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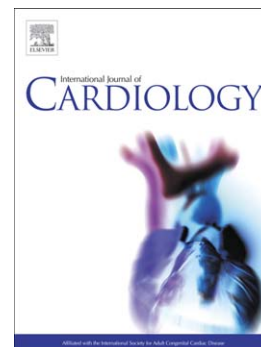
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**Predictive abilities of the HAS-BLED and ORBIT bleeding risk scores in non-warfarin  
anticoagulated atrial fibrillation patients: An ancillary analysis from the AMADEUS trial**

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Short title: The ORBIT and HAS-BLED scores in non-VKA anticoagulated AF patients

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**Abstract**

*Background* Simple bleeding risk scores have been proposed to predict bleeding events, in patients anticoagulated using non-warfarin anticoagulants. We compared the relative predictive values of two bleeding risk scores, HAS-BLED and ORBIT, in non-warfarin anticoagulated patients with atrial fibrillation (AF).

*Methods and Results* In a post-hoc ancillary analysis of 'clinically relevant bleeding' events amongst 2283 patients in the idraparinix arm in the AMADEUS trial. The two scores performed modestly in predicting both bleeding outcomes, although there was a trend for better HAS-BLED score performance in predicting any clinically relevant bleeding [c-indexes in HAS-BLED vs. ORBIT; 0.61 (95%CI; 0.58-0.64) vs. 0.58 (95%CI; 0.55-0.61); c-index difference = 0.03, z-score = 1.84, p = 0.06). Using the HAS-BLED score compared with the ORBIT score correctly and significantly reclassified 15.6% of the population (95% CI: 4.3 to 27.0; p = 0.007). Decision curve analyses confirmed the increasing ability to correctly identify patients who would bleed using the HAS-BLED score versus the ORBIT score, over a wide range of thresholds for any clinically relevant bleeding risk predictions.

*Conclusion* In this comparison of the HAS-BLED and ORBIT scores in a cohort of non-warfarin anticoagulated patients with AF, we show that the HAS-BLED score more accurately predicted any clinically relevant bleeding amongst patients with AF who were anticoagulated with a non-warfarin anticoagulant, when compared with the ORBIT score.

**Key words:** bleeding risk, HAS-BLED score, ORBIT score, atrial fibrillation, idraparinix

## Introduction

Assessment of bleeding risk is important in the management of patients with atrial fibrillation (AF). Two bleeding risk scores, the HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile international normalized ratio (INR), Elderly (age $\geq$ 65 years), Drugs or alcohol concomitant] and ORBIT [Older age ( $\geq$  74 years), Reduced hemoglobin/anemia (hemoglobin  $<$ 13 g/dl in men and  $<$ 12 g/dl in women or hematocrit  $<$ 40% for males and  $<$ 36% for females) (2 points), Bleeding history (2 points), Insufficient kidney function (glomerular filtration rate  $<$ 60 ml/min/1.73m<sup>2</sup>), Treatment with Antiplatelet] scores, have been derived and validated in AF populations, with the ORBIT score being proposed as a simple score that can be applied in AF patients on *any anticoagulant* (ie. whether using warfarin or non-warfarin anticoagulants) by not considering the 'labile INR' criterion that applies for warfarin users with the HAS-BLED score.<sup>1,2</sup> Of note, the L (labile INR) criterion in HAS-BLED is only applicable in a warfarin user, otherwise this criterion scores zero.

In the present analysis, these 2 bleeding scores were tested for their predictive abilities for clinically relevant bleeding amongst patients randomised to the idraparinux arm (ie. a non-warfarin anticoagulant) of the AMADEUS trial (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation)<sup>3</sup>.

## Methods

The AMADEUS trial design has previously been described<sup>3</sup>. The incidence of outcomes, any clinically relevant bleeding (the centrally adjudicated primary safety endpoint) are expressed as counts and/or percentages.

