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Cost-Effectiveness of Cardioversion and Antiarrhythmic Therapy in Nonvalvular Atrial Fibrillation

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Background: Physicians managing patients with nonvalvular atrial fibrillation must consider the risks, benefits, and costs of treatments designed to restore and maintain sinus rhythm compared with those of rate control with antithrombotic prophylaxis.

Objective: To compare the cost-effectiveness of cardioversion, with or without antiarrhythmic agents, with that of rate control plus warfarin or aspirin.

Design: A Markov decision-analytic model was designed to simulate long-term health and economic outcomes.

Data Sources: Published literature and hospital accounting information.

Target Population: Hypothetical cohort of 70-year-old patients with different baseline risks for stroke.

Time Horizon: 3 months.

Perspective: Societal.

Intervention: Therapeutic strategies using different combinations of cardioversion alone, cardioversion plus amiodarone or quinidine therapy, and rate control with antithrombotic treatment.

Outcome Measures: Expected costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness.

Results of Base-Case Analysis: Strategies involving cardioversion alone were more effective and less costly than those not involving this option. For patients at high risk for ischemic stroke (5.3% per year), cardioversion alone followed by repeated cardioversion plus amiodarone therapy on relapse was most cost-effective (\$9300 per QALY) compared with cardioversion alone followed by warfarin therapy on relapse. This strategy was also preferred for the moderate-risk cohort (3.6% per year), but the benefit was more expensive (\$18 900 per QALY). In the lowest-risk cohort (1.6% per year), cardioversion alone followed by aspirin therapy on relapse was optimal.

Results of Sensitivity Analysis: The choice of optimal strategy and incremental cost-effectiveness was substantially influenced by the baseline risk for stroke, rate of stroke in sinus rhythm, efficacy of warfarin, and costs and utilities for long-term warfarin and amiodarone therapy.

Conclusions: Cardioversion alone should be the initial

management strategy for persistent nonvalvular atrial fibrillation. On relapse of arrhythmia, repeated cardioversion plus low-dose amiodarone is cost-effective for patients at moderate to high risk for ischemic stroke.

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The management of patients with nonvalvular atrial fibrillation requires that physicians assess the risks and benefits of two principal treatment options: antithrombotic therapy with control of the ventricular response or cardioversion to restore sinus rhythm. Because a series of large-scale, randomized trials demonstrated the efficacy of warfarin (1–6) or aspirin (5–8) in reducing the frequency of thromboembolic events, antithrombotic therapy plus rate control is considered the standard of care for many patients (9–15). Furthermore, this management has been shown to be cost-effective (16, 17).

Restoration and maintenance of sinus rhythm in patients with nonvalvular atrial fibrillation frequently improve symptoms and exercise tolerance and, presumably, reduce the risk for thromboembolic stroke (18). Antiarrhythmic agents enhance the likelihood of restoring and maintaining sinus rhythm. However, relapse into atrial fibrillation often occurs, and the use of antiarrhythmic drugs may produce proarrhythmia and other potentially serious side effects (13, 19–21). Disch and colleagues (22) used decision analysis to evaluate the efficacy of cardioversion followed by amiodarone or quinidine ther-

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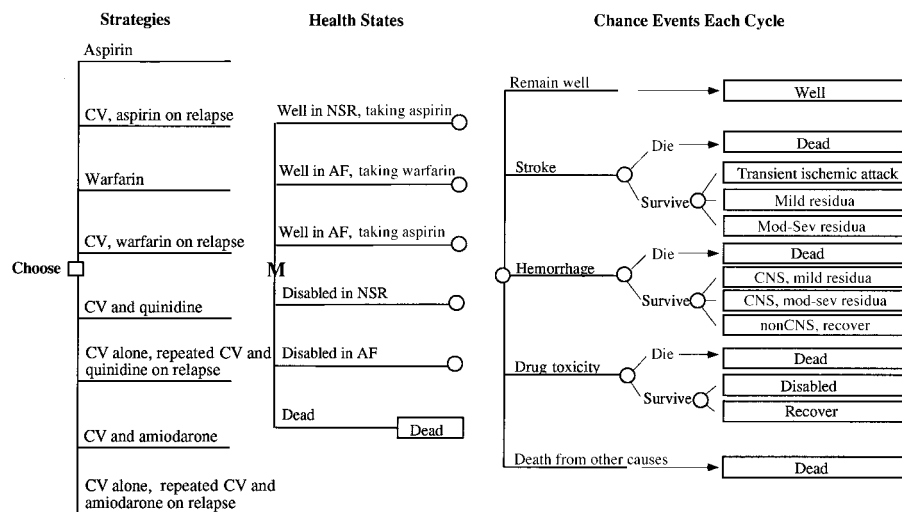


Figure 1. Simplified diagram of the Markov decision-analytic model. The square at left represents the decision to follow one of the treatment strategies. The *M* indicates the Markov process, which leads to one of several health states. Circles represent chance events that may occur during each cycle and result in continued good health, one of several temporary or permanent disabling events, or death. Health states in the figure are simplified, and each represents multiple states in the actual model (for example, "disabled in NSR" includes patients in sinus rhythm with disability due to stroke, intracerebral hemorrhage, or chronic pulmonary toxicity caused by amiodarone). AF = atrial fibrillation; CNS = central nervous system (intracranial); CV = cardioversion; Mod-Sev = moderate to severe; nonCNS = extracranial; NSR = normal sinus rhythm.

apy compared with rate control and warfarin therapy or no therapy in this population. They found that the strategy involving low-dose amiodarone provided the longest quality-adjusted survival. Similarly, Middlekauff and associates (23) described the superiority of amiodarone over warfarin or quinidine in reducing the frequency of adverse events in nonvalvular atrial fibrillation. However, these studies did not address whether the antiarrhythmic strategies achieved this benefit in a cost-effective manner.

Therefore, our goal was to evaluate the cost-effectiveness of cardioversion, with or without antiarrhythmic agents, compared with rate control and antithrombotic therapy in patients with nonvalvular atrial fibrillation. We performed this analysis by updating our previous decision-analytic model (22) and introducing the health-related costs for the treatments and outcomes of the therapeutic strategies.

