Cost-effectiveness of Therapies for Patients With Nonvalvular Atrial Fibrillation

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Background: The most appropriate treatment(s) for patients with atrial fibrillation remains uncertain.

Objective: To examine the cost-effectiveness of antithrombotic and antiarrhythmic treatment strategies for atrial fibrillation.

Methods: We performed decision and cost-effectiveness analyses using a Markov state transition model. We gathered data from the English-language literature using MEDLINE searches and bibliographies from selected articles. We obtained financial data from nationwide physician-fee references, a medical center’s cost accounting system, and one of New England’s larger managed care organizations. We examined strategies that included combinations of cardioversion, antiarrhythmic therapy with quinidine, sotalol hydrochloride, or amiodarone, and anticoagulant or antiplatelet therapy.

Results: For a 65-year-old man with nonvalvular atrial fibrillation, any intervention results in a significant gain in quality-adjusted life years (QALYs) compared with no specific therapy. Use of aspirin results in the largest incremental gain (1.2 QALYs). Cardioversion followed by the use of amiodarone and warfarin together is the most effective strategy, yielding a gain of 2.3 QALYs compared with no specific therapy. The marginal cost-effectiveness ratios of cardioversion followed by aspirin, with or without amiodarone, are $33,800 per QALY and $10,800 per QALY, respectively. Cardioversion followed by amiodarone and warfarin has a marginal cost-effectiveness ratio of $92,400 per QALY compared with amiodarone and aspirin. Strategies that include cardioversion followed by either quinidine or sotalol are both more expensive and less effective than competing strategies.

Conclusions: Cardioversion of patients with nonvalvular atrial fibrillation followed by the use of aspirin alone or with amiodarone has a reasonable marginal cost-effectiveness ratio. While cardioversion followed by the use of amiodarone and warfarin results in the greatest gain in quality-adjusted life expectancy, it is expensive (ie, has a high marginal cost-effectiveness ratio) compared with aspirin and amiodarone. Finally, for patients who are bothered little by symptoms of atrial fibrillation, cardioversion followed by either aspirin or warfarin without subsequent antiarrhythmic therapy is the treatment of choice.

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Over the last decade the management of patients with atrial fibrillation has become a subject of increasing interest. New antiarrhythmic agents have become available,1-8 large clinical trials9-13 have demonstrated the efficacy of antithrombotic therapy, and there has been increasing awareness that agents used to maintain sinus rhythm may have serious or fatal adverse effects.14-16

So powerful is the uncertainty as to the appropriate therapy in a patient with this arrhythmia that the National Institutes of Health (Bethesda, Md) has initiated a large multicenter clinical trial17 in which 5300 patients will be randomized either to remain in atrial fibrillation (with rate control and protection against thromboembolism) or will be restored to and maintained in sinus rhythm. Although results of this trial will not be available until the 21st century, clinicians need guidelines for managing their patients now.

Decision analysis18 offers an option by which such trade-offs can be approached, by estimating the incremental costs of various therapeutic options and comparing them with the efficacy of therapy. The latter is often expressed as life expectancy, adjusted for adverse events related to disease or therapy (ie, for quality of life).19 In this era of cost-containment such analyses provide guidelines about appropriate and cost-effective therapies.20

Physicians confronted with a patient with atrial fibrillation face several options: whether to administer cardioversion, and if so which (if any) drug to use to maintain
METHODS

BASIC MODEL

We constructed a Markov state transition model using a standard computer program (Decision Maker)\textsuperscript{26,27} to analyze decision trees and to perform sensitivity analyses. We evaluated 19 strategies that include combinations of cardioversion; antiarrhythmic therapy with quinidine (a prototypical type 1A agent), sotalol (a class III antiarrhythmic with β-blocking properties), or amiodarone (an antiarrhythmic agent with complex properties, including class III, β-blocking, and calcium channel blocking effects); and antiarrhythmic or antplatelet therapy. These strategies consist of: (1) allowing atrial fibrillation to persist with or without antithrombotic therapy; (2) cardioversion followed by 4 antithrombotic strategies, namely, warfarin in patients who revert to atrial fibrillation, long-term aspirin therapy (even if patients revert to atrial fibrillation), long-term aspirin therapy for sinus rhythm, with a crossover to warfarin for patients who revert to atrial fibrillation, and long-term antiplatelet therapy (even for patients who remain in normal sinus rhythm); and (3) cardioversion followed by the same 4 antithrombotic therapies but with the addition of antiarrhythmic therapy with quinidine, sotalol, or amiodarone.

