Anticoagulation in Patients with Mechanical Heart Valves: Less Is More?

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Valvular heart disease is diffused worldwide and is associated with significant morbidity and mortality.[1] Surgical valve replacement is the treatment of choice when valve repair is impossible. Both biological and mechanical prosthetic (biological and mechanical heart valves [BHV and MHV]) valves are available: BHVs have a shorter duration than MHVs but are associated with a lower thrombotic risk than MHVs, which require lifelong anticoagulation. Patients with MHVs are, therefore, exposed to a not negligible thromboembolic and bleeding risk, and the burden associated with the management of anticoagulation may substantially affect the quality of life. Unfortunately, direct oral anticoagulants were shown a lower safety and efficacy when compared with vitamin K antagonists (VKAs) in this setting, and no alternative life-long treatment to VKAs is recommended for MHV patients.[2,3]

In Western countries, a substantial change in the epidemiology of valvular disorders occurred in the last decades. Rheumatic heart disease progressively declined, whereas a high prevalence of degenerative valve diseases occurred, according to the increase in the median age of the population. Instead, rheumatic heart disease is still endemic in a large part of low- and middle-income countries of Asia and Africa, affecting several children and young adults.[4] Indeed, MHVs have been progressively less implanted in Western countries, where many patients were elderly with degenerative valvular diseases, treated with endovascular procedures or BHV implantation, mainly for aortic valve disease. In addition, very limited research on MHV management has been performed in the last years: guidelines still recommend managing VKAs based on evidence from old studies in very different clinical settings compared to the actual standard of care of cardiologic patients.

Therefore, we read with great interest the recent publication by Johansson et al,[5] who present data from a retrospective observational study evaluating the quality of anticoagulation in patients with MHV and the adverse events that occurred in relation to the quality of anticoagulation achieved. The study reported data from a cohort of MHV patients followed by the anticoagulation clinic (AC) of a Canadian tertiary care level university clinic for a median time of about 5 years. Almost 80% of patients received aortic MHV, most patients were males, with a median age of 61 years, and the median time of international normalized ratio (INR) time in therapeutic range (TTR) was 62.5%. Similarly, aortic MHVs were present in 78% of patients in a large Sweden cohort[6] and about 60% of cases in the Italian PLECTRUM cohort[7]; instead, patients with aortic MHV were only 15% in a sizeable Sub-Saharan cohort,[8] where the majority of patients were females and requiring mitral MHV implantation.

The study of Johansson et al[5] found an increased risk of adverse events according to the quality of anticoagulation. Patients with a TTR of less than 40% showed a higher incidence of ischemic stroke and embolism, major bleeding, and death. Interestingly, a TTR $<$40% is also associated with a higher rate of adverse events in the large Sub-Saharan cohort.[8] On the contrary, in the Italian cohort, the risk of thromboembolic complications was not significantly higher among patients with a TTR $<$47%, corresponding to the lowest quartile of the entire cohort.[7]

The relationship between the quality of anticoagulation expressed as TTR and the worst outcome of patients has been reported by several studies.[9] When VKAs are used in patients with atrial fibrillation or venous thromboembolism followed by ACs, good TTRs have been reported.[10,11] However, in the same setting, the worst quality of anticoagulation was reported for MHV patients. Even if patients' different clinical characteristics should be considered, the higher intensity of

