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Usefulness of the 2MACE score to predicts adverse cardiovascular events in patients with atrial fibrillation

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Abstract
We investigated the incidence of nonembolic adverse events in 2 cohorts of patients with atrial fibrillation (AF) and validated the 2MACE score ([metabolic syndrome, age ≥75] [doubled]; [myocardial infarction or revascularization, congestive heart failure {HF}, and stroke, transient ischemic attack or thromboembolism]) as predictor of major adverse cardiovascular events (MACEs). We recruited 2,630 patients with AF from 2 different cohorts (Murcia AF and FANTASIIA). The 2MACE score was calculated, and during a median of 7.2 years (Murcia AF cohort) and 1.01 years (FANTASIIA) of follow-up, we recorded all nonembolic adverse events and MACEs (composite of nonfatal myocardial infarction or revascularization and cardiovascular death). Receiver operating characteristic curves comparison, reclassification and discriminatory analyses, and decision curve analyses were performed to compare predictive ability and clinical usefulness of the 2MACE score against CHA_2DS_2-VASc. During follow-up, there were 65 MACEs in the Murcia cohort and 60 in the FANTASIIA cohort. Events rates were higher in the high-risk category (score ≥3) (1.94%/year vs 0.81%/year in the Murcia cohort; 6.01%/year vs 1.71%/year, in FANTASIIA, both $p < 0.001$). The predictive performance of 2MACE according to the receiver operating characteristic curve was significantly higher than that of CHA_2DS_2-VASc (0.662 vs 0.618, $p = 0.008$ in the Murcia cohort; 0.656 vs 0.565, $p = 0.003$ in FANTASIIA). Decision curve analyses demonstrated improved clinical usefulness of the 2MACE compared with the CHA_2DS_2-VASc score. In conclusion, in "real-world" patients with AF, the 2MACE score is a good predictor of MACEs. A score ≥3 should be used to categorize patients at "high risk," in identifying patients at risk of MACE.

Recently, the 2MACE score (2 points for metabolic syndrome and age ≥75, and 1 point for myocardial infarction [MI] or revascularization, congestive heart failure [ejection fraction ≤40%] and thromboembolism [stroke or transient ischemic attack]) has been described to stratify cardiovascular risk in patients with nonvalvular atrial fibrillation (AF). According to this clinical tool, patients with a score ≥3 (high risk) have a risk of almost 4-fold higher of having a cardiovascular adverse event.[1] Thus, this score may provide new information that would optimize the management and treatment of patients with AF, with important implications for clinical practice. In the present study, we investigated the incidence of nonembolic thrombotic adverse events in 2 "real-world" cohorts of patients with AF. In addition, we validated the 2MACE score as predictor of major adverse cardiovascular events (MACEs) in both populations, in comparison with the CHA_2DS_2-VASc score.

Methods

From May 1, 2007 to December 1, 2007 in our single anticoagulation center in a tertiary hospital in Murcia (South East Spain), we included consecutive patients with paroxysmal or permanent nonvalvular AF who were stable with Vitamin K Antagonist (VKA) (International Normalized Ratio [INR] 2.0 to 3.0) for at least the previous 6 months. At entry, all patients were receiving anticoagulation therapy with acenocoumarol (the commonest VKA used in Spain) and consistently achieved an INR between 2.0 and 3.0 during the previous 6 months. This inclusion criterion guarantees baseline homogeneity, and avoided any influence of fluctuant INR. For the same reason, we also excluded patients with rheumatic mitral valves or prosthetic heart valves, as well as those with any acute coronary syndrome, stroke, hemodynamic instability, hospital admissions, or surgical interventions in the preceding 6 months in the present analysis. In this cohort, follow-up was performed through routine visits to the anticoagulation clinic and through medical records. Importantly, no patient was lost to follow-up.

