International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: Results from the GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries

Benjamin A. Steinberg, MD, MHS, [a,b,c] Haiyan Gao, PhD, [d] Peter Shrader, MA, [c] Karen Pieper, MS, [c] Laine Thomas, PhD, [c] A. John Camm, MD, [e] Michael D. Ezekowitz, MB, ChB, DPhil, [f] Gregg C. Fonarow, MD, [g] Bernard J. Gersh, MB, ChB, DPhil, [h] Samuel Goldhaber, MD, [i] Sylvia Haas, MD, [j] Werner Hacke, MD, PhD, [k] Peter R. Kowey, MD, [l] Jack Ansell, MD, [m] Kenneth W. Mahaffey, MD, [n] Gerald Naccarelli, MD, [o] James A. Reiffel, MD, [p] Alexander Turpie, MD, [q] Freek Verheugt, MD, [r] Jonathan P. Piccini, MD, MHS, [b,c] Ajay Kakkar, MBBS, PhD, [d] Eric D. Peterson, MD, MPH, [b,c] and Keith A. A. Fox, MB, ChB [s], For the GARFIELD-AF ORBIT-AF Investigators ***Salt Lake City, UT; Durham, NC; London, United Kingdom; Wynnewood, PA; Los Angeles, CA; Rochester, MN; Boston, MA; Munich, Germany; Heidelberg, Germany; New York, NY; Palo Alto, CA; Hershey, PA; Hamilton, Canada; Amsterdam, The Netherlands; and Edinburgh, United Kingdom***

Background Atrial fibrillation (AF) is the most common cardiac arrhythmia in the world. We aimed to provide comprehensive data on international patterns of AF stroke prevention treatment.

Methods Demographics, comorbidities, and stroke risk of the patients in the GARFIELD-AF (n = 51,270), ORBIT-AF I (n = 10,132), and ORBIT-AF II (n = 11,602) registries were compared (overall N = 73,004 from 35 countries). Stroke prevention therapies were assessed among patients with new-onset AF (≤6 weeks).

Results Patients from GARFIELD-AF were less likely to be white (63% vs 89% for ORBIT-AF I and 86% for ORBIT-AF II) or have coronary artery disease (19% vs 36% and 27%), but had similar stroke risk (85% CHA_2DS_2-VASc ≥2 vs 91% and 85%) and lower bleeding risk (11% with HAS-BLED ≥3 vs 24% and 15%). Oral anticoagulant use was 46% and 57% for patients with a CHA_2DS_2-VASc = 0 and 69% and 87% for CHA_2DS_2-VASc ≥2 in GARFIELD-AF and ORBIT-AF II, respectively, but with substantial geographic heterogeneity in use of oral anticoagulant (range: 31%-93% [GARFIELD-AF] and 66%-100% [ORBIT-AF II]). Among patients with new-onset AF, non–vitamin K antagonist oral anticoagulant use increased over time to 43% in 2016 for GARFIELD-AF and 71% for ORBIT-AF II, whereas use of antiplatelet monotherapy decreased from 36% to 17% (GARFIELD-AF) and 18% to 8% (ORBIT-AF I and II).

Conclusions Among new-onset AF patients, non–vitamin K antagonist oral anticoagulant use has increased and antiplatelet monotherapy has decreased. However, anticoagulation is used frequently in low-risk patients and inconsistently in those at high risk of stroke. Significant geographic variability in anticoagulation persists and represents an opportunity for improvement. (Am Heart J 2017;194:132-40.)

From the [a]Division of Cardiovascular Medicine, University of Utah Health Sciences Center, Salt Lake City, UT, [b]Duke University Medical Center, Durham, NC, [c]Duke Clinical Research Institute, Durham, NC, [d]Thrombosis Research Institute, London, United Kingdom, [e]St George's University of London, London, United Kingdom, [f]Thomas Jefferson Medical College, Lankenau Medical Center, Wynnewood, PA, [g]UCLA Division of Cardiology, Los Angeles, CA, [h]Mayo Clinic, Rochester, MN, [i]Harvard Medical School and Brigham and Women's Hospital, Boston, MA, [j]Technical University of Munich, Munich, Germany, [k]University Hospital of Heidelberg, Heidelberg, Germany, [l]Lankenau Institute for Medical Research, Wynnewood, PA, [m]Department of Medicine, Hofstra Northwell School of Medicine, New York, NY, [n]Stanford University School of Medicine, Palo Alto, CA, [o]Penn State University School of Medicine, Hershey, PA, [p]Columbia University College of Physicians and Surgeons, New York, NY, [q]Department of Medicine, McMaster University, Hamilton, Canada, [r]Department of Cardiology, Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam, The Netherlands, and [s]Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom.

Trial Registration clinicaltrials.gov Identifiers: NCT01090362, NCT01165710, NCT01701817.
Submitted August 17, 2017; accepted August 17, 2017.