Methods

Model Design and Target Population

A Markov decision analysis (24, 25) was done to evaluate treatment strategies in a large cohort of 70-year-old patients (50% of whom are male) with nonvalvular atrial fibrillation (Figure 1). In a Markov model, patients move from one health state to another (for example, well, disabled, or dead) on the basis of transition probabilities determined from the best available information in the medical literature. As patients cycle through the model, they accumulate utilities (measured in quality-adjusted life-years [QALYs]) and costs. By simulating outcomes in large numbers of hypothetical patients, the model assesses expected costs and benefits for each strategy. We used DATA 3.0 software (TreeAge

Software, Inc., Williamstown, Massachusetts) to design the model. The cycle length was 3 months.

For our analysis, we considered patients with an initial diagnosis of persistent nonvalvular atrial fibrillation without absolute indications for or contraindications to anticoagulant therapy. In addition, we assumed that our cohort would not require restoration of sinus rhythm because of arrhythmia-related symptoms or hemodynamic compromise. Furthermore, we assumed that our cohort did not have significant left ventricular systolic dysfunction with its higher risk for proarrhythmia from quinidine. We evaluated the following therapeutic strategies.

1. Aspirin. All patients received aspirin (325 mg/d) plus a rate-controlling agent (metoprolol or diltiazem).
2. Cardioversion followed by aspirin therapy on relapse. All patients underwent electrical cardioversion and received aspirin on relapse of the arrhythmia.
3. Warfarin. All patients received warfarin (average dosage, 5 mg/d) and a rate-controlling agent similar to those used in the aspirin strategy.
4. Cardioversion followed by warfarin therapy on relapse. All patients had electrical cardioversion; those restored to sinus rhythm received aspirin. Warfarin therapy was started on recurrence of atrial fibrillation and was continued if cardioversion failed.
5. Cardioversion plus quinidine therapy. All patients underwent pharmacologic or electrical cardioversion; those restored to sinus rhythm received long-term therapy with quinidine and aspirin.
6. Cardioversion alone followed by repeated cardioversion plus quinidine therapy on relapse. All patients initially underwent electrical cardioversion without antiarrhythmic therapy. Patients in whom atrial fibrillation recurred underwent repeated cardioversion plus initiation of quinidine therapy.
7. Cardioversion plus amiodarone therapy. All patients underwent pharmacologic or electrical car-

dioversion; those who were restored to sinus rhythm received low-dose amiodarone and aspirin.

8. Cardioversion alone followed by repeated cardioversion plus amiodarone therapy on relapse. This strategy was similar to the quinidine arm (strategy 6) except that low-dose amiodarone was used instead of quinidine.

Our model tracks the short- and long-term clinical outcomes, adverse consequences (stroke, major hemorrhage, antiarrhythmic agent toxicities, and procedural risks) with their variable disabilities, and the attendant health care costs for each treatment strategy. By applying utilities for each health state entered and running the analysis until all cohort members enter the “dead” state, the model calculates quality-adjusted survival for each strategy. Of note, patients assigned to enter any of the cardioversion arms are also followed after reversion to atrial fibrillation. Additional details of the model, the strategies using cardioversion, and the components of the baseline assessment and long-term surveillance are described in the Appendix. We made several additional assumptions, as follows.

1. Patients relapsing into atrial fibrillation began receiving warfarin (except in the strategy using cardioversion followed by aspirin therapy on relapse). To adjust for delays in determining that atrial fibrillation had recurred, we assumed that patients would spend half of the 3-month model cycle in atrial fibrillation before initiation of warfarin therapy.

2. If antiarrhythmic therapy was discontinued because of adverse effects, we assumed that atrial fibrillation would recur at a rate similar to that of the patients undergoing cardioversion without concomitant antiarrhythmic prophylaxis (26).

3. The initial success rate of cardioversion was not affected by the concomitant use of antiarrhythmic agents.

4. In the strategies using quinidine and amiodarone, patients having a nonfatal, nonhemorrhagic stroke who were in sinus rhythm started receiving warfarin, but therapy with the antiarrhythmic drug continued. Patients experiencing the same event who were in atrial fibrillation still received warfarin or changed from aspirin to warfarin therapy.

5. In patients experiencing a major hemorrhage, warfarin therapy was discontinued and, after recovery, aspirin therapy was started. We assumed that the risk for major hemorrhage from warfarin was independent of the duration of therapy (27).

6. Warfarin and aspirin therapy altered the likelihood of stroke and hemorrhage but not their severity.

Probabilities and Rates

To enhance the compatibility of our results with those of other studies, we used similar assumptions

and values for the input variables, as reported elsewhere (16, 22). We updated the model with information from more recent studies in our variable specification. Base-case values, range of the estimates, and their sources for variables in our model are listed in **Table 1**. The following components deserve emphasis.

Stroke and Risk for Bleeding

We obtained the probabilities of adverse events, the efficacy of warfarin and aspirin therapy, and the rate of stroke with no therapy from the collaborative analysis (28) and review by Barnett and colleagues (34) of randomized trials in nonvalvular atrial fibrillation (1–5, 36). Stroke risk varies with patient age and the presence of other risk factors: previous stroke or transient ischemic attack, hypertension, diabetes, or evidence of heart disease (angina, previous myocardial infarction, or congestive heart failure) (28). Like Gage and associates (16), we analyzed the cost and benefits of each strategy according to three levels of risk for stroke: a high-risk group (65 years of age or older with two or more risk factors) with an annual risk for stroke of 5.3%, a moderate-risk group (one additional risk factor) with an annual risk for stroke of 3.6%, and a low-risk group (no risk factors other than age) with an annual risk for stroke of 1.6%. The Stroke Prevention in Atrial Fibrillation Investigators (8) recently reported a similar method for identifying patients with nonvalvular atrial fibrillation at variable risk for stroke according to clinical criteria.

