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Comparison of HAS-BLED with other risk models for predicting the bleeding risk in anticoagulated patients with atrial fibrillation

A PRISMA-compliant article

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Abstract

Background: The HAS-BLED, HEMORR$_2$HAGES, ATRIA, and ORBIT scores are used to predict bleeding risk in anticoagulated patients with atrial fibrillation (AF). Recently, these scores have been validated in various studies. Therefore, we aimed to compare the occurrence of major bleeding across different risk categories between HAS-BLED and any of HEMORR$_2$HAGES, ATRIA, or ORBIT scores.

Methods: A systemic literature search of PubMed and Embase databases was conducted to screen the relevant studies. We calculated and pooled the odds ratios (ORs) and 95% confidence intervals (CIs) for a comparative analysis of the occurrence of major bleeding.

Results: Nine studies fulfilled the inclusion criteria in this meta-analysis. Compared with HEMORR$_2$HAGES, there were 87% and 39% reduced rates of major bleeding in the HAS-BLED "low-risk" and "moderate-risk" groups, respectively. Compared with ATRIA, there was an 89% decreased rate of major bleeding in the HAS-BLED "low-risk" group. Compared with ORBIT, there were 84% and 44% reduced rates of major bleeding in the HAS-BLED "low-risk" and "moderate-risk" groups, respectively. Patients with HAS-BLED scores ≥3 showed an approximately 3-fold greater risk of major bleeding compared with patients with scores <3 (OR=3.00, CI: 1.21–7.43).

Conclusions: Compared with any of HEMORR$_2$HAGES, ATRIA, or ORBIT scores, the HAS-BLED score distributed more major bleeding events into the "low" or "moderate" risk categories.

Abbreviations: AF = atrial fibrillation, ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation, CI = confidence interval, HAS-BLED = Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly, HEMORR$_2$HAGES = Hepatic or renal disease, Ethanol abuse, Malignancy, Older, Reduced platelet count or function, Re-bleeding risk, Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke, INR = international normalized ratio, OR = odds ratio, ORBIT = Outcomes Registry for Better Informed Treatment, PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses, RCTs = randomized clinical trials.

Keywords: atrial fibrillation, bleeding, category, HAS-BLED

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1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide conferring an increased risk of stroke and thromboembolism. Patients with AF are associated with a higher disability and mortality rate compared with individuals without AF.[1–3] Given that AF may bring serious economic burden to our society, oral anticoagulation therapy is critical for those AF patients at high risk of embolic endpoints. To date, stroke risk scores are recommended for stroke prediction and guide the optimization of anticoagulation therapy and clinical decision making.[4,5] In spite of this, the severe bleeding complications of anticoagulation therapy are the relatively common cases in AF management. Therefore, it is necessary for clinicians to assess bleeding risk in AF patients with anticoagulant drugs.

Altogether, several bleeding risk prediction scores have been identified and published, and 4 of them (namely HAS-BLED, HEMORR$_2$HAGES, ATRIA, and ORBIT) target AF patients and have been appropriately validated.[6,7] Although these 3 bleeding risk scores employ different score cut-offs, all of them stratify AF patients into low, moderate, and high bleeding risk categories. In 2006, the HEMORR2HAGES score[8] was derived from previous risk assessment schemes,[9–11] and 11 risk factors (Hepatic or renal disease, Ethanol abuse, Malignancy, Older age [more than 75 years of age], Reduced platelet count or Function, Re-bleeding, Hypertension [uncontrolled], Anemia, Genetic factors, Excessive fall risk, Stroke) were selected from the National Registry of Atrial Fibrillation. In 2010, the HAS-BLED score[12] (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio [INR], Elderly [older than 65 years of age], Drugs/alcohol concomitantly) was first derived and validated in the prospective Euro Heart Survey on AF taking antithrombotic therapy, where patients were followed up for nearly 1 year. In 2011, the ATRIA score[13] in the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study group described a new bleeding risk score for AF, which included 5 weighted risk factors: anemia, renal disease, Elderly [75 years of age and older], any prior bleeding, hypertension. In 2015, O'Brien et al[14] derived and validated the ORBIT score (older [age ≥74 years], reduced hemoglobin/hematocrit/history of anemia, bleeding history, insufficient kidney function, and treatment with antiplatelet). More recently, the HAS-BLED, ATRIA, HEMORR2HAGES, and ORBIT scores have been validated in various studies. In the present study, we aimed to compare the occurrence of major bleeding events across 3 risk categories between HAS-BLED and any of HEMORR$_2$HAGES, ATRIA, or ORBIT scores.

2. Methods

The protocol and reporting of the results were based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement. This was a meta-analysis of published studies, and no ethical approval was warranted.

