






Antithrombotic treatment patterns and stroke prevention in patients with atrial fibrillation in Turkey: Inferences from GARFIELD-AF registry

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ABSTRACT

Objective: The corner stone of atrial fibrillation therapy includes the prevention of stroke with less adverse effects. The Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF) study provided data to compare treatment strategies in Turkey with other populations and every-day practice of stroke prevention management with complications.

Methods: GARFIELD-AF is a large-scale registry that enrolled 52,014 patients in five sequential cohorts at >1.000 centers in 35 countries. This study was initiated to track the evolution of global anticoagulation practice, and to study the impact of NOAC therapy in AF. A total of 756 patients from 17 enrolling sites in Turkey were in cohort 4 and 5. Treatment strategies at diagnosis initiated by CHA₂DS₂-VASc score, baseline characteristics of patients, treatment according to stroke and bleeding risk profiles, and INR values were analyzed in cohorts. Additionally, event rates during the first year follow up were evaluated.

Results: AF patients in Turkey were mostly seen in young women. Stroke risk according to the CHADS₂ score and CHA₂DS₂-VASc score compared with world data. The mean of risk score values, including HAS-BLED score were lower in Turkey than in the world data. The percentage of patients receiving FXa inhibitor with or without an antiplatelet usage was more than the other drug groups. All-cause mortality was higher in Turkey. Different from world data when HAS-BLED score was above 3, the therapy was mostly changed to antiplatelet drugs in Turkey.

Conclusion: In addition to deficiencies in available treatment options, patient care and clinical outcomes of patients with AF, the data of GARFIELD-AF provide data from Turkey about therapeutic strategies and best practices. (*Anatol J Cardiol* 2019; 21: 272-80)

Keywords: atrial fibrillation, anticoagulation, stroke

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. Atrial fibrillation is responsible for approximately 33% of arrhythmia-related hospitalizations. This arrhythmia is associated with a fivefold increase in the risk of cerebrovascular accident (stroke) and a two-fold increase in the risk of all-cause mortality. AF-related strokes are more serious and are more likely to be fatal or lead to long-term disability than strokes in people without this arrhythmia. Despite this fact, it is possible to reduce the risk of stroke with anticoagulant therapy (1-3). Risk stratification is important when considering anticoagulation, as the risk of stroke in AF patients is dependent on clinical predictors. A risk stratification scheme which is CHA₂DS₂-VASc (Cardiac failure, hypertension, age >75, diabetes, stroke, vascular disease, age 65-74 and sex category-female) to determine stroke risk has been widely used.

Traditional treatment with vitamin K antagonists (VKAs), which needs close monitoring for over or under dosing is giving way to non-vitamin K antagonist oral anticoagulants (NOACs), either direct factor Xa (FXa) inhibitors or direct thrombin inhibitors (DTIs). It remains problematic to use the international normalized ratio (INR) to maintain the intensity of anticoagulation, and less than two-thirds of patients on chronic VKA therapy are within the therapeutic window. Many patients with low stroke risk may be treated with anticoagulants, while too frequently patients at high stroke risk are left with no stroke prevention (4, 5).

The main aim of this registry is to describe real-life practice in the treatment of patients with AF. Stroke and systemic embolization rates were assessed. The objectives of the study also include outcome of patients, including bleeding, fluctuations of INR over time, and therapy persistence (6). In this paper, according to cohorts 4 and 5 in the Garfield-AF registry, we described baseline characteristics of patients in Turkey, and antithrombotic treatment strategies and rates of stroke were given. Additionally, clinical outcomes, including stroke/bleeding complications and incidence of therapy persistence in Turkey were mentioned (7).

Methods

Study population

Patients were enrolled prospectively and consecutively. GARFIELD-AF comprises 52,014 patients recruited over 6.5 years from 1310 enrolling sites in 35 countries. Patients are being enrolled in the registry in five independent, sequential cohorts. We analyzed cohort 4 and 5 in which the patients were included prospectively. Prospective cohort comprised a new diagnosis of non-valvular AF of up to 6 weeks prior to entry into the registry and an investigator-determined risk factor for stroke. Patients are followed up for a minimum of 2 years. Ex-

cluded from the registry were patients with transient AF, secondary to a reversible cause, and patients for whom follow-up was not possible. The study in the first cohort was started in December 2009, and follow-up was ended in the third quarter of 2018. Investigator sites were selected randomly and represent the different care settings in each participating country (office-based practice: hospital departments, including neurology, cardiology, geriatrics, internal medicine and emergency; anticoagulation clinics; and general or family practice). The data was extracted from the GARFIELD-AF registry database on 18 Oct 2017 (8, 9).