All patients undergoing cardioversion receive anticoagulant therapy with warfarin for 3 weeks before cardioversion and for an additional 3 weeks after cardioversion. For those receiving long-term aspirin therapy, aspirin is started after the use of warfarin is discontinued. In actual practice, anticoagulant therapy might be started a week or 2 before initiation of amiodarone to protect from embolic events the small percentage of patients who chemically undergo cardioversion early.

Antiarrhythmic therapy is discontinued in patients who revert to atrial fibrillation. In patients undergoing cardioversion, if atrial fibrillation recurs within 1 year repeated cardioversion is not attempted. If atrial fibrillation recurs after 1 year, we assumed that cardioversion would be repeated.

We model a patient’s prognosis as a sequence of health states that include cardiac rhythm, therapy being received, and complications of antiarrhythmic therapy, bleeding and embolic events. Patients in each health state are subject to similar chance events. These events include the risk of death from causes affecting the general population, drawn from age-, sex-, and race-specific mortality tables; embolic and bleeding events (that may both result in death or long-term morbidity that may resolve)\textsuperscript{1}. In addition, patients in certain health states are subject to special chance events such as success or failure of cardioversion, embolic complications specifically related to cardioversion, reversion to atrial fibrillation or maintenance of normal sinus rhythm, and adverse effects from antiarrhythmic therapy.

In the quinidine and sotalol strategies, patients undergo direct current electrical cardioversion, and, if it is successful, are immediately started on a regimen of either quinidine (eg, 324 mg of Quinaglute 3 times daily) or sotalol hydrochloride (80 mg twice daily, increased to 160 mg twice daily as tolerated)\textsuperscript{1}. Patients who fail to return to normal sinus rhythm with electrical cardioversion receive long-term treatment with warfarin or aspirin but do not receive an antiarrhythmic agent.

Unlike quinidine and sotalol, we assume that amiodarone (600 mg/d, decreasing to 400 mg/d after 7-10 days) is started 3 weeks before elective electrical cardioversion is scheduled.\textsuperscript{25} Therefore, we also considered the possibility that some patients may be withdrawn from treatment because of severe adverse effects before cardioversion.\textsuperscript{3} In that event, we assume electrical cardioversion is canceled and the patient receives long-term treatment with warfarin or aspirin.\textsuperscript{25} As mentioned earlier, some patients will chemically undergo cardioversion during the loading period, and therefore will not need electrical cardioversion. After successful cardioversion, the use of amiodarone is continued at a dosage of 200 mg/d.\textsuperscript{1}

Since amiodarone may interact with warfarin, making stable anticoagulant control more difficult,\textsuperscript{4} in sensitivity analyses we explored an increased risk of bleeding for patients receiving both amiodarone and warfarin. In the base case, we assumed no increased risk of bleeding because of this combination of drugs. We have also reflected a need for more intensive monitoring of anticoagulation during the amiodarone loading period by adding the cost of additional prothrombin time determinations to the overall cost of the cardioversion and amiodarone strategies.

A patient who underwent anticoagulation and is awaiting cardioversion who suffers a major bleeding event (without permanent morbidity) undergoes transesophageal echocardiography. If findings are negative, the patient undergoes cardioversion without restarting anticoagulant therapy. If the echo shows intracardiac thrombus (or “smoke”), cardioversion is canceled and anticoagulant therapy is resumed after a temporary discontinuation of 6 weeks, thus postponing the elective cardioversion.

ASSUMPTIONS

First, we have assumed that patients who fail to respond to 1 antiarrhythmic agent do not start therapy with an alternative antiarrhythmic. Without this assumption, the number of potential antiarrhythmic strategies would make analysis intractable. This assumption, in essence, decreases slightly the efficacy of each antiarrhythmic drug.

Second, if antiarrhythmic therapy is withdrawn because of adverse effects, the risk of reverting to atrial fibrillation is assumed to return to that of a similar cohort of patients who underwent cardioversion at the same time, but are not receiving antiarrhythmic therapy. We have also assumed that the efficacy of electrical cardioversion is the same regardless of which antiarrhythmic agent the patient receives.

