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Revised HAS-BLED score for bleeding prediction in atrial fibrillation patients with oral anticoagulants

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Abstract

Background: There were several limitations to the original HAS-BLED (oHAS-BLED) score in patients with atrial fibrillation (AF). This trial studied the revised HAS-BLED (rHAS-BLED) score for predicting bleeding events in anticoagulated AF patients.

Methods: This study retrospectively recruited anticoagulated AF patients in the Central Chest Institute of Thailand between 2014 and 2021. The rHAS-BLED score was oHAS-BLED using the estimated glomerular filtration rate of <60 ml/min/1.73 m^2 for abnormal renal function, SAMe-TT_2R_2 score of ≥3 for labile INR, and adding clinically relevant nonmajor bleeding (CRNMB) into bleeding history. The outcome was major bleeding (MB) and/or CRNMB at 1-year follow-up visit. The outcome between both groups was compared by using the chi-square test or Fisher's exact test. Receiver-operating characteristics curve was used to analyze the discrimination performances of both scores and the results were illustrated by using c-statistics.

Results: A total of 256 anticoagulated AF patients were enrolled. The average age was 73.6 ± 10.1 years. The average oHAS-BLED and rHAS-BLED scores were 1.7 ± 0.9 and 2.6 ± 1.2, respectively. Twenty patients in rHAS-BLED ≥3 (15.9%) and 9 patients in rHAS-BLED <3 (6.9%) experienced MB and/or CRNMB. The rHAS-BLED score of ≥3 increased the bleeding risk with statistical significance (OR 2.54, 95% CI 1.11–5.81, $p = .04$). The discriminative performance of the rHAS-BLED score was illustrated with c-statistics of 0.61 (95% CI 0.50–0.71).

Conclusions: The rHAS-BLED score could predict bleeding events in anticoagulated AF patients. However, a larger study is needed to confirm these results in the future.

KEYWORDS
atrial fibrillation, bleeding prediction model, oral anticoagulants, revised HAS-BLED, SAMe-TT_2R_2

1 | INTRODUCTION

Stroke prevention is of paramount importance in management in patients with atrial fibrillation (AF). Oral anticoagulants (OACs) are recommended in patients with a CHA_2DS_2-VASc score of 1 in males and 2 in females by standard clinical practice guidelines.[1–4] However, major bleeding especially intracranial bleeding is a catastrophic complication in those patients.

TABLE 1 Components in original HAS-BLED score

Components		Points
H	Uncontrolled hypertension SBP >160 mm Hg	1
A	Abnormal renal and/or hepatic function Dialysis, transplant, serum creatinine >200 μmol/L, cirrhosis, bilirubin >2 × ULN, AST/ALT/ALP >3 × ULN	1 point for each
S	Stroke Previous ischemic or hemorrhagic stroke	1
B	Bleeding history or predisposition Previous major hemorrhage or anemia or severe thrombocytopenia (platelet count <50,000/mm^3)	1
L	Labile INR TTR <60% in patients receiving VKA	1
E	Elderly Aged >65 years or extreme frailty	1
D	Drugs or excessive alcohol drinking Concomitant use of antiplatelet or NSAID and/or excessive alcohol per week	1 point for each

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; SBP, systolic blood pressure; TTR, time in therapeutic range; ULN, upper limit of normal; VKA, vitamin K antagonist.

Note: Nonsteroidal anti-inflammatory drug.

TABLE 2 Components in revised HAS-BLED score

Components		Points
H	Uncontrolled hypertension SBP >160 mm Hg	1
A	Abnormal renal and/or hepatic function Dialysis, transplant, eGFR <60 ml/min/1.73 m^2, cirrhosis, bilirubin >2 × ULN, AST/ALT/ALP >3 × ULN	1 point for each
S	Stroke Previous ischemic or hemorrhagic stroke	1
B	Bleeding history or predisposition Previous major or clinically relevant nonmajor bleeding or anemia or severe thrombocytopenia (platelet count <50,000/mm^3)	1
L	Labile anticoagulation control SAMe-TT$_2$R$_2$ score ≥3	1
E	Elderly Aged >65 years or extreme frailty	1
D	Drugs or excessive alcohol drinking Concomitant use of antiplatelet or NSAID and/or excessive alcohol/week	1 point for each

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; SBP, systolic blood pressure; ULN, upper limit of normal.