Discrimination and clinical usefulness were assessed for the HAS-BLED and the ORBIT score. Discrimination was studied with the concordance (c) index, which is identical to the area under the receiver-operating characteristic (ROC) curve, and Net reclassification improvement (NRI)<sup>4</sup>. As originally proposed, the NRI seeks to quantify whether a new marker provides clinically relevant improvements in prediction and has recently become a popular measure of incremental usefulness of markers added to risk prediction models.<sup>5</sup> Thus, to avoid confusion and biases that categorization of the data can cause, we calculated NRI for continuous scores.

Clinical usefulness was assessed using decision curve analyses (DCA)<sup>6</sup>. This analysis estimates a “net benefit” for a prediction model that provides individual risk estimate. The DCA demonstrates identification of patients who will have any clinically relevant bleeding, based on the predictions of one risk score, compared with another score. On the DCA, the x-axis shows threshold values for any clinically relevant bleeding risk. The clinician may use the threshold to classify patients as high or low risk at a value to proceed with some action, such as increased patient monitoring or additional medical therapy. The y-axis represents the net benefit for the different threshold values of any clinically relevant bleeding risk. Thus, the interpretation of the net benefit is in units of true positives and represents the sum of

how many patients are correctly identified to be 'high risk' (true positive: i.e., bleeding) minus a weighted number of patients incorrectly identified as high risk (false positive: i.e., none bleed). We plotted a slanted grey line which represents the classification of all patients as high risk (i.e., bleed); and a horizontal line representing the classification of all patients as low risk (i.e., none bleed), with the latter resulting in a net benefit of 0. The prediction models that are the farthest away from the slanted grey line (i.e., assume all bleed) and the horizontal line (i.e., assume none bleed) demonstrates the higher net benefit. Statistical analyses were performed with R software<sup>7</sup> and SPSS (version 21.0).

## Results

A total of 2,283 patients (mean age  $\pm$  standard deviation [SD]; 70.1  $\pm$  9.0 years) in AMADEUS were randomized to the idraparinux arm. Overall, 74 major bleeding events and 346 clinically relevant bleeding events occurred during the follow-up period (311  $\pm$  161 days). Specific bleeding data for each risk score are shown in Table 1.

There was modest discriminative ability for any clinically relevant bleeding, as reflected by the c-indexes in ROC curve analysis; c-indexes of 0.61 in HAS-BLED score (95% confidence interval [CI]: 0.58 to 0.64,  $p < 0.001$ ) and 0.58 in ORBIT score (95% CI: 0.55 to 0.61,  $P < 0.001$ ) [Figure 1]. Comparison of c-indexes revealed a non-significant trend for better discriminative ability of the 2 tested scores for any clinically relevant bleeding (HAS-BLED vs. ORBIT, c-index difference 0.03, z-score = 1.84,  $p = 0.06$ ). For the secondary outcome of major bleeding, c-indexes for the HAS-BLED score was 0.59 (95% CI: 0.53 to 0.65,  $P = 0.007$ ) and ORBIT score, 0.58 (95% CI: 0.52 to 0.65,  $P = 0.014$ ), with no significant difference between the two scores (c-index difference 0.01, z-score = 0.27,  $p = 0.79$ ).

For the primary outcome of any clinically relevant bleeding, using the HAS-BLED score compared with the ORBIT score correctly (and significantly) reclassified 15.6% of the population (95% CI: 4.3 to 27.0;  $p = 0.007$ ). For the secondary outcome of major bleeding, using the HAS-BLED score compared with the ORBIT score non-significantly reclassified - 3.7% (95% CI: -26.5 to 19.2;  $p = 0.753$ ) of the population.

The decision-curve analysis (DCA) demonstrated identification of patients who will have any clinically relevant bleeding, based on the predictions of HAS-BLED score, compared with



ORBIT score (Figure 2). The intersection of the y-axis and the slanted grey line represents the overall risk of any clinically relevant bleeding (15%). Being farthest away from the slanted grey line (i.e., assume all bleed) and the horizontal line (i.e., assume none bleed), the HAS-BLED score (broken red line) demonstrates the higher net benefit, followed by the ORBIT score (broken black line). Thus, the HAS-BLED score outperformed the ORBIT using DCA, over a wide range of thresholds probability for any clinically relevant bleeding.

