



## Original Article

# Risk profiles and one-year outcomes of patients with newly diagnosed atrial fibrillation in India: Insights from the GARFIELD-AF Registry



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## ABSTRACT

**Background:** The Global Anticoagulant Registry in the FIELD—Atrial Fibrillation (GARFIELD-AF) is an ongoing prospective noninterventional registry, which is providing important information on the baseline characteristics, treatment patterns, and 1-year outcomes in patients with newly diagnosed non-valvular atrial fibrillation (NVAF). This report describes data from Indian patients recruited in this registry. **Methods and results:** A total of 52,014 patients with newly diagnosed AF were enrolled globally; of these, 1388 patients were recruited from 26 sites within India (2012–2016). In India, the mean age was 65.8 years at diagnosis of NVAF. Hypertension was the most prevalent risk factor for AF, present in 68.5% of patients from India and in 76.3% of patients globally ( $P < 0.001$ ). Diabetes and coronary artery disease (CAD) were prevalent in 36.2% and 28.1% of patients as compared with global prevalence of 22.2% and 21.6%, respectively ( $P < 0.001$  for both). Antiplatelet therapy was the most common antithrombotic treatment in India. With increasing stroke risk, however, patients were more likely to receive oral anticoagulant therapy [mainly vitamin K antagonist (VKA)], but average international normalized ratio (INR) was lower among Indian patients [median INR value 1.6 (interquartile range {IQR}: 1.3–2.3) versus 2.3 (IQR 1.8–2.8) ( $P < 0.001$ )]. Compared with other countries, patients from India had markedly higher rates of all-cause mortality [7.68 per 100 person-years (95% confidence interval 6.32–9.35) vs 4.34 (4.16–4.53),  $P < 0.0001$ ], while rates of stroke/systemic embolism and major bleeding were lower after 1 year of follow-up.

**Conclusion:** Compared to previously published registries from India, the GARFIELD-AF registry describes clinical profiles and outcomes in Indian patients with AF of a different etiology. The registry data show that compared to the rest of the world, Indian AF patients are younger in age and have more diabetes and CAD. Patients with a higher stroke risk are more likely to receive anticoagulation therapy with VKA but are underdosed compared with the global average in the GARFIELD-AF.

**Clinical trial registration—URL:** <http://www.clinicaltrials.gov>. Unique identifier: NCT01090362.

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## 1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide,<sup>1</sup> with a prevalence of 1–2% in the general population. AF is an important contributor to all-cause mortality, cognitive decline, and stroke. The likelihood of nonvalvular AF (NVAf) increases with advancing age and is often accompanied by the presence of diabetes and cardiovascular comorbidities, such as heart failure and coronary artery disease (CAD). In the recently published Real-life global survey evaluating patients with atrial fibrillation (REALISE-AF) registry from India, the most common underlying cardiovascular risk factors in patients with AF were hypertension (50.8%) and diabetes (20.4%). In addition, a high proportion of patients had a history of valvular heart disease (40.7%).<sup>2,3</sup>

India has over 1.2 billion inhabitants<sup>4</sup> and is undergoing remarkable economic changes in the recent years and is making important inroads into improving cardiovascular health care despite finite resources. By the year 2050, however, the aging population (60–80 years) is projected to increase by 326% and for patients  $\geq 80$  years, by 700%.<sup>5</sup> As aging is a risk factor for AF, this change, along with other age-associated cardiovascular disease, is likely to add to already high index levels of AF associated with rheumatic heart disease.<sup>6,7</sup>

To date, most of our understanding of NVAf is based on observational studies from North America and western Europe.<sup>8</sup> Recently published registry data from the Indian Heart Rhythm Society (IHRS-AF) registry<sup>9</sup>; Randomised Evaluation of Long-Term Anticoagulation Therapy registry<sup>10</sup>; and REALISE-AF registry<sup>2,3</sup> have described patients with rheumatic valvular heart disease (RVHD) as well as those with NVAf.

Global Anticoagulant Registry in the FIELD—Atrial Fibrillation (GARFIELD-AF)<sup>11</sup> is one of the first studies to evaluate patients with only NVAf in India—thereby allowing a comparison of similar patients from the rest of the world. Patients in the GARFIELD-AF were enrolled from 35 countries between 2010 and 2016 and are currently being followed up until 2018 when all patients will have had a minimum follow-up of 2 years and up to 8 years. This article describes the trends in stroke prevention treatment and records the burden of disease and one-year outcomes associated with NVAf in India.

