

# Anticoagulant selection in relation to the SAME-TT2R2 score in patients with atrial fibrillation: The GLORIA-AF registry

---

**(GLORIA-AF) Ntaios, George; ...; Kes, Vanja Basic; Kalan, Marica Bracic; Brkljacic, Diana Delic; Knezevic, Aleksandar; Kovacic, Dragan; Nazlić, Jurica; Persic, Viktor; Pivac, Nediljko; ...**

*Source / Izvornik:* **Hellenic Journal of Cardiology, 2021, 62, 152 - 157**

**Journal article, Published version**

**Rad u časopisu, Objavljena verzija rada (izdavačev PDF)**

<https://doi.org/10.1016/j.hjc.2020.11.009>

*Permanent link / Trajna poveznica:* <https://um.nsk.hr/um:nbn:hr:220:642947>

*Rights / Prava:* [In copyright](#)/[Zaštićeno autorskim pravom.](#)

*Download date / Datum preuzimanja:* **2025-01-22**



*Repository / Repozitorij:*

[Repository of the Sestre milosrdnice University  
Hospital Center - KBCSM Repository](#)



Contents lists available at ScienceDirect

# Hellenic Journal of Cardiology

journal homepage: <http://www.journals.elsevier.com/hellenic-journal-of-cardiology/>



## Original Article

# Anticoagulant selection in relation to the SAME-TT<sub>2</sub>R<sub>2</sub> score in patients with atrial fibrillation: The GLORIA-AF registry



George Ntaios<sup>1,\*</sup>, Menno V. Huisman<sup>2,\*</sup>, Hans-Christoph Diener<sup>3</sup>, Jonathan L. Halperin<sup>4</sup>, Christine Teutsch<sup>5</sup>, Sabrina Marler<sup>6</sup>, Venkatesh K. Gurusamy<sup>5</sup>, Milla Thompson<sup>7</sup>, Gregory Y.H. Lip<sup>8,\*</sup>, Brian Olshansky<sup>9,\*</sup>, on behalf of the GLORIA-AF Investigators

<sup>1</sup> Department of Internal Medicine, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

<sup>2</sup> Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands

<sup>3</sup> Department of Neurology, University of Duisburg-Essen, Essen, Germany

<sup>4</sup> Icahn School of Medicine at Mount Sinai, New York, NY, USA

<sup>5</sup> Boehringer Ingelheim International GmbH, Ingelheim, Germany

<sup>6</sup> Boehringer Ingelheim Inc., Ridgefield, CT, USA

<sup>7</sup> Boehringer Ingelheim Finland Ky, Helsinki, Finland

<sup>8</sup> Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, UK

<sup>9</sup> University of Iowa, Mercy Hospital, Mason City, Iowa and Covenant Hospital, Waterloo, IA, USA

## ARTICLE INFO

### Article history:

Received 18 September 2020

Received in revised form

4 November 2020

Accepted 19 November 2020

Available online 15 December 2020

### Keywords:

SAME-TT<sub>2</sub>R<sub>2</sub>

atrial fibrillation

non-vitamin-K antagonist oral

anticoagulants

vitamin-K-antagonist oral anticoagulants

## ABSTRACT

**Aim:** The SAME-TT<sub>2</sub>R<sub>2</sub> 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<sub>2</sub>R<sub>2</sub> 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<sub>2</sub>R<sub>2</sub> 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<sub>2</sub>R<sub>2</sub> 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<sub>2</sub>R<sub>2</sub> scores >2 and 27.5% in those with scores ≤2.

**Conclusions:** The lack of a clear association between the SAME-TT<sub>2</sub>R<sub>2</sub> 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<sub>2</sub>R<sub>2</sub>-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.

© 2021 Hellenic Society of Cardiology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

\* Corresponding author. George Ntaios MD, MSc (Stroke Medicine), PhD, Department of Internal Medicine, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece. T: +30 241 3502888, F: +30 241 3501557.

