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Source / Izvornik: **Journal of Thrombosis and Thrombolysis, 2023, 57, 39 - 49**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1007/s11239-023-02866-y>

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:220:023108>

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# Validating the predictive ability of the 2MACE score for major adverse cardiovascular events in patients with atrial fibrillation: results from phase II/III of the GLORIA-AF registry

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Accepted: 8 July 2023  
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## Abstract

The 2MACE score was specifically developed as a risk-stratification tool in atrial fibrillation (AF) to predict cardiovascular outcomes. We evaluated the predictive ability of the 2MACE score in the GLORIA-AF registry. All eligible patients from phase II/III of the prospective global GLORIA-AF registry were included. Major adverse cardiac events (MACEs) were defined as the composite outcome of stroke, myocardial infarction and cardiovascular death. Cox proportional hazards were used to examine the relationship between the 2MACE score and study outcomes. Predictive capability of the 2MACE score was investigated using receiver-operating characteristic curves. A total of 25,696 patients were included (mean age 71 years, female 44.9%). Over 3 years, 1583 MACEs were recorded. Patients who had MACE were older, with more cardiovascular risk factors and were less likely to be managed using a rhythm-control strategy. The median 2MACE score in the MACE and non-MACE groups were 2 (IQR 1–3) and 1 (IQR 0–2), respectively ( $p < 0.001$ ). The 2MACE score was positively associated with an increase in the risk of MACE, with a score of  $\geq 2$  providing the best combination of sensitivity (69.6%) and specificity (51.6%), HR 2.47 (95% CI, 2.21–2.77). The 2MACE score had modest predictive performance for MACE in patients with AF (AUC 0.655 (95% CI, 0.641–0.669)). Our analysis in this prospective global registry demonstrates that the 2MACE score can adequately predict the risk of MACE (defined as myocardial infarction, CV death and stroke) in patients with AF. Clinical trial registration: <http://www.clinicaltrials.gov>. Unique identifiers: NCT01468701, NCT01671007 and NCT01937377

**Keywords** Atrial fibrillation · Risk stratification · Myocardial infarction · Cardiovascular mortality

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Menno V. Huisman and Gregory Y. H. Lip are co-Chairs of the GLORIA-AF registry.

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The members of on behalf of the GLORIA-AF Investigators are listed in acknowledgement section.

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## Highlights

- Patients with atrial fibrillation are at high risk for major adverse cardiac events.
- The 2MACE score can adequately predict the risk of major adverse cardiac events in patients with atrial fibrillation.
- These high-risk patients may benefit from intense and integrated care management strategies

## Introduction

Atrial fibrillation (AF) is substantially burdened with a high risk of mortality and cardiovascular events [1]. These have been long established, with frameworks such as the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and ABC pathway in place for stroke risk stratification and AF management, respectively [1, 2]. More recent evidence suggests that AF is independently associated with a 2-fold risk of major adverse cardiovascular events (MACE) such as myocardial infarction (MI) and revascularisation procedures such as percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery, even in those without a prior history of coronary artery disease (CAD) [3–5]. The risk of MI increases by 47% in the presence of AF, with this excess risk rising to 71% in those with no previous cardiac history [6]. Of note, risk of MACE in patients with AF has been shown to be lower in those who are appropriately anticoagulated [7, 8]. The extent of this issue has inadvertently been met with a focus on establishing a reliable method for stratifying the risk of MACE, to identify high-risk subsets of AF patients.

A previous study by Pastori et al. led to the derivation of the 2MACE score for use in patients with AF, based on clinical predictors associated with MACEs such as fatal/non-fatal MI, cardiac revascularisation and cardiac mortality [9]. The 2MACE score comprises 2 points each for metabolic syndrome and age equal to or greater than 75, and 1 point each for MI/revascularisation, congestive heart failure (ejection fraction  $\leq 40\%$ ), thromboembolism (stroke/transient ischemic attack [TIA]), thus ranging from 0 to 7. A score of 3 or more is considered high-risk, corresponding with a nearly 4-fold increase in the risk of MACE [9].