Reprint requests: Benjamin A. Steinberg, MD, MHS, Division of Cardiovascular Medicine, University of Utah Health Sciences Center, 30 N 1900 E, Room 4A100, Salt Lake City, UT 84132. E-mail: benjamin.steinberg@hsc.utah.edu:

0002-8703

https://doi.org/10.1016/j.ahj.2017.08.011

The prevalence of atrial fibrillation (AF) in the United States has been projected to increase 2.5-fold by 2050 to 5.6 million individuals and was estimated at 33.5 million worldwide in 2010.[1-3] International population-based studies have identified an 18% rise in disability-adjusted life-years attributable to AF globally.[2] This growth has been attributed to several factors, including aging populations, more chronic cardiovascular disease, and increasing prevalence of AF risk factors, such as obesity.[4] However, although prior studies have provided evidence of regional differences in incidence and demographics, no in-depth data on this worldwide epidemic have been reported.

In this setting, several disease-specific, prospective observational registry programs were created to better understand AF populations, their demography, treatments, and clinical outcomes. Internationally, the Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF) registry enrolled patients from around the globe and culminated in a population of more than 57,000 patients recruited over the course of 5 phases in 35 countries. The largest in the United States, the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) program, includes 2 phases of enrollment totaling nearly 25,000 patients. Collaboration between the programs will yield powerful insights regarding AF population characteristics globally, treatments, and outcomes among regions, and allow for investigation of phenomena too rare to explore in individual cohorts. In this analysis, we compared the baseline populations from the GARFIELD-AF and ORBIT-AF programs, including comparisons of baseline stroke and bleeding risk profiles, as well as variations in the prescribing practice for stroke prevention by region and by stroke-risk profile.

Methods

These analyses include data from all 5 enrollment cohorts of the GARFIELD-AF registry and both phases of the ORBIT-AF program. Separate data from each program are presented side-by-side for comparison.

GARFIELD-AF

GARFIELD-AF is an international prospective noninterventional registry of patients who were enrolled within 6 weeks of diagnosis of nonvalvular AF. Patients were included if they had at least 1 additional risk factor for stroke as defined by the patient's physician. This could include a CHA_2DS_2-VASc risk factor or an alternative characteristic that the physician felt increased the patient's risk of stroke (and was not collected). Neither treatment with stroke prevention therapy nor minimum $CHADS_2$ or CHA_2DS_2-VASc score was required for inclusion.

To reflect real-world care delivery, site makeup in GARFIELD-AF varied according to geography. For each country, delivery care patterns were assessed, and randomly selected generalist and specialty providers were invited to participate so that the balance of sites, by country, reflected local AF care. These could include primary care physicians, internal medicine, geriatricians, cardiologists, and/or neurologists.

Patient demographic, medical history, AF history, electrocardiographic and laboratory data, imaging, and medical and interventional treatments were prospectively recorded in a Web-based case report form. Patients were enrolled chronologically in 5 consecutive cohorts beginning in December 2010 with the completion of enrollment in July 2016. Follow-up will conclude in 2018, with a minimum of 2-year follow-up (for cohort 5) and a maximum of 7-year follow-up (for patients enrolled in cohort 1).

As a sensitivity analysis, the design of the GARFIELD-AF program included a retrospective cohort of patients with known AF as part of cohort 1. As in prior analyses from GARFIELD-AF, data from that retrospective cohort are not included in this analysis. The complete design and methods of the GARFIELD-AF registry have been described in detail previously.[5] All patients in GARFIELD-AF signed written informed consent, and GARFIELD-AF received regulatory approval pursuant to local policies.

ORBIT-AF

The ORBIT-AF program included 2 separate, observational US registries: ORBIT-AF I and ORBIT-AF II. The ORBIT-AF I cohort was enrolled from 2010 to 2011 and included adult patients with electrocardiographically proven AF not due to a reversible cause. Enrollment in ORBIT-II occurred between 2013 and 2016 and had additional inclusion criteria: patients either had to have a recent diagnosis of AF (<6 months) and/or they had to have recently transitioned to a non–vitamin K oral anticoagulant (NOAC; <3 months). Because of these differences in entry criteria, the 2 ORBIT-AF cohorts are presented separately here.

Patients were enrolled in each phase of ORBIT-AF from a nationally representative sample of sites providing care for patients with AF in the United States, and there was significant overlap between sites participating in ORBIT-AF I and ORBIT-AF II. They included primary care physicians, cardiologists, electrophysiologists, and neurologists. Similar clinical data were collected in each phase of ORBIT-AF: baseline demographics, medical history, vital signs, laboratory data, imaging and electrocardiographic data, AF symptoms and history, and medical and interventional therapies received. These data elements were entered into a Web-based case report form.