In addition, we also included consecutive patients with AF from the FANTASIIA (Spanish acronym for "Fibrilación Auricular: influencia del Nivel y Tipo de Anticoagulación Sobre la Incidencia de Ictus y Accidentes hemorrágicos") registry. This registry is an observational, multicenter, national, and prospective study of the general characteristics and current situation of a Spanish nonvalvular AF population between June 2013 and March 2014. Patients enrolled in FANTASIIA were receiving anticoagulant therapy (VKA or nonvitamin K antagonist oral anticoagulants [NOAC]) for at least 6 months before enrollment, and were followed in 50 outpatient clinics by 81 investigators. The follow-up was carried out in 3 visits, at 1, 2, and 3 years. At each visit, clinical and laboratory data were collected from patients.

At baseline, stroke risk (CHA_2DS_2-VASc) and bleeding risk (HAS-BLED Hypertension [uncontrolled, >160 mmHg systolic], Abnormal renal and liver function [dialysis, transplant, creatinine >2.26 mg/dL or >200 µmol/L and/or cirrhosis or bilirubin >2x normal with AST/ALT/AP >3x normal], Stroke history, Bleeding [prior major bleeding or predisposition to bleeding], Labile INR [unstable/high INRs, time in therapeutic range <60%], Elderly [age >65], Drugs or alcohol [medication usage predisposing to bleeding such as antiplatelet agents or nonsteroidal anti-inflammatory drugs and/or alcohol intake ≥8 units/week]) were calculated in these 2 cohorts, and a complete medical history was recorded. The time in therapeutic range was calculated at 6 months after entry in both populations according to the Rosendaal method. The 2MACE score was also calculated at baseline, as described by Pastori et al.[1] To define the metabolic syndrome, we used the established definition of the World Health Organization.[2,3]

The *primary end points* were MACEs (the composite of nonfatal MI or cardiac revascularization and cardiovascular death [death caused by sudden death, progressive congestive heart failure, fatal MI, or procedure-related death]), and these were recorded during the follow-up period. We excluded from MACE all embolic events; that is, stroke or transient ischemic attack and peripheral embolism were not included. The investigators identified, confirmed, and recorded all adverse events and outcomes.

The study protocol was approved by the Ethics Committee from University Hospital Morales Meseguer and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave informed consent to participation in the study.

Categorical variables were expressed as frequencies and percentages. Continuous variables were presented as median and interquartile range (IQR), or mean ± standard deviation if distribution was normal according to the Kolmogorov-Smirnov test. Cox proportional hazard regression models were used to determine the association between higher values of the 2MACE score and MACE. Survival analyses by Kaplan-Meier estimates were performed to assess differences in event-free survival distributions between subgroups of cardiovascular risk categories. Finally, receiver operating characteristic (ROC) curve was carried out to evaluate the predictive ability (expressed as c-index) of the 2MACE score. Comparisons of ROC curves between 2MACE score and CHA_2DS_2-VASc score were carried out by the method of DeLong et al.[4] Additionally, we used the methods described by Zhou et al[5] to calculate the weighted summary area under the ROC curve under the fixed effects model and random effects model. Integrated discriminatory improvement and net reclassification improvement were performed according to the methods described by Pencina et al.[6] Finally, clinical usefulness and net benefit of the 2MACE score in comparison with CHA_2DS_2-VASc were estimated using decision curve analysis.[7,8]

In all analyses, p values <0.05 were accepted as statistically significant. Statistical analyses were performed using SPSS Statistics 19.0 for Windows (SPSS Inc., Chicago, IL), MedCalc v. 16.4.3 (MedCalc Software bvba, Ostend, Belgium), and STATA v. 12.0 (Stata Corp., College Station, TX) for Windows.

Results

Baseline clinical characteristics are shown in Table 1. We included 693 patients (49.6% male; median age 75, IQR 69 to 80 years) followed up for a median of 7.2 years (IQR 6.2 to 7.9) from our AF cohort and 1,937 patients (55.8% male; mean age 73.84 ± 9.48 years) followed up for a median of 1.01 years (IQR 0.99 to 1.05) from the FANTASIIA registry. CHA_2DS_2-VASc and HAS-BLED were calculated at entry, with median values of 4 (IQR 3 to 5) and 2 (IQR 2 to 3), respectively, in our cohort, and 4 (IQR 3 to 5) and 2 (IQR 1 to 3) in the FANTASIIA registry. The median time in therapeutic range at 6 months after inclusion was 80% (IQR 66 to 100) and 63.03% (IQR 43.3 to 80) in both our population and the FANTASIIA registry. Baseline clinical characteristics associated with the development of a MACE during follow-up are shown in Supplementary Tables 1 and 2.

