What Scoring System Should We Use to Assess Bleeding Risk in Atrial Fibrillation?

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Although anticoagulation therapy can reduce the risk of stroke in patients with atrial fibrillation (AF), it is associated with bleeding events. Clinicians must always consider the benefit of anticoagulation therapy against the risk of major bleeding. Various clinical factors contribute to bleeding risk, including older age, malignancy, renal or liver dysfunction, and use of antiplatelet drugs or intensity of anticoagulation, and a new scoring system that can be used to reliably stratify patients according to their risk of a major bleeding event was proposed by Gage et al (HEMORR2HAGES). However, this system is complex and thus not widely used in clinical practice. To compensate for the limited clinical applicability, 2 bleeding risk classification systems were developed and tested in large cohorts of AF patients: the HAS-BLED system and the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) system. HAS-BLED was validated in a retrospective analysis of 7,329 patients enrolled in the SPORTIF trial, and its principle advantage is ease of use in clinical practice. HAS-BLED is recommended by the European Society of Cardiology for clinical assessment of bleeding risk in patients with AF. More recently, the Outcomes Registry for Better Informed Treatment (ORBIT) system was developed in a large observational cohort. A patient’s ORBIT score equals the total points given when any of the following factors exist: Older age (1 point), Reduced Hb/Hct/anemia (2 points), Bleeding history (2 points), Insufficient renal function (1 point), and Treatment with antiplatelets (1 point). The originators claimed that the predictive performance of the ORBIT score is superior to that of the HAS-BLED and ATRIA scores in anticoagulated AF patients. Because patient characteristics factor into bleeding risk, it is unclear whether ORBIT scores, which were validated in a specific registry cohort, are truly applicable to all AF patients.

This issue of the Journal includes the validation study of Esteve-Pastor et al, which was undertaken to test the HAS-BLED and ORBIT scores for prediction of major bleeding events and mortality in 2 “real world” anticoagulated AF patient cohorts: an electrical cardioversion (ECV) cohort (mean age, 66.9 years) and a FANTASIA cohort (mean age, 73.9 years). Stroke risk, according to CHA2DS2-VASc scores, was moderate (median 3) in the former group and high (mean 3.7) in the latter. Predictive accuracy was tested by the c-statistic, which showed the ORBIT score not to be statistically superior to the HAS-BLED score for predicting major bleeding events or death among AF patients treated with acenocoumarol and direct oral anticoagulants.

There have been numerous head-to-head comparisons of the ORBIT, HAS-BLED, ATRIA, and HEMORR2HAGES scoring systems (Table). Overall, the HAS-BLED score has been well validated in various cohorts, and the c-statistic has shown it to have increased predictive value. In contrast, the ORBIT score was originally validated in ORBIT-AF registry and ROCKET-AF trial patients, and was shown to better calibrate bleeding risk and to be more widely applicable than the existing HAS-BLED and ATRIA scores. Recent studies validated the ORBIT and HAS-BLED scores for predicting bleeding risk in a cohort of warfarin and non-warfarin anticoagulated (idaraparinux: a factor Xa inhibitor) AF patients re-enrolled in the AMADEUS trial. In both groups, the HAS-BLED score outperformed the ATRIA and ORBIT scores. It is important to understand that with the ORBIT system, 2 points are assigned to bleeding history and 2 points are assigned to reduced Hb/Hct/anemia; age ≥75 years is assigned 1 point. As the authors noted, the most important limitation of the ORBIT system is that anemia and insufficient kidney function may coexist in patients ≥75 years of age, and this overlap can increase the score in these patients. The incidence of bleeding events can be fairly high in a large cohort incorporating a large elderly and/or high risk population; the resulting ORBIT scores would then be quite high. In fact, the c-statistic of the ORBIT score was quite high in the FANTASIA registry patients reported by Esteve-Pastor et al, the ORBIT registry, and the ROCKET registry, which had many elderly and/or high risk patients and high annual rates of major bleeding events. In contrast, the HAS-BLED score includes points for age 65–75 years, uncontrolled hypertension, abnormal liver function, stroke, labile INR, nonsteroidal anti-inflammatory drug use, and alcohol abuse. Theoretically, this means that the HAS-BLED score stratifies the bleeding risk more precisely than the ORBIT score, especially among patients deemed to be low risk because they are <75 years of age. Notably, the prognostic performance of the HAS-BLED score was very good in the AMADEUS trial because the population was relatively young and at relatively low risk for...
bleeding. According to the Japanese registry data, the Japanese AF population tends to be at low risk for stroke, and the annual incidence of major bleeding tends to be low.\(^6\)\(^,\)\(^7\)\(^,\)\(^8\) Therefore, in Japanese, the HAS-BLED score may better predict a major bleeding event than the ORBIT score. Nonetheless, caution should be exercised when we consider using these scoring systems for clinical prognostication. The difference in the c-statistic between ORBIT and HAS-BLED (and others) is small, and the prognostic performance of these scores is less than satisfactory (c-statistics of only 0.60–0.70) (Table).\(^2\)\(^,\)\(^4\)\(^,\)\(^6\)\(^,\)\(^7\)\(^,\)\(^9\) Nevertheless, these scores have clinical utility because we can use them to assess bleeding risk in individual patients who are starting or continuing anticoagulants and also to identify and manage a patient’s modifiable risk factors. Esteve-Pastor et al\(^7\)  

