A Pharmacoeconomic Perspective on Stroke Prevention in Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is predictive of higher costs for stroke care, in part due to the influence of AF on stroke severity. Costs associated with severe strokes, which are more likely in patients with AF, are about twice those of mild strokes. Thus, adequately weighing the costs associated with stroke care is important when making prevention and treatment recommendations for patients diagnosed with AF. Costs associated with AF are estimated at $6.65 billion annually, which breaks down to 44% for hospitalizations, 29% for the incremental inpatient costs of AF as a comorbid diagnosis, 23% for outpatient treatment of AF, and 4% for medications. A diagnosis of AF should be followed by careful consideration of the treatment plan. Clinicians who tend to underuse warfarin should consider whether the patient has valid contraindications to warfarin or if the risk of stroke would be unacceptably high using the alternative—low-dose aspirin. Optimal use of anticoagulation in patients with AF is projected to result in substantial savings in direct costs. Optimization of anticoagulation therapy in only half of the suboptimally anticoagulated patients with AF would save approximately $1.3 billion annually. New and emerging oral alternatives to warfarin promise to combine the advantages of oral dosing and effective anticoagulation with improvements in safety, leading to reduced monitoring and dose adjustment. As these agents become available, treatment decisions will likely incorporate economic considerations, such as the costs of medication, patient monitoring, and treatment of bleeding events.

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For author information and disclosures, see end of text.

Although several risk factors for stroke are responsive to preventative measures, and overall risk of stroke can be significantly lowered by controlling factors like smoking, body weight, blood pressure, and blood glucose, stroke continues to be the third-leading cause of death in the United States.[1] The burden of stroke, from the perspective of life-years lost, diminished quality of life, and direct and indirect medical costs, is quite large. The direct and indirect costs of stroke care are estimated to be $73.7 billion (2010 US dollars), and the mean lifetime cost of ischemic stroke per patient is estimated at $140,048 (which includes inpatient care, rehabilitation, and any follow-up care needed to cope with lasting deficits). Race and economic status also play a significant role in the economics of stroke care. According to 1 study, socioeconomic status may underlie 39% of the excess risk of stroke reported in African Americans.[2] African Americans are also estimated to have the highest per capita cost for stroke care ($25,782), followed by Hispanics ($17,201) and non-Hispanic whites ($15,597).[1] Costs must be considered when making recommendations for stroke prevention and treatment in patients with AF. Comorbidities like AF and ischemic heart disease predict higher costs for stroke care. Furthermore, the costs of severe strokes are typically twice those of mild strokes. Thus, the costs of stroke care versus stroke risk reduction should be understood and considered throughout the course of AF management.

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Anticoagulation Therapy Is Underused in Patients With AF Who Are at Risk of Stroke

There is a consistent and systematic underuse of anticoagulation despite evidence supporting its use for stroke prevention in patients with AF.[3] Randomized trials have demonstrated that a relatively low intensity of anticoagulant therapy can largely eliminate the risk of stroke attributable to AF. **Figure 1** illustrates the risk reduction achieved using monitored warfarin treatment in patients with AF.[4]

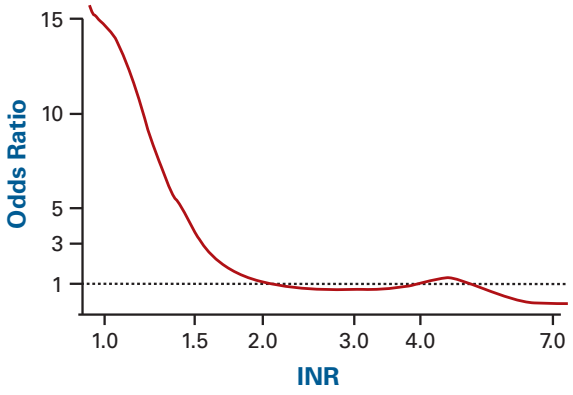
The reasons for underuse of anticoagulation are still emerging, but in many cases there is an underlying concern that the benefits of prescribing antithrombotic therapy shown in clinical trials may not translate into everyday practice, namely that the risk of hemorrhage associated with anticoagulants may be higher in certain patient populations, particularly the elderly. Many randomized trials exclude the majority of potential participants, more than 90% in