E-mail address: [gntaios@med.uth.gr](mailto:gntaios@med.uth.gr) (G. Ntaios).

Peer review under responsibility of Hellenic Society of Cardiology.

\* Drs Huisman and Lip are Chairs of the GLORIA-AF Registry and joint senior authors with Dr Olshansky.

## 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<sup>1</sup>. The achievement and maintenance of a therapeutic international normalized ratio (INR) in VKA-treated patients can be

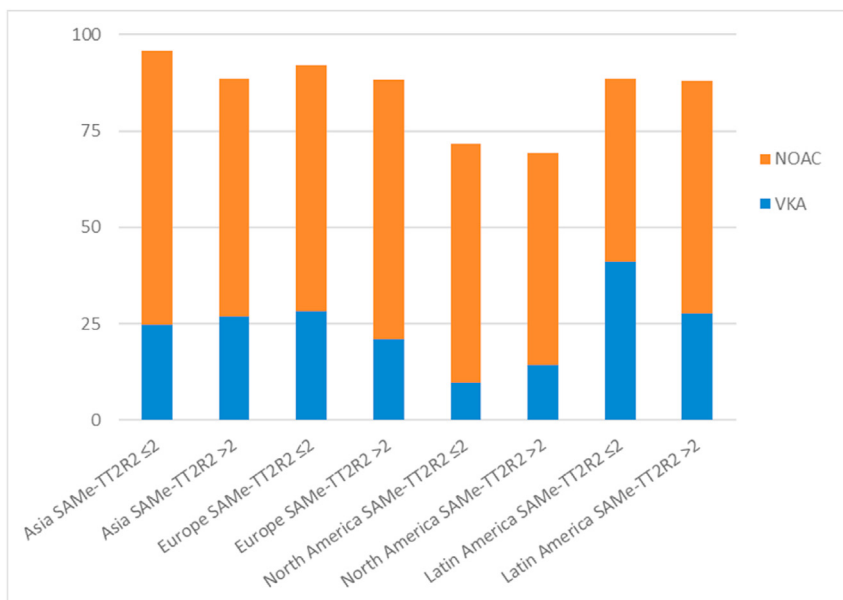
**Table 1**  
Baseline characteristics and their standardized differences by baseline SAME-TT<sub>2</sub>R<sub>2</sub> score for eligible anticoagulated patients in Phase III