To date, the 2MACE score has only been validated in a few cohorts, largely retrospective with small number of patients, and in limited settings [10]. Therefore, we aimed to evaluate its predictive ability in a large, global contemporary prospective cohort of newly diagnosed patients with AF from the GLORIA-AF (Global Registry on Long-Term Oral Anti-thrombotic Treatment In Patients With Atrial Fibrillation) registry.

## Methods

### Study design and population

GLORIA-AF is a prospective, observational, global registry programme of patients who were recruited from 935 participating centres across 38 countries in Asia, Europe, North America, Latin America, and Africa/Middle East. The study design has previously been described [11]. Briefly, consecutive adults with newly diagnosed AF (<3 months before baseline visit) and an increased risk of stroke (CHA<sub>2</sub>DS<sub>2</sub>-VASc  $\geq 1$ ) were enrolled. This study focused on patients from GLORIA-AF phase II and III. These patients were enrolled between 2011 and 2020. Eligible patients with follow-up data in relation to MACE were included. Main exclusion criteria were presence of mechanical heart valve or valvular disease necessitating valve replacement, previous oral anticoagulation with vitamin K oral antagonist over 60 days, a reversible cause of AF, indication for anticoagulation other than AF, and life expectancy of less than 1 year. Ethics approval was obtained from local institutional review boards, informed consent was obtained from patients, and the study was performed in accordance with the Declaration of Helsinki.

### Data collection and definition

Data on demographics, comorbidities and therapies were collected at enrolment with standardised, prospectively designed data collection tools. Creatinine clearance (CrCl) was assessed using the Cockcroft-Gault equation [12]. AF classification was determined according to the European Society of Cardiology recommendations [1]. Severity of AF-related symptoms was ascertained using the European Heart Rhythm Association classification [13]. CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores were calculated as previously described [14–16]. The 2MACE score was determined by assigning 2 points for metabolic syndrome and age  $\geq 75$  years, and 1 point for previous MI or CABG, congestive heart failure and prior thromboembolism [10]. Metabolic syndrome was defined according to the World Health Organisation criteria as the presence of diabetes mellitus and 2 other risk factors including hypertension, hypercholesterolaemia or BMI over 30 kg/m<sup>2</sup> [17].

### Study outcomes and follow-up

Outcomes of interest were MACEs, defined as the composite outcome of pre-specified events including cardiovascular (CV) death, MI and stroke, and its individual components. MI was defined as the development of significant Q-waves in at least 2 adjacent electrocardiogram leads, or

at least 2 of the following 3 criteria: (i) typical prolonged severe chest pain of at least 30 min; (ii) electrocardiographic changes suggestive of MI including ST-changes or T wave inversion in the electrocardiogram; (iii) elevation of troponin or creatinine kinase-MB to more than upper level of normal or, if creatinine kinase-MB was elevated at baseline, re-elevation to more than 50% increase above the previous level. Stroke was defined as an acute onset of a focal neurological deficit of presumed vascular origin lasting for 24 h or more, or that resulting in death. In phase II, follow-up for the dabigatran cohort was for 2 years, with scheduled visits at 3, 6, 12, and 24 months. In phase III, follow-up for all patients was conducted for 3 years, with scheduled visits at 6, 12, 24, and 36 months. CV death was defined as death due to stroke, non-central nervous system arterial embolism, pulmonary embolism, MI, haemorrhage, sudden cardiac death, pump failure, peripheral embolus or aortic dissection/rupture. Subgroup analyses were performed in patients equal or greater than 75 years old, female sex and patients with prior stroke.

