EDITORIAL

Comparison of different oral anticoagulant regimens in patients with atrial fibrillation: is the risk of left atrial appendage thrombus formation truly comparable between regimens?

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In this issue of *Polish Archives of Internal Medicine*, Gawałko et al[1] have reported the incidence of thrombi and dense spontaneous echo contrast (SEC) in the left atrial appendage (LAA), with different anticoagulation regimens in patients with atrial fibrillation (AF).

The LAA is a common nidus for thrombus formation in patients with AF.[2] Given that only 10% of the clinically relevant emboli in nonvalvular AF originate outside the LAA, several methods such as computed tomography, transesophageal echocardiography (TEE), and the newly emerging cardiac magnetic resonance imaging are routinely used nowadays to exclude thrombi in the LAA in order to prevent thromboembolic complications.[3] Patients with AF are known to have a 4- to 5-fold increase in the risk of ischemic stroke than those without AF. Therefore, the significance of effective anticoagulation for the prevention of stroke cannot be overemphasized.

Warfarin is still the most commonly used oral anticoagulant; however, it has several limitations including food and drug interaction, dependence on liver function, and need for frequent monitoring of the coagulation status.[4] In contrast, the non–vitamin K antagonist oral anticoagulants (NOACs) provide more convenient therapeutic options and have demonstrated equivalent efficacy in comparison with warfarin in large phase III clinical trials.[5] However, extrapolating findings from the trials with idealized clinical settings to real-world practice is challenging, especially for anticoagulant therapies because of logistics and compliance issues.[4] Therefore, the attempt by Gawałko et al[1] to report the safety and efficacy of warfarin vs NOACs in terms of thrombus formation in the LAA in the real-world AF population is commendable.

In this observational analysis, the authors evaluated 859 consecutive patients with AF referred to the University Hospital, Warsaw, Poland, for AF ablation or direct current cardioversion.[1] Patients were excluded if they received no anticoagulant therapy or if it was discontinued for the past 3 weeks or if they underwent bridging with heparin before TEE. Of the 859 patients, 437 (51%) received warfarin; 191 (22%), dabigatran; 230 (27%), rivaroxaban; and 1 patient, apixaban. All TEE studies were performed within 48 hours of the procedure and assessed by 2 or 3 echocardiographists. The frequency of LAA thrombus and dense SEC was detected to be similar between the warfarin and NOAC groups. Between the dabigatran and rivaroxaban populations, the incidence of LAA thrombi was comparable, whereas dense SEC was more common in the dabigatran group, although the difference was not significant.

The choice of an oral anticoagulant is normally guided by the preference of the physician and the buying ability of the patient. Thus, the findings of this study suggesting a similar efficacy of warfarin and NOACs in preventing LAA thrombus formation is reassuring for the AF patients in general. However, many aspects of the complex interrelationship between the thrombotic events and anticoagulant therapy were not addressed in this study, which raises the obvious question of whether this evidence is truly conclusive and can be applied in real-world clinical practice or not.

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TEE remains the gold standard technique for evaluating LAA thrombus. However, it is typically interpreted based on the judgment of the reader rather than using any quantitative approach.[5] Moreover, the assessment is superior only when views are obtained from multiple imaging planes.[6] There are published reports where thrombi could not be detected by TEE due to portions of oddly shaped LAAs being out of the plane.[7] Thus, there is always the possibility of underreporting.

Gawałko et al[1] observed a comparable risk of LAA thrombus formation with dabigatran and rivaroxaban therapies. This observation can be an artefact for several reasons; first, the study population receiving rivaroxaban was younger, mostly had paroxysmal AF, and were healthier in terms of left ventricular ejection fraction (LVEF) and LAA-emptying velocity. Secondly, renal elimination of these 2 drugs varies greatly, with 80% for dabigatran and 35% for rivaroxaban.[8] Thus, even minor impairment or variation in kidney function would create a big difference in bioavailability and subsequent functional efficacy of one of these agents over the other. Also, only 6% to 7% of the gastrointestinal absorption of dabigatran implies that a slight fluctuation in digestion may have a profound effect on the plasma level.[8]

The authors reported a single estimated glomerular filtration rate value for the study populations, and missed on addressing the subtle but important issue of drug absorption. Also, the temporality of the renal function test in relation to the TEE study is not clear. Lastly, while comparing the 2 NOACs, a comparable pharmacokinetics of these 2 drugs has to be established because the oral bioavailability of rivaroxaban is dependent on intestinal P-glycoprotein transporters and the conversion of the prodrug dabigatran etexilate to the active compound is mediated by the caroboxylesterase enzyme in the liver; genetic variations in both cases can affect the plasma level of these drugs.[9]

Another limitation of this trial is the lack of information on the time in therapeutic range (TTR) for the anticoagulants. The European Society of Cardiology Working Group on Thrombosis Anticoagulation Task Force has recommended an average TTR of more than 70% for warfarin.[10] Similarly, compliance was not verified for any of the agents.[1] In our experience, thromboembolic events are mostly associated with a subtherapeutic international normalized ratio with warfarin therapy and discontinuation of the NOAC due to noncompliance or for other planned procedures. In a series of consecutive patients with AF receiving LAA isolation, we observed 18 thromboembolic events; suboptimal anticoagulation was associated with all 18 cases and follow-up TEE revealed LAA thrombus in one of these patients (unpublished data). Fukuda et al[11] reported similar findings; 16 of the 231 patients included in the analysis had left atrial (LA) thrombus detected and 13 of the 16 patients had subtherapeutic anticoagulation.

LVEF is a known predictor of LAA thrombus formation. Normal LVEF has been seen to be associated with the absence of thrombi in the appendage,[12] whereas LVEF of less than 30% was reported to be linked with an increased risk for LAA thrombus (odds ratio, 8.32; 95% confidence interval, 1.18–36.29; $P = 0.011$).[13] In the current study, LVEF data were available for a small fraction of the study population. This can be the reason why it was not detected as a predictor of LAA thrombus in the multivariate regression analysis.

Last but not least, a wide variation in the dosage of anticoagulants was reported in the study population.[1] In a meta-analysis of contemporary randomized trials, Wang et al[14] detected a significantly reduced risk of thromboembolic events with a standard dose (dabigatran, 150 mg twice daily, and rivaroxaban, 20 mg once daily) compared with low-dose NOACs. Additionally, a case report revealed LAA thrombus developing during low-dose NOAC therapy.[15] It would have been more informative if the authors would have specified the dosage schedule of the anticoagulants in patients with LAA thrombus.

On the basis of the findings from this study and other published reports, we believe that an optimal anticoagulant regimen in patients with AF is still a field with many unchartered territories. We are not certain why some patients develop LA thrombus with a reduced dose of an anticoagulant, where others do not. It is also intriguing to see some subjects remaining stroke-free without anticoagulant therapy for a long period, while others experience thromboembolic events after discontinuing a few doses. Does the answer lie in the genetics of the individuals? Future trials on a large global population including all ages, races, and sexes will possibly provide the answers. Until then, we must cautiously interpret the available data, given all the limitations and variations of the results.

Note The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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