	SAME-TT <sub>2</sub> R <sub>2</sub> ≤ 2 n = 11,884	SAME-TT <sub>2</sub> R <sub>2</sub> > 2 n = 5,581	Standardized difference
<b>Demographics</b>			
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
<b>Race</b>			
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
<b>Insurance status</b>			
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
<b>Comorbidities</b>			
Body mass index (kg/m <sup>2</sup> ), 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
<b>NYHA I</b>			
	203 (8.4%)	138 (9.6%)	0.0430
<b>NYHA II</b>			
	1,325 (54.7%)	759 (52.8%)	-0.0370
<b>NYHA III</b>			
	520 (21.5%)	316 (22.0%)	0.0131
<b>NYHA IV</b>			
	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%)	1,586 (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
<b>Smoking</b>			
<b>Nonsmoker</b>			
	6,821 (57.4%)	3,078 (55.2%)	-0.0453
<b>Current smoker</b>			
	180 (1.5%)	1,369 (24.5%)	0.7277
<b>Past smoker</b>			
	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	1,392 (11.7%)	404 (7.2%)	-0.1532
<b>Creatinine clearance (ml/min), mean ± SD</b>			
	86.0 ± 200.5	80.3 ± 39.9	-0.0394
<b>Creatinine clearance &lt;15 ml/min</b>			
	70 (0.6%)	42 (0.8%)	0.0200
<b>Creatinine clearance 15 to &lt;30 ml/min</b>			
	188 (1.6%)	122 (2.2%)	0.0444
<b>Creatinine clearance 30 to &lt;50 ml/min</b>			
	1,235 (10.4%)	722 (12.9%)	0.0793
<b>Creatinine clearance 50 to &lt;80 ml/min</b>			
	3,854 (32.4%)	1,723 (30.9%)	-0.0335
<b>Creatinine clearance ≥80 ml/min</b>			
	4,215 (35.5%)	1,893 (33.9%)	-0.0326
<b>Type of NVAf</b>			
<b>Paroxysmal</b>			
	6,204 (52.2%)	3,115 (55.8%)	0.0725
<b>Persistent</b>			
	4,354 (36.6%)	1,947 (34.9%)	-0.0365
<b>Permanent</b>			
	1,326 (11.2%)	519 (9.3%)	-0.0614
<b>Categorization of NVAf</b>			
<b>Symptomatic</b>			
	3,475 (29.2%)	1,930 (34.6%)	0.1148
<b>Minimally symptomatic</b>			
	3,930 (33.1%)	1,893 (33.9%)	0.0180
<b>Asymptomatic</b>			
	4,479 (37.7%)	1,758 (31.5%)	-0.1304
<b>Type of site</b>			
<b>GP/primary care</b>			
	600 (5.0%)	337 (6.0%)	0.0433
<b>Specialist office</b>			
	3,856 (32.4%)	1,341 (24.0%)	-0.1878
<b>Community hospital</b>			
	3,679 (31.0%)	1,731 (31.0%)	0.0013
<b>University hospital</b>			
	3,439 (28.9%)	1,910 (34.2%)	0.1139
<b>Outpatient health care center</b>			
	184 (1.5%)	79 (1.4%)	-0.0110
<b>Anticoagulation clinic</b>			
	74 (0.6%)	28 (0.5%)	-0.0162
<b>Physician specialty</b>			
<b>GP/PCP/Geriatrician</b>			
	651 (5.5%)	148 (2.7%)	-0.1435
<b>Cardiologist</b>			
	9,702 (81.6%)	5,077 (91.0%)	0.2739
<b>Internist</b>			
	594 (5.0%)	144 (2.6%)	-0.1269
<b>Neurologist</b>			
	320 (2.7%)	133 (2.4%)	-0.0197
<b>CHADS<sub>2</sub> score, mean ± SD</b>			
	1.9 ± 1.2	1.9 ± 1.1	0.0222
<b>CHADS<sub>2</sub> score = 0</b>			
	964 (8.1%)	394 (7.1%)	-0.0397
<b>CHADS<sub>2</sub> score = 1</b>			
	4,051 (34.1%)	1,809 (32.4%)	-0.0355
<b>CHADS<sub>2</sub> score ≥ 2</b>			
	6,868 (57.8%)	3,378 (60.5%)	0.0557
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASC score, mean ± SD</b>			
	3.2 ± 1.5	3.2 ± 1.5	-0.0364
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASC score = 1</b>			
	1,408 (11.8%)	718 (12.9%)	0.0309
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASC score ≥ 2</b>			
	10,476 (88.2%)	4,863 (87.1%)	-0.0309

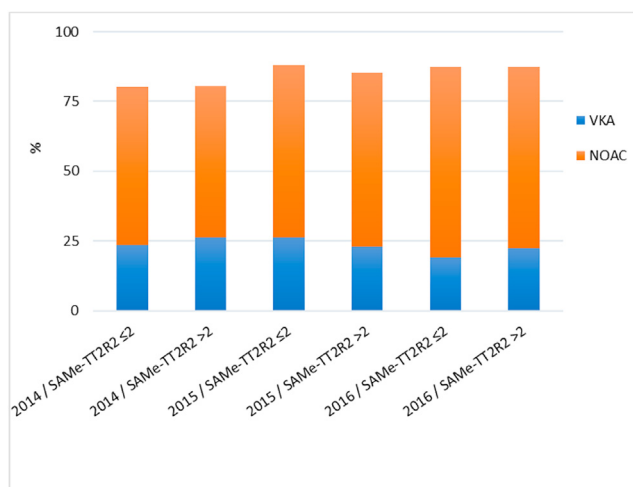
(continued on next page)