### Statistical analysis

Continuous variables were presented as median and interquartile range (IQR) and assessed for differences with Kruskal-Wallis test. Categorical variables were presented as count and percentage and assessed for differences with chi-squared test. The incidence rates (number of events/person-years at risk) with 95% confidence intervals for the outcomes of interest were calculated using previously described methods [18]. The relationship between the 2MACE score and study outcomes were analysed using Cox proportional hazards analyses.

Potential confounders were accounted for using a multivariable model with pre-specified selection of covariates including sex, creatinine clearance, type of atrial fibrillation, left ventricular hypertrophy, prior bleeding, peripheral artery disease, chronic obstructive pulmonary disease, AF ablation, oral anticoagulation use, antiplatelet use, anti-arrhythmic drug therapy, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, digoxin, statin and diuretic therapy.

Predictive capability of the 2MACE score for MACEs was investigated using receiver-operating characteristic curves, and the performance was tested against the CHA<sub>2</sub>DS<sub>2</sub>-VASc score using DeLong's method [19]. Area under the curve (AUC) was used to reflect the c-index, which represents the ability of scores to predict events. A two-sided p value of less than 0.05 was considered statistically significant. Statistical analyses were performed using R 4.0.3 (Vienna, Austria).

## Results

A total of 25,696 patients with 11,527 (44.9%) females and a median age of 71 (IQR 64–78) years were included. The patient flow is shown in Supplementary Fig. 1.

### Baseline characteristics

Baseline characteristics based on patients which reported MACEs are described in Table 1. Patients who suffered from a MACE were older, more likely to be male, and had higher BMI, poorer renal function by CrCl and greater burden of comorbidities including hypertension, hypercholesterolaemia, diabetes mellitus, CAD, prior MI, heart failure, left ventricular hypertrophy, prior thromboembolism, prior bleeding, peripheral artery disease and chronic obstructive pulmonary disease. As a result, patients who had a MACE had higher risk of stroke by CHA<sub>2</sub>DS<sub>2</sub>-VASc score, and major bleeding by HAS-BLED score. At baseline, MACE patients had a median 2MACE score of 2 (IQR 1–3) compared to 1 (IQR 0–2) in those without a MACE. The distribution of patients according to the 2MACE score is presented in Supplementary Fig. 2.

### Medication use and therapies

Those patients which reported a MACE were less likely to have received AF ablation and had lower uptake of anticoagulation and anti-arrhythmic drug compared to those which did not report the outcome. However, there was greater use of antiplatelet, angiotensin-converting enzyme inhibitor, beta-blocker, digoxin, diuretic and statin therapy among MACE patients (Supplementary Table 1).

### Relationship between 2MACE score and outcomes

During a median follow-up period of 3.0 (IQR 2.3–3.1) years, there were 1583 (6.2%) MACEs defined as a composite outcome of CV death, MI and stroke, 813 (3.2%) CV death, 432 (1.7%) MI and 681 (2.7%) stroke (Table 2). The incidence of MACEs per 100 person-years was 2.31 (95% CI, 2.20–2.43), of which CV death 1.17 (95% CI, 1.09–1.25), MI 0.62 (95% CI, 0.56–0.68) and stroke 0.98 (95% CI, 0.91–1.06).

The 2MACE score was associated with a significant increase in risk of MACE (HR 1.45 [95% CI, 1.40–1.50]), as well as separately for CV death or MI (HR 1.54 [95% CI, 1.48–1.60]), CV death (HR 1.59 [95% CI, 1.52–1.66]), MI (HR 1.46 [95% CI, 1.37–1.55]) and stroke (HR 1.29 [95% CI, 1.23–1.36]). After adjustment for confounders, an