In a Cox regression analysis, both HAS-BLED score  $\geq 3$  (i.e., high risk category) and ORBIT score  $\geq 3$  (i.e. high risk category) were predictors of any clinically relevant bleeding with hazard ratios of 2.2 (95% CI: 1.6 to 3.0;  $p < 0.001$ ) and 1.7 (95% CI: 1.2 to 2.4;  $p = 0.001$ ) (vs. low-risk category as baseline risk), respectively.

## Discussion

In this comparison of the HAS-BLED and ORBIT scores in a cohort of non-warfarin anticoagulated patients with AF, we show that the HAS-BLED score more accurately predicted any clinically relevant bleeding amongst patients with AF who were anticoagulated with a non-warfarin anticoagulant, when compared with the ORBIT score. Indeed, the HAS-BLED score demonstrated greater discriminative performance as reflected by the NRI and c-index, and its clinical usefulness reflected by DCA when compared with ORBIT score for the adjudicated outcome of any clinically relevant bleeding.

Clinically relevant bleeding was the centrally adjudicated primary safety endpoint in the AMADEUS trial and would be clinically meaningful and highly relevant to patients who are at risk of important bleeding events in daily clinical practice. The modest predictive performance of the scores for 'high risk' patients sustaining events should be put into context of the relatively 'low risk' clinical trial population studied (approx. 90% were 'low risk'). Also, notable differences between HASBLED and ORBIT include the different weighing for bleeding tendency or predisposition *in the ORBIT score*, as well as the lack of consideration of uncontrolled hypertension, abnormal liver function, prior stroke, concomitant use of NSAIDs and labile INRs (for a warfarin user). All these parameters are included in HASBLED, and allow physicians to consider more bleeding risk factors, and draw attention to those that are reversible or correctable.

However, the *principal objective* of this ancillary analysis was to assess how these 2 bleeding scores perform with non-warfarin anticoagulants. Notwithstanding the fact that the

development of idraparinux has ceased, this analysis is still relevant as ORBIT was introduced as a score that would be 'better' even when used for non-warfarin anticoagulants<sup>2</sup> – instead, our results suggest the opposite. Thus, further studies are needed to investigate that these scores in a broader spectrum of patients at high bleeding risk, in real-world clinical practice.

These results are in accordance with prior results from the warfarin arm of the AMADEUS cohort<sup>8</sup>, suggesting that despite some initial validations in warfarin-treated populations, the HAS-BLED and ORBIT schemes maintain their modest predictive performance in patients receiving other (non-warfarin) forms of anticoagulation. In the warfarin arm of the AMADEUS cohort<sup>8</sup>, there was a significant improvement in ORBIT score prediction performance by considering time in therapeutic range as a measure of 'labile INR' (a criterion included within the HAS-BLED score, but not ORBIT). Similar findings were reported by Proietti et al<sup>9</sup>, where the ORBIT score categorised a large proportion of AF patients who has sustained major bleeding on warfarin as being 'low risk', and that the predictive performance of the ORBIT score could be significantly improved by adding 'poor TTR' (or labile INR) as an added criterion. Based on these observations, the HAS-BLED score performs better than the ORBIT score for the outcome of any clinically relevant bleeding, whether using warfarin or non-warfarin anticoagulants.

Why use bleeding risk scores? These scores can help identify patients with common risk factors for bleeding, so in the case of HASBLED, would 'flag up' those patients potentially at risk of bleeding for more careful review and medical follow-up, and to draw attention to potentially reversible/ correctable bleeding risk factors<sup>11</sup>. Of note, bleeding risk scores

should not be used as an excuse to withhold oral anticoagulation, as such AF patients would derive even greater net clinical benefit from stroke prevention<sup>9</sup>. Rather than a focus on absolute bleeding rates, bleeding risk scores could facilitate clinical or electronic alerts to ‘flag up’ high risk patients, and to alert the clinician to address potentially modifiable bleeding risk factors<sup>11-13</sup>. Addressing the latter may minimise the risks of bleeding from antithrombotic therapy, and is an approach recommended in contemporary guidelines<sup>12</sup>. Indeed, the HAS-BLED score clearly fulfils this role, in contrast to other simple risk scores<sup>13</sup>.

