42] Death rates were highest in both registries in persistent/permanent atrial fibrillation, but also in a first-detected arrhythmia. However, 1-year stroke rates were higher in the EHS than in the EORP-AF (1.8% vs 0.6%, respectively).[41,42] Of note, in

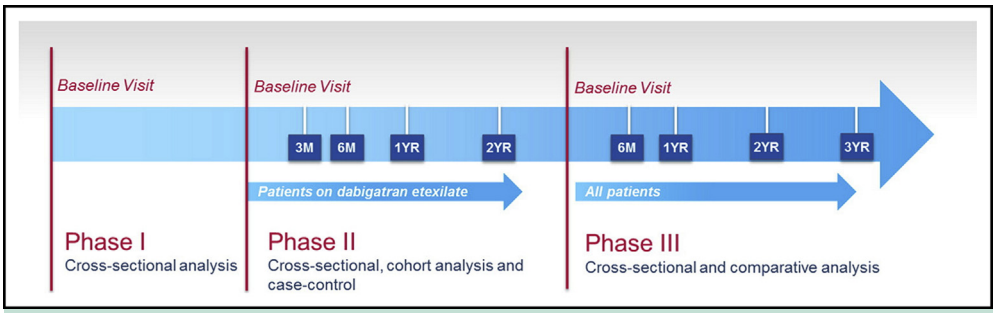

Figure 1 GLORIA-AF Registry design.[17] M = month; YR = year.

the EHS, anticoagulation was discontinued in 45% of patients with no reoccurrence of arrhythmia and in 63% patients who were considered cured.[42] This is of importance, because undertreatment resulted in a 2-fold increase in thromboembolic events compared with guideline-adherent management.[30]

North American Perspective. Oral anticoagulation was low in the US outpatient registry sponsored by the American College of Cardiology, the PINNACLE.[21] This registry was a nationwide, prospective quality improvement program designed to capture, report, and improve outpatient management in the pre-NOACs era. Between July 2008 and December 2009, the registry included 9113 patients from 20 US sites where overall oral anticoagulation was only 55.1%.[21] These results showed a great variation in oral anticoagulation prescribing across different US outpatient practices and near-random pattern of anticoagulation distribution.[43] In a larger analysis of 71,972 patients, subjects with paroxysmal atrial fibrillation were less commonly treated with oral anticoagulation than those with persistent arrhythmia (50.4% vs 64.3%, respectively) but more frequently with antiplatelet therapy or no antithrombotic drugs.[44] In contrast, 26.6% with CHA_2DS_2-VASc = 0 were prescribed oral anticoagulation, despite having no indications for such treatment.[45]

Atrial Fibrillation Registries Centered on Asia. Very low anticoagulation rates were reported from Asia, particularly China, where only approximately 20% of patients received oral anticoagulation, whereas 40% were receiving aspirin and 40% were untreated, resulting in an annual stroke risk of 9.28%.[46-50] By contrast, oral anticoagulation was associated with an annual stroke risk reduction by >50% and the adjusted net clinical benefit favoring oral anticoagulation therapy over antiplatelet or no therapy for all patients with CHA_2DS_2-VASc score ≥1.[46,51-54] In Japan, oral anticoagulation rates are better than in China, although anticoagulation control is generally suboptimal. In the J-RHYTHM Registry, despite a high overall oral anticoagulation at 87.3%, only 53% of patients met target international normalized ratio levels.[20,55-57]

