

ORIGINAL ARTICLE

Use of HAS-BLED Score in an Anticoagulation Outpatient Clinic of a Tertiary Hospital

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Abstract

Background: HAS-BLED score was developed to assess 1-year major bleeding risk in patients anticoagulated with vitamin K antagonists (VKA) due to atrial fibrillation (AF).

Objective: Of this study was to assess the ability of HAS-BLED score and its components to predict major bleeding in patients treated in an anticoagulation outpatient clinic of a tertiary hospital.

Methods: A retrospective cohort study on AF patients treated with VKA was conducted. Logistic regression analysis was performed to evaluate the ability of individual score components to predict major bleeding. The significance level adopted in all tests was 5%.

Results: We studied 263 patients with a mean age of 71.1 ± 10.5 years over a period of 237.6 patients-year. Median HAS-BLED score was 2 (1-3). The overall incidence of major bleeding was 5.7%, and it was higher among high-risk HAS-BLED score patients than in low risk patients (9.6 vs. 3.1%; $p = 0.052$). Area under the ROC curve was 0.70 ($p = 0.01$). Cut-off point ≥ 3 showed sensibility of 66.7%, specificity of 62.1%, positive predictive value of 9.6% and negative predictive value of 96.9%. Major bleeding-free survival was lower in high-risk group ($p = 0.017$). In multivariate analysis, concurrent antiplatelet use was the only independent predictor of major bleeding among score components (OR 5.13, 95%CI: 1.55-17.0; $p = 0.007$).

Conclusion: HAS-BLED score was able to predict major bleeding in this cohort of AF patients. Among score components, special attention should be given for concomitant antiplatelet use, which was independently associated to this outcome. Antiplatelets in AF patients under VKA anticoagulation should be used in selected patients with favorable risk-benefit assessment. (Int J Cardiovasc Sci. 2017;30(6):517-525)

Keywords: Atrial Fibrillation; Hemorrhage; Outpatient Clinics; Hospital.

Introduction

Atrial fibrillation (AF) is a common cardiac rhythm disturbance that increases in prevalence with advancing age: approximately 1% of patients with AF are under 60 years of age, whereas up to 12% of patients with AF are 75 to 84 years of age.¹ AF is associated with a broad spectrum of negative outcomes, such as heart failure and major cardiovascular events, including ischemic stroke, with increased cardiovascular and all-cause mortality.² Ischemic strokes related to AF usually result from cardioembolism of a large cerebral artery, and therefore

tend to be larger, more frequently fatal or associated with greater disability than strokes from other causes.³

Studies with oral anticoagulants (OAC) have shown reduction in all-cause mortality by 26% and in systemic thromboembolism by 64% with the use of vitamin K antagonists (VKA) compared with placebo or untreated controls.⁴ On the other hand, VKA are associated with increased risk of bleeding.⁵ Gomes et al⁶ demonstrated a 3.8% risk of hemorrhage per person-year with warfarin, especially within the first 30 days of therapy (11.8%), with almost 1% of all new users being admitted to hospital due to hemorrhagic complications during this period.

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DOI: 10.5935/2359-4802.20170081

Manuscript received February 11, 2017, revised manuscript April 06, 2017, accepted June 05, 2017

There are several risk scores available to assess bleeding risk in patients in treatment with VKA.⁷⁻¹² HAS-BLED score [Hypertension (uncontrolled), Abnormal renal/liver function, Stroke, Bleeding history or predisposition (anemia), Labile INR, Elderly (> 65 years), Drugs/alcohol concomitantly] offers a better prediction of bleeding compared with many other bleeding risk scores for AF patients, and has also been validated in several different cohorts, including large real-world and clinical trial populations.¹³ The score ranges from 0 to 9, with scores ≥ 3 indicating higher risk of bleeding. In this situation, thorough and regular patient follow-up is recommended.¹³ In addition, HAS-BLED score should be used to identify modifiable bleeding risk factors that might be addressed, but should not be used to exclude patients from OAC therapy, as suggested by CHA₂DS₂-VASc score [Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, Stroke, Vascular disease, Age 65-74 years, Sex category (i.e., female gender)].^{3,14,15} The objective of this study was to assess the ability of HAS-BLED score and its components to predict major bleeding in patients treated at an anticoagulation outpatient clinic of a tertiary hospital.