HAS-BLED score is used to predict bleeding events in those patients using OACs.[1–5] Labile international normalized ratio (INR) in this score is a cumbersome problem because it takes time for calculation during outpatient settings and cannot apply in patients using nonvitamin K OACs (NOACs).

Previous trials have shown that the SAMe-TT$_2$R$_2$ score has been used for the prediction of subtherapeutic INR in patients using vitamin K antagonists (VKAs) such as warfarin.[6–12] We previously proposed a simplified HAS-BLED score that incorporated the SAMe-TT$_2$R$_2$ score into the conventional HAS-BLED score and could predict bleeding risk in anticoagulated AF patients.[13,14] Moreover, abnormal renal function in HAS-BLED score is based on serum creatinine level which may not reflect the severity of renal impairment. To date, Kidney Disease: Improving Global Outcomes (KDIGO) classifies chronic kidney disease (CKD) according to glomerular filtration rate (GFR) and persistent albuminuria.[15] Renal function assessment

by using estimated glomerular filtration rate (eGFR) instead of serum creatinine is not used in the HAS-BLED score.

In addition, the HAS-BLED score has been studied in AF patients using VKAs, but there is scarce data on whether this score could predict bleeding events in those patients using NOACs.[5,16,17]

TABLE 3 Baseline characteristics of the patients

Demographic data	Total $n = 256$ n (%) or mean ± SD
Age (years)	73.6 ± 10.1
Male sex	141 (55.1)
Paroxysmal AF	83 (32.4)
CHA_2DS_2-VASc score	4.0 ± 1.7
SAMe-TT_2R_2 score	3.2 ± 0.8
Revised HAS-BLED score	2.6 ± 1.2
Original HAS-BLED score	1.7 ± 0.9
Time in therapeutic range (%)	52.8 ± 24.0
Medical history	
Diabetes mellitus	88 (34.4)
Hypertension	221 (86.3)
Dyslipidemia	225 (87.9)
Coronary artery disease	70 (27.3)
Peripheral artery disease	2 (0.8)
Chronic kidney disease	100 (39.1)
Previous stroke/TIA	49 (19.1)
History of heart failure	80 (31.3)
Liver disease	1 (0.4)
Pulmonary disease	13 (5.1)
Valvular heart disease	34 (13.3)
LVEF (%)	56.6 ± 19.4
Serum creatinine (mg/dL)	1.1 ± 0.3
eGFR (ml/min/1.73 m^2)	65.1 ± 19.0
Medications	
Beta-blockers	190 (74.2)
Nondihydropyridine CCBs	14 (5.5)
Digoxin	54 (21.1)
Antiplatelets	
Aspirin	11 (4.3)
$P2Y_{12}$ inhibitors	18 (7.0)
Oral anticoagulants	
Warfarin	110 (43.0)
NOACs	146 (57.0)
Amiodarone	22 (8.6)
Flecainide	3 (1.2)

Note: AF, atrial fibrillation; CCBs, calcium channel blockers; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; mg/dL, milligrams per deciliter; min, minute; ml, millimeter; *n*, numbers; NOACs, nonvitamin K antagonist oral anticoagulants; SD, standard deviation; TIA, transient ischemic attack.

Until now, the author did not know whether the use of eGFR, SAMe-TT_2R_2 score, and clinically relevant nonmajor bleeding (CRNMB) in the original HAS-BLED (oHAS-BLED) score could predict bleeding events in AF patients taking VKAs and NOACs. This study was conducted to use a revised HAS-BLED (rHAS-BLED) score for predicting bleeding events in anticoagulated AF patients.

