# External Validation of the ORBIT Bleeding Score and the HAS-BLED Score in Nonvalvular Atrial Fibrillation Patients Using Direct Oral Anticoagulants (Asian Data from the DIRECT Registry)

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**For Asian patients with nonvalvular atrial fibrillation (NVAF) using direct oral anticoagulants (DOACs), performance of contemporary various bleeding risk scores in a real-world setting is unknown. The objective of this study was to externally validate the ORBIT bleeding score and the HAS-BLED score in a large pooled real-world Asian population with NVAF using DOACs. We conducted a single-center prospective observational registry of NVAF patients treated with DOACs: the DIRECT registry (UMIN000033283). We assessed predictive and discriminative performance of the ORBIT bleeding and the HAS-BLED scores for major bleeding in 2,216 patients with NVAF using DOACs (63.6% male, median age 73 years, median $CHADS_2$ score 2). The overall incidence of major bleeding was 4.2% after a median follow-up of 315 days (interquartile range: 76 to 621). The ORBIT bleeding and the HAS-BLED scores both had modest discrimination ability to identify those who had bled versus who had not (C index = 0.64 [95% confidence interval {CI} 0.59, 0.70] and 0.62 [95% CI 0.57, 0.68], respectively). Calibration plots of the ORBIT bleeding score showed similar predictive performance compared with the HAS-BLED score (slope: 0.91 [95% CI 0.40, 1.43] vs 0.72 [95% CI 0.03, 1.40], intercept: 0.24 [95% CI −2.13, 2.61] vs 0.71 [95% CI −2.35, 3.76], respectively). In conclusion, the ORBIT bleeding score and the HAS-BLED score in a real-world of NVAF population with DOACs showed a modest discriminative performance and a similar predictive performance for major bleeding.**  **(Am J Cardiol 2019;124:1044−1048)**

Recently, the direct oral anticoagulants (DOACs) have been increasingly used, rather than vitamin K antagonists (VKA), for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF). However, despite the increased use of DOACs, validation data of the bleeding scores in a real-world setting are still sparse. Moreover, Asian population who are a higher risk of bleeding than Western population still lack updated data.[1] Therefore, we conducted the present study to validate the ORBIT bleeding score and the HAS-BLED score in a large pooled real-world Asian population with NVAF using DOACs.

## Methods

We conducted a single-center prospective observational registry of NVAF patients treated with DOACs: the DIRECT registry (UMIN000033283). All serial adult patients (aged ≥18 years) in our institution with NVAF who were users of dabigatran, rivaroxaban, apixaban, or edoxaban from June 2011 to November 2017 were enrolled. If a patient ever used DOACs during the study period, the first fill of DOACs was defined as the index medication. The treatment period was defined as the time from the first administration of a drug to last follow-up or 2 days after the drug discontinuation if the patient quitted the medication. The independent clinical event committee whose members were unaware of the treatment group adjudicated all clinical events. Written informed consent was obtained from all enrolled patients. This study was approved by the Osaka Police Hospital Ethical Committee.

The present study aimed to validate the ORBIT bleeding score and the HAS-BLED score for predicting major bleeding in the real-world Asian cohort: the DIRECT registry. Major bleeding was defined according to International Society on Thrombosis and Hemostasis criteria: (i) fatal bleeding and/or (ii) symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), and/or (iii) bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells.[2] Clinical events were monitored by questioning, physical examination, laboratory test, and electrocardiogram at each outpatient visits every 2 to 4 months. The primary analysis was performed under the intention-to-treat framework on the full analysis set of patients.

The ORBIT bleeding score is composed of 1 point for older (75 years or older), 2 points for reduced hemoglobin (<13 mg/dl in men and <12 mg/dl in women), hematocrit

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Funding: None.