Methods

A retrospective cohort study was conducted on patients on oral anticoagulation with VKA attending the outpatient anticoagulation clinic at Hospital de Clínicas de Porto Alegre (HCPA). This hospital is a tertiary care teaching hospital located in southern Brazil and most patients are low-income. All decisions regarding the management of anticoagulation are based on a protocol published by Kim et al.¹⁶ All patients who visited the clinic from January to March 2014 were screened for inclusion in the study. Non-valvular AF patients under VKA anticoagulation were included. Valvular AF was defined as AF associated to moderate to severe mitral stenosis or prosthetic heart valve.¹⁷ This study was approved by local Research Ethics Committee.

Ischemic stroke risk was estimated with the scores CHADS₂ (Congestive heart failure, Hypertension, Age > 75, Diabetes, Stroke) and CHA₂DS₂-VASc.^{18,19} High-risk for ischemic stroke was defined as a score ≥ 2 . As for the risk of major bleeding, patients were stratified into 2 groups according to individual HAS-BLED scores: (1) low-moderate risk group (score 0-2) and (2) high risk group (score ≥ 3).¹² The acronym HAS-BLED represents each of the bleeding risk factors and assigns 1 point

for each of the following: uncontrolled hypertension, abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile international normalized ratios, elderly, and concomitant drugs and/or alcohol abuse.¹³ Data were obtained by reviewing electronic health records during outpatient clinic visits, emergency visits and hospital admissions during the study period. Patients who were lost to follow-up, who died or whose anticoagulation therapy was discontinued were equally included in the analysis. Time in therapeutic range (TTR) was estimated through Rosendaal's linear interpolation method.²⁰

Laboratory test results and left ventricular ejection fraction (preferably assessed by echocardiogram) at the beginning of follow-up period were recorded. Anemia was defined by hemoglobin (Hb) below 13.0 g/L in men and 12.0 g/L in women.²¹ Uncontrolled hypertension was defined as systolic blood pressure > 160 mmHg.¹² Major bleeding was defined as any bleeding requiring hospitalization and/or causing a decrease in hemoglobin level > 2 g/dL and/or requiring blood transfusion.¹² Presence of chronic dialysis, renal transplantation or serum creatinine ≥ 200 $\mu\text{mol/L}$ (2.26 mg/dL) was classified as abnormal renal function.¹² Abnormal liver function was defined as previous clinical diagnosis of chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin > 2x upper limit of normal, in association with AST/ALT/ALP > 3 x upper limit of normal).¹²

Statistical analysis

Descriptive analyses were performed by absolute and relative frequency for qualitative variables, and mean \pm standard deviation and median (interquartile range, 25-75th percentile) for quantitative variables with symmetric and asymmetric distribution, respectively. Normality of the distribution of each variable was evaluated using Shapiro-Wilk test. Comparison between the groups was performed by Chi-square test. Fisher exact test was used in situations of low frequency. Area under the Receiver Operating Characteristic (ROC) curve was calculated to evaluate the ability of HAS-BLED score to predict major bleeding. Major bleeding-free survival between HAS-BLED groups was analyzed by Kaplan-Meier curves and compared using log-rank test. Logistic regression was performed to detect the adjusted association of HAS-BLED score components with the outcome major bleeding. Relation between candidate

variables and the outcome was initially investigated in a series of bivariate analyses ($p < 0.10$ for selection of candidate variables). Next, we used stepwise forward selection for variable inclusion until all retained variables were statistically significant at a $p < 0.05$. The significance level adopted in all tests was 5%. Data were analyzed in Statistical Package for Social Sciences (SPSS) software, version 21.0 (IBM, Armonk, NY, USA).

