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Comparison of the 2MACE and TIMI-AF Scores for Composite Clinical Outcomes in Anticoagulated Atrial Fibrillation Patients

Daniele Pastori, MD, PhD; José Miguel Rivera-Caravaca; María Asunción Esteve-Pastor, MD; Vanessa Roldán, MD; Francisco Marín, MD; Pasquale Pignatelli, MD, PhD; Francesco Violi, MD; Gregory Y.H. Lip, MD

Background: Two risk scores have been developed to predict composite outcomes in atrial fibrillation (AF): the 2MACE and TIMI-AF scores. The aim of this study was to compare the predictive ability of these scores in 2 separate warfarin-treated cohorts (one 'real world', one clinical trial) of AF patients.

Methods and Results: The 2MACE and TIMI-AF scores were calculated in the 'real-world' ATHERO-AF cohort (n=907), and in the randomized controlled AMADEUS trial (n=2,265). Endpoints were major adverse cardiovascular events (MACEs), net clinical outcomes (NCO) and a combination of them, namely "clinically relevant events" (CREs). ROC curves showed similar predictive ability for MACE for 2MACE and TIMI-AF, in both the ATHERO-AF (0.698 vs. 0.688, respectively P=0.783) and AMADEUS (0.657 vs. 0.569, respectively P=0.057) cohorts. Similarly, the TIMI-AF showed a comparable c-index with 2MACE for NCOs in the ATHERO-AF (0.676 vs. 0.667, P=0.737), and AMADEUS (0.666 vs. 0.663, P=0.859) cohorts. No differences were found between the 2 scores for the prediction of CREs (0.675 vs. 0.684, P=0.740 in ATHERO-AF and 0.669 vs. 0.667, P=0.889 in AMADEUS for 2MACE and TIMI-AF, respectively).

Conclusions: This study showed that the 2MACE and TIMI-AF scores had modest but significant predictive ability for composite outcomes in AF. The clinical usefulness of both scores was similar, but the 2MACE score may be simpler and easy to use.

Key Words: 2MACE; Atrial fibrillation; Cardiovascular events; Net clinical outcomes; TIMI-AF

Atrial fibrillation (AF) is the most common supraventricular arrhythmia in the general population, with an increasing incidence in the last decades. The natural history of AF is characterized by a high thromboembolic risk, and AF-related ischemic stroke is almost twice as likely to be fatal as non-AF stroke, together with more severe disabilities among survivors.[1] Oral anticoagulants (OAC), such as vitamin K and non-vitamin K antagonists (VKAs and NOACs), are effective in reducing the rate of ischemic stroke in AF.[2,3] In addition to thromboembolism, a high incidence of cardiac adverse outcomes, such as myocardial infarction (MI) is also evident in AF, compared with the general population.[4–6]

Hence, AF patients may experience a wide range of complications, related to both AF itself and OAC treatment, which is complicated by bleeding with a rate ranging from 1.3% to 7.2% per year.[7] The most feared bleeding complication is intracranial hemorrhage, which occurs in approximately 1% of patients on OAC, and is associated with a 50% increase in the risk of death.

Nevertheless, an important unsolved issue is that there remains a residual cardiovascular and mortality risk that is still evident even in well-managed anticoagulated AF patients.[8–10] Also, both ischemic and hemorrhagic events may occur in the same patient. What should be considered is that, independent of the type of event (ischemic or

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Institute of Cardiovascular Sciences, University of Birmingham, Birmingham (D.P., J.M.R.-C., M.A.E.-P., G.Y.H.L.), UK; I Clinica Medica, Atherothrombosis Center, Department of Internal Medicine and Medical Specialities, Sapienza University of Rome, Rome (D.P., P.P., F.V.), Italy; Department of Hematology and Clinical Oncology, Hospital General Universitario Morales Meseguer, Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca), Murcia (J.M.R.-C., V.R.); Department of Cardiology, Hospital Clínico Universitario Virgen de la Arrixaca, Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca), CIBER-CV, Murcia (M.A.E.-P., F.M.), Spain; and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg (G.Y.H.L.), Denmark

The first two authors contributed equally to this work (D.P., J.M.R.-C.).

