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Bleeding Risk Scores in Atrial Fibrillation: Helpful or Harmful?

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"In a false quarrel there is no true valour."
Much Ado About Nothing, by William Shakespeare.

The prevalence of atrial fibrillation (AF) in the United States is 12% in ages 75 to 84 years of age and is expected to continue to rise.[1] AF is known to increase the risk of stroke.[1] Among patients with AF, stroke and thromboembolism risk is mitigated with the addition of anticoagulants. However, this is associated with increased risk of bleeding, specifically intracranial hemorrhage in the setting of warfarin.[1–3] Because of this, prescribers are hesitant to anticoagulate, especially in the elderly population.[3]

There have been multiple risk stratification scoring systems utilized to assess bleeding risk including HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol), HEMORR2HAGES (History of bleeding, Hepatic or renal disease, Alcohol abuse, Malignancy, Older age, Reduced platelet count or function, Hypertension, Anemia, Genetic predisposition, Excessive fall risk, Stroke), ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) with the new addition of GARFIELD-AF (Global Anticoagulant Registry in the Field-Atrial Fibrillation).[2,4–6] In the past, HAS-BLED bas been found to be superior at determining any clinically relevant bleeding risk by receiver-operating characteristic analysis and decision curve analysis (C index: HAS-BLED: 0.6 versus HEMORR2HAGES: 0.55 versus ATRIA: 0.50).[2] However, more recently, the GARFIELD-AF risk model has been shown to be superior in major bleeding in comparison to HAS-BLED (C index: 0.66 GARFIELD-AF versus 0.64 HAS-BLED).[4,7] Proietti and colleagues sought to challenge GARFIELD-AF's superiority in this issue of the *Journal of the American Heart Association* (*JAHA*) and compared the predictive value of HAS-BLED with GARFIELD-AF risk model in the SPORTIF (Stroke Prevention Using the Oral Direct Thrombin Inhibitor Ximelagatran in Patients With Atrial Fibrillation Trial III and V) population.[7]

This study did show modest predictive value for major bleeding in both bleeding scores (C index: 0.58 HAS-BLED versus 0.56 GARFIELD-AF).[7] The high-risk HAS-BLED score (>3) patients had higher risk of major bleeding, clinically relevant nonmajor bleeding, and any bleeding in comparison to low-risk HAS-BLED patients.[7] In contrast, except for the major clinically relevant bleeding outcomes metric, the GARFIELD-AF score did not show a statistically significant difference for major bleeding and any bleeding in the high-risk patients compared with the low-risk patients. Lastly, there was a net benefit of 5% of any bleeding with HAS-BLED in comparison to GARFIELD-AF.[7] The authors concluded GARFIELD-AF was not superior to HAS-BLED, specifically in predicting any bleeding.

The patient populations of these 2 studies were substantially different. First, the patients in the study by Lip and colleagues were from the SPORTIF III and V controlled clinical trials, a more constrained population with strict inclusion and exclusion factors. As expected, the time in the therapeutic range in these controlled patients was 68.2%[7] compared with the time in the therapeutic range of patients in GARFIELD-AF, a real-world registry, of 55%.[8] Additionally, the patients in the SPORTIF III and V cohorts were sicker compared with GARFIELD-AF. Eighty-nine percent of patients in SPORTIF III and V had chronic AF as compared with 12.7% in GARFIELD-AF.[4,7] Further comparisons are shown in the Table. Even when externally validating the GARFIELD-AF risk model in the same study to the ORBIT-AF population, the predictive value fell (C index: 0.61).[4] The authors postulate that this was because of the longer duration of AF in the ORBIT-AF population compared with GARFIELD-AF, again distinguishing it from the SPORTIF III and V population where the duration of AF was >1 year in 81% of the patients.[4,9] Overall, both studies are valid, but, as one might expect, different risk scoring systems will have different results

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Table. Select Patient Characteristics in SPORTIF III and V Versus GARFIELD AF

Characteristic	SPORTIF III and V[9]	GARFIELD AF[4]
Age (y)	72	71
Female	30.5	44.5
Chronic AF	89.3	12.7
Prior stroke	20.6	7.8
Heart failure	37.3	22.5
Prior bleeding	5.6	2.6
Chronic kidney disease	25.9	12.0

AF indicates atrial fibrillation; GARFIELD, Global Anticoagulant Registry in the Field-Atrial Fibrillation; SPORTIF, Stroke Prevention Using the Oral Direct Thrombin Inhibitor Ximelagatran in Patients With Atrial Fibrillation Trial III and V.

when applied in diverse populations. Essentially, it is comparing apples to oranges. Thus, the readers of this article can conclude that in patients on warfarin, in a carefully controlled clinical trial, the HAS-BLED score performs better in minor bleeding compared with the GARFIELD-AF score. However, the GARFIELD-AF score, when applied to a less well-controlled registry, performs better than the HAS-BLED score.

