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Original Article

Anticoagulant selection in relation to the SAMe-TT_2R_2 score in patients with atrial fibrillation: The GLORIA-AF registry

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ABSTRACT

Aim: The SAMe-TT_2R_2 score helps identify patients with atrial fibrillation (AF) likely to have poor anticoagulation control during anticoagulation with vitamin K antagonists (VKA) and those with scores >2 might be better managed with a target-specific oral anticoagulant (NOAC). We hypothesized that in clinical practice, VKAs may be prescribed less frequently to patients with AF and SAMe-TT_2R_2 scores >2 than to patients with lower scores.

Methods and results: We analyzed the Phase III dataset of the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF), a large, global, prospective global registry of patients with newly diagnosed AF and ≥1 stroke risk factor. We compared baseline clinical characteristics and antithrombotic prescriptions to determine the probability of the VKA prescription among anticoagulated patients with the baseline SAMe-TT_2R_2 score >2 and ≤ 2. Among 17,465 anticoagulated patients with AF, 4,828 (27.6%) patients were prescribed VKA and 12,637 (72.4%) patients an NOAC: 11,884 (68.0%) patients had SAMe-TT_2R_2 scores 0-2 and 5,581 (32.0%) patients had scores >2. The proportion of patients prescribed VKA was 28.0% among patients with SAMe-TT_2R_2 scores >2 and 27.5% in those with scores ≤2.

Conclusions: The lack of a clear association between the SAMe-TT_2R_2 score and anticoagulant selection may be attributed to the relative efficacy and safety profiles between NOACs and VKAs as well as to the absence of trial evidence that an SAMe-TT_2R_2-guided strategy for the selection of the type of anticoagulation in NVAF patients has an impact on clinical outcomes of efficacy and safety. The latter hypothesis is currently being tested in a randomized controlled trial.

Clinical trial registration: URL: https://www.clinicaltrials.gov//Unique identifier: NCT01937377, NCT01468701, and NCT01671007.

1. Introduction

For many decades, vitamin-K antagonists (VKA) were the only anticoagulant choice for patients with non-valvular atrial fibrillation (NVAF), which remains one of the major etiologies of ischemic stroke[1]. The achievement and maintenance of a therapeutic international normalized ratio (INR) in VKA-treated patients can be

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Table 1
Baseline characteristics and their standardized differences by baseline SAMe-TT_2R_2 score for eligible anticoagulated patients in Phase III