2.1. Inclusion and exclusion criteria

The following inclusion criteria were applied to select the appropriate studies:

1. Type of studies: post hoc ancillary analysis of randomized clinical trials (RCTs) and observational studies focusing on the HAS-BLED score for predicting the bleeding risk;
2. Participants: adult nonvalvular AF patients with anticoagulation therapy;
3. Outcome: major bleeding; and
4. Settings of studies: not limited.

Exclusion criteria were used as follows:

1. studies that reported AF patients with certain interventions (e.g., cardioversion, catheter ablation, coronary interventions, or left-atrial appendage closure);
2. studies published in non-English language;
3. certain publication types (e.g., reviews, letters, case reports, comments, conference abstracts, and editorials); and
4. studies with duplicate or insufficient data.

2.2. Literature search

A comprehensive electronic search of the PubMed and Embase databases was conducted for relevant studies published in English from January 2010 to August 2019, in view of the first study on the HAS-BLED score being published in 2010.[12] We used the following search terms: "atrial fibrillation", "HAS-BLED", "HEMORR$_2$HAGES", "ATRIA" and "ORBIT". Further manual research was performed using reference lists, relevant journals, and conference abstracts.

2.3. Study selection and data extraction

All relevant studies were retrieved electronically and manually by 2 independent reviewers on the basis of the search strategy mentioned above. We first screened the titles and abstracts to select the appropriate studies, and then comprehensively reviewed the full text to check if these studies reported sufficient data. Studies that met the inclusion criteria were considered eligible for this meta-analysis. In situations of discrepancies, issues were resolved through discussion or consultation with a third reviewer.

Relevant data were extracted from each study according to the predetermined criteria, including the basic characteristics of studies (study type, demographic data, mean patient age, female ratio, and follow-up duration), the total number of AF patients and number of major bleeding events across 3 risk categories. If the major bleeding event number was unavailable in the study, it was calculated by using the following formula: Event number = (Total patient number) × (Event rate[per 100 patient years]) × (Follow-up duration[years]).[15]

2.4. Quality assessment

Two independent reviewers evaluated the quality of individual studies. QUADAS-2 was used for assessing the quality of the included studies in this meta-analysis. QUADAS-2 comprised 4 domains of patient selection, index test, reference standard, and flow and timing. The questions in each domain were assessed in terms of risk of bias, and the first 3 domains were also assessed in terms of applicability concerns. Included studies were separately graded as "good," "fair," or "poor."

2.5. Consistency test

The consistency of the included studies was evaluated using the Cochrane Q test complemented with I^2 values. For the Q statistic, substantial heterogeneity was defined as a $P < .1$. For the I^2

Table 1

Basic characteristics of Bleeding risk scores considered for this review.

Scoring system	Low	Moderate	High	Considered risk factors
$HEMORR_2HAGES$	0–1	2–3	≥4	liver/renal disease, Ethanol abuse, malignancy, age > 75 years, low platelet count or function, rebleeding risk, uncontrolled hypertension, anemia, genetic factors (CYP2C9), risk of fall or stroke, with 1 point for each risk factor present with 2 points for previous bleed.
HAS-BLED	0	1–2	≥3	Hypertension, Abnormal Renal/Liver Function (1 point each), Stroke, Bleeding History or Predisposition, Labile INR, Elderly Drugs/Alcohol concomitantly (1 point each); maximum 9 points
ATRIA	0–3	4	5–10	Anaemia, CKD with GFR < 30 mL/min or dialysis, Age≥75 years, Previous bleeding, Hypertension(3 points for anaemia and CKD, 2 points for age, 1 point for previous bleeding and hypertension)
ORBIT	0–2	3	≥4	Age≥75 years, reduced hemoglobin/hematocrit/history of anemia, bleeding history, insufficient kidney function, treatment with antiplatelet

ATRIA = anticoagulation and risk factors in atrial fibrillation, CKD = chronic kidney disease, GFR = glomerular filtration rate, HAS-BLED = Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly, $HEMORR_2HAGES$ = hepatic or renal disease, Ethanol abuse, Malignancy, Older, Reduced platelet count or function, Rebleeding risk, Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke, INR = international normalized ratio, ORBIT = Outcomes Registry for Better Informed Treatment.

statistic, 25% or less, 50%, and 75% or more indicated low, moderate, and high heterogeneity, respectively. In view of the heterogeneity among the included studies, appropriate models (fixed- or random-effect models) were chosen to ensure that the various statistics were estimated correctly.

2.6. Statistical analysis

The HAS-BLED, HEMORR2HAGES, ATRIA, and ORBIT scores stratified AF patients into low, moderate, and high bleeding risk categories (Table 1). Major bleeding events were measured as dichotomous outcome variables. For each study, the total number of AF patients and the number of major bleeding events were summarized across 3 risk categories, respectively. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated and pooled by assessing the occurrence of major bleeding risk. Additionally, the primary endpoints for AF patients were dichotomously defined and compared between HAS-BLED scores ≥3(high-risk) and scores < 3 (low and moderate-risk).