A total of 756 patients (Cohort 4: 317; Cohort 5: 439) were enrolled from 17 sites from October 2014 to July 2016 in Turkey. Turkey was included in the Asia population. New onset (36.9%), paroxysmal (28.3%), permanent (28.7%), and persistent AF (9.3%) patients were enrolled in the Turkey population. The data included patients from cohort 4 and 5. GARFIELD-AF show not only the changes in each cohort's treatment to prevent stroke over the follow-up period, but also differences in the time to introduction of NOACs.

Ethics statement

Independent Ethics Committee and hospital-based Institutional Review Board approvals were obtained. The registry has been conducted according to the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonisation-Good Pharmacoepidemiological and Clinical Practice guidelines. Written informed consent is obtained from all the study participants.

Statistical analysis

Descriptive summaries of the baseline characteristics from Cohort 4 and 5 were given. A one-sample Kolmogorov-Smirnov test was used to assess the distribution of data. Data are demonstrated as mean±standard deviation for normally distributed continuous variables (age, BMI, pulse, blood pressure), median (interquartile range, IQR) for skew-distributed continuous variables; frequencies and percentages for categorical variables. The multiple variables (all cause death, stroke, bleeding, congestive heart failure, acute coronary syndrome) were included in the Cox model. Treatment patterns were analyzed by cohort, and by cohort and CHA₂DS₂-VASc or HAS-BLED (uncontrolled hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile international normalized ratios, elderly (>65), drugs/alcohol concomitantly (1 point each)). The Wilcoxon rank-sum (Mann-Whitney U) test was used to test differences in medians. Categorical variables were compared using the Chi-Square test; normally distributed continuous variables were compared using the independent samples Students t test. Comparison of the GARFIELD-AF risk model with existing scores (CHA₂DS₂-VASc and HAS-BLED) were performed using two measures: display of C-index with 95% CI for a measure of discrimination. Both SAS software

V.9.4 (SAS Institute, Cary, NC, USA) and Stata Statistical Software V.14 (StataCorp, College Station, TX, USA) were used to perform statistical analysis.

Data collection

The electronic case report form (eCRF) was designed by Dendrite Clinical Systems Ltd (Henley-on-Thames, UK). Oversight of operations and data management was conducted by the sponsor and coordinating centre (Thrombosis Research Institute-TRI, London, UK), with support from Quintiles (Durham, North Carolina, USA), The University of Birmingham Department of Primary Care Clinical Sciences (Birmingham, UK), Thrombosis Research Group-Brigham and Women's Hospital (Boston, Massachusetts, USA), and AIXIAL (Paris, France).

Results

Baseline characteristics

A total of 756 patients (cohort 4; 317 and cohort 5; 439) were enrolled in the study for about 21.2 months in Turkey. The enrol-

ment period continued during October 2014 to July 2016. In terms of the baseline demographic data, the populations who were enrolled in cohorts 4 and 5 of GARFIELD-AF in Turkey showed some similarities with the global data. Overall, more women (50.5%) were included in the Turkey data ($p=0.001$). Similar with the world data, mean age (SD) at diagnosis was 64.9 ± 13.5 years. The higher percentage of younger patients (43.4% of patients were below 65 years) in Turkey was the main difference in the demographics. The time since AF diagnosis was 1.51 ± 1.62 weeks. The mean CHA_2DS_2 -VASc score in both cohorts were 2.9 ± 1.8 . Care setting specialty is mostly in cardiology setting in Turkey (95.6%). Most of the patients were treated in the public sector. New onset AF was 36.9% and 44.8% of the patients in Turkey and the world data respectively. Baseline characteristics are compared with global values and also p-values were given in Table 1.

The values of systolic/diastolic blood pressure, pulse, body mass index (28.7 ± 5.8 kg/m²) values were similar with world data. The percentages of diabetic patients were also similar. Despite being generally younger, patients in our cohort had a heavier burden of concomitant diseases such as acute coronary syn-

