Changing the Guard in Long-Term Anticoagulation: Clinical and Economic Implications

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The topic of anticoagulant prescription in patients with nonvalvular atrial fibrillation, for the primary and secondary prevention of stroke, provides a forum for discussion of current challenges in anticoagulation management and ways in which the introduction of ximelagatran will provide an opportunity to overcome many of them. Anticoagulation with warfarin has been shown to reduce stroke rates by 68%, providing significant net monetary savings. However, physician fear of hemorrhagic side effects, the need for regular INR monitoring, food and drug interactions, and patient noncompliance have all played a part in either suboptimal utilization or complete avoidance of anticoagulant therapy, even in patients at high risk for stroke. Ximelagatran, a new oral direct thrombin inhibitor, circumvents most of these problems and provides a more physician- and patient-friendly method of stroke prophylaxis. With the utilization of this new anticoagulation method, the incidence of stroke in high risk groups, and the corresponding quality-of-life and economic impact, can potentially be greatly reduced.
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Thrombosis plays a key role in the clinical manifestation of a number of common medical conditions including stroke, deep venous thrombosis (DVT), pulmonary embolism (PE), stroke prevention in atrial fibrillation (AF), and acute coronary syndromes (ACS). Long-term oral anticoagulation is pivotal to the treatment of these conditions, particularly DVT and PE, with warfarin being the only pharmacologic option currently available in the United States. With the anticipated release of the oral direct thrombin inhibitor ximelagatran,

Table 1
Advantages of Ximelagatran in the Clinical Setting

- No dose titration needed
- Rapid clinical effect
- No need to measure serial INRs during entire course of therapy, reducing costly clinic resource utilization
- One dose fits all
- Metabolism not affected by other medications
- Not impacted by dietary vitamin K

an anticoagulant will be available that overcomes many of the shortcomings of warfarin therapy (Table 1), hopefully spurring increased compliance and a resultant increase in safety and efficacy among affected patients. The topic of anticoagulant prescription in patients with nonvalvular atrial fibrillation (NVAF), for the primary and secondary prevention of stroke, provides a forum for discussion of current challenges in anticoagulation management and ways in which the introduction of ximelagatran will provide an opportunity to overcome many of them.

Atrial Fibrillation, Stroke, and Warfarin Therapy

AF is the most common chronic arrhythmia associated with an adverse prognosis. Approximately 2.2 million Americans suffer from chronic or recurrent forms of AF, affecting 6% of all Americans over the age of 65 years.[1] It is estimated that by the year 2050, 5.6 million Americans will suffer from AF.[2] AF is associated with a 1.5- to 1.9-fold increase in all-cause mortality risk, even after adjusting for other, preexisting cardiovascular conditions.[3] AF places patients at high risk for embolization of peripheral vascular beds, the most critical being the cerebrovascular circulation.

AF is also an independent risk factor for stroke, resulting in a 3- to 5-fold increase in risk.[4] The attributable risk of stroke associated with AF increases with age from 6.7% for those 50-59 years old to 36% for those over 80 years of age.[4] In all age groups, 10%-15% of strokes are related to AF and the rate rises to 25% in patients over 80 years old. Overall, elderly patients experience stroke at a rate of 5% in the general population.[4] In absolute numbers, AF is responsible for 75,000 strokes or transient ischemic attacks per year in the United States.[1,4]

Unfortunately, strokes that occur in association with AF have worse outcomes, with rates of death or significant neurological disability as high as 71%.[7] Patients with stroke require hospitalization at rates estimated anywhere from 54% to 71%. One-year mortality rates in stroke patients are as high as 31%, with a subsequent annual mortality of 9.1% over the next 5 years.[5,6] One-fifth of stroke survivors never improve enough to return home and 33% return to a physically restricted life at home, with less than half regaining full physical function.[7]