Mailing address: Gregory Y.H. Lip, Professor, MD, Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK. E-mail: g.y.h.lip@bham.ac.uk

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hemorrhagic), an AF patient who is being admitted or who has survived a complication is then more prone to stopping OAC,[11] resulting in a new event carrying an even greater degree of disability[12] and increased health-related costs. There is therefore the need for effective and simple clinical scores to predict composite outcomes in AF patients.[13]

Thus far, few risk stratification scores have been developed to predict composite cardiovascular outcomes in AF patients. The first is the 2MACE score, which is performed to predict the composite of major adverse cardiovascular events (MACE) including fatal/nonfatal MI, cardiac revascularization, and cardiovascular death in AF.[14] The 2MACE score has been recently validated in 3 cohorts of AF patients, showing good accuracy in predicting MACE occurrence.[15,16]

More recently, the TIMI-AF score was derived from the Effective Anticoagulation with Factor Xa Next Generation in AF-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) study, to predict the composite net clinical outcomes (NCO), including disabling stroke, life-threatening bleeding, and all-cause death.[17] This score is composed of several clinical and biochemical variables, such as age, reduced ejection fraction (EF), hemoglobin <13 g/dL, ethnicity (non-white race), baseline AF or flutter, prior ischemic stroke or MI, creatinine ≥110 μmol/L, male sex, diabetes mellitus and carotid disease history, for a maximum of 17 points.

The aim of our study was to compare the predictive ability of 2MACE and TIMI-AF scores towards composite outcomes, such as NCO and MACE, in 2 separate warfarin-treated cohorts (one 'real world', one clinical trial) of AF patients. As a secondary endpoint, we combined MACE and NCO into a composite variable that we termed "clinically relevant events" (CRE).

Methods

We included 2 cohorts of warfarin-anticoagulated AF patients: a 'real-world' cohort of consecutive AF patients from the Atherosclerosis in Atrial Fibrillation (ATHERO-AF) Study cohort,[18] and a cohort from the randomized clinical trial AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation).[19]

The ATHERO-AF study was an observational prospective study including non-valvular AF patients from the Atherothrombosis Center of the Department of Internal Medicine and Medical Specialties of Sapienza University of Rome, which was part of the cohort used to develop the 2MACE score. All patients were on treatment with VKAs after appropriate thromboembolic risk stratification. Exclusion criteria were prosthetic heart valves or the presence of any severe valvulopathies (i.e., severe mitral stenosis or regurgitation), severe cognitive impairment, chronic infections (human immunodeficiency virus infection, hepatitis C virus, hepatitis B virus), or systemic autoimmune disease, active cancer or liver insufficiency (e.g., cirrhosis). At entry, medical history was recorded for each patient. Cardiovascular risk factors, such as arterial hypertension,[20] diabetes,[21] and heart failure (HF),[22] were defined according to international guidelines.

The design of the AMADEUS trial has previously been described.[19] Briefly, this was a multicenter, randomized, open-label non-inferiority study with blinded assessment of outcomes that compared fixed-dose idraparinux with conventional anticoagulation by dose-adjusted VKA for the prevention of thromboembolism in AF patients with an indication for long-term anticoagulation. Exclusion criteria included inability to provide consent, contraindication or other requirement for anticoagulation, creatinine clearance <10 mL/min, breastfeeding, pregnancy, and recent or anticipated invasive procedures with potential for uncontrolled bleeding. For a proper analysis using the same criteria in both cohorts, only data from the VKA arm of the AMADEUS trial on an intention-to-treat basis were used.