	SAMe-$TT_2R_2 \le 2$	SAMe-$TT_2R_2 > 2$	Standardized difference
	n = 11,884	n = 5,581	
Demographics			
Age, mean ± SD, years	72.4 ± 9.4	68.3 ± 11.4	−0.3920
Female gender	4,936 (41.5%)	2,915 (52.2%)	0.2156
Race			
White	11,351 (95.5%)	1,546 (27.7%)	−1.9450
Asian	330 (2.8%)	2,181 (39.1%)	0.9972
Black/African American	20 (0.2%)	300 (5.4%)	0.3213
Insurance status			
Private	1,717 (14.4%)	835 (15.0%)	0.0145
Statutory/federal insurance	8,871 (74.6%)	4,002 (71.7%)	−0.0664
Self-pay/no coverage	429 (3.6%)	416 (7.5%)	0.1687
Comorbidities			
Body mass index (kg/m^2), mean ± SD	29.39 ± 6.41	27.76 ± 6.40	−0.2553
Dyslipidemia	5,077 (42.7%)	2,040 (36.6%)	−0.1264
Hepatic disease	91 (0.8%)	142 (2.5%)	0.1398
Congestive heart failure	2,424 (20.4%)	1,437 (25.7%)	0.1273
NYHA I	203 (8.4%)	138 (9.6%)	0.0430
NYHA II	1,325 (54.7%)	759 (52.8%)	−0.0370
NYHA III	520 (21.5%)	316 (22.0%)	0.0131
NYHA IV	45 (1.9%)	60 (4.2%)	0.1359
Ejection fraction ≤40%	973 (40.1%)	596 (41.5%)	0.0272
Diabetes mellitus	2,574 (21.7%)	1586 (28.4%)	0.1565
Arterial hypertension	8,950 (75.3%)	4,331 (77.6%)	0.0540
Abnormal kidney function	181 (1.5%)	97 (1.7%)	0.0170
Previous stroke	1,135 (9.6%)	656 (11.8%)	0.0715
Transient ischemic attack	651 (5.5%)	185 (3.3%)	−0.1057
Pulmonary embolism	70 (0.6%)	39 (0.7%)	0.0137
Deep venous thrombosis	168 (1.4%)	53 (0.9%)	−0.0430
Non-CNS arterial embolism	49 (0.4%)	20 (0.4%)	−0.0087
Smoking			
Nonsmoker	6,821 (57.4%)	3,078 (55.2%)	−0.0453
Current smoker	180 (1.5%)	1,369 (24.5%)	0.7277
Past smoker	4,482 (37.7%)	985 (17.6%)	−0.4602
Alcohol abuse (≥8 Units/week)	883 (7.4%)	357 (6.4%)	−0.0407
Coronary artery disease	2,052 (17.3%)	998 (17.9%)	0.0162
Myocardial infarction	1,127 (9.5%)	476 (8.5%)	−0.0333
Periphery arterial disease	348 (2.9%)	165 (3.0%)	0.0017
Prior bleeding	610 (5.1%)	252 (4.5%)	−0.0288
Cancer	1392 (11.7%)	404 (7.2%)	−0.1532
Creatinine clearance (ml/min), mean ± SD	86.0 ± 200.5	80.3 ± 39.9	−0.0394
Creatinine clearance <15 ml/min	70 (0.6%)	42 (0.8%)	0.0200
Creatinine clearance 15 to <30 ml/min	188 (1.6%)	122 (2.2%)	0.0444
Creatinine clearance 30 to <50 ml/min	1,235 (10.4%)	722 (12.9%)	0.0793
Creatinine clearance 50 to <80 ml/min	3,854 (32.4%)	1,723 (30.9%)	−0.0335
Creatinine clearance ≥80 ml/min	4,215 (35.5%)	1,893 (33.9%)	−0.0326
Type of NVAF			
Paroxysmal	6,204 (52.2%)	3,115 (55.8%)	0.0725
Persistent	4,354 (36.6%)	1,947 (34.9%)	−0.0365
Permanent	1,326 (11.2%)	519 (9.3%)	−0.0614
Categorization of NVAF			
Symptomatic	3,475 (29.2%)	1,930 (34.6%)	0.1148
Minimally symptomatic	3,930 (33.1%)	1,893 (33.9%)	0.0180
Asymptomatic	4,479 (37.7%)	1,758 (31.5%)	−0.1304
Type of site			
GP/primary care	600 (5.0%)	337 (6.0%)	0.0433
Specialist office	3,856 (32.4%)	1,341 (24.0%)	−0.1878
Community hospital	3,679 (31.0%)	1,731 (31.0%)	0.0013
University hospital	3,439 (28.9%)	1,910 (34.2%)	0.1139
Outpatient health care center	184 (1.5%)	79 (1.4%)	−0.0110
Anticoagulation clinic	74 (0.6%)	28 (0.5%)	−0.0162
Physician specialty			
GP/PCP/Geriatrician	651 (5.5%)	148 (2.7%)	−0.1435
Cardiologist	9,702 (81.6%)	5,077 (91.0%)	0.2739
Internist	594 (5.0%)	144 (2.6%)	−0.1269
Neurologist	320 (2.7%)	133 (2.4%)	−0.0197
$CHADS_2$ score, mean ± SD	1.9 ± 1.2	1.9 ± 1.1	0.0222
$CHADS_2$ score = 0	964 (8.1%)	394 (7.1%)	−0.0397
$CHADS_2$ score = 1	4,051 (34.1%)	1,809 (32.4%)	−0.0355
$CHADS_2$ score ≥ 2	6,868 (57.8%)	3,378 (60.5%)	0.0557
CHA_2DS_2-VASc score, mean ± SD	3.2 ± 1.5	3.2 ± 1.5	−0.0364
CHA_2DS_2-VASc score = 1	1,408 (11.8%)	718 (12.9%)	0.0309
CHA_2DS_2-VASc score ≥ 2	10,476 (88.2%)	4,863 (87.1%)	−0.0309
HAS-BLED, mean ± SD	1.3 ± 0.8	1.2 ± 0.9	−0.1571