All statistical analyses were performed using Review Manager (RevMan) version 5.3 software (Copenhagen, the Nordic Cochrane Center, the Cochrane Collaboration).

3. Results

3.1. Study selection

A total of 508 records were identified through the search strategy (Fig. 1). We initially retrieved 501 records through the electronic database search and identified 7 additional records in the manual search. After reading the titles and abstracts of studies, we included 86 full-text studies for further review. Finally, 9 eligible

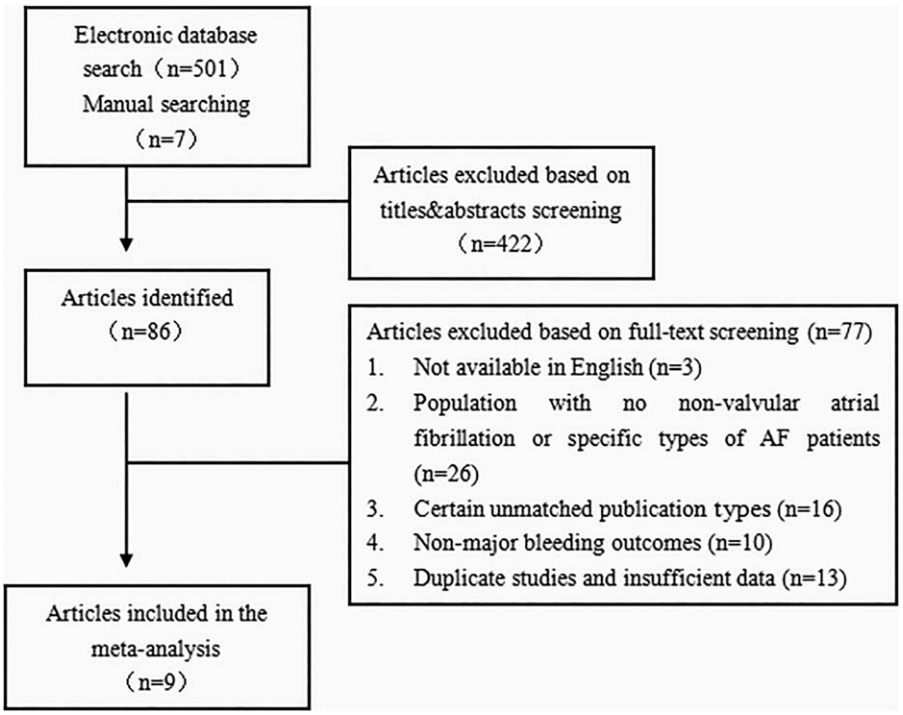

Figure 1. An overview of the research strategy.

Table 2

Basic characteristics of all included studies.

Study (author-year)	Data source	Participants	Anticoagulants	Age (years)	Female ratio	Follow-up time	Comparisons	Quality ratings
Olesen-2011	Danish National Patient Registry	44,771	VKAs	Mean 74	45%	Mean 3.5 years	HAS-BLED vs. HEMORR$_2$HAGES	good
Lip-2011	SPORTIF III and V	3665	Warfarin, ximelagatran	Mean 72	39%	Mean 499 days	HAS-BLED vs. HEMORR$_2$HAGES	good
Apostolakis-2012	Post hoc ancillary analysis of AMADEUS trial	2293	Warfarin, Acenocoumarol	Mean 70	35%	Mean 429 days	HAS-BLED vs. HEMORR$_2$HAGES/ATRIA	good
Roldan-2013	Outpatient anticoagulation clinic database	937	Acenocoumarol	Median 76	51%	Median 952 days	HAS-BLED vs. ATRIA	good
Apostolakis-2013	Post hoc ancillary analysis of AMADEUS trial	2283	Idraparinux	Mean 70	67%	Mean 311 days	HAS-BLED vs. HEMORR$_2$HAGES/ATRIA	good
Proietti-2016	Post hoc ancillary analysis of AMADEUS trial	3665	Warfarin	Median 71	30.5%	Median 1.6 years	HAS-BLED vs. ORBIT/HEMORR$_2$HAGES/ATRIA	good
Senoo-2016	Post hoc ancillary analysis of AMADEUS trial	2283	Idraparinux	Mean 70.1	67%	Mean 311 days	HAS-BLED vs. ORBIT	good
Esteve-Pastor-2016	ECV population	406	vitamin K antagonists (mostly with acenocoumarol); DOACs	Mean 66.9	30.8%	Median 1,005 days	HAS-BLED vs. ORBIT	good
	FANTASIIA population	1276		Mean 73.9	55.7%	Median 1.0 year		
Yao-2017	OptumLabs Data Warehouse	39,539	DOACs	Median 71	42%	Mean 0.6 year	HAS-BLED vs. ORBIT/ATRIA	good

AMADEUS = Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation, DOACs = direct oral anticoagulants, NA = not available, VKAs = vitamin K antagonists.

studies met all the inclusion criteria.[16–24] The basic characteristics of included studies are presented in Table 2.

