Predictors of NOAC versus VKA use for stroke prevention in patients with newly diagnosed atrial fibrillation: Results from GARFIELD-AF

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Introduction A principal aim of the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) was to document changes in treatment practice for patients with newly diagnosed atrial fibrillation during an era when non–vitamin K antagonist oral anticoagulants (NOACs) were becoming more widely adopted. In these analyses, the key factors which determined the choice between NOACs and vitamin K antagonists (VKAs) are explored.

Methods Logistic least absolute shrinkage and selection operator regression determined predictors of NOAC and VKA use. Data were collected from 24,137 patients who were initiated on AC ± antiplatelet (AP) therapy (NOAC [51.4%] or VKA [48.6%]) between April 2013 and August 2016.

Results The most significant predictors of AC therapy were country, enrolment year, care setting at diagnosis, AF type, concomitant AP, and kidney disease. Patients enrolled in emergency care or in the outpatient setting were more likely to receive a NOAC than those enrolled in hospital (OR 1.16 [95% CI: 1.04-1.30], OR: 1.15 [95% CI: 1.05-1.25], respectively). NOAC prescribing seemed to be favored in lower-risk groups, namely, patients with paroxysmal AF, normotensive patients, and those with moderate alcohol consumption, but also the elderly and patients with acute coronary syndrome. By contrast, VKAs were preferentially used in patients with permanent AF, moderate to severe kidney disease, heart failure, vascular disease, and diabetes and with concomitant AP.

Conclusion GARFIELD-AF data highlight marked heterogeneity in stroke prevention strategies globally. Physicians are adopting an individualized approach to stroke prevention where NOACs are favored in patients with a lower stroke risk but also in the elderly and patients with acute coronary syndrome. (Am Heart J 2019;213:35-46.)

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Atrial fibrillation (AF) is a strong independent risk factor for ischemic stroke, which often manifests in combination with other cardiovascular conditions, such as hypertension, diabetes, coronary artery disease, or heart failure, to further increase the thromboembolic risk.[1] AF-related stroke tends to be more severe and debilitating, requiring longer hospitalization (than stroke without AF), and so the costs of this arrhythmia to health care systems and to society are enormous.[2,3] Stroke prevention with either vitamin K antagonists (VKAs), usually warfarin, or non–vitamin K antagonist oral anticoagulants (NOACs) is a principal component in the management of AF patients with increased risk of stroke.[4-6] NOACs are at least as effective as VKAs for embolic stroke prevention but are associated with less bleeding (in particular, intracranial hemorrhage).[5,7] NOACs are also easier for patients to use and for physicians to manage because they can be given in fixed doses without routine coagulation monitoring.[8,9] However, VKAs (despite their recognized limitations including interactions with foods and/or drugs, a narrow therapeutic window, and difficulties in maintaining adequate time in therapeutic range) have remained the standard of care for stroke prevention in many settings because of their low acquisition costs and established monitoring services, which allow physicians to monitor patient adherence.[10-12]

The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF; ClinicalTrials.gov Identifier: NCT01090362) provided an opportunity to record prospectively the choice of the anticoagulant (AC) first prescribed in patients with newly diagnosed AF. Initial analyses revealed an increase in the use of ACs from 57.4% to 71.2% of patients between 2010 and 2016.[13,14] The aim of this analysis is to evaluate the factors (patient characteristics, year of enrolment by cohort, care settings, and geographic location) which have played a role in determining the choice of the AC type during these years of changing treatment practice.

Methods

Study design and participants

GARFIELD-AF is an ongoing prospective noninterventional registry of patients with newly diagnosed AF which is being conducted in 35 countries. The registry is designed to reflect patient management according to local practices, and all eligible patients were enrolled prospectively and consecutively into the study without exclusions according to comorbidities or treatment. Investigator sites were mainly selected randomly from a list of representative care settings in each participating country.[15] Treatment was neither mandated nor paid for by a sponsor, and no additional visits, tests or procedures were required to participate in the study. Adults ≥18 years were eligible for inclusion if they had nonvalvular AF diagnosed according to standard local procedures within 6 weeks of enrolment, had at least 1 risk factor for stroke as judged by the investigator, and provided written informed consent.[15] Risk factors for stroke were not prespecified nor limited to the components of existing risk stratification schemes, such as CHA_2DS_2-VASc. Patients with a transient reversible cause of AF and those for whom follow-up was not possible were excluded.