Table 1 (*continued*)

	$SAMe\text{-}TT_2R_2 \leq 2$	$SAMe\text{-}TT_2R_2 > 2$	Standardized difference
	n = 11,884	n = 5,581	
HAS-BLED <3	9,846 (82.9%)	4,616 (82.7%)	−0.0038
HAS-BLED ≥3	898 (7.6%)	381 (6.8%)	−0.0282
Treatment with amiodarone	825 (6.9%)	1640 (29.4%)	0.6085
Antithrombotic prescription			
VKA alone	2,795 (23.5%)	1,291 (23.1%)	−0.0092
VKA + antiplatelets	470 (4.0%)	272 (4.9%)	0.0447
NOAC alone	7,434 (62.6%)	3,486 (62.5%)	−0.0019
NOAC + antiplatelets	1,185 (10.0%)	532 (9.5%)	−0.0148

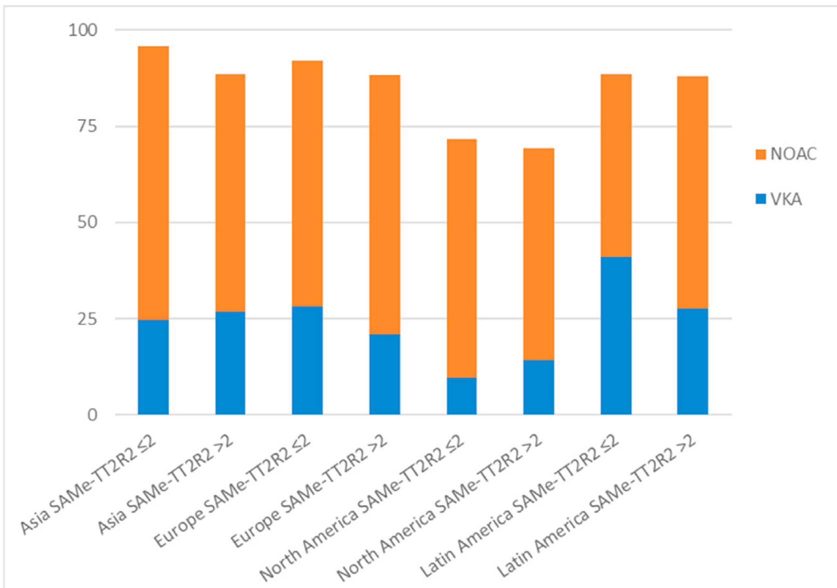

Figure 1. Proportion of patients treated with VKA and NOAC by baseline $SAMe\text{-}TT_2R_2$ score and region.

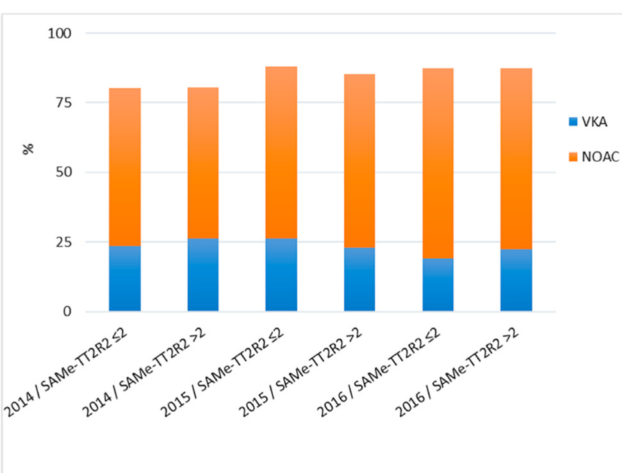

Figure 2. Proportion of patients treated with VKA and NOAC by baseline SAMe-TT2R2 score and enrollment year.

challenging because of numerous VKA-related limitations such as narrow therapeutic window, need for frequent INR measurements with consequent dose adjustments, and food-drug and drug-drug interactions[2].