**Table 1** (continued)

	SAME-TT <sub>2</sub> R <sub>2</sub> ≤ 2 n = 11,884	SAME-TT <sub>2</sub> R <sub>2</sub> > 2 n = 5,581	Standardized difference
HAS-BLED, mean ± SD	1.3 ± 0.8	1.2 ± 0.9	-0.1571
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-TT<sub>2</sub>R<sub>2</sub> score and region.



**Figure 2.** Proportion of patients treated with VKA and NOAC by baseline SAME-TT<sub>2</sub>R<sub>2</sub> 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<sup>2</sup>.

Common clinical factors determine if a patient can achieve effective and safe anticoagulation control on VKAs. The SAME-TT<sub>2</sub>R<sub>2</sub>

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-TT<sub>2</sub>R<sub>2</sub> 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)<sup>3</sup>. Patients with a SAME-TT<sub>2</sub>R<sub>2</sub> 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-TT<sub>2</sub>R<sub>2</sub> 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<sup>4</sup>.

In this context, we hypothesized that VKAs may be less frequently prescribed in patients with NVAF and a SAME-TT<sub>2</sub>R<sub>2</sub> 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
<b>Baseline SAME-TT<sub>2</sub>R<sub>2</sub></b>					
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)
<b>Region</b>					
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)
<b>Type of AF</b>					
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)
<b>BMI class</b>					
<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)
<b>Prior bleeding</b>					
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)
<b>Alcohol abuse</b>					
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)
<b>Cancer</b>					
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)
<b>Medical treatment reimbursed by</b>					
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<sup>5</sup>.

The design of GLORIA-AF, a global, noninterventional registry program with 3 phases, has been described in detail previously<sup>5</sup>. 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](https://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<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were used to assess the thromboembolic risk of the patients. The HAS-BLED bleeding score was used to assess the bleeding risk<sup>6</sup>. 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<sub>2</sub>R<sub>2</sub> scores were derived from the patient characteristics at baseline. Baseline characteristics for patients treated with oral anticoagulants were described based on the SAME-TT<sub>2</sub>R<sub>2</sub> 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  $\leq 10\%$  in absolute value will be considered as balanced between the groups<sup>7</sup>.

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<sub>2</sub>R<sub>2</sub> 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<sub>2</sub>R<sub>2</sub> score and other covariates, which are not SAME-TT<sub>2</sub>R<sub>2</sub> 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<sub>2</sub>R<sub>2</sub> 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<sub>2</sub>R<sub>2</sub> score of  $\leq 2$  and 5,581 (32.0%) with a score of  $> 2$ .

Patients with an SAME-TT<sub>2</sub>R<sub>2</sub> score of  $\leq 2$  were older (mean age ( $\pm$ SD) 72.4  $\pm$  9.4 vs 68.3  $\pm$  11.4) and were more often men (58.5% vs 47.8%) as compared to those with SAME-TT<sub>2</sub>R<sub>2</sub> score  $> 2$ . The mean CHADS<sub>2</sub> score was 1.9  $\pm$  1.1 and the mean CHA<sub>2</sub>DS<sub>2</sub>-VASc was 3.2  $\pm$  1.5 in both SAME-TT<sub>2</sub>R<sub>2</sub> groups. The mean HAS-BLED was 1.3  $\pm$  0.8 in patients with the SAME-TT<sub>2</sub>R<sub>2</sub> score of  $\leq 2$  and 1.2  $\pm$  0.9 for patients with SAME-TT<sub>2</sub>R<sub>2</sub> score of  $> 2$ .

