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EDITORIAL COMMENT

DOACs in Patients With Mitral Stenosis and Atrial Fibrillation

Time for a Randomized Clinical Trial*

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Data from the Framingham Heart Study demonstrated that the presence of mitral stenosis (MS) in patients with atrial fibrillation (AF) increases the risk of stroke more than 20-fold (1). More than 70 years ago, Wright and Foley (2) described the use of anticoagulants for acute treatment and in secondary prevention of thromboembolism in patients with rheumatic heart disease and AF. Only 2 types of anticoagulants were then available—vitamin K antagonists (VKAs) and heparin. Because long-term parenteral therapy with unfractionated heparin was impractical, the use of VKAs, in particular warfarin, eventually became the standard of care to prevent stroke and systemic embolism in patients with MS and AF. In 6 randomized clinical trials conducted in 2,900 patients with AF published between 1989 and 1993 (3), warfarin reduced the risk of stroke by 64% compared with placebo. However, because patients with AF and either MS or mechanical heart valve replacement were known to be at very high risk for thromboembolism if not anticoagulated, such patients were generally excluded from these older trials.

With the development of direct oral anticoagulants (DOACs) at the turn of the 21st century, randomized trials in AF were designed to show that the newer agents were noninferior to warfarin. Because an important statistical assumption in noninferiority testing, known as the "constancy assumption," requires the population to be similar to that which established the initial benefit of the active comparator (warfarin) over placebo (4), patients with MS or mechanical heart valves were excluded from each of the 4 large DOAC versus warfarin trials (5-8). This is a critical assumption to maintain the validity of the noninferiority comparison because violations have been shown to increase the rate of incorrectly concluding noninferiority in the presence of ineffective or even harmful treatment (9).

Thus, whether the clinical benefits of DOACs over warfarin in patients with AF (namely, reductions of 19% in stroke or systemic embolism, 10% in mortality, and 52% in intracranial hemorrhage [10]) extend to patients with MS is unknown. As such, neither regulatory authorities nor practice guidelines support the use of DOACs in patients with MS. Current practice guidelines also stipulate that DOACs are contraindicated in patients with mechanical heart valves largely on the basis of a single phase 2 trial of dabigatran that was stopped prematurely because of excess harm associated with this oral antithrombin (11).

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In this issue of the *Journal*, Kim et al. (12) begin to address the knowledge gap surrounding DOACs in patients with MS. The authors present a retrospective, observational analysis of patients enrolled in the national health insurance database of the Republic of Korea (participation is mandatory for all health care providers) between 2008 and 2017 who were identified with MS and AF using International Classification

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of Diseases-10th Revision codes and were treated with either warfarin or DOAC. Of the total 29,889 patients thereby identified, 39% who had prior mitral valve surgery and another 36% who did not receive any oral anticoagulation were excluded. The remaining 7,357 patients included 1,917 treated with DOAC and 5,440 treated with warfarin. Because patients were not randomized to anticoagulant therapy, the authors used 1:1 propensity matching to reduce the heterogeneity between the groups, leaving a total of 2,230 for analysis. These 2,230 patients were well-matched for the 10 baseline characteristics selected for use in the propensity score. The DOAC group consisted mostly of patients treated with rivaroxaban (42%) or dabigatran (33%), with only 192 and 84 patients treated with apixaban and edoxaban, respectively.

The primary efficacy endpoint of ischemic stroke or systemic embolism over a mean follow-up of 27 months occurred in 4.19%/year of patients treated with warfarin compared with 2.22%/year treated with a DOAC, while the annualized rates of the primary safety outcome of intracranial hemorrhage occurred in 0.93% and 0.49% of patients in the warfarin and DOAC groups, respectively. Annualized rates of all-cause mortality were 8.08% in the warfarin group and 3.45% in the DOAC group. The authors concluded that use of DOACs in this population is promising and call for a randomized trial to confirm their findings.

Given the paucity of information regarding the use of DOACs in patients with MS, these observational data are welcome and should be viewed as hypothesis-generating. While the authors provide a quantitative comparison of results, some of the hazard ratios presented appear overly optimistic (e.g., a 72% reduction in the risk of ischemic stroke or systemic embolism, 59% reduction in mortality) given the large magnitude of benefits compared with what was seen in a prior metanalysis (10), and likely are influenced by residual confounding. Use of DOACs in patients with MS is considered off-label in Korea (and globally). The reason(s) why the health care provider and patient elected to use a DOAC off-label instead of warfarin in the current population are unknowable; thus, the presence of confounding (by indication or contraindication) would be difficult, if not impossible, to fully overcome based on a limited number of baseline characteristics. Therefore, the quantitative results reported herein should be viewed with caution, as should any quantitative treatment comparisons that are derived from a nonrandomized observational study.

Several other caveats deserve consideration. Only 7.5% of the patients with MS and AF who were identified were included in this analysis, with more than one-third excluded because they received no anticoagulation. This suggests that many patients at higher risk of bleeding were excluded. The quality of warfarin management was not reported; the authors note that subtherapeutic levels of warfarin anticoagulation (41%) were more frequent than therapeutic levels (31%) in a recent observational study from Korea (13). In addition, 39% of patients were excluded from the analysis because of previous mitral valve surgery. Thus, one should also be cautious about extrapolating these results to patients who achieve a high level of time-in-therapeutic range with a VKA or who have had prior mitral valve surgery.

Retrospective analyses from observational insurance databases differ from randomized controlled trials (RCTs) in many ways. Inclusion criteria are not as rigorous when International Classification of Diseases coding is utilized, and details such as the severity and etiology of the disease state (in this case MS), are often not available. The reporting of clinical outcomes that rely on diagnosis codes submitted by a large variety of health care providers will have greater variability than blinded endpoint adjudication by a panel of independent experts.

However, the absence of negative signals in this observational report do warrant further confirmation. The event rates reported herein may be helpful to guide sample size calculations for future RCTs and trial entry criteria. To date, only 2 studies are listed on the government Clinical Trials website using DOACs in patients with MS: one trial from Pakistan was withdrawn (NCT03673605), whereas the second is comparing dabigatran versus warfarin in patients who underwent mitral valve placement with a bioprosthetic valve (NCT03183843). Given the evolving demographics of rheumatic heart disease (14), a large RCT in patients with MS would need to involve patients from regions of the world (e.g., Africa, South and Central Asia, Oceania, Latin America, and the Caribbean) where clinical research is challenged and DOACs have not generally been studied and/or have limited availability. Nevertheless, we agree with the authors and others (15) that the time has come to answer this question with an adequately powered RCT with significant implications for the health of vulnerable populations.

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