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### Prediction of long-term net clinical outcomes using the TIMI-AF score:

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## Accepted Manuscript

Prediction of long-term net clinical outcomes using the TIMI-AF score:  
Comparison with CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED

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**Prediction of long-term net clinical outcomes using the TIMI-AF score: Comparison with CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED**

**Cover title:** Prediction of net clinical outcomes by the TIMI-AF

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**Abstract**

*Background.* The TIMI-AF score was described to predict net clinical outcomes (NCOs) in atrial fibrillation (AF) patients receiving warfarin. However, this score derived from the ENGAGE AF-TIMI 48 trial, and no external validation exists in real world clinical practice. We tested the long-term predictive performance of the TIMI-AF score in comparison with CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED in a ‘real world’ cohort of anticoagulated AF patients.

*Methods.* We included 1156 consecutive AF patients stable on vitamin K antagonist (INR 2.0-3.0) during 6 months. The baseline risk of NCOs (composite of stroke, life-threatening bleeding, or all-cause mortality) was calculated using the novel TIMI-AF score. During follow-up, all NCOs were recorded and the predictive performance and clinical usefulness of TIMI-AF was compared with CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED.

*Results.* During 6.5 years (IQR 4.3-7.9), there were 563 NCOs (7.49%/year). ‘Low’ risk (6.07%/year) and ‘medium’ risk (9.49%/year) patients defined by the TIMI-AF suffered more endpoints than ‘low’ and ‘medium’ risk patients of CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED (2.37%/year and 4.40%/year for ‘low’ risk; 3.48%/year and 6.39%/year for ‘medium’ risk, respectively). The predictive performance of TIMI-AF was not different from CHA<sub>2</sub>DS<sub>2</sub>-VASc (0.678 vs. 0.677, p=0.963) or HAS-BLED (0.644 vs. 0.671, p=0.054). Discrimination and reclassification did not show improvement of prediction using the TIMI-AF score, and decision curves analysis did not demonstrate higher net benefit.

*Conclusions.* In VKA-experienced AF patients, the TIMI-AF score has limited usefulness predicting NCOs over a long-term period of follow-up. This novel score was not superior to CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED identifying ‘low risk’ AF patients.

**Keywords:** atrial fibrillation, anticoagulants, hemorrhage, stroke, mortality, risk prediction

## Introduction

Oral anticoagulation (OAC) in AF patients reduces the risk of stroke by 64% and the risk of all cause mortality by approximately 26% compared to control or placebo in trials <sup>1</sup>, with similar beneficial outcomes seen in everyday clinical practice <sup>1-5</sup>. For years, the Vitamin K Antagonists (VKAs, mainly warfarin and acenocoumarol) were the first option for OAC and thus, widely used worldwide.

Since the emergence of the Non-Vitamin K antagonist Oral Anticoagulants (NOACs, dabigatran, rivaroxaban, apixaban, and edoxaban), the landscape of stroke prevention has changed, with increasing use of OAC in many countries <sup>6</sup>. This is because the NOACs show relative efficacy, safety and convenience compared to VKA, without the need for routine anticoagulation monitoring <sup>7</sup>, such that recent guidelines for the management of AF have recommend the use of NOACs over VKAs in patients newly initiating OAC (Class IA) <sup>8,9</sup>.

OAC use requires a balance between thromboembolic and bleeding outcomes, which have often been expressed in relation to the net clinical benefit of the treatment. Recently, the TIMI-AF score (3 points = age  $\geq 75$  and left ventricular ejection fraction  $< 30\%$ ; 2 points = age 66-74, left ventricular ejection fraction 30-49%, hemoglobin  $< 13$  g/dL and non-white race; 1 point = unknown left ventricular ejection fraction, baseline AF or atrial flutter, prior ischaemic stroke, creatinine  $\geq 110$   $\mu\text{mol/L}$ , male sex, diabetes mellitus, carotid disease history and prior myocardial infarction) has been described to predict net clinical outcomes (the composite of disabling stroke, life-threatening bleeding, or all-cause mortality) in patients receiving warfarin therapy <sup>10</sup>. This score was derived from the ENGAGE AF-TIMI 48 trial cohort and no external validation exists as yet. Composite scores for stroke/thromboembolism/bleeding prediction have previously been described, but such an approach combining risk factors into a new risk score for composite events did not perform

much better than the established CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores for stroke and bleeding risk prediction, respectively <sup>11</sup>.

In the present study, we tested the long-term predictive performance of the TIMI-AF score and performed a comparison with CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores in a 'real world' cohort of anticoagulated AF patients.

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## Methods

For the present study from the Murcia AF Project, we included consecutive patients with paroxysmal, persistent or permanent AF who during the previous 6 months were stable on vitamin K antagonist (VKA; INR 2.0-3.0). The recruitment was carried out in our single anticoagulation center in a tertiary hospital in Murcia (South-east Spain) during a period of 7 months (from May 1, 2007 to December 1, 2007). At baseline, all patients were taking OAC with acenocoumarol (the commonest VKA used in Spain) and consistently achieved an INR between 2.0 and 3.0 during the previous 6 months (to ensure baseline homogeneity of the included cohort). We excluded patients with rheumatic mitral valves and 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.

