

Stroke Prevention: Measuring and Closing the Anticoagulation Gap

Stroke is a leading cause of death and disability in developed countries. In the United States, more than 700 000 Americans have a new or recurrent stroke every year.^{1,2} More than 4 million Americans now live with the aftereffects of stroke, including more than a million stroke survivors with serious impairments (eg, aphasia, hemiparesis, depression) or functional limitations (eg, needing help walking, being unemployable).^{2,3} These survivors are also at extremely high risk of recurrent stroke—14% of those who survive a first stroke or transient ischemic attack will have another event within 1 year.² Because stroke risk increases with age (after age 55 years, the risk doubles every decade),⁴ the prevalence of stroke will increase steadily in coming years as the number of Americans older than age 65 years continues to increase.

Atrial fibrillation (AF) is a medical condition that increases in prevalence with age, from about 0.1% in those younger than 55 years of age to 9% or more in those older than 80 years of age.⁵ This arrhythmia is associated with a 5- to 6-fold increased risk for stroke and accounts for 15% to 20% of all strokes.^{2,6} Strokes secondary to AF can be very debilitating, with individuals more than twice as likely to be left bedridden.² The rate of intracranial bleeding from randomized trials and observational studies ranges from 0.1% to 0.9% per year and largely depends on the international normalized ratio (INR) target range.⁷ By the year 2050, the number of US adults with AF will double from 2.3 million to 5.6 million,⁶ and this is considered one of the prime drivers of increasing stroke rates in coming decades.

Stroke remains one of the most preventable of all life-threatening health problems. Along with reduction of blood pressure and cholesterol, antithrombotic prophylaxis

against stroke in AF is a prime means of reducing thromboembolic complications. Anticoagulants and antiplatelet drugs are both widely used for this purpose in patients with AF, especially in the presence of additional risk factors for stroke. National guidelines have defined the patients and circumstances for which anticoagulation is recommended.⁸ Warfarin is especially effective in reducing stroke risk in AF patients (62% risk reduction vs 22% risk reduction with aspirin),⁹ but clinicians are reluctant to prescribe warfarin to an elderly patient because of this drug's narrow therapeutic index. Other risk factors for major hemorrhage include history of gastrointestinal bleeding, genetic differences in warfarin metabolism, INR variability, concurrent use of antiplatelet or nonsteroidal anti-inflammatory drugs, comorbid illness, and duration of anticoagulation therapy.⁷ Striking a balance between the risk of bleeding with excessive warfarin dosing and the risk of emboli with underdosing requires special monitoring and dose adjustment and an investment in time and resources that does not as frequently occur outside the clinical study or anticoagulation clinic setting.

This fear of bleeding and inconvenience of regular therapeutic monitoring is an apparent reason why warfarin use, although highly effective, remains underutilized. A recent Medicare-sponsored review of warfarin use in New York state, for example, found that 38% of patients who had AF and no contraindications for warfarin were not discharged taking warfarin and had no documented plan for warfarin administration.¹⁰ Similarly, a recent national survey of AF patients at 38 US hospitals showed that only 55% of those with high stroke risk received warfarin, and 21% received no antithrombotic treatment at all.¹¹ The strategy in the

Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study (RACE) was to examine the effects of rhythm and rate control in AF. Data from AFFIRM support the current guidelines that patients with paroxysmal AF receive warfarin if they have risk factors for stroke. Most strokes in AFFIRM occurred either during subtherapeutic INR rates or after terminating warfarin.¹²

Efforts are under way at many managed care organizations (MCOs) around the United States to implement, expand, and justify the cost of anticoagulation clinics or develop anticoagulation improvement strategies that include patient education, computerized patient records, outsourcing of monitoring, and use of portable monitors.^{11,13,14} These efforts are driven by the opportunity to reduce the substantial clinical burden of stroke, as discussed above, but also to lower the associated economic burden of disease. Even disregarding the long-term costs of stroke to patients and their families, the immediate costs that are typically paid for by MCOs or Medicare are substantial. The National Stroke Association recently summarized data from the National Center for Health Statistics to report that the average cost of caring for a stroke patient in the first 90 days poststroke is about \$15 000, with 43% of these costs for initial hospitalization, 16% for rehabilitation, 14% for physician services, 14% for hospital readmission, and 13% for other costs.¹⁵ This estimate comes close to the 12-week stroke costs of about \$14 000 calculated by Caro and colleagues in their recent study of ischemic stroke costs.¹⁶ Clearly, even when the significant nondirect, quality-of-life, and societal costs of stroke are neglected, the economic burden of this condition is huge and can be expected to grow in coming years.