The determination of the annual rate of stroke in patients with nonvalvular atrial fibrillation in whom sinus rhythm is maintained is controversial. Population studies (29, 33) of the rates of stroke in patients without previous atrial fibrillation may underestimate the risk if, independent of thromboembolic potential, nonvalvular atrial fibrillation is a marker for higher intrinsic stroke risk from multiple mechanisms (80–82). The age-adjusted 2-year incidence of stroke in patients without atrial fibrillation in the Framingham Study cohort (33) was 10 events per 1000 persons (annual base rate in sinus rhythm, 0.5%). Van Gelder and coworkers (31) followed 236 patients with chronic atrial fibrillation that was managed aggressively with sequential electrical cardioversion and serial antiarrhythmic drug therapy to maintain sinus rhythm. Warfarin prophylaxis was used before and after cardioversion. Two ischemic thromboembolic complications occurred during a mean of 3.7 years of follow-up in these patients, who had mixed causes for atrial fibrillation. Sinus rhythm was maintained for at least 3 years in most of the patients (thromboembolic complication rate, 0.2% per year). Van Gelder and colleagues (30) also described a thromboembolic complication rate

Table 1. Model Variables*

| Input Variable | Base-Case Value (Range) | Source or Reference Number |
|--|-------------------------|----------------------------|
| Stroke | | |
| Ischemic stroke with no therapy, %/y | | 8, 16, 28 |
| High risk | 5.3 (4.9–18) | |
| Moderate risk | 3.6 (2.6–4.6) | |
| Low risk | 1.6 (1.1–2.0) | |
| Ischemic stroke in sinus rhythm, %/y | 0.5 (0.1–2.0) | 8, 22, 29–33 |
| Efficacy (stroke risk reduction), % | | |
| Warfarin | 68 (50–79) | 28, 34 |
| Aspirin | 22 (0–40) | 5, 28, 34, 35 |
| Stroke outcome, % | | |
| Fatal | 25 (18–30) | 1–6, 36 |
| Residual deficit if stroke was nonfatal | | 37 |
| No deficit | 28 (20–40) | |
| Mild deficit | 28 (20–40) | |
| Moderate to severe deficit | 44 NA† | |
| Relative risk for recurrent stroke | 2 (1–3) | 38 |
| Relative risk for stroke with higher decade of age | 1.4 (1–2) | 28 |
| Hemorrhage | | |
| Bleeding rate, %/y | | |
| Warfarin therapy (age <75 years) | 1.4 (1.3–2.6) | 16 |
| Warfarin therapy (age ≥75 years) | 4.2 (2.5–6.8) | 27 |
| Aspirin therapy | 0.9 (0.8–1.0) | 16 |
| Hemorrhage outcome, % | | |
| Not involving the central nervous system | 85 (75–90) | 1–6, 36 |
| Fatal | 20 (15–25) | 1–6, 36, 37 |
| Residual deficit if intracranial hemorrhage was nonfatal | | 16, 28, 39 |
| Mild deficit | 67 (50–80) | |
| Moderate to severe deficit | 33 NA† | |
| Relative risk for recurrent bleeding | 1.5 (1–3) | 40 |
| Quinidine therapy | | |
| Reversion to atrial fibrillation | | |
| In first 6 months, % | 42 (35–49) | 22, 26, 41, 42 |
| After 6 months, %/y | 10 (5–20) | 22, 26, 41, 42 |
| Withdrawal and toxicity | | |
| Early, % | 25 (20–30) | 23, 41, 43–46 |
| Late, %/y | 1.5 (0–5) | 22, 41 |
| Serious toxicity, % | 3 (0–5) | 47 |
| Excess mortality, %/y | 1.4 (1.2–2.1) | 22, 23, 26, 42 |
| Reversion to atrial fibrillation if therapy is discontinued | | 26 |
| In first 6 months, % | 67 (50–75) | |
| After 6 months, %/y | 15 (10–20) | |
| Amiodarone therapy | | |
| Reversion to atrial fibrillation | | |
| In first 6 months, % | 30 (20–35) | 48–61 |
| After 6 months, %/y | 5 (2–10) | 22, 48–61 |
| Withdrawal and toxicity | | |
| Early, % | 3 (0–5) | 45, 62–65 |
| Late, %/y | 10 (6–16) | 22, 58, 62–66 |
| Withdrawal due to pulmonary toxicity, %‡ | 20 (7–40) | 22, 58, 62–66 |
| Irreversible pulmonary toxicity, % | 25 (10–50) | 66, 67 |
| Death from irreversible pulmonary toxicity, % | 20 (5–25) | 67 |
| Annual excess mortality, % | 0.1 (0–0.3) | 22, 68 |
| Reversion to atrial fibrillation if therapy is discontinued (same as quinidine, above) | | |
| Cardioversion | | |
| Pharmacologic conversion with quinidine, % | 7 (0–15) | 20, 41 |
| Pharmacologic conversion with amiodarone, % | 20 (10–40) | 53, 55, 56, 60 |
| Overall cardioversion success, % | 85 (80–90) | 26, 41, 42, 60 |
| Mortality, % | 0.01 (0–0.1) | 9, 22, 69 |
| Stroke risk in the first month after procedure, % | 0.27 (0–0.8) | 31, 69, 70 |
| Mortality | | |
| Relative risk | | |
| Nonstroke, nonhemorrhagic death | 1.3 (1–2) | 16, 28, 71 |
| Death if patient has previous disabling event | 2.3 (1.3–3.0) | 38 |
| Cost of care, \$ | | |
| Single event—ambulatory | | |
| Initiation of warfarin therapy (one cycle) | 125 (75–250) | Cost accounting |
| Initiation of amiodarone therapy (one cycle) | 500 (200–1000) | Cost accounting |
| Cardioversion | 550 (250–1100) | Cost accounting, 72 |
| Evaluation of mild amiodarone toxicity | 350 (250–500) | 66 |
| Single event—hospitalization | | |
| Telemetry unit admission | 2500 (1500–4000) | Cost accounting, 32, 72 |
| Cardioversion during admission | 450 (250–1000) | Cost accounting, 72 |
| Quinidine toxicity | 2200 (1100–4300) | Cost accounting |
| Amiodarone pulmonary toxicity | 7200 (5800–8700) | 66, 73 |
| Intracranial central nervous system events | | |
| No residua | 5700 (2800–11 400) | 16, 17, 74, 75 |
| Mild residua | 8400 (4100–16 600) | 16, 74, 75 |
| Moderate to severe residua | 34 000 (17 000–68 400) | 16, 17, 32, 74, 75 |