The time in therapeutic range (TTR) was calculated for the 2 cohorts by the linear interpolation method of Rosendaal et al.[23] Stroke and bleeding risk were assessed by the CHA_2DS_2-VASc and HAS-BLED scores, respectively.[24,25] The 2MACE score was calculated as previously described,[14] assigning 2 points for Metabolic syndrome and age ≥75 years, 1 point for MI/Arterial revascularization, Congestive heart failure (EF <40%), thromboEmbolism (stroke/transient ischemic attack), ranging from 0 to 7 points.[14] The TIMI-AF score was calculated according to Fanola et al.[17]

Study Outcomes

The primary endpoints for this study were MACE and NCO, including disabling stroke, life-threatening bleeding, and all-cause death.

As a secondary endpoint, we also analyzed the predictive value of the 2 scores on CREs, resulting from a combination of MACE and NCO. MACE were defined as the composite of fatal/nonfatal MI, cardiac revascularization, and cardiovascular death (death caused by sudden death, progressive congestive HF, fatal MI or procedure-related death). NCO included the composite of disabling stroke, major bleeding, and all-cause death. As CRE, we recorded the composite of MI, major bleeding, stroke and all-cause death.

In the ATHERO-AF cohort, the investigators identified, confirmed and recorded all adverse events, whereas in the AMADEUS cohort all adverse events were adjudicated by the original central adjudication committee, who were blinded to treatment assignment. The study protocol was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and all patients gave informed consent to participation. The study was approved by the ethical board of Sapienza University of Rome and by each center participating in the AMADEUS trial.

Statistical Analysis

Continuous variables are expressed as mean±standard deviation or median and interquartile range (IQR), as appropriate. Categorical variables are expressed as absolute frequencies and percentages. The Pearson Chi-squared test was used to compare proportions and correlations were tested using the Spearman's rho. Cox proportional hazard regression models were performed to determine the association between the 2MACE and TIMI-AF scores with the endpoints.

To investigated the predictive performance (expressed as c-indexes) of the 2 scores, we used receiver-operating characteristic (ROC) curves, and compared them as described by DeLong et al.[26] The calibration of the scores was assessed by the Hosmer-Lemeshow test.

Discrimination and reclassification analyses were performed by the integrated discrimination improvement (IDI) and the net reclassification improvement (NRI),

Table 1. Univariate Cox Regression Analyses for 2MACE and TIMI-AF Scores for Selected Outcomes

	2MACE	P value	TIMI-AF	P value
	HR (95% CI)		HR (95% CI)	
ATHERO-AF cohort				
MACE	1.52 (1.31–1.77)	<0.001	1.32 (1.19–1.47)	<0.001
NCO	1.35 (1.21–1.50)	<0.001	1.28 (1.19–1.39)	<0.001
CRE	1.37 (1.25–1.51)	<0.001	1.28 (1.19–1.37)	<0.001
AMADEUS cohort				
MACE	1.52 (1.23–1.86)	<0.001	1.23 (1.04–1.46)	0.014
NCO	1.52 (1.34–1.73)	<0.001	1.43 (1.30–1.58)	<0.001
CRE	1.55 (1.37–1.75)	<0.001	1.43 (1.30–1.57)	<0.001

CI, confidence interval; CRE, clinically relevant event; HR, hazard ratio; MACE, major adverse cardiovascular event; NCO, net clinical outcome.

Table 2. Receiver-Operating Characteristic Curves Comparison, IDI and NRI of the 2MACE and TIMI-AF for Predicting Different Outcomes