Results

A total of 263 patients were included in the study, corresponding to 38.5% of individuals attending in outpatient anticoagulation clinic. Demographic characteristics are detailed in Table 1. There were no patients using nonsteroidal anti-inflammatory drug (NSAIDs). Indications for anticoagulation among patients not included in the current cohort were: mechanical cardiac prosthesis (21.2%), deep vein thrombosis / pulmonary thromboembolism (19.0%), valvular AF (8.6%) and thrombus in the left ventricle (2.0%).

Mean follow-up was 329.9 ± 81.9 days. Of the 263 patients, 205 (77.9%) completed the follow-up, 25 (9.5%) were lost to follow-up, 21 (8.0%) stopped the anticoagulation and 12 (4.6%) died. Overall, 2,754 INR tests were performed during the study period, with a median of 10 INR tests per patient (range 7-13). Of these, 1,270 (46.1%) presented values between 2.0 and 3.0 over a treatment time of 237.6 patients-year. Median TTR was 62.5% (44.2-79.5%). Patients were under-anticoagulated (i.e., $INR < 2.0$) during a median of 18.9% of time (6.1-36.6%) and over-anticoagulated (i.e., $INR > 3.0$) during a median 9.6% of time (1.6-23.3%).

The incidence of major bleeding in all patients was 5.7% ($n = 15$), which represents 6.3 major bleedings/100-patients-year. The major bleeding sites were mucocutaneous ($n = 4$; 26.7%), genitourinary ($n = 4$; 26.7%), gastrointestinal ($n = 3$; 20.0%), intracranial ($n = 3$; 20.0%) and retroperitoneal ($n = 1$; 6.7%).

“Elderly” was the most prevalent HAS-BLED score component (72.2%), followed by “Labile INR” (47.1%). When the patients were divided according the HAS-BLED score in high and low-moderate risk for major bleeding, we observed that 104 patients (39.5%) were classified as high risk ($HAS-BLED \geq 3$). This group had a higher incidence of major bleeding compared with the low-moderate (9.6 versus 3.1%; $p = 0.052$).

The association of HAS-BLED score components with major bleeding incidence is described in Table 2. In multivariate logistic regression analysis, concurrent

Table 1 – Demographic characteristics of the patients

Variable	n = 263
Female sex	113 (43.0)
Age	71.2 (64.1-78.5)
Warfarin use	256 (97.3)
Hypertension	231 (87.8)
Heart failure / LVEF < 40%	149 (56.7)
Labile INR (TTR < 60%)	124 (47.1)
Diabetes	108 (41.1)
Previous stroke / TIA	96 (36.5)
Coronary artery disease	76 (28.9)
Antiplatelet therapy	64 (24.3)
Anemia	67 (25.5)
Peripheral artery disease	25 (9.5)
Major bleeding history	24 (9.1)
Hypertension, uncontrolled	22 (8.4)
Alcohol	21 (8.0)
Abnormal renal function	7 (2.7)
Abnormal liver function	2 (0.8)
CHADS ₂ score	3 (2-4)
CHA ₂ DS ₂ -VASc score	4 (3-5)
HAS-BLED score	2 (1-3)

LVEF: left ventricle ejection fraction; TIA: transient ischemic attack; INR: international normalized ratio; TTR: time in therapeutic range. CHADS₂: Congestive heart failure, Hypertension, Age > 75, Diabetes, Stroke; CHA₂DS₂-VASc: Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, Stroke, Vascular disease, Age 65-74 years, Sex category (i.e., female gender); HAS-BLED: Hypertension (uncontrolled), Abnormal renal/liver function, Stroke, Bleeding history or predisposition (anemia), Labile INR, Elderly (> 65 years), Drugs/alcohol concomitantly. Data presented as number (%) or median (interquartile range).

antiplatelet use was the only independent predictor of major bleeding among score components (OR 5.13, 95%CI: 1.55-17.0; $p = 0.007$).