**Table 1** Baseline characteristics

Baseline characteristics	MACE (n = 1583)	No MACE (n = 24,113)	p value
Age (years), median (IQR)	76.0 (69.0–81.0)	71.0 (64.0–77.0)	< 0.001
Female sex, n (%)	654 (41.3%)	10,873 (45.1%)	0.004
Heart rate (bpm), median (IQR)	78 (67–90)	76 (65–90)	0.004
sBP (mmHg), median (IQR)	130 (120–143)	130 (120–142)	0.392
BMI (kg/m <sup>2</sup> ), median (IQR)	26.7 (23.9–30.7)	27.6 (24.6–31.6)	< 0.001
CrCl (mL/min), median (IQR)	62.0 (44.1–83.3)	76.7 (58.4–99.6)	< 0.001
AF classification, n (%)			< 0.001
Paroxysmal	799 (50.5%)	13,495 (56.0%)	
Persistent	578 (36.5%)	8243 (34.2%)	
Permanent	206 (13.0%)	2375 (9.9%)	
EHRA classification, n (%)			< 0.001
I	584 (38.5%)	8073 (35.4%)	
II	469 (30.9%)	8677 (38.1%)	
III	365 (24.1%)	4670 (20.5%)	
IV	99 (6.5%)	1356 (6.0%)	
Comorbidities, n (%)			
Hypertension	1261 (79.8%)	18,034 (75.0%)	< 0.001
Hypercholesterolaemia	712 (46.2%)	9457 (40.3%)	< 0.001
Diabetes mellitus	494 (31.2%)	5423 (22.5%)	< 0.001
Coronary artery disease	517 (33.5%)	4279 (18.2%)	< 0.001
Prior myocardial infarction	333 (21.1%)	2088 (8.7%)	< 0.001
Congestive heart failure	564 (36.0%)	5014 (21.0%)	< 0.001
Left ventricular hypertrophy	349 (23.0%)	4362 (19.0%)	< 0.001
Prior thromboembolism	352 (22.2%)	3428 (14.2%)	< 0.001
Prior stroke	278 (17.6%)	2475 (10.3%)	< 0.001
Prior bleeding	116 (7.4%)	1234 (5.2%)	< 0.001
Peripheral artery disease	93 (5.9%)	631 (2.6%)	< 0.001
COPD	148 (9.4%)	1367 (5.7%)	< 0.001
2MACE score, median (IQR)	2 (1–3)	1 (0–2)	< 0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score, median (IQR)	4 (3–5)	3 (2–4)	< 0.001
HAS-BLED score, median (IQR)	2 (1–2)	1 (1–2)	< 0.001

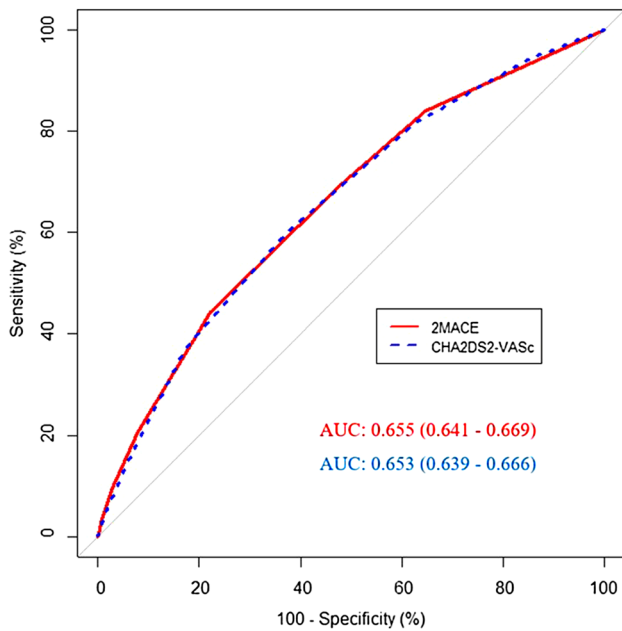
AF atrial fibrillation, BMI body mass index, COPD chronic obstructive pulmonary disease, CrCl creatinine clearance, EHRA European Heart Rhythm Association, IQR interquartile range, LVEF left ventricular ejection fraction, MACE major adverse cardiovascular event, sBP systolic blood pressure

