Relationship between HAS-BLED Score & Major Bleeding Events in Patients with Non-valvular Atrial Fibrillation on Warfarin: A Study at a Tertiary Care Teaching Hospital

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Authors' contributions:

This work was carried out in collaboration among all authors. Author CK designed the study, corrected the proposal and literature survey, supervised and guided methodology and analysis and finally corrected and modified the manuscript up to this final version. Authors VL, PC wrote the protocol, managed the literature survey, carried out data collection, performed the initial analysis and wrote the first draft of the manuscript. Authors NR, SG and VK Supported and modified the analyses of the study. All authors read and approved the final manuscript.

Original Research Article	

ABSTRACT

Background: Prevention of stroke and thrombo-embolism in patients with atrial fibrillation(AF) using oral vitamin K antagonists is closely related to risk of bleeding. The HAS-BLED score has been evaluated as a predictor of major bleeding risk in various populations. The present study was

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conducted to evaluate the usefulness of the HAS-BLED score for predicting 1-year major bleeding risk in a cohort of Sri Lankan patients with non valvular atrial fibrillation on warfarin.

Materials and Methods: This was a retrospective cohort study conducted at anticoagulation outpatient clinics of a tertiary care teaching hospital, which included ninety one patients with non valvular atrial fibrillation on warfarin for at least 18 months. The relevant data were collected using an interviewer administered questionnaire and medical records of the patient. HAS-BLED score was calculated 6 months after the initial diagnosis and start of warfarin, using the retrospective information. The occurrence of major bleeding events during the period of following 01year was documented. The results were analyzed by obtaining a p value through Fisher exact test and using logistic regression analysis to assess the independent risk factors.

Results: Out of 91 patients, 47.25% (43/91) were males and 52.74% (48/91) were females. The median HAS-BLED score was 2. In this cohort, 06(6.6%) were in a low risk, 59(64.8%) were in an intermediate risk and 26(28.6%) were in a high risk of bleeding according to HAS-BLED score. There were 2 major bleeding events in the one year period with one each occurring in intermediate and high risk groups. But, the association was not statistically significant(Fisher exact test is 1.000, P=1.000). Logistic regression analysis did not show any significance of individual components of the score as independent risk factors for bleeding.

Conclusion: The data of our study showed a limited value of HAS-BLED score, as it had no statistically significant relationship with the major bleeding events in patients in our cohort. However, further studies using greater samples are recommended to draw further conclusions in our population.

1. INTRODUCTION

Atrial fibrillation (AF) is the commonest cardiac arrhythmia which is associated with an increased risk of stroke and thromboembolism with an estimated prevalence of approximately 1% in the general population [1]. Stroke prevalence in Sri Lanka is 10.4/1000 persons with 2:1 male to female ratio and the world prevalence is 15 million/year [2,3].

Prevention of stroke and thrombo-embolism is one of the main tasks in atrial fibrillation (AF). Oral anticoagulation (OAC) therapy is the mainstay of management in patients with AF to prevent the risk of stroke and thromboembolism [4,5]. Oral anticoagulation therapy mainly consists of vitamin K antagonists (VKAs); often warfarin or acenocoumarol or phenprocoumon, which are dose adjusted to achieve an international normalized ratio (INR) of 2.0–3.0 [6]. The most serious side effect associated with the use of vitamin K antagonist is hemorrhage including intra cranial bleeding episodes which has become an added challenge to the clinician in the long term use of such drugs. Though the bleeding risk is less with new oral anticoagulants (NOACs) such as apixaban and dabigatran which are becoming popular in developed countries, we still depend on vitamin K antagonists such as warfarin in the management of these patients.

Bleeding risk gives information about the downside of anticoagulation treatment, with a bleeding incidence of 2.0 per 100 patient-years [7] Numerous individual clinical factors have been linked to an increased risk of hemorrhage including older age, anaemia, uncontrolled hypertension, diabetes, history of ischemic heart disease, cerebrovascular disease, renal disease & previous bleeding events etc [8].

