Pharmacoeconomics of Atrial Fibrillation and Stroke Prevention

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Abstract

Atrial fibrillation (AF) is a common arrhythmia that significantly increases the risk of stroke by the formation and embolism of left-atrial appendage thrombi. This risk can be substantially reduced with antithrombotic therapies such as aspirin or warfarin. Those with the highest risk receive the most benefit from adjusted-dose warfarin compared with aspirin or low-dose warfarin. Because of its efficacy in reducing strokes, adjusted-dose warfarin has been shown to be cost-effective in several different settings, but mostly for AF patients with at least 1 additional risk factor. Warfarin must be adjusted to international normalized ratios (INRs) within the target range of 2.0 to 3.0 to minimize the risk—as well as the cost—of stroke and bleeding. Subtherapeutic INR values occur commonly, but the consequences are increased risk of stroke and therefore increased costs. Of the several strategies available for managing anticoagulation, the key element to controlling costs is avoiding out-of-range values.

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Nearly 2.3 million adults in the United States have been diagnosed with atrial fibrillation (AF). Patients with AF have a 6-fold increased risk of stroke because of the formation and embolism of left atrial appendage thrombi. Each year 60 000 strokes occur as a result of this arrhythmia, producing a substantial impact on healthcare costs. Not only is the risk of stroke much higher in those with AF, but their strokes are more likely to be fatal, and stroke survivors have more severe disability and poorer functional outcome than those without AF.[1-3]

Although management of AF rate and rhythm with medications or procedures may improve symptoms associated with AF itself, this does not reduce stroke risk and thus is not a substitute for stroke prophylaxis with antithrombotic therapy.[4] Based on a meta-analysis of 16 randomized controlled trials, it is estimated that adjusted-dose warfarin (generally an international normalized ratio [INR] of 2.0-3.0) reduces the risk of stroke by 62% while aspirin reduces the risk by 22%.[5] Notably, cohort studies[6] and clinical trials of low-dose warfarin[7] indicate that the effectiveness of warfarin depends on maintaining the INR above 2.0.

While effective, warfarin therapy can be both risky and demanding. Targeting patients who could reasonably avoid warfarin can be accomplished by providing estimates of future stroke risk. For example, the Congestive Heart Failure, Hypertension, Age, Diabetes, and Stroke ($CHADS_2$) index is a model of stroke risk for AF patients that has been well validated in multiple cohorts and settings.[8] This index is determined by adding points for specific risk factors: 2 points for prior cerebral ischemia, and 1 point each for history of hypertension, diabetes mellitus, recent congestive heart failure, or ≥75 years of age. The annual stroke rate for patients not on antithrombotic therapy varies from 1.5% for a patient with a $CHADS_2$ score of 0 to as high as 18% for a score of 6 (**Table**).[8]

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The decision to use antithrombotic therapy involves a complex balancing of risks, benefits, and costs—all of which are highly uncertain. The key issues for stroke prevention in AF specifically involve the probabilities of stroke, bleeding complications, and death; the associated costs of all treatment options and outcomes; and the quality of life associated with treatment and disability.[9]

Decision and cost-effectiveness modeling can provide useful guidance in such situations and has been applied to the evaluation of antithrombotic therapy in AF.[10-13] These have shown that warfarin therapy is generally cost-effective and often cost-saving.[10-13] However, the economic value of antithrombotic therapy in terms of cost-effectiveness is most strongly influenced by 2 factors: stroke risk and perceived quality of life ("disutility") with warfarin.