**Table 2** Association between 2MACE score and major adverse cardiovascular events

Outcomes	n (%)	Incidence per 100 PYs (95% CI)	Relationship with 2MACE score		
			Univariate HR (95% CI)	aHR* (95%)	p value
MACE	1583 (6.2%)	2.31 (2.20–2.43)	1.45 (1.40–1.50)	1.33 (1.27–1.38)	< 0.001
CV death or myocardial infarction	1102 (4.3%)	1.59 (1.50–1.69)	1.54 (1.48–1.60)	1.36 (1.30–1.43)	< 0.001
CV death	813 (3.2%)	1.17 (1.09–1.25)	1.59 (1.52–1.66)	1.39 (1.31–1.47)	< 0.001
Myocardial infarction	432 (1.7%)	0.62 (0.56–0.68)	1.46 (1.37–1.55)	1.32 (1.22–1.43)	< 0.001
Stroke	681 (2.7%)	0.98 (0.91–1.06)	1.29 (1.23–1.36)	1.24 (1.16–1.32)	< 0.001

aHR adjusted hazard ratio, CI confidence interval, CV cardiovascular, HR hazard ratio, MACE major adverse cardiovascular event, PY person-years

\*Adjusted for gender, creatinine clearance, type of atrial fibrillation, left ventricular hypertrophy, prior bleeding, peripheral artery disease, chronic obstructive pulmonary disease, AF ablation, oral anticoagulation use, antiplatelet use, anti-arrhythmic drug therapy, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, digoxin, statin and diuretic therapy



**Fig. 1** Receiver-operating characteristic curves comparison for major adverse cardiovascular events (MACE) with the 2MACE and CHA<sub>2</sub>DS<sub>2</sub>-VASc score

increase in the 2MACE score remained associated to the occurrence of MACEs (aHR 1.33 [95% CI, 1.27–1.38]) and the single components of the composite outcome, namely CV death or MI (aHR 1.36 [95% CI, 1.30–1.43]), CV death (aHR 1.39 [95% CI, 1.31–1.47]), MI (aHR 1.32 [95% CI, 1.22–1.43]) and stroke (aHR 1.24 [95% CI, 1.16–1.32]).

**Predictive ability of 2MACE score**

Using receiver-operating characteristic curve analysis, the AUC of the 2MACE score for prediction of MACE was 0.655 (95% CI, 0.641–0.669) (Fig. 1). There was no statistical difference between the predictive ability of the 2MACE score and CHA<sub>2</sub>DS<sub>2</sub>-VASc score (0.653 [95% CI, 0.639–0.666]) for MACE (p=0.236). The sensitivity and specificity with corresponding HRs for MACEs occurrence

at each point of the 2MACE score is presented in Table 3. A cut-off of equal or more than 2 points for the 2MACE score provided good sensitivity (69.6%) and acceptable specificity (51.6%) with a HR of 2.47 (95% CI, 2.21–2.77).

**Subgroup analysis**

Results of the 2MACE score for prediction of MACEs in specific subgroups is shown in Fig. 2. Overall, the risk of MACEs increased with higher 2MACE score in each of the subgroups studied.

**Discussion**

The principal findings of our study from a global contemporary cohort of anticoagulated patients with AF were as follows: (i) the 2MACE score was associated with a significantly increased risk of MACE, CV death, MI and stroke, (ii) the predictive ability of the 2MACE score for MACE including stroke was adequate and comparable, but not superior to that of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score; and (iii) a 2MACE score of equal or greater than 2 may be useful for identifying high-risk subgroups.