Third, after a hemorrhagic event without permanent morbidity, anticoagulant or antplatelet therapy is discontinued for 6 weeks, after which treatment is resumed. However, after a hemorrhagic event with long-term morbidity, the use of both warfarin and aspirin is discontinued permanently, even if a subsequent embolic event were to occur; thus, the risk of subsequent embolization is increased. In patients not receiving anticoagulant therapy, any embolic event leads to long-term anticoagulation except in patients with long-term morbidity from a previous hemorrhagic event. Thus, patients who have a thromboembolic event while taking aspirin are started on a regimen of long-term anticoagulant therapy.

Fourth, patients with recurrent atrial fibrillation who are restarted on a regimen of warfarin once again face an increased risk of bleeding during the first cycle of anticoagulation.\textsuperscript{28}

Fifth, we assumed that events can be categorized into 3 groups: fatal, long-term, and short-term. Long-term events affect both subsequent survival and quality of life.\textsuperscript{25} Events with permanent morbidity decrease the quality of life to a fixed lower level, which stays constant until the patient dies or suffers an additional long-term event.
Short-term morbidities affect the quality of life for a limited period and then resolve.

Sixth, patients taking anticoagulants suffer the often not negligible inconvenience of frequent international normalized ratio determinations and worry about bleeding, trauma, and avoiding drug interactions. Thus, the quality of life of all patients being treated with warfarin is slightly diminished, ie, long-term anticoagulant therapy can be viewed as exacting a minimal loss of quality-adjusted life expectancy during those months in which it is given.30-33

Finally, we considered the impact of symptomatic atrial fibrillation on the quality of life, using a quality-adjustment factor varying from unity (describing patients who are asymptomatic) to lower values for patients who are markedly symptomatic (eg, poor exercise tolerance, fatigue, or palpitations). In sensitivity analyses we explored the effect of variations in this factor.

DATA USED IN THE ANALYSIS

We used data from the 5 recent trials9-13 examining warfarin prophylaxis in patients with nonvalvular atrial fibrillation to derive bleeding and thromboembolic risks (Table 1). We estimated the efficacy of warfarin from pooled primary data on 1393 patients with atrial fibrillation from these 5 trials.14 In our base-case analysis we used only data from the 2 primary prevention trials (Stroke Prevention in Atrial Fibrillation [SPAF] and Atrial Fibrillation, Aspirin, Anticoagulation Study [AFASAK])10,11 to determine the weighted average efficacy of aspirin to be 44%. In a recent meta-analysis that included data from a secondary prevention trial, the European Atrial Fibrillation Trial (EAFT),49 an average efficacy of 21% was calculated for aspirin.48 We explored this difference in sensitivity analyses.

QUINIDINE

Efficacy data from a meta-analysis by Coplen et al14 of randomized controlled trials addressing the efficacy and safety of quinidine were used to estimate the risk of reverting to atrial fibrillation following cardioversion. By 1 year, roughly 75% of untreated patients and 50% of patients treated with quinidine revert to atrial fibrillation. As shown in Figure 1, up to 25% of patients receiving quinidine after cardioversion subsequently discontinue treatment because of adverse effects.47-48

The meta-analysis by Coplen et al14 has raised concerns about the safety of quinidine in atrial fibrillation. The overall mortality rate was 2.9% per year in patients receiving quinidine compared with 0.8% per year in the control groups, a 3-fold increase. In a subsequent analysis, after removing noncardiovascular deaths, Falk48 found an excess cardiovascular mortality rate (primarily attributable to sudden death) of 1.2% per year.

