

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

Rivera-Caravaca, José Miguel; Marín, Francisco; Esteve-Pastor, María Asunción; Raña-Míguez, Paula; Anguita, Manuel; Muñoz, Javier; Cequier, Ángel; Bertomeu-Martínez, Vicente; Valdés, Mariano; Vicente, Vicente; Lip, Gregory Yoke Hong; Roldán, Vanessa

DOI:

[10.1016/j.amjcard.2017.09.003](https://doi.org/10.1016/j.amjcard.2017.09.003)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Rivera-Caravaca, JM, Marín, F, Esteve-Pastor, MA, Raña-Míguez, P, Anguita, M, Muñoz, J, Cequier, Á, Bertomeu-Martínez, V, Valdés, M, Vicente, V, Lip, GYH & Roldán, V 2017, 'Usefulness of the 2MACE Score to Predicts Adverse Cardiovascular Events in Patients With Atrial Fibrillation', *The American Journal of Cardiology*. <https://doi.org/10.1016/j.amjcard.2017.09.003>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Accepted Manuscript



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

Author: José Miguel Rivera-Caravaca, Francisco Marín, María Asunción Esteve-Pastor, Paula Raña-Míguez, Manuel Anguita, Javier Muñoz, Ángel Cequier, Vicente Bertomeu-Martínez, Mariano Valdés, Vicente Vicente, Gregory Yoke Hong Lip, Vanessa Roldán

PII: S0002-9149(17)31459-5
DOI: <http://dx.doi.org/doi: 10.1016/j.amjcard.2017.09.003>
Reference: AJC 22897

To appear in: *The American Journal of Cardiology*

Received date: 19-7-2017
Accepted date: 6-9-2017

Please cite this article as: José Miguel Rivera-Caravaca, Francisco Marín, María Asunción Esteve-Pastor, Paula Raña-Míguez, Manuel Anguita, Javier Muñoz, Ángel Cequier, Vicente Bertomeu-Martínez, Mariano Valdés, Vicente Vicente, Gregory Yoke Hong Lip, Vanessa Roldán, Usefulness of the 2MACE Score to Predicts Adverse Cardiovascular Events in Patients with Atrial Fibrillation., *The American Journal of Cardiology* (2017), <http://dx.doi.org/doi: 10.1016/j.amjcard.2017.09.003>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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

Short title: The 2MACE score in atrial fibrillation.

José Miguel Rivera-Caravaca^a, Francisco Marín^b, María Asunción Esteve-Pastor^b, Paula Raña-Míguez^c, Manuel Anguita^d, Javier Muñoz^c, Ángel Cequier^e, Vicente Bertomeu-Martínez^f, Mariano Valdés^b, Vicente Vicente^a, Gregory Yoke Hong Lip^{g*}, Vanessa Roldán^{a*}.
[*joint senior authors]

- a. Department of Hematology and Clinical Oncology, Hospital General Universitario Morales Meseguer, Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca), Murcia, Spain.
- b. Department of Cardiology, Hospital Clínico Universitario Virgen de la Arrixaca, Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca), CIBER-CV, Murcia, Spain.
- c. Universidade da Coruña, Instituto Universitario de Ciencias de la Salud, Instituto de Investigación Biomédica de A Coruña (INIBIC), La Coruña, Spain.
- d. Department of Cardiology, Hospital Universitario Reina Sofía, Córdoba, Spain.
- e. Department of Cardiology, Hospital de Bellvitge, CIBER-CV, Barcelona, Spain.
- f. Department of Cardiology, Hospital Universitario de San Juan, Alicante, Spain
- g. Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom, and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

Address for correspondence:

Francisco Marín

Department of Cardiology

Hospital Clínico Universitario Virgen de la Arrixaca

Ctra. Madrid-Cartagena s/n 30120, Murcia, Spain

Tel./fax: +34 968 38 10 27; E-mail: fcomarino@hotmail.com

Funding

This work was supported by Instituto de Salud Carlos III (ISCIII), Fondo Europeo de Desarrollo Regional (FEDER) (Research projects: PI13/00513 and P14/00253), Fundación Séneca (Grant number: 19245/PI/14) and Instituto Murciano de Investigación Biosanitaria (IMIB16/AP/01/06). José Miguel Rivera-Caravaca has received a grant from Sociedad Española de Trombosis y Hemostasia (Grant for short international training stays 2016).