The socio-economic implications of AF-related strokes are huge. It is estimated that the acute care cost of a moderate/severe stroke, minor stroke, and transient ischemic attack are $34,200, $7800, and $5300, respectively. The annual cost of care per stroke patient (based on 1985 estimates) with moderate to severe residua and minor residua were $18,000 and $2,000, respectively[8] The economic burden of stroke was estimated by the American Heart Association to be $51 billion in 1999.[9] Costs associated with the effects of stroke on lifestyle, including loss of employment, are more difficult to quantify and were not included in these calculations. An optimal treatment for AF should result in both reductions in stroke event rates and net cost savings. Anticoagulation with warfarin has been shown to reduce stroke rates by 68%, providing significant net monetary savings.[10]

Table 2 illustrates the annual stroke rate reduction in patients with AF, stratified by age group, with either no stroke risk factors or 1 or more risk factor, and changes in these rates with warfarin-therapy anticoagulation.[11]

Table 2
Annual Stroke Rates in Patients With Atrial Fibrillation: Age and Risk Factors (RFs)

		Event Rate, % (95% CI)	
Age Category	**Risk Category**	**Placebo**	**Warfarin**
< 65 years	No RFs	1.0 (0.3-3.1)	1.0 (0.3-3.0)
	1 or more RFs	4.9 (3.0-8.1)	1.7 (0.8-3.9)
65-75 years	No RFs	4.3 (2.7-7.1)	1.1 (0.4-2.8)
	1 or more RFs	5.7 (3.9-8.3)	1.7 (0.9-3.4)
> 75 years	No RFs	3.5 (1.6-7.7)	1.7 (0.5-5.2)
	1 or more RFs	8.1 (4.7-13.9)	1.2 (0.3-5.0)

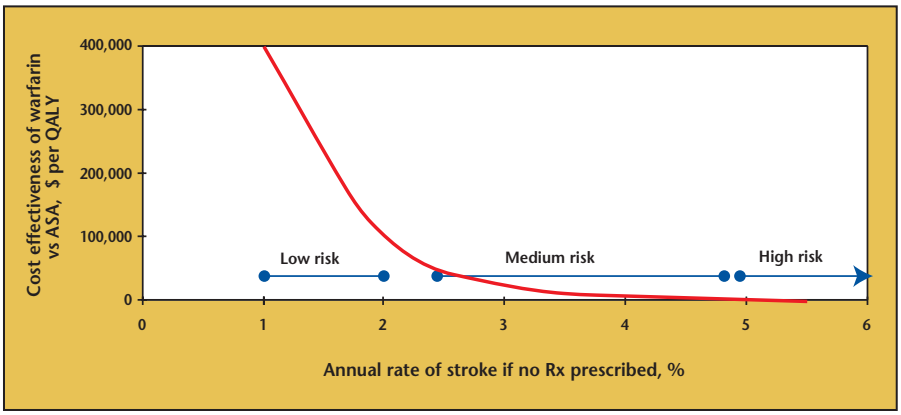


Figure 1. *Cost-effectiveness analysis of anticoagulation utilizing warfarin versus aspirin therapy in patients with nonvalvular atrial fibrillation. ASA, aspirin; QALY, quality-adjusted life years. Reproduced with permission from Gage et al.*[8]

A cost-benefit analysis by Gage and associates[8] compared the costs of warfarin prophylaxis therapy (including protime surveillance) in 1994 dollars to the costs of complications (death, stroke, transient ischemic attacks, and hemorrhage) over 10 years, in a 65-year-old patient with NVAF. In high-risk patients, treatment with warfarin resulted in a 0.5 quality adjusted life year advantage with a net savings of $2800. In medium-risk patients with NVAF, a 0.37 quality-adjusted life year advantage was achieved, with a net savings of $500. Effective treatment with anticoagulation results in both a quality-of-life year advantage and a cost savings (Figure 1).

Defining Levels of Risk

Patients with NVAF can be categorized by their relative risk of developing stroke. Risk factors for stroke include age, prior CVA, hypertension, diabetes, congestive heart failure, and left ventricular dysfunction. There are minor variations among the accepted classification schemes (Atrial Fibrillation Investigators,[12] American College of Chest Physicians,[13] and Stroke Prevention in Atrial Fibrillation Investigators[14]) that define stroke risk. Table 3 outlines the differing criteria.