3.2. Data analysis

3.2.1. HAS-BLED versus HEMORR2HAGES. *Low-risk category*: There were 88180 patients in the HEMORR2HAGES "low-risk" category, and 2232 patients(2.53%) experienced major bleeding events during follow-up. Among 25903 patients in the HAS-BLED "low-risk" category, 390 patients(1.51%) had major bleeding events during follow-up. The pooled RR values indicated that patients in the HAS-BLED "low-risk" category had a significantly higher risk of major bleeding compared to that in the HEMORR2HAGES "low-risk" category (OR = 0.13; 95% CI: 0.02–0.83; Fig. 2).

Moderate-risk category: 93762 patients were detected in the "moderate-risk category" of HEMORR2HAGES, and 3856 patients (4.11%) of them experienced major bleeding events during follow-up. One hundred seventeen thousand eight hundred thirty four patients were detected in the moderate-risk category of HAS-BLED, but only 3041 patients (2.58%) experienced the major bleeding events. The pooled RR values showed that the low-risk patients of HAS-BLED had an approximately 39% reduced risk of major bleeding than that of HEMORR2HAGES (OR = 0.61, CI: 0.47–0.80; Fig. 2).

High-risk category: A total of 21,928 patients were detected in the "moderate-risk category" of HEMORR2HAGES, and 2924 patients (1.33%) of them experienced the major bleeding events during follow-up. 80,060 patients were detected in the moderate-risk category of HAS-BLED, and 3805 patients (4.75%) experienced major bleeding events. The pooled results indicated that there was a non-significant increased risk of major bleeding in patients of the HEMORR2HAGES "high-risk" category (OR = 1.88, CI: 0.75–4.71; Fig. 2).

3.2.2. HAS-BLED versus ATRIA. *Low-risk category*: There were 35281 patients in the low-risk category of ATRIA, and 641 patients (1.82%) experienced the major bleeding events during follow-up. Among 11,194 patients in the low-risk category of HAS-BLED, only 62 patients (0.50%) had major bleeding events. When the RR values were pooled across these studies, the low-risk patients of HAS-BLED had a low-risk of major bleeding compared to that of ATRIA (OR = 0.11; 95%CI: 0.02–0.77; Fig. 3).

Moderate-risk category: A total of 4131 patients were detected in the moderate-risk category of ATRIA; 91 patients(2.2%) of which experienced major bleeding events during follow-up. Eighteen thousand four hundred ninety patients were detected in the moderate-risk category of HAS-BLED, and 355 patients (1.92%) had the major bleeding events. The pooled results indicated that the low-risk patients of ATRIA had a similar risk of major bleeding than that of HAS-BLED (OR = 0.96, CI: 0.51–1.84; Fig. 3).

High-risk category: The pooled analysis indicated that AF patients in the HAS-BLED "high-risk" category had no significantly higher risk of bleeding events compared to AF patients in the ATRIA "high-risk" category (OR = 1.84, CI: 0.63–5.32; Fig. 3).