Table 1. Comparison of baseline characteristics of Turkey patients with world

Baseline characteristics		Turkey n=(756)	World n=(52014)	P-value
Sex	Female, n (%)	382 (50.5)	22987 (44.2)	0.001^a
Age at diagnosis (years)	Mean±SD	64.9±13.5	69.7±11.5	0.27 ^b
Age group	<65, n (%)	328 (43.4)	15693 (30.2)	0.001^a
	65-74, n (%)	229 (30.3)	16948 (32.6)	0.024 ^a
	≥75, n (%)	199 (26.3)	19373 (37.2)	0.001^a
BMI (kg/m ²)	Mean±SD	28.7±5.8	27.8±5.7	1.000 ^b
Pulse (bpm)	Mean±SD	94.2±25.0	90.4±26.7	0.587 ^b
Systolic BP (mm Hg)	Mean±SD	124.2±16.7	133.5±19.8	0.253 ^b
Diastolic BP (mm Hg)	Mean±SD	75.5±10.9	79.7±12.9	0.240 ^b
Congestive heart failure	n (%)	216 (28.6)	10397 (20.0)	0.001^a
Coronary artery disease	n (%)	241 (31.9)	11232 (21.6)	0.001^a
Acute coronary syndrome	n (%)	94 (13.4)	4895 (9.5)	0.001^a
Carotid occlusive disease	n (%)	11 (1.7)	1543 (3.0)	0.001^a
Cirrhosis	n (%)	5 (0.7)	296 (0.6)	0.001^a
Diabetes	n (%)	168 (22.2)	11540 (22.2)	0.965 ^a
History of bleeding	n (%)	15 (2.1)	1317 (2.5)	0.001^a
Hypercholesterolemia	n (%)	231 (33.4)	20940 (41.6)	0.001^a
PE or DVT	n (%)	11 (1.5)	1356 (2.6)	0.001^a
Stroke/TIA	n (%)	81 (10.7)	5954 (11.4)	0.001^a
Systemic embolization	n (%)	11 (1.5)	337 (0.7)	0.001^a

^aBy Chi-Square test, ^bby independent samples Students t-test

SD - standard deviation, BMI - body mass index, BP - blood pressure, n - number, TIA - transient ischemic attack, PE - pulmonary embolism, DVT - deep venous thrombosis, bpm - beats per minute, CHF - congestive heart failure

drome, congestive heart failure and coronary artery disease. Additionally, history of systemic embolization was more frequent. Fewer patients in Turkey were smokers and consumers of alcohol. By contrast, a documented history of hypercholesterolemia, carotid occlusive diseases, pulmonary embolism/deep venous thrombosis and transient ischemic attacks (TIAs) or stroke was less frequent in the Turkish cohorts. Less history of bleeding was detected in our cohorts. Left ventricular ejection fraction values were similar in both groups. Mean ejection fraction in Turkish population was 52.7%. Patients with New York Heart Association (NYHA) functional capacity of Class III in cohort 4 were 55.9 % and Class II in cohort 5 was 57.9%.

Comparison of treatment strategies, antithrombotic patterns and stroke prevention

There were also some important differences in treatment strategy between Turkey and the rest of the world (Fig. 1).

Figure 2 shows comparison of prescribing patterns at diagnosis of AF in all cohorts. The percentage of patients receiving FXa inhibitor with or without an antiplatelet usage was more than the other drug groups. Stroke risk according to the CHADS₂ score and CHA₂DS₂-VASc score compared with world data. The mean of risk score values, including HAS-BLED

score were lower in Turkey than the world data (p=0.001, Table 2). Stroke risk of “0” and “5” according to CHADS₂ risk score was higher in the Turkey (p=0.001), also the CHA₂DS₂-VASc risk score of “zero” was higher in the Turkey group, the rest of the percentage of risk scores were similar with the world population (p=0.001) (Fig. 3).

The mean HAS-BLED score was 1.0±0.8. When compared with world data, the percentage of patients who have score 1 was similar in Turkey; however, other scores showed statistically significant difference (Fig. 4).

There were also some important differences in treatment strategies between Turkey and world. VKAs solo or with antiplatelet and antiplatelets were prescribed less in Turkish pa-

Table 2. Comparison of mean score values

		Turkey n=(756)	World n=(52014)	P-value
CHADS ₂ score	Mean±SD	1.7±1.3	1.9 (1.1)	0.001
CHA ₂ DS ₂ -VASc score	Mean±SD	2.9±1.8	3.2 (1.6)	0.001
HAS BLED score	Mean±SD	1.0±0.8	1.4 (0.9)	0.001