## 2. Methods

### 2.1. Study design

The GARFIELD-AF is an ongoing prospective noninterventional disease registry of patients with newly diagnosed, predominantly NVAf ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01090362) Identifier: NCT01090362).<sup>11</sup> Patients were enrolled into the GARFIELD-AF registry from over 1000 centers in 35 countries worldwide, from America, Europe, Africa, and Asia. Eligible patients included men and women aged  $\geq 18$  years with NVAf, diagnosed according to standard local procedures within the previous 6 weeks and with at least one additional risk factor for stroke. Risk factors were neither prespecified in the protocol nor were they limited to the components of existing risk stratification schemes. The registry excluded patients with a transient reversible cause of AF and those for whom follow-up was not envisaged or possible. Investigator sites were selected randomly and represented the different care settings in each participating country (office-based practice; hospital departments—neurology, cardiology, geriatrics, internal medicine, and emergency—anticoagulation clinics; and general or family practice).

### 2.2. Ethics statement

All patients provided written informed consent to participate. Independent ethics committee and hospital-based institutional review board approvals were obtained, as necessary, for the registry protocol. The registry is being conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonisation-Good Pharmacoepidemiological and Clinical Practice Guidelines.

### 2.3. Procedures and outcomes measures

Baseline data collected at screening included patients characteristics, medical history, care setting, type of AF, date and method of diagnosis, symptoms, and anticoagulant (AC) treatment [vitamin K antagonists (VKAs), factor Xa inhibitors (FXas), and direct thrombin inhibitors (DTIs), as well as antiplatelet (AP) treatment]. Ethnicity was classified by the investigator in agreement with the patient.<sup>11</sup>

Data on all components of the CHA<sub>2</sub>DS<sub>2</sub>-VASc [congestive heart failure (CHF), hypertension, diabetes, vascular disease, age 65–74 years, and female gender, age  $\geq 75$  years and previous systemic embolism]<sup>12</sup> and the HAS-BLED<sup>13</sup> risk stratification schemes were collected to assess the risks of stroke and bleeding retrospectively. Vascular disease was defined as peripheral artery disease and/or CAD with a history of acute coronary syndrome. Hypertension was defined as a documented history of hypertension or blood pressure  $> 140/90$  mmHg at rest.

### 2.4. Data collection

GARFIELD-AF data were collected using an electronic case report form (eCRF) and captured by trained personnel. The eCRF was designed by Dendrite Clinical Systems Ltd, Henley-on-Thames, UK, the group which is also responsible for the ongoing database program management. Oversight of operations and data management are managed by the sponsor and coordinating center Thrombosis Research Institute (TRI), with support from Quintiles (Durham, NC, USA), the University of Birmingham Department of Primary Care Clinical Sciences (Birmingham, UK), Thrombosis Research Group-Brigham and Women's Hospital (Boston, MA, USA), and AIXIAL (Paris, France).

The GARFIELD-AF protocol requires that 20% of all eCRFs are monitored against source documentation, that there is an electronic audit trail for all data modifications, and that critical variables are subjected to additional audit.<sup>14</sup>

### 2.5. Statistical analysis

This article describes the baseline characteristics, treatment patterns, and 1-year outcomes based on global data and for patients recruited in India; data for these analyses were extracted from the registry database on 18th October 2017. Continuous variables are expressed as mean  $\pm$  standard deviation (SD) and categorical variables as frequency and percentage. Use of antithrombotic therapy at baseline was analyzed by CHA<sub>2</sub>DS<sub>2</sub>-VASc and “modified” HAS-BLED (excluding fluctuations in the international normalized ratio) scores, calculated retrospectively from the data collected. Patients with missing values were not removed from the study.

Prothrombin time and international normalized ratio (INR) readings during the first year of follow-up were included in the analysis. Implausible INR values of less than 0.8 or greater than 20 were excluded. Patients on VKA treatment at enrollment, but with fewer than three readings during the follow-up, were excluded from the analysis. The distribution of INR values are described by

counts and percentages below, within, and above the therapeutic range, and by the mean, SD, median, and interquartile range (IQR).