The FANTASIIA registry was funded by an unconditional grant from Pfizer/Bristol-Myers-Squibb and by grants from the ISCIII/FEDER (RD12/0042/0068, RD12/0042/0010, RD12/0042/0069 and RD12/0042/0063).

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 CHA₂DS₂-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 CHA₂DS₂-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 CHA₂DS₂-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 $\leq 40\%$) 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 CHA₂DS₂-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 (CHA₂DS₂-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 \pm 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 CHA₂DS₂-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 CHA₂DS₂-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. CHA₂DS₂-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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 CHA₂DS₂-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 CHA₂DS₂-VASc and 2MACE scores. In previous studies, the predictive performance for non-stroke events of the CHA₂DS₂-VASc score has been investigated, and has proved to be useful predicting non-embolic adverse cardiovascular events.²¹⁻²⁵ Although in this study the CHA₂DS₂-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 CHA₂DS₂-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 FANTASIA 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 FANTASIA 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.

Accepted Manuscript

References

1. Pastori D, Farcomeni A, Poli D, Antonucci E, Angelico F, Del Ben M, Cangemi R, Tanzilli G, Lip GY, Pignatelli P, Violi F. Cardiovascular risk stratification in patients with non-valvular atrial fibrillation: the 2MACE score. *Intern Emerg Med* 2016; 11: 199-204.
2. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; 15: 539-553.
3. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Jr., Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; 112: 2735-2752.
4. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; 44: 837-845.
5. Zhou XH, Obuchowski NA, McClish DK. Statistical methods in diagnostic medicine. Second ed. New York: Wiley; 2002.
6. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008; 27: 157-172; discussion 207-112.
7. Vickers AJ, Cronin AM, Elkin EB, Gonen M. Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers. *BMC Med Inform Decis Mak* 2008; 8: 53.
8. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006; 26: 565-574.

9. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; 22: 983-988.
10. Medi C, Hankey GJ, Freedman SB. Stroke risk and antithrombotic strategies in atrial fibrillation. *Stroke* 2010; 41: 2705-2713.
11. Lip GY, Fauchier L, Freedman SB, Van Gelder I, Natale A, Gianni C, Nattel S, Potpara T, Rienstra M, Tse HF, Lane DA. Atrial fibrillation. *Nat Rev Dis Primers* 2016; 2: 16016.
12. Massera D, Wang D, Vorchheimer DA, Negassa A, Garcia MJ. Increased risk of stroke and mortality following new-onset atrial fibrillation during hospitalization. *Europace* 2016.
13. Polimeni L, Perri L, Saliola M, Basili S, Violi F. The risk of myocardial infarction in patients with atrial fibrillation: an unresolved issue. *Intern Emerg Med* 2010; 5: 91-94.
14. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd S, Howard VJ, Howard G, Herrington DM, Cushman M. Atrial fibrillation and the risk of myocardial infarction. *JAMA Intern Med* 2014; 174: 107-114.
15. Violi F, Soliman EZ, Pignatelli P, Pastori D. Atrial Fibrillation and Myocardial Infarction: A Systematic Review and Appraisal of Pathophysiologic Mechanisms. *J Am Heart Assoc* 2016; 5: e003347
16. Soliman EZ, Lopez F, O'Neal WT, Chen LY, Bengtson L, Zhang ZM, Loehr L, Cushman M, Alonso A. Atrial Fibrillation and Risk of ST-Segment-Elevation Versus Non-ST-Segment-Elevation Myocardial Infarction: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2015; 131: 1843-1850.
17. Marín F, Anguita Sánchez MP, Sanmartín Fernández M. Direct oral anticoagulants and cardiovascular prevention in patients with nonvalvular atrial fibrillation. *Expert Opin Pharmacother* 2016; 18: 67-77.

