

Cost-Effectiveness of Rhythm versus Rate Control in Atrial Fibrillation

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Background: Atrial fibrillation is the most common type of sustained cardiac arrhythmia, but recent trials have identified no clear advantage of rhythm control over rate control. Consequently, economic factors often play a role in guiding treatment selection.

Objective: To estimate the cost-effectiveness of rhythm-control versus rate-control strategies for atrial fibrillation in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM).

Design: Retrospective economic evaluation. Nonparametric bootstrapping was used to estimate the distribution of incremental costs and effects on the cost-effectiveness plane.

Data Sources: Data on survival and use of health care resources were obtained for all 4060 AFFIRM participants. Unit costs were estimated from various U.S. databases.

Target Population: Patients with atrial fibrillation who were 65 years of age or who had other risk factors for stroke or death, similar to those enrolled in AFFIRM.

Time Horizon: Mean follow-up of 3.5 years.

Perspective: Third-party payer.

Interventions: Management of patients with atrial fibrillation with antiarrhythmic drugs (rhythm control) compared with drugs that control heart rate (rate control).

Outcome Measures: Mean survival, resource use, costs, and cost-effectiveness.

Results of Base-Case Analysis: A mean survival gain of 0.08 year ($P = 0.10$) was observed for rate control. Patients in the rate-control group used fewer resources (hospital days, pacemaker procedures, cardioversions, and short-stay and emergency department visits). Rate control costs \$5077 less per person than rhythm control.

Results of Sensitivity Analysis: Cost savings ranged from \$2189 to \$5481 per person. Rhythm control was more costly and less effective than rate control in 95% of the bootstrap replicates over a wide range of cost assumptions.

Limitations: Resource use was limited to key items collected in AFFIRM, and the results are generalizable only to similar patient populations with atrial fibrillation.

Conclusion: Rate control is a cost-effective approach to the management of atrial fibrillation compared with maintenance of sinus rhythm in patients with atrial fibrillation similar to those enrolled in AFFIRM.

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A complete list of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) investigators has been published elsewhere (*Am Heart J.* 2002;143:991-1001).

*For a list of the Cardiac Outcomes and Research in Economics (CORE) investigators, see the Appendix, available at www.annals.org.

See related article on pp 720-726 and editorial comment on pp 727-729.

Atrial fibrillation is the most common sustained type of cardiac arrhythmia treated by physicians. Its prevalence increases with advancing age, affecting approximately 5% of those 65 years of age and older and 10% of those older than 80 years of age (1–3). As the U.S. population ages, it is expected that more than 5 million persons will be living with atrial fibrillation by the year 2050 (4). Despite significant advances in the effectiveness of treatments for atrial fibrillation and its associated comorbid conditions, disability and mortality from atrial fibrillation remain high (5–10).

The optimal approach to the rhythm management of atrial fibrillation remains unclear. There are 2 main approaches: Rhythm control uses electrical cardioversion, antiarrhythmic drugs, and, sometimes, nonpharmacologic therapies (for example, multisite atrial pacing, maze procedures, or radiofrequency ablation procedures) to maintain sinus rhythm; rate control uses atrioventricular nodal blocking agents (and, if needed, ablation of the atrioventricular junction and pacemaker implantation) for ventricular rate control.

Recently, several randomized, controlled studies have compared rate control versus rhythm control. In the largest

of these studies, investigators in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) randomly assigned 4060 patients with atrial fibrillation (mean age, 70 years) to either rate control or rhythm control (10–12). After a mean follow-up of 3.5 years, mortality did not differ significantly between the groups (hazard ratio for rate control vs. rhythm control, 0.87 [95% CI, 0.75 to 1.01]; $P = 0.08$), and the rate-control approach was associated with a lower risk for adverse drug effects (12). The results of the other large study were consistent with these findings (13). The RAtE Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) study randomly assigned 522 patients with persistent atrial fibrillation after electrical cardioversion to either rhythm control or rate control; the mean follow-up was 2.3 years (13). Patients in both treatment groups received oral anticoagulant drugs. There was a nonsignificant trend toward reduced death or other serious cardiovascular events in patients treated by the rate-control strategy.

Consequently, economic factors often play a substantial role in guiding treatment selection. Several authors have examined the incremental cost-effectiveness of rhythm-control versus rate-control strategies for treating

Context

Randomized trials show that rate control and rhythm control are similarly effective in the treatment of atrial fibrillation; therefore, economic issues will play a large role in the choice of therapy.

Contribution

This cost-effectiveness model shows that rate control saves costs compared with rhythm control.

Implications

From an economic perspective, unless specific clinical factors suggest a benefit of rhythm control for a particular patient, rate control seems to be the preferred strategy for the management of atrial fibrillation.

—The Editors

atrial fibrillation; however, their studies have been confined to modeling exercises of hypothetical scenarios that lack data on efficacy and resource use from randomized trials (14, 15).