Occurrence of major clinical events (primarily, stroke/systemic embolism (SE), major bleeding, and all-cause mortality) is described using the number of events, the proportion of patients with the event divided by the population at risk at the beginning of the follow-up period, person-time event rate (per 100 person-years), and 95% confidence interval (CI). We estimated person-year rates using a Poisson model, with the number of events. Only the first occurrences of each event were taken into account. Data analysis was performed at the TRI with SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

### 3. Results

#### 3.1. Baseline patient characteristics

In total, 52,014 patients with a new diagnosis of AF were enrolled in the GARFIELD-AF between March 2010 and August 2016. Of these, 1388 of patients were from India recruited between August 2012 and August 2016 from 26 centers Fig. 1. The mean (SD) time between enrollment and recruitment was 1.4 (1.5) weeks. The proportion of patients recruited by cohort is reported

in [Supplementary Figure S1](#). Indian patients with NVAF in this registry were almost entirely diagnosed and managed by cardiologists (81.7%), with a small number of patients diagnosed by internal medicine (15.0%), neurology (1.2%), and primary care physicians (1.9%). Approximately nine of 10 patients were managed in the hospital setting (90.1%); a small number of patients were first attended to by emergency services (2.7%). Approximately 8% of the patients made use of private medical insurance for their care.

The baseline clinical characteristics of patients recruited in India and all countries are summarized in [Table 1](#). In India, majority (59.9%) of the patients were men; mean age at diagnosis of NVAF was 65.8 years, and 26.3% of the patients were  $\geq 75$  years. Hypertension was the most prevalent risk factor for AF, seen in 68.5% of patients from India and in 76.3% of patients globally. A lower body mass index (BMI) (average of 24.3 kg/m<sup>2</sup>) was observed in patients from India compared with a global BMI average of 27.8 kg/m<sup>2</sup> ( $P < 0.001$ ). Despite this, diabetes was prevalent in over a third of Indian patients (36.2%), a significantly higher proportion than patients globally (22.2%,  $P < 0.001$ ).

Cardiovascular comorbidities, such as CAD, were higher for patients from India than globally (28.1% vs 21.6%,  $P < 0.001$ ) at the time of diagnosis of AF. Congestive heart failure (CHF) was



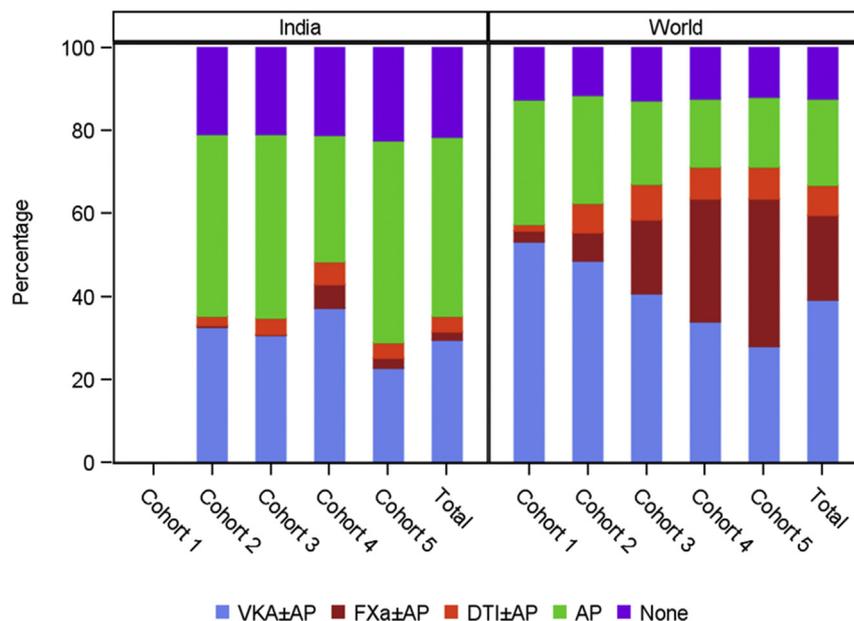
Fig. 1. GARFIELD-AF sites in India. GARFIELD-AF, Global Anticoagulant Registry in the FIELD—Atrial Fibrillation.

**Table 1**

Baseline characteristics of patients recruited from India and all countries in the GARFIELD-AF registry.