3.2.3. HAS-BLED versus ORBIT. *Low-risk category*: There were 36,488 patients in the low-risk category of ORBIT, and 626

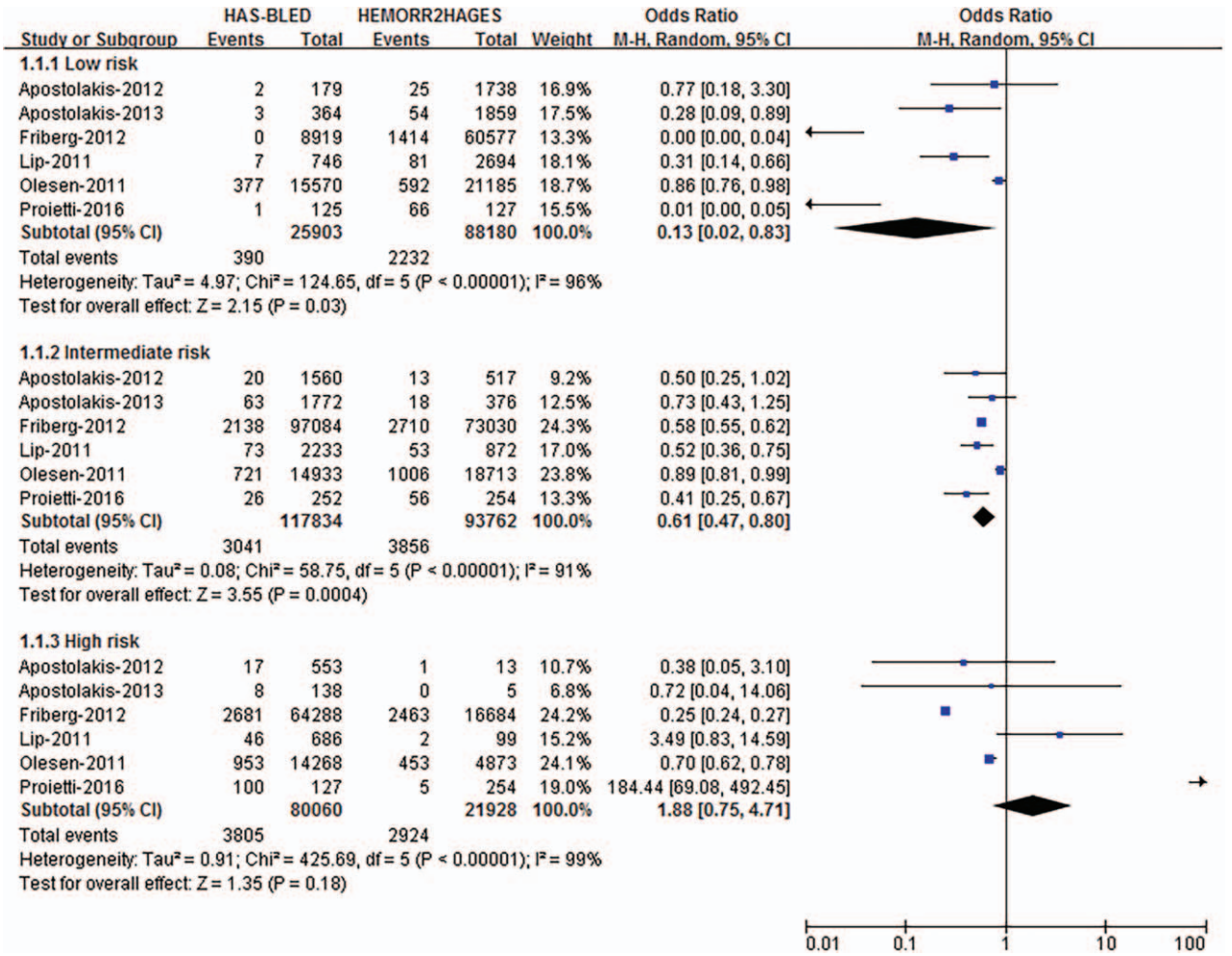

Figure 2. A comparative analysis of the occurrence of major bleeding across the 3 risk categories between HAS-BLED and HEMORR2HAGES. Note: HAS-BLED = Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; HEMORR$_2$HAGES = Hepatic or renal disease, Ethanol abuse, Malignancy, Older, Reduced platelet count or function, Re-bleeding risk, Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; M-H = Mantel-Haenszel; CI = confidence interval.

patients (1.72%) experienced the major bleeding events during follow-up. Among 11,558 patients in the low-risk category of HAS-BLED, only 68 patients (0.59%) had major bleeding events. In the pooled analysis, the low-risk patients of HAS-BLED had a low-risk of major bleeding compared to that of ORBIT (OR = 0.16; 95%CI: 0.04–0.67; Fig. 4).

Moderate-risk category: There were more AF patients in the ATRIA(5.27%) "high-risk" category experiencing the major bleeding events during follow-up than patients in the HAS-BLED (3.52%) "high-risk" category (OR = 0.56, CI: 0.43–0.72; Fig. 4).

High-risk category: The pooled analysis indicated that AF patients in the HAS-BLED "high-risk" category had a similar risk of major bleeding compared to AF patients in the ATRIA "high-risk" category (OR = 1.24, CI: 0.26–5.78; Fig. 4).

3.2.4. HAS-BLED scores <3 vs scores ≥3. The pooled RR values indicated that the occurrence of major bleeding events in AF patients with HAS-BLED scores ≥3 was significantly higher than that in patients with scores <3 (OR = 3.00, CI: 1.21–7.43; Fig. 5). The pooled results showed an approximately 3-fold greater risk of major bleeding events in AF patients with scores ≥3.

4. Discussion

AF is not immediately life-threatening but characterized by a high occurrence of embolic risks. Despite the clear net clinical benefits of oral anticoagulation therapy for reducing these embolic risks, the occurrence of bleeding events may be devastating.[19] Previously, a systematic review of randomized and observational studies presented a high rate of major bleeding events in AF patients receiving vitamin K antagonists (approximately 2 per 100 patient-years).[25] Therefore, it is indispensable to assess the bleeding risk using an appropriate approach. Although the HAS-BLED, HEMORR$_2$HAGES, ATRIA, and ORBIT scores have been specifically derived and validated in AF patients, there is still some uncertainty that which risk score is best to be introduced into clinical practice. In recent studies, the HAS-BLED score may perform better in predicting bleeding risk than the HEMOR-R$_2$HAGES or ATRIA scores in AF patients taking anticoagulation therapy.[18–20] Earlier meta-analysis indicated that the HAS-BLED score preformed better for evaluating major bleeding risks in AF patients due to a higher sensitivity when compared with the HEMORR$_2$HAGES or ATRIA scores.[26] Additionally, our previous meta-analysis also indicated that the HAS-BLED score