#### 3.1. Clinical risk profile and SAME-TT<sub>2</sub>R<sub>2</sub> score

Patients from Europe accounted for 60.8% of those with an SAME-TT<sub>2</sub>R<sub>2</sub> score of  $\leq 2$ ; 38.9% and 35.0% of patients with an SAME-TT<sub>2</sub>R<sub>2</sub> score  $> 2$  were from Asia and Europe, respectively. Fewer patients in the SAME-TT<sub>2</sub>R<sub>2</sub> score of  $\leq 2$  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<sub>2</sub>R<sub>2</sub> score  $> 2$  versus those with an SAME-TT<sub>2</sub>R<sub>2</sub> score  $\leq 2$ .

#### 3.2. SAME-TT<sub>2</sub>R<sub>2</sub> score and VKA use: Regional differences

The proportion of patients treated with VKAs was 28.0% with an SAME-TT<sub>2</sub>R<sub>2</sub> score of  $> 2$  and 27.5% with a score of  $\leq 2$ . Patients from Europe and Latin America who had an SAME-TT<sub>2</sub>R<sub>2</sub> score  $> 2$  were less often prescribed VKA when compared with an SAME-TT<sub>2</sub>R<sub>2</sub> score  $\leq 2$  (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<sub>2</sub>R<sub>2</sub> score  $> 2$  were more often prescribed VKA when compared

with those with an SAME-TT<sub>2</sub>R<sub>2</sub> score  $\leq 2$  (14.3% vs. 9.6%, respectively, standardized difference:  $-0.147$ ) (Fig. 1).

#### 3.3. SAME-TT<sub>2</sub>R<sub>2</sub> score and VKA use: Enrolment year

There were no important differences in the prescription rate of VKAs between patients with an SAME-TT<sub>2</sub>R<sub>2</sub> score  $> 2$  versus those with a score of  $\leq 2$  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<sub>2</sub>R<sub>2</sub> score  $> 2$  were less frequently prescribed VKA when compared with patients with a score  $\leq 2$  (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<sub>2</sub>R<sub>2</sub> 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<sub>2</sub>R<sub>2</sub> score and anticoagulant selection.

The lack of clear association between the SAME-TT<sub>2</sub>R<sub>2</sub> score and anticoagulant selection may indicate that other factors, not captured entirely by the SAME-TT<sub>2</sub>R<sub>2</sub> 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<sup>8–10</sup>. Accordingly, current clinical practice guidelines recommend NOACs in preference to VKA<sup>11–13</sup>. 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<sub>2</sub>R<sub>2</sub> 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<sup>14–17</sup>.

Another potential explanation for the results of our analysis is that although several validation studies in different populations suggest that the SAME-TT<sub>2</sub>R<sub>2</sub> score can predict the quality of anticoagulation in NVAf patients, there is still no trial evidence that an SAME-TT<sub>2</sub>R<sub>2</sub>-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<sub>2</sub>R<sub>2</sub>-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<sup>18</sup>. 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<sub>2</sub>R<sub>2</sub> score and anticoagulant selection. The lack of clear association between the SAME-TT<sub>2</sub>R<sub>2</sub> 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<sub>2</sub>R<sub>2</sub>-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

**Menno V. Huisman:** study concept; data collection, analysis, and interpretation; drafting of the manuscript

**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

**Sabrina Marler:** study concept; data collection, analysis, and interpretation; drafting of the manuscript

**Venkaatesh 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

## Funding source

This study was funded by Boehringer Ingelheim.

## Disclosures

George Ntaios: Speaker fees/Advisory Boards/Research support from Amgen; Bayer; BMS/Pfizer; Boehringer-Ingelheim; Elpen; Galenica; Sanofi; and Winmedica. The authors did not receive any fees directly or personally.

Menno V. Huisman: Grants from ZonMW Dutch Healthcare Fund; grants and personal fees from Boehringer-Ingelheim, Pfizer-BMS, Bayer Health Care, Aspen, Daiichi-Sankyo, outside the submitted work.

