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DOACs in Valvular Heart Disease: Latest Key Updates on PROACT Xa (Apixaban) and INVICTUS (Rivaroxaban)

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This letter serves to inform the readers of *Clinical and Applied Thrombosis/Hemostasis* regarding pivotal updates to a recent review article.[1] In this review, the authors critically evaluated the literature on the use of direct-acting oral anticoagulants (DOACs) in the setting of mechanical/bioprosthetic heart valves. Concerns surrounding the lack of adequate safety and efficacy data, as well as an official approval from the United States Food and Drug Administration (FDA) for these indications, should preclude the precarious use of DOACs in mechanical/bioprosthetic heart valves.

The review article mentioned the PROACT Xa study, which was at the time an ongoing randomized, open-label study of apixaban versus warfarin in patients with mechanical on-X aortic heart valves.[2] The international normalized ratio (INR) goal for warfarin was 2 to 3. The mechanical on-X valve had to be placed within 3 months prior to study enrollment, and patients were taking warfarin at baseline with or without low-dose aspirin. Patients with any other mechanical valve, an indication for higher-dose aspirin or a P2Y12 inhibitor, or on dialysis/creatinine clearance (CrCl) <25 mL/min, were excluded.

Study investigators had begun enrolling patients in April 2020, and the final randomized patient was to be followed for a minimum of 2 years.[2] On September 23, 2022, it was announced that the Data and Safety Monitoring Board (DSMB) recommended early cessation of the trial.[3] This decision was on the basis that rates of thromboembolism and valve thrombosis causing stroke were higher in the apixaban group, compared to the warfarin group. It was surmised that the trial would be unable to achieve noninferiority without increasing the risk of major bleeding events. Patients in the apixaban group were switched back to warfarin; other additional details were not made available by the investigators. A similar negative study in mechanical heart valves was previously found for another DOAC, dabigatran, in the RE-ALIGN study.[4]

Very recently, an open-label noninferiority trial of 4565 patients with rheumatic heart disease-associated atrial fibrillation (AF) was randomized to rivaroxaban or warfarin (INR goal 2-3) in the INVICTUS study.[5] Patients did not have mechanical heart valves, were not on any dual antiplatelets, nor had severe renal impairment (CrCl <15 mL/min); the mean CHA2DS2-VASc score was 1.9 ± 1.4. Initially, the composite primary outcome was stroke or systemic embolism. However, due to a higher-than-expected rate of death and a lower-than-expected rate of stroke based on blindly assessed outcomes, the composite outcome was revised to add death and myocardial infarction. After a mean follow-up of 3.1 years, patients receiving rivaroxaban compared to warfarin had a higher rate of permanent drug discontinuation (22.55% vs 5.98%)—the most common reasons cited as being the need for valve-replacement surgery and participant decision. The rivaroxaban group also had a higher rate of the composite outcome compared to the warfarin group (hazard ratio 1.25; 95% confidence interval 1.1-1.41), and the individual outcomes of ischemic stroke and death were significant.

As deduced in the original review article and this update, in patients with mechanical heart valves or rheumatic heart disease-associated AF, the gold standard is still warfarin.[1] As always, special precautions must be given to address the numerous drug, diet, and herb interactions.[6] As usual, diligent monitoring of INR and subsequent dosage adjustment are imperative in ensuring optimal patient care outcomes.[6]

Declaration of conflicting interests

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