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See page 1048 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2019.07.005

(<40% in men and <36% in women) or history of anemia, 2 points for bleeding history, 1 point for insufficient kidney function (estimate glomerular filtration rate [eGFR] <60 mg/dl/1.73 $m^2$), and 1 point for treatment with an antiplatelet agent.[3] The HAS-BLED score is composed of 1 point for hypertension (uncontrolled systolic blood pressure >160 mm Hg), 1 or 2 points for abnormal renal and/or liver function, 1 point for previous stroke, 1 point for bleeding history or predisposition (anemia), 1 point for labile INR (only applies to a VKA user; not applicable for a non-VKA user), 1 point for elderly (age ≥65 years), and 1 or 2 points for concomitant drugs (antiplatelet or nonsteroidal anti-inflammatory drugs) and/or alcohol excess.[4] In the DIRECT registry, we did not evaluate PT-INR in our daily clinical practice due to the use of DOAC. The criterion was therefore set to zero point in all patients.

Continuous variables are presented as mean ± standard deviation or median and interquartile range (IQR) as appropriate, and compared with Student's *t* test or Mann−Whitney *U* test. Binary variables are expressed as counts and percentages, and compared using chi-square test. In the whole database of 2,216 patients, there were missing values of the ORBIT bleeding and HAS-BLED scores variables in 587 cases: eGFR in 551 patients, creatinine in 80 patients, hemoglobin in 537 patients, and history of bleeding in 6 patients. To calculate the ORBIT bleeding and HAS-BLED scores, multiple imputation of missing values in 587 cases was performed taking into account the correlation between all potential predictors, and sensitivity analyses were done to account for missing values.[5] A regression model was used for the imputation including the following variables as a predictor: age, gender, height, body weight, diabetes, current smoking status, dyslipidemia, history of percutaneous coronary intervention or coronary artery bypass graft, peripheral vascular disease, creatinine, creatinine clearance, and eGFR. Outcome (major bleeding) was analyzed with Kaplan-Meier method stratified by the ORBIT bleeding and HAS-BLED scores. Receiver-operating characteristic curves were used to assess the discrimination ability of the ORBIT bleeding and HAS-BLED scores to predict major bleeding in the whole population.[6,7] Discrimination was studied with the concordance (C) index, which is identical to the area under the receiver-operating characteristic curve. The C index estimates the probability that, of 2 randomly chosen patients, the patient with the more favorable prognostic score will outlive the patient with the less-favorable prognostic score, and ranges from 0.5 (no discrimination) to a theoretical maximum of 1.[8,9] The predictive performance of the ORBIT bleeding and HAS-BLED scores was evaluated using calibration plots[10] by 0, 1, 2, 3, and ≥4 for the ORBIT bleeding score[3] and the HAS-BLED score.[4] Calibration refers to the agreement between observed major bleeding event rate per 100 patient-years in the DIRECT registry and original cohort event rate (ORBIT and HAS-BLED) per 100 patient-years.[3,4] The possible over- or underestimation of the predicted risks were graphically assessed with calibration plots. A p value <0.05 was considered statistically significant. All analyses were undertaken using SPSS 24.0 (IBM Corporation, Armonk, New York).

## Results

A total of 2,216 patients with NVAF using DOACs were included in this study and patient characteristics are shown in Table 1. The distributions of the ORBIT bleeding and HAS-BLED scores levels in the DIRECT registry are shown in Figure 1. The median ORBIT bleeding score was 2 (IQR: 1 to 4) and the median HAS-BLED score was 2 (IQR: 1 to 3). The cumulative event rate of major bleeding up to 2-year follow-up stratified by the ORBIT bleeding and HAS-BLED scores in the DIRECT registry is shown in Figure 2. In both scores, the stratifications well discriminated high bleeding risk patients in the real-world data. Results from the model calibration analysis comparing observed major bleeding rates in the DIRECT registry with reported major bleeding rates in the original derivation populations for the ORBIT bleeding and HAS-BLED scores are shown in Figure 3. The ORBIT bleeding and the HAS-BLED scores both had modest discrimination ability to identify those who had bled vs who had not (C index = 0.64 [95% confidence interval {CI} 0.59, 0.70] and 0.62 [95% CI 0.57, 0.68], respectively). Calibration plots of the ORBIT bleeding score showed a similar predictive performance compared with the HAS-BLED score (slope: 0.91 [95% CI 0.40, 1.43] vs 0.72 [95% CI 0.03, 1.40], intercept: 0.24 [95% CI −2.13, 2.61] vs 0.71 [95% CI −2.35, 3.76], respectively). In a sensitivity analysis, all analyses with the different iterations of the multiple imputation datasets and the original data yielded the similar results (Supplementary Figure 1).