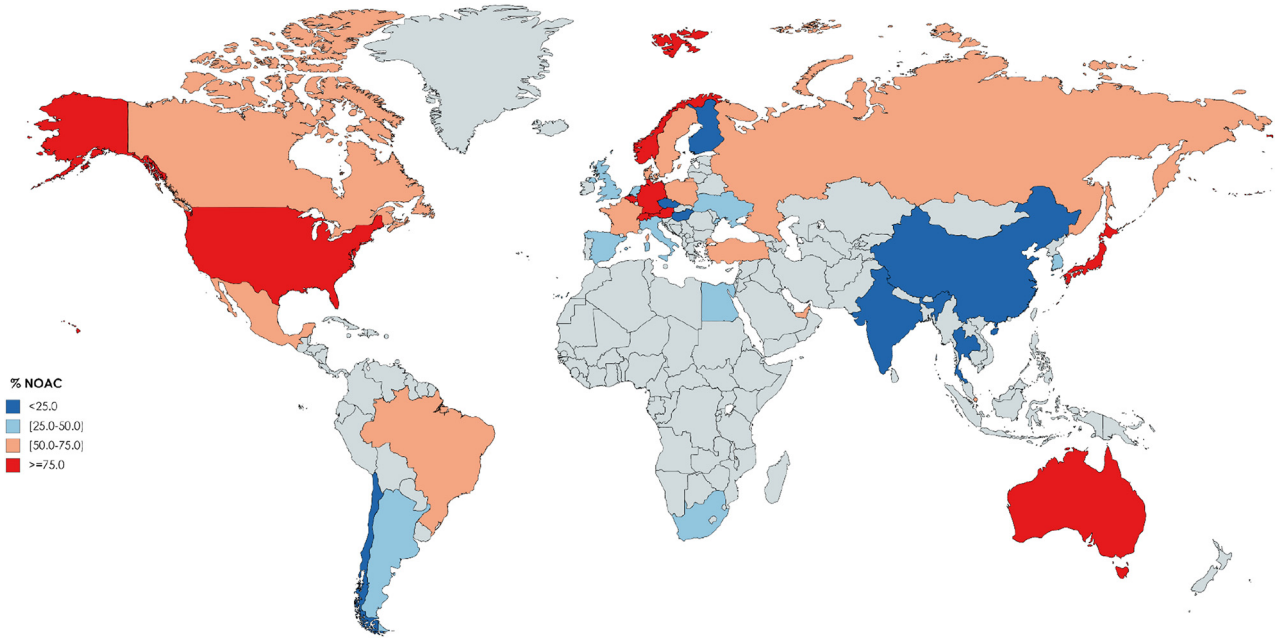
To study the evolution of antithrombotic management at diagnosis of AF, consecutive patients were enrolled prospectively into 5 sequential cohorts (representing the 5.5 years of enrolment) from March 2010 to July 2016; each cohort included approximately 10,000 participants. Supplementary Figure S1 shows the increasing NOAC use in AC recipients by date of enrolment in all countries from 2013 to 2016. In this report, the analysis focuses on the latter years of recruitment after at least 1 NOAC was licensed in all 35 countries in the GARFIELD-AF registry, that is, cohorts (C) C3 (2013-2014), C4 (2014-2015), and C5 (2015-2016), when NOAC prescribing rose from a median of 33.8% to 62.6% of patients on AC therapy.

Cross-sectional data at baseline including treatment patterns (NOAC relative to VKA) for all patients on an AC with or without antiplatelet (AP) therapy are reported. The data were extracted from the study database on October 2017. This article has been written according to the standards outlined by the Strengthening the Reporting of Observational Studies in Epidemiology statement. The registry is being conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonization–Good Pharmacoepidemiological and Clinical Practice guidelines. GARFIELD-AF data are captured using an electronic case report form designed by Dendrite Clinical Systems Ltd (Henley-on-Thames, UK). Data management and quality assurance processes have been described previously.[16]

Statistical analysis

Patients who were not prescribed AC at enrolment were excluded from these analyses. Patient characteristics and medical history were described according to the use of AC therapy, that is, NOAC ± AP or VKA ± AP therapy, respectively. Complete case analysis was used for the description of medication use. Data gathered on patients characteristics included demographics (gender, age, race), clinical findings and history (type of AF, alcohol use, smoking status, body mass index [BMI], diabetes, systolic and diastolic blood pressure [BP], heart rate, history of stroke and/or transient ischemic attack, history of systemic embolism, history of bleed, hypertension, cirrhosis, history of coronary artery bypass graft [CABG], heart failure, kidney disease, history of acute coronary syndrome [ACS], vascular disease, dementia, or

Figure 1



National variations in NOAC use in AC recipients at the time of diagnosis of AF (based on data collected between 2013 and 2016 for GARFIELD-AF cohorts 3 to 5).

hypo- or hyperthyroidism), and AP therapy. Age, BP, and heart rate were assessed as continuous variables.

Logistic least absolute shrinkage and selection operator regression determined predictors of NOAC and VKA use based on data collected at enrolment. Four models were generated, each adding additional information, to establish the association of treatment decision with patient (clinical and demographic) characteristics (model 1), then the addition of cohort (ie, year of enrolment) to patient characteristics (model 2), the addition of site of enrolment to the other 2 sets of information (model 3), and finally the addition of country to all covariates in models 1-3 combined (model 4). The linearity assumption was evaluated for each continuous measure by applying restricted cubic splines. The association between date of enrolment and NOAC use versus VKA use was estimated using a restricted cubic spline. The predicted values and 95% CIs from the unadjusted models displayed the relationship of increasing NOAC use with time. Data analysis was performed with SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

This work was supported by an unrestricted research grant from Bayer AG (Berlin, Germany) to the Thrombosis Research Institute (London, UK), which sponsors the GARFIELD-AF registry. The funding source had no involvement in the data collection, data analysis, or data interpretation. 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

Global prescribing trends

Of the 34,865 patients enrolled into GARFIELD-AF between April 2013 and August 2016, 24,137 patients who received AC ± AP therapy (NOAC [51.4%] or VKA [48.6%]) as their first treatment after diagnosis of AF were included in this analysis, and 10,717 patients on AP therapy only or no stroke prevention treatment were excluded.