SD - standard deviation

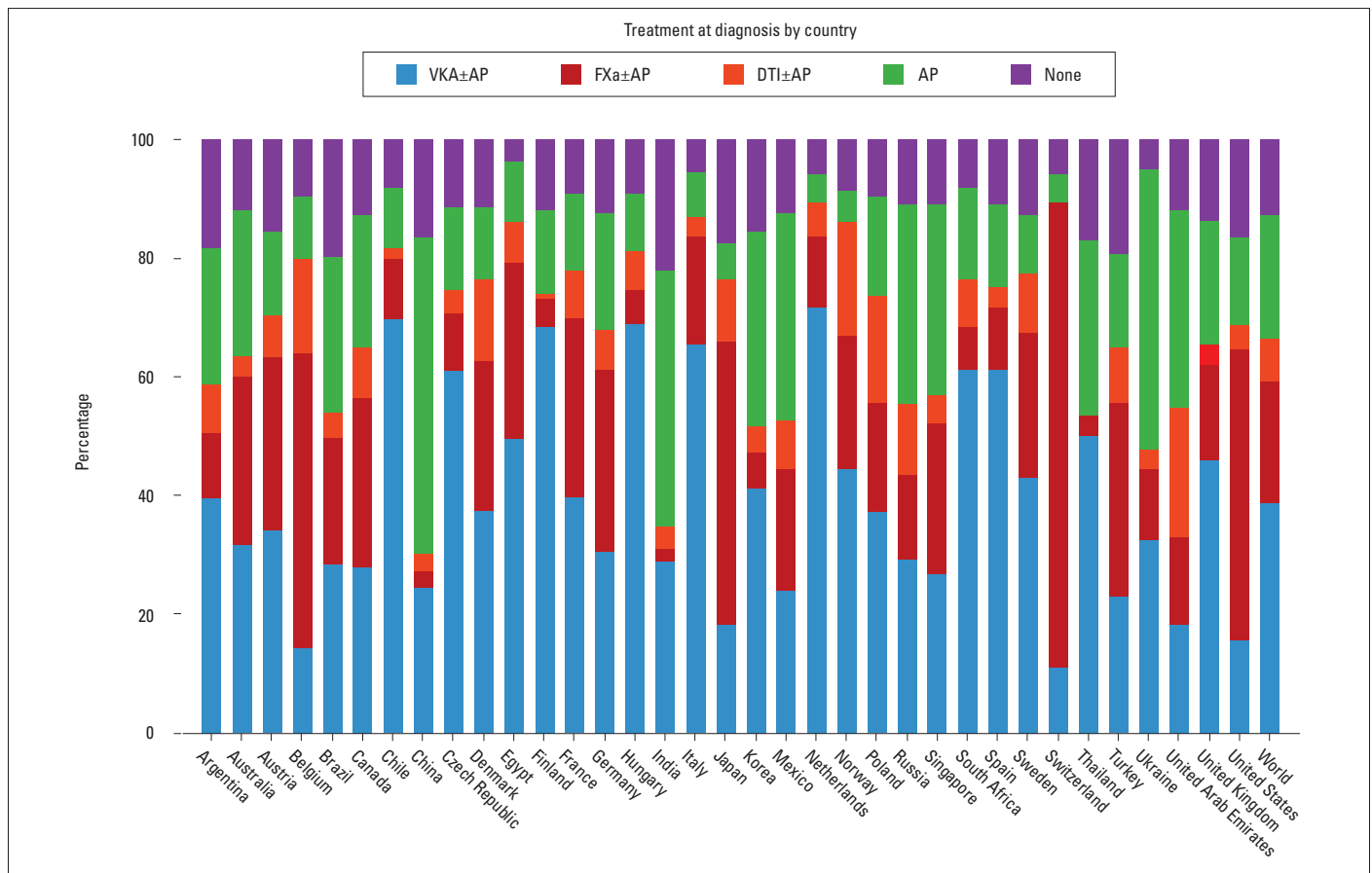


Figure 1. Treatment at diagnosis in different countries

VKA - vitamin K antagonists, AP - antiplatelets, FXa - factor Xa inhibitors, DTI - direct thrombin inhibitors

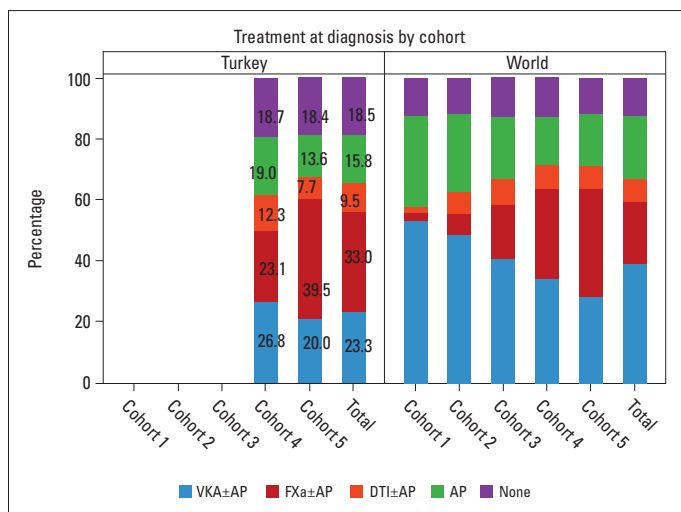


Figure 2. Prescribing patterns at diagnosis
VKA - vitamin K antagonists, AP - antiplatelets, FXa - factor Xa inhibitors, DTI - direct thrombin inhibitors

tients with CHA₂DS₂-VASc risk score zero. FXa inhibitors solo or with antiplatelet were prescribed more frequently in Turkey with low and high risk patients. Additionally, for all risk groups, DTI usage was more in Turkey than the world. By contrast, lack of any antithrombotic treatment seems to differ between two populations especially in very high risk patients (CHA₂DS₂-VASc risk score 6–9). Interestingly, the percentage of these very high risk patients using only antiplatelets was less in Turkey. In the overall data, most of the prescribed medicine consisted of FXa inhibitors with or without antiplatelets in Turkey, while VKAs solo or with antiplatelet usage was more common in world (Fig. 5).