Table 1. Baseline clinical characteristics

Variables	MURCIA AF (N = 693)	FANTASIIA (N = 1937)
Age (years), median (IQR)/mean (SD)	75 (69–80)	73.84 ± 9.48
Men	344 (49.6%)	1080 (55.8%)
Body-mass index (kg/m^2), median (IQR)/mean (SD)	75 (69–80)	28.95 ± 4.83
Hypertension	564 (81.4%)	1559 (80.5%)
Diabetes mellitus	166 (24.0%)	565 (29.2%)
Metabolic syndrome	170 (24.5%)	1047 (54.1%)
Heart failure	206 (29.7%)	561 (29.0%)
Coronary artery disease	139 (20.1%)	350 (18.1%)
Hypercholesterolemia	258 (37.2%)	1528 (78.9%)
Current smoking habit	104 (15.0%)	97 (5.0%)
History of stroke/TIA/thromboembolism	119 (17.2%)	329 (17.0%)
Hepatic impairment	5 (0.7%)	23 (1.2%)
Renal impairment	70 (10.1%)	376 (19.4%)
Previous medications		
Amiodarone	41 (5.9%)	240 (12.4%)
Digoxin	126 (18.2%)	353 (18.2%)
Beta-blockers	245 (35.4%)	1170 (60.4%)
ACE inhibitors /ARBs	370 (53.4%)	1387 (71.6%)
Calcium channel blockers	178 (25.7%)	467 (24.1%)
Diuretics	303 (43.7%)	1112 (57.4%)
Antiplatelets	127 (18.3%)	207 (10.7%)
Statins	187 (27.0%)	1065 (55.0%)
TTR (%) at 6 months, median (IQR)	80 (66–100)	63.03 (43.3–80)
CHA_2DS_2-VASc score, median (IQR)	4 (3–5)	4 (3–5)
HAS-BLED score, median (IQR)	2 (2–3)	2 (1–3)
2MACE score, median (IQR)	2 (1–3)	2 (0–3)

ACE inhibitors = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; IQR = interquartile range; SD = standard deviation; TIA = transient ischemic attack; TTR = time in therapeutic range.

Table 2. Distribution of major adverse cardiovascular events according to the cardiovascular risk categories

	MURCIA AF cohort				FANTASIIA cohort			
	2MACE score				2MACE score			
	Total *(n = 693)*	score < 3 *(n = 393)*	score ≥ 3 *(n = 300)*	*p*	Total *(n = 1937)*	score < 3 *(n = 1327)*	score ≥ 3 *(n = 610)*	*p*
MACE	65 (9.4%)	23 (5.9%)	42 (14.0%)	<0.001	60 (3.1%)	23 (1.7%)	37 (6.1%)	<0.001
annual rate (%/year)	1.30%/year	0.81%/year	1.94%/year		3.06%/year	1.71%/year	6.01%/year	
Non-fatal MI/revascularization	34 (4.9%)	13 (3.3%)	21 (7.0%)	0.026	22 (1.4%)	11 (0.8%)	11 (1.8%)	0.110
annual rate (%/year)	0.68%/year	0.46%/year	0.97%/year		1.12%/year	0.82%/year	1.79%/year	
Cardiovascular death	31 (4.5%)	10 (2.5%)	21 (7.0%)	0.005	38 (2.0%)	12 (0.9%)	26 (4.3%)	<0.001
annual rate (%/year)	0.62%/year	0.35%/year	0.97%/year		1.94%/year	0.89%/year	4.22%/year	

MACE = major adverse cardiovascular event; MI = myocardial infarction.

