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Opinion Paper

Is this the beginning of end for warfarin in bioprosthetic mitral valve recipients with atrial fibrillation? – New insights from RIVER trial

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ABSTRACT

Novel oral anticoagulants, with dabigatran in particular have failed in their quest to replace the traditional anticoagulation in the form of vitamin K antagonist in patients with mechanical valvular implants. However, the same had not been tried in bioprosthetic valve recipients until recently in a large trial where rivaroxaban was found to be non-inferior to warfarin on head-to-head basis. This commentary discusses the various aspects related to oral anticoagulation in bioprosthetic valve recipients in the light of recent clinical evidence.

Multiple novel oral anticoagulants (NOAC) have proven to be non-inferior or even superior in few aspects to vitamin K antagonists (VKA) for stroke prevention in non-valvular atrial fibrillation (AF) in addition to reducing bleeding events.[1] The utility of rivaroxaban, in particular has also been applied in coronary artery disease[2] and peripheral vascular disease.[3] Few NOAC trials involving mechanical prosthetic valve recipients for prevention of thromboembolic events had to be terminated in view of enhanced mortality.[4] Even though, previous trials like ARISTOTLE[5] and ENGAGE-AF TIMI-48[6] included few patients with bioprosthetic valves yet these were grossly underpowered for detecting meaningful benefit in this very population. This niche area of NOAC application was explored recently in a multicentric, randomized, open-label study presented at American heart association virtual scientific sessions 2020 where Guimarães et al[7] found rivaroxaban to be non-inferior to warfarin with respect to net clinical benefit at 1-year follow-up in 1005 bioprosthetic mitral valve (BMVx) recipients having AF. However, few reservations need in-depth explication while extrapolating the trial results to the real-world population.

RIVER trial population was at relatively lower thromboembolic risk (mean CHA_2DS_2-VASc score = 2.6 ± 1.4) and even lesser bleeding risk (mean HAS-BLED score = 1.6 ± 0.9) probably due to the selection bias (inclusion criteria ensured that patients having any risk factor(s) for bleeding got excluded). Also, 60% population was contributed by female sex who would otherwise qualify for a class IA recommendation for anticoagulation only if CHA_2DS_2-VASc exceeds 3.[8] Contrastingly, the ROCKET-AF[9] population was at a higher thromboembolic risk (mean CHA_2DS_2-VASc score = 3.5) and with females comprising 40% of study population. Despite the thromboembolic risk being modest at best, RIVER trial could not demonstrate the upper hand of rivaroxaban in terms of superiority analysis.

Moreover, 60% of the patients had undergone valvular surgery more than one year prior to randomization thereby reducing the anticoagulation need just to stroke prevention in atrial fibrillation and omitting the possible indication required for prevention of prosthetic valve thrombosis. The difference in the cumulative incidence of primary composite outcome (death, major cardiovascular events, or major bleeding) was maximal at 6 months follow-up in favour of rivaroxaban coinciding with the highest thrombogenic potential realized during the first 6 months post valve implantation requiring a certain level of anticoagulation. A notable observation was the similar ischemic stroke rates in the two groups (0.6% vs 1.4%; HR 0.43 [95% CI: 0.11–1.66]). However, rivaroxaban showed the real edge by outperforming warfarin in preventing haemorrhagic stroke (0% vs 1.0%). RIVER trial is also silent on the distribution of body weight among the trial participants. It is well known that the incidence of bleeding is directly proportional to

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rivaroxaban dose and inversely proportional to body weight. So going by the indirect logic lower dosage of rivaroxaban may be considered in frail patients to reduce bleeding risk, but lower doses of rivaroxaban (<15 mg) is also shown to be inferior for stroke prevention except in Japanese cohort.[10] Thus, titration and dose individualization may be more relevant in patients belonging to extremes of weight, keeping an Indian perspective in mind.[11,12] An important shining chunk in the rivaroxaban armour was the demonstration of superior clinical efficacy in patients with recent BMVx implant (within 3 months of randomization) and those receiving aspirin in addition to anticoagulation.

Although, the rationale for implanting BMVx in a relatively younger population (mean age: 59.3 ± 12.1 years) with AF is not mentioned in the trial data yet in real world scenario this sort of patient population is rather likely to receive mechanical prosthesis in view of higher longevity, durability and an invariable need for anticoagulation because of underlying AF. Moreover, the data of patients with rheumatic involvement who inherently have a higher thrombogenic potential is lacking. More clarity regarding percentage of rheumatic heart disease patients inducted among the study population would have made us wiser in the use of anticoagulation after valve surgery especially with mitral stenosis. Patients achieving time-in-therapeutic range (TTR) > 60% in both treatment arms had similar restricted mean survival time (RMST) thereby, implicating an equalized antithrombotic response irrespective of the anticoagulation strategy. This also emphasizes upon the need for regular compliance monitoring in improving clinical outcomes with respect to anticoagulant efficacy. The open-label design of RIVER trial too results in blinded outcome assessments being less feasible. Lastly, pharmacogenomic effect concerning anticoagulation in Brazilian population should have been taken into account while addressing the benefit of rivaroxaban in the BMVx recipients.[13]

Therefore, the RIVER trial results should be read in light of the above discussion and applied in perspective to valvular AF patients at moderate thromboembolic risk who have received mitral valve bioprosthesis at least a year ago and are not at high bleeding risk (HBR).

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Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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