### *Limitations*

It is difficult to fully claim that one score is definitely better than another one, given the various ways of assessing differences in predictive value. The results of comparisons between the two scores in the present study were statistically significant based on the NRI and DCA. Thus, we suggest that the HAS-BLED score is statistically better at predicting any clinical relevant bleeding than the ORBIT score, although both scores had modest prediction performance using the ROC analysis. Of note, the latter is now regarded to be insufficient alone when assessing predictive value, and should be supplemented with the NRI and - more recently - the DCA approaches<sup>4-6</sup>. All clinical factor-based risk scores in various clinical settings (eg. CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>VASc, Killip, TIMI etc) show broadly similar c-indexes (approx. 0.6) when used to predict those categorised at ‘high risk’ who actually sustain events<sup>11</sup>. Again, HAS-BLED offers simplicity and draws attention to the potentially reversible risk factors for bleeding – as recommended in guidelines<sup>11,12</sup>. Finally, HASBLED and ORBIT are bleeding risk scores derived and validated in patients with AF – and used to *predict* those patients potentially at high risk of bleeding and (with HAS-BLED) to *draw attention* to the reversible risk factors for bleeding. Both score are not used to define ‘bleeding severity’

after the bleeding event (eg. TIMI, GUSTO or BARC - which were also derived/validated in non-AF patients).

**In conclusion**, when compared with the ORBIT score, the HAS-BLED score more accurately predicted individuals with any clinically relevant bleeding in patients with AF who were anticoagulated with a non-warfarin anticoagulant. Given its simplicity, the HAS-BLED score should be recommended for bleeding risk assessment, whether using warfarin or non-warfarin anticoagulants.

#### **Declarations of interest**

Keitaro Senoo: Nothing to disclose.

Gregory YH Lip: Consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo.

Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo

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## FIGURE LEGENDS

**Figure 1 Receiver-operating characteristic (ROC) curves for any clinically relevant bleeding with the HAS-BLED and ORBIT scores**

**Figure 2 Decision Curves demonstrating identification of patients who will have any clinically relevant bleeding, based on the predictions of HAS-BLED score, compared with ORBIT score**

The x-axis shows threshold values for any clinically relevant bleeding risk. The y-axis represents the net benefit for the different threshold values of any clinically relevant bleeding risk.

Figure 1: Receiver-operating characteristic (ROC) curves for any clinically relevant bleeding between HAS-BLED and ORBIT scores