A description of the prescribing across all 35 countries is depicted in Figure 1 (and Supplementary Figure S2). The figure shows the marked variability in NOAC prescribing between countries, ranging from 6.1% (in Thailand) to 87.5% (in Switzerland) of all AC-treated patients (Figure 1). When evaluating prescribing trends over time between April 2013 and August 2016, NOAC use increased year on year in most but not all countries so that by the last quarter of enrolment, for example, NOACs represented 100.0% of AC prescribing in Austrian patients but only 9.4% of AC prescribing in Hungary (see Supplementary Figure S3).

Characteristics of the study population

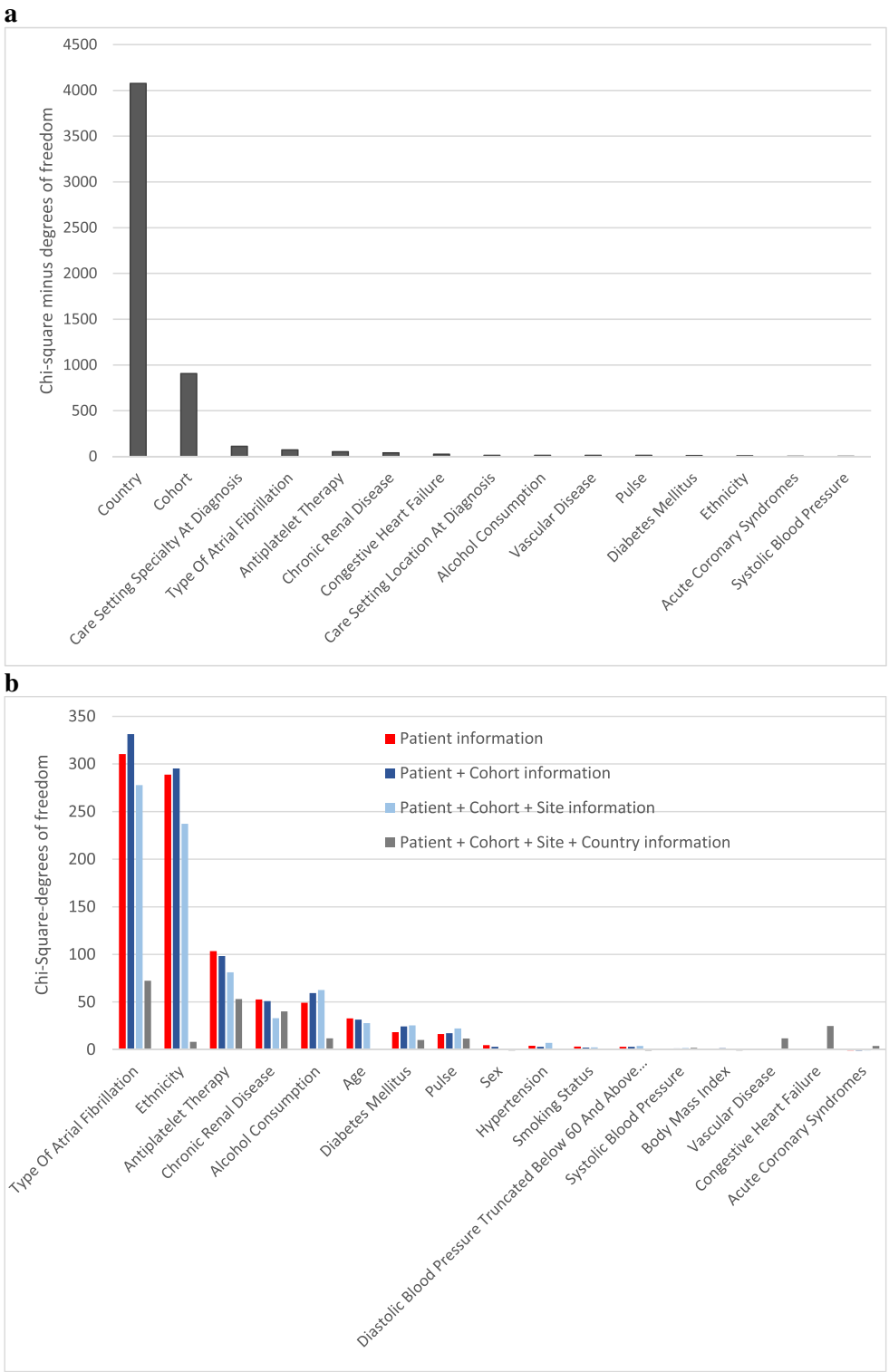
The baseline characteristics of patients on AC ± AP therapy are summarized in Table I as well as the care setting (Supplementary Table SI). The median age of patients at the time of initiating AC for stroke prophylaxis was 72.0 years for NOACs and 71.0 years for VKAs. More