2 | METHODS

This study retrospectively recruited anticoagulated AF patients treated for 1 year or more in the Central Chest Institute of Thailand between 2014 and 2021. The patients had contraindication of warfarin or duration of warfarin use below 1 year, each INR measurement during follow-up visit more than 6 months apart, OACs discontinuation due to surgery or other interventions, patients having prosthetic heart valve and/or mitral valve repair, thrombocytopenia, myeloproliferative disorders, hyperviscosity syndrome, pregnancy, and/or patients participating in any concealed studies were excluded. The study protocol was approved by Human Research Ethics Committee of Central Chest Institute of Thailand. This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice Guidelines. This trial was registered on the Thai Clinical Trials Registry (TCTR20200921001).

The baseline clinical data were collected from medical records. The choice of OACs was dependent on physicians' discretion. The following data were recorded: age, sex, baseline medical history, patterns of AF, types of OACs, time in therapeutic range (TTR) if the patients took warfarin (target INR 2–3), component parameters of CHA_2DS_2-VASc, SAMe-TT_2R_2, oHAS-BLED and rHAS-BLED scores. TTR was calculated by using the Rosendaal method.[18]

Each component of the SAMe-TT_2R_2 score was counted and recorded as S = female sex (1 point); A = age <60 years (1 point); Me = medical history >2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease (1 point); T = treatment (interacting drugs, e.g., amiodarone for rhythm control) (1 point); T_2 = tobacco use within 2 years (2 points); and R_2 = non-Caucasian race (2 points).[6,11,12]

The oHAS-BLED and CHA_2DS_2-VASc scores were defined according to recent European guidelines.[2] The rHAS-BLED score was oHAS-BLED using the eGFR of <60 ml/min/1.73 m^2 instead of serum creatinine >200 μmol/L, SAMe-TT_2R_2 score of 3 or more instead of labile INR, and adding CRNMB into bleeding history or predisposition. The components of oHAS-BLED and rHAS-BLED scores are shown in Tables 1 and 2.

The outcome was major bleeding (MB) and/or CRNMB at 1-year follow-up visit. MB was defined according to the International Society on Thrombosis and Haemostasis (ISTH).[19] The definition of CRNMB was non-MB requiring medical attention, a fall in hemoglobin level of 1 g/dL or more, or leading to blood transfusion of one unit or more.

This study determined 0.05 for type 1 error and 0.20 for type 2 error leading to the power of 0.90. The author estimated 18.6% and 37.5% for

bleeding events in patients with rHAS-BLED <3 and with a score of ≥3, respectively.[13] The ratio of estimated bleeding events in both groups was determined as 1. A total of 256 patients were calculated to compare two populations by chi-square test. The demographic data were analyzed by using descriptive statistics. The categorical data are presented as frequency and percentage. The continuous data are presented as mean ± standard deviation (SD). The outcome between both groups was compared by using the chi-square test or Fisher's exact test. The association between both groups was represented by odds ratio (OR) and 95% confidence interval (95% CI). Receiver-operating characteristics (ROC) curve was used to analyze the discrimination performances of oHAS-BLED and rHAS-BLED scores and the results were illustrated by using c-statistics. A *p* value of .05 or less was considered statistical significance.

3 | RESULTS

A total of 256 anticoagulated patients with AF were enrolled. The average age was 73.6 ± 10.1 years. Half of the patients were males. One-third of patients had paroxysmal AF. An average SAMe-TT_2R_2 score was 3.2 ± 0.8. An average TTR was 52.8 ± 24.0%. An average oHAS-BLED and rHAS-BLED scores were 1.7 ± 0.9 and 2.6 ± 1.2, respectively. Most patients had hypertension and dyslipidemia. About 40% of patients had CKD. Nearly 60% of patients were prescribed NOACs. The baseline characteristics of the patients are shown in Table 3 and the distribution of patients with revised and original HAS-BLED scores is illustrated in Figure 1.

Twenty patients in rHAS-BLED ≥3 (15.9%) and 9 patients in rHAS-BLED <3 (6.9%) experienced MB and/or CRNMB. The rHAS-BLED score ≥3 increased the bleeding risk with statistical significance (OR 2.54, 95% CI 1.11–5.81, $p = .04$) (Table 4).