AMIODARONE

Efficacy

We used data from the study by Gosselink et al2 of 89 consecutive patients with sustained atrial fibrillation or flutter treated with amiodarone to estimate the risk of reverting to atrial fibrillation following cardioversion. The cumulative percentage of patients remaining in sinus rhythm after 1, 2, and 3 years was 61%, 56%, and 53%, respectively. A recent meta-analysis pooling data from 6 studies of patients with resistant atrial fibrillation found 73%, 71%, and 60%, remaining in sinus rhythm after 3, 6, and 12 months, respectively, in close agreement with the data of Gosselink et al.2

Toxicity

In the base-case analysis, we used a declining annual risk of pulmonary toxicity, extrapolating from data in the literature.39 In sensitivity analysis, we explored the implication of a constant annual risk of pulmonary toxicity throughout the treated lifetime of the patient. In the study by Dusman et al59 the cumulative incidence of pulmonary toxicity was 9.1% at 5 years, while in the study by Chen et al,14 29% of 110 patients discontinued therapy by 3 years because of adverse effects, including pulmonary fibrosis (Figure 1). The mortality rate in patients with pulmonary fibrosis is 9.1%.50

SOTALOL

Efficacy

We used data from the Swedish multicenter trial conducted by Juul-Møller et al20 that compared the use of sotalol hydrochloride (160 mg twice daily) with quinidine. At 6 months after cardioversion, there was no significant difference in effectiveness, with 52% of 93 patients treated with sotalol and 48% of 79 patients receiving quinidine remaining in normal sinus rhythm. Hohnloser et al50 recently compared the use of quinidine and sotalol in a trial of pharmacological cardioversion. Although these patients did not undergo electrical cardioversion, the proportion of patients remaining in sinus rhythm after successful cardioversion was similar.51

Toxicity

Cardiovascular adverse effects from using sotalol include ventricular tachyarrhythmias (primarily torsades de points), sinus bradycardia, hypotension, exacerbation of congestive heart failure, and heart block. Central nervous system adverse effects include fatigue, dizziness, and headache.53-56 We used data from the study by Juul-Møller et al20 to predict the proportion of patients remaining on a regimen of sotalol (Figure 1).

As is the case with type IA antiarrhythmics, proarrhythmia is the most serious toxic effect from using sotalol.16 In a review examining data from 12 controlled clinical trials of sotalol in the treatment of patients with ventricular arrhythmias, Soyka et al53 found that almost half of the 4.3% of patients suffering proarrhythmic reactions had torsades de points. The incidence of proarrhythmia shows a strong dependence on dosage,61 with a 1.6% incidence of torsades de points at a daily dosage of 320 mg.57,58 Many reports describe a clustering of proarrhythmic events early in the course of treatment. However, to avoid a bias favoring sotalol over quinidine, we assumed, for both drugs, that the risk of proarrhythmia continues as long as the drug is continued. In sensitivity analyses, we examined an alternative assumption in which the risk of proarrhythmia is limited to the first year of therapy with sotalol.

Continued on next page
sinus rhythm; and whether to use long-term antithrombotic therapy, with warfarin or aspirin.²¹⁻²³ In this study, we considered a variety of strategies for the treatment of atrial fibrillation but focus on 3 antiarrhythmic drugs, reflecting their common use in the last decade.²¹,²²,²⁴ Quinidine is still widely used, although possibly decreasing in popularity.²⁵ Sotalol hydrochloride is generally well tolerated and is widely used for treatment of atrial fibrillation in Europe and Canada.²⁵ Amiodarone is highly effective in maintaining sinus rhythm; initial fears about toxicity have been tempered because that toxicity is in large part a function of dosage, and atrial fibrillation is being treated with a relatively low dosage.²¹

RESULTS

BASELINE ANALYSIS

Unless otherwise noted in the following sections, all strategies containing aspirin are followed by a crossover to warfarin in the event of recurrent atrial fibrillation. The base-case analysis was performed for a 65-year-old man with nonvalvular atrial fibrillation.

Effectiveness

“No treatment” provided the least quality-adjusted survival, 10.6 quality-adjusted life years (QALYs), while cardioversion followed by the use of amiodarone and warfarin yielded the highest life expectancy (12.8 QALYs). The simple addition of aspirin provided the largest incremental gain (1.2 QALYs compared with no treatment). These results are not discounted.

Cost-effectiveness Analysis

Table 3 lists the cost-effectiveness for each strategy (1995 dollars and QALYs), both discounted at 3% per year. The strategies are ranked by increasing cost, shown in the first results column. Cardioversion followed by aspirin therapy (without warfarin even in the event of reversion to atrial fibrillation) is the least expensive, while treatment with cardioversion, sotalol, and warfarin is roughly twice as expensive. Only 3 strategies are not dominated once marginal cost-effectiveness ratios are calculated: (1) cardioversion and aspirin followed by warfarin in patients who revert to atrial fibrillation; (2) cardioversion, amiodarone, and aspirin followed by warfarin in patients who revert to atrial fibrillation; and (3) cardioversion, amiodarone,
In 1995 dollars, as above.