Table 1
Patient characteristics in the DIRECT registry

| Variable | Total (n = 2,216) |
|---|---|
| Age (years) | 73 (65-79) |
| Men | 1410 (63.6%) |
| Body weight (kg) | 60 (50-69.6) |
| Hypertension | 1628 (73.5%) |
| Diabetes mellitus | 619 (27.9%) |
| Dyslipidemia | 1444 (65.2%) |
| eGFR (ml/min/1.73 $m^2$) | 64.9 (52.7-76.7) |
| Coronary artery disease | 439 (19.8%) |
| Peripheral artery disease | 158 (7.1%) |
| Heart failure | 525 (23.7%) |
| Prior stroke | 447 (20.2%) |
| Prior bleeding | 601 (27.1%) |
| Antiplatelet drugs | 477 (21.5%) |
| $CHADS_2$ score | 2 (1-3) |
| $CHA_2DS_2$-$VAS_c$ score | 3 (2-5) |

$CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack/thromboembolism (doubled); $CHA_2DS_2$-VASc = congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke/transient ischemic attack/thromboembolism (doubled), vascular disease (previous myocardial infarction, peripheral arterial disease, or aortic plaque), age 65 to 74 years, gender category (female); eGFR = estimated glomerular filtration rate.

Data are expressed as median (interquartile) or number (percentage). Hypertension was defined as blood pressure ≥140/90 mm Hg or the use of antihypertensive drug. Dyslipidemia was defined as treatment with medication or serum low-density lipoprotein cholesterol level ≥140 mg/dl.

## Discussion

Main findings of this study are as follows: (1) the ORBIT bleeding and the HAS-BLED scores showed modest discriminative performance for prediction of major bleeding in

| ORBIT score | n = 2216 |
|---|---|
| **O**lder than 74 (1) | 939 (42.4) |
| **R**educed hemoglobin (2) | 766 (34.6) |
| **B**leeding history (2) | 601 (27.1) |
| **I**nsufficient kidney function (1) | 879 (39.7) |
| **T**reatment with any antiplatelet drug (1) | 477 (21.5) |

| HAS-BLED score | n = 2216 |
|---|---|
| **H**ypertension (1) | 1628 (73.5) |
| **A**bnormal renal/liver function (1-2) | 737 (33.3) |
| **S**troke (1) | 447 (20.2) |
| **B**leeding history (1) | 601 (27.1) |
| **L**abile INR (1) | - |
| **E**lderly(≥65 years) (1) | 1732 (78.2) |
| **D**rug (antiplatelet or NSAIDs)/alcohol (1-2) | 477 (21.5) |