18. Fauchier L, Villejoubert O, Clementy N, Bernard A, Pierre B, Angoulvant D, Ivanes F, Babuty D, Lip GY. Causes of deaths and influencing factors in patients with atrial fibrillation. *Am J Med* 2016; 129: 1278-1287.
19. Potpara TS, Lip GY, Dagues N, Estner HL, Larsen TB, Blomstrom-Lundqvist C. Management of acute coronary syndrome in patients with non-valvular atrial fibrillation: results of the European Heart Rhythm Association Survey. *Europace* 2014; 16: 293-298.
20. Fauchier L, Lecoq C, Ancedy Y, Stamboul K, Saint Etienne C, Ivanes F, Angoulvant D, Babuty D, Cottin Y, Lip GY. Evaluation of 5 Prognostic Scores for Prediction of Stroke, Thromboembolic and Coronary Events, All-Cause Mortality, and Major Adverse Cardiac Events in Patients With Atrial Fibrillation and Coronary Stenting. *Am J Cardiol* 2016; 118: 700-707.
21. Bozbay M, Uyarel H, Cicek G, Oz A, Keskin M, Murat A, Yildirim E, Karaca G, Ergelen M, Eren M. CHA2DS2-VASc Score Predicts In-Hospital and Long-Term Clinical Outcomes in Patients With ST-Segment Elevation Myocardial Infarction Who Were Undergoing Primary Percutaneous Coronary Intervention. *Clin Appl Thromb Hemost* 2017; 23: 132-138.
22. Komatsu T, Tachibana H, Satoh Y, Ozawa M, Kunugita F, Ueda H, Nakamura M. Relationship between CHA2DS-VASc scores and ischemic stroke/cardiovascular events in Japanese patients with paroxysmal atrial fibrillation without receiving anticoagulant therapy. *J Cardiol* 2012; 59: 321-328.
23. Naccarelli GV, Panaccio MP, Cummins G, Tu N. CHADS2 and CHA2DS2-VASc Risk Factors to Predict First Cardiovascular Hospitalization Among Atrial Fibrillation/Atrial Flutter Patients. *Am J Cardiol* 2012; 109: 1526-1533.

24. Rozenbaum Z, Elis A, Shuvy M, Vorobeichik D, Shlomo N, Shlezinger M, Goldenberg I, kimhi O, Pereg D. CHA₂DS₂-VASc score and clinical outcomes of patients with acute coronary syndrome. *Eur J Intern Med* 2016; 36: 57-61.
25. Tasolar H, Cetin M, Balli M, Bayramoglu A, Otlu YO, Turkmen S, Akturk E. CHA₂DS₂-VASc-HS score in non-ST elevation acute coronary syndrome patients: assessment of coronary artery disease severity and complexity and comparison to other scoring systems in the prediction of in-hospital major adverse cardiovascular events. *Anatol J Cardiol* 2016; 16: 742-748.

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

Figure 2. Decision curves for the 2MACE and CHA₂DS₂-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%)
<i>Previous medications</i>		
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 ₂ DS 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.

Accepted Manuscript

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

	MURCIA AF cohort				FANTASIA cohort			
	2MACE score			<i>p</i>	2MACE score			<i>p</i>
	Total (<i>n</i> = 693)	score < 3 (<i>n</i> = 393)	score ≥ 3 (<i>n</i> = 300)		Total (<i>n</i> = 1937)	score < 3 (<i>n</i> = 1327)	score ≥ 3 (<i>n</i> = 610)	
MACE	65 (9.4%)	23 (5.9%)	42 (14.0%)	<0.001	60 (3.1%)	23 (1.7%)	37 (6.1%)	<0.001
<i>annual rate (%/year)</i>	1.30%/year	0.81%/year	1.94%/year		3.06%/year	1.71%/year	6.01%/year	
Non-fatal	34 (4.9%)	13 (3.3%)	21 (7.0%)	0.026	22 (1.4%)	11 (0.8%)	11 (1.8%)	0.110
MI/revascularization	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
<i>annual rate (%/year)</i>	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 CHA₂DS₂-VASc and 2MACE scores.

