

Oral anticoagulation for atrial fibrillation and high risk of bleeding in daily practice: What clinical considerations?

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The benefits of oral anticoagulants in reducing the risk of stroke associated with atrial fibrillation (AF) have been demonstrated by randomized controlled trials (RCTs). Indeed, in patients with so-called “nonvalvular AF” the role of warfarin, with appropriate monitoring of the international normalized ratio vs. antiplatelets and, more recently the advantages of direct anticoagulants (DOACs) have been validated [1]. Taking into account all the RCTs comparing DOACs to warfarin, the use of DOACs was associated with statistically significant reductions in the risk of stroke/thromboembolism and intracranial hemorrhages, but not in major bleeding and gastrointestinal bleeding [1].

The risk of bleeding remains a major concern and an important barrier to full implementation of oral anticoagulants in patients at risk, particularly in elderly frail patients [2], in patients with advanced kidney disease [1], and in patients with severe co-morbidities such as cancer [3]. While RCTs are important for gathering high-level evidence for recommendations of consensus guidelines [4], assessment of management of AF patients in daily clinical practice through observational studies and “all-comer” registries is essential for defining what barriers may exist to full implementation of guidelines in daily practice.

In the present issue of the Journal, Maciorowska et al. [5] report on a group of 3598 patients enrolled in the POL-AF registry, a multicenter cross-sectional study enrolling consecutive patients with AF hospitalized for urgent or planned reasons (mainly AF and/or heart failure) in 10 Polish cardiology

centers. The authors specifically focused on patients presenting a clinical profile with high risk of bleeding, as evaluated by a HAS-BLED score ≥ 3 . The high HAS-BLED group accounted for around 29% of the entire patient population and was characterized by older age and more comorbidities, particularly coronary artery disease, peripheral artery disease, and chronic kidney disease. In the high HAS-BLED patient group, 14.5% of the patients did not receive anticoagulants. Among the patients treated with DOACs, the proportion of patients with inappropriate dose reduction was impressive, ranging from 8 to 47%, according to different used agents. The study highlights that even nowadays, despite around 10 years of experience in using DOACs in AF patients, the clinical profile: “at risk of bleeding” and/or a history of bleeding constitute important barriers to the provision of adequate antithrombotic prophylaxis for preventing stroke. The available data do not allow us to identify the number of patients who had true contraindications to anticoagulation (severe bleeding due to a non-correctable or non-reversible cause) as opposed to only an increased risk of bleeding, expressed by at high HAS-BLED score [6]. This has important implications since in the presence of absolute contraindications to long-term anticoagulation, use of left atrial appendage occluders is justified and appropriately applied [7, 8]. Notably, according to the ESC guidelines [9] a high bleeding risk score should not contraindicate anticoagulation in the long term; however, it, should prompt

Table 1. Scores for estimating bleeding risk and cut-offs for defining a high risk of bleeding

Risk scores proposed in the literature	Number of risk factors and associated scores	Cut-off for high risk of bleeding
HAS-BLED	9 RF: systolic BP >160 mm Hg (1) — severe renal/hepatic disease (1 each) — stroke (1) — bleeding (1) — labile INR (1) — age >65 (1) — APT/NSAIDs (1) — alcohol excess (1)	≥3
ORBIT	5 RF: age ≥75 (1) — reduced Hb/Hct/anemia (2) — bleeding history (2) — reduced renal function (1) — APT (1)	≥4
HEMORRHAGES	12 RF: hepatic/renal disease (1) — ethanol abuse (1) — malignancy — age >75 (1) — low Plt (1) — re-bleeding risk (2) — hypertension (1) — anemia (1) — genetic factors (1) — increased falls risk (1) — stroke (1)	≥4
ABC	3 RF: age — biomarkers (GDF-15 or cystatin C/CKD-EPI, cTnT-Hs, Hb) — previous bleeds	≥2
ATRIA	5 RF: anemia (3) — severe renal disease (3) — age ≥75 (2) — prior bleed (1) — hypertension (1)	≥5
Alfalfa-MB	7 RF: age >65 (10), history of bleeding (7.9) — anemia (4.8) — vascular disease (6.9) — no PPI (8.6) — antiplatelet therapy/NSAIDs (8.6) — rivaroxaban (4.2)	≥18.3