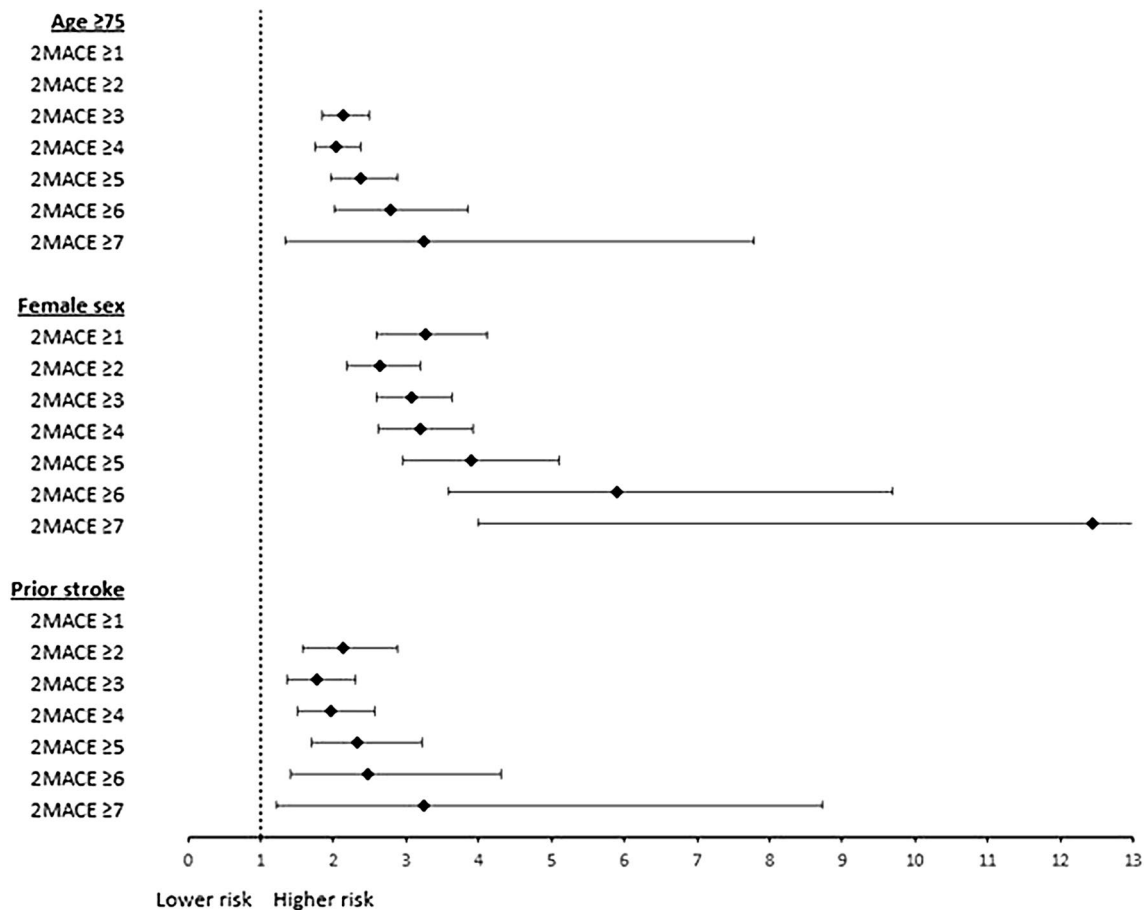
To date, this is the largest study validating the predictive performance of the 2MACE score in a global prospective cohort of anticoagulated patients who were predominantly treated with non-vitamin K antagonist oral anticoagulants. Further, as this was based on a multi-centre registry, the results are more likely to be applicable to a wider range of patients from different geographical regions and ethnicities, as opposed to that from most existing studies which were based on single-centre cohorts, mostly on vitamin K antagonists.