Common clinical factors determine if a patient can achieve effective and safe anticoagulation control on VKAs. The $SAMe\text{-}TT_2R_2$ score was developed to help identify those at high-risk for poor anticoagulation control and thus higher risk of stroke or peripheral embolism as estimated by the time in therapeutic INR range (TTR). The $SAMe\text{-}TT_2R_2$ score consists of the following: Sex (female), Age (<60 years); Medical history (≥2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic, or renal disease); Treatment (interacting drugs like amiodarone for rhythm control) [all 1 point]; current Tobacco use (2 points); and Race (2 points for non-Caucasian)[3]. Patients with a $SAMe\text{-}TT_2R_2$ score >2 could best avoid a “trial of VKA” and start directly with a non-vitamin-K-antagonist oral anticoagulant (NOAC).

The recent 2020 Guidelines of the European Society of Cardiology about the management of atrial fibrillation suggest that the $SAMe\text{-}TT_2R_2$ score could be used to aid decision-making: patients with a score of >2 points are prone to low TTR while on VKA and can be monitored more closely with more frequent INR measurements or can be supported with more intensive education or counselling to improve TTR. Alternatively, if there are concerns, they may skip a “trial of VKA” and start directly with a NOAC[4].

In this context, we hypothesized that VKAs may be less frequently prescribed in patients with NVAF and a $SAMe\text{-}TT_2R_2$ score of >2 as compared to patients with a score of 0-2. We tested this hypothesis in a large, contemporary, prospective, global registry of newly diagnosed NVAF patients with ≥1 stroke risk factors.

Table 2
Log-binomial regression analysis for the prediction of VKA prescription. Only patients who were anticoagulated were included in the analysis

	Patients N	VKA use N (%)	NOAC use N (%)	Univariate analysis	Multivariate analysis
				Relative risk (95% CI) for prescription of VKA use	Relative risk (95% CI) for prescription of VKA use
Baseline SAMe-TT$_2$R$_2$					
Score >2	5581	1563 (28.0)	4018 (72.0)	1.019 (0.968, 1.073)	0.907 (0.856, 0.961)
Score ≤2	11884	3265 (27.5)	8619 (72.5)	1.0 (ref)	1.0 (ref)
Region					
Asia	2609	798 (30.6)	1811 (69.4)	1.022 (0.957, 1.091)	1.138 (1.054, 1.226)
Europe	9182	2747 (29.9)	6435 (70.1)	1.0 (ref)	1.0 (ref)
North America	4261	734 (17.2)	3527 (82.8)	0.576 (0.535, 0.619)	0.604 (0.560, 0.650)
Latin America	1413	549 (38.9)	864 (61.1)	1.299 (1.206, 1.395)	1.355 (1.254, 1.461)
Type of AF					
Paroxysmal	9319	2179 (23.4)	7140 (76.6)	1.0 (ref)	1.0 (ref)
Persistent	6301	1968 (31.2)	4333 (68.8)	1.336 (1.268, 1.407)	1.271 (1.207, 1.339)
Permanent	1845	681 (36.9)	1164 (63.1)	1.579 (1.470, 1.692)	1.372 (1.276, 1.472)
BMI class					
<18.5	199	58 (29.1)	141 (70.9)	1.015 (0.802, 1.250)	1.035 (0.820, 1.269)
18.5−<25	4484	1288 (28.7)	3196 (71.3)	1.0 (ref)	1.0 (ref)
25−<30/Missing	6807	1907 (28.0)	4900 (72.0)	0.975 (0.919, 1.036)	0.992 (0.934, 1.053)
30−<35	3559	954 (26.8)	2605 (73.2)	0.933 (0.869, 1.002)	0.982 (0.914, 1.055)
≥35	2416	621 (25.7)	1795 (74.3)	0.895 (0.824, 0.971)	1.031 (0.948, 1.119)
Prior bleeding					
Yes	862	248 (28.8)	614 (71.2)	1.043 (0.933, 1.158)	1.044 (0.936, 1.156)
No/Unknown	16603	4580 (27.6)	12023 (72.4)	1.0 (ref)	1.0 (ref)
Alcohol abuse					
Yes(≥8U/week)	1240	300 (24.2)	940 (75.8)	0.867 (0.781, 0.957)	0.881 (0.795, 0.972)
No(<8U/week/Unknown)	16225	4528 (27.9)	11697 (72.1)	1.0 (ref)	1.0 (ref)
Cancer					
Yes	1796	478 (26.6)	1318 (73.4)	0.959 (0.883, 1.038)	1.050 (0.968, 1.135)
No/Unknown	15669	4350 (27.8)	11319 (72.2)	1.0 (ref)	1.0 (ref)
Medical treatment reimbursed by					
Self−pay/No coverage	845	221 (26.2)	624 (73.8)	0.944 (0.837, 1.056)	0.785 (0.696, 0.880)
Not self−pay/Unknown	16620	4607 (27.7)	12013 (72.3)	1.0 (ref)	1.0 (ref)

