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EDITORIAL COMMENT

Left Atrial Appendage Occlusion as an Alternative to Anticoagulants in Ibrutinib-Induced Hemorrhagic Pericardial Effusion*

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Atrial fibrillation (AF) affects 3% to 5% of the population older than 65 years of age and is responsible for up to one-fifth of all ischemic strokes.[1] Among patients with AF, the annual rate of stroke rate varies from 2% to 10% depending on the baseline risk.[2] AF incidence is even higher in patients with malignancies, often as a consequence of surgery, chronic inflammation, and chemotherapy. In addition, in the setting of cancer patients, AF is associated with a significantly higher risk of thromboembolism and heart failure, even after adjusting for known risk factors.[3]

Ibrutinib—a potent inhibitor of B cell proliferation—has been recently approved for several blood diseases including chronic lymphocytic leukemia, mantle cell lymphoma, Waldenstrom macroglobulinemia, and marginal cell lymphoma.[4] Of note, ibrutinib provides a significant survival benefit in these categories of patients, thus implying a therapy that lasts for years. However, its long-term use is associated to some bothersome side effects. The most common is new onset AF, being reported up to 16% and generally higher than that observed with other chemotherapeutic agents.[5] Moreover, ibrutinib is metabolized primarily by CYP450 CYP3A, so that CYP3A inducers and inhibitors affect both its efficacy and toxicity.[4] Thus, significant drug-drug interactions between ibrutinib and medications commonly used to manage AF—including direct oral anticoagulants—have been reported. Finally, ibrutinib affects several platelet-signaling pathways and increases the risk of bleeding—in a population already at high hemorrhagic risk due to older age and hematologic disorder—even without concomitant use of anticoagulants.[4,6]

In this issue of *JACC: Case Reports*, the case described by Jeelani et al[7] well depicts a not so uncommon scenario that the clinician has to keep in mind when prescribing ibrutinib. Despite presenting with an unusual bleeding problem—hemorrhagic pericardial effusion—the bleeding complication was clearly linked to the concomitant use of ibrutinib and apixaban. The real challenge that emerges in these patients is how to manage antithrombotic therapy to reduce AF-related cardioembolic risk without inducing a bleeding complication. As previously anticipated, different mechanisms explain the ibrutinib-related increased bleeding risk. Besides the well-known drug-related thrombocytopenia, ibrutinib selectively inhibits platelet signaling and functions interacting with the collagen receptor glycoprotein VI as well as impairs platelet adhesion to von Willebrand factor.[4-6] On the other hand, with regard to the correct anticoagulant therapy to prevent AF-related cardioembolic risk, it has been speculated that ibrutinib: 1) may increase the levels of warfarin via its effects on CYP3A4; 2) may potentially increase the plasma level of dabigatran, a direct thrombin inhibitor; and 3) may increase plasma levels of factor Xa inhibitors, such as rivaroxaban, apixaban, and

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edoxaban, and consequently the risk of bleeding.[8] Low-molecular-weight heparin represents a valuable alternative option, but fluctuations in kidney function may increase the risk of bleeding. In the case described by Jeelani et al,[4] the patient had a CHA_2DS_2-VASc score of 4, thus implying the choice of an antithrombotic strategy that, after the occurrence of hemorrhagic pericardial effusion, could provide a definitive and long-lasting protection against thromboembolism without affecting the bleeding diathesis.

Left atrial appendage occlusion (LAAO) appears as the most logical strategy stroke prevention strategy in these patients. The LAA is the source of thromboemboli leading to ischemic strokes in in more than 90% of cases, as demonstrated by many studies with transesophageal echocardiography or autopsy.[9,10] Although both European and American guidelines of AF management are still very cautious in considering LAAO as a primary choice of stroke prevention in AF[11,12]—leaving the strength of recommendation of LAAO only in Class IIb—an extensive experience has accumulated over time, on the one side confirming and reinforcing LAAO efficacy in preventing AF-related thromboembolism and on the other side confirming its increasing safety in experienced centers.

One issue to be faced after LAAO relates to the correct antithrombotic management in the first weeks and months after LAA closure. In the very first studies, LAAO was compared with oral anticoagulation and even those patients randomized to LAAO received warfarin and low-dose aspirin for at least 45 days after device implantation.[13,14] Later on—as avoiding oral anticoagulation is the main driver of proposing LAAO—the nonrandomized ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) study, in which patients receiving the LAAO device were managed with aspirin associated with a thienopyridine for 6 months followed by aspirin,[15] first demonstrated an annualized ischemic stroke rate of 1.7%, 77% less than expected. Only 1 (0.7%) case of device thrombus hesitating in ischemic stroke was observed. Even more important is long-term antithrombotic management after LAAO. Although 10% to 20% of patients usually withdraw even single antiplatelet therapy due to their hemorrhagic risk,[16,17] as reported in different registries, this issue has never been appropriately addressed in randomized studies. In addition, it is not clear the time course of device embolization and whether endothelization is a permanent phenomenon over time.

Another point to consider is whether AF induced by ibrutinib carries the same thromboembolic risk as that seen in patients with spontaneous AF with comparable CHA_2DS_2-VASc score. Recent studies have shown that in patients with a history of AF, thromboembolism occurs in both AF and sinus rhythm,[18,19] suggesting that spontaneous AF may identify a substrate prone to thrombus formation but may not be the actual cause. It remains unclear, however, whether AF provoked by ibrutinib similarly identifies a substrate at risk for thrombus formation, and thus whether patients with ibrutinib-related AF require aggressive stroke prevention. But in the absence of data to the contrary, we consider these patients at high risk of both stroke and bleeding complications. LAAO is therefore a highly attractive option in this setting.

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