During the follow-up, 58 patients from our population had a stroke (8.4%, i.e., 1.16%/year) and 106 had a major bleeding event (15.3%, 2.12%/year). In the FANTASIIA registry, 15 patients had a stroke (0.77%/year), whereas 65 had a major bleeding event (3.36%/year). In this period, there were 65 MACEs (9.4%; 1.30%/year) in our cohort. Of these, 31 (4.5%, 0.62%/year) were cardiovascular deaths and 34 (4.9%, 0.68%/year) were nonfatal MI or revascularizations. Regarding the FANTASIIA cohort, 60 patients had a MACE (3.10%; 3.06%/year); 38 (2%; 1.94%/year) were cardiovascular deaths and 22 (1.4%; 1.12%/year) were nonfatal MI or revascularizations (Table 2).

When we calculated the 2MACE score as described by Pastori et al,[1] the median value in our cohort was 2 (IQR 1 to 3), and 300 patients (43.3%) had a score ≥3 (i.e., high risk). In the FANTASIIA registry, we found a median 2MACE score of 2 (IQR 0 to 3) and 610 patients (31.5%) with a score ≥3. In our cohort, patients with 2MACE score ≥3 had 42 MACEs, which resulted into an annual event rate of 1.94%/year for this group. In the population of the FANTASIIA registry, 37 patients with 2MACE score ≥3 had a MACE (6.01%/year). Cox regression analysis performed in our cohort showed that patients categorized as high risk (score ≥3) had significantly higher risk of MACE (hazard ratio 2.88, 95% confidence interval [CI] 1.73 to 4.80; p <0.001) (Supplementary Figure 1). The overall risk for each score point was 1.50 (95% CI 1.30 to 1.74, p <0.001) in our cohort, and 1.52 (95% CI 1.28 to 1.80, p <0.001) in the FANTASIIA registry.

ROC curve analysis demonstrated that the 2MACE score had a good performance to predict MACE in patients with AF in our cohort, with a c-index of 0.662 (95% CI 0.625 to 0.697, p <0.001). This analysis showed the 2MACE score >2 as the best combination of sensitivity (64.6%) and specificity (60.0%). The cohort of the FANTASIIA registry showed similar results, and the 2MACE score had a c-index of 0.656 (95% CI 0.593 to 0.719, p <0.001), with the score ≥3 presenting the best combination of sensitivity (61.7%) and specificity (69.5%).

Comparisons of the ROC curves of 2MACE and CHA_2DS_2-VASc scores proved that the 2MACE score had better predictive ability to predict MACE, both in our Murcia cohort (0.662 vs 0.618, p = 0.008) and in the FANTASIIA cohort (0.656 vs 0.565, p = 0.003) (Table 3, Supplementary Figure 2). Additionally, the weighted summary area under the ROC curve under the fixed effects model and random effects model also demonstrated a good performance of the 2MACE to predict MACE, even including the internal derivation and the external validation cohorts of Pastori et al into the models (fixed effects 0.668, 95% CI 0.641 to 0.696; random effects 0.674, 95% CI 0.634 to 0.715, both p <0.001) (Figure 1).

Table 3. Comparison of the receiver operating characteristic curves, integrated discriminatory improvement, and net reclassification improvement of the CHA_2DS_2-VASc and 2MACE scores

	C-index	95% CI	*p**	IDI	*p*	NRI	*p*
MURCIA AF cohort							
2MACE	0.662	0.625–0.697	0.008	0.0188	<0.001	0.2517	<0.001
CHA_2DS_2-VASc	0.618	0.581–0.655					
FANTASIIA cohort							
2MACE	0.656	0.593–0.719	0.003	0.0110	<0.001	0.3720	0.002
CHA_2DS_2-VASc	0.565	0.526–0.605					

CI = confidence interval; IDI = integrated discriminatory improvement; NRI = net reclassification improvement.
* For c-index comparison.