The area under the ROC curve for HAS-BLED score ability to predict major bleeding was 0.70 (95%CI: 0.53-0.86; $p = 0.01$). A score cut-off point ≥ 3 presented sensibility of 66.7%, specificity of 62.1%, positive predictive value of 9.6% and negative predictive value of 96.9%. Major bleeding-free survival Kaplan-Meier curves according HAS-BLED score categories are

shown in Figure 1. High-risk patients, i.e. HAS-BLED score ≥ 3 , had a significantly lower major bleeding-free survival ($p = 0.017$).

The magnitude of the risks associated to each score component is presented in Figures 2 and 3 in univariate and multivariate analysis, respectively. In multivariate analysis, only the concurrent use of antiplatelet agents independently predicted the occurrence of major bleeding among the score components. Antiplatelets used during follow-up and their indications are described in Figure 4 and Table 3.

Discussion

In this study, a significant association between high HAS-BLED scores (i.e. score ≥ 3) and major bleeding during

follow-up was observed. The only independent variable of HAS-BLED score associated with this adverse event was concomitant use of antiplatelet agents. Our findings corroborate the use of HAS-BLED score as a predictor of bleeding, and the importance of an adequate assessment of modifiable risk factors for bleeding.

Current literature suggest that increments in HAS-BLED score values are associated with progressively increased risk of bleeding, with little difference in hemorrhage rates between patients in use of OAC and controls. Because many risk factors for bleeding are also risk factors for stroke, the use of OACs is wrongly contraindicated for many patients with high risk of stroke (and consequently high risk of bleeding),³ thereby losing benefit of stroke prevention and maintaining a high risk of bleeding even without use of OAC.

Table 2 – HAS-BLED components and associated major bleeding incidence

Variable		n (%)	Bleeding, n (%)	p
Hypertension, uncontrolled	Yes	22 (8.4)	3 (13.6)	.119*
	No	241 (91.6)	12 (5.0)	
Abnormal renal function	Yes	7 (2.7)	2 (28.6)	.054*
	No	256 (97.3)	13 (5.1)	
Abnormal liver function	Yes	2 (0.8)	1 (50.0)	.111*
	No	261 (99.2)	14 (5.4)	
Stroke	Yes	96 (36.5)	5 (5.2)	1.0 [†]
	No	167 (63.5)	10 (6.0)	
Bleeding history	Yes	24 (9.1)	0 (0)	.374*
	No	239 (90.9)	15 (6.3)	
Predisposition (anemia)	Yes	67 (25.5)	7 (10.4)	.067*
	No	196 (74.5)	8 (4.1)	
Labile INR (TTR < 60%)	Yes	124 (47.1)	10 (8.1)	.196 [‡]
	No	139 (52.9)	5 (3.6)	
Elderly (> 65 years)	Yes	190 (72.2)	12 (6.3)	.767*
	No	73 (27.8)	3 (4.1)	
Drugs (antiplatelets) [‡]	Yes	64 (24.3)	9 (14.1)	.003*
	No	199 (75.7)	6 (3.0)	
Alcohol	Yes	21 (8.0)	2 (9.5)	.341*
	No	242 (92.0)	13 (5.4)	

INR: international normalized ratio; TTR: time in therapeutic range; *Fisher exact test; [†]Chi-square test; [‡]There were no patients using nonsteroidal anti-inflammatory drug (NSAIDs). Data presented as number (%).