Regardless of the risk classification scheme used, the majority of patients with NVAF have at least 1 stroke-risk factor and should be treated with anticoagulation therapy, unless a contraindication exists.[15] See Figure 2.

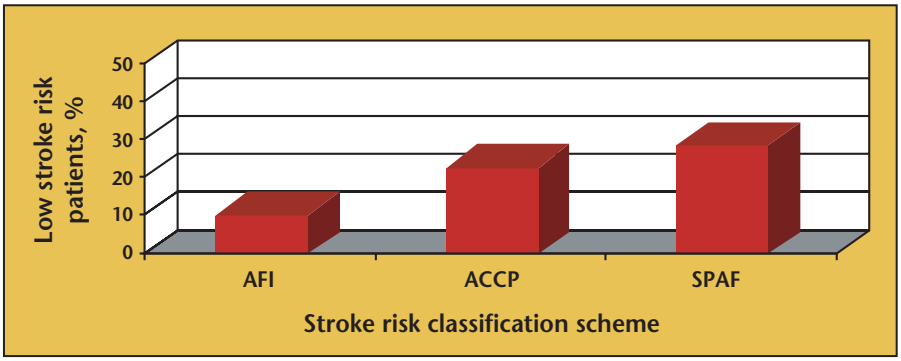
Resistance to Therapy

With the aging of the American population, an increased incidence and prevalence of AF is expected. Success in primary and secondary stroke prevention will have serious implications in terms of life expectancy, quality of life, and cost to society. However, despite widespread access to tools enabling physicians to easily categorize and identify patients at higher risk, the majority of eligible patients for anticoagulation are not receiving therapy. In addition, many of those who are treated are falling outside the narrow therapeutic international normalized ratio (INR) window for warfarin, placing them at increased risk for hemorrhage or thrombosis.[16] Unlike trends showing greater utilization over time of statin therapy in patients with coronary artery disease or angiotensin-con-

Table 3
Criteria for Classification as a Low Stroke Risk

- **Atrial Fibrillation Investigators (AFI):** None of the following: age ≥ 65 years; prior CVA or history of hypertension, diabetes, or left ventricular dysfunction
- **American College of Chest Physicians (ACCP):** None of the following: age > 75 years; prior CVA, hypertension, or heart failure
- **Stroke Prevention in Atrial Fibrillation (SPAF) Investigators :** None of the following: women > 75 years; prior CVA, systolic blood pressure > 160 mm Hg or recent heart failure or fractional shortening < 25% on echocardiography

Figure 2. *Proportion of patients with atrial fibrillation classified as at "low risk" for stroke. ACCP, American College of Chest Physicians; AFI, Atrial Fibrillation Investigators; SPAF, Stroke Prevention in Atrial Fibrillation Investigators. Reproduced with permission from Go et al.*[15]



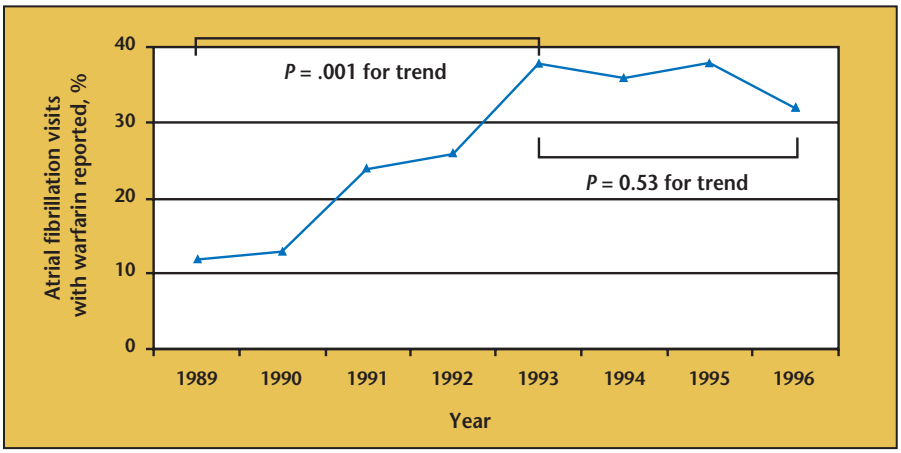


Figure 3. *Reported percentage of atrial fibrillation patients receiving warfarin therapy, excluding patients with contraindications to warfarin, apparent low risk for stroke, and visits to physicians other than cardiologists and primary care physicians. Reproduced with permission from Stafford and Singer.*[17]