At inclusion, a complete medical history was recorded. The time in therapeutic range (TTR) was calculated at 6 months after entry by the linear interpolation method of Rosendaal. Stroke risk and bleeding risk were assessed using the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores<sup>12,13</sup>. The risk of net clinical outcomes was calculated using the novel TIMI-AF score, giving 3 points to age  $\geq 75$  and left ventricular ejection fraction  $< 30\%$ ; 2 points to age 66-74, left ventricular ejection fraction 30-49%, hemoglobin  $< 13$  g/dL and non-white race, and 1 point to unknown left ventricular ejection fraction, baseline AF or atrial flutter, prior ischaemic stroke, creatinine  $\geq 110$   $\mu\text{mol/L}$ , male sex, diabetes mellitus, carotid disease history and prior myocardial infarction, as described by Fanola *et al.*<sup>10</sup> (Online Table 1).

### *Study outcomes*

The *primary endpoint* for this study was net clinical outcome (composite of disabling stroke, life-threatening bleeding, or all-cause mortality). As *secondary endpoints* we analyzed ischaemic strokes, major bleeds and deaths. Ischaemic stroke was defined as the sudden

onset of a focal neurological deficit in a location consistent with the territory of a major cerebral artery resulted of an obstruction documented by imaging, surgery or autopsy. Major bleeding was defined based on 2005 International Society on Thrombosis and Haemostasis (ISTH) criteria<sup>14</sup>. The follow-up was performed by personal interview at each visit to the anticoagulation clinic and through medical records. The investigators had full access to patients' clinical histories including Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) and therefore identified, confirmed and recorded all adverse events. Last follow-up visit was carried out on January 26, 2016 and no patient was lost.

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

#### *Statistical analysis*

Continuous variables were expressed as mean  $\pm$  standard deviation (SD) or median and interquartile range (IQR) as appropriate, whilst categorical variables were expressed as absolute frequencies and percentages. The Pearson Chi-squared test was used to compare proportions.

Cox proportional hazard regression models were performed to determine the association between higher values of the TIMI-AF, CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores, and primary/secondary endpoints. Differences in event-free survival by the different risk categories of TIMI-AF, CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED were reflected by Kaplan-Meier curves.

To evaluate the predictive ability (expressed as c-indexes) of the different risk scores, receiver operating characteristic (ROC) curves were applied. The methods of DeLong *et al.* were used for the ROC curves and ROC curves comparisons<sup>15</sup>. Discrimination and



reclassification performances were evaluated by the integrated discrimination improvement (IDI) and the net reclassification improvement (NRI), as described by Pencina *et al*<sup>16</sup>. The clinical usefulness and the net benefit of the risk scores were estimated using the decision curve analysis (DCA), according to the method proposed by Vickers *et al*<sup>17,18</sup>.

A p value <0.05 was accepted as statistically significant. Statistical analyses were performed using SPSS v. 19.0 (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.

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## Results

Over a median follow-up of 6.5 years (IQR 4.3-7.9), 1156 patients (49.3% male; median age 76, IQR 71-81 years), were followed-up. Baseline clinical characteristics are summarized in Table 1. At entry, median CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores were 4 (IQR 3-5) and 2 (IQR 2-3), respectively. The median TIMI-AF score was 6 (IQR 4-7). Median TTR at 6 months after entry was 80% (IQR 66-100). During follow-up, there were 97 (8.4%, 1.30%/year) ischaemic strokes, 168 major bleeds (14.5%, 2.24%/year), and 470 deaths (40.7%, 6.25%/year). The net clinical outcomes endpoint was recorded in 563 patients (48.7%, 7.49%/year).

### *Ischaemic stroke and bleeding*

In the analysis of the 97 ischaemic stroke events, 1% were categorized as 'medium' risk by the CHA<sub>2</sub>DS<sub>2</sub>-VASc (i.e. score=1) and 99% as 'high' risk patients (i.e. score  $\geq 2$ ); importantly no 'low risk' patients by CHA<sub>2</sub>DS<sub>2</sub>-VASc suffered a stroke. Using the TIMI-AF score, 56.7% of the ischaemic strokes occurred in 'low risk' patients (i.e. score 0-6), 33.0% occurred in 'medium risk' patients (score 7-9 points), and 10.3% in 'high' risk patients (score  $\geq 10$ ).

For bleeding events, 11.3% of major bleeds were in the 'low risk' patients according to the HAS-BLED score (score 0-1), whilst 29.2% of major bleeds were in the 'medium risk' category (score=2); however, the vast majority of bleeding events (59.5%) were sustained in 'high risk' patients (score  $\geq 3$ ). Using the TIMI-AF score, 53.6% of major bleedings were sustained in 'low risk' patients, 37.5% in 'medium risk' patients, and 8.9% in 'high risk' patients.