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Table 1—Continued

| Input Variable | Base-Case Value (Range) | Source or Reference Number |
|---|-------------------------|-----------------------------|
| Extracranial hemorrhage | 4200 (1900–8400) | 16, 17 |
| Death | 7500 (0–15 000) | 16, 17, 32, 75 |
| Annual care | | |
| Aspirin | 270 (140–530) | Cost accounting |
| Warfarin | 500 (250–1000) | Cost accounting, 16, 17, 32 |
| Conversion to sinus rhythm without use of an antiarrhythmic agent | 325 (170–650) | Cost accounting |
| Quinidine | 1100 (600–2300) | Cost accounting, 32 |
| Amiodarone | 1700 (800–3400) | Cost accounting, 32, 66, 73 |
| Warfarin therapy added to any regimen | 250 (100–500) | Cost accounting |
| Stroke or intracranial bleeding | | |
| Mild residua | 2200 (1100–4300) | 16 |
| Moderate to severe residua | 19 400 (1000–38 900) | 16, 17, 32 |
| Pulmonary toxicity caused by amiodarone | 4000 (2000–8000) | 76 |
| Utilities for health states and therapies | | |
| Permanent quality-of-life adjustments | | |
| Treatment strategy | | |
| Aspirin | 0.998 (0.96–1.0) | 16, 77, 78 |
| Warfarin | 0.987 (0.92–1.0) | 22, 77, 78 |
| Well in sinus rhythm | 1.0 (0.98–1.0) | Estimate |
| Quinidine | 0.996 (0.96–1.0) | Estimate |
| Amiodarone | 0.987 (0.92–1.0) | Estimate |
| Stroke or intracranial bleeding | | |
| Mild residua | 0.76 (0.14–1.0) | 16, 78 |
| Moderate to severe residua | 0.39 (0.0–1.0) | 16, 78 |
| Chronic pulmonary toxicity | 0.6 (0.4–1.0) | 79 |
| Short-term quality-of-life adjustment | | |
| Utility for short-term events | 0.5 (0.0–0.5) | Assumption |
| Telemetry admission, <i>d</i> | 4 (3–5) | Assumption, 22 |
| Major extracranial hemorrhage, <i>wk</i> | 2 (1–4) | Assumption, 22 |
| Stroke or intracranial bleeding, <i>wk</i> | | |
| No residua | 1 (0–2) | Assumption, 22 |
| Mild residua | 1 (0–2) | Assumption |
| Moderate to severe residua | 4 (2–8) | Assumption, 16 |
| Amiodarone pulmonary toxicity, <i>wk</i> | 2 (0–4) | 22 |
| Hospitalizations resulting in death, <i>wk</i> | 2 (0–4) | Assumption |

* NA = not applicable.

† Sensitivity analysis could not be performed on this variable because the probability is dependent on the sum of events with mild or no residual deficit.

‡ Pulmonary toxicity estimates are a series of path probabilities as described in the text.

of 1% per year in a group of 342 patients with sequential cardioversions who were followed for 4.1 years. However, six of nine complications occurred as an initial event before inclusion in the study. We selected a base-case annual rate of stroke in sinus rhythm of 0.5% (33) with a range of 0.1% to 2.0% (8, 22, 29, 30, 32) for our model.

Antiarrhythmic Drug Toxicity

We updated toxicity data for quinidine by using the review by Grace and Camm (41) and the study by Reimold and associates (42). The older literature (1987 or earlier) on amiodarone toxicity summarized by Wilson and Podrid (58) revealed annual withdrawal rates resulting from significant adverse effects of 1% to 16% (average, 9.4% per year). Recent larger-scale studies of low-dose amiodarone in the setting of left ventricular dysfunction (62–64) or postinfarction ventricular arrhythmias (65) offer additional information on the drug's toxicity. Our calculation from these studies yielded an annual total withdrawal rate of 12.2%. Given these data, we chose an annual withdrawal rate of 10%, with one fifth of the annual withdrawal rate related to pulmonary toxicity. Furthermore, we decided that pulmonary toxicity would be irreversible in 25% of

patients; 20% of this group would die of the complication (66, 67), and the remainder would have some degree of permanent pulmonary injury and compromise in quality of life. This sequence of probabilities as constructed in our model yields an annual excess mortality rate on base-case assumptions of 0.1%, a value consistent with the estimates of Sopher and Camm (68). We evaluated the influence of these variables across a broad range of estimates in our sensitivity analysis.

Mortality

We adjusted the mortality rates from causes other than those explicitly identified in the model for age and sex according to data from the National Center for Health Statistics (83). We also applied relative risks of 1.3 to nonstroke, nonhemorrhagic death in nonvalvular atrial fibrillation (16, 28, 71) and 2.3 to mortality with a previous disabling event (38). Finally, although most of the mortality reduction from warfarin or aspirin therapy in nonvalvular atrial fibrillation results from the prevention of events included explicitly in our model, we adjusted the model to reflect the overall vascular mortality benefit (33% and 17% with warfarin and aspirin,

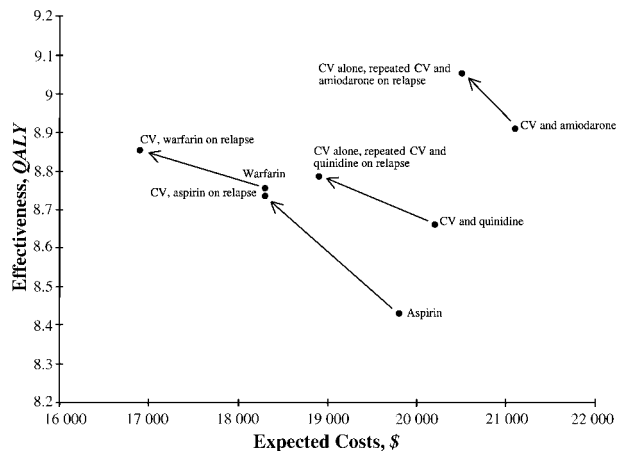


Figure 2. Cost and effectiveness of eight treatment strategies in patients at moderate risk for ischemic stroke. Strategies involving cardioversion (CV) alone as the initial approach are more effective and less expensive than other strategies. QALY = quality-adjusted life-year.

respectively) compared with no therapy in this population (16, 28, 35).

Costs and Utilities

Our analysis included all health-related costs (in 1996 U.S. dollars) associated with each strategy, assessed from a societal perspective and discounted at 3% per year (Table 1). The sources for our cost estimates included inflation-adjusted values from the published literature (16, 17, 32, 66, 72–75, 84, 85), Medicare reimbursement rates (professional and technical costs), and our hospital cost-accounting system (86) for individual laboratory tests and daily inpatient care. We obtained the cost of medications from an annually published reference book (87) and assigned a cost of treating chronic pulmonary toxicity caused by amiodarone that was similar to the cost of treating a chronic condition (76).