This supplement is based on presentations related to anticoagulation therapy made at the 5th World Stroke Congress held in Vancouver, British Columbia, Canada, on June 23-26, 2004. The presentations are relevant to the ongoing problem of the anticoagulation treatment gap in US clinical

practice and the resulting missed opportunities for reducing stroke rates and lowering healthcare costs.

In the first of 2 presentations made in Vancouver, J. Jaime Caro, MDCM, FRCPC, FACP, described the creation of a new economic model that allows estimation of the direct costs for AF-related stroke in the United States. His model is relevant to *AJMC* readers for several reasons. First, it takes the perspective of Medicare in analyzing stroke costs, accounting for only those expenses that would normally be reimbursed by the Centers of Medicare and Medicaid Services. Although such a narrow focus certainly misses costs typically associated with stroke over the long term—from long-term costs for nursing home care to drug costs to indirect costs related to lost productivity—Dr Caro's streamlined analysis provides managed care decision makers with a solid base to build their own estimates of system costs for AF-related stroke. The second practical feature of this economic model is its element of realism in projecting separate stroke rates, bleed rates, and costs for 2 different groups of patients receiving warfarin. Thus, Dr Caro's analysis not only projects costs for "ideal" patients who are well controlled taking warfarin, it also estimates costs for the "real-life" patients who are receiving warfarin outside the anticoagulation clinic setting. The distance between these 2 estimates essentially defines, for the first time, the hard cost of the anticoagulation gap. Because the economic model is set on the national scale, the absolute numbers generating in Dr Caro's analysis—for example, the total of \$8 billion in AF-related stroke costs—are perhaps less relevant than the relative sizes of the costs in his various treatment populations. Analysis of these projections allows readers to gauge the potential savings that might be associated with shifting more of their AF patients to more optimal warfarin therapy as seen in the anticoagulation clinic setting.

In fact, Dr Caro's second presentation relieves us of the burden of performing our own calculation of this potential savings with anticoagulation optimization. The economic model is designed to ask a series of "what if" questions about how many strokes

could be avoided and how much money could be saved if (1) more patients received warfarin or if (2) more patients already taking warfarin were managed in an anticoagulation clinic. Again, the answers revealed in this model provide a good sense for the scale of potential clinical and economic gains to be had in anticoagulation optimization.

The other presentation summarized comes from Gregory W. Albers, MD, who provides a first look at the pooled analysis of data from the 2 major trials with the new oral direct thrombin inhibitor, ximelagatran. The Stroke Prevention Using an Oral Direct Thrombin Inhibitor in Atrial Fibrillation (SPORTIF III and V) trials compared adjusted-dose warfarin with fixed-dose ximelagatran in more than 7000 AF patients with at least 1 additional stroke risk factor. The pooled analysis showed that this new agent is essentially equivalent (noninferior) in efficacy to extremely well-controlled warfarin in reducing the risk of stroke and systemic embolic events, but without the need for monitoring and with a reduced level of major and minor bleeding. The primary event rates were 1.65% per year for warfarin and 1.62% per year for ximelagatran ($P = .941$). Intracranial hemorrhage rates were 0.20% per year and 0.11% per year with warfarin and ximelagatran, respectively. The major downside of ximelagatran therapy was transient asymptomatic elevation of liver enzymes in 6.1% of patients, implying a potential need for monitoring of some patients early in therapy. Dr Albers concluded that SPORTIF shows that ximelagatran offers a possible alternative to standard dose-adjusted warfarin therapy.

The practical significance of SPORTIF is only clarified by its juxtaposition to the Caro economic model in this supplement. Although the Caro model puts a price tag on the longstanding anticoagulation gap between the ideal and the real, the author readily admits that closing this gap with warfarin will be extremely difficult. The investments needed to expand warfarin clinics or introduce novel monitoring systems for warfarin are likely beyond the reach of most MCOs—and, in any event, the deeply ingrained attitudes of clinicians toward this old agent would be difficult to change. The SPORTIF pooled data, howev-

er, suggest that a nonwarfarin anticoagulant may soon be available to help close the anticoagulation gap.

If a direct thrombin inhibitor can be shown to share warfarin's efficacy while remaining free of this drug's hematological, logistical, and historical baggage, then it may allow significantly more at-risk AF patients to receive quality stroke prophylaxis. This increase in the number of AF patients receiving optimal anticoagulation could, as outlined in Dr Caro's economic model, dramatically reduce stroke rates. The cost implications of using ximelagatran instead of warfarin remain uncertain, but would likely depend on this drug's price, its relative impact on bleeding rates, the need for liver monitoring, and, of course, the payer's perspective. As novel anticoagulants and antiplatelets continue their evaluations in mid- and late-stage clinical trials, we look forward to the publication of future anticoagulation models that consider the potential impacts of various nonwarfarin agents on health system stroke rates and costs.

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