### *Net clinical outcomes*

For the ‘net clinical outcomes’ endpoint, 0.4% were sustained by ‘low risk’ patients as defined by CHA<sub>2</sub>DS<sub>2</sub>-VASc and 8.2% as defined using HAS-BLED. More than half (51%) of the events were suffered by ‘low risk’ patients as defined using the TIMI-AF score. Corresponding figures for the ‘medium risk’ categories recorded 2.1% of events by CHA<sub>2</sub>DS<sub>2</sub>-VASc, 36.2% by HAS-BLED and 40.3% by TIMI-AF.

Using CHA<sub>2</sub>DS<sub>2</sub>-VASc, the ‘high risk’ category, had 97.5% of the recorded outcomes, whilst the ‘high risk’ HAS-BLED and TIMI-AF categories accounted for 55.6% and 8.7% of the events, respectively (Table 2).

### *Survival analyses*

Cox regression analyses demonstrated a relative risk of *ischaemic stroke* of 1.45 (95% CI 1.28-1.64, p<0.001) for each CHA<sub>2</sub>DS<sub>2</sub>-VASc score point, 1.65 (95% CI 1.41-1.93, p<0.001) for HAS-BLED, and 1.23 (95% CI 1.12-1.35, p<0.001) for TIMI-AF. The risk of *major bleeding* per each score point was 1.18 (95% CI 1.07-1.30, p<0.001) for CHA<sub>2</sub>DS<sub>2</sub>-VASc, 1.49 (95% CI 1.31-1.93, p<0.001) for HAS-BLED, and 1.23 (95% CI 1.12-1.35, p<0.001) for TIMI-AF. Finally, the risk of *net clinical outcomes* was 1.34 (95% CI 1.27-1.41, p<0.001) for CHA<sub>2</sub>DS<sub>2</sub>-VASc, 1.46 (95% CI 1.34-1.57, p<0.001) for HAS-BLED, and 1.25 (95% CI 1.20-1.30, p<0.001) for TIMI-AF with each score point (Online Table 2).

Figure 1 shows Kaplan-Meier survival analyses with the different risks of each category for, CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED and TIMI-AF scores. This analysis also demonstrates that both ‘low risk’ (annual rate 6.07%/year) and ‘medium risk’ (9.49%/year) patients defined by the TIMI-AF sustained more primary endpoints than the ‘low risk’ and ‘medium risk’ category patients using CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED (annual rates of

2.37%/year and 4.40%/year for 'low' risk; 3.48%/year and 6.39%/year for 'medium' risk, respectively) (Table 2).

#### *Prediction of net clinical outcomes*

The TIMI-AF score demonstrated a modest predictive performance for net clinical outcomes, with a c-index of 0.677 (95% CI 0.649-0.704). The predictive performance of CHA<sub>2</sub>DS<sub>2</sub>-VASc was similar (c-index = 0.678, 95% CI 0.650-0.705) and non-significantly different from the c-index of TIMI-AF (0.678 vs. 0.677, p=0.963). The HAS-BLED score showed a slight worse predictive performance, but also not significantly different from TIMI-AF (0.644 vs. 0.677, p=0.054) (Figure 2).

A summary of the ROC curve comparisons, as well as IDI, NRI and median improvement analyses are detailed in Table 3. Based on the IDI, the TIMI-AF score showed for net clinical outcomes a non-significant improvement of 1.2% (p=0.418) and 2.3% (p=0.119) against CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED, respectively. In the same way, the NRI showed a *non-significant* positive reclassification over CHA<sub>2</sub>DS<sub>2</sub>-VASc (0.5%, p=0.925) and HAS-BLED (10.5%, p=0.139) scores. The median improvement of the TIMI-AF score over CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED at 6.5 (IQR 4.3-7.9) years of follow-up was non-significant (<0.1%, p=0.249 and 1.9%, p=0.090; respectively) (Table 3).

In order to assess the clinical usefulness in real practice, we plotted DCAs which graphically demonstrated no net benefit of the TIMI-AF in comparison to the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores (Figure 3).

## Discussion

The principal finding of the present study investigating the predictive performance of the TIMI-AF score was that this novel score is not superior compared with the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores to predict adverse net clinical outcome events in a 'real world' cohort of VKA-experienced AF patients who had stable INRs at inclusion. Second, the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores performed better in identifying 'low risk' patients. Consequently, our data suggest that the clinical usefulness of the TIMI-AF score in the 'real world' is limited.