Table I. Baseline characteristics of patients stratified by first AC treatment following diagnosis of AF

Variable at enrolment	NOAC (n = 12,395)	VKA (n = 11,742)
Gender, n (row %)		
Male	6951 (52.2)	6360 (47.8)
Female	5444 (50.3)	5382 (49.7)
Age at AF diagnosis (y), median (IQR)	72.0 (64.0-79.0)	71.0 (64.0-78.0)
Age group, n (row %)		
<75 y	7451 (50.6)	7284 (49.4)
≥75 y	4944 (52.6)	4458 (47.4)
Ethnicity, n (row %)		
Caucasian	7867 (51.0)	7553 (49.0)
Hispanic/Latino	530 (35.8)	951 (64.2)
Asian (not Chinese)	3205 (58.4)	2288 (41.7)
Chinese	176 (26.8)	481 (73.2)
Afro-Caribbean/mixed/other	300 (54.6)	250 (45.4)
Alcohol consumption, n (row %)		
Abstinent	5332 (48.8)	5605 (51.3)
Light	3642 (52.8)	3259 (47.2)
Moderate	1159 (58.0)	839 (42.0)
Heavy	207 (48.9)	216 (51.1)
BMI, median (IQR)	27.0 (24.0-31.0)	27.0 (24.0-31.0)
Pulse (beat/min), median (IQR)	85.0 (70.0-107.0)	85.0 (72.0-104.0)
Systolic blood pressure (mm Hg), median (IQR)	132.0 (120.0-145.0)	131.0 (120.0-145.0)
Diastolic blood pressure (mm Hg), median (IQR)	80.0 (70.0-88.0)	80.0 (70.0-90.0)
Type of AF, n (row %)		
New onset (unclassified)	4814 (47.7)	5272 (52.3)
Paroxysmal	4057 (61.2)	2568 (38.8)
Persistent	2078 (51.2)	1980 (48.8)
Permanent	1446 (42.9)	1922 (57.1)
Heart failure, n (row %)		
No	10,073 (51.9)	9356 (48.1)
Yes	2321 (49.3)	2386 (50.7)
Acute coronary syndrome, n (row %)		
No	11,280 (51.9)	10,477 (48.1)
Yes	1056 (47.0)	1191 (53.0)
Vascular disease, n (row %)		
No	10,711 (52.0)	9880 (48.0)
Yes	1634 (47.4)	1810 (52.6)
History of stroke/TIA, n (row %)		
No	11,024 (51.6)	10,328 (48.4)
Yes	1370 (49.2)	1414 (50.8)
Hypertension, n (row %)		
No	2924 (54.6)	2428 (45.4)
Yes	9439 (50.5)	9266 (49.5)
Diabetes, n (row %)		
No	9730 (52.7)	8746 (47.3)
Yes	2664 (47.1)	2996 (52.9)
Chronic kidney disease, n (row %)		
None or mild (grades I and II)	10,763 (52.8)	9632 (47.2)
Moderate to severe (grades III to V)	1202 (45.8)	1421 (54.2)
AP therapy, n (row %)		
No	10,357 (53.4)	9034 (46.6)
Yes	2038 (42.9)	2708 (57.1)
CHA_2DS_2-VASc score, median (IQR)	3.0 (2.0-4.0)	3.0 (2.0-4.0)
CHA_2DS_2-VASc categories, n (row %)		
≤1	1669 (57.4)	1237 (42.6)
2-3	5479 (51.3)	5200 (48.7)
>3	4970 (49.9)	4984 (50.1)
HAS-BLED score,* median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)

TIA, transient ischemic attack.
*The risk factor "Labile INRs" is not included in the HAS-BLED score because it is not collected at baseline. As a result, the maximum HAS-BLED score at baseline is 8 points (not 9).

Figure 2



Relative significance (measures as Wald χ^2 statistic minus the number of degrees of freedom) associated with NOAC versus VKA prescribing based on 2a. Model 4 including country, site characteristics, cohort, and patients' baseline characteristics. 2b. All models including patient characteristics are presented in descending order of significance.

patients of Asian ethnicity (not Chinese) were prescribed NOACs than VKAs. VKAs seemed to be favored for the treatment of Hispanic/Latino and Chinese populations. Patients with new-onset (unclassified) AF and permanent AF were preferentially prescribed VKAs, whereas NOACs appeared to be more frequently prescribed in patients with paroxysmal AF. Fewer patients on NOACs than VKAs received concomitant antiplatelet therapy (16.4% vs 23.1%). Patients in both groups had a median CHA_2DS_2-VASc score of 3, although a slightly higher proportion of patients on VKA had diabetes, and vascular disease. Conversely, a greater proportion of patients on NOACs (13.8%) than on VKAs (10.8%) had a low stroke risk (CHA_2DS_2-VASc $\leq$1).