In our analysis, 6.2% of the entire study population had a MACE, at an incidence rate of 2.31 events per 100 person-years. This was lower compared to the internal derivation cohort (10.9%) but similar to that of the external validation cohort (6.2%) in the study by Pastori et al. [9]. These differences may be attributable to the cohort sizes which were significantly smaller in contrast to the GLORIA-AF

**Table 3** Sensitivity, specificity and hazard ratios for MACE at different thresholds of the 2MACE score

2MACE score	Sensitivity (%)	Specificity (%)	HR (95% CI)	p value
≥ 1	84.1	35.4	2.89 (2.50–3.33)	<0.001
≥ 2	69.6	51.6	2.47 (2.21–2.77)	<0.001
≥ 3	44.3	77.8	2.81 (2.53–3.12)	<0.001
≥ 4	20.7	92.0	2.97 (2.62–3.38)	<0.001
≥ 5	9.2	97.2	3.49 (2.92–4.17)	<0.001
≥ 6	2.6	99.3	4.12 (3.00–5.66)	<0.001
≥ 7	0.3	99.9	4.81 (2.00–11.57)	<0.001

CI confidence interval, HR hazard ratio, MACE major adverse cardiovascular event



**Fig. 2** Results of the 2MACE score for prediction of MACE in subgroups of patients equal of greater than 75 years, female sex and patients with prior stroke

cohort, variations in the baseline characteristics and the differing follow-up durations. Nonetheless, it illustrates that AF patients remain at high residual risk of MACE despite being on oral anticoagulation [20–22]. This highlights the need for a more holistic or integrated care approach to AF management [23] and other chronic long term conditions [2, 24, 25]. In AF, such an approach has been associated with improved clinical outcomes [26, 27], leading to its incorporation into guidelines [28].

Our data demonstrated that an increase in the 2MACE score was positively associated with a graded increase in the risk of MACE. A 2MACE score of equal or greater than 2 had the best combination of sensitivity (69.6%) and specificity (51.6%) for MACE in our study, similar to the Murcia AF cohort [29]. Both sensitivity and specificity were inversely related, with sensitivity highest at 84.1% for a 2MACE score of equal or more than 1 (i.e. the probability for ruling out MACE was highest with lower scores), and specificity highest at 99.9% for a score equal or more than 7 (i.e. the probability of ruling out false positive results was highest with higher scores). In contrast, a 2MACE score of equal or

more than 3 resulted in the best balance between the 2 in the validation studies by Pastori et al. (sensitivity 83%, specificity 68%) and Polovina et al. (sensitivity 74.6%, specificity 81.8%) [9, 30]. The corresponding sensitivity for each of the 2MACE scores were higher in their studies but these figures could represent spectrum effects associated with the clinical variability between study populations, which can influence performance of such tools [31].

Overall, we found that the 2MACE score had a moderate predictive ability for MACE in patients with AF. Although the c-index for predicting MACE was high at 0.79 (95% CI, 0.71–0.90) in the internal derivation cohort, this was 0.66 in the external validation cohort in the study by Pastori et al. [9]. Similarly, Rivera-Caravaca et al. derived c-indexes of 0.662 (95% CI, 0.625–0.697) and 0.656 (95% CI, 0.593–0.719) for discriminating MACE in the Murcia AF and FANTASIIA cohorts, on par with our results [29]. In contrast, the 2MACE score performed better in the analysis by Polovina et al. [30], with a marginally higher c-statistic of 0.699 (95% CI, 0.648–0.750). Notable differences between this study compared to the others included the younger population, lower

CHA<sub>2</sub>DS<sub>2</sub>-VASc score, exclusion of patients with known CAD and the large proportion of patients who were managed with a rhythm control strategy, suggesting that this was lower risk population, and also raising the question whether the 2MACE score performs better in lower risk populations.

In addition to the above, the 2MACE score has been utilised in other real-world studies. In the ATHERO-AF study, the 2MACE score was utilised to categorise patients into low- and high-risk groups using a cut off of equal or more than 3 [32]. Further, it has been evaluated in AF cohorts with comorbidities such as chronic kidney disease and obstructive sleep apnoea to stratify CV risk with reasonable reliability [10, 33].

