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COMMENTARY

Should bleeding be a concern in antiphospholipid syndrome?

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Antiphospholipid syndrome (APS) is an acquired prothrombotic condition that requires long-term anticoagulation due to the high rate of recurrent thrombosis [1]. Besides the high thrombotic risk, the risk of bleeding complications is not negligible.

In this issue, Gaspar et al. report on the prevalence, severity, and damage associated with bleeding events in a cohort of patients with APS followed for 4 decades. The study showed that 40% of patients experienced at least 1 bleeding event during follow-up. The incidence rate of overall bleeding was 6.9 events per 100 patient-years and that of major bleeding was 1.6 event per 100 patient-years. A total of 11% of the bleeding episodes resulted in accrual damage, ie, a clinical complication that lasted for at least 6 months or resulted in permanent harm. Nearly 8% of the patients in this cohort experienced damage after a bleeding event, most of which was related to cerebral events. The authors highlight the importance of including bleeding in damage assessment tools such as the Damage Index for APS (DIAPS) [2].

Rates of major bleeding in APS vary from 1 to 10 events per 100 patient-years across studies [3] and are mainly associated with anticoagulation. The reported variations in major bleeding risk can be attributed to several factors, including the nature of the study (observational or randomized trial), the underlying characteristics of APS (triple or nontriple antiphospholipid [aPL] positivity), the type and dosage of anticoagulation used (moderate or high-intensity vitamin K antagonist [VKA], combined therapy with antiplatelet agents, or direct oral anticoagulant [DOAC]).

Observational studies have reported an overall risk of bleeding ranging from 1.5 [4] to 3.2 events per 100 patient-years [5] in patients with APS undergoing anticoagulation, which is comparable to the risk reported in non-APS anticoagulated patients [5,6]. In subgroups of patients using more intense VKA regimens, with a target international normalized ratio (INR) above 3.0, the rates of minor and major bleeding events appear to be higher. Different studies have reported major bleeding rates of 6 [7] and 10.5 events per 100 patient-years [6] among patients using high-intensity VKA (INR: 3-4). A large observational cohort study demonstrated that most bleeding episodes occurred in patients on antithrombotic treatments, with 33% of them at a target INR above 3 [1]. Of note, in a cohort of high-risk patients with APS, particularly those with triple aPL positivity, the major bleeding associated with oral anticoagulant therapy was low at 0.8% per patient-year [8].

Interventional studies suggest that the risk of bleeding remains high regardless of the intensity of anticoagulation. Crowther et al. [9] reported a bleeding rate of 2.2 events per 100 patient-years in individuals using moderate-intensity VKA dosage (INR: 2-3) and 3.6 events per 100 patient-years in those using high-intensity VKA (hazard ratio [10]: 1.0; 95% CI: 0.2-4.8). Finazzi et al. found a similar risk of major bleeding (odds ratio [OR]: 0.73; 95% CI: 0.23-2.31) and an increased risk of minor bleeding with high-intensity VKA (OR: 2.30; 95% CI: 1.16-4.58) in a comparison with moderate-intensity VKA [11]. The combination of VKA and single antiplatelet therapy was also associated with increased risk of major bleeding (14% per patient-year) when compared with standard-dose VKA alone (2% per patient-year), with a rate ratio of 7.42 (95% CI: 0.91-60.7) [12].

Major bleeding is associated with high morbidity and mortality in patients with APS. In a large observational cohort followed for 10 years, Cervera et al. reported that up to 25% of major bleeding events were cerebral and 16% were fatal. Overall, 20% of deaths related to APS in this cohort were attributed to bleeding [1]. In a recent cohort of patients with APS and a previous stroke, 14% of patients had intracerebral or subarachnoid hemorrhage. Cerebral hemorrhage occurred later in the course of APS, mainly 4 years after diagnosis,