Relationship between baseline variables and choice of anticoagulant

A complete list of variables associated with prescribing choice selected in all 4 least absolute shrinkage and selection operator regression models are described (see Supplementary Table SII). Overall, the final model (including all baseline variables) predicted AC prescribing with the greatest accuracy (C statistic of 0.81). When evaluating all 4 sets of factors in this model, the country in which the patient was enrolled far outweighed all other factors in terms of statistical significance (Figure 2, *a*). When country was not included in the model, the year of enrolment was the most significant factor followed by the setting in which patients were enrolled (Supplementary Table SII). Overall, patients' (demographic and clinical) characteristics were statistically the least significant factors in determining choice of AC.

Figure 2, *b* shows the relative importance of the patient characteristics in all 4 models. Type of AF, concomitant antiplatelet therapy, and kidney disease were strongly associated with the choice of AC therapy in each model. Similarly, alcohol use, diabetes, and heart rate also remained significantly associated with AC choice in each model. Ethnicity, which is highly correlated with geographic location, was one of the strongest predictors of the choice of AC in all models, except the final model which included country. The age of patients at the time of diagnosis of AF also became a nonsignificant predictor of AC choice in the presence of country, yet vascular disease and heart failure were significant in the presence of country.

Factors determining the choice of NOAC or VKA

Results obtained from the final model suggest that patients enrolled in the emergency care setting or in the outpatient setting (ie, at an office or anticoagulation clinic) were more likely to receive a NOAC than a VKA prescription as their first treatment for stroke prevention than patients enrolled in the hospital (OR 1.16 [95% CI: 1.04-1.30], OR: 1.15 [95% CI: 1.05-1.25], respectively). Overall, neurologists were most likely to prescribe NOACs. Compared with cardiologists, primary care physicians and internists were less likely to initiate treatment with NOACs (OR: 0.55 [95% CI: 0.50-0.62], OR: 0.89 [95% CI: 0.81-0.97], respectively) (Supplementary Figure S4).

Model 4 found that patient characteristics which predicted NOAC prescribing included year of enrolment (designated by cohort), ACS, paroxysmal AF (relative to new onset AF), increasing age (as assessed over 5-year increments) in patients up to 75 years and beyond 75 years, and normotensive patients (defined by a systolic blood pressure up to 120 mm Hg) (Figure 3 and Supplementary Table SIII). Conversely, factors which predicted a VKA prescribing included moderate to severe kidney disease, vascular disease, heart failure, diabetes, concomitant antiplatelet therapy, permanent AF, and Chinese ethnicity (Figure 3).