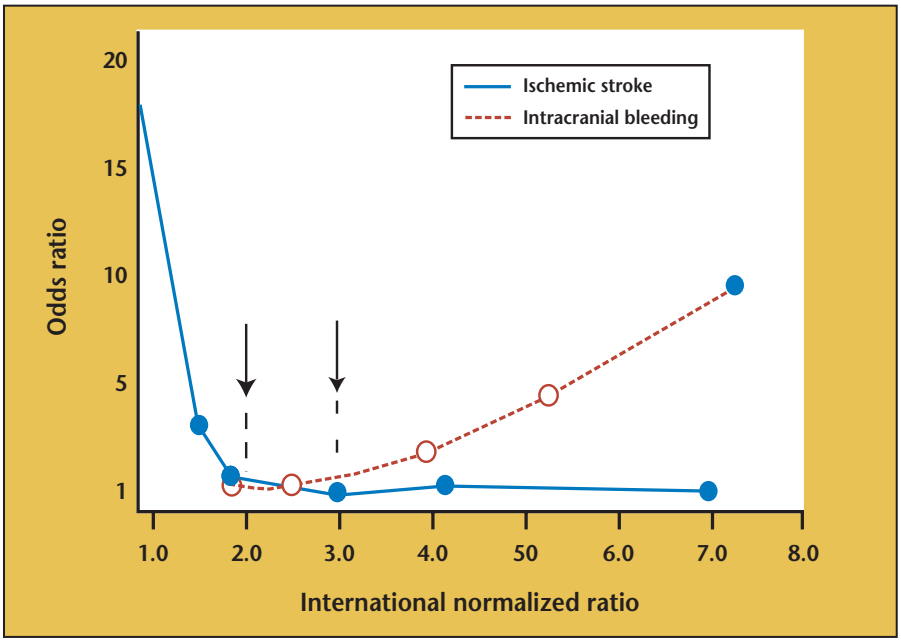


Figure 4. *Risk of stroke and intracranial bleeding, based on international normalized ratio. Arrows indicate boundaries of therapeutic window for warfarin. Data from Hylek et al.*[18,19]

verting enzyme inhibitors and ß-blockers in patients with heart failure, use of anticoagulation in patients with AF has not increased significantly (Figure 3). The majority of patients who are eligible for anticoagulation remain untreated.[17]

There are a variety of reasons to explain the resistance to treating eligible patients. From the practitioner's perspective, there may be a lack of appreciation for the risk:benefit ratio of anticoagulation in patients with NVAF. Primary care physicians may be unprepared to distinguish a high-risk patient subset from a low-risk patient subset and may have the misconception that older patients are at too high a risk for hemorrhagic complications. From a patient perspective, warfarin is commonly associated with rat poison and frequent protime monitoring often represents too much of an inconvenience. Rates of patient discontinuation, both in clinical trials and practice, are well over 20%.[16] A variety of warfarin-use predictors have been evaluated and illustrate the issues that must be addressed in order to effectively treat patients with AF (Table 4). Beyond a history of stroke, the presence of other stroke-risk factors including hypertension, heart failure, atherosclerosis, valvular disease, and diabetes have an impact on utilization of warfarin. In addition, advanced age (> 80 years) has been associated with decreased use of warfarin, though this population is at a particularly high risk of thrombotic complications and would benefit most from anticoagulation. Care from a family physician or gen-

Table 4
Predictors of Warfarin Use

- **Effect**
  - **Increased Use**
    - CVA
    - Patients seen by cardiologist or internist
  - **Decreased Use**
    - Age > 80 years
    - Residence in the southern United States
    - Care by family physician or general practitioner
    - Residence in rural area
- **No Effect**
  - Sex
  - Race
  - Payment source
  - Hypertension
  - Congestive heart failure
  - Atherosclerosis
  - Valvular disease
  - Diabetes

Data from Stafford and Singer[17] and Gage et al. *Stroke* 2000;31:822-827.