So, it is necessary to assess the risk of bleeding in the patients with atrial fibrillation on anticoagulation therapy. For that, several scores of bleeding risk are used in general clinical practice. HAS-BLED, ATRIA, ORBIT, $HEMORR_2$ HGES are commonly used bleeding scores. From these scores, HAS-BLED score has been a reliable clinical tool to predict the bleeding risk of the atrial Fibrillation patients that helps to determine the oral anticoagulant dose since the incidence of bleeding is higher with increasing HAS BLED Score [7,8,9].

HAS-BLED score is calculated using the information on several characteristics of the patient, which include hypertension, abnormal renal function and abnormal liver function, prior stroke, history of bleeding, labile international normalized ratio(INR), elderly (defined as age 65 years), drug therapy, and alcohol intake[10].

HAS-BLED categorizes bleeding risk into 03 groups according to the points obtained using

above criteria. HAS BLED score of 0 indicates low risk of bleeding whereas score of 1-2 & 3 or more than 3 indicates intermediate and high risk of bleeding respectively.

There was no evidence of previous studies conducted to evaluate the association of the HAS-BLED score to major bleeding events in patients with atrial fibrillation on warfarin in Sri Lanka.

So, our study wanted to assess the ability of HAS-BLED score and its components to predict the 1-year major bleeding risk in a cohort of patients with non valvular atrial fibrillation on warfarin, with the aim of identifying any differences or similarities when compared to the pattern of western population.

2. MATERIALS AND METHODS

This was a retrospective cohort study and all the patients with non valvular atrial fibrillation who were on warfarin for at least 18 months were recruited from two anticoagulation outpatient clinics attached to Colombo South Teaching Hospital, Sri Lanka. Patients who had hospital admissions or surgical intervention in the first 06 months after diagnosis of AF, patients with prosthetic heart valves, acute coronary syndrome, stroke,(ischaemic or embolic), valvular AF, or hemodynamic instability & cancer patients receiving chemotherapy or radiotherapy were excluded from the study.

Out of 220 patients, ninety one(91) patients who satisfied the eligibility criteria were included in the study. A Questionnaire was provided to each patient and information was gathered by an interviewer. At the same time relevant clinical details were collected from the medical records. HAS-BLED score was calculated using the

retrospective information obtained from each patient. The score was applied at a point where 06 months have elapsed from the initial diagnosis and start of warfarin. INR values during those 06 months were taken into consideration to decide on the score for labile INR, during application of the score.

The occurrence of major bleeding events during the time period of following one year was documented.

2.1 Definition of Major Bleeding

We applied the same definition of major bleeding used in Euro Heart Survey in 2010, which is any bleeding requiring hospitalization and/ or causing a decrease in hemoglobin level of >2 g/dL and/ or requiring blood transfusion that was not a haemorrhagic stroke.

2.2 Calculation of HAS BLED Score

For each patient, the HAS-BLED score was calculated as the sum of points obtained after adding 1 point for the presence of each individual factor.

Risk of bleeding was categorized according to the calculated HAS BLED Score.

Score - 0→ Low risk of bleeding
Score - 1-2 → Intermediate risk of bleeding
Score ≥ 3 → High risk of bleeding

Data analysis was performed with SPSS, version 21.The presence of any differences between the groups with and without major bleeding during 01 year after applying the score was tested by Fisher exact test. The association between individual components of the HAS-BLED score and major bleeding events was evaluated by

	Condition	points
H	Hypertension (uncontrolled, >160 mmHg systolic)	1
A	Abnormal Renal function (Dialysis, transplant, Creatinine>2.26 mg/dL or >200 µmol/L	1
	Abnormal liver function (Cirrhosis or bilirubin >2×normal or AST/ALT/AP >3×Normal)	1
S	Stroke (prior history of stroke)	1
B	Bleeding (prior major bleeding or predisposition to bleeding)	1
L	Labile INR (Unstable /High INR), Time in therapeutic range <60%	1
E	Elderly (Age >65 years)	1
D	Prior alcohol or drug usage history (≥8 drinks/week)	1
	Medication usage predisposition to bleeding (antiplatelet agents, NSAIDs)	1

logistic regression analysis by obtaining an odds ratio with a 95% confidence interval(CI) for each component.