The TIMI-AF has been proposed to predict net clinical outcomes in AF patients taking OACs. This composite of events includes strokes, major bleeds, and all-cause deaths. Although this score could give physicians an overview of the risk of suffering an adverse clinical event of importance in AF patients, it will be difficult to reflect the individual risk of each event. For example, "high risk" patients according to the TIMI-AF score could have a higher risk of either disabling stroke, life-threatening bleeding or death. However, it cannot show if the risk of stroke is higher than the risk of bleeding or on the contrary, if the risk of bleeding is higher than the risk of stroke. Clinical decision-making could be quite different depending on if patients have a high risk of stroke or high risk of bleeding. Indeed, previous studies demonstrated that thromboembolic and bleeding risk classifications are correlated but not exchangeable and thus, the advantage of a strategy combining risk assessment is questionable<sup>19</sup>.

Predictors of adverse events incorporated in the TIMI-AF score are well known to be associated with stroke and major bleeding, and most are already included in the widely used CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores<sup>12,13</sup>. This is the case of age, hemoglobin (as a way to assess anemia), history of previous stroke, renal function, sex, diabetes mellitus or history of coronary disease. Surprisingly, hypertension, a demonstrated risk factor of stroke and

bleeding in AF has not been included in this novel score. Indeed, hypertension is strongly related with AF and in the original article of TIMI-AF, hypertension was the commonest comorbidity, present in >90% of patients. In fact, the intimate association between hypertension, stroke and bleeding in AF is well known<sup>20-23</sup>.

One of the main advantages of CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED compared with the TIMI-AF is the prediction of low risk patients, even for net clinical outcomes. An issue of special interest is to define what annual rate of events we might assume to categorize patients as low risk. Using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, low risk patients (i.e. score 0 in males, 1 in females) generally have a stroke risk of <1%/year<sup>24-26</sup>. In the same line, low risk (score 0-1) using HAS-BLED also have a risk of major bleeding, of <1%/year<sup>27</sup>. In the original article of Fanola *et al.* the TIMI-AF 'low risk' patients had an annual event rate 3-fold higher (3.53%)<sup>10</sup>. In our study, low risk patients categorized by the TIMI-AF score had a high event rate for net clinical outcomes of 6.07%/year, which was higher than the rates observed with low risk patients of CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED (2.37%/year and 4.40%/year, respectively).

Importantly, the TIMI-AF was also described to aid selection of the type of oral anticoagulation treatment. According to this score, high risk (score  $\geq 10$ ) and intermediate risk (score 7-9) patients should be preferably treated with edoxaban, while low risk patients (score 0-6) should be treated with either warfarin or NOACs. To date, there are no head-to-head trials demonstrating the superiority of a NOAC against others, so there is no evidence supporting the use of edoxaban in particular in high-medium risk patients. Additionally, our study showed that low risk patients categorized by the TIMI-AF score had an appreciable annual event rate, and are not 'truly low risk'; hence, warfarin might still not be the optimal OAC treatment for them<sup>28-30</sup>.

How do trial cohorts translate to real world practice? The TIMI-AF score was developed using the data from AF patients from the ENGAGE AF-TIMI 48 trial. AF patients

in ‘real world’ clinical practice tend to be older, with many associated comorbidities and polypharmacy, and variable treatment adherence and follow-up, whereas in clinical trials, patients are often carefully selected with specific inclusion/exclusion criteria and carefully followed up in a protocol-based manner<sup>31,32</sup>. Usually, AF patients in clinical trials undergo various procedures and follow-up appointments by protocol, which is uncommon in the real world. This is exemplified by (eg.) the inclusion of carotid disease or the percentage of left ventricular ejection function in the final model of the TIMI-AF score. However, an echocardiogram is not needed for routine risk assessment and therefore not necessary for OAC selection<sup>9</sup>. Awaiting additional tests or multiple biomarker assays simply to define high(er) risk can delay the onset of OAC initiation, particularly in the first weeks of diagnosis when the risk is higher<sup>33</sup>.

#### *Limitations*

This study is limited by its single centre design and the recruitment of a Caucasian based population. At baseline, all patients were stable with VKA (all INR the 6 months previous at entry between 2 and 3) to ensure baseline homogeneity. For the same reason patients with rheumatic mitral valves, prosthetic heart valves, acute coronary syndrome, stroke, hemodynamic instability, hospital admissions or surgical interventions in the preceding 6 months were not included. Thus, these strict selection criteria may not reflect ‘typical’ clinical practice, but the long follow-up and the standard care received make our cohort suitable to test our hypotheses. Our dataset was collected in a prospective manner, but the statistical analyses presented in this study have been performed retrospectively. Of note, participant patients were carefully followed-up and all events (even very early ones) were recorded.

The TIMI-AF score was derived from the ENGAGE AF-TIMI 48 trial, a trial comparing outcomes in patients receiving VKA versus edoxaban. In the present study we only included patients receiving VKA, and thus we only investigated the role of the TIMI-AF score as risk prediction tool, but not as prediction scheme for choosing between NOAC and VKA.