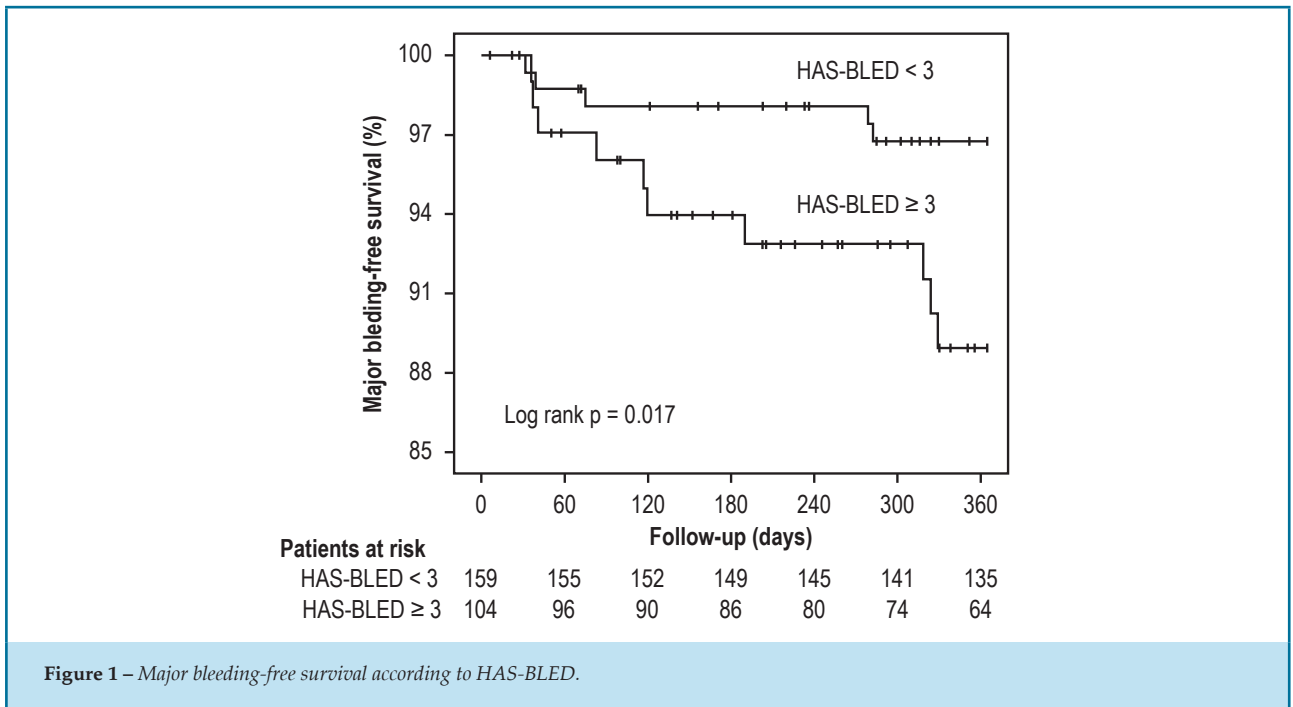


Figure 1 – Major bleeding-free survival according to HAS-BLED.