3. RESULTS

Out of ninety one(91) patients recruited for the study, 43 (47.25%) were males and 48(52.75%) were females. Majority(45.1%, n=41) of the study population was above 65 years of age. Socio demographic and other baseline clinical characteristics of the study population are shown in Table 1.The frequency distribution of the HAS-BLED score showed a median of 2 in the cohort (Table 2).

The risk classification according to HAS-BLED score showed that, out of 91 patients ,06 (6.6%) were in the low risk of bleeding, a majority,59 (64.8%) were in the intermediate risk and 26(28.6%) patients were in the high risk of bleeding (Table 3).

In the study cohort, during the one year period after calculating the HAS-BLED score, there were two(02) major bleeding events and seventeen (17) minor bleeding events (Table 4).

Out of 17 patients who experienced minor bleeding, 01 (16.67%) was in low risk, 08 (13.56%) were in the intermediate risk and another 08 (30.77%) were inthe high risk category (Table 5).

Two(02) major bleeding events(2.2%) occurred during 01 year period were episodes of haematuria which needed hospital admission for management. One patient was in intermediate risk group (Table 6) who had a HAS BLED score of 01which was due to heavy alcohol intake. The other patient was in high risk category who had a score of 03 due to uncontrolled hypertension, labile INR and anti platelet drugs. Both patients were males between 40-50 years of age.

Table 1.Distribution of demographic and other baselineclinical characteristics

Characteristic	Frequency	Percentage
Sex		
Male	43	47.25
Female	48	52.75
Age		
30-40	1	1.1
41-50	8	8.8
51-60	28	30.7
61-65	13	14.3
>65	41	45.1
Hypertension	91	100.0
Diabetes Mellitus	29	31.9
History of stroke	12	13.2
Renal impairment	0	0
Liver impairment	0	0
Hyperthyroidism	1	1.1
Hypothyroidism	5	5.5
cancer	0	0
Smoking	12	13.2
Alcohol use	28	30.8
NSAIDs	67	73.6
Statin use	41	45.1

Table 2.Frequency distribution of HAS-BLED score

Score	Frequency	Percentage (%)
0	6	6.6
1	27	29.7
2	32	35.2
3	21	23.1
4	4	4.4
5	1	1.1
6	0	0
7	0	0
8	0	0
9	0	0
Total	91	100.0

The median HAS-BLED score is 2

Table 3.Distribution of risk classification according to HAS-BLED score

Risk category	Frequency	Percentage (%)
Low risk (0)	6	6.6
intermediate risk (1-2)	59	64.8
High risk (≥3)	26	28.6
Total	91	100.0

Table 4.Distribution of bleeding events

Minor bleeding events	No. of patients
Gum bleeding	10
Ecchymotic patches	04
Nasal bleeding	03
Major bleeding events	
Haematuria	02

Table 5. Distribution of minor bleeding events in each risk category

Risk category	No of patients	Minor bleeding episodes	Percentage (%)
Low	06	1	(1/6) 16.67
Intermediate	59	8	(8/59) 13.56
High	26	8	(8/26) 30.77
Total	91	17	

Table 6. Distribution of major bleeding events in each risk category

Risk category	No of patients	Major bleeding episodes	Percentage (%)
Low	06	0	0
Intermediate	59	01	1.69
High	26	01	3.85
Total	91	02	

Table 7. Distribution of major bleeding events in low vs intermediate/high risk categories

Risk category	No of patients	Major bleedingepisodes	(%)
Low	06	0	0
Intermediate/high	85	02	2.35

Fisher exact test -1.000(p=1.000)

Table 8. Regression analysis for individual components of the HASBLED score

Individual Characteristics of HASBLED score	Odds ratio(Confidence interval(CI)- 95%)
Hypertension (uncontrolled, >160mmHg systolic)	11.714 (0.659-208.108)
Labile INR (Unstable /High INR), Time in therapeutic range <60%	1.070 (0.065-17.642)
Prior alcohol or drug usage history (≥8drinks/week)	13.833 (0.767-249.655)
Medication usage predisposition to bleeding(antiplatelet agents, NSAIDs)	0.435 (0.026-7.222)

When intermediate and high risk groups were considered as one group versus low risk (Table 7), major bleeding episodes have occurred in 2/85 (2.35%) patients in the preceding group. Anyhow, significant association between risk category and major bleeding could not be found (Fisher exact test is 1.000, P=1.000) in our population.