	2MACE score			TIMI-AF score			TIMI-AF vs. 2MACE							
	C-index	95% CI	P value	C-index	95% CI	P value	Z statistic*	P value*	IDI	95% CI	P value	NRI	95% CI	P value
ATHERO-AF cohort														
MACEs	0.698	0.667–0.728	<0.001	0.688	0.657–0.718	<0.001	0.275	0.783	–0.010	–0.056/0.018	0.597	–0.014	–0.194/0.214	0.935
NCOs	0.667	0.636–0.698	<0.001	0.676	0.645–0.707	<0.001	0.335	0.738	0.007	–0.017/0.034	0.547	–0.059	–0.179/0.173	0.925
CREs	0.675	0.644–0.706	<0.001	0.684	0.652–0.714	<0.001	0.332	0.740	0.003	–0.023/0.031	0.866	–0.024	–0.161/0.165	0.836
AMADEUS cohort														
MACEs	0.657	0.637–0.677	<0.001	0.569	0.548–0.596	0.048	1.901	0.057	–0.007	–0.020/0.000	0.030	–0.181	–0.371/–0.039	<0.001
NCOs	0.663	0.643–0.682	<0.001	0.666	0.645–0.682	<0.001	0.166	0.869	0.008	–0.011/0.028	0.328	0.049	–0.134/0.187	0.527
CREs	0.669	0.649–0.689	<0.001	0.667	0.647–0.686	<0.001	0.144	0.886	0.005	–0.009/0.023	0.458	0.045	–0.138/0.154	0.667

*C-index comparison. IDI, integrated discriminatory improvement; NRI, net reclassification improvement. Other abbreviations as in Table 1.

according to Pencina et al.[27] The clinical usefulness and the net benefit of the risk scores were estimated using decision curve analysis (DCA).[28,29]

A P-value <0.05 was accepted as statistically significant. Statistical analyses were performed using SPSS v. 22.0 (SPSS, Inc., Chicago, IL, USA), MedCalc v. 16.4.3 (MedCalc Software bvba, Ostend, Belgium), STATA v. 12.0 (Stata Corp., College Station, TX, USA) and survIDINRI package for R v. 3.3.1 for Windows.

Results

Baseline clinical characteristics of the 2 populations are summarized in **Table S1**. In the ATHERO-AF and AMADEUS cohorts, mean age was 72.3±9.1 and 70.2±9.1 years, and the number of males was 58.1% and 65.5%, respectively. All patients were treated with VKAs in the ATHERO-AF cohort, and only the VKA arm of the AMADEUS trial was used for this analysis.

The median follow-up was 34.2 (IQR 19.0–53.6) months in the ATHERO-AF cohort, and 12.2 (IQR 6.3–15.3) months in the AMADEUS trial.

No differences in baseline risk factors for clinical outcomes were found between the 2 cohorts, as shown by the similar values for CHA_2DS_2-VASc, HAS-BLED, 2MACE, and TIMI-AF scores (**Table S1**).

During the follow-up, 43 (1.90%) patients in the AMADEUS cohort suffered a MACE, 119 (5.3%) patients suffered a NCO and 127 (5.6%) had a CRE. In the ATHERO-AF cohort, 59 (6.5%) patients suffered a MACE, 120 (13.2%) patients suffered a NCO and 151 (16.6%) had a CRE (**Table S2**).

Predictive Value of 2MACE and TIMI-AF for Study Outcomes

Univariate Cox regression analyses showed that both the 2MACE and TIMI-AF scores were significantly associated with an increased risk of MACE, NCO and CRE in the ATHERO-AF and AMADEUS cohorts (**Table 1**).

Comparing the 2MACE and TIMI-AF Scores

ROC curves comparison did not find significant differences in the predictive performance of the 2 scores for MACE, in both the ATHERO-AF (2MACE 0.698 vs. TIMI-AF 0.688, P=0.783) and AMADEUS (2MACE 0.657 vs. TIMI-AF 0.569, P=0.057) cohorts. Similarly, the TIMI-AF score had a non-significant difference in c-index to the 2MACE for NCO in the ATHERO-AF (0.676 vs. 0.667, P=0.738), and