In one model, patients were stratified into those with lone AF (ie, no other risk factors) and those with AF and at least 1 additional risk factor. The investigators found that for patients ≤65 years of age with AF only, warfarin was not cost-effective, but for those with AF and an additional risk factor or for those >75 years of age, warfarin was more cost-effective than aspirin.[10] In terms of stroke rate without therapy, warfarin was cost-saving at an annual rate of 4.6% or greater and cost-effective at an annual rate between 2.1% and 4.6% (marginal cost-effectiveness ratio below $66 000 per quality-adjusted life-year saved). Below an annual stroke rate of 2.1% warfarin was not estimated to be cost-effective and, indeed, at a 1.1% stroke rate, aspirin was superior to warfarin in terms of both cost and effectiveness.[10]

Consideration of patients' preferences for warfarin versus aspirin therapy has been assessed using preference-based utility assignments for each therapy. A utility assignment is based on a patient's response to a series of questions about willingness to accept some trade-off, such as chronic warfarin therapy to avoid a specific health state, such as stroke or death. Although warfarin appears clinically and economically unattractive for very-low-stroke-risk patients and cost-effective for higher-stroke-risk patients, modest individual variation in negative utility ("disutility") for warfarin therapy can sway the balance.[12] Patients' judgment of the disutility of warfarin can be highly variable depending on their experience (especially prior experience with bleeding) and the way in which risks and benefits are explained. Studies of patient decision aids that enhance patients' knowledge and expectations of therapy options, benefits, and risks showed that patients tended to make conservative decisions regarding therapy (ie, aspirin over warfarin) when fully informed of the choices.[14]

Table. Annual Stroke Rates for Patients with AF According to the $CHADS_2$ Score

$CHADS_2$ Score	Adjusted Stroke Rate (%) (95% CI)
0	1.9 (1.2-3.0)
1	2.8 (2.0-3.8)
2	4.0 (3.1-5.1)
3	5.9 (4.6-7.3)
4	8.5 (6.3-11.1)
5	12.5 (8.2-17.5)
6	18.2 (10.5-27.4)

AF indicates atrial fibrillation; $CHADS_2$, Congestive Heart Failure, Hypertension, Age, Diabetes, and Stroke; CI, confidence interval.
Source: Reference 8.

To summarize, cost-effectiveness models indicate that warfarin can be cost-effective or, indeed, cost-saving for a wide variety of patients with AF. The exception to warfarin's robust cost-effectiveness includes patients under age 65 with AF only because their annual stroke risks without therapy are <2.1%. However, patient perception of the disutility of warfarin can have a significant impact on the overall value of anticoagulation. Thus, patients must be informed about the implications of therapy and be allowed to express their preferences, regardless of risk.

Making Antithrombotic Therapy for AF Cost-Effective in Routine Practice

For warfarin to be effective and cost-effective, it must be used appropriately. Despite the strong clinical and cost-effectiveness evidence for warfarin therapy, rates of use in eligible high-risk patients with AF were low in most studies and ranged from 22% to 79%.[15-23] Moreover, up to 60% of those receiving warfarin have INRs that are below the recommended therapeutic target range of 2.0 to 3.0.[17,18,23]

Barriers to appropriate high-quality anticoagulation have been linked to patient,

physician, and healthcare system factors. In general, patients who were less likely to receive warfarin tended to be older,[24] have language barriers or disability,[21] or were located in rural settings.[22] Physicians have widely varied perceptions of the risks and benefits of warfarin therapy, and they report uncertainty about antithrombotic therapy guidelines for AF patients.[15] Physician surveys indicated that healthcare systems barriers to optimal anticoagulation include delays in laboratory reports for INRs, the general inconvenience of monitoring, and the lack of consultant services in anticoagulation management.[15] While excessive anticoagulation is an especially worrisome issue because of potential bleeding complications, studies suggest that underanticoagulation is much more common,[25] possibly because of a desire to avoid excessively high INRs.