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

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

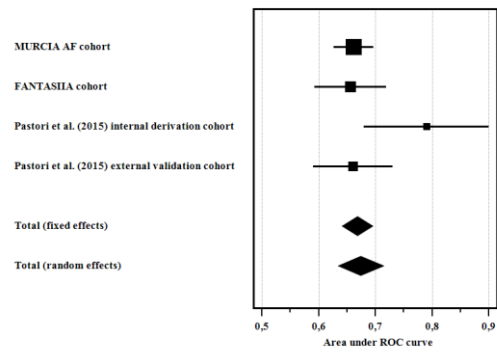


Figure 1.tif

Accepted Manuscript

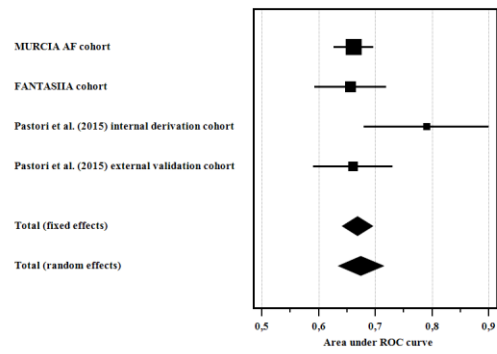


Figure 1_bestsetConverted.png

Accepted Manuscript

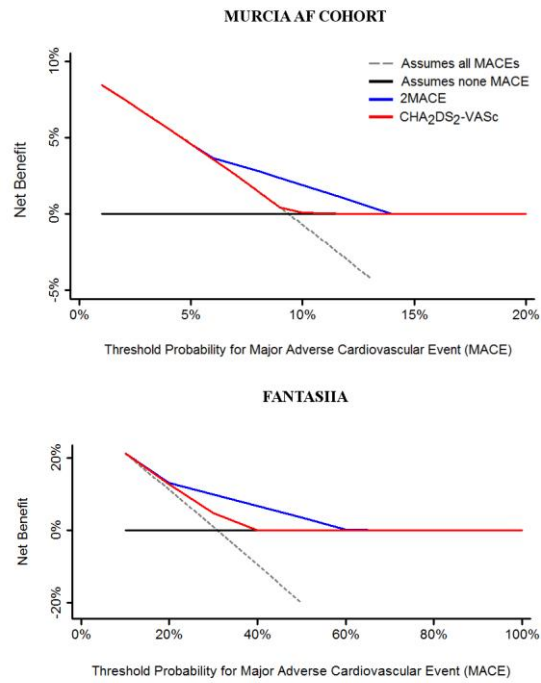


Figure 2.tif

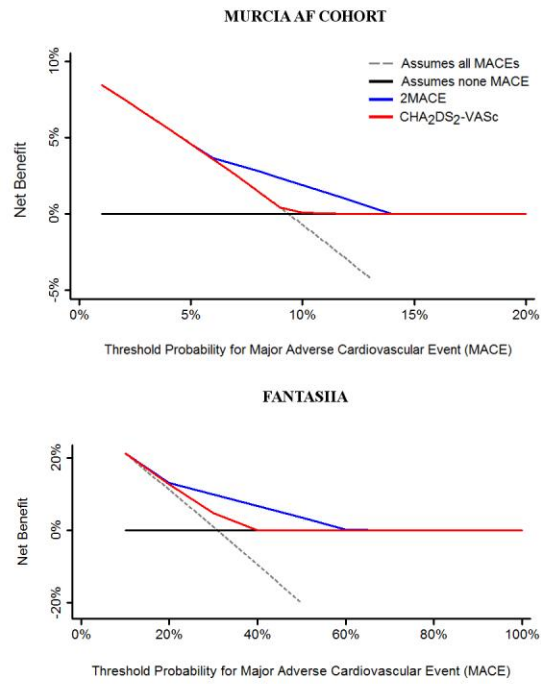


Figure 2_bestsetConverted.png