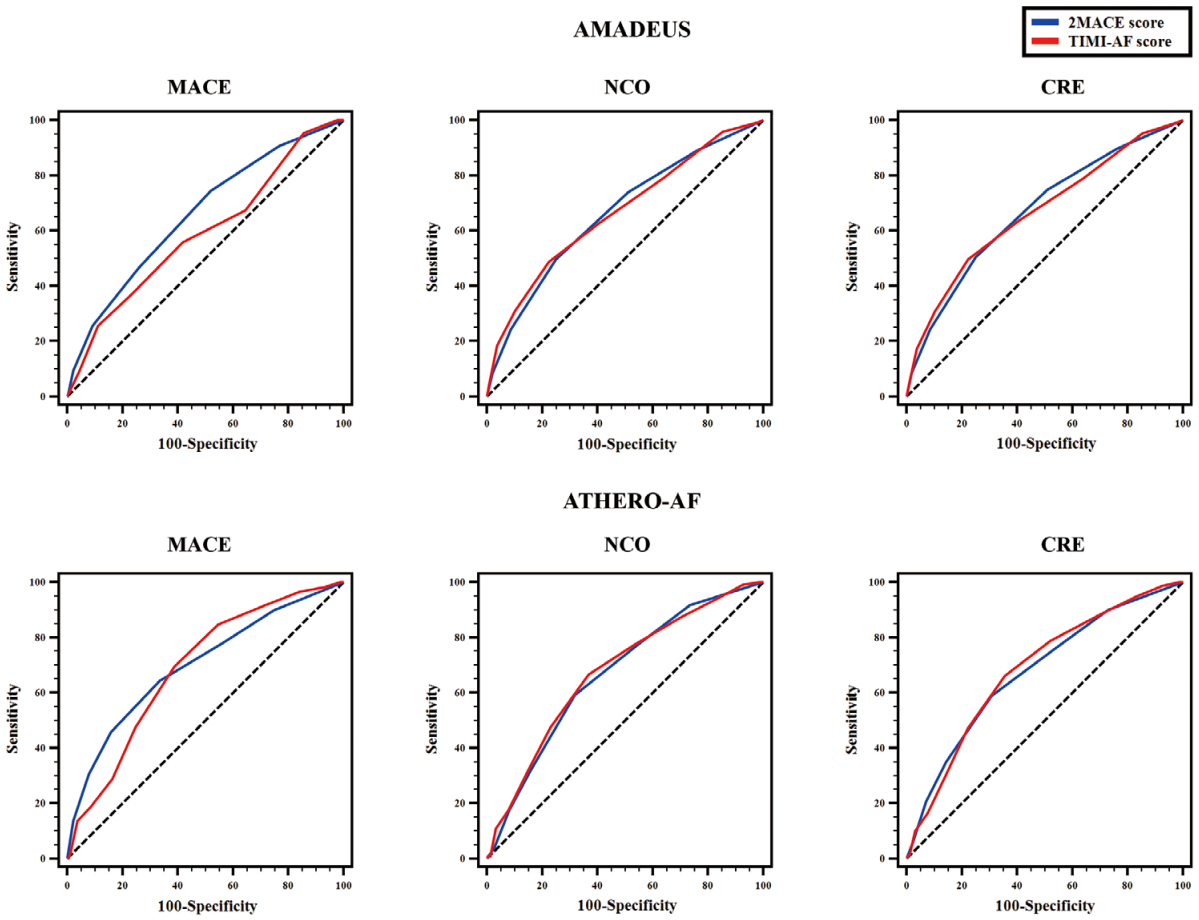

Figure 1. Receiver-operating characteristic curves comparison for major adverse cardiovascular events (MACE), net clinical outcomes (NCO) and clinically relevant events (CRE) in the AMADEUS cohort (**Upper**) and ATHERO-AF cohort (**Lower**). The blue line indicates the 2MACE score and red line is the TIMI-AF score.

AMADEUS (0.666 vs. 0.663, P=0.869) cohorts. No significant differences were found between the 2 scores for CRE prediction (0.675 vs. 0.684, P=0.740 in the ATHERO-AF and 0.669 vs. 0.667, P=0.886 in the AMADEUS for 2MACE and TIMI-AF, respectively) (**Table 2**, **Figure 1**).