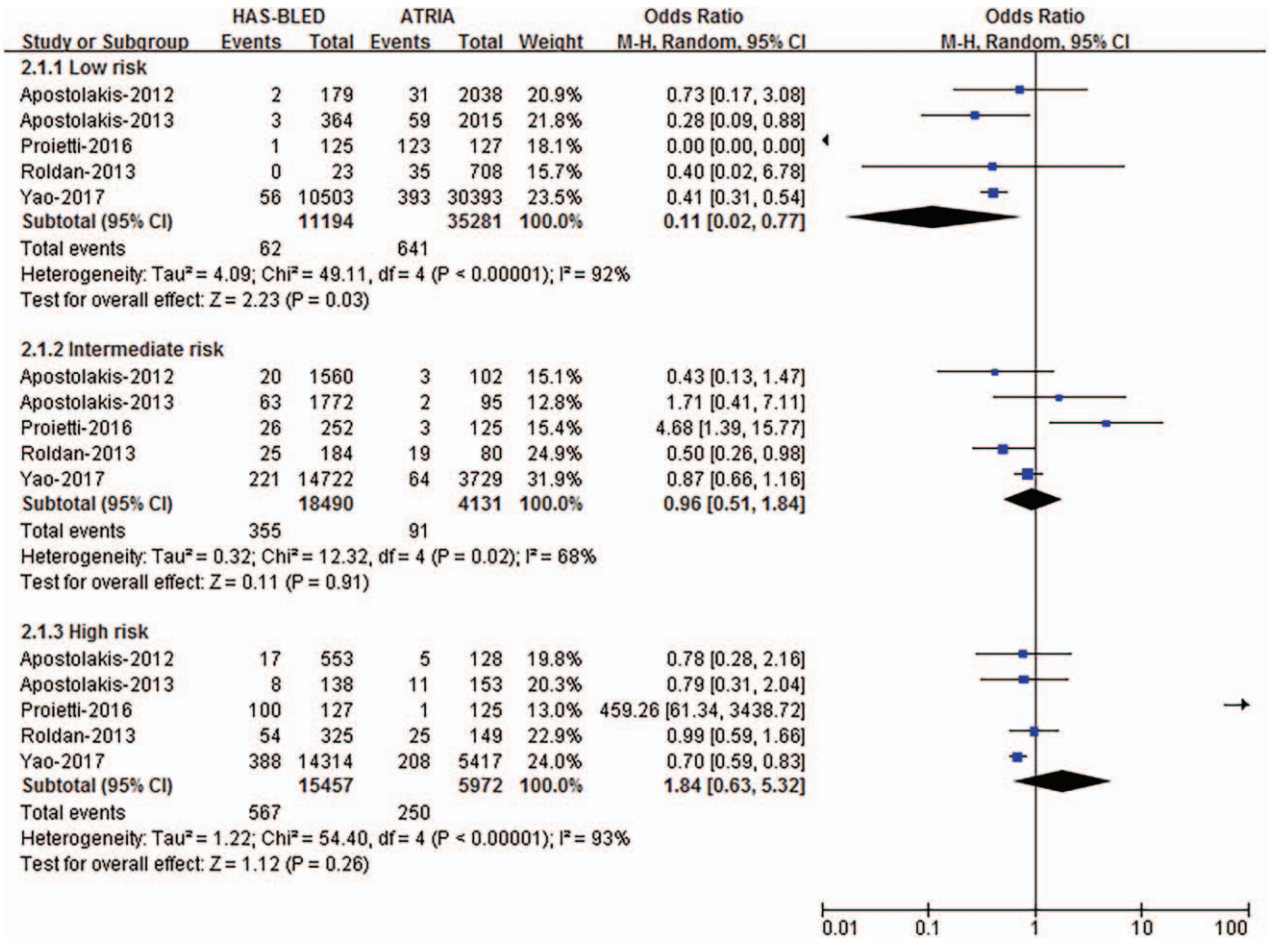

Figure 3. A comparative analysis of the occurrence of major bleeding across the 3 risk categories between HAS-BLED and ATRIA. Note: HAS-BLED = Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; M-H = Mantel-Haenszel; CI = confidence interval.

was superior to the HEMORR$_2$HAGES or ATRIA scores for bleeding risk prediction, evaluated by C-statistic and further reflected by the positive net reclassification improvement and integrated discrimination improvement values.[27] Compared with HAS-BLED, the ORBIT score does not perform better in predicting bleeding risk in anticoagulated AF patients.[28] However, there is still no comprehensive meta-analysis comparing the occurrence of major bleeding events between the same risk categories (namely low, moderate, and high-risk category) among the HAS-BLED, HEMORR2HAGES, ATRIA, and ORBIT scores.