This paper reports an economic analysis based on the results of AFFIRM. The objective was to estimate the incremental cost-effectiveness of rhythm-control versus rate-control strategies from AFFIRM.

METHODS**AFFIRM Study Sample**

AFFIRM included 4060 patients with atrial fibrillation whose treatment was block randomized by center to be either rhythm control or rate control (12). Similar to patients with atrial fibrillation in the general population, most of the patients in AFFIRM were older men (men represented 61% of the sample) with common associated cardiovascular comorbid conditions (history of hypertension [71%], coronary artery disease [39%], and congestive heart failure [9%]). The mean age (\pm SD) for all patients was 69.7 ± 9.0 years, and 75% were 65 years of age or older. The qualifying event was the first episode of atrial fibrillation in 34% of patients and recurrent atrial fibrillation in the remaining 66% of patients.

The overriding principles for enrollment of patients in AFFIRM were based on the clinical judgment of the investigator and were as follows: Atrial fibrillation was likely to be recurrent, atrial fibrillation was likely to cause morbidity or death, long-term treatment for atrial fibrillation was warranted, anticoagulation was not contraindicated, the patient was eligible for at least 2 drug trials in both treatment strategies, and treatment in both strategies could be initiated immediately after randomization. Additional information on the design, inclusion and exclusion criteria, and results of AFFIRM are available elsewhere (10–12).

The economic analysis described here compares costs

and effects of the 2 management strategies among patients enrolled in AFFIRM from the perspective of a third-party payer. The outcome was the incremental cost-effectiveness ratio comparing rhythm control and rate control, measured in dollars per life-year gained.

Survival

We obtained data on survival from the time of randomization to the end of study follow-up and use of specific health care resources for all 4060 AFFIRM patients. For patients who were lost to follow-up, withdrew from the study, or had incomplete follow-up, all available data were included in the analysis. Patients were censored at withdrawal or loss to follow-up. We derived the within-study mean survival time for each treatment group by using the Kaplan–Meier product limit estimator to account for censoring during follow-up (16). To obtain an unbiased estimate of mean survival, exposure was truncated at 5.65 years, which was the longest follow-up observed in AFFIRM (17).

Resource Use and Costs

We estimated costs by multiplying the number of each resource used by its unit cost (18). All unit costs for resources were estimated in U.S. dollars for the year 2002. Price estimates from earlier years were adjusted by applying the Consumer Price Index, Medical Care component (19). For each measure of resource use, 3 different unit costs were derived and considered in separate analyses: a base case for the most likely scenario, a low estimate, and a high estimate. The analysis considered costs of all hospitalizations, cardiac procedures, cardioversion, short-stay and emergency department visits, and medications used to treat atrial fibrillation from the perspective of a third-party payer.

Hospital Costs

At each follow-up visit during the study, the total number of hospitalized days since the last visit was recorded, along with the primary reason (cardiovascular or noncardiovascular cause) for hospitalization. The mean cost per hospital day was estimated from the Healthcare Cost and Utilization Project (HCUP) statistics for the 1995 HCUP-3 Nationwide Inpatient Sample (20) for Diseases of the Circulatory System, excluding any diagnosis associated with a mean patient age of younger than 18 years, for cardiovascular and noncardiovascular causes. The low and high estimates of the per diem for hospital days were based on the 25th and 75th percentile of mean charges, respectively. The HCUP prices were adjusted to represent costs by using a cost-to-charge ratio of 0.575, which is based on the 2002 estimate from the Centers for Medicare & Medicaid Services (21).

In addition, physician charges for subsequent hospital care as a level II visit (Current Procedural Terminology [CPT] [22] code 99232) were applied for each hospital day recorded. In the base case, an average estimate for the phy-

sician fee payment for this CPT code was calculated from the 2002 Physician Fee Schedule Payment Amount File National/Carrier for facility-based procedures for all carriers and localities listed in the database (23). In the sensitivity analysis, we used the minimum physician fee across carriers and localities for each procedure as the low cost estimate. We based the high cost estimate on the standard billed charge from the Marshfield Clinic, an ambulatory care facility in Marshfield, Wisconsin. This clinical center recruited most patients in the study and provides an estimate of charges for centers in the United States. Although these estimates are based on data from 1 facility, they are a reasonable estimate for the high-cost scenario, in between billed charges from a teaching hospital and a private clinic.

Costs of Cardiac Procedures

At each follow-up visit during the study, the number of cardiac procedures (percutaneous transluminal coronary angioplasty, coronary artery bypass graft surgery, pacemakers, valve surgery, ablation) performed since the previous follow-up visit was recorded. No information was available from AFFIRM to describe the number of arteries revascularized during percutaneous transluminal coronary angioplasty interventions or coronary artery bypass graft surgeries. We assumed that only 1 lesion was treated for each percutaneous transluminal coronary angioplasty procedure. We estimated the number of arteries revascularized during bypass surgery as a weighted average from the National Hospital Discharge Survey (NHDS) data set for 2000 (24, 25).