Complete details of the ORBIT-AF I and ORBIT-AF II registry designs have been previously described.[6,7] Each

Table I. Selected comparisons between the GARFIELD-AF and ORBIT-AF registry programs

	GARFIELD-AF[5]	ORBIT-AF I[6]	ORBIT-AF II[7]
Enrollment period	2010-2016	2010-2011	2013-2016
Geography	Worldwide (35 countries, primarily non-US)	US only	US only
Size (approx.)	51,270	10,000	13,400
AF criteria	New onset <6 wk	New onset or prevalent (any type)	New onset (≤6 m) or new NOAC (≤3 m)
AF diagnosis	Nonvalvular AF diagnosed according to standard local procedures	AF, valvular or nonvalvular	AF, valvular or nonvalvular
Stroke risk inclusion criteria	1 additional risk factor required (physician-defined)	No requirement	No requirement

Abbreviations: *AF*, atrial fibrillation; *GARFIELD-AF*, Global Anticoagulant Registry in the FIELD – Atrial Fibrillation; *ORBIT-AF*, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; *NOAC*, non-Vitamin K antagonist oral anticoagulant.

phase of ORBIT-AF was approved separately by the Duke University institutional review board as well as by governing oversight groups pursuant to local regulations. All patients provided written informed consent.

Registry methods compared

Notable distinguishing characteristics of each registry design are shown in Table I. Importantly, GARFIELD-AF included only patients with a diagnosis of AF within 6 weeks of enrollment, whereas ORBIT-AF I enrolled patients irrespective of time since diagnosis, and ORBIT-AF II only required a recent diagnosis (<6 months) for patients *not* recently switched to a NOAC. The additional distinguishing characteristic of the GARFIELD-AF registry was a requirement for at least 1 investigator-defined risk factor for stroke in addition to AF—this was not required in either ORBIT-AF phase. Lastly, GARFIELD-AF excluded patients with valvular AF (as defined by local practice), whereas both ORBIT-AF registries allowed valvular and nonvalvular AF.

Patient involvement

Patients were not involved in the design, recruitment, or conduct of this analysis; however, outcomes measured by these registries are informed by previously described patient priorities. These include clinically relevant events such as stroke and major bleeding. Study burden to patients was minimized, as no additional follow-up visits or testing was performed beyond those carried out as part of routine clinical care.

Statistical methods

Summary statistics of the baseline populations of GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II are described using percentages or means (95% CIs), as appropriate. These included baseline demographics, vital signs, medical history, laboratory and imaging data, as well as baseline medical therapies. Comparison statistical tests are not calculated because the large sample sizes are likely to yield statistically significant differences that may or may not be clinically relevant.

For analyses of patients with new-onset AF, all cohorts were limited to patients diagnosed with AF within 6 weeks of enrollment. ORBIT-AF I included a small number of these patients, and so this cohort was excluded from this analysis of patients stratified by CHA_2DS_2-VASc.

Analyses of the data from GARFIELD-AF were performed by the Thrombosis Research Institute using SAS software (version 9.4; SAS Institute, Cary, NC). Analyses of the deidentified data from ORBIT-AF were performed by the Duke Clinical Research Institute using SAS software (version 9.3; SAS Institute, Cary, NC). The Thrombosis Research Institute and the GARFIELD-AF registry are supported by an unrestricted research grant from Bayer AG, Berlin, Germany. The ORBIT-AF 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 paper, and its final contents.

Results

Patient demographics and clinical characteristics

The prospective population of GARFIELD-AF included 51,270 patients from 1,314 sites in 35 countries (including the United States). The ORBIT-AF I population included 10,132 patients from 174 US sites, and ORBIT-AF II included 11,602 patients from 242 US sites. Baseline characteristics of these 3 groups are shown in Table II. Patient age (mean 70-74 years) and female sex (about 42%-44%) were roughly balanced across the studies. However, there was variability in ethnic makeup across studies (63% of patients were white in GARFIELD-AF vs 85%-89% in ORBIT-AF I and II). Coronary artery disease was less common in the international GARFIELD-AF cohort (19% vs 36% and 27% for ORBIT-AF I and II, respectively). However, more than three-quarters of all patients had hypertension, and approximately one-fifth had diabetes in all studies. Patient characteristics, stratified by enrolling provider type (generalist vs

Table II. Demographics, past medical history, and risk scores among all patients in GARFIELD-AF, ORBIT-AF I, and ORBITAF II