### **Conclusions**

In VKA-experienced AF patients with stable INR at study entry, the TIMI-AF score has limited usefulness to predict net clinical outcomes over a long-term period of follow-up. This novel score was not superior to CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED for identifying ‘low risk’ AF patients.



**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. No fees are received personally.

There is nothing to disclose for other authors.

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**References**

1. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007;146(12):857-867.
2. Chao TF, Liu CJ, Tuan TC, et al. Impact on Outcomes of Changing Treatment Guideline Recommendations for Stroke Prevention in Atrial Fibrillation: A Nationwide Cohort Study. *Mayo Clin Proc.* 2016;91(5):567-574.
3. Lip GY, Laroche C, Popescu MI, et al. Improved outcomes with European Society of Cardiology guideline-adherent antithrombotic treatment in high-risk patients with atrial fibrillation: a report from the EORP-AF General Pilot Registry. *Europace.* 2015;17(12):1777-1786.
4. Diez-Manglano J, Gomes-Martin J, Al-Cheikh-Felices P, Perez SI, Diez-Angulo R, Clemente-Sarasa C. Adherence to guidelines and mortality in atrial fibrillation. *Int J Cardiol.* 2014;176(2):430-436.
5. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med.* 2010;123(7):638-645.e634.
6. Huisman MV, Rothman KJ, Paquette M, et al. The Changing Landscape for Stroke Prevention in AF: Findings From the GLORIA-AF Registry Phase 2. *J Am Coll Cardiol.* 2017;69(7):777-785.
7. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet.* 2014;383(9921):955-962.
8. Macle L, Cairns J, Leblanc K, et al. 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol.* 2016;32(10):1170-1185.

9. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893-2962.
10. Fanola CL, Giugliano RP, Ruff CT, et al. A novel risk prediction score in atrial fibrillation for a net clinical outcome from the ENGAGE AF-TIMI 48 randomized clinical trial. *Eur Heart J*. 2017;38(12):888-896.
11. Lip GYH, Lane DA, Buller H, Apostolakis S. Development of a novel composite stroke and bleeding risk score in patients with atrial fibrillation: the AMADEUS Study. *Chest*. 2013;144(6):1839-1847.
12. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest*. 2010;137(2):263-272.
13. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138(5):1093-1100.
14. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694.
15. 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(3):837-845.
16. 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(2):157-172; discussion 207-112.

17. 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.
18. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making.* 2006;26(6):565-574.
19. Marcucci M, Lip GY, Nieuwlaat R, Pisters R, Crijns HJ, Iorio A. Stroke and bleeding risk co-distribution in real-world patients with atrial fibrillation: the Euro Heart Survey. *Am J Med.* 2014;127(10):979-986.e972.
20. Lip GY. Atrial Fibrillation in Patients With Hypertension: Trajectories of Risk Factors in Yet Another Manifestation of Hypertensive Target Organ Damage. *Hypertension.* 2016;68(3):544-545.
21. Guo Y, Wang H, Tian Y, Wang Y, Lip GY. Multiple risk factors and ischaemic stroke in the elderly Asian population with and without atrial fibrillation. An analysis of 425,600 Chinese individuals without prior stroke. *Thromb Haemost.* 2016;115(1):184-192.
22. Lip GY, Lane DA. Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores. *J Thromb Haemost.* 2016.
23. Esteve-Pastor MA, Rivera-Caravaca JM, Lip GYH. Hypertension and Atrial Fibrillation: Balancing Stroke and Bleeding Risks. *Am J Hypertens.* 2017;30(11):1063-1065.
24. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. *Thromb Haemost.* 2012;107(6):1172-1179.
25. Nielsen PB, Chao TF. The risks of risk scores for stroke risk assessment in atrial fibrillation. *Thromb Haemost.* 2015;113(6):1170-1173.

26. Olesen JB, Torp-Pedersen C. Stroke risk in atrial fibrillation: Do we anticoagulate CHADS2 or CHA2DS2-VASc  $\geq 1$ , or higher? *Thromb Haemost.* 2015;113(6):1165-1169.
27. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol.* 2011;57(2):173-180.
28. Shahid F, Shantsila E, Lip GYH. What do the guidelines suggest for non-vitamin K antagonist oral anticoagulant use for stroke prevention in atrial fibrillation? *European Heart Journal Supplements.* 2016;18(suppl\_1):I18-I24.
29. Roldan I, Marin F. On the Way to a Better Use of Anticoagulants in Nonvalvular Atrial Fibrillation. Proposed Amendment to the Therapeutic Positioning Report UT/V4/23122013. *Rev Esp Cardiol (Engl Ed).* 2016;69(6):551-553.
30. Diener HC, Aisenberg J, Ansell J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2. *Eur Heart J.* 2017;38:860-868.
31. Freedman B, Lip GY. "Unreal world" or "real world" data in oral anticoagulant treatment of atrial fibrillation. *Thromb Haemost.* 2016;116(4):587-589.
32. Potpara TS, Lip GY. Postapproval Observational Studies of Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation. *JAMA.* 2017;317(11):1115-1116.
33. Garcia DA, Lopes RD, Hylek EM. New-onset atrial fibrillation and warfarin initiation: high risk periods and implications for new antithrombotic drugs. *Thromb Haemost.* 2010;104(6):1099-1105.