The main reason for the lack of anticoagulant usage in patients with CHA₂DS₂-VASc>=2 was physicians’ choice in Turkey similar with world population. Patient refusal was another frequently seen reason for not to use anticoagulants (Turkey; 9%

vs world; 10.6%). Physicians’ choice of drug was more related with concern over patients’ compliance and falling risk in Turkey (11.1%). All-cause mortality was higher in Turkey. The most common causes of deaths were congestive heart failure and malignancies in both groups of patients. Stroke/systemic embolism were more common in the world than Turkey. While stroke rates and bleeding rates were lower in Turkey, yet mortality was higher (Table 3). One possible explanation may be the higher standard care with high percentage of NOAC and OAC usage.

The data about bleeding and INR were not enough to compare with the world data. HAS-BLED score also had important role in the selection of drug type during AF. The prescription of FXa inhibitors solo or with antiplatelet was more in Turkey than in the world data; even, the score was between 0 and 3. Different from the world data was when HAS-BLED score was above 3, the therapy was mostly changed to antiplatelet drugs in Turkey. Lack of using any anticoagulants or antiplatelet was 25% in Turkey and 4.4% in the world data when HAS-BLED score was between 4 and 9 (Fig. 6).

Discussion

Analysis of the baseline data from GARFIELD-AF registry provided very important findings for stroke prevention strategies in AF patients in Turkey compared to the world wide GARFIELD-AF cohorts. To prevent the burden on the Turkish medical health-care system, which may result from aging and increasing multimorbid population, one must understand the baseline characteristics of AF patients, risk and frequency of treatment strategies in the overall Turkish population. The GARFIELD-AF registry data show how distant everyday clinical practice is from the current guidelines. This large, global, observational study investigated prospectively the changing pattern of antithrombotic therapy

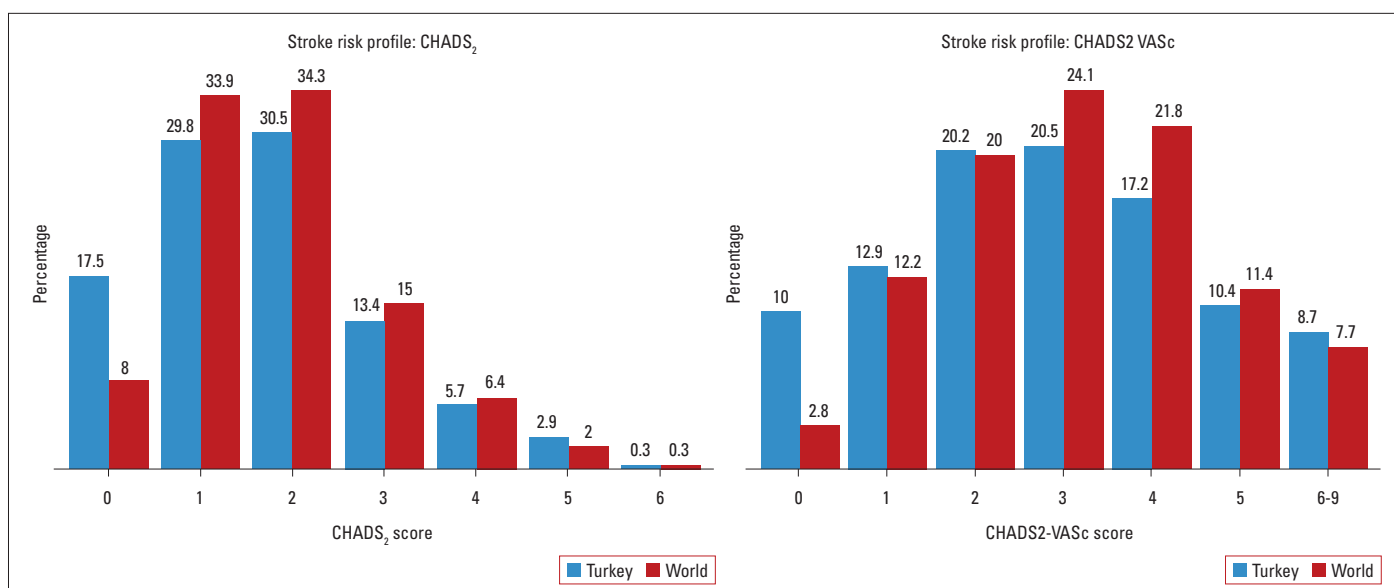


Figure 3. Comparison of CHADS₂ and CHA₂DS₂-VASc scores in Turkey and world population