	GARFIELD-AF (n = 51,270)	ORBIT-AF I (n = 10,132)	ORBIT-AF II (n = 11,602)
Age, y	69.7 (69.6, 69.8)	73.5 (73.2, 73.7)	70.3 (70.1, 70.5)
Female	22,669 (44.2)	4293 (42.4)	4822 (41.6)
Race			
White	31,595 (63.2)	9041 (89.2)	9917 (85.5)
Black/African American	232 (0.5)	506 (5.0)	571 (4.9)
Hispanic	3315 (6.6)	425 (4.2)	641 (5.5)
Asian		61 (0.6)	218 (1.9)
Non-Chinese	11,379 (22.7)		
Chinese	2684 (5.4)		
Hypertension	39,025 (76.3)	8411 (83.0)	9229 (79.6)
Diabetes	11,317 (22.1)	2982 (29.4)	3034 (26.2)
Prior stroke/TIA	5858 (11.4)	1528 (15.1)	1249 (10.8)
CAD	6633 (19.4)	3645 (36.0)	3084 (26.6)
Prior CABG	1599 (3.2)	1487 (14.7)	1024 (8.8)
PAD	2806 (5.5)	1355 (13.4)	924 (8.0)
CHF	10,260 (20)	3297 (32.5)	2437 (21.0)
NYHA I	1792 (19.2)	1045 (31.9)	789 (33.2)
NYHA II	4536 (48.5)	1504 (45.9)	1148 (48.4)
NYHA III	2605 (27.8)	663 (20.2)	410 (17.3)
NYHA IV	423 (4.5)	64 (2.0)	26 (1.1)
BMI, kg/m^2	27.8 (27.7, 27.8)	30.5 (30.4, 30.7)	31.2 (31.0, 31.3)
Heart rate, beat/min	90.4 (90.2, 90.7)	71.9 (71.7, 72.2)	75.1 (74.8, 75.4)
SBP, mm Hg	133.5 (133.3, 133.7)	126.5 (126.2, 126.8)	127.8 (127.5, 128.2)
DBP, mm Hg	79.7 (79.6, 79.8)	73.0 (72.8, 73.3)	74.7 (74.5, 74.9)
Time from AF diagnosis			
<6 wk	51,270 (100)	370 (3.7)	4574 (39.4)
Mean time from diagnosis to enrollment (wk)	2.0 (1.9, 2.2)	303.4 (296.8, 310.1)	84.5 (80.9, 88.1)
CHA_2DS_2-VASc scores			
Low: 0	1404 (2.8)	225 (2.2)	476 (4.1)
Moderate: 1	6095 (12.2)	705 (7.0)	1269 (10.9)
High: ≥2	42,453 (85.0)	9202 (90.8)	9856 (85.0)
HAS-BLED scores			
Low: 0	5386 (14.6)	613 (6.6)	1670 (14.4)
Medium: 1-2	27,419 (74.2)	6443 (69.1)	8174 (70.6)
High: ≥3	4171 (11.3)	2271 (24.3)	1731 (15.0)
Specialty			
Primary/general practice	7339 (14.3)		
Internal medicine	9211 (18.0)	1978 (19.5)	925 (8.0)
Geriatrics	198 (0.4)		
Cardiology	33,650 (65.6)	6610 (65.2)	7999 (69.0)
Electrophysiology		1544 (15.2)	2591 (22.3)
Neurology	870 (1.7)		86 (0.7)

Values are presented as n (%) or mean (95% CI), unless noted otherwise.
TIA, Transient ischemic attack; *CAD*, coronary artery disease; *CABG*, coronary artery bypass grafting; *PAD*, peripheral arterial disease; *CHF*, congestive heart failure; *NYHA*, New York Heart Association; *BMI*, body mass index; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure.

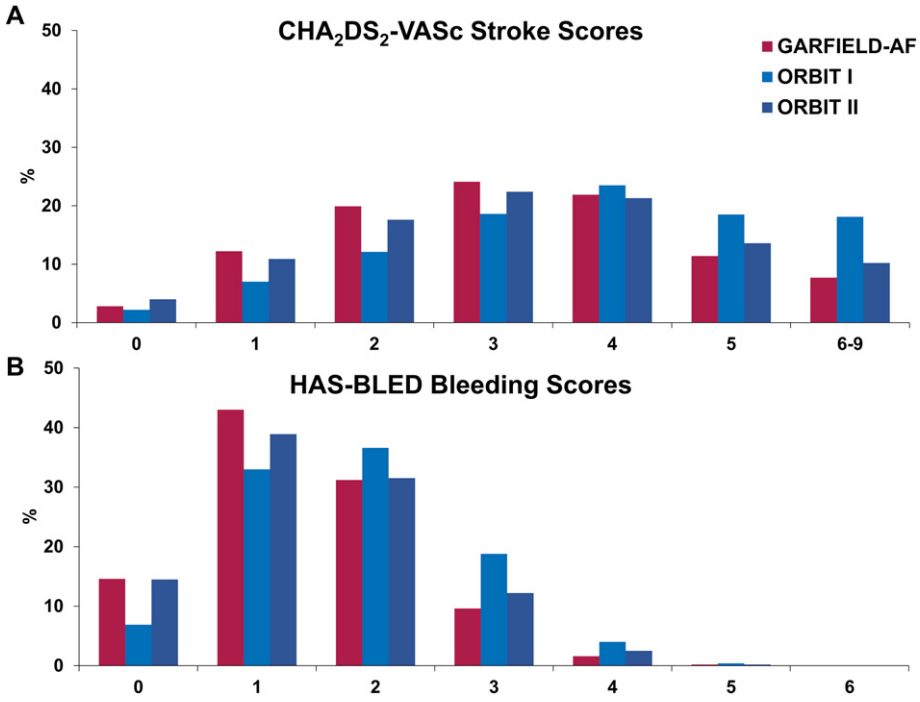
cardiologist), are provided in the Supplemental Material (Table S1).