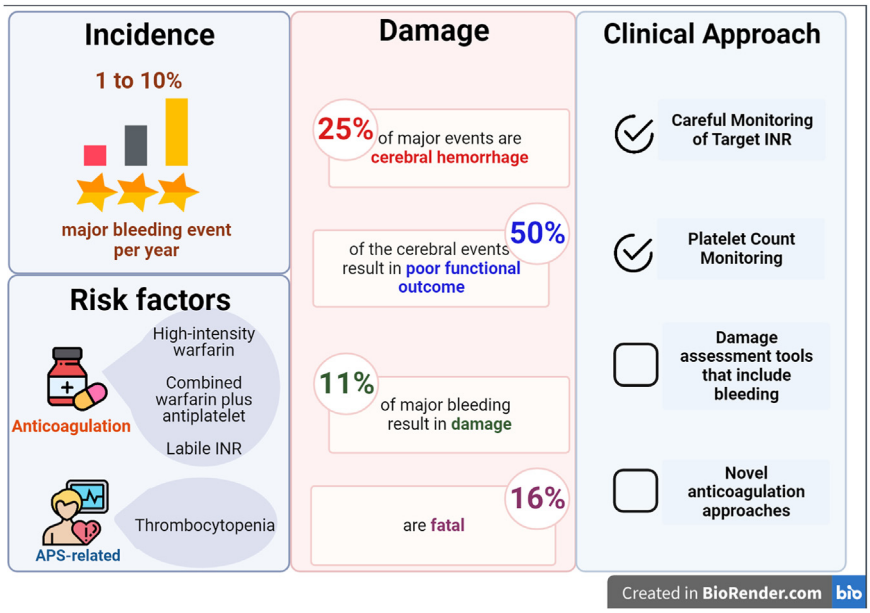

FIGURE Epidemiology, adverse outcomes, and clinical approach to bleeding risk in APS. APS, antiphospholipid syndrome.

leading to poor functional outcome in more than 50% of cases and stroke-related death in 17% of cases [12].

Although the difficulty in achieving a stable INR may be a reason for the development of bleeding complications in APS [1], AVK is currently the primary therapy for the disease. The use of DOACs has been associated with a higher risk of thrombosis, particularly arterial thrombosis, compared with VKA use in several studies [13], raising concerns about the treatment of thrombotic APS with DOACs. Currently, the available evidence does not support the routine use of existing DOAC regimens in patients with thrombotic APS [14]. Furthermore, in a recent meta-analysis of randomized controlled trials, the odds of major bleeding (OR: 1.02; 95% CI: 0.42-2.47; P = .97; I^2 = 0%) and clinically relevant nonmajor bleeding (OR: 1.90; 95% CI: 0.78-4.66; P = .16; I^2 = 0%) were not significantly different between DOACs and VKA [13].

Furthermore, while most cases of bleeding episodes in APS are attributed to long-term anticoagulation therapy, some aspects of the disease also contribute to an increased risk of bleeding. APS-related causes of bleeding involve inflammation of capillaries, hypoprothrombinemia, and thrombocytopenia. Capillary inflammation leads to most cases of diffuse alveolar hemorrhage, a rare condition associated with high morbidity and mortality [15]. Lupus anticoagulant–associated hypoprothrombinemia syndrome is also rare and occurs when lupus anticoagulant targets prothrombin, accelerating its clearance and leading to hypoprothrombinemia and severe bleeding events [16]. Finally, thrombocytopenia may occur in up to 30% of cases, contributing to a poorer prognosis [17,18]. Figure summarizes the epidemiology, adverse outcomes, and clinical approach to bleeding risk in APS.

Prolonged anticoagulation therapy is associated with an increased risk of bleeding complications. Careful monitoring of target INR is essential, as is vigilance for the onset of additional hemostatic disorders, particularly thrombocytopenia. Novel approaches to anticoagulation, such as factor XI inhibitors, are under clinical investigation to evaluate their efficacy in patients at risk for thromboembolic events [19]. These drugs have been associated with low bleeding rates [19], suggesting a potential strategy for safer anticoagulation.

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F.A.O. was responsible for the concept of the manuscript, the review of the bibliography, and the writing.

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There are no competing interests to disclose.

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