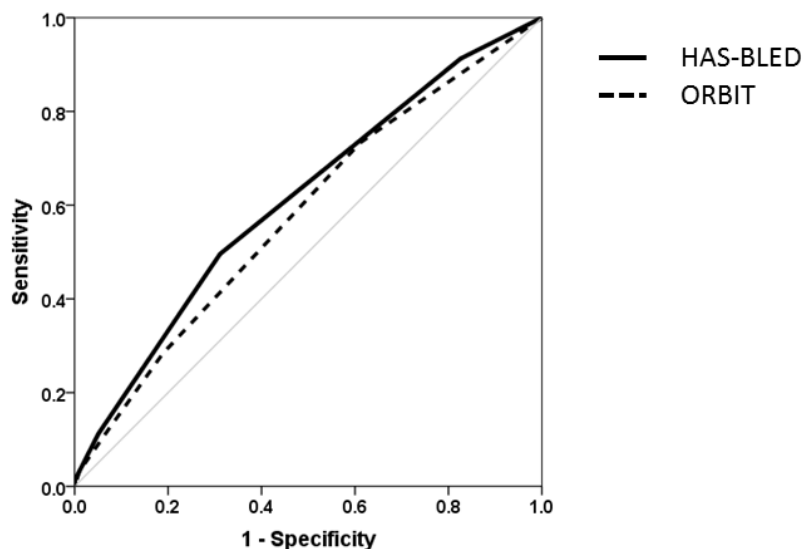
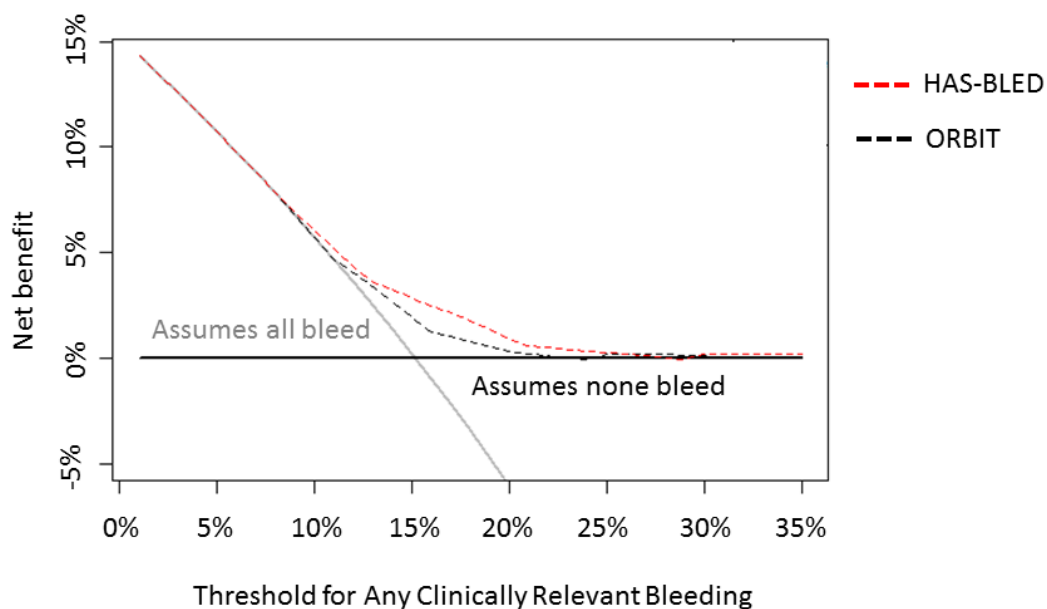




Figure 2: Decision Curves demonstrating identification of patients who will have any clinically relevant bleeding, based on the predictions of HAS-BLED score, compared with ORBIT score



**Table 1** Bleeding events in the AMADEUS trial population stratified according to the HAS-BLED and ORBIT bleeding risk scores

	N	Any clinically relevant bleeding N (%)	Major bleeding N (%)
<b>HAS-BLED</b>			
0	364	30 (8.2)	3 (0.8)
1	1139	144 (12.6)	38 (3.3)
2	633	132 (20.9)	25 (3.9)
3	131	34 (26.0)	8 (6.1)
4	7	5 (71.4)	0 (0)
<b>ORBIT</b>			
0	845	92 (10.9)	19 (2.2)
1	975	156 (16.0)	33 (3.4)
2	286	57 (19.9)	10 (3.5)
3	147	30 (20.4)	8 (5.4)
4	29	11 (37.9)	4 (13.8)
5	1	0 (0)	0 (0)

HAS-BLED score= Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile international normalized ratio (INR), Elderly (age $\geq$ 65 years), drugs or alcohol concomitant

ORBIT score= Older age ( $\geq$  74 years), reduced hemoglobin/Anemia [(hemoglobin  $<$ 13 g/dl in men and  $<$ 12 g/dl in women) or (hematocrit  $<$ 40% for males and  $<$ 36% for females) (2 points)], Bleeding history (2 points), Insufficient kidney function [glomerular filtration rate  $<$ 60 ml/min/1.73m<sup>2</sup>], Treatment with Antiplatelet.