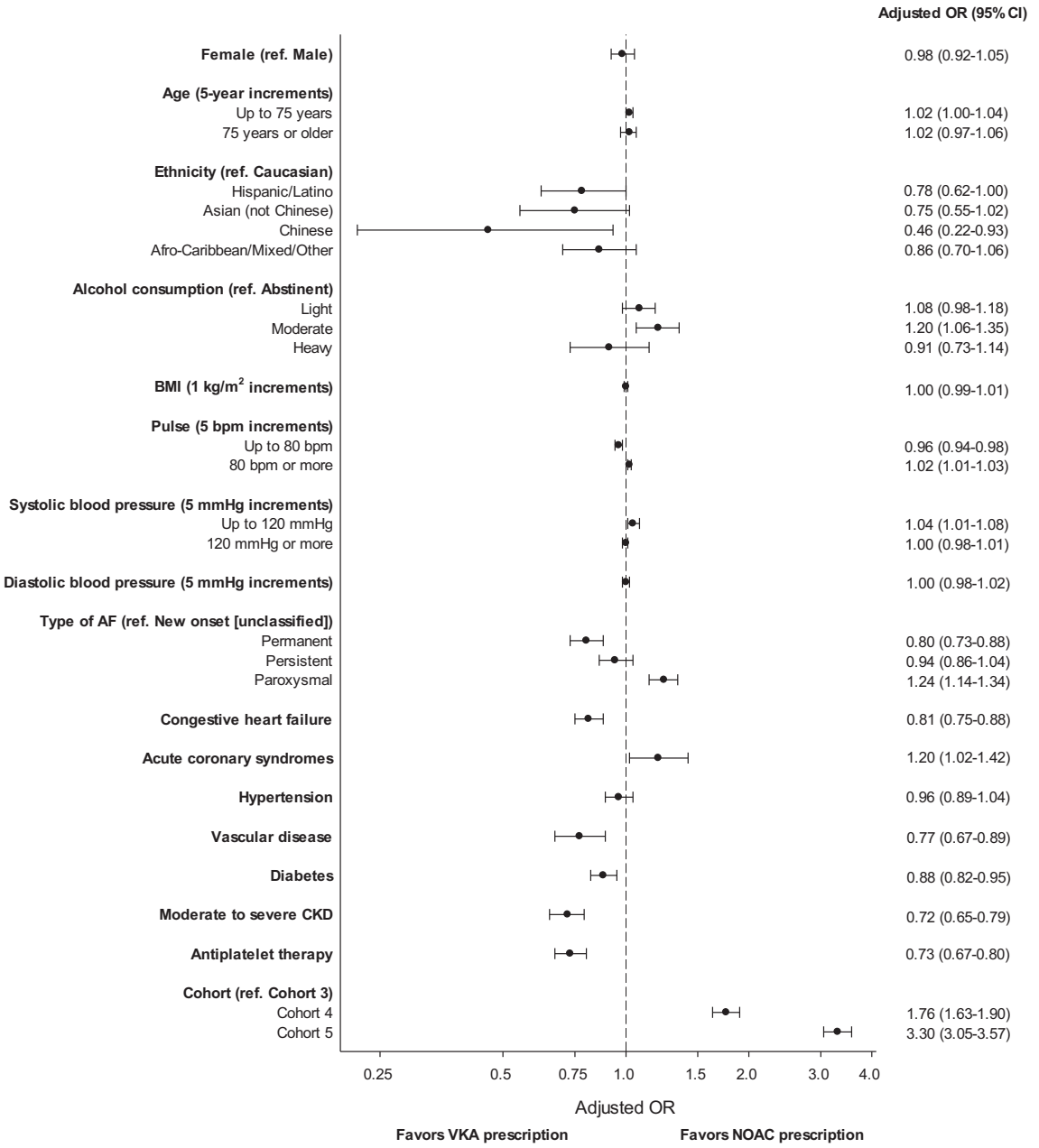
Discussion

There is still much to learn about how NOACs are being used in clinical practice and their impact on short- and long-term outcomes in patients with AF. A principal aim of the GARFIELD-AF registry was to document changes in treatment practice at a national and global level for patients with newly diagnosed AF during an era when NOACs are becoming more widely adopted.[14,15] Although the indications and eligibility of patients for NOACs and VKAs are well codified by prescribing information, clinical guidelines, expert opinion, and a wealth of published data,[7,17-20] the large global data set from GARFIELD-AF provides an opportunity to evaluate the key drivers of NOAC and VKA prescribing across a range of care settings in everyday practice.

Unsurprisingly, the registry recorded enormous variability in prescribing practice reflecting the heterogeneity in the organization of health care across the globe.[5] NOACs were most commonly used as an initial treatment for stroke prevention in countries where there is a high per capita spend on health via Medicare (such as in the United States) or universal health care coverage. Whereas in participating centers in other countries with more restricted public funding (including Hungary, Czech Republic, Ukraine, Spain, Argentina, Brazil, Chile, Egypt, South Africa, India, China, and Thailand), VKA was most commonly used.

For participating centers in some countries, early and broad access to NOACs meant that NOACs had already become the preferred option by the start of the analysis (ie, April 2013). These countries included Japan, the United States, Belgium, France, Germany, Austria, Switzerland, and Norway (Supplementary Figure S3). However, for countries such as the United Kingdom, state-funded reimbursement for NHS patients was only made available in 2014 after the National Institute for Health and Care Excellence guideline was updated.[21] In Canada, an initial disconnect between recommended NOAC therapy and insurance coverage resulted in a delay

Figure 3



Adjusted ORs for NOAC prescription among OAC recipients by baseline characteristics and cohort of enrolment.

in patient access to NOACs.[22] Consistent with the published observations from national registries,[23-27] GARFIELD-AF recorded an initially slow but nevertheless steady rise in NOAC prescribing between 2013 and 2016 at participating centers in many countries including Australia, Netherlands, Denmark, Sweden, Finland, Russia, Poland, Italy, Turkey, United Arab Emirates, Mexico, Singapore, and Korea (Supplementary Figure S3). Key drivers for this change included new guidelines from the European Society of Cardiology,[4] European Heart Rhythm Association,[28] and American College of Cardiology/American Heart Association[29] as well as national policy documents (such as the Canadian guidelines and National Institute for Health and Care Excellence) based on reappraisal of the evidence on NOACs.

At a national level, it was observed that physician-specific prescribing habits and the care setting came to the fore in determining the choice of AC.

Consistent with other published studies,[24,30,31] both cardiologists and neurologists (rather internists) were clearly early adopters of NOACs for stroke prevention,[32] acting as "anticoagulant champions" for physicians less familiar with these new therapies.[33] Equally, the lack of uptake of NOACs in some fields of medicine and clinical settings may have been the consequence of limited or restricted funding, or prescribing regulations. For example, the prescribing choices of primary care physicians and general physicians who work in smaller community hospitals and practices serving poorer communities[32] may be restricted because of financial constraints on funding and insurance limitations or because of the imposed need to restrict prescription to the best informed health care professionals.