2. Methods

The Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) was designed to generate evidence on patients with recently diagnosed NVAF treated in routine clinical practice. The aim of this multinational, multicenter, prospective, noninterventional registry is to provide long-term effectiveness and safety data on NOAC and VKA for stroke prevention in patients with NVAF in nearly 50 countries[5].

The design of GLORIA-AF, a global, noninterventional registry program with 3 phases, has been described in detail previously[5]. Phase III consists of a cross-sectional and comparative analyses part involving a 3-year follow-up of all patients independent of antithrombotic therapy. Ethical approvals were obtained from the Institutional Review Boards as required at participating sites. The GLORIA-AF study is listed at Clinicaltrials.gov (Nos. NCT01937377, NCT01468701, and NCT01671007).

The phase III of GLORIA-AF enrolled adult patients with newly diagnosed NVAF (i.e., NVAF diagnosed within 3 months of the baseline visit; Latin America <4.5 months) and a CHA$_2$DS$_2$-VASc score of ≥1 between 2014 and 2016. Patients with mechanical heart valves, prior VKA therapy for >60 days, life-expectancy ≤1 year at recruitment, a comorbidity other than NVAF for which the chronic use of VKAs is indicated and NVAF due to a generally reversible cause were excluded. The CHADS$_2$ and CHA$_2$DS$_2$-VASc scores were used to assess the thromboembolic risk of the patients. The HAS-BLED bleeding score was used to assess the bleeding risk[6]. Patients were recruited from outpatient settings from university hospitals, community hospitals, specialist offices, and general practice offices. Sites were chosen to reflect physicians who typically identify and manage patients with newly diagnosed NVAF cases in each participating country.

2.1. Data collection and quality control

All clinical data were collected and processed using a web-based external vendor managed Infosario Outcome EDC® system to ensure that data were complete, accurate, internally consistent, logical, and in compliance with the requirements of the protocol. Study data were entered into the EDC system by the study staff using a secured network and the study physician electronically signed the case report forms to confirm accuracy and completeness of the entered information. Extensive data quality standards were in place to address any systematic data issues identified.

2.2. Statistical Analysis

Baseline data were summarized descriptively. Continuous variables were reported as mean and standard deviation. Categorical variables were reported as absolute frequencies and percentages. SAMe-TT$_2$R$_2$ scores were derived from the patient characteristics at baseline. Baseline characteristics for patients treated with oral anticoagulants were described based on the SAMe-TT$_2$R$_2$ score (>2 versus ≤2). Rather than relying on statistical significance testing (p-values), emphasis was put on estimation using confidence intervals (CI) to measure effect size and to gauge precision, given that P-values confine the interpretation of the results as significant and non-significant, whereas CI move the interpretation of the results to the effect size and its range of plausible values given by the data under study. P-values are dependent on sample size, however, standardized differences are independent of sample size and it is an intuitive index to compare baseline characteristics. Interpretation was based on the value of standardized difference. The focus will be on the variables with highest standardized differences, while differences ≤10% in absolute value will be considered as balanced between the groups[7].

