Assessing Bleeding Risk in Atrial Fibrillation Patients: Comparing a Bleeding Risk Score Based Only on Modifiable Bleeding Risk Factors against the HAS-BLED Score. The AMADEUS Trial

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Abstract

Background The HAS-BLED (hypertension, abnormal renal/liver function, previous stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly and drugs/alcohol consumption) score has been validated in several scenarios but the recent European guidelines does not recommend any clinical score to assess bleeding risk in atrial fibrillation (AF) patients and only focus on modifiable clinical factors.

Purpose The aim of this study was to test the hypothesis that the HAS-BLED score would perform at least similarly to an approach only based on modifiable bleeding risk factors (i.e. a 'modifiable bleeding risk factors score') for predicting bleeding events.

Methods We performed a comparison between the HAS-BLED score and the new 'modifiable bleeding risk factors score' in a post hoc analysis in 4,576 patients included in the AMADEUS trial.

Results After 347 (interquartile range, 186–457) days of follow-up, 597 patients (13.0%) experienced any clinically relevant bleeding event and 113 (2.5%) had a major bleeding. Only the HAS-BLED score was significantly associated with the risk of any clinically relevant bleeding (Cox’s analysis for HAS-BLED ≥ 3: hazard ratio 1.38; 95% confidence interval [CI], 1.10–1.72; p = 0.005). The ‘modifiable bleeding risk factors score’ ≥ 2 were non-significantly associated with any clinical relevant bleeding. The two scores had modest ability in predicting bleeding events. The HAS-BLED score performed best in predicting any

Keywords
- atrial fibrillation
- guideline
- risk score
- haemorrhage
- vitamin k antagonist

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Note: The review process for this article was fully handled by Christian Weber, Editor in Chief.
clinically relevant bleeding (c-indexes for HAS-BLED, 0.545 [95% CI, 0.530–0.559] vs. the ‘modifiable bleeding risk factors score’, 0.530 [95% CI, 0.515–0.544]; c-index difference 0.015, z-score = 2.063, p = 0.04). The HAS-BLED score with one, two and three modifiable factors performed significantly better than the ‘modifiable bleeding risk factors scores’ with one, two and three modifiable risk factors.

Conclusion When compared with an approach only based on modifiable bleeding risk factors proposed by European Society of Cardiology (ESC) guidelines, the HAS-BLED score performed significantly better in predicting any clinically relevant bleeding in this clinical trial cohort. While modifiable bleeding risk factors should be addressed in all AF patients, the use of a formal bleeding risk score (HAS-BLED) has better predictive value for bleeding risks, and would help decision-making in identifying ‘high risk’ patients for scheduling reviews and follow-up.

Introduction
Oral anticoagulation treatment is essential in the prevention of ischemic events and mortality in atrial fibrillation (AF) patients.1 AF patients have higher intrinsic risk of bleeding events while taking oral anticoagulation therapy.2 Thus, it would be important to assess bleeding risk in all AF patients.3 Various bleeding risk scores have been proposed in the last decade with different degrees of complexity. The HAS-BLED (hypertension, abnormal renal/liver function, previous stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly and drugs/alcohol consumption) score4 has been validated in patients with and without anticoagulation treatment, as well as in both AF and non-AF patients.5,6 Indeed, HAS-BLED score had the best predictive performance for intracranial haemorrhage compared with other bleeding scores.7 Nevertheless, the recent European Society of Cardiology (ESC) clinical guidelines do not recommend any particular bleeding risk score to predict haemorrhagic events but focus only on reversing the modifiable bleeding risk factors (class IIa, level of evidence B) in AF patients.8 A long list of modifiable, potentially modifiable, non-modifiable and biomarker bleeding risk factors are tabulated in the guidelines, making it less practical for everyday clinical practice in busy wards or clinics.

The aim of this study was to test the hypothesis that the HAS-BLED score would perform at least similarly to an approach only based on modifiable bleeding risk factors (i.e. ‘modifiable bleeding risk factors score’) proposed by ESC AF guidelines for predicting clinically relevant bleeding events in an anticoagulated clinical trial cohort of AF patients.

Methods
Study Population
The study design of AMADEUS clinical trial has been previously described.9 In brief, this clinical trial was a multi-centre, randomized, open-label non-inferiority clinical trial with blinded assessment of the outcome that compared a fixed dose of idraparinux with conventional vitamin K antagonist (VKA) treatment for the prevention on thromboembolic events in long-term anticoagulated AF patients. Exclusion criteria included the inability to provide consent, contraindication for anticoagulation therapy, alcohol abuse, terminal renal dysfunction (creatinine clearance < 10 mL/min), breastfeeding, pregnancy and recent or anticipated invasive procedures with potential for uncontrolled bleeding.