some cases, because of advanced age or relative contraindications to anticoagulation. Thus, the efficacy of anticoagulation is often demonstrated under ideal circumstances (ie, patients enrolled in the 5 studies examined in a landmark meta-analysis were at low risk of bleeding and the intensity of their anticoagulation was carefully regulated, which is frequently not the case in patients with AF).[5] For many other patients, anticoagulation therapy is used inappropriately. As shown in **Table 1**, a survey of hospital pharmacy representatives reveals some of the reasons for inappropriate use of specific anticoagulant agents.[6] Inappropriate dosing (53.7%) and monitoring (36.6%) were especially important factors in relation to warfarin use, while 50% of respondents indicated that direct thrombin inhibitors were used for inappropriate indications.

Overall, several studies report that typical implementation of anticoagulation therapy is approximately 60% in patients with AF. In 1 study, underuse of antithrombotic therapy in patients with nonvalvular AF was specifically associated with advanced age, female gender, and rural residency.[7] Compared with younger patients, the odds of receiving antithrombotic therapy were 1.7 times lower (95% confidence interval [CI], 1.2-2.5) for patients older than 75 years of age (P <.01). For females, the odds of receiving antithrombotic therapy were 1.5 times lower (95% CI, 1.0-2.1) than that in male patients (P = .05), and patients discharged from a rural healthcare setting were 1.7 times less likely (95% CI, 1.2-2.5) to receive anticoagulation than patients discharged from urban hospitals (P <.05). In 195 ideal anticoagulation candidates (ie, those who had nonvalvular AF, no contraindication to anticoagulation, and ≥1 stroke risk factor), 46% received warfarin and 23% received aspirin, while 31% received no antithrombotic therapy. In 111 ideal anticoagulation candidates older than 75 years of age, only 41% received warfarin, while 22% used aspirin.

Many clinicians interpret the results of large clinical trials with caution when considering the individual needs and characteristics of their patients with AF. However, this approach often develops into an overall trend of systematic underuse of anticoagulation. To avoid this, clinicians must decide whether their patients who are not receiving anticoagulation truly have a strong contraindication to warfarin, because the alternatives are aspirin (which may not offer adequate protection against stroke) or no treatment (ie, no protection against stroke).

Figure 1. Odds Ratios for Stroke According to INR Value in Patients With Atrial Fibrillation[4]



Unadjusted odds ratios were calculated by dividing the estimated density of patients who had a stroke at a given international normalized ratio (INR) by the estimated density of control patients with the same INR. The resulting ratio was then divided by the ratio at an INR of 2.0.
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Real-World Compliance With Recommendations

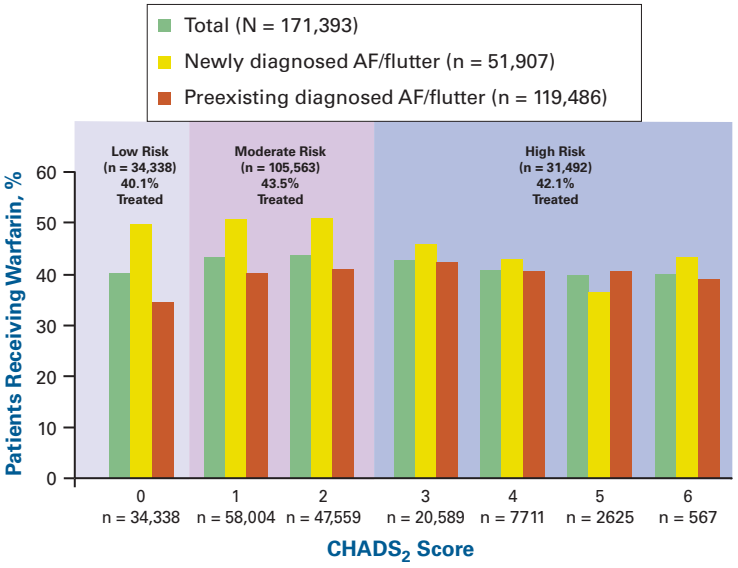
A recent examination of clinician compliance with anticoagulation guidelines in patients with AF found that warfarin was used in only 42.6% of the overall study population.[8] Compliance was slightly higher in patients with newly diagnosed AF or atrial flutter (49.6%) compared with those with