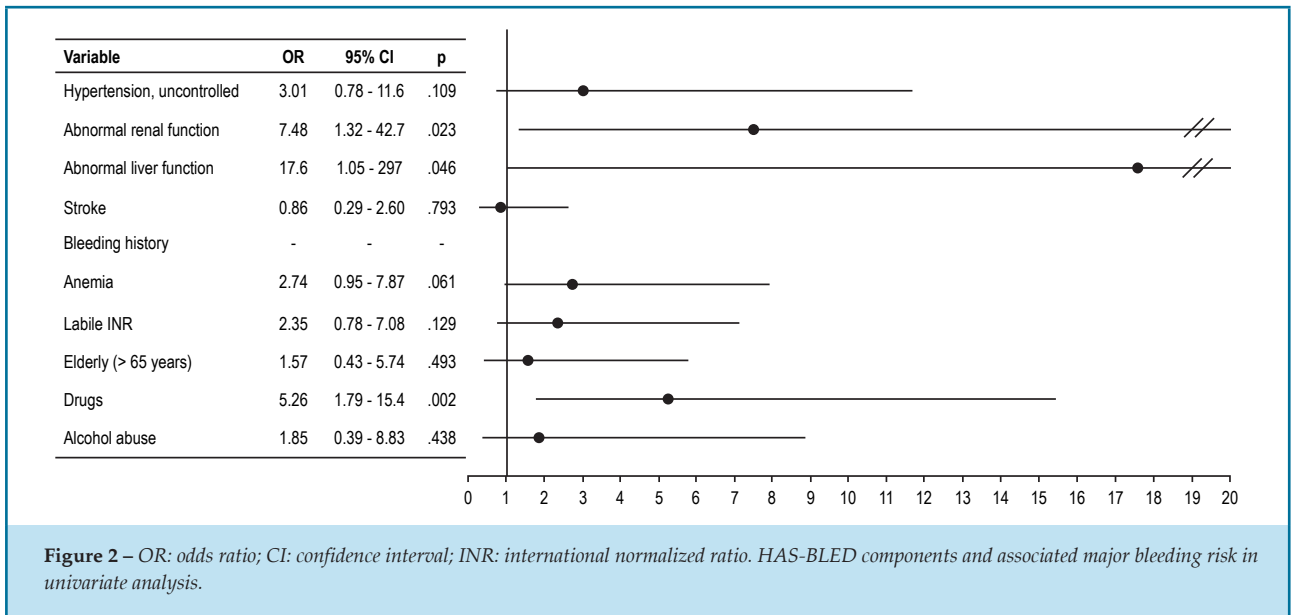
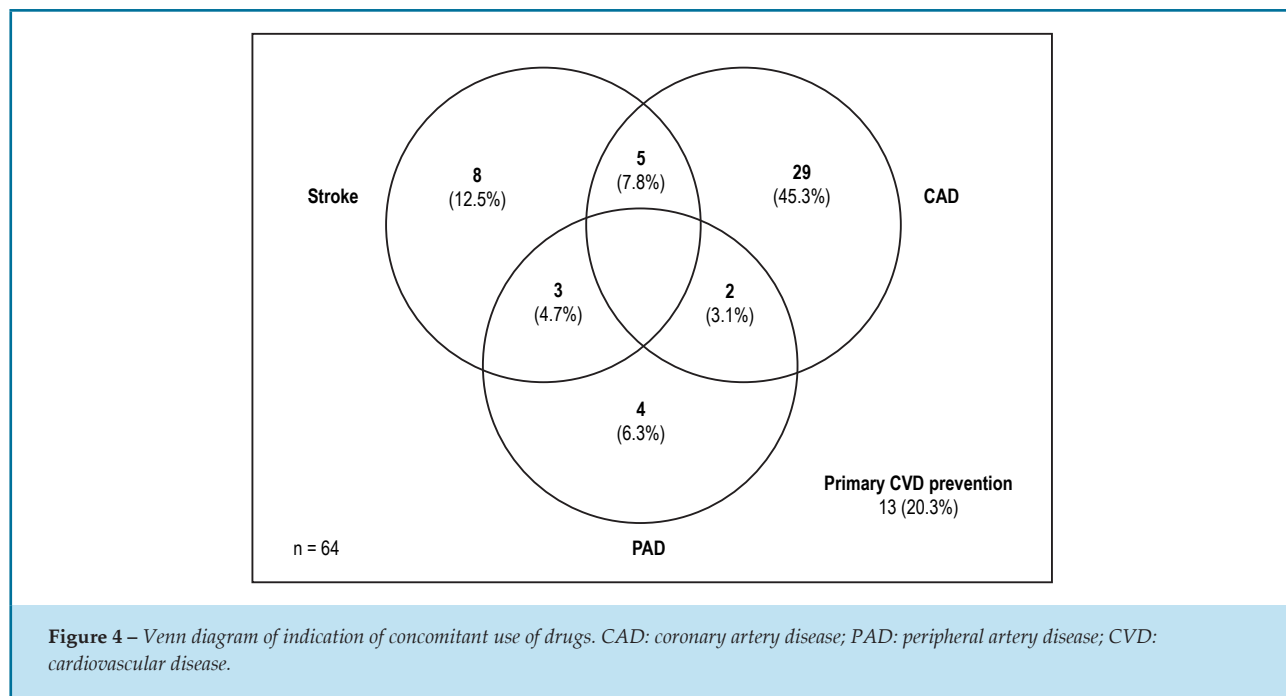