We performed a log-binomial regression analysis to estimate risk ratios in the cohort of patients who were anticoagulated to identify the association between the SAMe-TT_2R_2 score and prescription of VKA. We use the term “probability ratio” rather than “risk ratio” as our measure describes drug use rather than adverse outcomes. Both univariate and multivariate log-binomial regression analyses were performed to evaluate the crude as well as the adjusted probability ratios together with 95% CIs. The variables included in this analysis were the SAMe-TT_2R_2 score and other covariates, which are not SAMe-TT_2R_2 components, as follows: the type of AF (paroxysmal vs. persistent vs. permanent), body mass index class, reimbursement status, geographical region (Asia, Europe, North America, and Latin America), other comorbidities [prior bleeding and cancer], and alcohol abuse. No covariate selection procedure was employed, rather all variables that might have an impact on the prescription pattern were included in the model. Statistical analyses were performed with the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

The baseline characteristics and their standardized differences by baseline SAMe-TT_2R_2 score are summarized in Table 1. Among 21,597 patients who were enrolled in 38 countries, there were 21,248 who were eligible for the analysis. Of these, 17,465 (82.2%) were treated with oral anticoagulation (45.0% women) and were included in the analysis. Among OAC-treated patients, 4,828 (27.6%) received VKA and 12,637 (72.4%) received NOAC. Out of 17,465 OAC-treated patients, 11,884 (68.0%) patients had an SAMe-TT_2R_2 score of ≤2 and 5,581 (32.0%) with a score of >2.

Patients with an SAMe-TT_2R_2 score of ≤2 were older (mean age (±SD) 72.4 ± 9.4 vs 68.3 ± 11.4) and were more often men (58.5% vs 47.8%) as compared to those with SAMe-TT_2R_2 score >2. The mean $CHADS_2$ score was 1.9 ± 1.1 and the mean CHA_2DS_2-VASc was 3.2 ± 1.5 in both SAMe-TT_2R_2 groups. The mean HAS-BLED was 1.3 ± 0.8 in patients with the SAMe-TT_2R_2 score of ≤2 and 1.2 ± 0.9 for patients with SAMe-TT_2R_2 score of >2.

3.1. Clinical risk profile and SAMe-TT_2R_2 score

Patients from Europe accounted for 60.8% of those with an SAMe-TT_2R_2 score of ≤2; 38.9% and 35.0% of patients with an SAMe-TT_2R_2 score >2 were from Asia and Europe, respectively. Fewer patients in the SAMe-TT_2R_2 score of ≤2 underwent NVAF ablation (0.9% vs 4.2%) and there was a higher prevalence of hyperlipidemia (42.7% vs 36.6%) and cancer (11.7% vs 7.2%) than those with a score of >2. There was high prevalence of congestive heart failure (25.7% vs 20.4%), diabetes mellitus (28.4% vs 21.7%), hepatic disease (2.5% vs 0.8%), and chronic kidney disease (27.1% vs 22.0%) in an SAMe-TT_2R_2 score >2 versus those with an SAMe-TT_2R_2 score ≤2.

3.2. SAMe-TT_2R_2 score and VKA use: Regional differences

The proportion of patients treated with VKAs was 28.0% with an SAMe-TT_2R_2 score of >2 and 27.5% with a score of ≤2. Patients from Europe and Latin America who had an SAMe-TT_2R_2 score >2 were less often prescribed VKA when compared with an SAMe-TT_2R_2 score ≤2 (21.0% vs. 28.2%, for Europe, standardized difference: −0.169; 27.8% vs. 41.1%, for Latin America, standardized difference: −0.283). Patients from North America with an SAMe-TT_2R_2 score >2 were more often prescribed VKA when compared with those with an SAMe-TT_2R_2 score ≤2 (14.3% vs. 9.6%, respectively, standardized difference: −0.147) (Fig. 1).

3.3. SAMe-TT_2R_2 score and VKA use: Enrolment year

There were no important differences in the prescription rate of VKAs between patients with an SAMe-TT_2R_2 score >2 versus those with a score of ≤2 with regard to the enrollment year (26.4% vs. 23.5%, for 2014, standardized difference: 0.067; 23.0% vs. 26.4%, for 2015, standardized difference: −0.079; 22.3% vs. 19.1%, for 2016, standardized difference: 0.079) (Fig. 2).