**Figure legends**

**Figure 1.** Kaplan-Meier analysis for net clinical outcomes according to the risk categories of each score.

Dashed lines = TIMI-AF; Solid lines = CHA<sub>2</sub>DS<sub>2</sub>-VASc; Crossed lines = HAS-BLED

Green lines = Low Risk; Purple lines = Medium Risk; Orange lines = High Risk

TIMI-AF categories were defined as low risk (score = 0-6), medium risk (score = 7-9), and high risk (score  $\geq 10$ ). CHA<sub>2</sub>DS<sub>2</sub>-VASc categories were defined as low risk (score = 0), medium risk (score = 1), and high risk (score  $\geq 2$ ). HAS-BLED categories were defined as low risk (score = 0-1), medium risk (score = 2) and high risk (score  $\geq 3$ ).

**Figure 2.** ROC curves comparison for net clinical outcomes

**Figure 3.** Decision curves for the TIMI-AF, CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores.

This analysis shows the clinical usefulness of each score based on a continuum of potential thresholds for net clinical outcomes (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 net clinical outcome.

**Table 1.** Baseline clinical characteristics.

	TIMI-AF score			CHA <sub>2</sub> DS <sub>2</sub> -VASc score			HAS-BLED score		
	<i>Low risk</i>	<i>Medium Risk</i>	<i>High risk</i>	<i>Low risk</i>	<i>Medium risk</i>	<i>High risk</i>	<i>Low risk</i>	<i>Medium Risk</i>	<i>High risk</i>
N = 1156	N = 727	N = 368	N = 61	N = 13	N = 52	N = 1091	N = 161	N = 491	N = 504
Male sex, n (%)	350 (48.1)	180 (48.9)	40 (65.5)	13 (100)	48 (92.3)	508 (46.6)	93 (57.8)	219 (44.6)	258 (51.2)
Age (years), median (IQR)	74 (68-79)	79 (75-83)	80 (77-84.5)	58 (53-63.5)	63 (57.3-68)	77 (72-81)	64 (59-77)	76 (71-81)	78 (73-82)
<b>Comorbidities, n (%)</b>									
Hypertension	598 (82.3)	313 (85.1)	52 (85.2)	0 (0.0)	22 (42.3)	941 (86.3)	51 (31.7)	435 (88.6)	477 (94.6)
Diabetes mellitus	136 (18.7)	141 (38.3)	38 (62.3)	0 (0.0)	2 (3.8)	313 (28.7)	31 (19.3)	116 (23.6)	168 (33.3)
Heart failure	105 (14.4)	210 (57.1)	55 (90.2)	0 (0.0)	2 (3.8)	368 (33.7)	40 (24.8)	150 (30.5)	180 (35.7)
Prior stroke/TIA	98 (13.5)	103 (28.0)	24 (39.3)	0 (0.0)	0 (0.0)	225 (20.6)	5 (3.1)	26 (5.3)	194 (38.5)
Renal impairment	43 (5.9)	62 (16.8)	23 (37.7)	1 (7.7)	3 (5.8)	124 (11.4)	2 (1.2)	8 (1.6)	118 (23.4)
Prior myocardial infarction	93 (12.8)	97 (26.4)	38 (62.3)	0 (0.0)	3 (5.8)	225 (20.6)	27 (16.8)	62 (12.6)	139 (27.6)
Current smoking habit	103 (14.2)	58 (15.8)	16 (26.2)	5 (38.5)	6 (11.5)	166 (15.2)	24 (14.9)	62 (12.6)	91 (18.1)
Concomitant antiplatelet treatment	93 (12.8)	90 (24.5)	24 (39.3)	1 (7.7)	6 (11.5)	200 (18.3)	5 (3.1)	18 (3.7)	184 (36.5)
TTR at 6 month (%), median (IQR)	80 (66-100)	80 (61.3-100)	71 (57-83)	80 (73-85)	80 (60-100)	80 (66-100)	80 (80-100)	80 (66-100)	68 (50-83)
TTR <65% at 6 month, n (%)	168 (23.1)	95 (25.8)	19 (31.1)	2 (15.4)	15 (28.8)	265 (24.3)	7 (4.3)	71 (14.5)	204 (40.5)

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IQR = interquartile range; TIA = transient ischemic attack; TTR = time in therapeutic range.

CHA<sub>2</sub>DS<sub>2</sub>-VASc = cardiac failure or dysfunction, hypertension, age  $\geq 75$  [doubled], diabetes, stroke [doubled] – vascular disease, age 65-74 years and sex category [female];

HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly age.

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**Table 2.** Distribution of net clinical outcomes according to risk categories of each score.