Table 3. Event rates during the first year of follow-up (rates per 100 person-years)

	Turkey events	Rate (95% CI)	World events	Rate (95% CI)
Death	38	5.59 (4.07 to 7.69)	2140	4.34 (4.16 to 4.53)
Cardiovascular death	24	3.53 (2.37 to 5.27)	799	1.62 (1.51 to 1.74)
Non-cardiovascular death	12	1.77 (1.00 to 3.11)	793	1.61 (1.50 to 1.72)
Undetermined cause	2	0.29 (0.07 to 1.18)	548	1.11 (1.02 to 1.21)
Stroke/SE	8	1.18 (0.59 to 2.36)	657	1.34 (1.24 to 1.45)
Major bleeding	1	0.15 (0.02 to 1.05)	411	0.84 (0.76 to 0.92)
Acute coronary syndrome	6	0.89 (0.40 to 1.97)	377	0.77 (0.69 to 0.85)
New or worsening congestive heart failure	30	4.47 (3.13 to 6.40)	834	1.71 (1.60 to 1.83)

CI - confidence interval, SE - systemic embolism

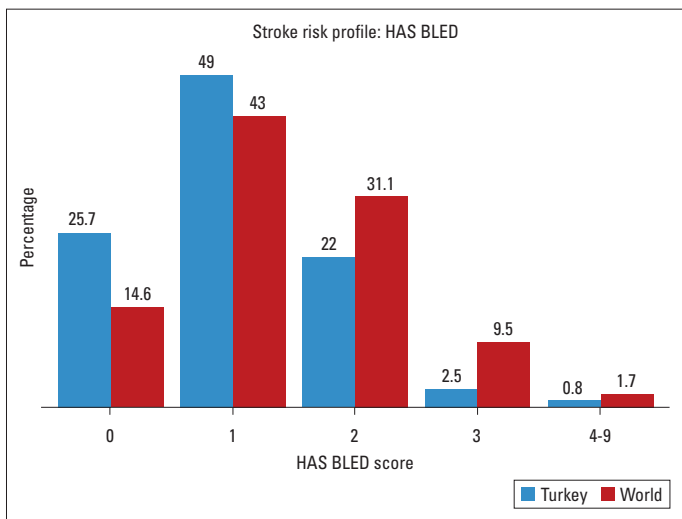


Figure 4. Stroke risk profiles according to HAS-BLED score.

over the past 5 years, before and after the introduction of NO-ACs. Additionally, the study provides information regarding AF demographics, co-morbidities, treatments and outcomes in the developing countries (6, 8).

In this study, Turkey data showed that there were higher percentages of younger patients from Turkey who have been evaluated mostly in cardiology clinics. Despite being generally younger, patients had a burden of concomitant diseases such as acute coronary syndrome, history of systemic embolization, congestive heart failure and coronary artery disease. Oral anticoagulation choices predominantly consist of FXa inhibitors with or without APs, while VKAs solo or with antiplatelet usage was more common in the world data. FXa inhibitors solo or with antiplatelet were prescribed more frequently in Turkey with low and high risk patients. Different from the world data, when HAS-BLED score is above 3, the therapy was mostly changed to antiplatelet drugs in Turkey. Lack of using any anticoagulants or antiplatelet was 25% in Turkey when HAS-BLED score was between 4 and 9.