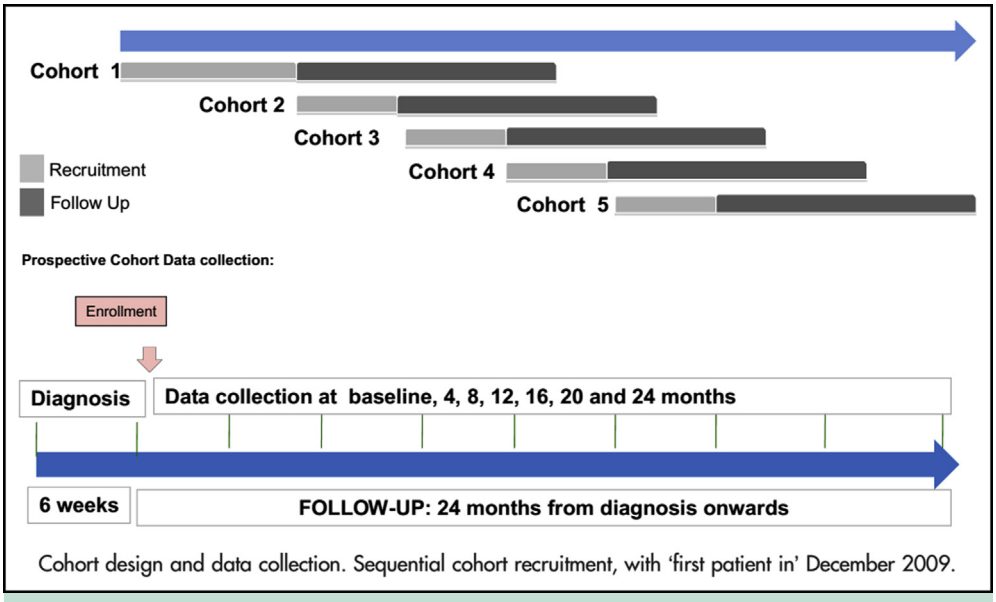

Figure 2 GARFIELD Registry design.[18]

Industry-Sponsored or Funded Registries

Suboptimal adherence to guidelines and regional differences in treatment patterns have also been observed in industry-sponsored or funded registries. GLORIA-AF is one of the largest, currently ongoing registries, which was initiated in 2011 and aims to enroll up to 56,000 patients from approximately 50 countries worldwide.[17] It has an innovative inception cohort design consisting of 3 overlapping phases (**Figure 1**; **Tables 2** and **3**). The first phase of the study includes a period before NOACs introduction, the second phase begins immediately after approval of NOACs in a given country, and the third phase starts after propensity score comparisons in a region, between patient populations taking vitamin K antagonist versus NOACs, to ensure baseline characteristics of those patients can be reasonably compared.[17] Such a registry design allows collection of data where there is dynamically changing clinical practice and available treatment methods with a reduced study bias. It also allows description of the pre-NOACs era[58] and the early period immediately after first NOACs approval,[59] and can further inform about changing prescription patterns as the landscape of NOACs availability changes. It also implements a "new user" design, which includes only incident cases of atrial fibrillation (diagnosed within the previous 3 months) to limit the potential for confounding factors, such as disease comorbidity.[17,59]

A report from phase I (between May 2011 and January 2013) of GLORIA-AF showed oral anticoagulation at 64.1% and 20.3% in Europe and China, respectively.[58] Although results of phase II (between November 2011 and February 2014) comprising more than 10,000 patients were still showing regional differences in antithrombotic treatment patterns, the overall oral anticoagulation uptake substantially increased to 80% (32.3% vitamin K antagonist and 47.7% NOACs).[59] The highest oral anticoagulation rates were observed in Europe at 90.2%, followed by 78.2% in North America and 57.4% in Asia.[59] A considerable number of patients were still treated with antiplatelet therapy (5.7% in Europe, 14.1% in North America, and 25.8% in Asia) or remained untreated (4.1% in Europe, 7.6% in North America, and 16.9% in Asia).

GARFIELD-AF is another large-scale, ongoing, international registry initiated by the Thrombosis Research Institute, London.[18] The registry design is to enroll patients in 5 independent, sequential, and prospective (but overlapping) cohorts, and 4 of the cohorts enroll only subjects with newly diagnosed arrhythmia (**Figure 2**; **Tables 2** and **3**).[18]

Data from the first of 5 registry cohorts with 10,614 patients enrolled between 2009 and 2011 showed that 60.3% of patients received oral anticoagulation (45.2% vitamin K antagonist alone, 4.5% NOACs), whereas 25.3% were given antiplatelet therapy alone and 14.4% did not use any antithrombotic drugs.[60] Contraindications to oral anticoagulation were reported in only 7.8% of patients, yet 40.7% of eligible patients with a CHA_2DS_2-VASc score ≥ 2 were not given oral anticoagulation, whereas 38.7% of those with a score of 0 received anticoagulation.

Oral anticoagulation uptake in GARFIELD-AF has improved over time. It was 57.4% in 2010 and increased to 71.1% in 2015. At the same time, NOACs uptake increased from 4.1% to 37%.[61] Of note, the 2-year all-cause mortality was 3.83 per 100 person-years and was far more frequent than the incidence of stroke or major bleeding (1.25 and 0.70 per 100 person-years, respectively).[62] The cause of death was cardiovascular in 40.5% of cases, and congestive heart failure with sudden cardiac death was responsible for 10.8% and 7.5% of deaths, respectively.[62]

COMPARING THE REGISTRIES

Direct comparison of registries is not straightforward (**Tables 1-3**). There are different inclusion criteria for atrial fibrillation and its duration. For example, in GLORIA-AF and GARFIELD-AF, only new-onset arrhythmia (<6 weeks in GARFIELD-AF and <3 months in GLORIA-AF) is permitted, whereas it is <12 months in PREFER-AF and arrhythmia detected by implantable pacemaker/cardioverter-defibrillator is also allowed.[17,18,63]