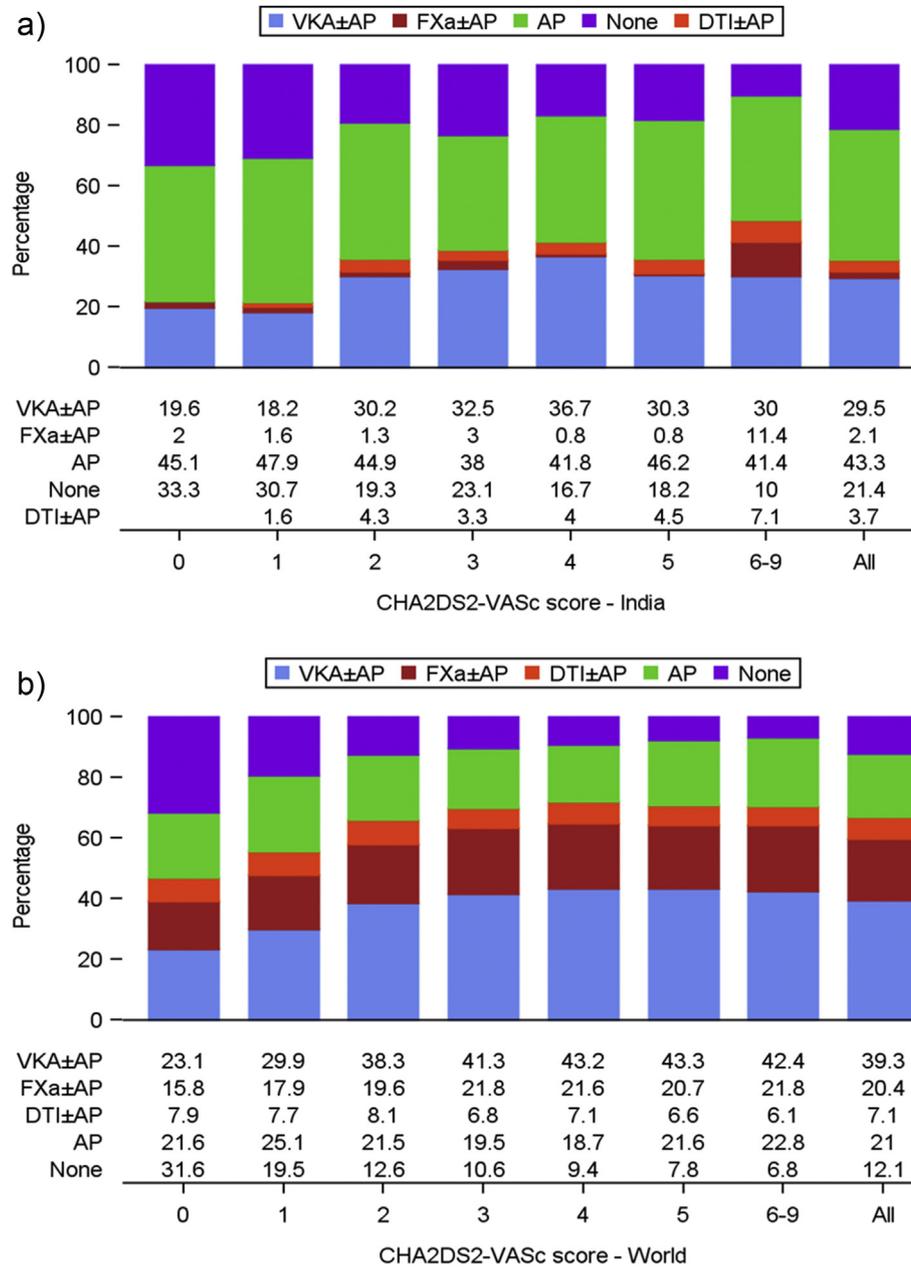
Variable	India (N = 1388)	All countries (N = 52,014)	P-Value <sup>b</sup>
Mean age (SD), years	65.8 (12.2)	69.7 (11.5)	<0.001
Age ≥75 years, %	26.3	37.2	<0.001
Women, %	40.1	44.2	0.002
Mean BMI (SD), kg/m <sup>2</sup>	24.3 (4.3)	27.8 (5.7)	<0.001
Smoking, current/Ex, %	16.0	34.6	<0.001
Alcohol consumption, %	16.4	44.5	<0.001
Diabetes mellitus, %	36.2	22.2	<0.001
History of hypertension, %	68.5	76.3	<0.001
Hypercholesterolaemia, %	13.6	41.6	<0.001
Coronary artery disease, %	28.1	21.6	<0.001
Congestive heart failure, %	15.5	20.0	<0.001
Prior stroke/transient ischemic attack, %	9.1	11.4	0.005
Vascular disease <sup>a</sup> , %	14.1	14.8	0.452
Chronic kidney disease <sup>l</sup> (grade ≥3), %	5.2	10.3	<0.001
Type of AF, %			
Paroxysmal	16.4	27.5	<0.001
Permanent	8.5	12.8	<0.001
Persistent	10.4	14.9	<0.001
New/unclassified	64.6	44.8	<0.001
Care setting at diagnosis, %			
Cardiology	81.7	65.7	<0.001
Geriatrics	0.3	0.4	<0.001
Internal medicine	15.0	18.0	<0.001
Neurology	1.2	1.7	<0.001
Primary care/general practice	1.9	14.2	<0.001
Median time since diagnosis (IQR), weeks	0.70 (0.20–2.00)	1.40 (0.50–3.20)	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASC scores, mean (SD)	2.9 (1.5)	3.2 (1.6)	<0.001
HAS-BLED, mean (SD)	1.5 (0.9)	1.4 (0.9)	0.002