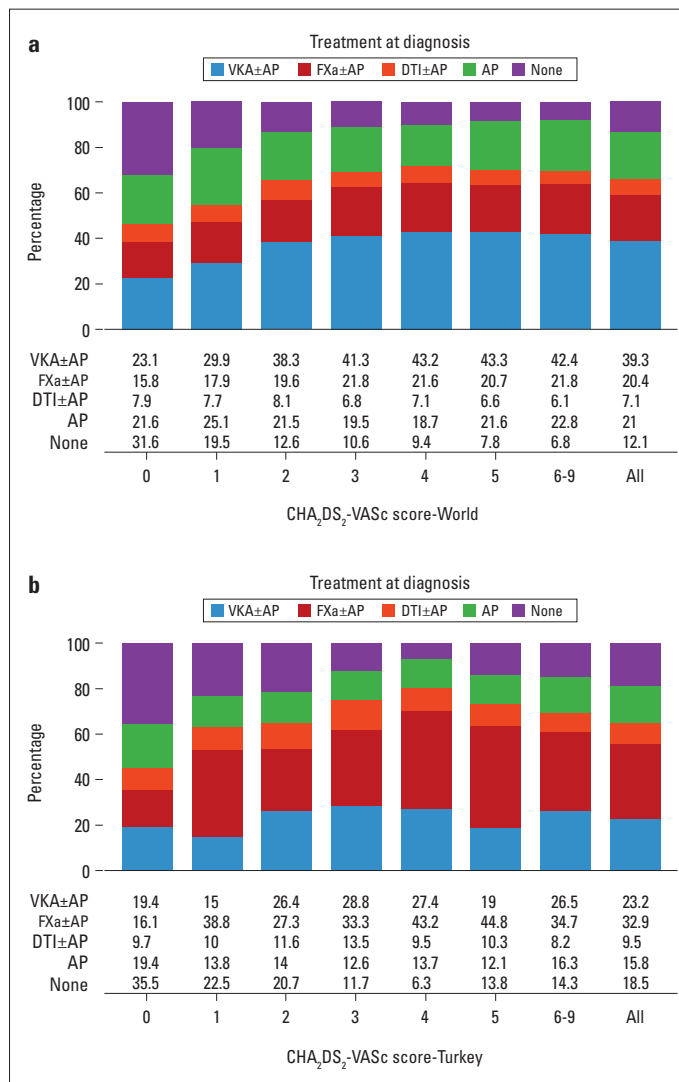


Figure 5. Comparing data from world and Turkey- Treatment at diagnosis according to CHA₂DS₂-VASc risk scores. VKA - vitamin K antagonists, AP - antiplatelets, FXa - factor Xa inhibitors, DTI - direct thrombin inhibitors

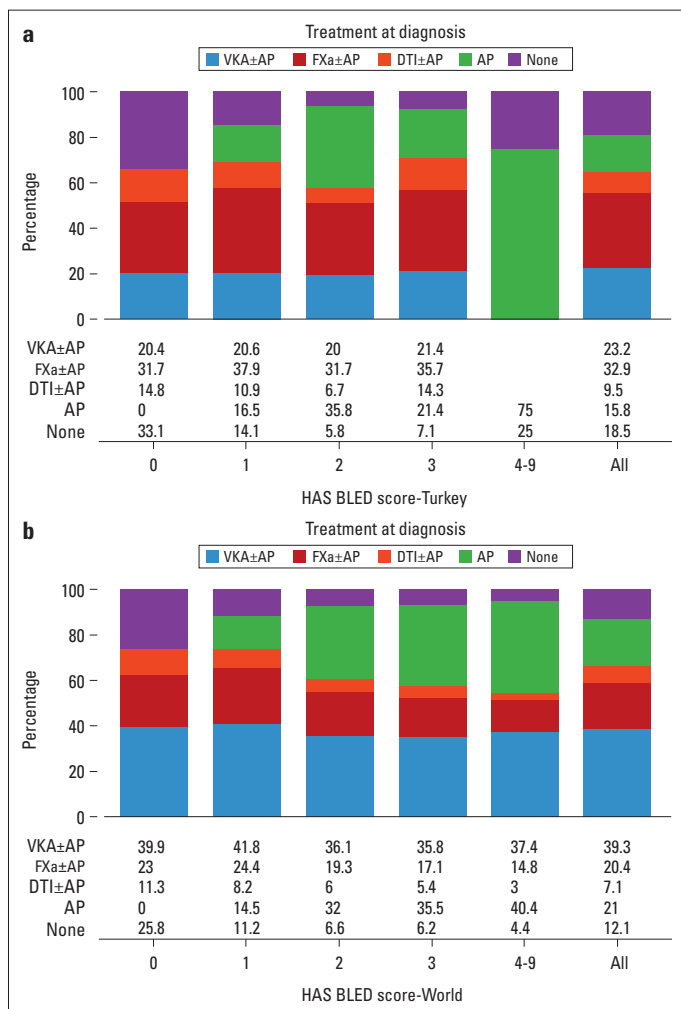


Figure 6. Comparing data from world and Turkey- Treatment at diagnosis according to HAS-BLED scores.

VKA - vitamin K antagonists, AP - antiplatelets, FXa - factor Xa inhibitors, DTI - direct thrombin inhibitors

TRAF (Turkish Atrial Fibrillation cohort) study (7) was conducted over Turkish claims, and from these data, 507136 subjects were analyzed. This study suggested that prevalence and the incidence of non-valvular AF in Turkey were lower than that reported in Western healthcare system. In this study, they found a higher frequency of non-valvular AF in women. This was thought to be related with obesity, metabolic syndrome and cardiovascular diseases in Turkish women over the age of 40 years. Death rate at one year was 7.04% in study group (7). Similarly in GARFIELD-AF, the study the percentage of women patients and patients less than 65 years were higher.

Another multicenter epidemiological study (AFTER) (10) was conducted over 2242 consecutive patients with at least one attack from 17 different tertiary health care centers. While congestive heart failure and hyperlipidemia were higher than other comorbidities in GARFIELD-AF, hypertension was the most common comorbidity in AFTER study consistent with TRAF study. Diabetes mellitus as a comorbidity was similar in both studies. Moreover,

they found that 50% of the patients were on VKAs at the time of the study where this was 23.3% in GARFIELD-AF.