The discrimination and reclassification analyses also gave similar results for both scores in the 2 cohorts and the 3 endpoints, with the only exception of TIMI-AF compared with 2MACE in predicting MACE in the AMADEUS cohort, whereby IDI showed a small but significant lower sensitivity (−0.7%, P=0.030) and a negative continuous reclassification (−18%, P<0.001) (**Table 2**).

DCA demonstrated comparable net benefits and clinical usefulness between 2MACE and TIMI-AF for predicting MACE, NCO and CRE (**Figure 2**).

The calibration of the scores was fairly good, as shown in **Table S3**.

Subgroup Analysis

We also investigated the annual event rate of each endpoint according to subgroup categories of both scores. Thus, we categorized both cohorts into low and high risk according to the 2MACE score (0–2 and ≥3 points, respectively), and into 3 groups according to the original work of the TIMI-AF score (0–6, 7–9 and 10–12 points, respectively). Overall, annual event rates were increased for the high-risk categories of each score (**Table 3**).

We also investigated the predictive ability of each score according to age categories. Briefly, both scores showed lower predictive value in patients aged ≥75 years compared with those aged <75 years in the ATHERO-AF cohort. In contrast, the 2MACE and TIMI-AF scores showed lower predictive performance in patients <75 years compared with those patients aged ≥75 years in the AMADEUS trial (**Table S4**).

When we separately analyzed fatal events, we found no difference between the 2MACE and TIMI-AF scores in predicting all-cause death in the ATHERO-AF cohort (n=66). Thus, the c-index for the 2MACE was 0.66 (95% CI 0.63–0.69, P<0.001) and 0.70 (95% CI 0.67–0.73, P<0.001) for the TIMI-AF score (P=0.239 for the difference). Similarly, c-index comparisons did not show differences between 2MACE and TIMI-AF scores in predicting all-cause death in the population included in the AMADEUS (0.67 [95% CI 0.65–0.69] vs. 0.67 [95% CI 0.66–0.69], P=0.890).