Table. Reported Comparisons of the ORBIT, HAS-BLED, ATRIA, and HEMORR2HAGES Scoring Systems

| Journal (Year)       | Chest (2010)\(^2\) | J Am Coll Cardiol (2011)\(^3\) | Eur Heart J (2015)\(^4\) | Am J Med (2016)\(^5\) | Int J Cardiol (2016)\(^6\) | Circ J (2016)\(^7\) |
|----------------------|---------------------|-------------------------------|--------------------------|------------------------|--------------------------|----------------------|
| Validated bleeding score | HAS-BLED, HEMORR\(\times\)HAGES | HAS-BLED HEMORR\(\times\)HAGES | ORBIT HAS-BLED ATRIA | ORBIT HAS-BLED ATRIA | ORBIT HAS-BLED | ORBIT vs. HAS-BLED |
| Patient pool         | Euro Heart Survey   | SPORTIF III & V (North American RCT) | ORBIT-AF AF registry (USA) | ROCKET-AF trial (worldwide RCT) | AMADEUS trial (worldwide RCT) | AMADEUS trial (worldwide RCT) |
| n=3,978              | Warfarin: 64.8%     | Vitamin K antagonist: 50%    | ORBIT-AF: n=7,411 Warfarin: 93.5% |   | n=2,293 Warfarin | n=2,283 Idraparinux |
| Warfarin alone: 24%  | No antithrombotic therapy: 10.2% | Dabigatran: 6.5% | ROCKET-AF: Warfarin: 50% | ROCKET-AF: Warfarin: 50% | Warfarin | Acenocoumarol: 91.6% |
| Mean age             | 66.8 years         | Bleeding event group (n=234): 73.9 years | ORBIT-AF: 75 years ROCKET-AF 73 years (median) | 71 years | 70.1 years | ECV patients at a single center FANTASIA registry (Spain) |
| CHADS\(_2\) score    | Bleed group: 2.1±1.2 | No bleed group: 1.6±1.3 | Bleeding event group: 2.6±1.2 | No bleeding event group: 2.2±1.2 | ORBIT-AF CHADS\(_2\) ≤0–1: 25.1% CHADS\(_2\) ≥2: 74.9% | ROCKET-AF 3.5±0.9 |
| CHADS\(_2\)-VASc score | –                  | –                             | ORBIT-AF: No major bleeding: 4.0 (9–5) Bleeding: 5.0 (4.0–6.0) ROCKET-AF – | 3 (2–4) | 3 (2–4) | ECV: 2 (1–2) FANTASIA: 2.2±1.2 |
| History of stroke/ TIA | 9.1%               | 21.0%                         | ORBIT-AF: 16.3% ROCKET-AF: 55% | 25.1% | 23% | ECV: 5.7% FANTASIA: 12.9% (previous embolism) |
| Antiplatelet use     | 12.8% in warfarin group | 21.5% (aspirin use only) | ORBIT-AF: 37.4% ROCKET-AF: 38.5% | 16.5% (aspirin use only) | – | ECV: 16.5% FANTASIA: 10.9% (antiplatelet agents and NSAIDs) |
| Annual major bleeding event rate | 1.5% | 3.2% | ORBIT-AF: 4.0% ROCKET-AF Warfarin: 3.4% Rivaroxaban: 3.6% | 1.3% | 3.2% | ECV: 1.6% FANTASIA: 3.6% |
| C-statistic          | HAS-BLED: 0.72 HEMORR\(\times\)HAGES: 0.66 | HAS-BLED: 0.65 HEMORR\(\times\)HAGES: 0.62 | ORBIT-AF HAS-BLED: 0.67 ATRIA: 0.66 ROCKET-AF ORBIT: 0.62 HAS-BLED: 0.59 ATRIA: 0.60 | ORBIT: 0.61 HAS-BLED: 0.65 | ORBIT: 0.58 HAS-BLED: 0.61 | ECV ORBIT: 0.82 HAS-BLED: 0.77 FANTASIA ORBIT: 0.70 HAS-BLED: 0.63 |

Values are mean±SD or median and interquartile range unless otherwise indicated. DOACs, direct oral anticoagulants; ECV, electrical cardioversion; NSAIDs, nonsteroidal anti-inflammatory drugs; TIA, transient ischemic attack.
note that the HAS-BLED score seems to better identify low-risk patients than the ORBIT score. The HAS-BLED score can accurately stratify bleeding risk in patients who are at low, moderate/intermediate, and high risk for stroke or who are taking warfarin or a non-warfarin anticoagulant or are using an antiplatelet concomitantly. Moreover, the HAS-BLED score alone can draw attention to the reversible risk factors, such as uncontrolled hypertension, liable INR, alcohol abuse, and concomitant nonsteroidal anti-inflammatory drug use. Although the ORBIT score is simpler, the HAS-BLED score has specific advantages that are important for “real world” clinical practice.

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