Five patients in oHAS-BLED ≥3 (12.5%) and 24 patients in oHAS-BLED <3 (11.1%) experienced MB and/or CRNMB. The oHAS-BLED score ≥3 increased the bleeding risk with no statistical significance (OR 1.14, 95% CI 0.41–3.20, $p = .79$) (Table 4). Each of the CRNMB events is described separately in Table 5.

The discriminative performances of rHAS-BLED and oHAS-BLED scores were illustrated with c-statistics of 0.61 (95% CI 0.50–0.71) and 0.51 (95% CI 0.40–0.62), respectively (Figure 2).

4 | DISCUSSION

Based on current knowledge, the HAS-BLED score is a useful bleeding prediction model in AF patients with OACs especially VKAs.[1–5,16,17] However, this score has some limitations, such as labile INR is defined as poor TTR that is difficult to calculate in clinical practice and cannot apply in those patients using NOACs. In addition, serum creatinine alone cannot indicate accurate renal function. To date, renal function is accurately classified by eGFR.[15] CRNMB is another important outcome in many outpatient settings because it needs to attend in hospitals. The rHAS-BLED score was created by using the eGFR instead of serum creatinine, SAMe-TT_2R_2 score of 3 or more instead of labile INR, and adding CRNMB into bleeding history or predisposition.

This study showed that patients with an rHAS-BLED score of ≥3 experienced significantly increased MB and/or CRNMB compared with those had a score of<3 with a c-statistics of 0.61, while those with an oHAS-BLED score of ≥3 experienced increased bleeding outcomes with no statistical significance.

This study including AF patients with VKAs and NOACs may be leading to nonsignificant increased bleeding outcomes in oHAS-BLED score ≥3. The patients with NOACs had lower oHAS-BLED scores than those with VKAs because of no INR measurement. Those patients may have bleeding events regardless of INR level. A previous study has demonstrated that the SAMe-TT_2R_2 score could use instead of labile INR in the HAS-BLED score.[14] The clinical profile of those patients in the SAMe-TT_2R_2 score is another predictor of bleeding events.[13] This led to the rHAS-BLED score predicting bleeding events regardless of INR measurement.

Several bleeding risk assessments defined renal impairment following the eGFR and can predict bleeding events in AF patients.[20,21] The use of eGFR less than 60 ml/min/1.73 m^2 led to more accurate bleeding risk prediction than serum creatinine because some patients having serum creatinine <200 μmol/L might have eGFR less than 60 ml/min/1.73 m^2. So, this study used the eGFR instead of serum creatinine in the rHAS-BLED scoring system for improving bleeding prediction.

The MB in this study was defined following the ISTH definition because previous contemporary bleeding risk score trials used

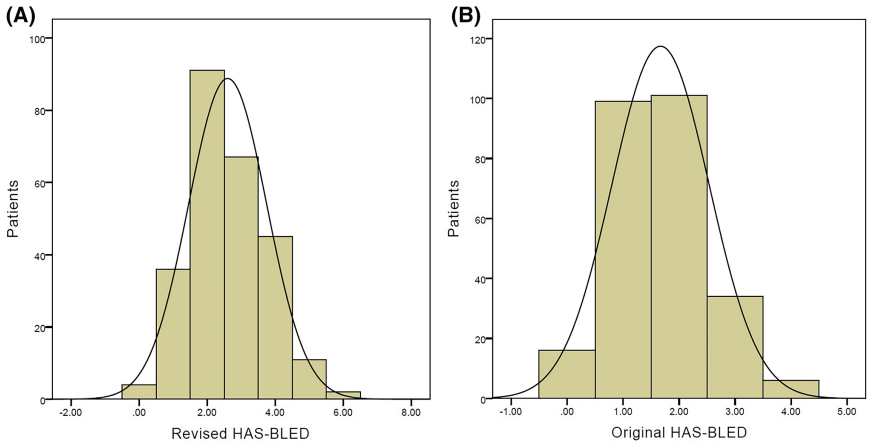

FIGURE 1 The distribution of patients with revised HAS-BLED (A) and original HAS-BLED (B)

TABLE 5 Clinically relevant nonmajor bleeding events in AF patients

CRNMB events	*n* (%)
LGIB	3 (17.6)
Hematuria	1 (5.9)
Anemia	13 (76.5)

Abbreviations: CRNMB, clinically relevant nonmajor bleeding; *n*, numbers; LGIB, lower gastrointestinal bleeding.