Distributions of stroke (CHA_2DS_2-VASc) and bleeding (HAS-BLED) risk scores for each of the overall populations are shown in Figure 1. These distributions were minimally skewed toward lower stroke risk for GARFIELD-AF compared with the ORBIT-AF cohorts. Overall, >85% of patients in both registry programs had high stroke risk (CHA_2DS_2-VASc ≥2), whereas high bleeding risk (HAS-BLED score ≥3) was present in 11% (GARFIELD-AF) to 24% (ORBIT-AF I) of patients.

Treatment of patients with new-onset AF

Among patients with AF diagnosed within 6 weeks, stroke prevention therapies are shown in Figure 2. Use of NOACs, with and without antiplatelet therapies, increased over the study periods of both the GARFIELD-AF (3% NOAC in 2010 to 43% in 2016) and ORBIT-AF programs (2% NOAC in ORBIT-AF I in 2010 to 71% NOAC in ORBIT-AF II in 2016). Use of antiplatelet therapy alone for stroke prevention decreased over time in both programs (from 36% to 17% in GARFIELD-AF and from 18% to 8% in the ORBIT-AF program).

Figure 1



Distribution of CHA_2DS_2-VASc stroke risk (**A**) and HAS-BLED (**B**) bleeding risk in the GARFIELD-AF and ORBIT-AF programs.

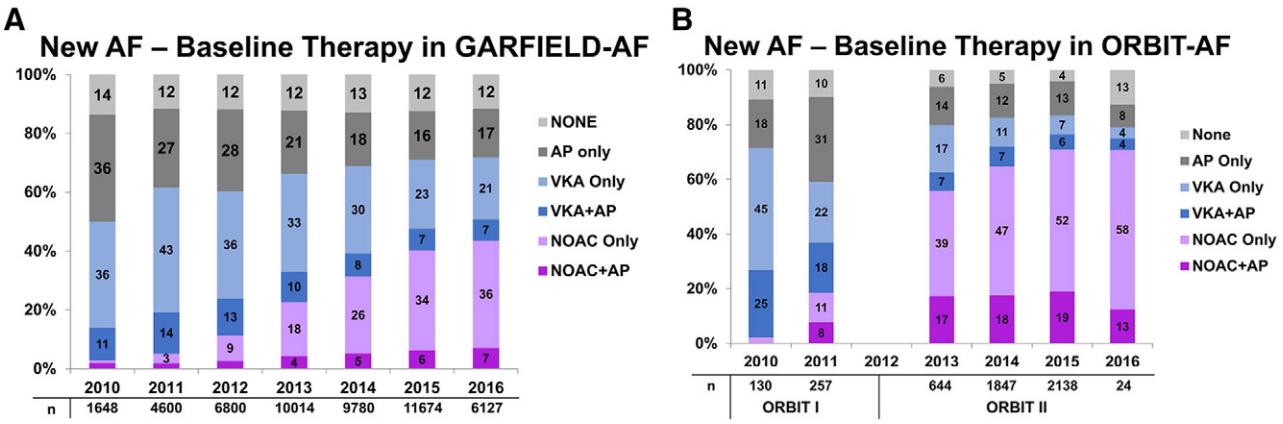
Use of oral anticoagulation therapy (OAC) at baseline increased with increasing CHA_2DS_2-VASc score (Figure 3) (because of very low numbers of ORBIT-AF I patients in some categories, that cohort was excluded). Nearly half of patients with CHA_2DS_2-VASc score of 0 and new-onset AF received OAC (47% for GARFIELD-AF, 57% for ORBIT-AF II). Among patients with CHA_2DS_2-VASc $\geq$2, 69% and 87% of patients in GARFIED-AF and ORBIT-AF II, respectively, were treated with OAC. Among patients with new AF and CHA_2DS_2-VASc score $\geq$2, there was significant geographic variability in use of OAC across countries, from 31% to 93% in GARFIELD-AF and, across states within the United States, from 66% to 100% in ORBIT-AF II (Figure 4). For such patients in GARFIELD-AF enrolled from the United States, OAC use was 72% compared with 84% for the comparable ORBIT-AF US cohort.

Discussion

These analyses represent a global assessment of AF care, encompassing >70,000 patients from the GARFIELD-AF and ORBIT-AF I and II cohorts. Despite baseline differences in ethnic composition, overall comorbidities and risk profiles among patients with AF globally appear consistent across cohorts. Additionally, there have been major shifts in therapies for prevention of stroke in this population, including a move away from antiplatelet monotherapy and toward oral anticoagulation with NOACs around the world. However, the use of oral anticoagulation is common in patients with a low stroke risk (CHA_2DS_2-VASc score 0-1) but not consistently implemented in patients with a high stroke risk (CHA_2DS_2-VASc $\geq$2). Regional differences in treatment (both within the United States and between countries) may account for some of the undertreatment in higher-risk patients.