Hans-Christoph Diener: Received honoraria for participation in clinical trials; contribution to advisory boards or oral presentations from: Abbott, Bayer Vital, BMS, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Pfizer, Portola, Sanofi-Aventis, and WebMD Global. Financial support for research projects was provided by Boehringer Ingelheim. Chairs the Treatment Guidelines Committee of the German Society of Neurology and contributed to the EHRA and ESC guidelines for the treatment of AF.

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.

Christine Teutsch; Sabrina Marler; Venkaatesh K. Gurusamy; and Milla Thompson: are employees of Boehringer Ingelheim.

Gregory Y. H. Lip: Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseeon, 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.

Brian Olshansky: Consulting fees from Boehringer Ingelheim and Lundbeck; and has served as DSMB Chair for Amarin (REDUCE IT Trial).

## References

1. Tsioufis C. Ischemic stroke in atrial fibrillation patients: don't put the blame always on heart. *Hellenic J Cardiol.* 2020;61(3):208–209.
2. Kourlaba G, Stefanou G, Tsalamandris S, et al. Incidence and cost of bleeding events requiring hospitalization in patients with atrial fibrillation treated with acenocoumarol in Greece. *Hellenic J Cardiol.* 2020. S1109-9666(20)30159-7.
3. Apostolakis S, Lane DA, Buller H, Lip GY. Comparison of the CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores for the prediction of clinically relevant bleeding in anticoagulated patients with atrial fibrillation: the AMADEUS trial. *Thromb Haemostasis.* 2013;110(5):1074–1079.
4. Hindricks G, Potpara T, Dagres N, et al. ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2020, 2020.
5. Huisman MV, Lip GY, Diener HC, et al. Design and rationale of Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation: a global registry program on long-term oral antithrombotic treatment in patients with atrial fibrillation. *Am Heart J.* 2014;167(3):329–334.
6. Pisters R, Lane DA, Nieuwlaar R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138(5):1093–1100.
7. Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research. *Commun Stat Simulat Comput.* 2009;38(6):1228–1234.
8. Ntaios G, Papavasileiou V, Makaritis K, Vemmos K, Michel P, Lip GYH. Real-World Setting Comparison of Nonvitamin-K Antagonist Oral Anticoagulants Versus Vitamin-K Antagonists for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Stroke.* 2017;48(9):2494–2503.
9. Ntaios G, Papavasileiou V, Diener HC, Makaritis K, Michel P. Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke or transient ischemic attack: An updated systematic review and meta-analysis of randomized controlled trials. *Int J Stroke.* 2017;12(6):589–596.
10. Diener HC, Ntaios G, O'Donnell M, Easton JD. Non-vitamin-K oral anticoagulants (NOACs) for the prevention of secondary stroke. *Expert Opin Pharmacother.* 2018;19(14):1597–1602.
11. Kirchhof P, Benussi S, Kotecha D, et al. ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37(38):2893–2962, 2016.
12. January CT, Wann LS, Calkins H, et al. AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *Circulation.* 2019, 0(0):CIR.0000000000000665.
13. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest.* 2018;154(5):1121–1201.
14. McIntyre WF, Conen D, Olshansky B, et al. Stroke-prevention strategies in North American patients with atrial fibrillation: The GLORIA-AF registry program. *Clin Cardiol.* 2018;41(6):744–751.
15. Lim GB. Registries reveal real-world use of anticoagulant drugs in AF. *Nat Rev Cardiol.* 2017;14:189.
16. Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. *Br J Clin Pharmacol.* 2017;83(9):2096–2106.
17. van den Heuvel JM, Hövels AM, Büller HR, Mantel-Teeuwisse AK, de Boer A, Maitland-van der Zee AH. NOACs replace VKA as preferred oral anticoagulant among new patients: a drug utilization study in 560 pharmacies in The Netherlands. *Thromb J.* 2018;16, 7-7.
18. <https://gtr.ukri.org/projects?ref=MR%2FR020892%2F1>. Accessed May 30, 2019.