AF, atrial fibrillation; BMI, body mass index; IQR, interquartile range; SD, standard deviation.

<sup>l</sup> Renal function was assessed according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative classification by investigators at baseline.<sup>a</sup> Peripheral artery disease or coronary artery disease.<sup>b</sup> P-values were calculated for India vs all other countries.**Fig. 2.** Antithrombotic treatment in patients enrolled in five sequential cohorts: C1 (2010–2011), C2 (2011–2012), C3 (2013–2014), C4 (2014–2015), and C5 (2015–2016), comparison of India versus world data from the GARFIELD-AF registry. GARFIELD-AF, Global Anticoagulant Registry in the FIELD–Atrial Fibrillation.

prevalent in 15.5% of Indian patients and 20.0% of patients globally ( $P < 0.001$ ). Nearly one-tenth of the patients had a history of transient ischaemic attack or prior stroke in India and all countries. In this registry of NVAF, a very low percentage of patients had RVHD globally (0.1%) and none from India. Prevalence of chronic kidney disease was 5.2% in India and 10.3% globally ( $P < 0.001$ ).

The mean ( $\pm$ SD) CHA<sub>2</sub>DS<sub>2</sub>-VASC scores in India and all countries were 2.9 (1.5) and 3.2 (1.6), respectively ( $P < 0.001$ ). [Figure S2](#) in the [Supplementary Material](#) shows the distribution of patients across the range of CHA<sub>2</sub>DS<sub>2</sub>-VASC scores in India and all countries. Proportionately, there were more Indian patients with low stroke risk (CHA<sub>2</sub>DS<sub>2</sub>-VASC  $\leq 3$ ).



**Fig. 3.** Treatment of newly diagnosed AF by CHA<sub>2</sub>DS<sub>2</sub>-VASc score in (A) India and (B) all countries included in the GARFIELD-AF registry. AF, atrial fibrillation; GARFIELD-AF, Global Anticoagulant Registry in the FIELD–Atrial Fibrillation.

Approximately two-thirds of Indian patients (64.6%) had a new unclassified type of AF diagnosed. The most prevalent form of AF was paroxysmal AF (16.4%) in patients; followed by persistent (10.4%) and permanent AF (8.5%).

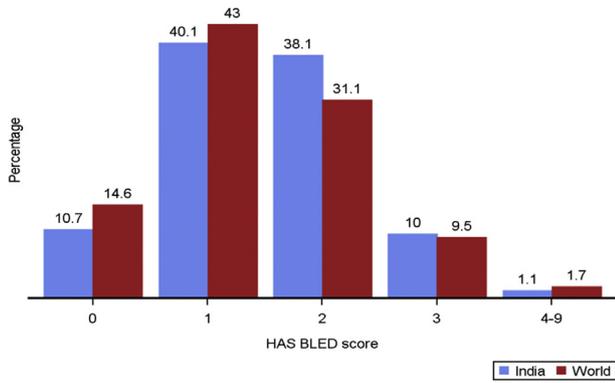
**3.2. Antithrombotic treatment**

Fig. 2 shows the patterns of antithrombotic treatment in each cohort for India and all countries. Overall, patients were enrolled in four sequential cohorts (C): 317 in C2 (2011–2012), 334 in C3 (2013–2014), 242 in C4 (2014–2015), and 495 in C5 (2015–2016). In India and globally, antithrombotic therapy was prescribed to approximately 80% of the patients, whereas approximately 20% of the patients were not prescribed antithrombotic treatment. The most common antithrombotic treatment in India was AP therapy alone, in around 40% of the patients within each cohort. The most

commonly prescribed oral AC for stroke prevention at diagnosis of AF was VKA ± AP therapy (in approximately 40% overall), and only few patients received Novel Oral Anticoagulant (NOAC) ± AP therapy (approximately 6%); this trend did not change appreciably over time in India.