Our data add to those of several administrative claims analyses demonstrating anticoagulation underutilization for patients with AF.[8,9] Although those studies capture large numbers of patients, claims data are primarily limited in the granularity of data available and usually isolated to single-country data sets. The present analyses also complement those of a worldwide epidemiology study assessing the global health burden and cost of AF.[2] Those investigators demonstrated increasing prevalence and associated disease morbidity from AF from 1990 to 2010. However, specific population characteristics were outside the scope of that analysis. Our data provide details of the AF

Figure 2



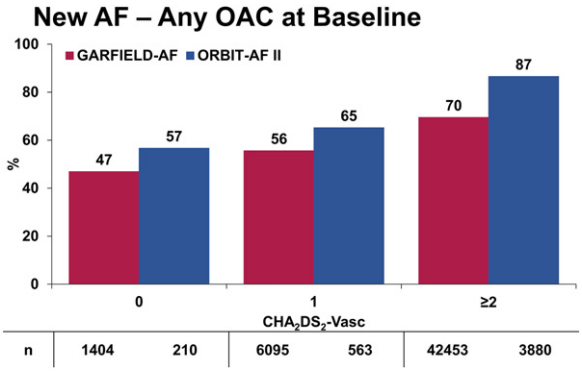
Antiplatelet and anticoagulation therapies in patients with new-onset AF within 6 weeks in (**A**) GARFIELD-AF and (**B**) ORBIT-AF. *AP*, antiplatelet; *VKA*, vitamin K antagonist.

population worldwide, as well as potential insights into the contributors to AF-associated health care expenditures. Both in the United States and around the world, patients with AF in our analysis were predominantly elderly, with high rates of cardiovascular risk factors as well as manifest cardiovascular disease.

We identified promising trends in oral anticoagulation for AF. Major, randomized clinical trials have demonstrated noninferiority or superiority of each NOAC compared with warfarin for stroke prevention,[10-13] and a meta-analysis of these trials demonstrated very favorable risk-benefit profile for NOACs as a class.[14] Based on these data, shifting from warfarin to NOACs at the population level should decrease thromboembolic and bleeding rates for patients with AF. Additional analyses from these cohorts will examine whether such improvements are realized in clinical practice. These data also reflect a progressive shift away from antiplatelet therapy for stroke prevention in AF, as it is increasingly recognized to be of little benefit and not insignificant risk.[15-17]

Our data demonstrated that for patients with new onset AF, nearly half of patients at low-risk of stroke were anticoagulated, yet only two-thirds of patients at high risk of stroke received appropriate OAC therapy. There may be several explanations for this paradox. The low-risk patients with new-onset AF may be receiving OAC in the setting of cardioversion, which could be appropriate for patients of any CHA_2DS_2-VASc score. However, risk-treatment paradoxes are well documented in local cohorts of AF patients, where the lowest-risk patients often receive aggressive therapy.[18] Physicians may perceive lower risk of causing harm in these patients, although their potential benefit is also lower. Our data