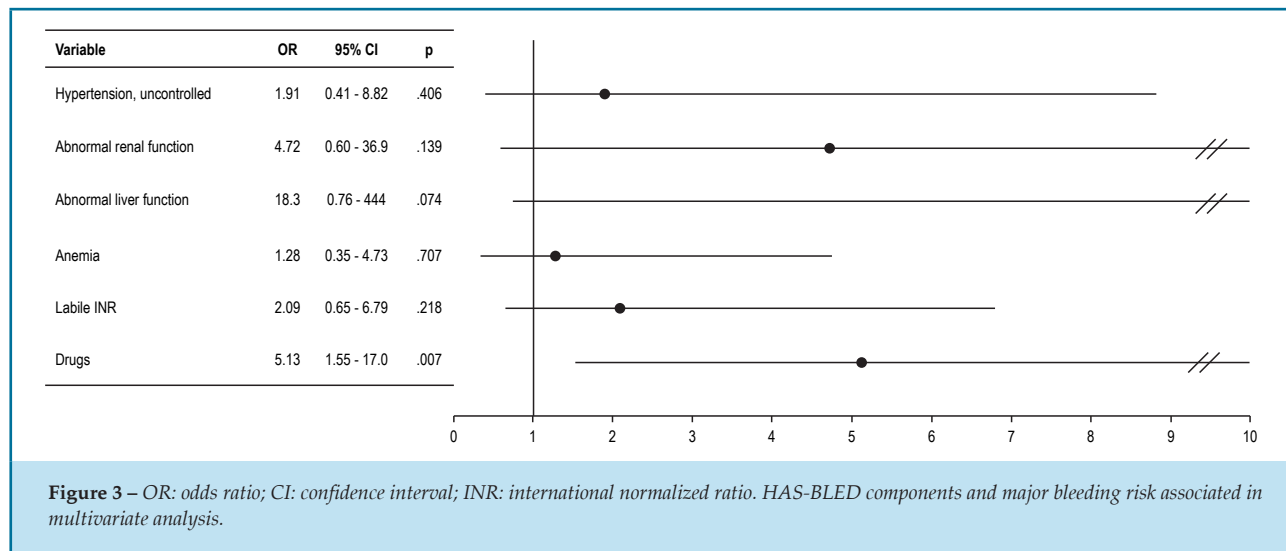


