Intensity and Quality of Warfarin Anticoagulation in Chinese Patients
Setting the Record Straight

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North American and European guidelines for the use of warfarin for stroke prevention in patients with atrial fibrillation recommend routine coagulation monitoring and dose adjustment to achieve an international normalized ratio (INR) between 2 and 3.\textsuperscript{1,2} The quality of warfarin anticoagulation control is most commonly evaluated by calculating the time in therapeutic range (TTR) using the linear interpolation method of Rosendaal et al.\textsuperscript{3} Asian guidelines recommend a lower INR,\textsuperscript{4} based on the belief that Asian patients are more sensitive to the anticoagulant effects of warfarin and that they have unacceptably high rates of bleeding when the INR is maintained between 2 and 3. High-quality evidence to support targeting a lower INR range in Asian patients is lacking.

In this issue, Ho et al\textsuperscript{5} report the results of a hospital-based registry of 8754 patients with nonvalvular atrial fibrillation and a CHA\textsubscript{2}DS\textsubscript{2}-VASc score $>1$ (mean enrolled between July 1997 and December 2011 who were followed up for a mean of 3 years). Patients with incomplete follow-up were not included. Clinical outcomes were obtained from the territory-wide information network of all public hospitals in Hong Kong. One thousand four hundred twenty-eight patients in the registry were treated with warfarin, and their median TTR on an INR target of 2 to 3 was 38.8%. Three thousand six hundred patients were treated with aspirin, 393 patients were treated with dabigatran, and 3338 patients received no antithrombotic therapy.

Overall rates of ischemic stroke (7.74% per year), intracranial hemorrhage (ICH; 0.75% per year), and death (18.3% per year) were remarkably high, reflecting the high age (mean, 79.5 years) and CHA\textsubscript{2}DS\textsubscript{2}-VASc score (mean, 4.1) of this registry population. Ischemic stroke rates were the highest in patients who received no antithrombotic therapy (10.38% per year), intermediate in those who received aspirin (7.95% per year), and the lowest in those who received dabigatran (2.24% per year). Among patients receiving warfarin, the TTR was a key determinant of outcome; annual stroke rates were the highest among those with a TTR in the bottom quartile (7.34% per year) and were the lowest in those with a TTR in the top quartile of the population (3.1% per year). Annual ICH rates were the highest (1.37% per year) in patients with a TTR in the bottom quartile of the population and were progressively lower among those with a TTR in the upper 3 quartiles (0.86% per year, 0.82% per year, and 0.74% per year, respectively). The rate of ICH in patients on aspirin (0.80% per year) was similar to that in patients in the upper 3 quartiles of TTR for warfarin. The lowest rate of ICH was in patients who received dabigatran (0.32% per year), which compared favorably with the rate in those who received no antithrombotic therapy (0.53%/yr). An association was also evident between TTR and death.

The data by Ho et al\textsuperscript{5} are observational, which limit the validity of comparisons of event rates between different treatment groups, but, nevertheless, contain several important lessons. First, only 1 in 5 patients with atrial fibrillation received guideline-recommended anticoagulant therapy for stroke prevention. Failure to treat the vast majority of at-risk patients results in an enormous burden of potentially preventable stroke in Hong Kong Chinese. Second, among those who received warfarin for stroke prevention, the quality of anticoagulation was poor, and poor anticoagulant control was associated with high rates of ischemic stroke and ICH. Third, aspirin was the most commonly used antithrombotic treatment, despite overwhelming evidence from randomized controlled trials indicating that it is relatively ineffective for stroke prevention in atrial fibrillation. High-quality evidence from randomized controlled trials indicates that well-controlled warfarin\textsuperscript{6} and apixaban\textsuperscript{7} are much more effective than aspirin, and that apixaban did not increase major bleeding compared with aspirin in the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke (AVERROES) trial.\textsuperscript{7} Finally, the low event rates observed with dabigatran are consistent with the results of a recently published Asian subgroup analysis from the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, which demonstrated that dabigatran compared with warfarin provided substantial improvements in efficacy, and lower rates of major and intracranial bleeding.\textsuperscript{8}

What are the implications of these findings for clinical practice? The results by Ho et al\textsuperscript{5} add to the accumulating and now compelling evidence that anticoagulation offers important benefits to East Asian patients with atrial fibrillation. Healthcare providers and patients in Asian countries must take note, and urgently implement readily available and highly effective treatments to reduce the enormous burden of preventable stroke. Establishment of specialized warfarin management clinics might improve the efficacy and safety of warfarin anticoagulation but would be costly, and a strong case can be made to abandon vitamin K antagonists in favor of non–vitamin K antagonists in the majority of patients with atrial fibrillation in Asian countries. Non–vitamin K antagonists are...
at least as effective and are safer than warfarin\textsuperscript{9–12}, and we suspect that they would prove to be highly cost-effective in high-risk East Asian patients with atrial fibrillation in countries where the newer agents are reasonably priced. Warfarin will still be needed in patients with absolute indications for a vitamin K antagonist (eg, mechanical heart valves) and those with contraindications to non–vitamin K antagonist oral anticoagulants (eg, interacting drugs and severe renal impairment).

What are the implications for future research? The data presented by Ho et al\textsuperscript{5} alert clinicians and patients to the requirement to evaluate better methods of healthcare delivery, so that highly effective, evidence-based therapies are appropriately implemented. At the same time, there also remains a need for further studies to understand the risk factors better, causes, and consequences of bleeding in patients with atrial fibrillation who are treated with antithrombotic therapy because fear of bleeding remains an important barrier to the appropriate use of anticoagulant therapy in this population.

Disclosures
Dr Eikelboom has received honoraria and research support from companies that market non–vitamin K antagonist oral anticoagulants, including Bayer, Boehringer Ingelheim, Bristol-Myers Squib, Daiichi-Sankyo, Janssen, and Pfizer. Dr Hart has served as a consultant and has received research support from Bayer.

References

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