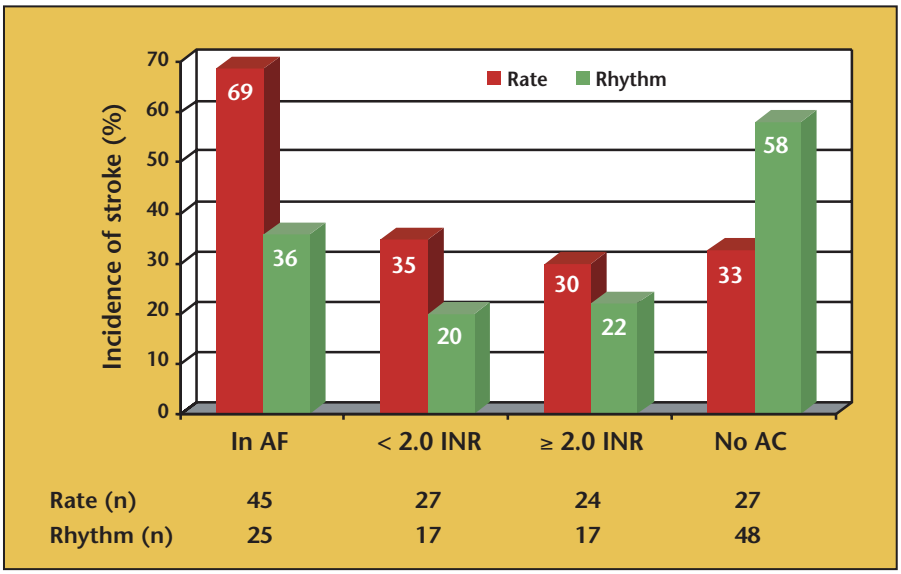


Figure 5. *Incidence of stroke in the rate control versus rhythm management arms of the AFFIRM study. AC, anticoagulation; AF, atrial fibrillation, INR, international normalized ratio. Data from Wyse et al.*[20]

eral practitioner has also been associated with decreased utilization of anticoagulation. It is clear that one challenge we face is to educate clinicians, particularly primary care providers, so that they better identify the higher risk patient and translate this knowledge into greater utilization of anticoagulation therapy.

To minimize stroke and hemorrhage risk, warfarin must be maintained within a narrow therapeutic window (Figure 4). INR levels below 2.0 are associated with higher stroke rates and levels above 3.0 with increasing rates of intracranial hemorrhage. Compounding the problem of this narrow therapeutic window is the high intrapatient variability of the anticoagulant effect of warfarin.[18,19] This variability can be partially explained by the high potential for drug and food interactions with warfarin, variability in the accuracy of protime measures, and lack of patient compliance. Over the course of therapy, reports of patients prescribed warfarin have shown that 26%-32% of INR measures fell below the target INR range, placing those patients at an increased risk of thrombotic complications. Measures were above the target INR in 9%-19% of patients, exposing them to a risk of hemorrhagic complications.[16] INRs fell within the desired 2.0-3.0 range in only 50%-55% of those patients measured. Data from the AFFIRM trial, which compared the benefits of rate and rhythm control in patients with NVAF, revealed that 65% of patients in the rhythm control group and 54% within the rate control group, who had strokes during the study period, had either stopped taking warfarin or were not maintaining therapeutic INR levels. Total strokes in the rhythm management arm and the rate control arm occurred in 78% and 54% of patients, respectively (Figure 5).[20]

The contemporary process for treating and monitoring patients on warfarin anticoagulation in clinics around the country is labor and resource intensive. Lifelong therapy with warfarin mandates close and regular INR monitoring, which is generally performed in an office setting. Each instance of INR monitoring requires a series of labor-intensive actions and reimbursement from most payers covers only a fraction of the real cost of the process (Figure 6). This process repeats at a frequency of every 3 to 6 weeks and represents an accident waiting to happen. A breach in protocol at any stage of the cycle can have an adverse effect on anticoagulation management, which is necessary to mitigate the risk of an adverse clinical event. The