Overall, prescribing of AC therapy for stroke prevention in AF patients appears to be more common in the outpatient setting.[34] The GARFIELD-AF registry and a number of other studies[33] have found that patients who are managed in the outpatient setting are more likely to receive NOAC therapy than patients treated in emergency care or in the hospital setting. The prescribing policy of many hospitals and clinics with established monitoring services for VKA may have restricted NOAC prescribing until after a trial period with a VKA. In the Netherlands, for example, a nationwide network of anticoagulant clinics monitors the vast majority of patients on anticoagulants, and so the availability of these ancillary services has meant that the uptake of NOACs has been relatively slow compared with neighboring Belgium.[33]

The variation in the choice of AC also reflects the differing values and preferences among physicians and patients.[35-37] Many physicians and patients express a preference for NOACs due to reduced potential for food and drug interactions and reduced need for monitoring.[38] However, other studies have also described the preferential use of VKAs by physicians in the outpatient setting[38] because of the availability of portable home testing, which allows patients to self-manage their treatment and provides physicians with information to assess patients' compliance to treatment.[39]

Consistent with observations from the national Danish registry,[27] GARFIELD-AF shows that NOACs seemed to be favored for the management of patients with a low stroke risk (CHA_2DS_2-VASc 0 or 1) as well as the elderly and patients with ACS. VKAs were more often prescribed in patients with CKD, diabetes, heart failure, and permanent AF.[40] It is well recognized that VKAs are the treatment of choice[41,42] in cases of severe renal failure and severe cardiac structural alterations.

Ethnicity was found to be significant in the model of patient characteristics but became borderline when country was added to the model. Not surprisingly, there is a strong correlation between these 2 factors. It is interesting to note the striking difference in NOACs used across the Asian countries. Thus, we have separated the Chinese Asian ethnicity. Because some ethnicity remained in the presence of country, it is possible that the remaining differences are between health care systems. In the case of Asian countries, it may be that the differences noted are driven by the lack of reimbursement of NOACs in China.

It is likely that concerns may exist regarding the increased risk of major bleeding complicating VKA therapy in the elderly[43] and especially those with a high risk of fall or dementia. Our analyses also provide evidence about ongoing concerns regarding the prescription of NOACs for patients with renal dysfunction. However, it may only be a question of time before the favorable findings from recent randomized clinical trials (RCTs) with NOACs are influencing clinical practice. Subgroup analyses from RCTs with rivaroxaban or apixaban have shown the benefits of these NOACs when compared to warfarin.[44,45] Data from phase III trials also suggest that the preservation of renal function was significantly better with rivaroxaban than warfarin.[46] These findings were corroborated by Yao et al (2017) in a US retrospective cohort analysis of the Opted-Labs Data Warehouse database,[47] which compared the impact of NOACs (apixaban, dabigatran, and rivaroxaban) and warfarin on renal outcomes. The authors found that the use of NOACs was associated with reduced risks of progressive renal impairment, manifest as $\geq$30% decline in eGFR, doubling of serum creatinine, and acute kidney disease developing over time.

Although use of NOACs was more common than VKAs in patients with ACS, a separate unpublished GARFIELD-AF analysis found that antiplatelet therapy (either alone, ie, without OAC, or in combination with OAC) is used in approximately two-thirds of patients in this setting. The value of NOACs in patients with vascular disease, recently described in published studies,[48] has yet to be realized in everyday clinical practice.

GARFIELD-AF showed that VKAs are more likely to be used in combination with AP therapy than NOACs, although the evidence from many studies suggests that stopping AP therapy would almost certainly diminish the bleeding risk without increasing CVD risk.[49] In a separate GARFIELD-AF analysis, an overall decline over time was seen in the nonindicated use of AP therapy (both as a monotherapy and in combination with AC).[50]

Strengths and limitations

This study describes real-world clinical practices in AC prescribing for a well-defined cohort of patients with newly diagnosed nonvalvular AF and at least 1 risk factor for stroke. However, in contrast to RCTs, AF patients with many concomitant diseases were not excluded from this noninterventional registry. This observational study was sufficiently large to identify hospital and other care settings which were representative in each country. With patients recruited within 6 weeks of diagnosis of AF, the registry provided a record of almost all patients treated in

each participating center with nonvalvular AF, that is, including some high-risk patients who died shortly after diagnosis. GARFIELD-AF mitigated some of the limitations inherent to observational studies through the standardization of clinical definitions and the rigorous audit (using both remote and onsite monitoring) to ensure the completeness and accuracy of the data collected. This is a unique feature because GARFIELD-AF is a prospective global disease registry and regional differences and country-related variations of drug prescribing patterns had been anticipated. Other studies addressing the predictors of NOAC use where smaller, retrospective, limited to selected patient populations, limited to single countries or regions within a country, or monocenter observations. A small study of Guerriero et al was limited to 967 patients in South Italy and assessed the predictive role of age, gender, and number and type of co-treatments for NOAC versus warfarin prescription in elderly patients. In contrast to our findings, age was negatively associated with NOAC initiation.[51] A German claim data analysis of 16,804 elderly nursing home residents identified previous stroke, bleeding events, and a recent hospitalization as predictors for NOAC prescription instead of VKA.[52] An analysis of health insurance data of the Canadian Province of Quebec showed that initiation with NOACs was less likely for patients ≥80 years old (OR 0.55, 95% CI 0.41-0.73) or with CHA_2DS_2-VASc ≥2 (OR 0.49, 95% CI 0.42-0.57).[53] Another group of authors addressed the effect of NOACs on prescribing practices for AF in older adults by using the database of their hospital, the academic medical center in St Louis, MO, USA. Consistent with our results, they observed an increase of NOAC use over, time but in contrast to GARFIELD-AF, the rate of NOAC uptake was attenuated by increasing age.[54] The group of Urbaniak et al used the Norwegian Prescription Database to analyze the prescription patterns of NOACs in Norway, and they report that AF patients <70 years old had higher odds of NOAC prescribing (OR 1.19-1.29, depending on age category) in contrast to patients >74 years old (OR 0.51-0.77).[26] The aim of a Canadian study was to identify factors that predict selection of a NOAC by resident physicians when faced with patients with nonvalvular AF. The most consistent predictor for prescribing a NOAC in all clinical scenarios was self-reported comfort level.[55] The ORBIT-AF II study group also aimed to describe the factors associated with selection of NOACs versus warfarin in patients with new-onset AF. Their findings related to patient characteristics are not too different from our observations in GARFIELD-AF; however, ORBIT-AF II is limited to patients in United States, whereas GARFIELD-AF is a global registry. The impact of the health insurance status on the prescription pattern could be analyzed in more detail in ORBIT-AF II. This would have been too confounded in GARFIELD-AF due to reimbursement differences in each country.[56] None of these publications addressed the role of different countries as a predictor of treatment, which was the most important factor in GARFIELD-AF with 35 contributing countries. We also show the uptake of NOAC use by country, and we provide information on the impact of the care setting specialty (cardiology, geriatrics, internal medicine, neurology, primary care/general practice) and the location of enrolment (anticoagulation clinic/thrombosis center, emergency room, hospital, office).