What is more important, however, is that this challenge by Lip and colleagues illustrates what Shakespeare would call a "false quarrel." That is, when it comes to risk stratification bleeding scores, the reality is that no scoring system has clinical impact. They should not change a physician's decision to prescribe anticoagulants to patients at high risk of stroke. They help identify people at higher risk of bleeding, which should guide physicians to monitor for bleeding more carefully. However, they should not be used to exclude patients from anticoagulation. This fact is recognized by the European Society of Cardiology[10] and the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines.[1] Specifically, from the AHA/ACC/HRS guideline: "Although these scores may be helpful in defining patients at elevated bleeding risk, their clinical utility is insufficient for use as evidence for the recommendations in this guideline."[1]

The reasons for the lack of clinical impact by bleeding risks scores is partially because of the parallel nature of bleeding risk scores and stroke risk scores such as CHA2DS2-VASc (Congestive heart failure, Hypertension, Age, Diabetes Mellitus, Prior Stroke, Vascular disease, Sex category).[11] For example, with increasing age, the risk of stroke and major bleeding increase. Because a bleeding risk score can help justify withholding anticoagulation from a high-risk patient, they may actually harm patients. This editorial will further discuss the reasons why previously developed bleeding risk scoring systems, such as HAS-BLED and GARFIELD-AF, have minimal clinical impact, especially in modern anticoagulation therapy.

First, the net clinical benefit of anticoagulation in patients with AF has been studied. Friberg and colleagues showed that increased thromboembolism risk was associated with increased risk of bleeding, likely because many of the risk factors involved in the risk stratification scores overlap.[11] In this study, the only patients who did not benefit from anticoagulation were patients with a CHA2DS2VASc score of 0 or 1, patients in whom anticoagulation is not recommended by either the European Society of Cardiology or AHA/ACC/HRS guidelines.[1,10,11] In fact, a patient with a CHA2DS2VASc score of 5 and an HAS-BLED score of 5 would have a net clinical benefit of 3% per year even when weighting intracranial hemorrhage as 1.5 times the clinical impact of a stroke.[11] In a study by Oleson and colleagues, bleeding risk does increase with higher HAS-BLED scores.[12] However, net clinical benefit, measured in deaths or hospitalizations for thromboembolism or bleeding, significantly favored warfarin in all patients with a CHA2DS2VASc score >1.[12] Thus, even when accounting for bleeding risk, warfarin therapy would provide net clinical benefit to those in whom guidelines recommend anticoagulation. The risk is that despite guideline statements to the contrary, bleeding risk scores could be used to justify withholding therapy from high-risk patients, which places patients at risk of stroke.

Second, the use of bleeding risk scores has been less valuable in patients receiving direct-acting oral anticoagulants (DOACs). In recent studies, DOACs have been shown to reduce thromboembolic risk and reduce bleeding risk, most importantly intracranial hemorrhage, in comparison to warfarin.[1,11] These medications have fewer dietary effects and more predictable drug levels without frequent blood draws, providing improved ease of use for patients.[1] Because of this, the prescription of DOACs is increasing, gradually supplanting warfarin use. The study by Lip and colleagues in this issue of *JAHA* only compares the HAS-BLED and GARFIELD-AF bleeding scores with warfarin-treated patients. There is a paucity of evidence supporting the use of bleeding risk scores in patients on DOACs. GARFIELD-AF and ORBIT-AF had very few patients on DOACs.[4,13] Most bleeding risk scores were validated with warfarin.[2,4,5,13] In a large study of patients on DOACs in a Danish registry, HAS-BLED, ATRIA, and ORBIT-AF were equally moderately predictive (C index: 0.58–0.61).[14] The sensitivity and specificity of the HAS-BLED score in this population were 62.8 and 53.5, respectively.[14] The positive predictive value of the HAS-BLED score in this study was 3.0%, meaning that one would need to "flag up" 100 patients to predict 3 bleeds.[14] Additionally, in this study, major bleeding and clinically relevant minor bleeding were grouped.[14] Another study evaluated the use of DOACs with the bleeding risk score in a population of 39 539 Medicare Advantage patients.[6] The

HAS-BLED, ORBIT-AF, and ATRIA risk scores showed only modest predictive value for the bleeding scores in patients on dabigatran, apixaban, rivaroxaban, or edoxaban. In fact, in this study, the CHA2DS2-VASc thromboembolic risk score was a better predictor of bleeding than these bleeding risk scores.[6] This finding is consistent with the fact that bleeding risk scores parallel stroke risk scores. What we can conclude from these studies of DOACs is that while HAS-BLED can "flag up" patients at risk, it raises that flag too frequently, even when there is no bleeding problem. If anything, we should recognize that patients with a high risk of stroke are also at a high risk of bleeding.

In summary, in this study using a population of patients in a controlled clinical trial, the HAS-BLED score outperformed the GARFIELD-AF score with respect to minor bleeding. What is clear from these data is that scoring systems are dependent on the population studied and minor differences can be seen when comparing scores in diverse populations. However, we argue that none of the risk stratification bleeding scores are clinically impactful. The authors argue that bleeding risk scores allow physicians to "flag up" high-risk patients for more aggressive monitoring. Given the modest predictive value of the bleeding risk scores, one could argue that all patients, regardless of their score, should be monitored closely. The HAS-BLED score should be used to identify modifiable risk factors for bleeding including those not identified in risk scores, such as history of gastric ulcers. As such, bleeding risks scores serve only to allow physicians to justify excluding a high-risk patient from potentially life-threatening therapy. Hence, current guidelines from AHA/ACC/HRS and European Society of Cardiology do not support their use in the decision making for antithrombotic therapy in patients with AF.[1,10] Further studies are needed to determine whether these scores hold up in the setting of lower-risk DOAC treatment. Additionally, if bleeding scores are to gain relevance, randomized clinical trials should be performed using bleeding risk scores to guide anticoagulation therapy. In the end, the "quarrel" should not be over HAS-BLED versus GARFIELD-AF; the "valour" rests in emphasizing the appropriate prescription of anticoagulation in patients at risk of stroke.

Disclosures

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