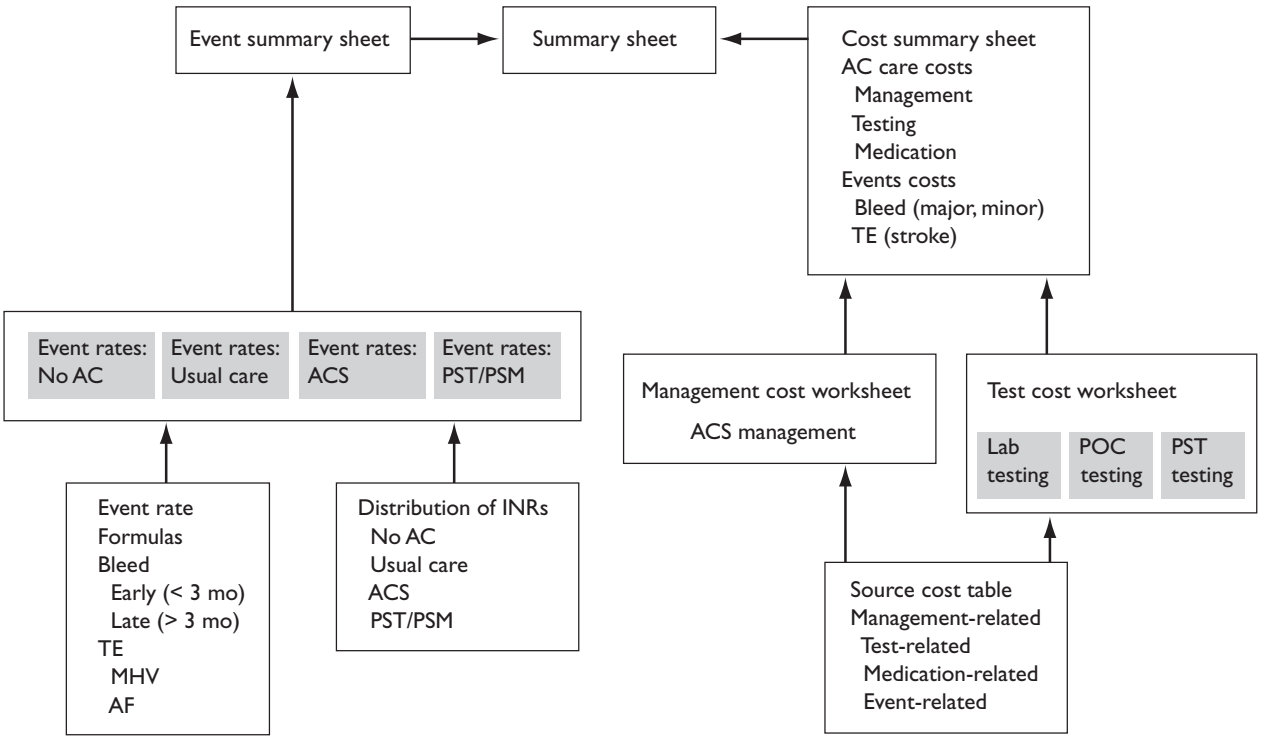
Two strategies that have been promoted to improve appropriate, high-quality anticoagulation in patients with AF are anticoagulation services and patient self-testing with or without self-management.[26] The rationale for a specialized clinic with personnel trained to manage anticoagulation is that it provides an organizational structure that assures levels of monitoring, dose adjustments, and follow-up that is not practical in a busy general practice. There is evidence that such services can improve care in specific settings. For example, in a report, a community hospital instituting an anticoagulation clinic increased the proportion of eligible patients with AF who received warfarin from 45% to 63%, and increased the proportion of patients with INRs in the target range.[27]

When evaluated in trials in more general clinical settings, anticoagulation services have not been as uniformly effective. In the Managing Anticoagulation Services Trial (MAST), clusters of practices affiliated with managed care organizations were randomized to an intervention in which an anticoagulation service was made available (intervention cluster) or not (control cluster).[25] The main outcome measure was the proportion of time that warfarin-treated patients with AF were within the therapeutic range of INRs (2.0-3.0) in each cluster. Although the study demonstrated that anticoagulation services successfully managed anticoagulation in patients with AF, there was no significant difference in the time patients spent in the therapeutic range of INRs between the intervention and the control clusters. This lack of effect may be explained partly by the reduction in the institutional commitment at several sites after extensive reorganization, high patient turnover limiting follow-up measurements of INR, and the lack of physician acceptance of and referrals to the anticoagulation services in the intervention clusters.[25] This study illustrates the local challenges within institutions and organizations that need to be overcome before the value of anticoagulation services can be proved.