We obtained the adjustments for quality of life from published studies (16, 17, 66, 74, 77, 78, 84, 85) (Table 1). If more than one condition coexisted, the lowest utility estimate was used. We assigned similar utilities to warfarin and amiodarone therapy because of the frequent laboratory surveillance and potential risks associated with each drug. We also made short-term adjustments from the total quality-adjusted life expectancy for hospitalizations by applying a utility of 0.5 for the duration of these events. The utility for chronic bronchitis (79) was used as the quality-of-life adjustment for chronic pulmonary toxicity caused by amiodarone.

Results

Base-Case Analysis

Strategies involving cardioversion alone were more effective and less costly than those not involv-

ing this option. As shown in Figure 2, the dominance of cardioversion alone as initial therapy was independent of subsequent decisions about treating relapse of atrial fibrillation. Because these relations were consistent across all risk strata of ischemic stroke, we omitted strategies not involving cardioversion alone from our subsequent presentation of results.

Figure 3 shows the effectiveness of the four strategies using initial cardioversion without antiarrhythmic drugs across the rate of ischemic stroke with no therapy. Cardioversion alone followed by repeated cardioversion plus amiodarone therapy on relapse is the most beneficial intervention for patients at moderate and high risk for stroke. In contrast, cardioversion alone followed by aspirin therapy on relapse was the most effective strategy in patients at lowest risk for stroke (<2% per year).

The expected costs, quality-adjusted survival (QALYs), and cost-effectiveness comparisons for the base-case analysis as stratified by risk for ischemic stroke with no therapy are given in Table 2. For the highest-risk cohort (5.3% per year), cardioversion alone followed by repeated cardioversion plus amiodarone therapy on relapse was more expensive than cardioversion followed by warfarin therapy on relapse (\$21 200 compared with \$18 400)

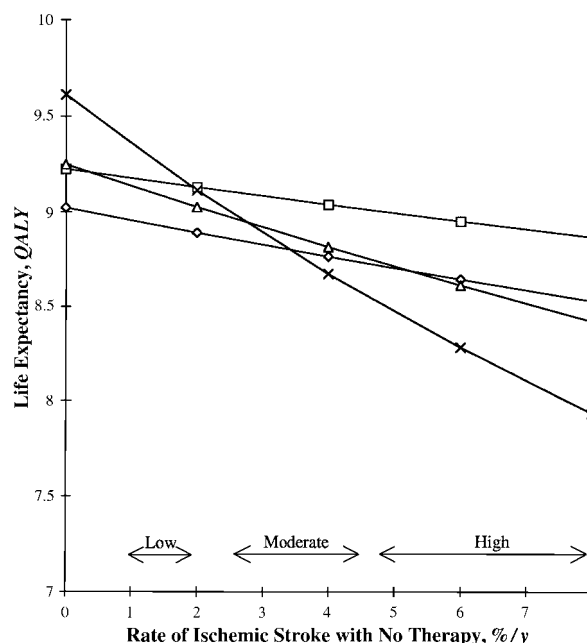


Figure 3. Sensitivity analysis of the rate of ischemic stroke with no therapy and the effectiveness of strategies involving cardioversion alone. Risk groups are shown with their respective ranges (arrows). At the lowest rates of stroke, cardioversion followed by aspirin therapy on relapse (crosses) provided the most benefit in quality-adjusted life-years (QALYs). Cardioversion alone followed by repeated cardioversion plus amiodarone therapy on relapse (squares) offered the most benefit for patients at moderate to high risk for ischemic stroke with no therapy. Although the range of ischemic stroke extends to 18% per year in the high-risk category, the upper bound in the figure is 8% per year for illustration purposes. Diamonds represent cardioversion alone followed by repeated cardioversion plus quinidine therapy on relapse; triangles represent cardioversion followed by warfarin therapy on relapse.

Table 2. Incremental Cost-Effectiveness Ratios in Base-Case Estimates, Stratified by Risk for Ischemic Stroke*

| Intervention | Total Cost | Total Effectiveness | Incremental Cost | Incremental Effectiveness | Incremental Cost-Effectiveness† |
|---|------------|---------------------|------------------|---------------------------|---------------------------------|
| | \$ | QALY | \$ | QALY | \$/QALY |
| High risk (5.3% per year) | | | | | |
| Cardioversion followed by warfarin therapy on relapse | 18 400 | 8.68 | – | – | – |
| Cardioversion followed by repeated cardioversion plus quinidine therapy on relapse | 19 900 | 8.68 | – | – | Dominated |
| Cardioversion followed by repeated cardioversion plus amiodarone therapy on relapse | 21 200 | 8.98 | 2800 | 0.30 | 9300 |
| Cardioversion followed by aspirin therapy on relapse | 21 300 | 8.41 | – | – | Dominated |
| Moderate risk (3.6% per year) | | | | | |
| Cardioversion followed by warfarin therapy on relapse | 16 900 | 8.86 | – | – | – |
| Cardioversion followed by aspirin therapy on relapse | 18 300 | 8.76 | – | – | Dominated |
| Cardioversion followed by repeated cardioversion plus quinidine therapy on relapse | 18 900 | 8.79 | – | – | Dominated |
| Cardioversion followed by repeated cardioversion plus amiodarone therapy on relapse | 20 500 | 9.05 | 3600 | 0.19 | 18 900 |
| Low risk (1.6% per year) | | | | | |
| Cardioversion followed by aspirin therapy on relapse | 14 000 | 9.21 | – | – | – |
| Cardioversion followed by warfarin therapy on relapse | 14 800 | 9.07 | – | – | Dominated |
| Cardioversion followed by repeated cardioversion plus quinidine on relapse | 17 700 | 8.92 | – | – | Dominated |
| Cardioversion followed by repeated cardioversion plus amiodarone on relapse | 19 600 | 9.15 | – | – | Dominated |

* Dashes indicate that calculation of the incremental cost, incremental effectiveness, or incremental cost-effectiveness ratio is not appropriate. After eliminating interventions that are dominated (those that have higher costs and lower effectiveness), the calculations when entered compare that strategy to the next most effective option at lower cost. The values are discounted at 3%. QALY = quality-adjusted life-year.