Ancillary costs (eg, for electrocardiograms, echocardiograms, and chest radiography) were the same for all groups.

**Quinaglute, 324-mg tablet 3 times daily at $0.10 per tablet.**

††Amiodarone, 200-mg tablet once a day at $2.12 per tablet.

‡‡Sotalol hydrochloride, 160-mg tablet twice daily at $2.17 per tablet.

<table>
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<tr>
<th>Strategies</th>
<th>Cost, $</th>
<th>Effectiveness (Quality-Adjusted Life Expectancy), QALY</th>
<th>Marginal Cost (Additional Cost Beyond Next-Cheapest Strategy), $</th>
<th>Marginal Effectiveness (Additional Quality-Adjusted Life Expectancy), QALY</th>
<th>Marginal Cost-effectiveness Ratio, $ per Additional Quality-Adjusted Year of Life Expectancy‡</th>
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* Ellipses indicate not applicable.

† Information on inpatient variable costs was obtained through the Clinical Cost Manager, Transition Systems Inc, Boston, Mass, for fiscal years 1986-1988. The 1995 costs were obtained by inflating these data at the rate appropriate for medical costs at each year using the medical component of the consumer price index (6.6% for 1987, 6.5% for 1988, 7.7% for 1989, 9.0% for 1990, 8.7% for 1991, 7.4% for 1992, 5.9% for 1993, and 4.3% for 1994). Physicians’ costs were based on average charges for medical service for the first day ($151/d) and subsequent days ($84/d), on an average collection rate of 54% for physicians’ fees.

‡‡Sotalol hydrochloride, 160-mg tablet twice daily at $2.17 per tablet.

††Amiodarone, 200-mg tablet once a day at $2.12 per tablet.

# Bronchoscopy with transbronchial biopsy, cytopathology with interpretation, pulmonary function tests with diffusion capacity.

¶ Surveillance laboratory studies for patients receiving amiodarone includes chest radiography and thyroid function tests every 6 months.

§ Bronchoscopy with transbronchial biopsy, cytopathology with interpretation, pulmonary function tests with diffusion capacity, and chest radiography.

**Quinaglute, 324-mg tablet 3 times daily at $0.10 per tablet.**

††Amiodarone, 200-mg tablet once a day at $2.12 per tablet.

‡‡Sotalol hydrochloride, 160-mg tablet twice daily at $2.17 per tablet.
and warfarin. All other strategies are either dominated (ie, they are both more expensive and less effective) or are excluded by extended dominance (ie, having a higher marginal cost-effectiveness ratio [mCER] than other viable but more expensive strategies).

SENSITIVITY ANALYSIS

Quality of Life in Atrial Fibrillation

For a patient severely debilitated by atrial fibrillation (eg, quality-adjustment factor of 0.80 compared with the base-case of 0.95), the mCER of treatment with cardioversion, amiodarone, and aspirin decreases to $12 700 per QALY, while the mCER of cardioversion, amiodarone, and warfarin use increases slightly to $98 200 per QALY. For a patient who is asymptomatic (eg, quality-adjustment factor of 1.0), the strategy of cardioversion, amiodarone, and aspirin is dominated, while the mCER of cardioversion, amiodarone, and warfarin use increases to $146 900 per QALY. More important, in the asymptomatic patient cardioversion without subsequent antiarrhythmic therapy becomes a viable strategy. Cardioversion followed by warfarin (without antiarrhythmic therapy) would have an mCER of $43 100 per QALY, while cardioversion followed by aspirin therapy continues to have a low mCER of $10 200 per QALY. Thus, for a patient with few or no symptoms related to atrial fibrillation, cardioversion followed by treatment with amiodarone is expensive, while cardioversion followed by either aspirin or warfarin use, both without subsequent antiarrhythmic therapy, are relatively inexpensive for the health benefits gained.