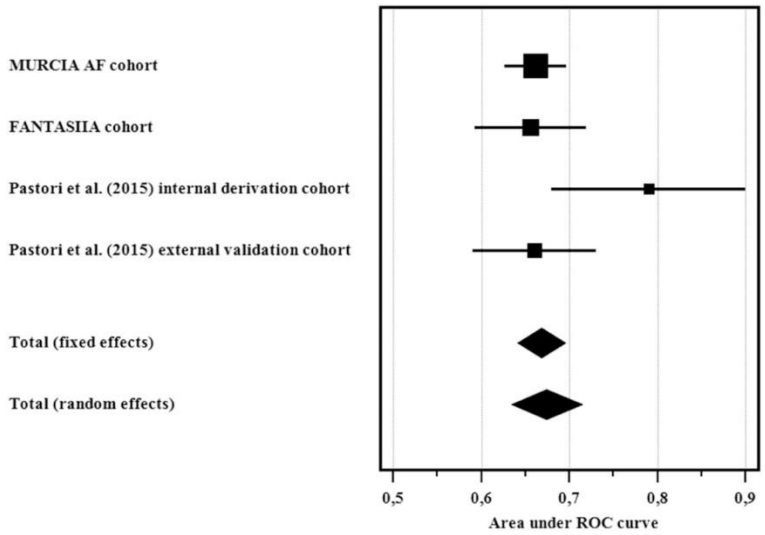

Figure 1. Weighted summary area under the receiver operating characteristic curve.

Reclassification analyses showed significant improvement in sensitivity and important positive reclassification of the 2MACE score compared with the CHA_2DS_2-VASc score, based on the integrated discriminatory improvement and net reclassification improvement (Table 3).

Finally, decision curve analyses graphically demonstrate that the overall risk of MACE in the MURCIA AF cohort was approximately 9%, according to the intersection of the y-axis and the slanted dash gray line. In the FANTASIIA population, the overall risk was around 30%. In both cohorts, as the lines of the 2MACE score are farthest away from the slanted dash gray lines (i.e., assume all MACE) and the horizontal black lines (i.e., assume none MACE), the 2MACE score demonstrates improved clinical usefulness and a higher net benefit compared with the CHA_2DS_2-VASc score (Figure 2).

