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Usefulness of the 2MACE Score to Predicts Adverse Cardiovascular Events in Patients with Atrial Fibrillation.

Short title: The 2MACE score in atrial fibrillation.

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Abstract

We investigated the incidence of non-embolic adverse events in 2 cohorts of AF patients and validated the 2MACE score [(metabolic syndrome, age ≥75) [doubled]; (myocardial infarction (MI)/revascularization, congestive heart failure (HF) and stroke/TIA/thromboembolism)] as predictor of major adverse cardiovascular events (MACEs). We recruited 2630 AF patients from two 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 non-embolic adverse events and MACEs (composite of non-fatal MI/revascularization and cardiovascular death). ROC curves comparison, reclassification/ discriminatory analyses and decision curve analysis, were performed to compare predictive ability and clinical usefulness of 2MACE score against CHA_2DS_2-VASc. During follow-up, there were 65 MACEs in the Murcia cohort and 60 in FANTASIIA. 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 ROC curve was significantly higher from 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 to the CHA_2DS_2-VASc score. In conclusion, in 'real world' AF patients, 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.

Keywords: atrial fibrillation, myocardial infarction, mortality, risk assessment.

Introduction

Recently, the 2MACE score [2 points for Metabolic Syndrome and Age ≥75, and 1 point for Myocardial Infarction/revascularization, Congestive heart failure (ejection fraction ≤40 %) and thrombo-Embolism (stroke/TIA)] has been described to stratify cardiovascular risk in non-valvular AF patients. According to this clinical tool, patients with a score ≥3 (high risk) have a risk almost 4-fold higher of suffering 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 non-embolic thrombotic adverse events in two 'real world' cohorts of AF patients. 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/permanent non-valvular AF who were stable with VKA (INR 2.0-3.0) 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 AF patients 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 non-valvular AF population between June 2013 and March 2014. Patients enrolled in FANTASIIA were receiving anticoagulant therapy (VKA or Non-vitamin K Oral Anticoagulants [NOAC]) for at least 6 months before enrolment, and were followed in 50 outpatient clinics by 81 investigators. The follow-up was carried out in three 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) were calculated in these two cohorts, and a complete medical history was recorded. The time in therapeutic range (TTR) was calculated at 6 month 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] For defining the metabolic syndrome (MetS), we used the established definition of the World Health Organization (WHO).[2, 3]

The *primary endpoints* were MACEs (the composite of nonfatal myocardial infarction [MI]/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; i.e. stroke/transient ischaemic 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 (SD) 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 were 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 DeLong *et al.* method.[4] Additionally, we used the methods described by Zhou *et al.*[5] for calculating the weighted summary area under the ROC curve under the fixed effects model and random effects model. Integrated discriminatory improvement (IDI) and net reclassification improvement (NRI) 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 (DCA).[7, 8]

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

Results

Baseline clinical characteristics are shown in Table 1. We included 693 patients (49.6% male; median age 75, IQR 69-80 years) followed-up for a median of 7.2 years (IQR 6.2-7.9)

from our AF cohort and 1937 patients (55.8% male; mean age 73.84 ± 9.48 years) followed-up for a median of 1.01 years (IQR 0.99-1.05) from FANTASIIA registry. CHA_2DS_2-VASc and HAS-BLED were calculated at entry, with median values of 4 (IQR 3-5) and 2 (IQR 2-3), respectively in our cohort and 4 (IQR 3-5) and 2 (IQR 1-3) in the FANTASIIA registry. The median TTR at 6 months after inclusion was 80% (IQR 66-100) and 63.03 (IQR 43.3-80) in both, our population and FANTASIIA. Baseline clinical characteristics associated with the development of a MACE during follow-up are shown in Supplementary Tables 1 and 2.

During the follow-up, 58 patients from our population suffered from a stroke (8.4%, i.e. 1.16%/year) and 106 suffered from a major bleeding event (15.3%, 2.12%/year). In the FANTASIIA registry, 15 patients had a stroke (0.77%/year) while 65 suffered from a major bleeding event (3.36%/year). In this period there were 65 MACE (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 non-fatal MI/revascularizations. Regarding the FANTASIIA cohort, 60 patients suffered a MACE (3.10%; 3.06%/year); 38 (2%; 1.94%/year) were cardiovascular deaths and 22 (1.4%; 1.12%/year) were non-fatal MI/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 1-3), 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 0-3) and 610 patients (31.5%) with a score ≥3. In our cohort, patients with 2MACE score ≥3 suffered 42 MACEs, which resulted into an annual event rate of 1.94%/year for this group. In the population of FANTASIIA, 37 patients with 2MACE score ≥3 suffered 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 (HR 2.88, 95% CI 1.73-4.80; p<0.001) (Supplementary Figure 1). The overall risk for each score point was 1.50 (95% CI 1.30-1.74, p<0.001) in our cohort, and 1.52 (95% CI 1.28-1.80, p<0.001) in the FANTASIIA registry.

ROC curve analysis demonstrated that the 2MACE score had a good performance for predict MACE in AF patients of our cohort, with a c-index of 0.662 (95% CI 0.625-0.697, 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 0.593-0.719, 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 for 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 for 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 0.641-0.696; random effects: 0.674; 95% CI 0.634-0.715, both p<0.001) (Figure 1).