† The incremental cost-effectiveness ratio was calculated by dividing the incremental cost by the incremental effectiveness. Discrepancies in the value for cost-effectiveness ratio are due to round-off error.

but was also more effective (8.98 QALYs compared with 8.68 QALYs). Thus, the incremental cost-effectiveness of cardioversion alone followed by repeated cardioversion plus amiodarone therapy on relapse was \$9300 per QALY.

In the cohort at moderate risk for stroke (3.6% per year), the expected costs of cardioversion alone followed by repeated cardioversion plus amiodarone on relapse remained higher than those of cardioversion with warfarin on relapse (\$20 500 compared with \$16 900), but the benefit was more modest (9.05 QALYs compared with 8.86 QALYs) with a cost-effectiveness of \$18 900 per QALY. As in the high-risk cohort, cardioversion followed by warfarin therapy on relapse dominated strategies using quinidine or aspirin. For the cohort at lowest risk for ischemic stroke (1.6% per year), cardioversion followed by aspirin on relapse dominated all other strategies.

Sensitivity Analysis

Although baseline risk for ischemic stroke had the most impact on cost-effectiveness, several other variables substantially influenced the cost-effectiveness of cardioversion alone followed by amiodarone therapy on relapse (**Figure 4**). A major advantage presumed to be associated with the restoration and maintenance of sinus rhythm is a significant reduction in the risk for stroke. We estimated an annual base-case risk for stroke in patients in sinus rhythm of 0.5% (range, 0.1% to 2.0%). In patients at moderate risk for stroke, the marginal cost-effectiveness varied substantially (\$11 800 per QALY to well over

\$100 000 per QALY) as the variable approached the threshold value (1.7% per year). At the threshold value, the comparison strategies are equally effective. For the high-risk cohort, the cost-effectiveness calculation ranged from \$6200 per QALY to \$93 700 per QALY.

The utility for long-term amiodarone therapy in the moderate-risk cohort altered the marginal cost-effectiveness dramatically (\$15 200 per QALY when the utility was 1.0 to more than \$100 000 per QALY near the threshold value of 0.93). The high-risk group, in contrast, did not reach the threshold, but the cost-effectiveness calculation varied from \$8300 per QALY to \$54 000 per QALY across the range of the sensitivity analysis.

The annual cost of amiodarone therapy (base case, \$1700 per year [range, \$800 to \$3400 per year]) also caused large variation in cost-effectiveness estimates. Values ranged from \$2300 per QALY to \$50 100 per QALY in the moderate-risk cohort and \$1000 per QALY to \$30 700 per QALY in the high-risk cohort. The annual cost of warfarin therapy (base case, \$500 per year [range, \$250 to \$1000 per year]) induced less variation in the calculation. However, the efficacy of warfarin in reducing the rate of ischemic stroke (base case, 68% [range, 50% to 79%]) changed the cost-effectiveness from \$9600 per QALY to \$31 400 per QALY in moderate-risk patients and from \$3800 per QALY to \$17 600 per QALY in high-risk patients. Finally, the utility for long-term warfarin therapy modestly affected the calculations. Across the range for this

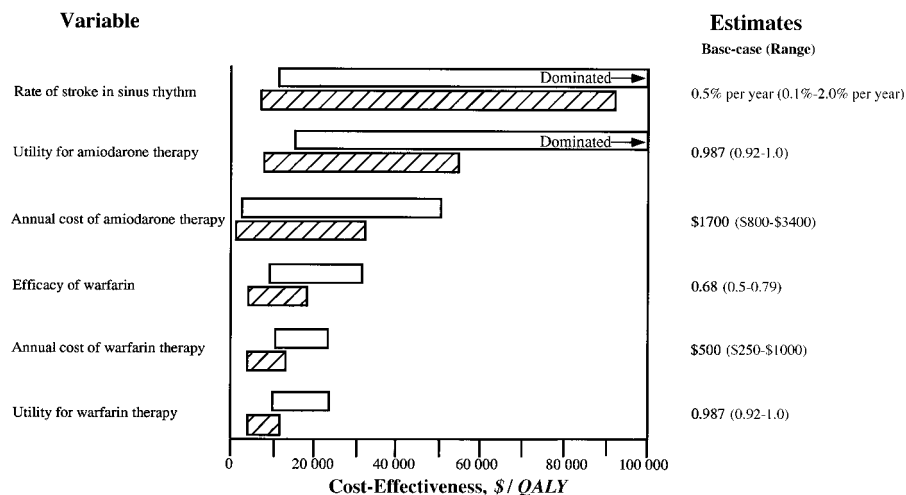


Figure 4. Tornado diagram of variables with significant influence on cost-effectiveness. The diagram showed variables identified in the sensitivity analysis that substantially affect the incremental cost-effectiveness when evaluated across the range of estimates from **Table 1**. The analysis includes cardioversion alone followed by repeated cardioversion plus amiodarone therapy on relapse compared with cardioversion followed by warfarin therapy on relapse. The analysis was performed at base-case estimates for moderate risk (white bars; 3.6% per year) and high risk (striped bars; 5.3% per year) for ischemic stroke with no therapy. "Dominated" means that the incremental cost-effectiveness ratio reaches the threshold value beyond which the comparison strategy is less costly and more effective. See text for details. QALY = quality-adjusted life-year.

variable (base case, 0.987 [range, 0.92 to 1.0]), the cost-effectiveness in moderate-risk patients and high-risk patients varied from \$9000 to \$24 000 per QALY and \$5600 to \$11 300 per QALY, respectively.

Finally, we evaluated the influence of age on our results by analyzing the model with a starting age of 65 or 75 years. For patients at moderate or high risk for ischemic stroke, cardioversion alone followed by repeated cardioversion plus amiodarone therapy on relapse was cost-effective regardless of starting age. Furthermore, as in the base-case analysis, cardioversion with aspirin on relapse dominated all other strategies in the low-risk cohort for both starting ages.

Discussion

We evaluated the cost-effectiveness of strategies directed at re-establishing and maintaining sinus rhythm compared with anticoagulation and control of the ventricular response in patients with nonvalvular atrial fibrillation. We found that cardioversion alone should be the initial step in the management of these patients. For patients at moderate to high risk for stroke, the best overall strategy among those we considered was cardioversion alone followed by repeated cardioversion plus amiodarone therapy on relapse of the arrhythmia. Our model also predicts that strategies using cardioversion and quinidine prophylaxis offer no advantage in quality-adjusted survival unless the rate of ischemic stroke is very high and amiodarone is contraindicated. Moreover, our study supports consideration of a single cardioversion attempt and long-term aspirin prophylaxis, even on relapse of arrhythmia, for patients at the lowest risk for ischemic stroke.