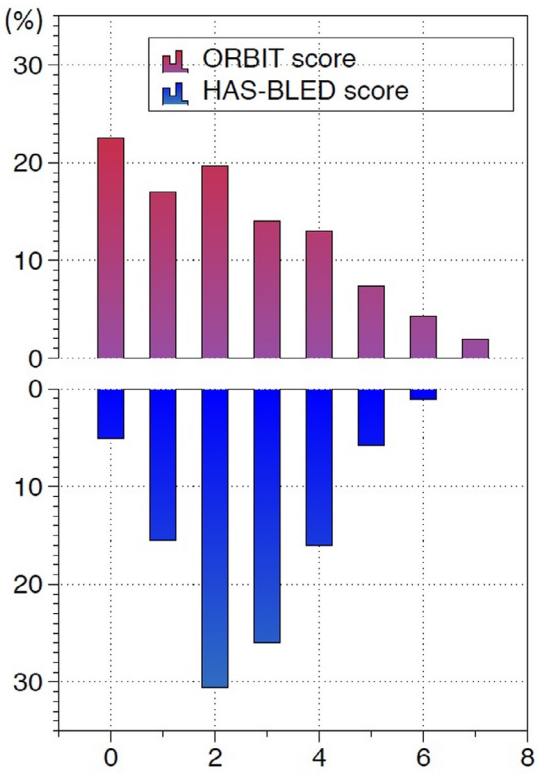


Figure 1. Distribution of the ORBIT bleeding and HAS-BLED scores in the DIRECT registry. NSAIDs = nonsteroidal anti-inflammatory drugs.

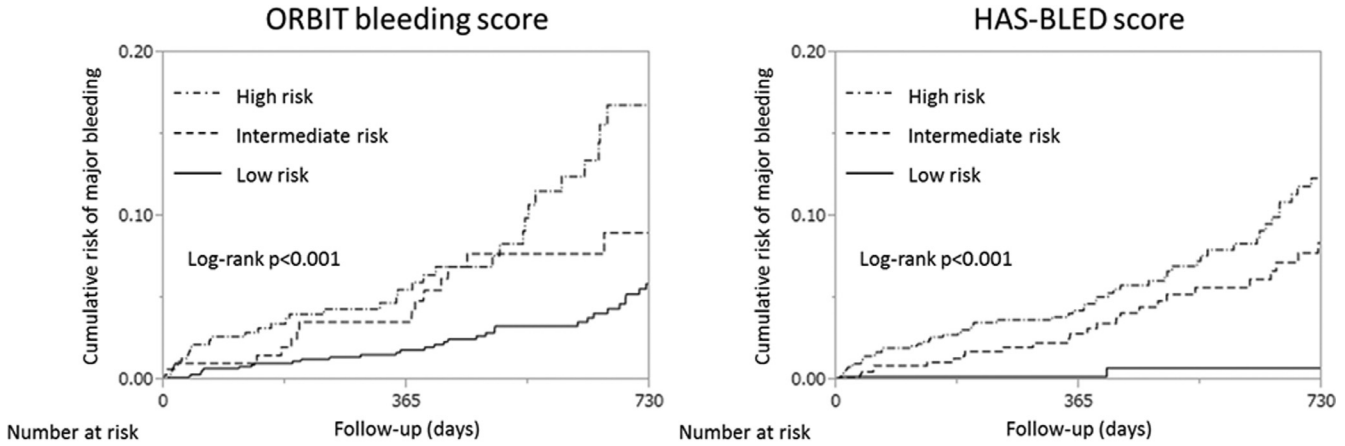


Figure 2. Cumulative risk of major bleeding up to 2-year follow-up for each risk classification score. The ORBIT bleeding score of 0 to 2 is classified as "low risk," whereas "intermediate risk" is a score of 3 and a score ≥4 is "high risk."[3] The HAS-BLED score of 0 to 1 is categorized as "low risk," a score of 2 is "intermediate risk," and a score of ≥3 is "high risk."[21]

a real-world Asian NVAF population with DOACs; (2) in this population, the ORBIT bleeding score had a similar predictive performance compared with the HAS-BLED score.

A recent meta-analysis showed that DOAC had a favorable risk-benefit profile, with significant reductions in stroke, intracranial hemorrhage, and mortality, and with similar major bleeding risk to warfarin.[11] Because its favorable relative efficacy and safety of DOACs was consistent across a wide range of patients, DOACs accounted for nearly 3/4 of all oral anticoagulation for stroke prevention in patients with a new diagnosis of NVAF in our contemporary clinical practice.[12] However, bleeding risk may still be one of the major concerns of clinical physicians. Individualized approach for bleeding risk assessment would help us to flag up patients at a high bleeding risk and thus