**3.3. Risk profiles and treatment patterns**

Fig. 3 shows the distribution of antithrombotic therapies according to the CHA<sub>2</sub>DS<sub>2</sub>-VASc scores. In India with increasing stroke risk, there was a marked increase in the proportions (from 20% to 50%) of patients receiving oral AC ± AP therapy and fewer patients receiving no therapy (from 31.6% to 6.8%). The proportions of patients receiving AP therapy alone remained consistent despite the increasing risk of stroke.



**Fig. 4.** HAS-BLED scores at baseline in patients with newly diagnosed AF: India versus all countries included in the GARFIELD-AF registry. AF, atrial fibrillation; GARFIELD-AF, Global Anticoagulant Registry in the FIELD–Atrial Fibrillation.

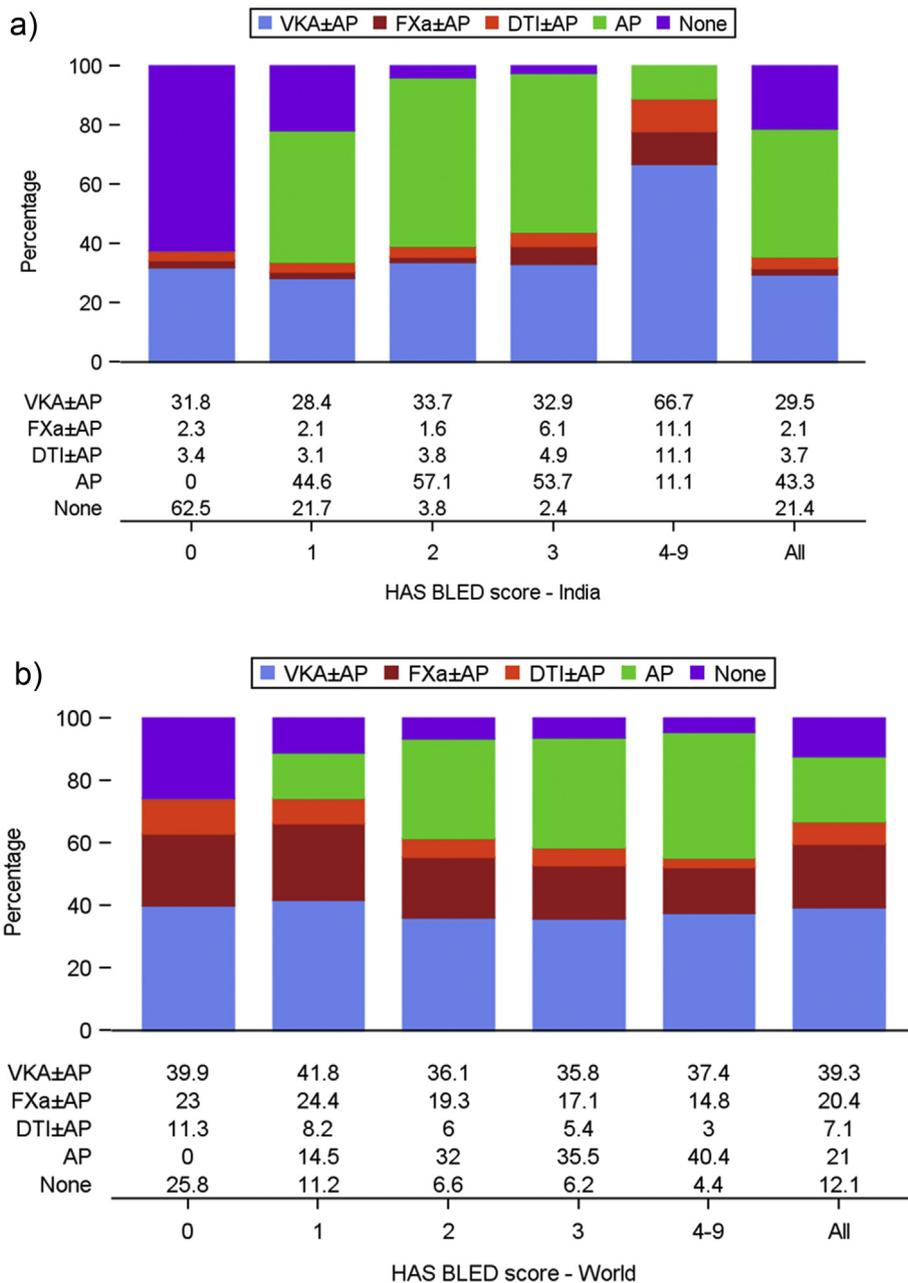
3.4. Thromboembolic and bleeding profiles