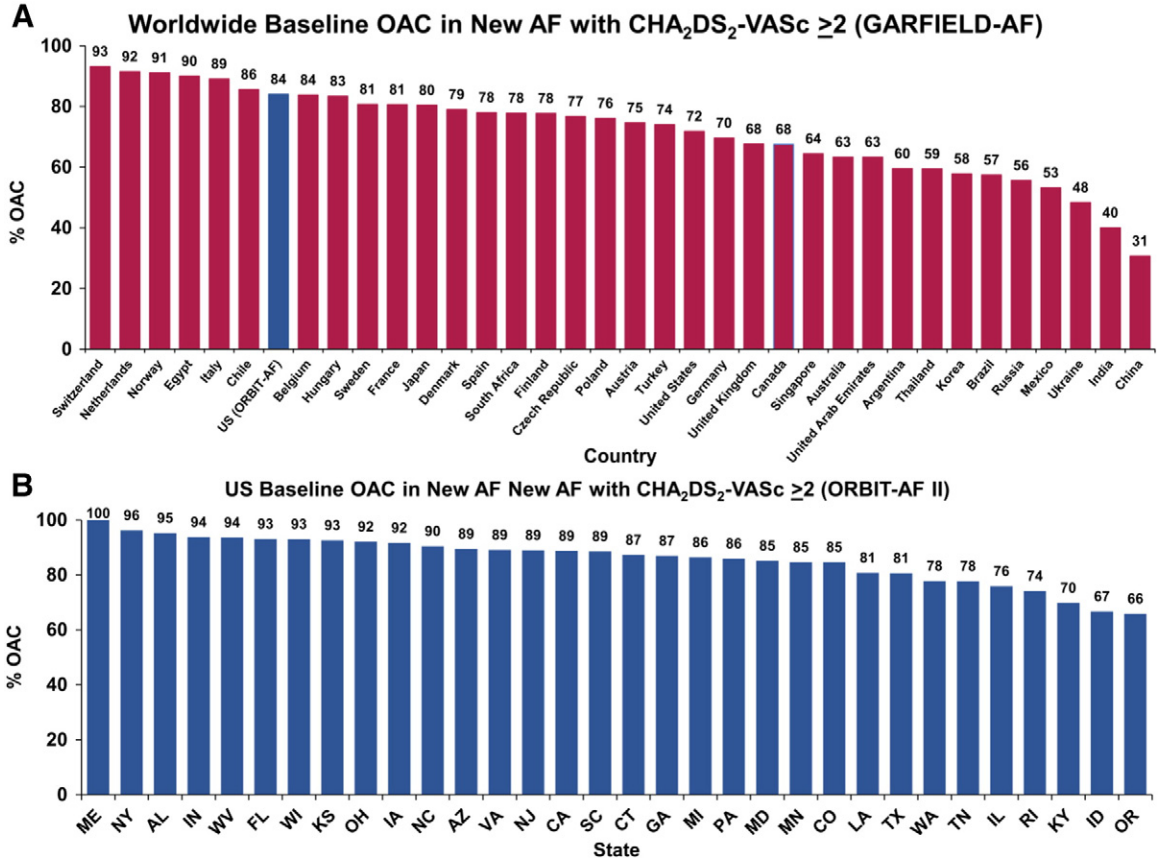
Figure 3



Baseline use of OAC in patients with new-onset AF by CHA_2DS_2-VASc risk strata in GARFIELD-AF and ORBIT-AF II. Data from ORBIT-AF I were excluded because of very low numbers of patients in some strata.

demonstrate that this is not an isolated phenomenon. Among patients with CHA_2DS_2-VASc score of 1, OAC use rose to 55% in the GARFIELD-AF cohort and 65% in the ORBIT-AF II group. The appropriate target treatment rate is difficult to gauge, as there are few data to guide therapy in this "intermediate"-risk group—therefore, the latest US and European guidelines carry much weaker recommendations for these patients.[19,20] Nevertheless, the overtreatment with anticoagulation of patients at very low risk of stroke (CHA_2DS_2-VASc = 0) would convey a significantly increased risk of bleeding in these patients, with likely little benefit in terms of thromboembolism prevention. In contrast, suboptimal

Figure 4



Baseline use of OAC in patients with new-onset AF and CHA_2DS_2-VASc ≥2 within 6 weeks by country (**A**) and by state or territory of the United States (**B**) with at least 20 patients. Data in panel **A** are derived from GARFIELD-AF and ORBIT-AF; data in panel **B** are from ORBIT-AF II alone.

implementation of anticoagulation prophylaxis in patients at the highest stroke risk (CHA_2DS_2-VASc ≥2) likely risks potentially preventable thromboembolic events.

Our analysis of regional variability in OAC use demonstrates significant heterogeneity and may account, in part, for the apparent undertreatment of high-risk patients. Furthermore, variability in treatment appears not only at the country level across the GARFIELD-AF study but also more locally at the state level in the ORBIT-AF program. This suggests that such differences in treatment result from local practice variation and not necessarily system-wide differences in management among locales, and represents an opportunity for education and improvement in quality of care for patients. As the burden of disease continues to increase, it remains imperative to appropriately implement treatments, targeted to local care delivery models, to improve outcomes and reduce health care costs worldwide.

Limitations

There may be sampling and/or selection biases in these observational, registry data. Additionally, there was a geographic imbalance in enrollment of patients, and some regions may be overrepresented, with the potential for regional differences in diagnoses and treatments. Lastly, differences in design and enrollment criteria must be considered when comparing GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II. Data were acquired via medical record review, and each study had its own data verification and auditing protocol.

Conclusions

Despite regional, ethnic, and other differences, patients with AF worldwide demonstrate similar risk profiles and manifest a significant burden of comorbid cardiovascular

disease. The use of NOACs in patients with AF is increasing worldwide, with a concomitant decrease in the use of antiplatelet therapies. However, among new-onset AF, oral anticoagulation is commonly used in the lowest-risk patients, for unclear reasons. Furthermore, it is inconsistently prescribed to patients with a high risk of stroke. The significant geographic variability in the use of OAC represents an opportunity for education and implementation of consistent guideline-based recommendations.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2017.08.011.