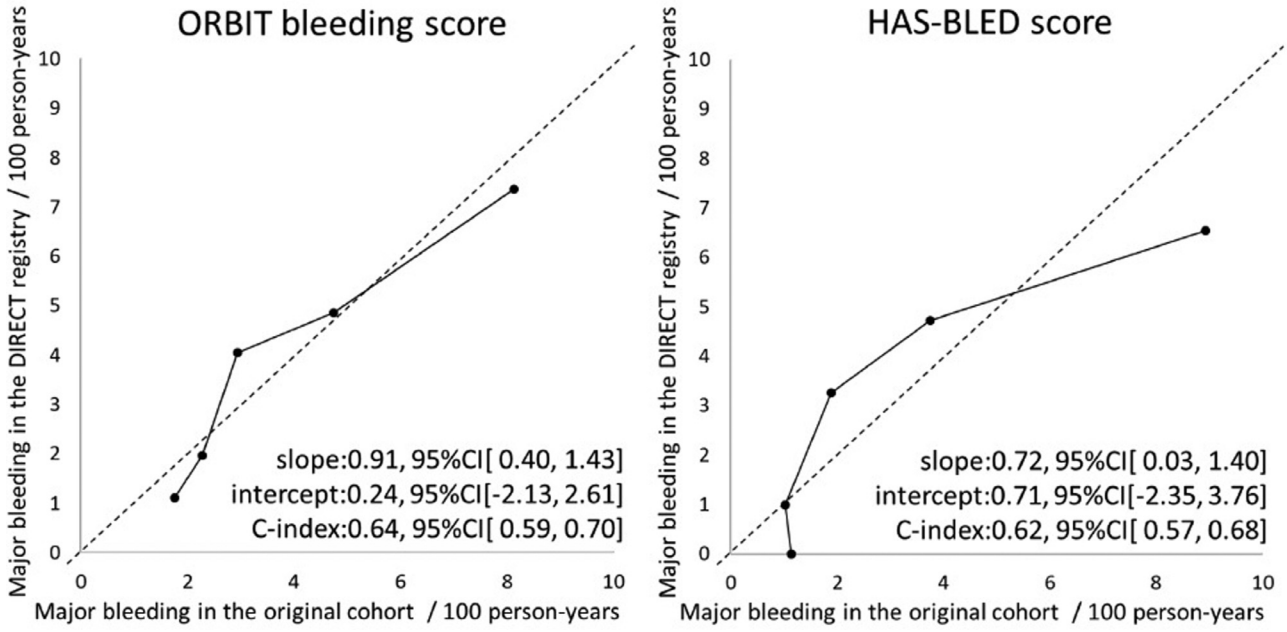


Figure 3. Calibration plot at cross-validation of the ORBIT bleeding and HAS-BLED scores. The predictive performance of the ORBIT bleeding and HAS-BLED scores was evaluated using calibration plots[10] by 0, 1, 2, 3, and ≥4 for the ORBIT bleeding score[3] and the HAS-BLED score.[4] Horizontal axis shows major bleeding rates in the original cohort, whereas vertical axis indicates observed major bleeding rate in the DIRECT registry per 100 person-years. For each plot, slope, intercept, and c-index are reported, with confidence interval (CI).

enable careful follow-up as well as to address the potentially reversible bleeding risk factors.[13,14]

The HAS-BLED score[4] and the ORBIT bleeding score[3] are useful tools to estimate the risk of major bleeding.[15–18] The HAS-BLED score has been validated in various populations including AF and non-AF cohorts treated with various drugs (e.g., aspirin, VKA, and non-VKA anticoagulants).[4] The ORBIT bleeding score was created from the ORBIT-AF registry that consisted of 10,132 AF patients taking warfarin and dabigatran.[3] It is a simple score and thus could be adapted to both warfarin and DOACs users. It was validated in the ROCKET-AF randomized and strictly controlled population treated with warfarin or rivaroxaban. Although the ORBIT and HAS-BLED scores showed similar discrimination in the external validation population, the ORBIT score showed superior calibration.[3] In contrast, a recent meta-analysis including 7 trials with 8,079 patients concluded that the ORBIT bleeding score was not superior than the HAS-BLED score for prediction of major bleeding events in anticoagulated AF patients.[19] Nevertheless, trials included in this meta-analysis were all from Western cohorts (USA, England, Spain, and the Netherlands) and mainly evaluated VKA.