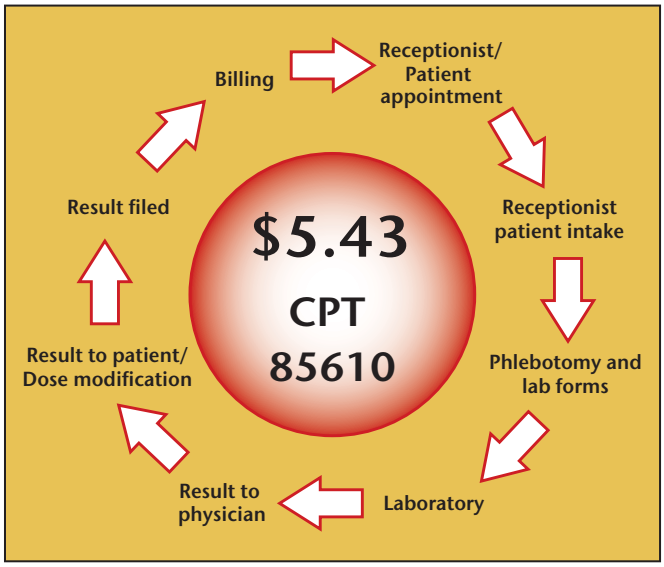


Figure 6. *Process of in-office warfarin-therapy monitoring versus reimbursable Medicare expense. $5.43 represents the amount paid to physicians per in-office protime evaluation, based on the Medicare billing code, CPT 85610.*

medical/legal consequences of anticoagulation-related, serious, adverse clinical events are significant and are a frequent source of litigation.

Ximelagatran as an Alternative to Warfarin Therapy

The introduction of the oral direct thrombin inhibitor, ximelagatran, will simplify the anticoagulation process, which should yield an increase in the number of eligible patients with NVAF receiving anticoagulation treatment. Differences, including prompt onset and offset of the anticoagulant effect, a wider therapeutic window, predictable pharmacokinetics, low potential for drug and food interactions (metabolism independent of the Cytochrome P450 pathway), and the lack of need for dosing adjustments or coagulation monitoring, make ximelagatran much more physician- and patient-friendly than warfarin. These factors should help physicians and patients to overcome resistance to effective anticoagulation treatment, particularly in the elderly patient population, where resistance to warfarin therapy and the benefits of anticoagulation are greatest. Liver-function-test abnormalities observed within the first 6 months of ximelagatran therapy will mandate close periodic monitoring, similar to recommendations for surveillance that are standard in the utilization of statin therapy.

It is expected that physician acceptance of ximelagatran as an effective treatment for stroke prophylaxis in patients with NVAF will be widespread. With "one dose fitting most" and no need for frequent INR surveillance, ximelagatran is anticipated to become the anticoagulant of choice for eligible patients. Many, if not most, patients eligible for anticoagulation, but not receiving warfarin, will be treated with ximelagatran. Hence, an overall reduction

Table 5
Stroke Cost Variables

Input Variable	Base Case
Stroke parameters	
Rate of stroke without therapy, % per patient-year*	
High risk	5.3
Medium risk	3.6
Low risk	1.6
Proportion of ischemic strokes, %	
Fatal	24
Moderate to severe†	19
Minor†	32
Without permanent residua†	25
Stroke risk reduction with prophylaxis, %	
Warfarin	68
Aspirin	22
Hemorrhage parameters	
Rate of major hemorrhage, % per patient-year	
Warfarin	1.4
Aspirin	0.9
No therapy	0.8
Proportion of major hemorrhages, %	
Fatal	20
Moderate to severe intracranial hemorrhage†	3
Mild intracranial hemorrhage†	8
Without permanent residua†	69
Mortality parameters	
Demographics used to estimate age/sex-specific mortality rate	
Age at start of 10-year interval	65
Sex, % male	50
Relative risk of non-stroke, nonhemorrhage death	
Atrial fibrillation	1.3
Atrial fibrillation and a prior stroke	2.3
Cost parameters	
Cost of eliciting each patient's preferences, US $	50
Annual cost of prophylaxis, US $	
Warfarin (including monitoring)	800
Aspirin	10
Acute (one time) cost of neurological event, US $	
Moderate to severe	34,200
Minor	7800
Transient ischemic attack	5300
Chronic (annual) cost of a neurological event, US $	
Moderate to severe residua	18,000
Minor residua	2000

Adapted with permission from Gage et al.[8]
All US $ amounts based on 1994 value.
* Rate of stroke increased by a factor of 1.4 per decade of life (compounded monthly). Rates shown are for patients aged 65 years.
†These events are not fatal.