Table 1. Perceived Reasons for Inappropriate Anticoagulant Use[6]

Anticoagulant	Inappropriate Dose, %	Inappropriate Indication, %	Inadequate Monitoring, %	Failure to Comply With Guidelines, %
Unfractionated Heparin (n = 12)	41.7	41.7	8.3	8.3
Warfarin (n = 27)	53.7	2.4	36.6	7.3
Low Molecular Weight Heparin (n = 26)	75.0	22.2	0	2.8
Direct Thrombin Inhibitor (n = 6)	33.3	50.0	0	16.7
Factor Xa Inhibitor (n = 4)	71.4	28.6	0	0

Adapted from Vats V, Nutescu EA, Theobald JC, Wojtynek JE, Schumock GT. *Am J Health Syst Pharm.* 2007;64:1203-1208.

Figure 2. Underutilization of Anticoagulation in Patients With AF[8]



Warfarin use within 30 days of the first atrial fibrillation (AF) diagnosis assessed according to stroke risk, estimated by $CHADS_2$ (congestive heart failure, hypertension, age [older than 75 years], diabetes, stroke) score.
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preexisting AF or atrial flutter (39.5%). Anticoagulation use was less than 50% across all groupings of congestive heart failure, hypertension, age at least 75 years, diabetes mellitus, and stroke ($CHADS_2$) scores, specifically 42.1% of high-risk patients ($CHADS_2$ score 3-6), 43.5% of moderate-risk patients, and 40.1% of low-risk patients (Figure 2).

Despite guideline recommendations that anticoagulation should be provided in accordance with a patient's risk of stroke, some patients who would benefit most from anticoagulation, due to a high risk of stroke, did not receive treatment.[9] In contrast, recent results from the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) study show that low-risk patients derive a benefit from anticoagulation beyond that obtained from dual antiplatelet therapy.[10] As shown in Table 2, even with a $CHADS_2$ score equal to 1, there was a significant benefit with warfarin compared with aspirin plus clopidogrel. Given these results, the European Society of Cardiology now recommends an oral anticoagulant over aspirin, even in low-risk patients with AF and $CHADS_2$ equal to 1.[11]

Treatment of AF Represents a Significant Healthcare Burden

The use of healthcare resources and other costs attributable to AF has been examined in terms of hospital inpatient stays, physician office visits, emergency department visits, and hospital outpatient department visits.[12] Figure 3 shows the findings from case-control analyses conducted to estimate the annual incremental costs of AF. Regression models assessed the impact of AF on hospitalization costs (estimated in 2005 US dollars). The total annual

Table 2. ACTIVE-W: Stroke Rates After Treatment With Warfarin Versus Clopidogrel + Aspirin[10]

$CHADS_2$ Score	Stroke Rate W/Aspirin (/100 pt-y)[a]	Number (%) of Patients in ACTIVE-W[b]	Stroke Rate W/Clopidogrel + Aspirin (/100 pt-y)	Stroke Rate W/Warfarin (/100 pt-y)	Relative Risk (Clopidogrel + Aspirin Vs Warfarin)[c]
0	0.8	178 (3)	1.90	0.80	3.02
1	2.2	2436 (36)	1.21	0.40	3.11
2	4.5	2286 (34)	1.93	1.86	1.04
3	8.6	1107 (17)	2.79	1.72	1.62
4	10.9	490 (7)	6.73	3.25	2.07
5	12.3	183 (3)	11.65	2.69	7.01
6	13.7	26 (0.4)	0	0	N/A