A recent report from Danish national registry consisting of 57,930 AF patients provided real-world evidence regarding the discriminative performance of HAS-BLED, ATRIA, and ORBIT scores.[20] In terms of discrimination, the study showed *C*-statistics at 1-year follow-up for ATRIA as 0.59 (95% CI 0.57 to 0.60), HAS-BLED 0.58 (95% CI 0.57 to 0.59), and ORBIT 0.61 (95% CI 0.59 to 0.62), with ORBIT displaying a statistically significant difference from both ATRIA and HAS-BLED ($p < 0.001$). At the 2.5-year follow-up, comparable statistics were obtained. An analysis from the FANTASIIA registry also showed similar discriminative performance of ORBIT and HAS-BLED scores for predicting major bleeding.[21] These data, however, apply to a predominantly white European population, and differential efficacy and safety benefits may be evident between Asians and non-Asians. Asian population was reportedly at higher bleeding risk than Western population.[1] When treated with VKA, Asian patients had an increased intracranial hemorrhage risk compared with Western patients (hazard ratio 4.06 [95% CI 2.47 to 6.65]).[1] Thus, precise assessment of bleeding risk would be of paramount importance especially in Asian cohorts.

Results of the present study demonstrated similar discriminative performance, and similar or slightly better predictive performance of the ORBIT score in comparison with the HAS-BLED score, which is quite similar to the findings in Western population.[20] One possible explanation is that the ORBIT derivation cohort was more similar to the study cohort and the HAS-BLED derivation cohort was less similar to the present study cohort. We also need to keep in mind the fact that "labile INR" was all set to "zero" in the present analysis, which could have confounded or underestimated the performance of the HAS-BLED score due to our optimistic assumption. The "labile INR" is not applicable for patients on DOACs. It is not, therefore, surprising that this scoring has no anymore advantage over the more simplified score not necessarily in this special ethnic group (Asian population). In the current era of DOAC, the HAS-BLED score needs to be re-evaluated also in the other ethnic groups.

In Asian population with a higher risk of bleeding, particularly intracranial, existing bleeding risk scores provided modest discriminative performance that is similar to lower bleeding risk cohorts primarily comprised of patients with European ancestry. This finding further emphasizes the need to improve bleeding risk prediction in AF patients treated with anticoagulation, in particular for Asians who

are at high risk of bleeding which cannot not be satisfactorily forecasted with existing risk scores.

Several limitations should be acknowledged. First, our study was a single-center prospective observational registry. Second, the present data suffer from a potential selection bias. Specifically, we included only NVAF patients treated with DOACs. Therefore, patients who were inappropriate for DOACs were not investigated (e.g., end-stage renal failure). Third, owing to lack of laboratory data (i.e., PT-INR), we defined the "modified" HAS-BLED score that had, however, a quite optimistic assumption ("labile INR" was set to "zero"). Adherence to DOACs might have similar meaning to the "labile INR" in the era of VKA. However, it was not investigated in the present study. Further investigations answering these limitations should be conducted.

In conclusion, 2 contemporary bleeding risk scores, the ORBIT bleeding score and the HAS-BLED score, showed a modest discriminative performance and a similar predictive performance for major bleeding in NVAF patients treated with DOACs.

## Disclosures

Y. Sotomi, A. Hirata, A. Hirayama, and Y. Higuchi received speaker honoraria from Bayer, Daiichi-Sankyo, Amgen Astellas BioPharma, Boehringer Ingelheim, Bristole-Myers Squibb, Abbott Vascular Japan, Boston Scientific Japan, TERUMO, Cardinal Health, and Medtronic. Y. Sakata reports grants and personal fees from Daiichi-Sankyo, Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb. The other authors have nothing to disclose.