Although most of the registries include only nonvalvular atrial fibrillation, PREFER-AF or ORBIT-AF also permitted valvular arrhythmia.[19,63] GLORIA-AF requires at least 1 stroke risk factor in the CHA_2DS_2-VASc scale, whereas GARFIELD-AF does not use any stroke risk scales, enrolling patients with at least 1 risk factor at the discretion of physicians. PREFER-AF and ORBIT-AF enroll "all comers," regardless of the presence or absence of stroke risk factors.[17,18,63] To omit the influence of previous anticoagulation, GLORIA-AF excluded patients with a history of vitamin K antagonist therapy ≥ 60 days, whereas the rest of the registries are recruiting patients irrespective of previous or current oral anticoagulation (**Table 3**).

Comparison of anticoagulation rates requires consideration of several factors, the most important of which seem to be the calendar year and time period of data collection. Indeed, oral anticoagulation uptake is gradually, but constantly increasing worldwide, and thus more recent reports show higher oral anticoagulation rates.[59,61] However, registry design, regional contribution, and availability of approved medications also are important (**Table 3**).[17,59] The impact of site and setting also may play a role, for example, registries from the region of Asia/Pacific may report lower oral anticoagulation rates.[59,60] The proportions of inpatients and outpatients, academic institutions, participating physician specialties, patients of different ethnicities, different health care providers, and funding of the registries need to be considered.[59,60,63,64] Indeed, in several registries, oral anticoagulation was high where cardiologists were responsible for treatment.[25,26,38,41,59,65] When a broader spectrum of care settings was analyzed, including patients treated by other specialists, then the overall oral anticoagulation was lower.[60,66]

Finally, there are various atrial fibrillation guidelines issued by different organizations, which may differ with

respect to stroke prevention recommendations.[67] For example, American guidelines permit the use of aspirin or even no antithrombotic treatment in some patients (eg, with CHA_2DS_2-VASc = 1).[36]

QUO VADIS? HAS CLINICAL PRACTICE CHANGED?

Since the EHS more than a decade ago (2003-2004), the overall use of oral anticoagulation has increased, from 67% in the EHS to 80% in the EORP-AF (2012-2013), 82.3% in the PREFER-AF (2012-2013), 80% in the GLORIA-AF (2011-2014), and 71.1% in the GARFIELD-AF (2010-2015).[38,39,41,59,61,65] On the basis of data from the GLORIA-AF, NOACs are currently gradually replacing vitamin K antagonist both in Europe, where more patients are prescribed NOACs, and in North America, where the use of NOACs is twice as high as warfarin.[59]

Possible reasons for an increase in oral anticoagulation prescription over the last years may be the increasing availability of NOACs, but also new guidelines and increased awareness of atrial fibrillation and stroke burden. This is also reflected by the decreasing number of patients being prescribed aspirin or those untreated.[25,40] Contemporary registries also demonstrate that by performance improvement efforts, any treatment gaps can be identified and bridged.[38,39,41,59,61,65,68] In the GWTG program, as a result of tailored feedback and clinical decision support, anticoagulation rates reached 95%.[68]

However, despite best efforts, guideline-adherent thromboprophylaxis is still suboptimal. Indeed, approximately half of truly low-risk patients are overtreated with oral anticoagulation, whereas one third of high-risk patients are not anticoagulated.[38,39,59,65] Potential reasons are complex and include fear of bleeding complications, especially in certain patient populations (the elderly and those with low body weight, anemia, and chronic kidney disease), a perception that certain patterns of atrial fibrillation are more benign (paroxysmal or asymptomatic arrhythmia), subtherapeutic international normalized ratio values, lack of good international normalized ratio monitoring, and finally even cultural or habitual differences in treatment patterns.[16,56,57,69-71]

Contraindications (~10% of patients) and refusal to accept oral anticoagulation are important because these are often subjective and change over time.[72] These patients are generally older and more frail, with multiple comorbidities, but also at higher risk of stroke. In the ORBIT-AF registry, the most frequent reasons for warfarin forgoing were physician preference/choice (47.7%) and patient preference/refusal (21.1%).[60,73]

CONCLUSIONS

Although differences among registries on atrial fibrillation are evident, their main findings are similar and consistent, thus giving us a comprehensive insight into current clinical practice. Despite a gradual increase in anticoagulation rates worldwide, gaps in stroke prevention are still apparent, whereas guideline-adherent thromboprophylaxis improves outcomes.[30,40] The long-term mortality of patients with atrial fibrillation is relatively high, exceeding both ischemic and bleeding events, mainly due to comorbid disease.[41,42,62]

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