Efficacy of Aspirin

A wide range of efficacy has been reported for aspirin. In the base-case analysis, we used an efficacy of 44% based on the Stroke Prevention in Atrial Fibrillation and Atrial Fibrillation, Aspirin, Anticoagulation Study trials. A recent meta-analysis that included data on secondary prevention of stroke from the European Atrial Fibrillation Trial reported an efficacy of 21%. As the efficacy of aspirin decreases, the mCER of cardioversion followed by amiodarone and warfarin therapy decreases, while that of cardioversion followed by amiodarone and aspirin therapy increases. Below an efficacy of 37% for aspirin, cardioversion and amiodarone followed by aspirin use was dominated by cardioversion, amiodarone, and warfarin therapy (ie, both more costly and less effective). At an efficacy of 20% the nondominated strategies were: (1) cardioversion followed by aspirin, (2) cardioversion followed by warfarin, and (3) cardioversion, amiodarone, and warfarin having mCERs of $2500 per QALY, $11 800 per QALY, and $15 400 per QALY, respectively.

Annual Excess Mortality Associated With Use of Quinidine

If there were no excess cardiovascular mortality associated with the use of quinidine, as some investigators suggest (vs base-case of 1.2% per year), the mCER of cardioversion and treatment with quinidine and aspirin would be $10 700 per QALY. Because a cheaper strategy would have improved efficacy, cardioversion followed by amiodarone and aspirin use would be dominated, while cardioversion followed by amiodarone and warfarin therapy would cost $730 400 per QALY. As the annual excess mortality from quinidine increases, the mCER of the quinidine strategy increases, while that of the amiodarone strategy decreases. At mortality rates higher than 0.5% per year the quinidine strategy is dominated.

Incidence of Amiodarone-Related Pulmonary Toxicity

The mCER of cardioversion followed by amiodarone and aspirin therapy increases as the probability of pulmonary fibrosis increases. Above an 18% 5-year cumulative probability of pulmonary toxicity (vs 9.1% in the base-case), the mCER exceeds $50 000 per QALY, approaching $99 000 per QALY at a 25% 5-year cumulative probability of pulmonary toxicity.

Mortality From Amiodarone-Related Pulmonary Toxicity

Figure 2 shows a 3-way sensitivity analysis examining both the 5-year cumulative probability of amiodarone-related pulmonary toxicity (vertical axis) and its associated mortality (horizontal axis). The family of curves represents a series of different thresholds for willingness to pay. In the shaded region to the upper right, where both the probability of pulmonary fibrosis and the probability of death from pulmonary fibrosis are high, cardioversion followed by warfarin therapy is preferred. As one moves farther into the unshaded region to the lower left, where both the probability of pulmonary fibrosis and its associated mortality are low, the mCER of cardioversion followed by amiodarone and aspirin use becomes...
progressively less, making it a more attractive strategy. The base-case values for these 2 variables fall well within the amiodarone region.

Any Amiodarone Toxicities Requiring Drug Withdrawal

As mentioned earlier, the mCER of cardioversion followed by amiodarone therapy increases as the risk of any toxicity increases. At a risk of toxicity requiring amiodarone withdrawal that is twice that of the base-case, the mCER of cardioversion followed by amiodarone and aspirin is $55,300 per QALY.

Quality of Life With Amiodarone

While amiodarone is well tolerated in general, a number of adverse reactions may not necessitate drug discontinuation but may impair quality of life. These include mild bradycardia; hyperthyroidism and hypothyroidism; gastrointestinal tract adverse effects; dermatologic disorders including rash, photosensitivity, hair loss, and an unusual blue-gray discoloration of the skin; neurologic toxic effects, such as fatigue, tremor, ataxia, and peripheral neuropathy; and ophthalmologic adverse effects consisting mainly of corneal microdeposits (caused by secretion of amiodarone by the lacrimal gland). The mCERS of cardioversion and amiodarone followed by either the use of aspirin or warfarin increase as the quality of life while taking amiodarone decreases. At a quality-adjustment factor of 0.98, the mCERs of both these strategies exceed $100,000 per QALY.