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 IDI and NRI (Table 3).

Finally, decision curve analyses (DCA) graphically demonstrates 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 grey 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 grey 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 to the CHA_2DS_2-VASc score (Figure 2).

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 two different cohorts of AF patients.

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 myocardial infarction due to 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 AF patients at increased risk of cardiovascular events.[20] As well as CHA_2DS_2-VASc and HAS-BLED are widely used in clinical practice to estimate, respectively, the risk of ischemic stroke and bleeding, the new 2MACE score has proved to be useful for 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 non-stroke events of the CHA_2DS_2-VASc score has been investigated, and has proved to be useful predicting non-embolic 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 our both cohorts of patients, the 2MACE score had a similar c-index as 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 while 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 two different contexts. First, in AF patients 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 centre. Second, all patients were treated with VKA (INR 2.0-3.0) 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 presents in this study may be low, since the follow-up is yet only of 1 year and the planned complete follow-up for three years is ongoing. Although our datasets were collected prospectively, all statistical analyses were performed retrospectively. This led us to define the MetS according to the WHO criteria, since at the end of follow-up we did not have the waist circumference of all patients.

In conclusion, in 'real world' AF patients, 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.

Conflicts of interest

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

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.

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.

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.

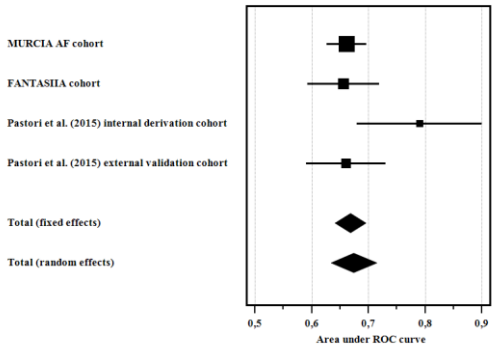

Figure 1.tif

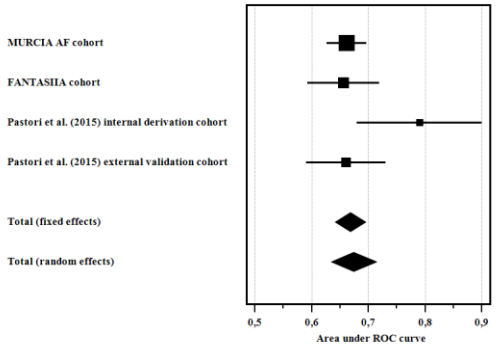

Figure 1_bestsetConverted.png

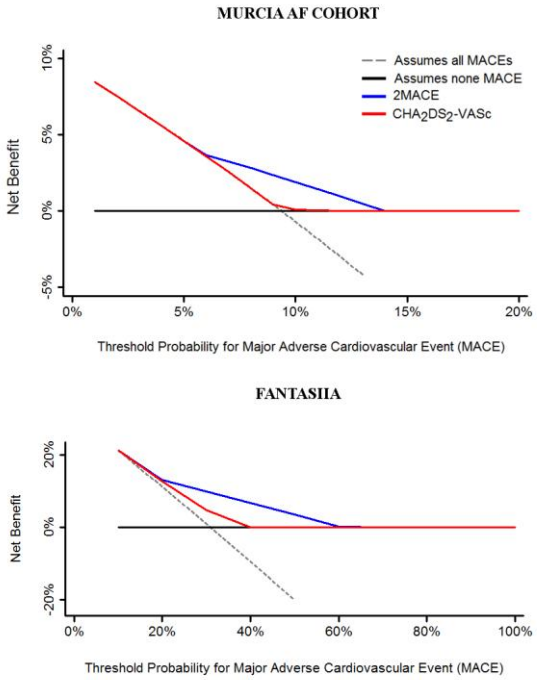

Figure 2.tif

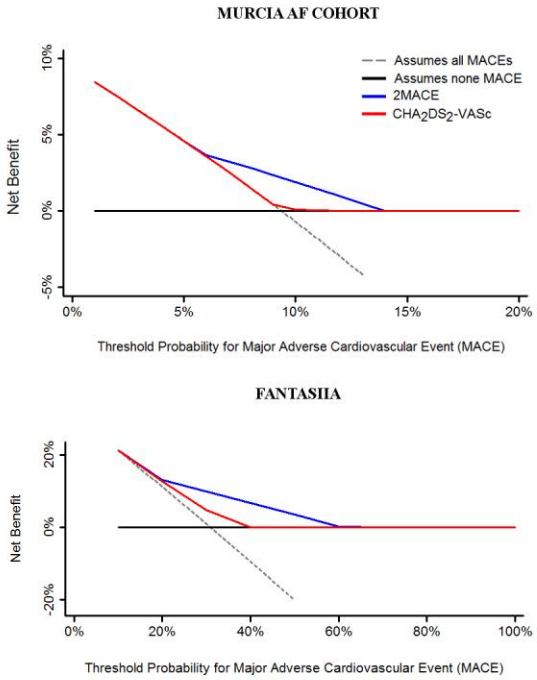

Figure 2_bestsetConverted.png