Assessment of Bleeding Risk Scores
The HAS-BLED score was calculated assigning 1 point to the following factors:4 hypertension, abnormal renal and/or liver function, previous stroke, bleeding history or predisposition (anaemia), labile INR (if the time in therapeutic range [TTR] assessed by the method of Rosendaal was lower than 70%), elderly (age ≥ 65 years) and concomitant drugs (anti-platelet or non-steroidal anti-inflammatory drugs [NSAIDs]) and/or alcohol excess. A HAS-BLED score of 0–1 was categorized as ‘low risk’, HAS-BLED = 2 as ‘moderate/intermediate risk’ and a HAS-BLED score ≥ 3 as ‘high risk’.

The approach based on modifiable bleeding risk factors proposed by ESC AF guidelines for predicting bleeding events was designated as a ‘modifiable bleeding risk factors score’ and calculated taking into account only the modifiable risk factors by assigning 1 point to the following: hypertension, labile INR defined as TTR < 70% and medication predisposing to bleeding (anti-platelets drugs and NSAIDs).

Definition of End Points
We used data from all the AMADEUS cohort (VKA and idraparinux patients). The main safety outcome of our analysis was any clinically relevant bleeding. The principal safety outcome of the AMADEUS trial was any clinically relevant bleeding event, subclassified as major bleeding and clinically relevant non-major bleeding. Major bleeding was defined following the ISTH (International Society of Thrombosis and Haemostasis) criteria.10 Clinically relevant non-major bleeding was defined as repetitive epistaxis for more than 5 minutes in 24 hours, haematuria, hematemeses and subcutaneous hematomas of more than 25 cm² if spontaneous or more than 100 cm² if after trauma. All adverse events were adjudicated by the original central adjudication committee, who were blinded to treatment assignment. The study protocol was performed according to the Declaration of Helsinki and all patients gave
informed consent to participation. The trial was stopped prematurely because of excess of clinically relevant bleeding in idraparinux arm.

**Statistical Analysis**

Normal distribution of continuous variables was tested with the Kolmogorov–Smirnov method. Quantitative variables were described using the mean ± standard deviation (SD) or median (interquartile range [IQR]). Clinically relevant bleeding events by each bleeding score were calculated as the overall rate of events per 100 patient-years. Cox’s proportional hazard regression models were performed to evaluate the relationship between high HAS-BLED and the ‘modifiable bleeding risk factors score’ and any clinically relevant bleeding. Kaplan–Meier analyses investigated differences in any clinically relevant bleeding event–free survival for different risk categories of HAS-BLED and the new ‘modifiable bleeding risk factors score’, and compared with the log-rank test. Receiver operating characteristic (ROC) curves (expressed as c-indexes) and ROC curves comparisons were performed for the HAS-BLED and the new ‘modifiable bleeding risk factors score’ to evaluate their predictive ability, as described by DeLong et al. Statistical significance was defined as p < 0.05. Statistical analyses were performed with SPSS statistical package version 22.0 (SPSS Inc., Chicago, IL) and MedCalc v. 16.4.3 (MedCalc Software bvba, Ostend, Belgium) for Windows.

**Results**

We analysed 4,576 patients: 2,283 patients with warfarin and 2,293 patients treated with idraparinux (66.5% male; median age, 71 years; IQR, 64–77). Demographic and clinical characteristics of the AMADEUS population are summarized in Table 1. Of these, 977 (21.4%) had concomitant treatment with anti-platelets or NSAID, 3,530 (77.1%) had hyper-tension (73.4%) patients in warfarin group had TTR < 70%. Considering modifiable risk factors as defined by the 2016 ESC AF guidelines, 540 (11.8%) patients had no modifiable risk factors, 2,193 (47.9%) had one modifiable risk factor, 1,532 (33.5%) had two modifiable risk factors and 311 (6.8%) had three modifiable risk factors. Median of HAS-BLED in the cohort was 2 (IQR, 2–3) and the median of the ‘modifiable bleeding risk factors score’ was 1 (1–2).

After 347 (IQR, 186–457) days of follow-up, 597 patients (13.0%) experienced a clinically relevant bleeding event and 113 (2.5%) had an episode of major bleeding. Incidence of bleeding events according to bleeding risk scores categories is shown in Table 1. HAS-BLED score appears to better classify low-risk patients than the ‘modifiable bleeding risk factors score’, with a lower annual incidence of bleeding events.