Excess Mortality Associated With Use of Sotalol

If the excess mortality risk attributable to sotalol is zero (base case, 0.8% per year), cardioversion followed by sotalol and aspirin therapy has an mCER of $42,000 per QALY, while cardioversion followed by sotalol and warfarin use has an mCER of $109,500 per QALY. Assuming that the risk of proarrhythmic events continues as long as the patient receives sotalol, if the excess mortality risk is more than 0.18% per year the sotalol strategies soon become both more expensive and less effective than the corresponding amiodarone strategies (i.e., dominated). However, if the risk of proarrhythmic events is limited to the first year, the mCERS of cardioversion followed by sotalol and either aspirin or warfarin therapy are $74,200 per QALY and $109,500 per QALY, respectively, at the baseline rate of 0.8% per year. If the excess mortality exceeds 1.8% in the first year of treatment, the sotalol strategies are both more expensive and less effective than the amiodarone strategies.

Quality of Life With Sotalol

Sotalol’s β-blocking characteristics cause up to 15% of patients to note fatigue, altered mental status, and parasthesias, while as many as 6% of patients experience impotence. In the base-case, in which no adjustment is made for the negative impact these adverse effects have on quality of life, none of the sotalol strategies are preferred over cardioversion followed by amiodarone and either aspirin or warfarin therapy. Furthermore, none of the sotalol strategies are preferred over cardioversion followed by warfarin use (Table 3). Therefore, in sensitivity analyses that examine decrements in the quality of life for both sotalol and amiodarone, sotalol is still never a preferred strategy.

Discount Rate

The traditional discount rate used in cost-effectiveness analyses has been 5% per year. However, in light of significant changes in economic fundamentals, analysts have suggested recently that 3% may be a more representative discount rate. In our base-case we presented results using a discount rate of 3% per year. At a discount rate of 3% per year, for all 3 of the nondominated strategies, the mCER increases; at a discount rate of 0, they decrease. At discount rates of 0%, 3%, and 5% per year, respectively, the mCERS of these strategies are as follows: cardioversion and aspirin use, $9700 per QALY, $10,800 per QALY, and $11,500 per QALY; cardioversion followed by amiodarone and aspirin therapy, $29,400 per QALY, $33,700 per QALY, and $36,800 per QALY; and cardioversion followed by amiodarone and warfarin use, $64,900 per QALY, $92,400 per QALY, and $122,300 per QALY.

The selection of therapeutic strategies for managing patients with nonvalvular atrial fibrillation must be individualized. Clinical risk factors for thromboembolism and hemorrhage should influence decisions, especially for patients who are not candidates for cardioversion (e.g., very high risk of recurrent atrial fibrillation). For most patients, however, cardioversion followed by the use of amiodarone and long-term use of either aspirin or warfarin have similarly high quality-adjusted life expectancies (12.8 QALYs and 12.9 QALYs, respectively). Despite similar outcomes, the mCERS of these 2 strategies differ greatly. Thus, while cardioversion followed by amiodarone and aspirin therapy has a reasonable mCER of $33,700 per QALY (falling well below society’s demonstrated willingness to pay for other health care interventions), cardioversion followed by amiodarone and warfarin use is relatively expensive, having an mCER of $92,400 per QALY.

Despite the continued popularity of quinine, we found it to be a poor choice of therapy because of the substantial excess cardiovascular mortality, the high incidence of adverse effects requiring discontinuation of the drug, and its modest efficacy in maintaining sinus rhythm. All other things being equal, the excess cardiovascular mortality associated with quinine must be less than 0.5% per year for it to be a reasonable use of society’s limited resources. Similarly, sotalol is limited by its risk of proarrhythmic events and sudden cardiac death. Even if this risk is limited to the first year of therapy, sotalol appears expensive, with mCERS of $74,200 per QALY and $109,500 per QALY for cardioversion followed by sotalol and aspirin or warfarin therapy, respectively.