AF indicates atrial fibrillation; ACTIVE-W, Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events; $CHADS_2$, congestive heart failure, hypertension, age (older than 75 years), diabetes, stroke; RR, relative risk.
[a]Annual rate of stroke among 2580 aspirin-treated patients with AF.
[b]Patients had evidence of peripheral vascular disease or coronary artery disease and were aged >55 years.
[c]Influence of baseline $CHADS_2$ score on RR (*P* trend = .29).
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costs for AF were estimated at $6.65 billion: $2.93 billion (44%) for hospitalizations (principal discharge diagnosis was AF), $1.95 billion (29%) for the incremental inpatient cost of AF as a comorbid diagnosis, $1.53 billion (23%) for outpatient treatment of AF, and $235 million (4%) for medications. Overall, the treatment of AF represents a significant healthcare burden, and the costs of treating AF in the inpatient setting outweigh the costs of treating AF in the office, emergency department, or hospital outpatient settings.

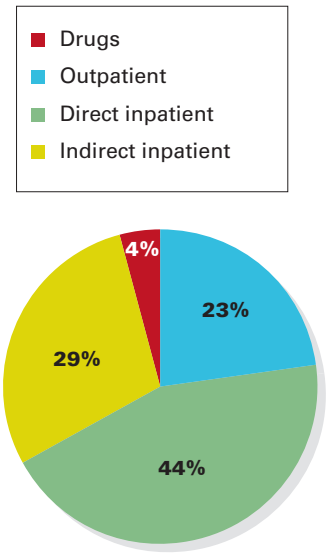
Cost Considerations in AF Symptom Control

Using a rate-control strategy for symptomatic treatment of AF has been shown to be more cost-effective than using a rhythm-control strategy in patients with AF. The analysis by Marshall et al[13] combined data from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study and unit cost estimates from various US databases in patients who were similar to those in the AFFIRM population. Patients in the rate-control group used fewer resources, including hospital days, pacemaker procedures, cardioversions, short-stay visits, and emergency department visits. The overall cost of rate-control therapy was less than that of rhythm control by a difference of $5077 per person. In addition to being more costly, rhythm control was less effective than rate control over a wide range of assumptions. For a case-base scenario, the probability that rhythm control was cost-effective relative to rate control was less than 0.01, even when analyzed at a value of $100,000 per life-year gained.

Optimal Use of Anticoagulation Can Reduce the Costs of AF Care

Beyond the anticipated benefits to patients in terms of mortality and quality of life, it has been projected that optimal use of anticoagulation in patients with AF would lead to substantial savings in direct costs.[14] This cost analysis is illustrated in Figure 4. The model estimated that 2.3 million patients in the United States have AF. An estimated 1.3 million of those patients are not receiving oral anticoagulants and about half of that group are assumed to be using aspirin. Moreover, about 70% of the patients who are using anticoagulation receive it in a routine medical care setting without special support, while only 30% of patients using anticoagulation therapy receive it in an anticoagulation clinic. As shown in Figure 4, during the first year of AF care, 58,392 strokes were estimated to occur in the patients not using anticoagulants, while 38,468 were estimated in the patients with AF who were receiving anticoagulation therapy.