On Cox's regression analysis, a HAS-BLED score ≥3 was associated with a 1.38-fold greater hazard for any clinical relevant bleeding (95% confidence interval [CI], 1.10–1.72; p = 0.005). On similar Cox’s regression analysis, a ‘modifiable bleeding risk factors score’ ≥2 was non-significantly associated with any clinical relevant bleeding (hazard ratio, 1.13; 95% CI, 0.95–1.34; p = 0.17). Also, ‘modifiable bleeding risk factors score’ ≥3 was non-significantly associated with any clinically relevant bleeding (p = 0.06). Kaplan–Meier curves are shown in Fig. 1.

**Predictive Performance and Comparing HAS-BLED versus ‘Modifiable Bleeding Risk Factors Score’**

We observed modest discriminative ability for any clinically relevant bleeding for both scores, as reflected by c-indexes of 0.545 in HAS-BLED score (95% CI, 0.530–0.559; p < 0.001) and 0.530 in ‘modifiable bleeding risk factors score’ (95% CI, 0.515–0.544; p = 0.01). The HAS-BLED score performed significantly better in predicting any clinically relevant bleeding, as reflected by the comparison of the area under the curve analyses (DeLong’s test, p = 0.04).

We also assessed the predictive performance of the HAS-BLED score with one, two and three modifiable risk factors compared with the ‘modifiable bleeding risk factors score’ with one, two and three modifiable risk factors. For all

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**Table 1** Baseline clinical characteristics of the AMADEUS population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 4,576</th>
</tr>
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<tbody>
<tr>
<td>Male sex (%)</td>
<td>3,042 (66.5)</td>
</tr>
<tr>
<td>Age (y, IQR)</td>
<td>71 (64–77)</td>
</tr>
<tr>
<td>Type of AF (%)</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>1,634 (35.7)</td>
</tr>
<tr>
<td>Permanent</td>
<td>2,484 (54.3)</td>
</tr>
<tr>
<td>Persistent</td>
<td>438 (9.6)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>3,530 (77.1)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>897 (19.6)</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>1,072 (23.4)</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>1,048 (30.8)</td>
</tr>
<tr>
<td>Previous stroke/TIA (%)</td>
<td>580 (12.7)</td>
</tr>
<tr>
<td>Use of NSAID (%)</td>
<td>236 (5.2)</td>
</tr>
<tr>
<td>Use of anti-platelets (%)</td>
<td>840 (18.4)</td>
</tr>
<tr>
<td>Time in therapeutic range (IQR)</td>
<td>58 (45–70)</td>
</tr>
<tr>
<td>CHA2DS2-VASc score (IQR)</td>
<td>3 (2–4)</td>
</tr>
<tr>
<td>HAS-BLED score (IQR)</td>
<td>2 (2–3)</td>
</tr>
<tr>
<td>Low/Intermediate: ≤ 3 (%)</td>
<td>2,866 (62.6)</td>
</tr>
<tr>
<td>High: ≥3 (%)</td>
<td>1,710 (37.4)</td>
</tr>
<tr>
<td>Modifiable bleeding risk factors score (IQR)</td>
<td>1 (1–2)</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; CHA2DS2-VASc, congestive heart failure or left ventricular dysfunction (1); hypertension (1), age ≥75 (2) or 65–74 (1), diabetes mellitus (1), prior stroke/TIA or systemic embolism (2), vascular disease (peripheral artery disease, myocardial infarction, aortic plaque) (1), sex category (i.e. female sex) (1); HAS-BLED, hypertension (1), abnormal renal and/or liver function (1), prior stroke (1), bleeding history or predisposition (1), labile INR (1), elderly (1), drugs or excess alcohol (1); IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; TIA, transient ischaemic attack. Note: Numeric values are expressed as median (interquartile range) or number (percentage %).

Modifiable bleeding risk factors: hypertension (1); time in therapeutic range < 70% (1); use of anti-platelets/NSAID (1).
comparisons, the HAS-BLED score performed significantly better than the ‘modifiable bleeding risk factors score’ for any clinically relevant bleeding (Table 2).

**Discussion**

In this ancillary analysis of the AMADEUS trial, we compared the ability of HAS-BLED and an approach only based on modifiable bleeding risk factors proposed by the ESC AF guidelines, to predict serious bleeding events in a clinical trial cohort, where safety outcomes are well-defined and adjudicated. We demonstrate that HAS-BLED score performed significantly better than the ‘modifiable bleeding risk factors score’ in predicting any clinically relevant bleeding in anticoagulated AF patients.