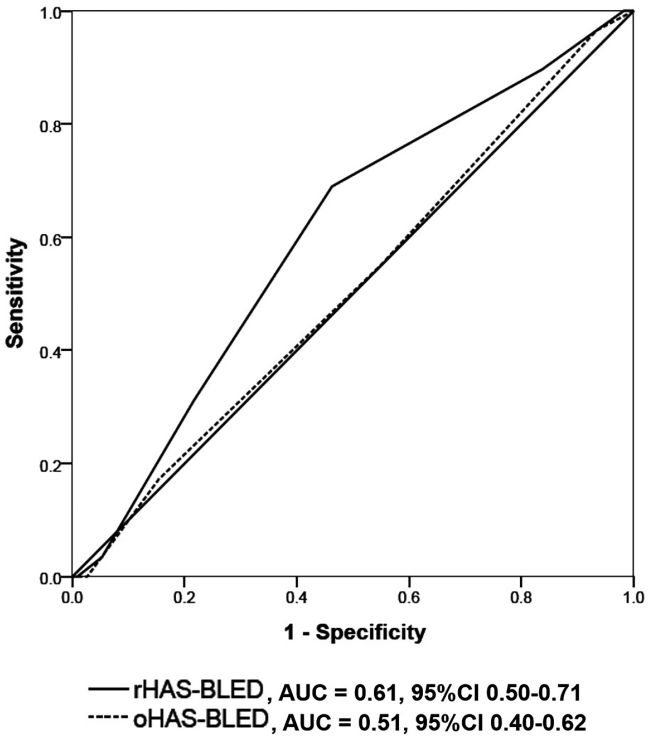

FIGURE 2 Comparison of ROC curve between revised and original HAS-BLED scores

this definition.[16,19,20] Until now, the CRNMB has not been defined by standard definition. The definition of CRNMB in this study was modified from the ISTH MB definition including the situation where patients need medical attention.

The c-statistics of rHAS-BLED and oHAS-BLED scores were lower than previous contemporary scoring trials.[5,16,17] Prior trials showed that patients with any clinically relevant bleeding had a lower area under the curve than those with MB.[22] Because this study included CRNMB in the combined outcome, the c-statistics was lower than expected.

However, this study had some limitations. First, this trial was a retrospective study. The missing data might not be stated in the medical records and the selection bias could not be excluded. Second, this study had small patients leading to nonsignificant increased bleeding events in the oHAS-BLED score. Nevertheless, this study was the first trial illustrating the useful bleeding prediction of this scoring system in patients with VKAs and NOACs. Finally, this study included only Thai AF patients, so the results could not be generalizable to other racial patients.

TABLE 4 Outcomes in AF patients with revised and original HAS-BLED scores

Outcomes	MB and/or CRNMB	OR (95% CI)	*p* value
Revised HAS-BLED			
Score ≥3, *n* = 126	20 (15.9)	2.54 (1.11–5.81)	0.04
Score <3, *n* = 130	9 (6.9)		
Original HAS-BLED			
Score ≥3, *n* = 40	5 (12.5)	1.14 (0.41–3.20)	0.79
Score <3, *n* = 216	24 (11.1)		

Note: 95% CI, 95% confidence interval; AF, atrial fibrillation; CRNMB, clinically relevant nonmajor bleeding; MB, major bleeding; *n*, numbers; OR, odds ratio.

5 | CONCLUSIONS

The rHAS-BLED score could predict bleeding events in anticoagulated AF patients. However, a larger study is needed to confirm these results in the future.

CONFLICT OF INTEREST

The author declares no conflict of interest in this article.

DATA SHARING AND DATA AVAILABILITY

The data summaries provided and analyzed for this study are included in this published article. Further details of the data are available from the corresponding author on reasonable request, after deidentification from any patient.

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