Table 6
Estimated Global Costs of Stroke

- 24% of NVAF patients are high risk and eligible for anticoagulation but not treated (480,000 pts)
- 5.3% annual stroke rate = 25,440 strokes/yr
  - 24% are fatal (6105 pts/yr)
  - 19% with moderate to severe disability (4833 pts/yr) with 5-year care costs = $124,200/pt
  - 32% with minor disability (8140 pts/yr) with 5-year care costs of $17,800/pt
  - 25% with no residual disability (6360 pts/yr) with 5-year care costs of $5300/pt
- Costs of care per year for high-risk patients with AF eligible for but not receiving AC = $735,000,000 per year in 1985 dollars
- **Estimated cost in 2004 dollars = $2,205,000,000**

in AF-related stroke is expected. This reduction of stroke incidence will reduce both mortality associated with NVAF and the incidence of possible lifelong, debilitating effects associated with nonfatal stroke. Based on these reductions, global cost savings can be anticipated.

Gage and associates,[8] taking into account the mortality and morbidity rates of stroke, the cost of acute-care hospitalization, and chronic supportive care, calculated the costs associated with strokes of varying severity. See Table 5.

These economic data, along with the incidence of stroke in untreated NVAF patients and an estimate of the number of eligible patients not receiving anticoagulation, allow the calculation of overall cost of avoidable strokes. Using a very conservative figure for the eligible, untreated portion of the NVAF population at 24% (estimate range of 24% to 60%), the estimated cost of stroke is over $2 billion dollars. Using the 60% untreated estimate, the avoidable cost of strokes increases to over $5 billion dollars in the United States alone (Table 6).

These cost savings will prove very attractive to both governmental and private payer groups, who, for the most part, bear the economic burden of stroke. These agencies will benefit by treating those patients who are eligible for anticoagulation but are not receiving warfarin at the present time. Extra savings could also be anticipated through the treatment of patients in whom it is difficult to consistently maintain a therapeutic INR.

Conclusion

The development of an oral direct thrombin inhibitor, ximelagatran, provides clinicians with an effective and more efficient tool for preventing stroke in patients with NVAF. The current warfarin-based anticoagulation system is onerous and inefficient, leading to physician resistance and resultant underutilization. Lack of therapeutic anticoagulation in higher risk NVAF patients leads to unacceptably high stroke rates. Ximelagatran will allow us to deal more effectively with difficult-to-treat patients and hopefully extend the reach of effective anticoagulation to those who have declined warfarin treatment in the past. Perhaps the greatest challenge will be to educate our colleagues in identifying those patients with stroke risk factors, including age, coronary artery disease, hypertension, diabetes, heart failure, and prior stroke, in order to ensure use of effective anticoagulation therapy. ■

Main Points

- The economic burden of stroke was estimated by the American Heart Association to be $51 billion in 1999.
- Warfarin, which is currently the only pharmacologic anticoagulation therapy available in the United States, significantly reduces the rate of stroke across all age groups, in patients with 1 or more risk factors.
- Physician fear of hemorrhagic side effects, the need for regular international normalized ratio monitoring, food and drug interactions, and patient noncompliance have all played a part in either suboptimal utilization or complete avoidance of anticoagulant therapy, even in patients at high risk for stroke.
- The introduction of a new oral direct thrombin inhibitor, ximelagatran, will simplify the anticoagulation process. This should yield an increase in the number of eligible patients with nonvalvular atrial fibrillation receiving anticoagulation treatment, thereby reducing the overall economic burden of both stroke treatment and the intensive patient monitoring required with warfarin therapy.

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