Eckman and colleagues (32) recently reported their evaluation of the cost-effectiveness of 19 treatment strategies in nonvalvular atrial fibrillation. Us-

ing similar methods, their analysis was based on patients who were younger than ours (65 rather than 70 years of age) and on a risk for ischemic stroke with no therapy of 4.5% per year, a value intermediate to our moderate- and high-risk base-case estimates. They found cardioversion alone followed by warfarin therapy should atrial fibrillation recur to be the treatment of choice for patients who were bothered little by symptoms. Although cardioversion with amiodarone prophylaxis was cost-effective in their study, they did not consider strategies involving cardioversion alone and delay in the application of antiarrhythmic drugs until the recurrence of atrial fibrillation. This approach is clinically relevant because of the unpredictability of arrhythmia relapse and the reluctance of many physicians to recommend long-term treatment with antiarrhythmic agents as initial therapy (88, 89). Furthermore, our study provides insight into the impact of the variable risk for stroke, as estimated by clinical factors (8, 28), on choosing the optimal strategy.

Our study demonstrates the progressively more favorable cost-effectiveness of cardioversion alone followed by repeated cardioversion plus amiodarone therapy on relapse in patients at increasing risk for stroke (**Table 2, Figure 3**). In the base-case analysis, the cost-effectiveness of this strategy is \$18 900 per QALY and \$9300 per QALY for patients at moderate and high risk for stroke, respectively. These estimates are well within the range in which other accepted technologies and treatments are considered to be appropriate expenditures of medical resources (90). For example, adjusted to 1996 U.S. dollars, the cost-effectiveness of propranolol therapy in mild hypertension is \$13 000 per QALY (91) and the cost of hemodialysis for end-stage renal disease is \$53 000 per QALY (92).

Our estimates of the cost-effectiveness of cardioversion alone followed by repeated cardioversion

plus amiodarone therapy on relapse are substantially influenced by several factors. Amiodarone is expensive, and obligatory office visits and laboratory surveillance add to the annual cost of care. These costs and the potential decrease in quality of life caused by long-term amiodarone therapy significantly altered the incremental cost-effectiveness calculations (**Figure 4**). In patients at moderate risk for stroke, a utility of amiodarone therapy of less than 0.93 resulted in a preference for cardioversion followed by warfarin therapy on relapse. Likewise, the range of estimates for the annual cost and patient utility for long-term warfarin treatment shifted the cost-effectiveness assessment. These insights from our sensitivity analysis emphasize the relevance of patient preferences and the costs of prophylactic strategies on decision making in this setting.

The rate of ischemic stroke in patients with nonvalvular atrial fibrillation in whom sinus rhythm is restored and maintained, with or without antithrombotic prophylaxis, is unknown. Recent echocardiographic studies (81, 82) suggested a multifactorial pathogenesis of stroke with this condition, including such clinical factors as previous stroke, hypertension, or the presence of dense aortic plaque. These diverse predisposing factors have prompted some authorities to advise long-term warfarin therapy even if sinus rhythm is restored (18). In our model, all patients in sinus rhythm received daily aspirin. However, our cohort did not include patients with previous ischemic stroke—a clear indication for long-term warfarin prophylaxis regardless of whether sinus rhythm is restored. Nevertheless, our sensitivity analysis revealed the important influence of estimates for the rate of stroke in sinus rhythm on the cost-effectiveness calculation (**Figure 4**).

Information on the long-term efficacy and safety of low-dose amiodarone prophylaxis in nonvalvular atrial fibrillation is limited. In the absence of results of ongoing, randomized trials (93–95), we relied on conclusions from a decision analysis (22), a meta-analysis (60), and more recent observational studies (54, 57) to estimate the probability of maintaining sinus rhythm with amiodarone therapy. In most instances, patients in these studies had atrial fibrillation of variable duration from mixed causes (valvular and nonvalvular) that was often refractory to other antiarrhythmic agents. This suggests that amiodarone may show even greater efficacy in such a population as our hypothetical cohort (96, 97). Moreover, the risk for ischemic stroke increases with time as patients age and acquire additional comorbid conditions. In the Stroke Prevention in Atrial Fibrillation III Study (8), patients deemed free of clinical risk factors on enrollment developed them at a rate of 6% per year. Our investigation suggests that patients with increasing risk for stroke during long-

term surveillance would derive additional benefit from maintenance of sinus rhythm.

Our study has several limitations. As in most cost-effectiveness studies, we incorporated a series of simplifying assumptions. Our cohort was restricted to patients with persistent nonvalvular atrial fibrillation who would have been eligible for randomized trials evaluating the efficacy and safety of warfarin or aspirin in this condition. This implies that our cohort would not include patients with hemodynamic or symptom-related compromise from arrhythmia or those with contraindications to anti-thrombotic therapy. In addition, our model is not designed for patients with transient (paroxysmal) atrial fibrillation or, at the other extreme, permanent atrial fibrillation, in which the probability for restoration and maintenance of sinus rhythm is low. Furthermore, the benefit of cardioversion alone as the initial approach would be significantly reduced if the rate of relapse to atrial fibrillation without antiarrhythmic prophylaxis was even greater than our estimates. Strategies using antiarrhythmic agents as initial therapy would be more attractive in this subset or in patients in whom a cardioversion attempt had already failed. Finally, it is unknown whether strategies using sequential cardioversions (31, 98) and newer antiarrhythmic agents (such as sotalol, propafenone, or flecainide) would offer a similar or more cost-effective alternative to amiodarone in nonvalvular atrial fibrillation.

In conclusion, our study supports a management strategy in patients with persistent nonvalvular atrial fibrillation that incorporates an initial cardioversion attempt without concomitant antiarrhythmic therapy. If relapse occurs, repeated cardioversion plus low-dose amiodarone therapy to maintain sinus rhythm provides a cost-effective alternative to anticoagulation and rate control in patients at moderate to high risk for ischemic stroke. Cardioversion alone followed by repeated cardioversion and quinidine therapy on relapse is an inferior option unless risk for stroke is high and amiodarone is contraindicated or is considered unappealing by the patient. For patients at low risk for ischemic stroke, cardioversion alone and long-term aspirin therapy seems to be the best strategy. Finally, to optimize safety and benefit, the decision to recommend any treatment approach requires careful assessment of individual patient features and preferences.