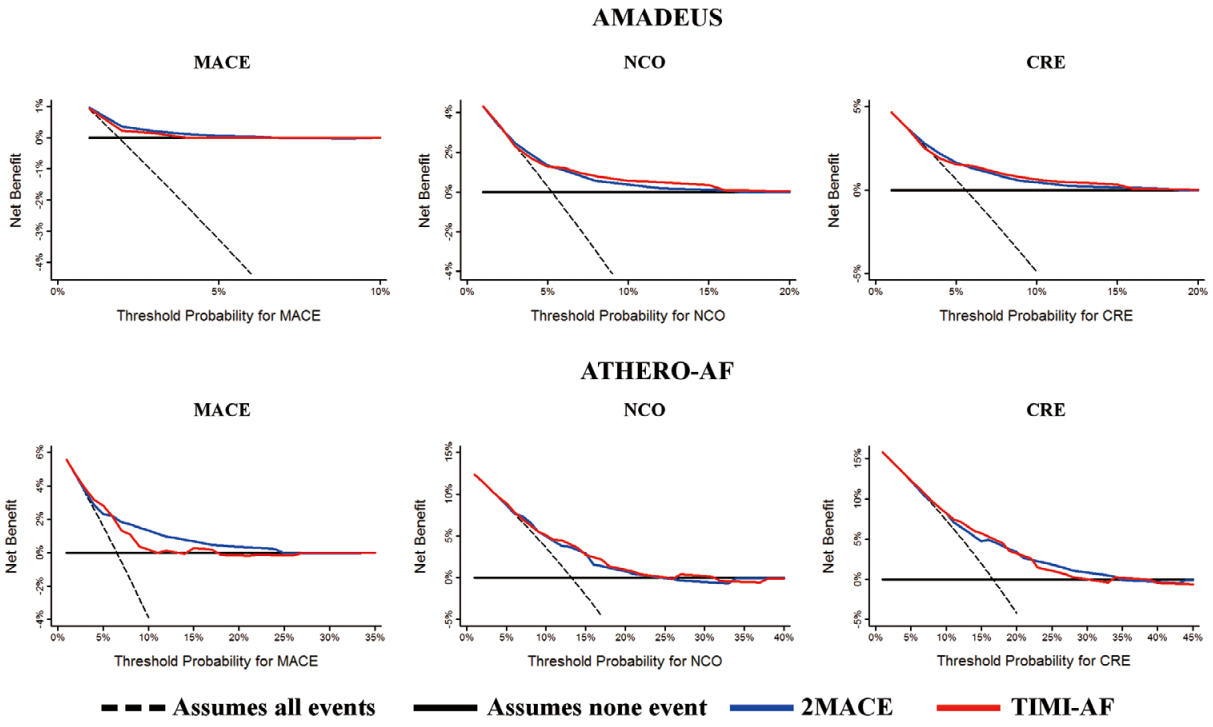

Figure 2. Decision curve analysis for the 2MACE (blue line) and TIMI-AF (red line) scores for MACE, NCO and CRE in the AMADEUS cohort (**Upper**) and ATHERO-AF cohort (**Lower**). This analysis shows the clinical usefulness of each score based on a continuum of potential thresholds for the endpoints (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 an endpoint. Abbreviations as in Figure 1.

Table 3. Annual Rates of Endpoints According to Subgroup Categories of the 2 Scores

	MACE (%/year)	NCO (%/year)	CRE (%/year)
ATHERO-AF cohort			
2MACE groups			
2MACE 0–2 points	1.15	2.69	3.41
2MACE ≥3 points	3.76	7.07	8.86
TIMI-AF groups			
TIMI-AF 0–6 points	1.43	2.92	3.71
TIMI-AF 7–9 points	3.38	7.46	9.50
TIMI-AF 10–12 points	9.75	15.9	18.4
AMADEUS cohort			
2MACE groups			
2MACE 0–2 points	1.37	3.59	3.77
2MACE ≥3 points	3.35	9.88	10.72
TIMI-AF groups			
TIMI-AF 0–6 points	1.56	3.53	3.70
TIMI-AF 7–9 points	2.93	10.18	11.15
TIMI-AF 10–12 points	3.70	22.22	22.22

Abbreviations as in Table 1.

Finally, a comparison of the 2MACE and TIMI-AF scores with $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores is provided in **Table S5**. This showed that the HAS-BLED score was generally inferior to both the 2MACE and TIMI-AF scores in predicting outcomes in the ATHERO-AF cohort, and the CHA_2DS_2-VASc score was superior to TIMI-AF for MACE in the AMADEUS cohort.

Discussion

In this study, which included 2 separate cohorts of anticoagulated AF patients from the "real world" and a clinical trial, our principal finding was that the 2MACE and TIMI-AF scores showed a similar predictive ability towards NCO and CRE. There was a higher sensitivity of 2MACE in re-classifying high-risk patients for MACE in the AMADEUS trial.

The present analysis was a unique opportunity to test both the 2MACE and TIMI-AF scores in 2 separate VKA-treated cohorts of AF patients.

With respect to the 2MACE score, our results for the AMADEUS cohort, were in keeping with recent validation studies showing a c-index of 0.65–0.69 in predicting MACE in all cohorts in which it was tested.[15,16] Altogether, these findings confirm the usefulness of this score in predicting cardiovascular outcomes in AF. This has clinical relevance, as recent evidence confirmed that AF is a risk factor for myocardial ischemia,[6] and that almost 50% of deaths in AF patients are attributable to cardiac causes, and only a minority to thromboembolism and bleeding (5–6% each).[30]

In addition, the c-indexes for the TIMI-AF score found in our 2 cohorts were very similar to those obtained from the original internal validation.[17] Of note, the TIMI-AF score includes up to 11 laboratory and instrumental variables, resulting into a score that is difficult to remember and apply. Moreover, laboratory analyses such as creatinine and hemoglobin may rapidly and significantly change over time, thus not reflecting the real risk of patients in long-term follow-up. This is graphically exemplified by our DCA, showing that the use of the TIMI-AF score does not provide any clinical advantage over the 2MACE score for the prediction of any of the composite outcomes considered in this study.