Over a median follow-up period of 3 years, a total of 1583 (6.2%) MACE were observed in the GLORIA-AF cohort, of which the majority were MI and CV death, with stroke being less frequent. Given this, it seems prudent to have a risk-prediction tool for CV events, the same way several exist for stroke risk-stratification. Nonetheless, we did not demonstrate a significant difference in the predictive ability of the 2MACE compared to CHA<sub>2</sub>DS<sub>2</sub>-VASc score for MACE in this cohort. As per previous studies, the 2MACE score was significantly associated with an increased risk of all outcomes with the strongest association with CV death.

The 2MACE score is a convenient tool that can be used with ease, as the variables it encompasses are clinical and readily available from patient histories. Our study validates the ability of this tool in predicting the risk of MACE in patients with AF. The potential for improving its predictive performance exists and studies focusing on this are already underway. In a recent study, incorporation of microRNAs which have been implicated in thromboembolic disease, in the 2MACE score significantly improved its predictive performance, increasing the c-statistic to 0.762 [29]. The biomarker-based risk scores are also non-specific and may be predictive of outcomes beyond what they were proposed for [34]. However, such biomarkers are not widely used and focus on clinical variables that are easily accessible may enhance clinical uptake and utility. The specific role of the 2MACE score in influencing treatment decisions has not been formally tested. Nonetheless, the score highlights high-risk patients who may benefit the most from optimisation of their cardiovascular risk profile. Ultimately, the benefits and risk of each treatment will need to be balanced at an individual level though we have shown that the 2MACE score can be used to provide vital information in terms of risk. More research is needed to evaluate the role of the 2MACE score to guide the management of patients with AF.

## Limitations

Although the GLORIA-AF registry was a prospective registry, our analysis was conducted retrospectively and should

therefore be interpreted with caution. Moreover, there was possible misclassification and selection biases due to the observational study design. Data on medication compliance and control of CV risk factors which may have influenced outcomes was not available. Given that only patients with newly diagnosed AF were enrolled, the results presented here may not be applicable to the wider AF population. Though used for comparison in this study, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score was not designed for the prediction of MACEs. Lastly, even though our results complement current evidence and provide useful insights, a direct comparison with other studies on this subject should be avoided due to differences in the definitions and study outcomes.

## Conclusion

The results of this large global prospective study indicate that the 2MACE score can adequately predict the risk of MACE such as MI, CV death as well as stroke in AF patients, in the short- and intermediate term, and supports its use as a risk-stratification tool for MACE in the AF cohort. It may be used to identify high-risk patients who will stand to benefit from more intense and integrated care measures in terms of lifestyle and risk factor modification as well as management strategies such as a rhythm control approach.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s11239-023-02866-y>.

**Acknowledgements** This publication is based on research using data from Boehringer Ingelheim that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication. The authors thank the patients who participated in this trial, their families, the investigators, study co-ordinators, and study teams.

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**Author contributions** WYD and GYHL contributed to study conception and design. WYD contributed to data analysis and interpretation of data. WYD and AMF drafted the manuscript. GFR, MP, DP, MVH and GYHL revised the manuscript critically for important intellectual content. All authors approved the final version of the submitted manuscript.

**Funding** The GLORIA-AF registry was sponsored by Boehringer Ingelheim GmbH. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

**Data availability** Data supporting this study are available through the data contributors Boehringer Ingelheim through Vivli, Inc.

**Code availability** Not applicable.

## Declarations

**Conflict of interest** MVH: Researchgrants from Dutch Healthcare Fund, Dutch Heart Foundation, Bayer Health Care, Pfizer-BMS, Leo Pharma, and consulting fees from Boehringer Ingelheim, BayerHealth Care, Pfizer-BMS. GYHL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees were received personally. Other authors declare no conflict of interest.

**Ethical approval** Patients provided written informed consent; the GLORIA-AF study protocol was approved by the appropriate ethics review boards.

**Consent to participate** See Acknowledgements.

**Consent for publication** See Acknowledgements.

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