Relevant disclosure information

B. A. S. reports consulting for Janssen and BMS-Pfizer and research support from Janssen. H. G., P. S., K. P., and L. T. report no disclosures. A. J. C. has advised and conducted studies on behalf of Bayer, Boehringer Ingelheim, Pfizer/BMS, and Daiichi Sankyo. M. D. E. reports serving as a consultant for AstraZeneca, Eisai, Pozen Inc, Boehringer Ingelheim, ARYx Therapeutics, Pfizer, Sanofi, Bristol-Myers Squibb, Portola, Daiichi Sanko, Medtronic, Merck, Johnson & Johnson, Gilead, Janssen Scientific Affairs, and Armetheon and received grants from Boehringer Ingelheim, Bayer, Daiichi Sanko, Pfizer, and Bristol-Myers Squibb. G. C. F. reports consulting for Janssen, Medtronic, and St Jude Medical. B. J. G. reports Data Safety Monitoring Board–Mount Sinai St Luke's, Boston Scientific Corporation, Teva Pharmaceutical Industries Ltd, St Jude Medical Inc, Janssen Research & Development LLC, Thrombosis Research Institute, Duke Clinical Research Institute, Duke University, Kowa Research Institute Inc, Cardiovascular Research Foundation, and Medtronic and general consulting for Janssen Scientific Affairs, Xenon Pharmaceuticals, and Sirtex Medical Limited. S. G. reports research support from BiO2 Medical, Boehringer-Ingelheim, BMS, BTG EKOS; Daiichi, Janssen, NHLBI, and Thrombosis Research Institute and serving as a consultant to Agile, Bayer, Boehringer-Ingelheim, BMS, Daiichi, Janssen, Portola, and Zafgen. S. H. reports personal fees from Aspen, personal fees from Bayer Healthcare, personal fees from BMS, personal fees from Daiichi-Sankyo, personal fees from Pfizer, and personal fees from Sanofi outside the submitted work. W. H. reports honoraria for serving on executive committees for Johnson & Johnson and Bayer. P. R. K. reports being a consultant for Johnson and Johnson. J. A. reports advisory activity and/or honoraria from Bristol Myers Squibb, Pfizer, Janssen, Daiichi Sankyo, and Boehringer Ingelheim. K. W. M.'s financial disclosures can be viewed at http://med.stanford.edu/profiles/kenneth-mahaffey. G. N. reports research support from Janssen and serving as consultant to Glaxo-Smith-Kline, Janssen, and Daiichi-Sankyo. J. A. R. reports research support from Janssen and Medtronic; consulting for Medtronic, Janssen, In Cardia Therapeutics, Acesion, and Portola; and being in the speaker's bureau for Janssen and Boehringer Ingelheim. A. T. reports being consultant to Bayer Pharma and speaker's bureau for Janssen and Portola. F. V. reports honoraria for speaker fees and consultancy honoraria from AstraZeneca, Medtronic, Bayer Healthcare, Boehringer-Ingelheim, BMS/Pfizer, and Daiichi-Sankyo. J. P. P. reports funding for clinical research from Abbott Medical, ARCA biopharma, Boston Scientific, Gilead, Janssen Pharmaceuticals, and Spectranetics and serves as a consultant to Allergan, GlaxoSmithKline, Johnson & Johnson, Medtronic, and Spectranetics. A. K. reports grants and personal fees from Bayer Healthcare and personal fees from Boehringer-Ingelheim Pharma, Daiichi Sankyo Europe, Sanofi SA, and Janssen. E. D. P. reports significant Research Grant support from Eli Lilly & Company, Janssen Pharmaceuticals, Inc, and the American Heart Association, and modest Consultant/Advisory Board support from Boehringer Ingelheim, Bristol-Myers Squibb, Janssen Pharmaceuticals, Inc, Pfizer, and Genentech Inc. K. A. A. F. reports research grant and honoraria from Bayer and Janssen.

References

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285(18):2370-5.
2. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation 2014;129(8):837-47.
3. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006;114(2):119-25.
4. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA 2004;292(20):2471-7.
5. Kakkar AK, Mueller I, Bassand JP, et al. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). Am Heart J 2012;163(1):13-19 e1.
6. Piccini JP, Fraulo ES, Ansell JE, et al. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. Am Heart J 2011;162(4):606-612 e1.
7. Steinberg BA, Blanco RG, Ollis D, et al. Outcomes registry for better informed treatment of atrial fibrillation II: rationale and design of the ORBIT-AF II registry. Am Heart J 2014;168(2):160-7.
8. Dlott JS, George RA, Huang X, et al. National assessment of warfarin anticoagulation therapy for stroke prevention in atrial fibrillation. Circulation 2014;129(13):1407-14.
9. Wilke T, Groth A, Pfannkuche M, et al. Real life anticoagulation treatment of patients with atrial fibrillation in Germany: extent and causes of anticoagulant under-use. J Thromb Thrombolysis 2015;40(1):97-107.
10. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139-51.

11. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981-92.
12. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365(10): 883-91.
13. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369(22): 2093-104.
14. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383(9921):955-62.
15. Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database Syst Rev 2007;3:CD006186.
16. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011;364(9):806-17.
17. Ben Freedman S, Gersh BJ, Lip GY. Misperceptions of aspirin efficacy and safety may perpetuate anticoagulant underutilization in atrial fibrillation. Eur Heart J 2015;36(11):653-6.
18. Sandhu RK, Bakal JA, Ezekowitz JA, et al. Risk stratification schemes, anticoagulation use and outcomes: the risk-treatment paradox in patients with newly diagnosed non-valvular atrial fibrillation. Heart 2011;97(24):2046-50.
19. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2014;130(23):e199-67.
20. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC: endorsed by the European Stroke Organisation (ESO). Eur Heart J 2016. [pii: ehw210. Epub ahead of print].