This study, however, also has limitations. Firstly, although patients were recruited consecutively, informed consent was required, thereby introducing a level of bias in the patient selection. Secondly, comorbidities (such as cancer) and other factors, which would have likely impacted on the choice of treatment, were not comprehensively reported. Thirdly, the impact of drug costs and levels of reimbursement could not be quantified accurately, but this is likely to be a main driver limiting access to NOACs for a broad cross section of eligible patients. Finally, there are likely to be other factors relating to patient preferences, which were not reported.

Conclusions

GARFIELD-AF shows that prescribing of NOACs has increased substantially during the course of the study. With this change, an overall increase in AC prescribing was also observed. GARFIELD-AF highlighted marked differences in the stroke prevention strategies which are adopted around the world. This heterogeneity may be explained by substantial differences in health systems across countries as well as differences between specialty practice and differences in patient characteristics. In the years shortly after approval of NOACs for stroke prevention, prescribing of NOACs seems to have been favored in the lower-risk groups, such as patients with paroxysmal AF and/or a low stroke risk (CHA_2DS_2-VASc 0 or 1), but also in the elderly and patients with ACS, whereas physicians now appear to prefer prescribing VKAs in patients with permanent AF, moderate to severe kidney disease, or heart failure and those with vascular disease and diabetes mellitus. It is likely that further changes in AC prescribing may evolve as physicians' experience with NOACs mature for stroke prevention as well as other indications and as initial concerns over the safety and reversibility abate. However, the countries and the cohorts reflecting the time of enrolment were the strongest predictors of NOAC versus VKA prescription for stroke prevention in patients with newly diagnosed atrial fibrillation.

CRediT authorship contribution statement

Sylvia Haas: Conceptualization, Investigation, Resources, Methodology, Writing - original draft, Writing - review & editing. **A John Camm:** Conceptualization, Investigation, Resources, Methodology, Writing - original draft, Writing -

review & editing. **Jean-Pierre Bassand:** Conceptualization, Investigation, Resources, Methodology, Writing - review & editing. **Pantep Angchaisuksiri:** Investigation, Resources, Writing - review & editing. **Frank Cools:** Investigation, Resources, Writing - review & editing. **Ramon Corbalan:** Investigation, Resources, Writing - review & editing. **Harry Gibbs:** Investigation, Resources, Writing - review & editing. **Barry Jacobson:** Investigation, Resources, Writing - review & editing. **Yukihiro Koretsune:** Investigation, Resources, Writing - review & editing. **Lorenzo G Mantovani:** Conceptualization, Methodology, Writing - review & editing. **Frank Misselwitz:** Conceptualization, Methodology, Writing - review & editing.
Elizaveta Panchenko: Investigation, Resources, Writing - review & editing. **Hany Ibrahim Ragy:** Investigation, Resources, Writing - review & editing. **Janina Stepinska:** Investigation, Resources, Writing - review & editing. **Alexander GG Turpie:** Conceptualization, Investigation, Resources, Methodology, Writing - review & editing. **Jitendra PS Sawhney:** Investigation, Resources, Writing - review & editing. **Jan Steffel:** Investigation, Resources, Writing - review & editing. **Toon Wei Lim:** Investigation, Resources, Writing - review & editing. **Karen S Pieper:** Conceptualization, Methodology, Formal analysis, Writing - review & editing. **Saverio Virdone:** Methodology, Formal analysis, Writing - review & editing. **Freek WA Verheugt:** Conceptualization, Investigation, Resources, Methodology, Writing - review & editing. **Ajay K Kakkar:** Conceptualization, Funding acquisition, Investigation, Resources, Methodology, Supervision, Writing - review & editing.

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Declaration of interests

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.03.013.

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