## Acknowledgment

We thank Ayaka Murakami; Yoko Inoue; Tomoe Yamamoto; Ayako Fukao; Nanao Matsusaki, MD; Satoshi Suzuki, MD; Tomoaki Kobayashi, MD; Yuma Hamanaka, MD; Junichi Ohno, MD; Takashi Omatsu, MD; Yasuharu Takeda, MD, PhD; Nobuhiko Makino, MD, PhD; Takaharu Hayashi, MD, PhD; and Shimpei Nakatani, MD, PhD for their invaluable supports for data collection and management.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.005.

1. Shen AY, Yao JF, Brar SS, Jorgensen MB, Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. *J Am Coll Cardiol* 2007;50:309–315.
2. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692–694.
3. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey KW, Chang P, Fonarow GC, Pencina MJ, Piccini JP, Peterson ED. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J* 2015;36:3258–3264.
4. 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;138:1093–1100.
5. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR, Mack M, Feldman T, Morice MC, Ståhle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 2013;381:639–650.
6. Harrell FE Jr., Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA* 1982;247:2543–2546.
7. Pencina MJ, D'Agostino RB Sr. Evaluating discrimination of risk prediction models: the C statistic. *JAMA* 2015;314:1063–1064.
8. Metz CE. Basic principles of ROC analysis. *Semin Nucl Med* 1978;8:283–298.
9. Obuchowski NA. Receiver operating characteristic curves and their use in radiology. *Radiology* 2003;229:3–8.
10. Vergouwe Y, Steyerberg EW, Eijkemans MJ, Habbema JD. Validity of prognostic models: when is a model clinically useful? *Semin Urol Oncol* 2002;20:96–107.
11. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. 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;383:955–962.
12. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, Hylek E, Kowey PR, Mahaffey KW, O'Brien EC, Singer DE, Peterson ED, Piccini JP. Outcomes registry for better informed treatment of atrial fibrillation I, patients. Factors associated with non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with new-onset atrial fibrillation: results from the outcomes registry for better informed treatment of atrial fibrillation II (ORBIT-AF II). *Am Heart J* 2017;189:40–47.
13. Lip GY, Lane DA. Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores. *J Thromb Haemost* 2016;14:1711–1714.
14. Sotomi Y, Hirata A, Amiya R, Kobayashi T, Hirayama A, Sakata Y, Higuchi Y. Bleeding risk of add-on anti-platelet agents to direct oral anticoagulants in patients with nonvalvular atrial fibrillation (from 2216 patients in the DIRECT registry). *Am J Cardiol* 2019;123:1293–1300.
15. Lip GY, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E, Lane D, Levi M, Marin F, Palareti G, Kirchhof P, European Heart Rhythm Association. Bleeding risk assessment and management in atrial fibrillation patients. Executive summary of a position document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] working group on thrombosis. *Thromb Haemost* 2011;106:997–1011.
16. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, ESC Scientific Document Group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893–2962.
17. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864–2870.
18. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007;69:546–554.
19. Wang C, Yu Y, Zhu W, Yu J, Lip GYH, Hong K. Comparing the ORBIT and HAS-BLED bleeding risk scores in anticoagulated atrial fibrillation patients: a systematic review and meta-analysis. *Oncotarget* 2017;8:109703–109711.
20. Lip GYH, Skjoth F, Nielsen PB, Kjaeldgaard JN, Larsen TB. The HAS-BLED, ATRIA, and ORBIT bleeding scores in atrial fibrillation patients using non-vitamin K antagonist oral anticoagulants. *Am J Med* 2018;131. 574.e513−574.e527.
21. Esteve-Pastor MA, Garcia-Fernandez A, Macias M, Sogorb F, Valdes M, Roldan V, Muniz J, Badimon L, Roldan I, Bertomeu-Martinez V, Cequier A, Lip GY, Anguita M, Marin F, Investigators F. Is the ORBIT bleeding risk score superior to the HAS-BLED score in anticoagulated atrial fibrillation patients? *Circ J* 2016;80:2102–2108.