Figure 3. Distribution of Inpatient and Selected Outpatient Costs Associated With AF[12]



The treatment of atrial fibrillation (AF) represents a significant cost burden in healthcare. A combined total of $6.65 billion (US dollars) was spent in 2005 for AF treatment in the inpatient, emergency department, and hospital outpatient settings.
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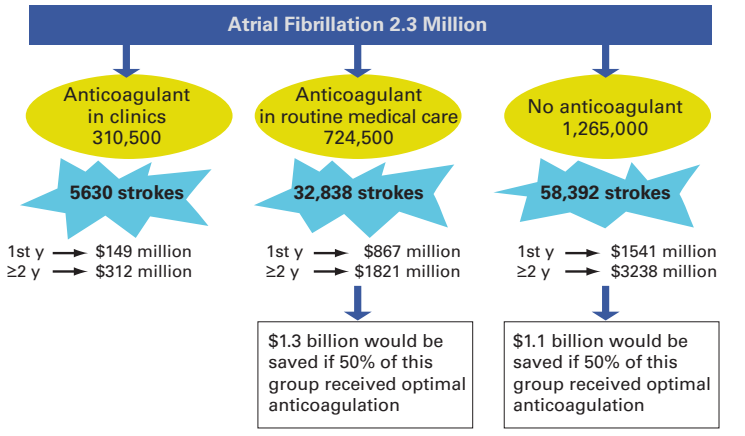
The total direct costs associated with these AF-related strokes are estimated at approximately $8 billion.[14] Many factors that follow a stroke must be taken into account for such an analysis. For instance, about 50% of stroke survivors can be anticipated to return home after discharge, 25% will require special skilled nursing care, and another 20% will go to rehabilitation centers; the remainder will require services from a skilled nursing facility. Among patients who return home, only about half of those have no need for further care (other than follow-up physician visits). The remainder of those who return home will need home healthcare (25%), day care (10%), or will go through a rehabilitation program (15%). The initial estimate of $8 billion for AF-related strokes includes $2.6 billion during the first year and another $5.4 billion in Medicare-covered costs thereafter. At the individual level, the total financial cost of a stroke is about $3435 per patient annually. The estimated cost savings of anticoagulation, projected at the individual patient level, are also illustrated in Figure 4. For patients using an anticoagulation clinic, the cost of a stroke was estimated at $1485, compared with $3710 for patients receiving anticoagulation as part of routine medi-

Figure 4. Improvements in Anticoagulant Utilization Could Yield Both Clinical and Economic Gains[14]



Projected costs for patients in the 3 main treatment groups reflect the varying stroke rates in those groups.
Adapted from Caro JJ. *Am J Manag Care.* 2004;10:S451-S461.

cal care. The estimate for patients not using anticoagulants was $3778. The surprisingly small cost difference between anticoagulation in routine medical care compared with no anticoagulation therapy stems from the costs associated with treating complications of anticoagulation therapy, like gastrointestinal bleeding.

However, these savings estimates do not consider the costs associated with a dedicated anticoagulation clinic capable of delivering such a level of stroke reduction. As shown in Figure 4, a second analysis from this study found that approximately $1.3 billion would be saved if only half of the patients receiving anticoagulation through routine medical care were given optimal anticoagulation therapy.[14] Much of this cost reduction would be anticipated to arise from decreases in the expenses associated with the treatment of warfarin-related bleeding, which can often entail surgery, intensive care unit stays, or blood transfusions. These savings should be weighed against the costs of maintaining an anticoagulation clinic.

Over the long term, an anticoagulation management clinic can be anticipated to cost less and provide greater efficacy compared with the costs of managing warfarin therapy in a routine-care setting. Community-based studies have reported significant variation in the effectiveness of anticoagulation depending on the management approach used. By some estimates, the average patient receiving warfarin maintains an international normalized ratio (INR) within the target therapeutic range for less than half of the time. Sullivan et al[15] compared estimated lifetime costs and health benefits of stroke prevention with warfarin managed through usual care versus anticoagulation management services with dedicated anticoagulation professionals (eg, a physician or pharmacist). Patients were elderly (mean age, 70 years) and had AF and high risk of stroke. This analysis found that using an anticoagulation management service improved effectiveness by 0.057 quality-adjusted life-year—a significant enhancement in the cost-effectiveness of warfarin therapy. Compared with routine care, an anticoagulation management service reduced costs by $2100 (2004 US dollars). This improvement supports the notion that it is preferable to use warfarin therapy within the context of an anticoagulation management service and that greater consideration toward therapies that do not require monitoring may be appropriate when anticoagulation management services are not accessible. Improved stroke prophylaxis in a rapidly growing population of older, high-risk patients is achievable through the addition of patient-monitoring technology strategies, like a formally organized anticoagulation monitoring program.