Fig. 4 shows the HAS-BLED risk profile of patients in India and all countries. As reflected in the mean HAS-BLED scores, patients in India have a slightly higher risk of bleeding compared with the global average (SD): 1.5 (0.9) vs 1.4 (0.9) ( $P = 0.002$ ).

Fig. 5a shows that Indian patients with highest risk of bleeding are more likely to receive AC ± AP than patients with no risk or low risk of bleeding. An increase in patients receiving NOAC therapy is shown for the highest risk patients (particularly HAS-BLED score of 4–9).

3.5. INR readings and time in therapeutic range

A total of 368 INR readings were analyzed from 407 Indian patients receiving VKA; excluding those who had <3 INR readings. Globally, 158,121 INR readings were analyzed from a total of 20,182



**Fig. 5.** Treatment of newly diagnosed AF by HAS-BLED score in (A) India and (B) all countries included in the GARFIELD-AF registry. AF, atrial fibrillation; GARFIELD-AF, Global Anticoagulant Registry in the FIELD–Atrial Fibrillation.

**Table 2**  
Event rates per 100 person-years for stroke, major bleeding, and all-cause mortality.

	India (N = 1388)		All countries (N = 52,014)		P-value <sup>a</sup>
	Events	Rate (95% CI)	Events	Rate (95% CI)	
All-cause mortality	100	7.68 (6.32–9.35)	2140	4.34 (4.16–4.53)	<0.0001
Cardiovascular death	44	3.38 (2.52–4.54)	799	1.62 (1.51–1.74)	<0.0001
Noncardiovascular death	19	1.46 (0.93–2.29)	793	1.61 (1.50–1.72)	0.6621
Undetermined cause	37	2.84 (2.06–3.92)	548	1.11 (1.02–1.21)	<0.0001
Stroke/systemic embolism	11	0.85 (0.47–1.53)	657	1.34 (1.24–1.45)	0.1230
Major bleeding	4	0.31 (0.12–0.82)	411	0.84 (0.76–0.92)	0.0364
Acute coronary syndrome	5	0.38 (0.16–0.92)	377	0.77 (0.69–0.85)	0.1072

CI, confidence interval.

<sup>a</sup> P-values were calculated for India vs all other countries using Kaplan–Meier analysis with the generalized Wilcoxon test producing the P-value.

patients receiving VKA in total, with the same exclusion. Overall, the median INR value was 1.6 (IQR: 1.3–2.3) in India and 2.3 (IQR 1.8–2.8), globally ( $P < 0.001$ ). Approximately two-thirds of INR readings (64.1%) in India were <2.0 and 25.2% between 2.0 and 3.0 (Supplementary Table S1).

### 3.6. Events rates at 1-year follow-up and clinical outcomes

Event rates per 100 person-years during the first year after diagnosis of AF in GARFIELD-AF are presented in Table 2. Patients from India had markedly higher rates of all-cause mortality compared with all countries [7.68 per 100 person-years (95% CI 6.32–9.35) vs 4.34 (4.16–4.53),  $P < 0.0001$ ]. Rates per 100 person-years of stroke/systemic embolism and major bleeding were lower in India compared with global average in the GARFIELD-AF [0.85 (0.47–1.53) vs. 1.34 (1.24–1.45),  $P = 0.1230$  and 0.31 (0.12–0.82) vs 0.84 (0.76–0.92),  $P = 0.0364$ ]. Overall, the incidence of cardiovascular events was higher in Indian patients. The causes of death during the first year of follow-up are presented in Supplementary Table S2. Of all the cardiovascular causes of death, the most common were sudden or unwitnessed death (27.3%) and congestive heart failure (25%). Among the noncardiovascular causes of death, respiratory failure was the most frequent (26.3%). All stroke events of a known type were primary ischemic (0.79%)

## 4. Discussion

This is the first report of the GARFIELD-AF data of patients from India. The GARFIELD-AF describes an Indian population which is older than those described in previous registries from India.<sup>2,9,10,15–18</sup> None of the patients in the GARFIELD-AF registry had RVHD compared with 40%–60% of patients from other registries from India,<sup>9,10,19,20</sup> thus representing an etiologically different form of AF than has been previously published.