A recently published The New Oral Anticoagulants-TURKEY (NOAC-TURK) study (11) was designed to evaluate current patterns of NOACs treatment in Turkey. A total of 2,862 patients from 21 different centers of Turkey under the treatment NOACs for at least three months were included in the study. They mentioned the importance of adequate anticoagulation management according to CHA₂DS₂-VASC and HAS-BLED scores to provide more benefit and less adverse effect. Stroke risk calculated with CHA₂DS₂-VASC score was lower (2.9±1.8) in Turkey than in the global data. However, CHA₂DS₂-VASC score had similar values in other studies such as NOAC-TURK (3.3±1.6) or ReAl-life Multicenter Survey Evaluating Stroke prevention strategies in non-valvular atrial fibrillation (RAMSES) study (12) (3.3±1.6) that evaluated Turkey population. In the RAMSES study, anti-thrombotic therapy use was 91% and 72% of the patients received OAC therapy. Overuse of OAC therapy was a problem; they detected that 72% of the patients with a CHA₂DS₂-VASC score of 0 were on OAC therapy. GARFIELD-AF registry showed that NOACs were preferred over VKAs for stroke prophylaxis in Turkish patients with NVAf. In this study, Turkish people with lower risk groups were found to be prescribed FXa inhibitors more often than world countries. Overuse of NOACs is also a problem where it is 23.7% with or without antiplatelet in Turkey in patients with CHA₂DS₂-VASC score of 0. However, in the presence of high stroke risk, the percentages of anticoagulated patients were similar with other countries. The overall anticoagulant use for all CHA₂DS₂-VASC groups was 65.6% in Turkey and 66.8% in the world. The most preferred OAC was VKAs in ORBIT-AF and GARFIELD trials (world data), whereas NOAC use was more common in the GLORIA-AF trial (8, 13, 14). Previous studies have reported that the limitations of warfarin therapy may have prevented physicians in Turkey from prescribing OAC therapy (10). In GARFIELD-AF physicians' choice had an effect of 32.3% in the selection of therapy. The rate of prescribing OACs was 60% in the GARFIELD study, 60.9% in the Euro Heart Survey, and 71.4% in the Central Registry of the German Competence Network on Atrial Fibrillation (6, 15, 16). GARFIELD-AF showed that, for stroke prophylaxis in NVAf patients in Turkey, NOACs are preferred over VKAs. Besides widely use of NOACs, the 27.1% of patients who have CHA₂DS₂-VASC > 2 still received no OAC therapy and the results were consistent with the RAMSES study. Concerns about bleeding events may probably lead physicians to overprescribe antiplatelet agents. In GARFIELD-AF, patients with HAS-BLED score 4 to 9, antiplatelet prescription was 75%. The current data in recent registries show that the risk of major bleeding does not differ between aspirin and VKAs (17). GARFIELD-AF showed that major bleeding rate during the first year of follow-up were 0.47 (event rate/100 person-years) in patients with CHA₂DS₂-VASC risk score >4 and mortality rate was higher in this group. Death from cardiovascular causes was mostly from congestive heart failure in Turkey (54.17%).

Despite younger age, high mortality rates can be explained by more patients with heart failure, coronary artery disease and stroke. Additionally, most of the patients seem to be enrolled during hospitalization for an index event rather than during outpatient visits in Turkey. Bassand et al. (18) evaluated risk factors for death, stroke and bleeding in 28.628 patients from the GARFIELD-AF registry and similarly they found the cardiovascular causes of death was mostly from congestive heart failure. This registry proved that primary ischemic stroke not including systemic embolism was the frequent cause of stroke.

Further analyses are required to assess the impact of changes in treatment and compliance over time. As Turkey data about bleeding complications and stroke events INR value follow-up were limited or missing, it is hard to compare the types of stroke during the follow up and also severity of bleeding with world data. We concluded from the missing data about stroke events that not only cardiologist evaluation is enough for diagnosing stroke events but also neurologist should be aware of stroke events and consult the cardiologist. Follow-up data from GARFIELD-AF may provide interesting and valuable insights into the stroke prevention management.

Conclusion

The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF Registry) provides international data about therapeutic strategies and best practices for anticoagulation in stroke prevention among those with AF. The Turkish cohort included a relatively larger percentage of young patients, yet despite being younger, the patients had a notable burden of concomitant diseases. FXa inhibitors alone or with antiplatelet were prescribed more frequently in Turkey with low- and high-risk patients. Newer oral anticoagulant (NOAC) therapy was replaced with antiplatelets when the bleeding risk was higher. We need to evaluate regional differences to provide adequate therapy and improve clinical outcomes.

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