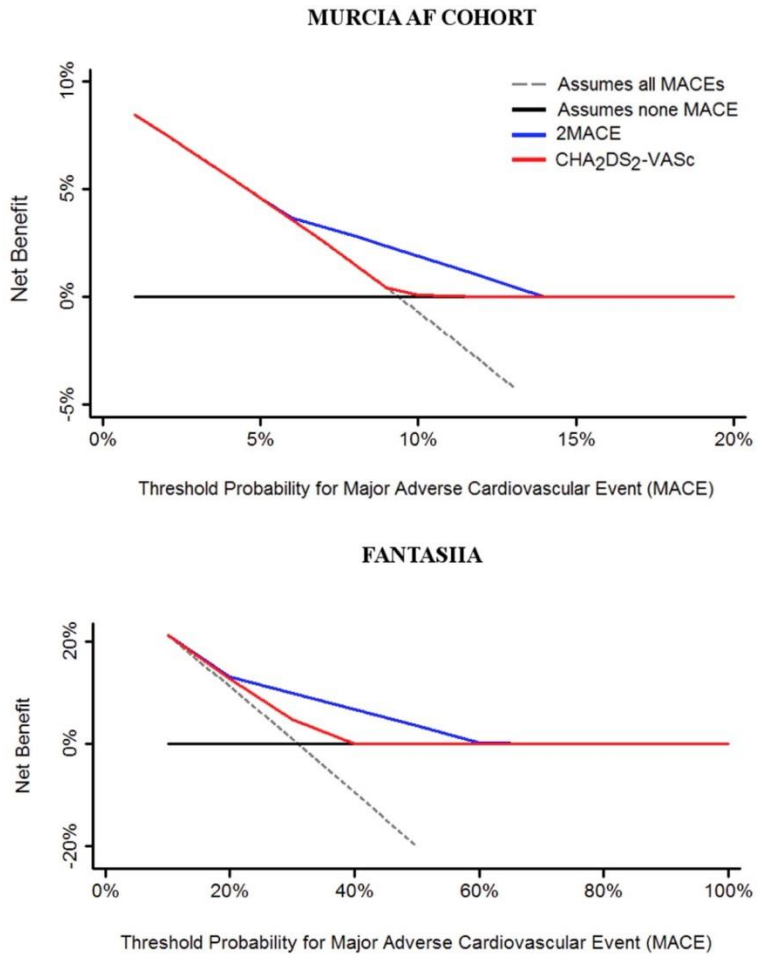

Figure 2. Decision curves for the 2MACE and CHA_2DS_2-VASc scores.
This analysis shows the clinical usefulness of each score based on a continuum of potential thresholds for major adverse cardiovascular events (x-axis) and the net benefit of using the model to stratify patients at risk (y-axis) relative to assuming that no patient will have a major adverse cardiovascular event.

Discussion

In this first study validating the 2MACE score in "real-world" patients taking both VKA and NOACs, we show that this novel score has a moderate predictive performance for MACEs in 2 different cohorts of patients with AF.

Patients with AF are under a high risk of ischemic stroke and mortality.[9–12] Our study confirms that other adverse cardiovascular events are frequent in these patients, with an incidence close to 3%/year in a population taking VKAs or NOACs, a rate which is even higher than that for stroke. This has been highlighted in previous studies that show that AF is associated with a risk of MI because of the coexistence of atherosclerotic risk factors and is associated with the presence of some biomarkers also present in patients with coronary heart disease.[13–19]

Given this information, it seems useful to have a simple clinical risk score to easily classify those patients with AF at increased risk of cardiovascular events.[20] CHA_2DS_2-VASc and HAS-BLED are also widely used in clinical practice to estimate, respectively, the risk of ischemic stroke and bleeding; the new 2MACE score has proven to be useful in predicting MACE, with implications for clinical practice by aiding decision-making about antithrombotic therapies.

We have also compared the predictive ability for MACE of CHA_2DS_2-VASc and 2MACE scores. In previous studies, the predictive performance for nonstroke events of the CHA_2DS_2-VASc score has been investigated, and has proven to be useful in predicting nonembolic adverse cardiovascular events.[21–25] Although in this study the CHA_2DS_2-VASc score remained a modest c-index for MACE, the 2MACE score demonstrates significantly better predictive performance for these events. In addition, this novel score demonstrates better discrimination and reclassification ability, as well as higher net benefit and clinical usefulness in comparison with CHA_2DS_2-VASc.

In the present study, in both cohorts of patients, the 2MACE score had a similar c-index with the external validation cohort of Pastori et al (i.e., 0.66). Indeed, a score >2 in the Murcia AF cohort showed the best combination of sensitivity and specificity, whereas in the original article by Pastori et al the best combination was obtained by a score ≥3,[1] as was also confirmed in the FANTASIIA cohort. Importantly, we show that the 2MACE score can be useful in 2 different contexts. First, in patients with AF taking VKA or NOAC from a multicenter registry in the short-term follow-up. Second, in AF patients well controlled with VKA and during a long-term follow-up period. These observations potentially add value to this novel score for use in daily clinical practice.

This study has several limitations that should be noted. First, the Murcia AF cohort is a Caucasian-based population from a single center. Second, all patients were treated with VKA (INR 2.0 to 3.0) during the previous 6 months to ensure homogeneity at baseline. We acknowledge that this inclusion criterion may not reflect "typical" clinical practice, but the long follow-up and the standard care received make this cohort suitable. The FANTASIIA observational registry includes patients taking VKA or NOAC, and its design is multicenter. However, individual incidence rates of MACE present in this study may be low, because the follow-up is only 1 year, and the planned complete follow-up for 3 years is ongoing. Although our datasets were collected prospectively, all statistical analyses were performed retrospectively. This led us to define the metabolic syndrome according to the World Health Organization criteria, because at the end of follow-up we did not have the waist circumference of all patients.

In conclusion, in "real-world" patients with AF, the 2MACE score is a good predictor of MACE. A score ≥3 should be used to categorize patients at "high risk," in identifying patients at risk of MACE.

Disclosures

GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo.

Other authors state that they have no conflict of interest.

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