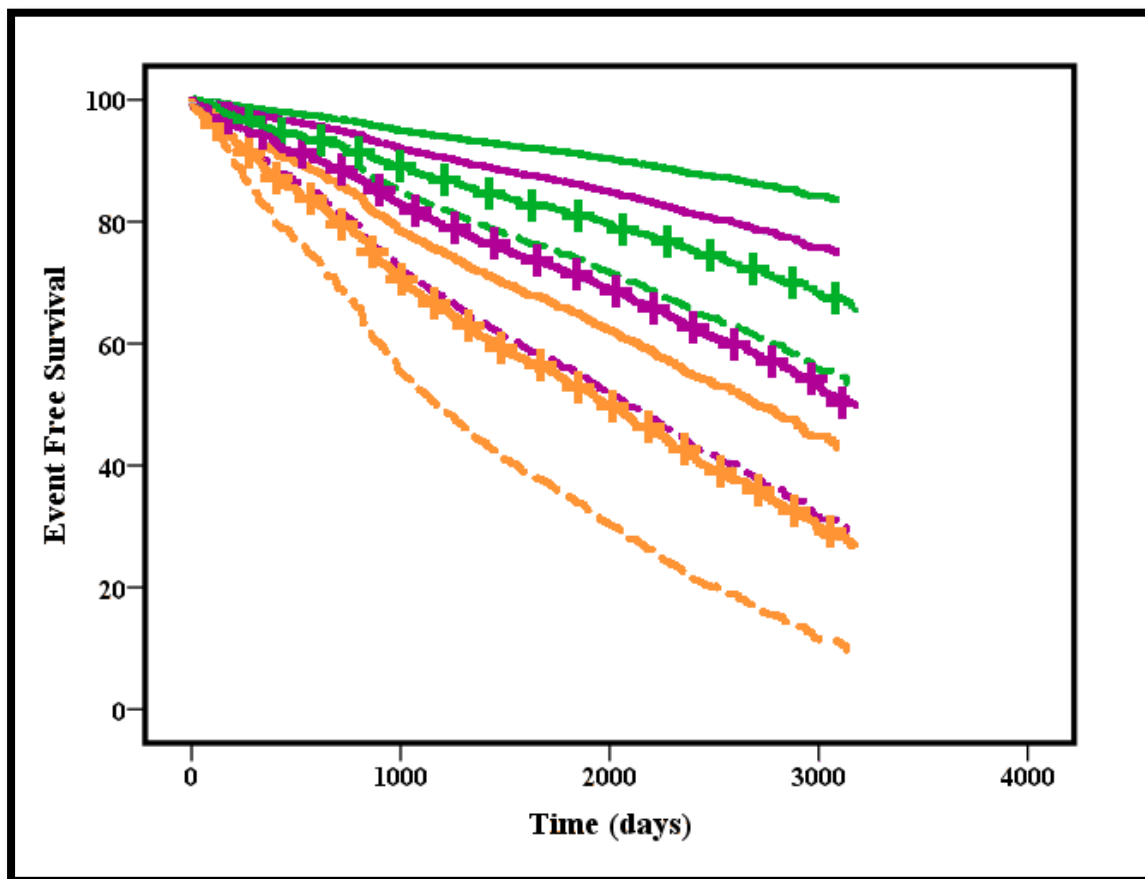
Risk categories	TIMI-AF score		CHA <sub>2</sub> DS <sub>2</sub> -VASc score		HAS-BLED score	
	N (%)	annual rate (%/year)	N (%)	annual rate (%/year)	N (%)	annual rate (%/year)
<b>Net Clinical Outcomes (N = 563)</b>						
Low Risk	287 (51.0)	6.07	2 (0.4)	2.37	46 (8.2)	4.40
Medium Risk	227 (40.3)	9.49	12 (2.1)	3.48	204 (36.2)	6.39
High Risk	49 (8.7)	12.36	549 (97.5)	7.75	313 (55.6)	9.55

**Table 3.** ROC curves comparison, IDI, NRI and median improvement of the TIMI-AF score in comparison with CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores for prediction of net clinical outcomes.

	<b>C-index</b>	<b>95% CI</b>	<b><i>p</i></b>	<b><i>z</i> statistic*</b>	<b><i>p</i>*</b>	<b>IDI</b>	<b><i>p</i></b>	<b>NRI</b>	<b><i>p</i></b>	<b><i>Median improvement</i></b>	<b><i>p</i></b>
	vs. TIMI-AF score										
CHA <sub>2</sub> DS <sub>2</sub> -VASc	0.678	0.650-0.705	<0.001	0.046	0.963	0.012	0.418	0.005	0.925	<0.001	0.249
HAS-BLED	0.644	0.615-0.671	<0.001	1.925	0.054	0.023	0.119	0.105	0.139	0.019	0.090