No Monitoring Costs Associated With New and Emerging Anticoagulant Agents

New classes of anticoagulant agents may soon serve as alternatives to warfarin. They offer oral dosing and good efficacy, coupled with the advantage of a lower bleeding risk, which eliminates much of the expense of monitoring, potentially reducing the total cost of anticoagulation therapy.[16] Apixaban, rivaroxaban, and edoxaban, factor Xa inhibitors, as well as dabigatran, a direct thrombin inhibitor, offer several important advantages over warfarin.[16-18] None of these agents require the close laboratory monitoring that is required with warfarin therapy. They also have more predictable pharmacodynamics than warfarin, which should simplify dosing.[17] These agents could emerge as alternatives to warfarin in patients with AF. Pharmacoeconomic considerations, in addition to efficacy and safety issues, need to be assessed when these new anticoagulants are evaluated for use in the management of AF.[16]

Conclusion

The high risk of stroke associated with AF leads to significantly higher morbidity and mortality in patients with AF and negatively impacts the quality of life for many patients in this population. There is a strong connection between advancing age and onset of AF; it is anticipated

that any increase in average life span will be accompanied by increases in the personal and financial impact of AF, particularly with regard to the risk of stroke and the long-term consequences for stroke survivors. Fortunately, using evidence-based antithrombotic therapy can greatly diminish the incidence of stroke in patients with AF. Making an individualized comparison between risks and benefits associated with antithrombotic therapy lies at the heart of every decision to use it and the choice of antithrombotic agent. The risk of stroke in patients with AF is easily estimated using the $CHADS_2$ scoring system. Evidence-based US guidelines currently recommend warfarin for patients who are determined to be at high or intermediate risk; however, the use of warfarin is complicated by a continuous need for laboratory monitoring due to the narrow therapeutic window and an association with bleeding events. Aspirin, an alternative agent, is less effective than warfarin for primary prevention of stroke in patients with AF, and it is currently only recommended in the United States for patients at low or intermediate risk of stroke. The European Society for Cardiology (ESC) now recommends using a newly developed 9-point scoring system called the CHA_2DS_2VASc score to estimate the risk of stroke in AF patients.[11,19] The CHA_2DS_2VASc system stratifies the contribution of age to stroke risk by assigning 2 points (A_2) to patients aged at least 75 years, but only 1 point (A) to patients aged 65 to 74 years. It includes the contributions of vascular disease (V) and sex category (Sc) to stroke risk as well, assigning 1 point for each. The CHA_2DS_2VASc score also assigns 2 points for a previous stroke (S_2) and 1 point each for congestive heart failure (C), hypertension (H), or diabetes (D).[19] This scoring system takes the influence of clinically relevant nonmajor risk factors into account when estimating individual risk of stroke. Using the CHA_2DS_2VASc score, the ESC now states that warfarin is the preferred therapy for patients with AF who have a risk score as low as 1 point.[11]

Warfarin is currently underused, and opportunities to achieve additional reduction in the total burden of stroke in the United States are lost in many patients with AF. There are a number of reasons for underuse of warfarin, most having to do with the need for INR monitoring and associated risks of major bleeding events or inadequate anticoagulation. New and emerging antithrombotic agents that combine antithrombotic efficacy with improved safety and less stringent monitoring requirements are likely to shift treatment decisions toward the costs of treatment. As more patients are diagnosed with AF, subsequent treatment decisions will focus more on the anticipated course of care for an entire episode, looking not only to the silo of drug and monitoring costs, but also to the billions of dollars that are estimated to go into the treatment of stroke victims.

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