While strategies containing amiodarone are favored in this analysis, in the United States this agent is approved by the Food and Drug Administration only for the treatment of refractory ventricular arrhythmias. In Europe, how-
ever, amiodarone is often the drug of choice for patients with atrial fibrillation. Although long-term adverse effects are associated with the use of amiodarone, the most serious ones may be dosage related and occur less commonly at the lower dosages prescribed for atrial fibrillation. The likelihood of amiodarone-related pulmonary toxic effects and death must increase substantially before cardioversion followed by the long-term use of warfarin is favored. However, increases in either the probability of pulmonary toxic effects or associated mortality may increase the mCER of the amiodarone strategies beyond society’s willingness to pay. As a worst-case scenario, we performed a separate analysis using data from studies of patients treated with higher dosages of amiodarone for ventricular arrhythmias. In a study in which most patients were receiving maintenance dosages of more than 400 mg/d, a pulmonary-associated mortality rate of 23% was observed, while Herre and colleagues found a 25% cumulative incidence of pulmonary fibrosis over 5 years. Using these worst-case data, we found cardioversion followed by amiodarone and warfarin to have a quality-adjusted life expectancy of 9.7 QALYs compared with 10.00 QALYs under the base-case assumptions. This small decrement in quality-adjusted life expectancy is sufficient to drop the amiodarone strategies from their nondominated positions, leaving cardioversion and long-term use of either aspirin or warfarin as the only viable strategies, with mCERs of $10,800 per QALY and $44,900 per QALY, respectively.

There are few published data describing the risk of thromboembolism in patients with atrial fibrillation who revert to normal sinus rhythm. A previously published decision analysis66 assumed that these patients have a risk of stroke similar to that of individuals who have never had atrial fibrillation, 0.1% per year (compared with 1.33% in patients with atrial fibrillation receiving warfarin, and 5.0% per year in patients with atrial fibrillation who were not receiving warfarin). Such a low figure is unlikely to be correct and biases that analysis strongly in favor of cardioversion. Atrial fibrillation can be a marker for other disorders that are themselves associated with an increased risk of stroke (eg, diabetes, hypertension, or history of myocardial infarction). Based on data describing patients with normal sinus rhythm who have a similar distribution of risk factors for noncardioembolic stroke as patients with nonvalvular atrial fibrillation, we determined that patients with a history of atrial fibrillation who have normal sinus rhythm have an annual stroke rate of 1.7%. This also is in close agreement with the 2% per year risk of embolic events noted by Petersen and Gotfredsen7 in patients with paroxysmal atrial fibrillation (R.H.F., written communication, November 29, 1995), but more than 10 times the rate assumed by Disch et al.66 We also examined the possibility that warfarin might be less effective, while aspirin might be more effective in preventing stroke in patients who have been converted to normal sinus rhythm than in patients who are currently in atrial fibrillation due to the different mechanism of stroke in these patients. Either a decrease in the effectiveness of warfarin or an increase in the effectiveness of aspirin in preventing noncardioembolic events would produce a dramatic increase in the mCER of cardioversion followed by warfarin rather than aspirin therapy.

In the same decision analysis comparing quinidine and amiodarone with allowing the patient to remain in atrial fibrillation while taking warfarin, Disch and coworkers66 concluded that the optimal strategy was cardioversion followed by the use of amiodarone. However, they did not consider the role of continued warfarin therapy after cardioversion (to prevent stroke should atrial fibrillation recur) and the role of aspirin alone for the post-cardioversion patient. They also did not distinguish symptomatic from minimally symptomatic patients. We found the most effective strategies to be cardioversion and amiodarone use in conjunction with either aspirin or warfarin therapy. Furthermore, Disch et al did not consider or compare costs, an important consideration when strategies have only slightly different expected outcomes. When costs were included in our analysis, the optimal strategy studied by Disch et al was dominated and thereby eliminated from consideration, being both less effective and more expensive than the strategy of cardioversion followed by amiodarone and long-term use of aspirin. Consideration of antiarrhythmic therapies alone in the management of nonvalvular atrial fibrillation is not sufficient. Decisions regarding the optimal treatment of these patients must include combinations of both antiarrhythmic and antithrombotic therapies.

If future studies of low-dose amiodarone therapy continue to support the trend suggesting less toxic effects in patients with atrial fibrillation than in patients treated with higher maintenance doses for ventricular arrhythmias, cardioversion followed by low-dose amiodarone and aspirin therapy while the patient remains in normal sinus rhythm should be considered a reasonable therapeutic intervention. Finally, despite the present array of antiarrhythmic agents available, for patients who are inconvenienced little by symptoms of atrial fibrillation, cardioversion followed by the use of aspirin or cardioversion followed by the use of warfarin without subsequent antiarrhythmic therapy may well be the treatments of choice.

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