3.4. Multivariable analysis

In the multivariable analysis, patients with an SAMe-TT_2R_2 score >2 were less frequently prescribed VKA when compared with patients with a score ≤2 (adjusted probability ratio 0.907; 95%CI: (0.856 and 0.961). Factors associated with an increased prescription of VKA use were the geographical region and type of NVAF (Table 2).

4. Discussion

This is the first global study to assess the association between the SAMe-TT_2R_2 score and the type of oral anticoagulant use in a large, prospective, multinational cohort of nonvalvular AF patients anticoagulated in routine clinical practice. We found no clear association between the SAMe-TT_2R_2 score and anticoagulant selection.

The lack of clear association between the SAMe-TT_2R_2 score and anticoagulant selection may indicate that other factors, not captured entirely by the SAMe-TT_2R_2 likely have more influence on prescriptive choices in clinical practice. Such a factor may be the safety and efficacy profile of VKAs and NOACs. There is solid evidence from randomized controlled trials as well as from real-world studies, showing that NOACs are safer and at least as effective as VKAs[8-10]. Accordingly, current clinical practice guidelines recommend NOACs in preference to VKA[11-13]. Because of overwhelming evidence favoring NOACs over VKAs, treating physicians may have largely adopted the related recommendations and prefer to start directly with an NOAC among NOAC-eligible NVAF patients, even in patients with a favorable SAMe-TT_2R_2 score who would be expected to maintain a good level of anticoagulation control on VKA. This is in line with recent reports of sharply increasing trends of NOAC prescription over VKA worldwide[14-17].

Another potential explanation for the results of our analysis is that although several validation studies in different populations suggest that the SAMe-TT_2R_2 score can predict the quality of anticoagulation in NVAF patients, there is still no trial evidence that an SAMe-TT_2R_2-guided strategy for the selection of the type of anticoagulation in NVAF patients has an impact on clinical outcomes of efficacy and safety. In this context, a large, randomized trial that assesses a SAMe-TT_2R_2-guided strategy on the quality of anticoagulation and on clinical outcomes (e.g., thromboembolism and bleeding) would determine its utility in routine clinical practice. Such an ongoing trial, the TREATS-AF trial, is being conducted in Thailand[18]. The geographical variation regarding VKA prescription may be conceivably related to local prescription and reimbursement policies, but this needs to be confirmed in future studies.

4.1. Limitations

While we did not perform region-specific analyses, the large sample size of prospectively recruited patients from nearly 50 countries with extensive data quality review and broad physician and site selection worldwide enhanced the value of this study.

5. Conclusion

In this large, prospective, multinational cohort of nonvalvular AF patients anticoagulated in routine clinical practice, we found no clear association between the SAMe-TT_2R_2 score and anticoagulant selection. The lack of clear association between the SAMe-TT_2R_2 score and anticoagulant selection may be attributed to the relative efficacy and safety profiles between NOACs and VKAs as well as to the absence of trial evidence that an SAMe-TT_2R_2-guided strategy for the selection of the type of anticoagulation in NVAF patients has an impact on clinical outcomes of efficacy and safety. The latter hypothesis is currently being tested in a randomized, controlled trial.

Author contributions

George Ntaios: study concept; data collection, analysis, and interpretation; drafting of the manuscript

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Hans-Christoph Diener: study concept; data collection, analysis, and interpretation; drafting of the manuscript

Jonathan L. Halperin: study concept; data collection, analysis and interpretation; drafting of the manuscript

Christine Teutsch: study concept; data collection, analysis, and interpretation; drafting of the manuscript

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Venkatesh K. Gurusamy: study concept; data collection, analysis, and interpretation; drafting of the manuscript

Milla Thompson: study concept; data collection, analysis, and interpretation; drafting of the manuscript

Gregory Y. H. Lip: study concept; data collection, analysis, and interpretation; drafting of the manuscript

Brian Olshansky: study concept; data collection, analysis, and interpretation; drafting of the manuscript

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Jonathan L. Halperin: Consulting activities with Boehringer Ingelheim, for advisory activities involving anticoagulants, and he is a member of the Executive Steering Committee of the GLORIA-AF Registry.

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Gregory Y. H. Lip: Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo. He has been a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. The authors did not receive any fees directly or personally.

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