Appendix

Cardioversion Followed by Warfarin Therapy on Relapse

Initially, patients received rate-controlling agents and prophylactic warfarin for 1 month (99, 100). Ambulatory

cardioversion was performed, and patients in whom sinus rhythm was not restored continued to receive warfarin and rate-controlling agents (if necessary). Patients in whom sinus rhythm was restored continued warfarin therapy for 1 additional month and were evaluated in the office setting. If sinus rhythm was maintained, daily aspirin therapy was substituted for warfarin therapy. If relapse into atrial fibrillation was seen during outpatient surveillance, patients started therapy with warfarin and rate-controlling agents.

Cardioversion Followed by Aspirin Therapy on Relapse

A sequence similar to that in the strategy using warfarin therapy was applied, except that aspirin was used if atrial fibrillation recurred.

Cardioversion plus Quinidine Therapy

After therapeutic anticoagulation was ensured for 1 month, patients were admitted to a hospital telemetry bed to optimize the safety of antiarrhythmic therapy (45, 101). Pharmacologic cardioversion was attempted by using sustained-action quinidine (average dose, 900 to 1200 mg/d). Patients who tolerated quinidine but in whom cardioversion could not be pharmacologically induced underwent electrical cardioversion by standard techniques (102) on the third hospital day. Patients who converted to sinus rhythm continued to receive quinidine, completed an additional 24 hours of telemetry unit surveillance (19, 45), and continued to receive warfarin for another month; those in whom cardioversion failed discontinued quinidine therapy and received rate-controlling agents and warfarin. If sinus rhythm was maintained at a 1-month office assessment, daily aspirin was substituted for warfarin to provide thromboembolism prophylaxis should atrial fibrillation recur. On recurrence of atrial fibrillation, quinidine therapy was stopped and patients began to receive warfarin and rate-controlling agents. If patients who remained in sinus rhythm discontinued quinidine therapy because of adverse effects, aspirin therapy was maintained until relapse of atrial fibrillation was detected in ambulatory surveillance.

Cardioversion plus Amiodarone Therapy

As in the quinidine strategy, all patients underwent a cardioversion sequence. Unlike patients in the quinidine strategy, however, patients started amiodarone therapy on an ambulatory basis after 1 month of anticoagulation. Our dosing regimen was similar to those used by Van Gelder and colleagues (31) and Tieleman and associates (55): Amiodarone therapy is initiated at 600 mg/d for 3 weeks, followed by 200 mg/d thereafter. Patients who could not tolerate amiodarone received warfarin and rate-controlling therapy. Patients who did not convert to sinus rhythm during the loading period underwent ambulatory electrical cardioversion. No inpatient surveillance was performed because of the negligible risk for proarrhythmia with amiodarone (20, 103). If sinus rhythm was maintained at a 1-month office assessment, daily aspirin was substituted for warfarin. On recurrence of atrial fibrillation, amiodarone therapy was stopped and patients began to receive

warfarin and rate-controlling agents. If patients who remained in sinus rhythm required discontinuation of amiodarone therapy because of adverse effects, aspirin therapy was maintained until relapse of atrial fibrillation was detected in ambulatory surveillance. In all cardioversion strategies, we assumed that most physicians would maintain therapy with a rate-controlling agent but at approximately half the dose used in the aspirin and warfarin strategies (13).

Cardioversion Alone Followed by Repeated Cardioversion plus Quinidine Therapy on Relapse

Electrical cardioversion was attempted after 1 month of therapeutic anticoagulation. If sinus rhythm was restored, patients received daily aspirin. If electrical cardioversion did not achieve sustained sinus rhythm, a second attempt was made in the first cycle of the model using the cardioversion and quinidine therapy strategy. Patients who did not convert to sinus rhythm with quinidine therapy after repeated cardioversion received warfarin and rate-controlling agents. Patients who developed recurrent atrial fibrillation after initially successful cardioversion received anticoagulation and underwent the second cardioversion sequence using quinidine. A second cardioversion was not performed on the few patients who experienced a disabling event before relapse into atrial fibrillation. Final relapse into atrial fibrillation was managed with warfarin and rate-controlling agents.

Cardioversion Alone Followed by Repeated Cardioversion plus Amiodarone Therapy on Relapse

This strategy was almost the same as cardioversion alone followed by repeated cardioversion plus quinidine on relapse, except that amiodarone was initiated in an outpatient setting and pharmacologic or electrical cardioversion did not require hospitalization for telemetry monitoring.

Baseline Assessment and Surveillance

A baseline assessment, which was common to all strategies, included a comprehensive history, physical examination, and laboratory evaluation (electrocardiography, transthoracic echocardiography, chest radiography, complete blood count, electrolyte levels, creatinine concentration, urinalysis, liver profile, prothrombin time, and thyroid-stimulating hormone levels). Initiation of warfarin required frequent prothrombin time sampling during the first month followed by monthly determinations thereafter (104, 105). Patients in the aspirin or warfarin arms or those who reverted to permanent atrial fibrillation in the cardioversion strategies received biannual intermediate-length office visits and annual complete blood count and Holter monitoring.

Surveillance of patients maintaining sinus rhythm was done through an intermediate-length office visit every 3 months and routine monitoring, including annual electrocardiography, complete blood count, and Holter monitoring. Patients receiving quinidine also underwent an annual liver profile and quinidine measurement. Serious side effects related to quinidine therapy, such as presyncope or syncope, prompted hospital admission. Surveillance for

the numerous potential side effects of amiodarone therapy required office visits every 3 months and laboratory studies according to published recommendations (58, 59, 96). These included baseline pulmonary function studies and ophthalmologic examination; annual Holter monitoring and ophthalmologic examination; and biannual complete blood count, liver function studies, thyroid-stimulating hormone measurement, electrocardiography, and chest radiography. If acute pulmonary toxicity resulted from amiodarone therapy, patients were hospitalized for complete evaluation and treatment (106). Finally, patients maintaining sinus rhythm upon discontinuation of therapy with either antiarrhythmic agent required office visits every 3 months to detect recurrent atrial fibrillation and the need to initiate warfarin therapy.

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