Logistic regression analysis showed odds ratio and 95% confidence interval(CI) of each individual component associated with major bleeding (Table 8) and represented the independent risk of each characteristic to bleeding. But, none of the above characteristics were significant as independent risk factors.

Odds ratio could not be calculated for the characteristics; abnormal renal and liver function, prior major bleeding or predisposition to bleeding, since there were no subjects who have got points to those characteristics in HASBLED score.

Odds ratio for stroke was 0 since there were no major bleeding events recorded among the patients who have got points for 'S' in HAS-BLED (thosewho had prior history of stroke).

4. DISCUSSION

In this study, we tried to evaluate the clinical usefulness of HAS-BLED score for assessing the 1-year risk of major bleeding in a cohort of patients with non valvular atrial fibrillation on warfarin.

Though, previous studies conducted in other countries have concluded that the HAS-BLED score is a better predictive tool for major bleeding events in patients with AF on warfarin, a significant relationship between the HAS-BLED score and the major bleeding events in warfarinized AF patients could not be found in our study.

Our study was a single center study and we recruited all the patients with atrial fibrillation from the anticoagulation outpatient clinics, from which only ninety one satisfied the eligibility criteria. Most of the previous studieswere multicentric and a greater number of patients had been included as the study population. In the studies, Mitesh Shah et al. [11] & Jonas Bjerring et al. [12], 205,836 &132,372 subjects respectively have been recruited whereas all other studies have also recruited thousands of subjects.

Also, we used only the retrospective data available in hospital medical records and patients' history to calculate the score and assess the bleeding history of following one year. But in some studies they have followed up the patients for major bleeding episodes for number of years. In the studies conducted by Mitesh Shah et al. [11], Gregory YH et al. [13], Jonas Bjerring et al. [12] & Juan M Ruiz-Nodar [14], patients have been followed up for major bleeding events for 09, 10, 12 & for 07 years respectively.

The proportions of patients falling into risk categories according to HAS-BLED score was variable among all the studies.In our study, majority of patients fell into the intermediate risk category(59/91, 64.8%). Similar studies such as Gregory Y H et al. [15], PillerGallego et al. [8] and Gregory Y H et al. [13] had also obtained a majority of patients in the intermediate risk category followed by high and low risk categories

resembling our study.Juan M Ruiz-Nodar [14] has shown a majority of subjects in high risk category (71%) whereas the study by Jonas Bjerring et al. [12] had a majority of subjects in low risk category.

In previous studies, most of the major bleeding episodes had been experienced by the patients in intermediate risk category [11,13,15,16].In our study, two major bleeding events were observed in intermediate/high risk category, and none was seen in the low risk category; but the association was not statistically significant ((Fisher exact test is 1.000 ,P=1.000)) in our study population.

Odds ratios(by logistic regression analysis)of individual components which were associated with the 02 bleeding events, namely heavy alcohol intake, hypertension, labile INR and antiplatelet drugs did not show statistically significant correlation as independent risk factors in our study, though they have been highlighted in some studies.

Our findings did not point out a significant correlation between HAS-BLED score and 1-year bleeding risk in patients with non valvular atrial fibrillation on warfarin. This may be due to the small sample size and limited number of bleeding events. However, it is interesting to know whether the behavior of the asian population is different to patients from other parts of the world. Studies done in the south asian region are currently not available for comparison.

5. LIMITATIONS

Since the sample size and major bleeding events were limited in our study we could not draw concrete conclusions.

6. CONCLUSION

Though we made some important observations similar to previous studies, the findings of our study showed a limited value of HAS-BLED score as it has no statistically significant relationship with the major bleeding events in our patient cohort. However, Due to the limitations of our study, further retrospective or prospective multi-centrestudies using a greater sample size is recommended to draw better conclusions in our population.

DISCLAIMER

This manuscript was presented in a Conference : Annual academic sessions of college of

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CONSENT

Written informed consent was taken from each patient prior to the study.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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