In this meta-analysis, the major bleeding events were measured as dichotomous outcome variables and compared between the same risk categories among the HAS-BLED, HEMORR2HAGES, ATRIA, and ORBIT scores. Our pooled data suggested that in the "low" or "moderate" risk categories, the occurrence of major bleeding evaluated by HAS-BLED was lower than that evaluated by any of HEMORR$_2$HAGES, ATRIA, or ORBIT scores. The pooled analysis also indicated that AF patients in the HAS-BLED "high-risk" category had no significant increased risks of bleeding events compared to AF patients in the "high-risk" category of the HEMORR2HAGES, ATRIA, or ORBIT scores. According to the HAS-BLED score, there was a stepwise increase in major bleeding events in conjunction with increasing scores across 3 risk categories. The increasing trend toward the risk of major bleeding events was supported by the average incidence rates of events across 3 risk categories ($P_{trend} < .001$). Our meta-analysis demonstrated a clear relationship between increasing HAS-BLED scores and higher rates of major bleeding events. We also observed a powerful predictive value of the HAS-BLED score for the "high-risk" category of AF patients. Patients with HAS-BLED scores ≥3 (high-risk) showed an approximately 3-fold greater bleeding risk compared with patients with scores <3 (low and moderate-risk). In addition, the HAS-BLED score is also proposed as a practical tool for predicting bleeding risk in AF patients after percutaneous coronary interventions,[29–33] or patients with ischemic stroke.[34,35] For example, Konishi et al[29] indicated that the incidence of both death and major bleeding was higher in the HAS-BLED scores ≥3 group than in the scores <3 group.

A cohort of 13,559 patients with AF was used to quantify the net clinical benefit of warfarin therapy balancing stroke against serious bleeding. Although the net clinical benefit was only 0.68% for all the participants, there was an even higher rate (>2%) for AF patients with a history of stroke or in the elderly with high stroke risk.[36–38] These results indicated that the advantages of anticoagulation therapy for stroke prevention usually far outweighed the disadvantages (e.g., the elevation in