Additional methods have been established to improve the quality of INR monitoring for patients receiving warfarin. An example is patient self-monitoring or self-management, where patients are instructed to use a device that measures INR based on a finger-stick blood sample obtained at home. Patients alert their physicians or other providers who then adjust the doses accordingly. Or, some patients can be taught to adjust their own doses based on an algorithm. There is evidence that this method is a very effective means of managing anticoagulation. For example, in a randomized trial of patient self-monitoring/self-management versus usual care, INRs were more frequently within the target range in the self-management group.[28] In addition to being a more effective monitoring strategy, the self-management group of patients in this trial also reported better quality-of-life measurements and increased satisfaction compared with the usual-care group.[28]

A Web-based monitoring system to facilitate patient self-monitoring is currently being tested. Patients use a Web browser to transfer their INR results and any other symptoms directly to their healthcare providers. Patients may be alerted electronically or by telephone regarding the next step in the warfarin adjustment, if needed.[29] Although this method is not suitable for all patients because it requires computers and Internet access, the additional convenience should improve the quality of

Figure. Overview of the ACME Model



ACME indicates Anticoagulation Management Event/Cost; AC, anticoagulation; TE, thromboembolism; ACS, anticoagulation services; PST/PSM, patient self-test/patient self-management; POC, point of care; MHV, mechanical heart valve; AF, atrial fibrillation; INR, international normalized ratio.

anticoagulation management and stroke prevention.

Estimating the Local Costs and Health Impacts of Anticoagulation Management

As shown in the MAST study, the value of different approaches to anticoagulation management depends on local resources and constraints. A tool developed to help local providers assess the costs and outcomes of various methods of anticoagulation management is the Anticoagulation Management Event/Cost (ACME) model (**Figure**).[30] ACME is a series of linked spreadsheets that allow the user to choose among 4 approaches to anticoagulation: no treatment, usual physician management, anticoagulation service, or patient self-testing/self-management. Based on projections of event rates derived from large cohort studies and costs derived from Medicare and published literature, the model estimates the utilization costs (management, testing, and medication), and the costs of stroke or bleeding events. The user enters the resource costs and the resulting distribution of INR values for patients for each strategy. The ACME model displays the costs associated with no treatment versus the costs associated with anticoagulation within the target range. The results show the benefits of avoiding low INR values and the trade-off between increased costs of anticoagulation management compared with the decreased lifetime costs associated with reducing the number of strokes.[30]

The strategies for anticoagulation management need to be tailored to the patients, the physicians or care providers, and the resources available locally. Ultimately the goal is to increase the proportion of time that patients are within the therapeutic range of

anticoagulation at a cost that is within the means of the local healthcare system.

The Future of AF and Stroke Prevention

By the year 2050, the number of adults with AF may be as high as 5.6 million, and 50% of them will be >80 years.[31] Thus there will be an increasing proportion of AF patients at risk for stroke. New alternatives to anticoagulants are needed to improve stroke prevention. Thrombin inhibitors, which do not require monitoring, currently are being tested in clinical trials to determine whether these agents are as efficacious as warfarin.[32] These therapies may be costly. They may be a good value, however, if they reduce management costs or if they reduce event costs by making high-quality therapy more reliable or by increasing the number of patients willing to receive the most effective treatment.

Conclusions

The increased risk of stroke in patients with AF requires risk assessment and consideration of patient preferences to guide decisions regarding appropriate antithrombotic therapy. For patients at high risk for AF, anticoagulation with warfarin is cost-effective in the long term, but it must be adjusted appropriately to keep the INRs in the therapeutic range. Although new alternatives to antithrombotic therapies may be available soon, the choices of available therapies and the approaches to management depend on local constraints and resources.

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