Bleeding risk assessment in AF patients while taking anticoagulation treatment is essential in daily clinical practice to identify patients with different risks of bleeding to help determine the risk–benefit balance of anticoagulation treatment. Bleeding risk in AF patients is not a static ‘on-off’ phenomenon but is a dynamic process, and all patients should be periodically checked at every patient contact for changes in their bleeding risk profile.11

The HAS-BLED score is a formal risk bleeding score that includes modifiable, potentially modifiable and non-modifiable risk factors.12 To assess the different risks of AF patients,
a simple, dynamic and validated scale is necessary—not only at the beginning of the therapy but also throughout the patient pathway, where antithrombotic treatment is being used. The HAS-BLED score has been validated in different scenarios and compared with other more complex bleeding scores, and this score has been shown to have the best predictive performance for major bleeding. The NICE guidelines recommend formal bleeding risk assessment of AF patients with HAS-BLED and formal ischemic risk assessment with CHA2DS2-VASC.

In the 2016 ESC clinical guidelines, no formal bleeding risk score was recommended and only focus on modifiable risk factors was emphasized. Uncontrolled hypertension, concomitant anti-platelet/NSAID use and poor anticoagulation quality (lability INR) are the commonest bleeding risk factors and should be identified to guarantee the safety of oral anticoagulation. Although these factors could be the cornerstone of bleeding risk, they would have a synergistic effect with other factors, whether non-modifiable or biomarker based.

In this study, we observed that the HAS-BLED score had significantly better predictive performance than the new ‘modifiable bleeding risk factors score’ proposed by the ESC guidelines and, of note, the latter approach was not significantly associated with the adjudicated principal trial safety end point of any clinically relevant bleeding. For that reason, the use of a formal risk score with the inclusion of routinely recorded clinical factors improves the quality of AF patient management, helps in decision-making with a simple clinical tool and avoids the misuse of bleeding scores. The appropriate and responsible use of a clinical score is to ‘flag up’ the patient at risk for more regular follow-up visits and reviews, and the HAS-BLED score should be appropriately and responsibly used in this manner in everyday clinical practice.

Limitations
The results of our study are based on a post hoc analysis of the AMADEUS trial and should be interpreted as hypothesis generating. In addition, patients at high risk of bleeding (patients with excess alcohol abuse, extreme liver biochemical abnormalities or renal dysfunction and patients with history of major bleeding events) were excluded from the trial. Indeed, this was a retrospective analysis and no available clinical trials have evaluated prospectively the impact of an approach only based on modifiable bleeding risk factors (i.e. the new ‘modifiable bleeding risk factors score’) on patient bleeding events.

Conclusion
In the first validation of an approach only based on modifiable bleeding risk factors score proposed by ESC AF guidelines in an anticoagulated clinical trial cohort, the HAS-BLED score performed significantly better than new ‘modifiable bleeding risk factors score’ in predicting adjudicated ‘any clinically relevant bleeding’ events. While modifiable bleeding risk factors should be addressed in all AF patients, the use of a formal bleeding risk score (HAS-BLED) with the inclusion of routinely recorded clinical factors aids AF patient management and decision-making for scheduling reviews and follow-up of high-risk patients with a simple clinical tool.

What Is Known about This Topic
- Recent European Society of Cardiology (ESC) guidelines do not recommend any specific bleeding score.

What Does This Paper Add
- In this analysis from the AMADEUS trial, we compared HAS-BLED with a ‘modifiable bleeding risk factors score’ in atrial fibrillation patients enrolled in the AMADEUS trial.
- HAS-BLED score performed significantly better than a ‘modifiable bleeding risk factors score’ in predicting any clinically relevant bleeding, which were adjudicated outcomes in this anticoagulated clinical trial cohort.
- While modifiable bleeding risk factors should be addressed in all AF patients, the use of a formal bleeding risk score (HAS-BLED) helps AF patient management and decision-making for scheduling reviews and follow-up of ‘high-risk’ patients with a simple clinical tool.

Funding
J. M. R.-C. has received a grant from Sociedad Española de Trombosis y Hemostasia (grant for short international training stays 2016). Sanofi SA provided the dataset of the AMADEUS trial. The analysis of the dataset was conducted fully independent of any industry or other grant support.

Note
The fast-track review process for this paper was fully handled by Christian Weber, Editor in Chief.

Conflicts of Interest
G. Y. H. L.: Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. No fees are received personally. There is nothing to disclose for other authors.

Author Contribution
M. A. E.-P. had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, drafted the manuscript and made critical revision. J. M. R.-C., V. R. and A. S. interpreted the analysed data and made critical revision. F. M. and G. Y. H. L. drafted the manuscript and made critical revision. All authors gave final approval of the manuscript.
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