Figure 2 – OR: odds ratio; CI: confidence interval; INR: international normalized ratio. HAS-BLED components and associated major bleeding risk in univariate analysis.

The rate of major bleeding found in our study (6.3/100 patients-year) was higher than previously reported (1.4-2.4/100 patients-year).²² This may be explained by the median TTR found in this cohort (62.5%), which is in the lower limit of 60-65% of currently accepted rate.²³ Connolly et al.²³ suggest that this is the minimal threshold in which there is significant benefit of using OAC as compared with double antiplatelet therapy, with lower TTR

being associated with both stroke and hemorrhage rates that are comparable to those observed in AF patients treated with clopidogrel plus acetylsalicylic acid (ASA).

Another possible explanation for the high bleeding rate among our patients was the proportion of patients under concomitant use of antiplatelet drugs (24.3%). The majority of them had no clear indication to maintain antiplatelet use once OAC therapy has been initiated.



As shown in Figure 4, the reasons for concurrent use of antiplatelets were coronary artery disease (CAD, 56.2%), stroke (25.0%), primary cardiovascular disease (CVD) prevention and peripheral artery disease (PAD, 14.1%). Current guidelines recommend discontinuation of antiplatelet therapy in most cases when OAC is indicated; exceptions include acute coronary syndrome (ACS) and stent implantation, though even in these cases antiplatelet drugs should be discontinued as soon as possible.²⁴ This is based on low quality evidence that suggest that patients with stable CAD have increased bleeding risk with OAC

plus antiplatelet agent without further decrease in major adverse cardiovascular events in comparison with OAC alone.^{15,25} According to the 2016 US Preventive Services Task Force review,²⁶ ASA for the primary prevention of cardiovascular events has been shown to be safe and effective in the very strict group of adults ranging 50-59 years old who have an estimated cardiovascular risk > 10% and a low bleeding risk according to American Heart Association (AHA) score. Regarding PAD and stroke,²⁷⁻²⁹ current evidence indicates no benefit of adding ASA to VKA.

Table 3 – Antiplatelet agents used during follow-up and their indications

Drug(s)	n = 64	Indication
ASA	13 (20.3)	Cardiovascular disease primary prevention
	12 (18.8)	CAD with previous ACS > 1 year
	11 (17.2)	CAD without previous ACS
	8 (12.5)	Stroke
	4 (6.3)	CAD with previous ACS > 1 year + Stroke
	3 (4.7)	PAD
	3 (4.7)	Stroke + PAD
	1 (1.6)	CAD with previous ACS > 1 year + PAD
	1 (1.6)	CAD without previous ACS + Stroke
	1 (1.6)	CAD without previous ACS + PAD
ASA + Clopidogrel	4 (6.3)	CAD with previous ACS < 1 year
Cilostazol	1 (1.6)	PAD
Ticlopidine	1 (1.6)	CAD without previous ACS
Clopidogrel	1 (1.6)	CAD with previous ACS < 1 year

ASA: acetylsalicylic acid, CAD: coronary artery disease, ACS: acute coronary syndrome, PAD: peripheral artery disease. Data presented as number (%).

There are some limitations in our study that deserve to be mentioned. First, retrospective design may have influenced the quality and consistency of the data collected. Besides, review of the medical records could only identify events (cardiovascular and bleeding) that occurred at our hospital or that have been spontaneously reported by the patients during clinical care. This may underestimate adverse events occurrence. Second, the relative small sample size associated with the short follow-up period may have underestimated the occurrence of adverse events, especially events related to AF, which have a longer latency period. Yet, we believe that this may be a conservative bias, given the elevated event rates observed in this limited sample. Third, the higher rates of bleeding found in this study could have overestimated the prediction power of the score. Finally, the fact that the study was conducted at a single center can limit external validity of our findings.

Conclusion

HAS-BLED may be a useful and applicable tool to assess bleeding risk in our population, particularly to aid

the identification of potentially modifiable factors such as concomitant use of antiplatelet agents. We highlight that HAS-BLED should not be used as the single instrument to either initiate OAC or exclude patients from OAC therapy. Hospitals and clinical care facilities should implement protocols for regular assessment of patients using OAC, and HAS-BLED may have a major role helping to reduce complications associated with this therapy. Further research is needed to assess the impact of score-based protocols for modifying bleeding risk factors and rates in anticoagulation outpatient clinics.

Author contributions

Conception and design of the research: Pivatto Júnior F. Acquisition of data: Beltrame RCF, Giasson FTB, Gomes BS, Pivatto Júnior F. Analysis and interpretation of the data: Beltrame RCF, Giasson FTB, Amon LC, Scheffel RS, Pivatto Júnior F. Statistical analysis: Pivatto Júnior F. Writing of the manuscript: Beltrame RCF, Scheffel RS. Critical revision of the manuscript for intellectual content: Beltrame RCF, Giasson FTB, Silva ALFA, Gomes BS, Amon LC, Blaya MB, Scheffel RS, Pivatto Júnior F. Supervision / as the major investigator: Pivatto Júnior F.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

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