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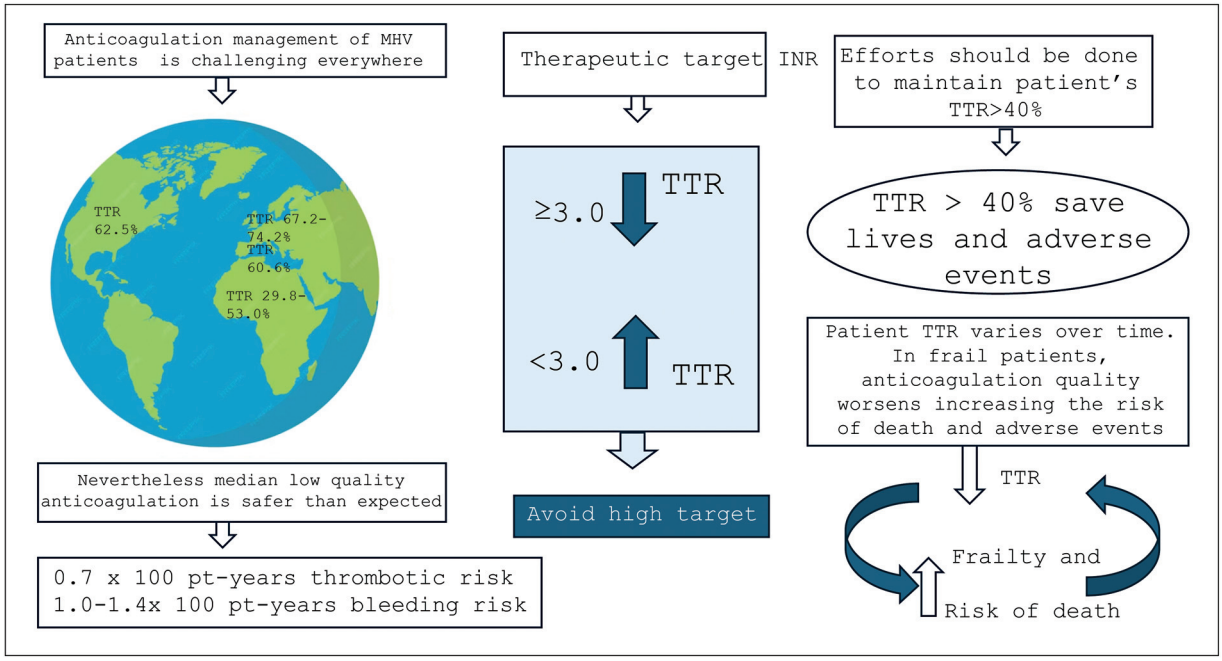

anticoagulation recommended for MHV patients may play a vital role in this phenomenon. When the quality of anticoagulation was analyzed according to the intended target INR levels, a progressive decline of the achieved TTR was found as the INR therapeutic range increased.[7] In the Italian PLECTRUM cohort, when the target INR ranged between 2.0 and 3.0, a TTR of 71.5% was obtained. Instead, the TTR declined to 58.6 and 46.0% when the target INR range was maintained between 2.5–3.5 and 3.0–4.0, respectively. The association of poor anticoagulation with low TTR and the risk for thromboembolic complications among MHV patients has been found in several studies[6–8] and confirmed by Johansson and colleagues. When the TTRs' determinants were analyzed, a target INR range of 2.5 to 3.5 or higher was associated with a lower quality of anticoagulation.[12]

During the last decades, international guidelines on the management of VKAs in MHV patients progressively reduced their recommendation on the optimal intensity of antithrombotic treatment for MHV. Previous recommendations were based on evidence from retrospective observational studies performed more than 30 years ago. The introduction of lower thrombogenic MHV and the improved medical treatment of patients of the last decades may explain the reduced thrombotic risk observed over time and allow the evolution of clinical recommendations. Indeed, during the 1990s, the intensity of anticoagulation recommended to prevent thromboembolic complications in MHV patients was a target INR range of 3.0 to 4.5,[11,12] but was promptly reduced to 2.5 to 3.5 for the elevated bleeding risk a few years later.[13] Further reduction in INR therapeutic range was suggested for patients with aortic valves and low thrombotic risk.[14] Moreover, the use of a more intense antithrombotic regimen plus low-dose aspirin, which was previously recommended, is now limited to patients who had a thromboembolic event during well-conducted anticoagulation, i.e., INR in the therapeutic range, and to patients with a particular high thrombotic risk.[15,16]

Anticoagulation management of patients on VKAs in daily practice is challenging, particularly for MHV patients with elevated INR therapeutic range. Available data suggest that an acceptably low thrombotic risk is achieved when a TTR >40% is obtained. When anticoagulation is maintained in an INR range between 2.0 and 3.0, a more stable anticoagulation could be obtained, with a higher TTR, lower adverse events, and a better clinical outcome. In addition, fewer INR determinations are required, with longer intervals between blood controls and reduced anticoagulation treatment burden. From an AC's perspective, keeping the patients' median INR values centered in the assigned therapeutic ranges and promptly acting in case of under or over-therapeutic values are valuable practices for improving anticoagulation control.[17] These aspects are relevant for patients living in low- and middle-income countries, where the accessibility to laboratories to obtain INR determination is complex and seriously expensive due to the inefficacy, or even to the absence, of an adequate health system.

Is it time for a further reduction in anticoagulation intensity in MHV patients? The results of the ongoing LIMIT Study (ClinicalTrials.gov, identifier NCT03636295) will probably help answer this question better.

Conflict of Interest
None declared.

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