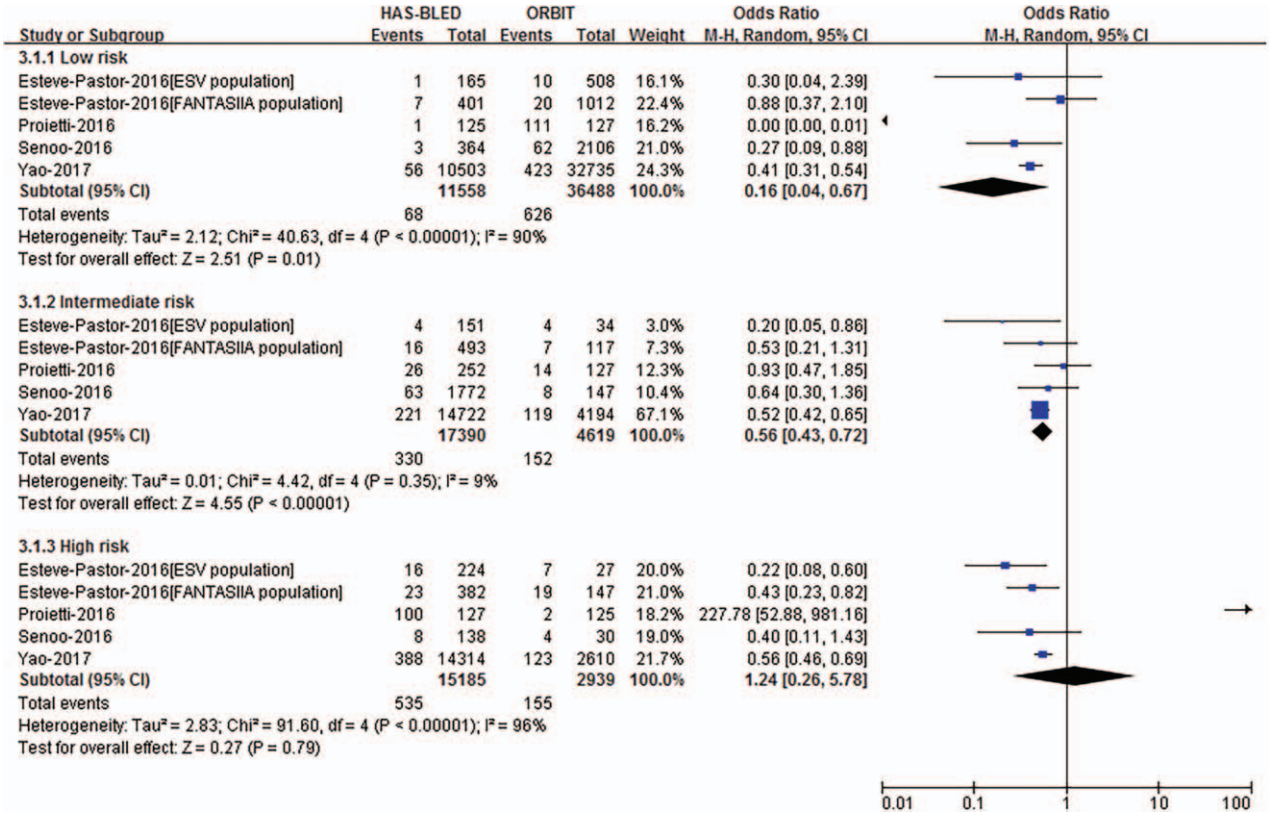

Figure 4. A comparative analysis of the occurrence of major bleeding across the 3 risk categories between HAS-BLED and ORBIT. Note: HAS-BLED = Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; ORBIT = Outcomes Registry for Better Informed Treatment; M-H = Mantel-Haenszel; CI = confidence interval.

bleeding risk). Therefore, the HAS-BLED score is not used to help us discontinue anticoagulation therapy in AF patients, but rather, to identify the potential bleeding risk factors. Given that the HAS-BLED score distributes more AF patients and a higher incidence of endpoint events into the "high-risk" category, we may search for appropriate measures (e.g., correcting reversible risk factors, and providing appropriate follow-up services) to reduce the occurrence of bleeding risk in anticoagulated patients with AF, particularly for patients at the "high-risk" category.

4.1. Limitations

Several limitations of this meta-analysis were detailed as follows. First, our included studies were observational prospective or retrospective studies. Large scale randomized controlled trials would be necessary to further validate the current results. Second, the HAS-BLED, HEMORR2HAGES, ATRIA, or ORBIT scores are derived and validated in independent studies with methodological differences. Various definitions of major bleeding events

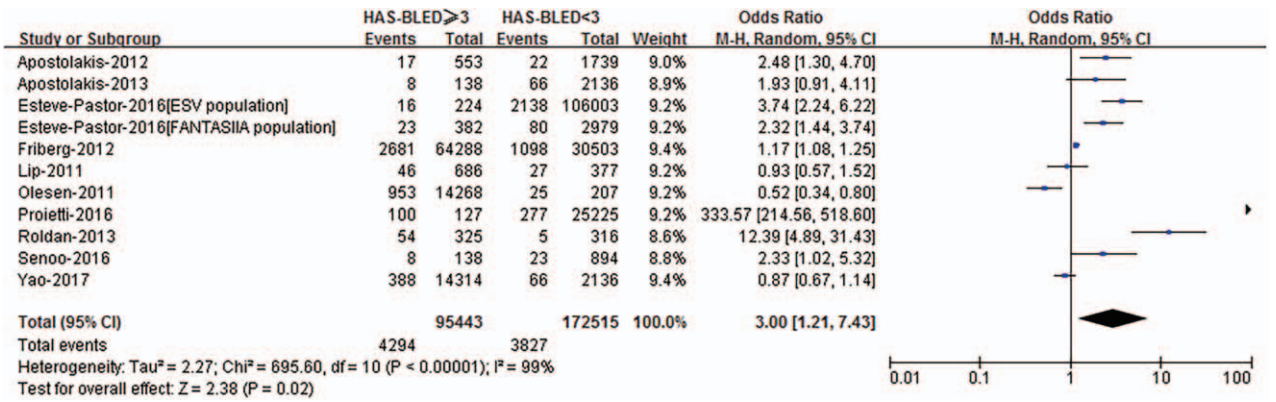

Figure 5. Forest plot for a comparative analysis of the occurrence of major bleeding risk in anticoagulated patients with AF between HAS-BLED scores ≥3 and scores <3. Note: AF = atrial fibrillation; HAS-BLED = Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; M-H = Mantel-Haenszel; CI = confidence interval.

(e.g., International Classification of Diseases-10 or 2005 International Society of Thrombosis and Haemostasis criteria) also complicated the synthesis of RR values. Third, although the high heterogeneity of the individual studies was observed obviously, there were limited studies regarding this topic and not all ethnic groups were represented in our included studies. Finally, our participants and interventions of studies were adult nonvalvular AF patients with anticoagulation therapy. Of note, anticoagulant drugs in our study included warfarin and non-warfarin agents. Further meta-analysis should perform the subgroup analysis based on the type of anticoagulants.

5. Conclusions

In the "low" or "moderate" risk categories, the occurrence of major bleeding events in AF individuals evaluated by the HAS-BLED scores was lower than that in patients evaluated by any of the HEMORR2HAGES, ATRIA, or ORBIT scores. With regard to the HAS-BLED score, there is a stepwise increase in major bleeding in conjunction with increasing scores across 3 risk categories. The incidence of major bleeding events was higher in the high HAS-BLED score group than in the low and moderate HAS-BLED score group.

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Validation: Junquan Zeng, Xiaoping Wang.
Writing – original draft: Junquan Zeng, Peng Yu.
Writing – review & editing: Jianyong Ma, Changai Zeng.

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