Abbreviations: APT: antiplatelet; BP: blood pressure; cTnT-hs: high-sensitivity cardiac troponin T; GDF-15: growth differentiation factor 15; HB: hemoglobin; Hct: hematocrit; INR: international normalized ratio; NSAIDs: nonsteroidal anti-inflammatory drugs; Plt: platelets; PPI: proton pump inhibitor; RF: risk factors

correction of modifiable risk factors for bleeding and increase patient monitoring and surveillance. However, this is often not applied to clinical practice where physicians are often particularly worried by the risk of bleeding, even more worried about bleeding than the risk of stroke [6], which is at odds with views and values of empowered patients, who usually prioritize the prevention of cardiometabolism [1].

The HAS-BLED score has been commonly used since it was advised by 2020 ESC Guidelines [1, 9], but other risk scores have been also proposed [6], with some differences in terms of the number of risk factors considered and requirements for defining a condition of high-risk for bleeding (Table 1).

In daily practice, decision-making is frequently conditioned by the physician's perceptions rather than objective evidence. It was recently shown how frailty assessment in AF patients [10] may show an important disagreement between the physician's perceptions and objective definitions of frailty. Physician's perceptions may have important implications such as lack of prescription of anticoagulants in patients at risk but without clear contraindications or prescription of DOACs at low inappropriate dosing, as highlighted by Maciorowska et al. [5] and by Diemberger et al. [10]. Additionally, we can expect that physician's perceptions of bleeding risk may strongly affect, together with the occurrence of minor bleeding adherence and persistence to anticoagulants, an issue that still requires substantial improvement, even if the situation is currently better with DOACs as compared to the past when only vitamin K antagonists were available [1].

Observational studies exploring the "real world" practice are important since they highlight that inappropriate provision of stroke prevention in AF patients at risk of stroke is still a problem [5, 11], and targeted educational programs should be planned. With this regard, it is important to recognize that prescription of aspirin or low molecular-weight heparin is not uncommon in real-world registries [11]. In these registries, low molecular heparin is frequently employed, despite the lack of evidence, in

patients with AF and active cancer, which is a setting of difficult management considering the risk of bleeding and the lack of randomized studies [3, 12]. It is noteworthy that none of the scores proposed for estimating the risk of bleeding (Table 1) includes active cancer or a history of cancer, thus making any decision-making problematic. As a matter of fact, in the study by Maciorowska et al. [5], malignant neoplasms were strong predictors of non-use of anticoagulants. In the same study, the proportion of patients characterized as being at high risk of bleeding was important, accounting for around one-third of patients hospitalized for AF in cardiology wards [5], with even higher estimates expected in settings such as Internal Medicine, Geriatrics or Neurology wards [11].

Clinical management of patients at high risk of bleeding is challenging and requires a holistic integrated approach, also with involvement of different specialists, and it should follow all the pillars of the A-B-C pathway suggested by consensus guidelines [1, 9, 13]. It is well known that patients at high risk of bleeding may be concomitantly at high thromboembolic risk [1]. According to guidelines, pillars A (avoid stroke), B (better symptoms management) and C (cardiovascular and comorbidities management) should be followed, since adherence to A-B-C is associated with better outcomes in the long term [13], and this approach should be coupled with minimization of bleeding risk, by correcting modifiable risk factors (e.g.: hypertension) and by avoiding, if possible, concomitant treatment with aspirin [14] or other drugs that increase the hemorrhagic risk. Furthermore, it should be stressed that the bleeding risk may change over time, and HAS-BLED assessment should consider its dynamic changes [1, 6].

In conclusion, the availability of DOACs allowed for an increase in the effective prevention of stroke and, particularly, of disabling strokes in AF patients, but patients at high risk of bleeding still represent a clinical challenge that requires an evidence-based approach rather than relying on perceptions. There is an interesting perspective of uncoupling hemostasis and thrombosis by factor XI inhibitors [15], but their efficacy and safety in AF need to be confirmed by dedicated RCTs.

*“Things should be made as simple as possible,
but not simpler”*

This famous line attributed to Albert Einstein can also be applied to decision-making in medicine, which is often problematic, as in the case of anticoagulation in patients at high risk of bleeding. Such cases be approached in a conscientious, responsible way, taking into account the risks and benefits of potential therapeutic decisions, and, discussed with appropriately informed and empowered patients.

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