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

**Figure 1.** Kaplan-Meier analysis for net clinical outcomes according to the risk categories of each score.

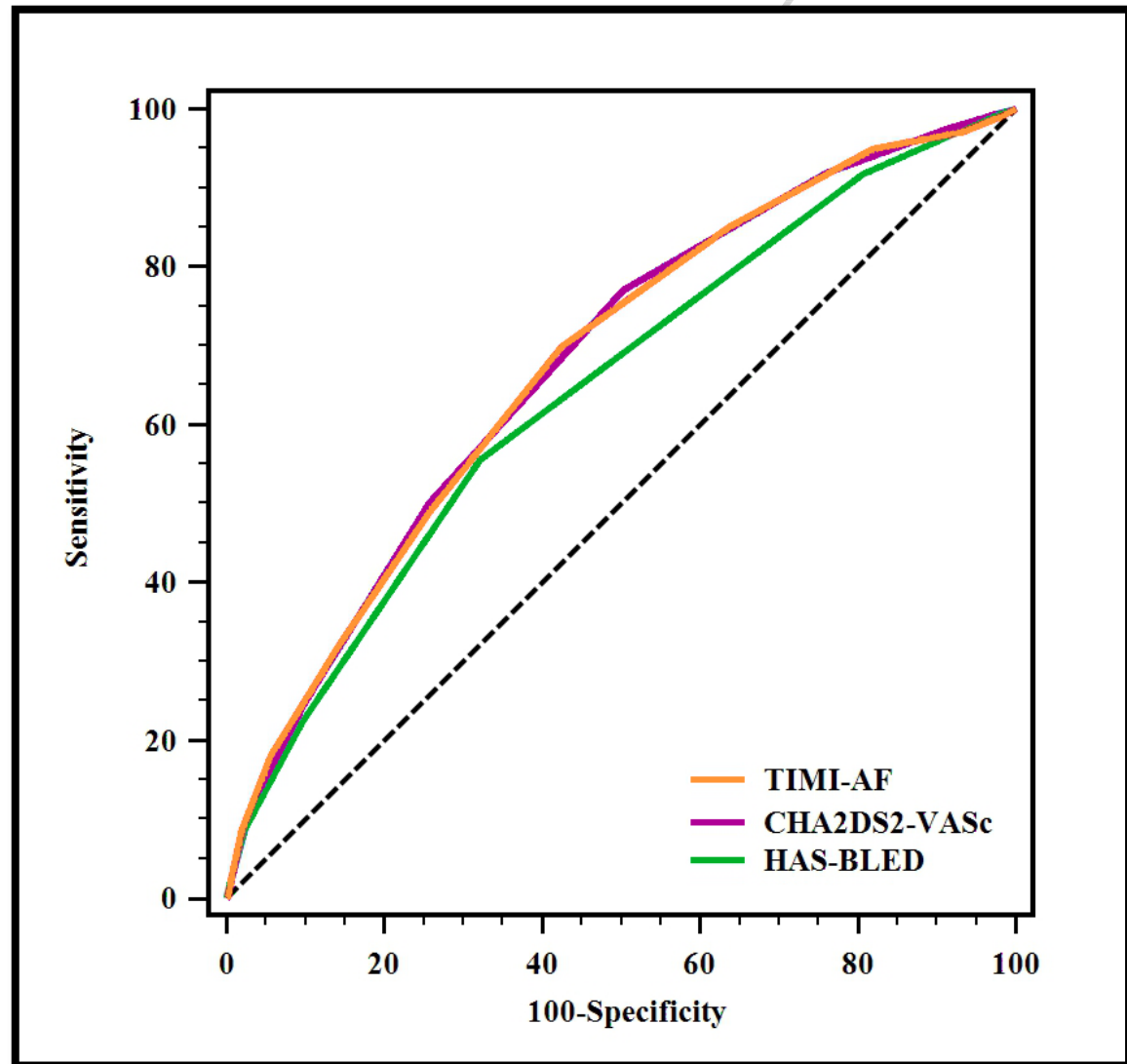


Dashed lines = TIMI-AF; Solid lines = CHA<sub>2</sub>DS<sub>2</sub>-VASc; Crossed lines = HAS-BLED

Green lines = Low Risk; Purple lines = Medium Risk; Orange lines = High Risk

TIMI-AF categories were defined as low risk (score = 0-6), medium risk (score = 7-9), and high risk (score  $\geq 10$ ). CHA<sub>2</sub>DS<sub>2</sub>-VASc categories were defined as low risk (score = 0), medium risk (score = 1), and high risk (score  $\geq 2$ ). HAS-BLED categories were defined as low risk (score = 0-1), medium risk (score = 2) and high risk (score  $\geq 3$ ).

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**Figure 2.** ROC curves comparison for net clinical outcomes

**Figure 3.** Decision curves for the TIMI-AF, CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores.

This analysis shows the clinical usefulness of each score based on a continuum of potential thresholds for net clinical outcomes (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 net clinical outcome.

