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Balancing the Risk of Hemorrhage vs Thromboembolism in Patients With Atrial Fibrillation

How To Navigate Between Scylla and Charybdis?

According to mythology, Scylla and Charybdis were two sea monsters placed on opposite sides of the Strait of Messina, between Calabria and Sicily in Italy. Sailors' navigation was extremely difficult since these monsters were very close to each other and attempts to avoid Scylla implied passing very closely to Charybdis and vice versa. This imaginary scenario well depicts the difficulties that a practicing physician may encounter when deciding on the intriguing trade-off between benefits and risks of antithrombotic prophylaxis in the challenging and complex setting of "real-world" patients affected by nonvalvular atrial fibrillation (AF).[1]

In this issue of *CHEST* (see page 1093), Pisters et al[2] report on the development of a novel, easy, and practical risk score to estimate the 1-year risk for major bleeding, which uses the acronym HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly). The authors tested this score (also called the Birmingham AF Bleeding Risk Schema) on a cohort of 3,678 real-world patients enrolled in the Euro Heart Survey on AF. At discharge, around 65% of patients were on oral anticoagulation (OAC) treatment (13% of them also taking aspirin and/or clopidogrel), 24% on antiplatelet therapy alone, and 10% without any antithrombotic therapy, with unadjusted bleeding rates of 1.75%, 0.97%, and 1.42% per year, respectively.

This study is particularly interesting because the risk of bleeding was assessed on real-world patients with AF included in a registry, thus in a much-less-selected population than that represented in randomized clinical trials on OACs, where, quite often, up to one-third of patients with AF were not enrolled, mainly because they were judged to be at high risk of bleeding.[3] During treatment with OACs, the absolute risk of major bleeding complications for patients followed by specialized anticoagulation services ranges from 0.32% to 2.1% per year, with a risk of fatal bleeding ranging from 0% to 0.25% per year, and this implies that the risk of major bleeding and the risk of intracranial hemorrhage are increased by 0.3% to 0.5% per year and by 0.2% per year, respectively, in comparison with controls.[3,4]

However, these data cannot necessarily be extrapolated to real-world clinical practice, where patients' care may be less accurate and rigorous.[4] A series of bleeding-risk stratification schemes have been previously developed and proposed to estimate the risk of major bleeding during OAC treatment,[3,4] but most of them were not necessarily specific for patients with AF, were derived from historic cohorts without subsequent prospective validation, and did not appear to be user friendly.[2-4] The study by Pisters et al[2] indicates that a very simple risk score, HAS-BLED, is able to predict the bleeding risk with consistent accuracy, performing better than the more complicated HEMOR$_2$RAGES (Hepatic or renal disease, Ethanol abuse, Malignancy, Older age [> 75 years], Rebleeding, Reduced platelet count or function, Hypertension [uncontrolled], Anemia, Genetic factors, Excessive fall risk, and Stroke) scheme (which also requires genetic assessment[4]) when tested in the overall population and in all the subgroups of patients, apart from those receiving both OAC and antiplatelet treatments.[2]

While the HAS-BLED score is a very simple and useful tool to be applied in daily practice, the article also stimulates questions about how to further improve our prediction of the risk of bleeding. In our view, and according to what the authors reported, assessment of the bleeding risk in the elderly will merit further evaluation. Indeed, the use of antithrombotic treatments in the elderly is quite problematic but relevant given the increasing prevalence of AF with age.[1] However, biologic age is perhaps more relevant than chronologic age. For example, a frail 60-year-old patient with multiple comorbidities and polypharmacy would be at greater bleeding risk than a fit, healthy 90-year-old subject with no previous illnesses who still goes ballroom dancing.

The risk of bleeding, and specifically the risk of intracranial hemorrhage, is particularly increased in the elderly.[3-6] Whereas the prevalence of bleeding is reported to be 0.2% to 1.0% patient-years overall among patients who are anticoagulated, this rate increases to 1.1% patient-years in patients aged ≥ 75 years.[3] Fang et al[5] reported an adjusted odds ratio of 2.5 for intracranial hemorrhage in patients aged

≥ 85 vs a reference group of patients aged 70 to 74 years. However, the risk of major bleeding is not limited to use of OACs, since the occurrence of major hemorrhage may be similar with both warfarin or aspirin use.[7] The relatively small numbers of bleeding events and the limited number of very elderly patients in the study by Pisters et al[2] suggest the need for collecting long-term data on larger populations of elderly patients with AF to assess how much the bleeding risk is increased at ages ≥ 65 years, thus providing further tools for improving decision making in the elderly. Perhaps a future refinement of HAS-BLED would address this.

A decision-making process based on balancing the individual risk of bleeding and the risk of stroke is difficult, and the risk factors for bleeding and stroke largely overlap. For example, a history of previous stroke is one of the determinants of the HAS-BLED risk score. The impact of bleeding in decision making is considerable because physicians are less likely to prescribe OACs to any patient after observing a case of major bleeding during treatment with these agents, but the same powerful influence does not appear to exist in the case of a thromboembolic stroke occurring in a patient without OAC prescription.[8] Therefore, any method for predicting the risk of bleeding in an individual patient may be of special value.[3]

Now, how do we make decisions in balancing the risks of hemorrhage and thromboembolism? Stroke risk assessment is well served by many studies into stroke risk factors and the value of stroke risk stratification schema. Indeed, the same investigators recently proposed the CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke or transient ischemic attack, Vascular disease, Age 65-74 years, and Sex category [female]) score[9] to improve identification of "truly low-risk" patients and to incorporate risk factors not included in the commonly used $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke or transient ischemic attack) risk score.

In our view, the availability of such simple stroke and bleeding-risk assessments is the basis for helping to improve "personalized care," but perhaps should also take into account the balance between risks and benefits of all the available treatments, the patient's context and comorbidities, the patient's cognitive state and likelihood of compliance to therapy, as well as the patient's values and preferences, where the problematic trade-off of stroke vs hemorrhagic risk may not coincide with the physician's priorities.[10] Thus, a dialogue between the patient, the patient's relatives, and a physician well aware of the complexity of this problem and of the potential options appears to be mandatory for appropriately directing the helm between Scylla and Charybdis.

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