The use of antithrombotic therapy and its monitoring are major challenges for the health-care system in India because of poor INR monitoring and lack of compliance by patients.<sup>9</sup> In India, the most commonly prescribed antithrombotic for stroke prevention (regardless of stroke risk) was AP therapy alone, although AP is no longer recommended by Asian guidelines.<sup>21</sup> The European Society of Cardiology and National Institute for Health and Clinical Excellence guidelines also restrict the use of aspirin and other AP therapies for patients who refuse anticoagulation.<sup>22</sup>

There was, however, a notable increase in VKA prescribing (and marked reduction in patients receiving no antithrombotic therapy) with increasing stroke risk. By contrast, NOACs were seldom prescribed, except for a slight increase in NOAC prescribing in patients with the highest risk of stroke. This could be due to the later approvals of NOACs in India. Possible economic limitations and other factors in India could also be affecting prescribing practices. NOACs are more

expensive in comparison with VKA; however, in the long term, NOACs might prove to be the more cost-effective treatment choice compared with VKA treatment,<sup>23</sup> primarily because of lower monitoring costs and reduced numbers of patients with stroke and SE.<sup>22</sup> Practical guidelines on the management of stroke prevention in AF (SPAF) with NOACs in Asians, including Indians, have been published recently by Dalal et al<sup>24</sup> for the SPAF Academy India experts. Unlike many countries, the GARFIELD-AF registry has not observed any definitive increase in NOACs prescribing in India over time (as shown in Fig. 2). Of note, there are only 4000 cardiologists in India, and the ratio of physicians to cardiac patients is disproportionately low<sup>25</sup> compared with other countries. This could also be a factor influencing antithrombotic therapy prescription patterns in India.

In India, the rate of all-cause mortality was higher than the global rate. This is due to the higher rate of cardiovascular deaths. The higher mortality was predominantly due to sudden death, CHF, myocardial infarction, and stroke. Comorbidities such as hypertension, CAD, and diabetes possibly resulted in higher mortality in AF, and these outcome results were comparable to the published results from the IHRS-AF registry.<sup>9</sup>

## 5. Conclusions

In conclusion, the global GARFIELD-AF registry continues to provide important information on the homogeneity and heterogeneity of baseline characteristics and treatment patterns in patients with newly diagnosed AF. Compared to the rest of the world, Indian patients are younger but associated with more diabetes and CAD. Patients with a higher stroke risk are likely to receive AC therapy with warfarin (compared with global average in the GARFIELD-AF registry), but tend to be underdosed as suggested by the INR. The registry provides evidence of higher mortality in newly diagnosed AF in India as compared with the global average in GARFIELD-AF.

### What is already known?

- The combined prevalence of valvular and NVAF treated with vitamin K antagonists only in tertiary care centers of India.

### What this study adds?

- The prevalence of NVAF in the community and treatment with both vitamin K antagonists and NOACs.
- Treatment with NOACs in nonvalvular AF was missing in the past.

## Conflicts of interests

The authors have read the journal's policy and have the following competing interests: JPSS reports receiving personal fee from Pfizer, AstraZeneca, Novartis, Sanofi, and BMS. The authors VAK, VB, RD, PJ, MC, VV, RM, GV, KC, and JA have none to disclose. KSP reports receiving personal fees from the Thrombosis Research Institute, during the conduct of the study. AJC reports receiving personal fee from Bayer, Boehringer Ingelheim, Pfizer/BMS, and Daiichi Sankyo outside the submitted work. AKK reports receiving grants from Bayer AG, during the conduct of the study; grants and personal fees from Bayer AG; personal fees from Boehringer Ingelheim Pharma, Daiichi Sankyo Europe, Janssen Pharma, Sanofi SA, and Verseon outside the submitted work.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ihj.2018.09.001>.

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