Is It Time to Reevaluate Current International Normalized Ratio Targets for Asian Patients Following Mechanical Heart Valve Replacement?

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The optimal international normalized ratio (INR) target for warfarin therapy has evolved through decades of use as additional information sheds light on the best balance between preventing pathologic thrombus formation while limiting bleeding complications. The INR target recommended in evidence-based guidelines for most warfarin indications is currently 2.5, with a range of 2.0 to 3.0. For patients with mechanical mitral valve replacements, a slightly higher target of 3.0, with a range of 2.5 to 3.5, is recommended. Despite its history of use, is this one-size-fits-all approach to INR targets appropriate for achieving desired outcomes for patients with differing sensitivity to warfarin's anticoagulant effect—particularly patients of Asian descent? This question is addressed in research published by Huang et al elsewhere in JAMA Network Open. Specifically, the study by Huang et al sought to identify the optimal INR for patients of Asian ancestry after mechanical aortic valve replacement (AVR) and/or mitral valve replacement (MVR). Using a large electronic medical record database in Taiwan, the authors identified patients who received mechanical AVR and/or MVR between January 1, 2001, to December 31, 2018. These patients were followed up from the first INR examination after surgery discharge. Primary outcomes were composites of bleeding or thromboembolic events. To facilitate estimation of INR values at the time of outcome events, only outcomes occurring between 1 day before to 7 days after the date of measured INR tests were included. The association between INR and bleeding/thromboembolic events was assessed. Patients who received AVR alone (n = 474) were analyzed separately from those receiving MVR alone or combined MVR-AVR (n = 426). For both the AVR-alone and the combined MVR and MVR-AVR groups, the familiar U-shaped distribution of outcome events emerged, with increased thromboembolic events at low INR values and increased bleeding events at higher INRs. In the AVR-alone group, using various 0.5-INR point ranges (reference INR, 2.0-2.5), the adjusted odds of thromboembolic events were significantly higher when the INR was less than 1.5 (adjusted odds ratio [aOR]: 2.55; 95% CI, 1.37-4.73), and bleeding events were significantly higher with INRs of 3.0 or greater (aOR, 3.48; 95% CI, 1.95-6.23). A separate regression model created using a restricted cubic spline variable and a reference INR of 2.0 estimated the lowest risk of thromboembolic events at INRs between 2.0 and 2.6 and the lowest risk of bleeding events at INRs between 1.8 and 2.4. In the combined MVR and MVR-AVR group (reference INR, 2.5-3.0), the odds of bleeding events were significantly higher when the INR was 3.5 or greater (aOR, 2.25; 95% CI, 1.35-3.76). However, no significant association was observed between INR and thromboembolic events. Using the RCS variable and a reference INR of 2.5, the lowest risk of thromboembolic events was estimated at INRs between 2.1 and 2.7 and the lowest risk of bleeding events at INRs between 2.1 and 2.8. A number of previous studies have documented lower warfarin requirements in Chinese patients (3 mg/d) compared with White patients (4-6 mg/d), suggesting that Chinese patients have increased sensitivity to warfarin. In a cohort of Hong Kong Chinese patients receiving warfarin therapy, an INR between 1.8 and 2.4 appeared to be associated with the lowest rates of major bleeding or thromboembolic events. In patients who achieved similar INR control, the hazard ratio for intracranial hemorrhage (ICH) for Asian individuals was 4.06 (95% CI, 2.47-6.65) compared with White patients. Thus, the study by Huang et al seems to confirm earlier evidence suggesting that the optimal INR target in Asian patients may be lower than that recommended in evidence-based guidelines. A critical question is how much lower?
Huang et al\textsuperscript{2} do not directly answer this question, but they suggest that the rate of thromboembolic events at INRs between 1.5 and 2.0 was not significantly higher than at INRs between 2.0 and 2.5 for patients with AVR. For patients with MVR, they suggest that the rate of thromboembolic events at INRs between 2.0 and 2.5 was not significantly higher than at INRs between 2.5 and 3.0. This seems to indicate target INR ranges of 1.5 to 2.5 for AVR and 2.0 to 3.0 for MVR and MVR-AVR may be reasonable. However, these suggestions are not based on high certainly evidence, as Huang et al\textsuperscript{2} analyzed observational data. Even with the sophisticated regression models used to minimize bias, there is likely to be residual confounding, and their results require confirmation in randomized clinical trials. Unfortunately, it is unlikely that these types of trials will be conducted in the near future, if ever. What can clinicians do now for their Asian patients taking warfarin following mechanical heart valve replacement? One approach might involve continuing to use conventional, evidence-based guideline INR targets for Asian patients but being slow to increase warfarin doses for INRs slightly less than the lower limit of the INR range and quick to reduce warfarin doses for INRs exceeding the upper limit. In addition, clinicians could aggressively address modifiable bleeding risk factors, such as uncontrolled hypertension, unnecessary use of daily aspirin and/or nonsteroidal anti-inflammatory drugs, and the use of herbal drugs associated with antiplatelet and/or antithrombotic effects, many of which are used by an estimated 1 in 4 Chinese patients receiving anticoagulants.\textsuperscript{6} Another option to consider is prescribing lower tablet strengths of warfarin (eg, 1- or 2-mg tablets) to Asian patients to allow more precise titration of the INR response among this population given the demonstrated increased sensitivity to warfarin.

Direct oral anticoagulants, such as apixaban or rivaroxaban, are contraindicated in patients with mechanical heart valves based on the results of the Randomized, Phase 2 Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) trial, in which patients with mechanical heart valves receiving dabigatran had increased rates of thromboembolic and bleeding complications compared with warfarin.\textsuperscript{8} Thus, warfarin remains the anticoagulant of choice in this patient population. Huang et al\textsuperscript{2} have provided important confirmatory evidence to previous work suggesting that Asian patients may experience improved outcomes with INR targets lower than those recommended in current evidence-based guidelines.

**ARTICLE INFORMATION**

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