Indeed, a recent real-world validation of the TIMI-AF score demonstrated that it has limited usefulness even in predicting NCO over a long-term period of follow-up and was not superior to CHA_2DS_2-VASc or HAS-BLED, particularly for identifying low-risk patients.[31]

Thus, the use of the 2MACE score rather than TIMI-AF may be clinically more convenient, given that it showed at least similar predictive ability for NCO and a higher sensitivity for MACE in VKA-treated patients, together with a lower number of clinical variables to be calculated.

Our findings have clinical implications. We acknowledge that testing scores for endpoints that were not the same as those they were derived for may appear as a conceptual issue. Thus, although the TIMI-AF score included severe events such as disabling stroke and life-threatening bleeding, the 2MACE was designed for cardiac outcomes, and included also potentially non-severe events such as cardiac revascularization.

Notably, investigation of composite outcomes in AF is clinically relevant for several reasons because some risk factors, such as age, renal impairment, and hypertension, increase the risk of both ischemic and bleeding complications, as well as cardiovascular/all-cause deaths. Also, every complication occurring in the history of a patient suffering from AF contributes to increasing the risk of death, irrespective of the type of event. Additionally, despite good anticoagulation, the rate of cardiac outcomes and death is still high in AF, suggesting that reduction of a single endpoint (i.e., ischemic stroke) is probably not enough as part of the holistic management of these patients.[32]

For all these reasons, we combined the endpoints of the 2 scores in the so-called CRE to investigate the overall risk of any type of complication. Both scores showed a significant predictive ability for CREs, suggesting that they may be used to assess the global risk of a patient with AF.

Hence, the application of a risk stratification score for composite outcomes can help decision-making, leading to a significant reduction not only of thromboembolism, but also of cardiac outcomes and overall death.[30] For instance, AF patients initially categorized as 'low-risk' for thromboembolism, such as those with CHA_2DS_2-VASc 0 and 1, may still be at important risk of MACE or NCO. Apart from cardiovascular prevention drugs, such patients could also benefit from NOACs, which seems to favorably affect the risk of all-cause death, mainly by reducing fatal bleeding.[30]

Study Limitations

This study has some limitations that should be noted. Even if the TIMI-AF score was developed in a cohort with slightly different characteristics compared with the ATHERO-AF and AMADEUS cohorts, these 2 cohorts disclosed a similar baseline thromboembolic and bleeding risk, as shown by the CHA_2DS_2-VASc and HAS-BLED scores, making results comparable. Although we provided comparisons with the $CHADS_2$, the CHA_2DS_2-VASc and HAS-BLED scores were not developed for composite outcomes, and are not currently recommended for predicting MACE or NCO in AF. Also, the length of follow-up was different between the 2 cohorts, but the annual rates of events were similar. Despite data from both cohorts being collected prospectively, the results from our study should be regarded as exploratory post-hoc analyses.

Finally, most of patients included in the 2 cohorts were Caucasian, and thus the generalizability of the results to patients with non-white ethnicity is unclear.

Conclusions

This study showed that the 2MACE and TIMI-AF scores had modest but significant predictive ability for composite outcomes in AF patients. The clinical usefulness of both scores is similar, but the 2MACE score may be simpler and easier to use.

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Authors' Conflict of Interests

None declared related to this manuscript.

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None.

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Supplementary Files

Supplementary File 1

Table S1. Baseline characteristics of the study cohorts

Table S2. Annual rates of each outcome in the 2 cohort studies

Table S3. Results from the Hosmer-Lemeshow test for calibration of the scores

Table S4. Predictive performance of 2MACE and TIMI-AF scores according to age groups

Table S5. Comparison of 2MACE and TIMI-AF score with $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores

Please find supplementary file(s);
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