We included the costs of the most frequent cardiac procedures in the analysis. Hospital costs include the costs of all facility personnel except physicians. Physician costs consisted of a physician fee for diagnostic and therapeutic procedures, as well as any applicable anesthesia fee. Perfusionist fees for open-heart cardiac procedures were not included because these costs are included in the hospital costs.

The analysis included costs for pacemakers and implantable cardioverter defibrillators (ICDs) because they have high unit cost (24, 25). In the base case, the hardware cost (that is, device and electrode or electrodes costs) for the most widely used single-chamber and dual-chamber device was assigned on the basis of the list price as of June 2003 (not adjusted to 2002 dollars) supplied by the 3 largest device manufacturers (Medtronic, Inc. [Minneapolis, Minnesota]; Guidant Corporation [St. Paul, Minnesota]; St. Jude Medical [Sylmar, California]). For the sensitivity analysis, the low estimate excluded the cost of hardware, and the high estimate was based on the maximum cost provided by these manufacturers.

The costs for all catheter ablation procedures were based on the CPT codes for His bundle ablation procedures. Estimates for the physician professional fee payment for the CPT codes associated with each procedure were

included in the base-case, low, and high scenarios, and were calculated as described earlier for hospital days.

Costs of Cardioversions

At each follow-up visit during the study, the number of cardioversion attempts since the previous follow-up visit was recorded. The 3 categories of cardioversion were electrical procedures, pharmacologic procedures, and procedures using a combination approach. The base-case estimate for outpatient electrical cardioversion was based on the average payment made to St. Joseph Hospital in Marshfield, Wisconsin, between October 2002 and September 2003. The same cost was applied irrespective of the number of shocks or duration of anesthesia delivered at any single session. For electrical cardioversions for which neither a short-stay visit nor an emergency department visit or hospital days was recorded, a facility charge was also assigned. For the sensitivity analyses, no hospital payment was assigned for the low estimate; the billed hospital charges at St. Joseph Hospital were assumed for the high estimate.

We assumed that pharmacologic cardioversions consisted of outpatient amiodarone therapy (200 mg/d for 30 days) without a hospitalization. For sensitivity analyses of pharmacologic cardioversions, use of propafenone (at 1800 mg) and ibutilide (20% at 1 mg and 80% at 2 mg) was assumed for the low and high estimates, respectively (see section on medications for source of cost estimates).

The cost for combined electrical and pharmacologic cardioversion was the sum of the cost for each, as described earlier. The estimates for the physician fee payment for the CPT codes associated with any category of cardioversion in the base-case, low, and high scenarios were calculated as described earlier for hospital days.

Costs of Short-Stay and Emergency Department Visits

At each follow-up, the number of short-stay visits and emergency department visits since the last follow-up visit was recorded. A single cost was assigned to represent the fee paid to facilities for each short-stay and emergency department visit. This cost was based on the average Medicare costs for facilities, weighted by the frequency of groups in the Ambulatory Surgical Center payment files for level I and level II in the Healthcare Common Procedure Coding System (26). For the sensitivity analyses, the low estimate was the minimum payment, and the high estimate was the maximum payment from the same source. In addition, for each short-stay visit recorded, a physician professional fee for a level III emergency department visit (CPT 99283) was assigned (low and high scenarios were calculated as described earlier under hospital days).

Medication Costs

During the study, information was obtained at each follow-up visit on patient medication use since the previ-

Table 1. Mean Survival Time, Total Costs, and Incremental Cost-Effectiveness Ratio

Variable	Rate Control (n = 2027)	Rhythm Control (n = 2033)	Increment (Rhythm Control – Rate Control)	Incremental Cost-Effectiveness Ratio of Rhythm Control vs. Rate Control, \$/life-year*	Bootstrap Replicates in Which Rhythm Control Is Dominated by Rate Control, %†
Mean survival time, y	4.67‡	4.60‡	–0.08‡	–	
Costs, \$*					
Base case	20 546	25 623	5077	Rhythm dominated by rate§	95
Low estimate	8083	10 272	2189	Rhythm dominated by rate§	95
High estimate	27 488	32 969	5481	Rhythm dominated by rate§	95

* 2002 U.S. dollars.

† Ninety-five percent of the bootstrap samples were observed in the northwest quadrant of the scatter plot (Figure). This does not imply that the incremental cost-effectiveness ratio is statistically significant in the northwest quadrant.

‡ Values have been rounded.

§ Rhythm control is both more costly and less effective than rate control.

ous visit. Only medications used for treating atrial fibrillation (that is, rate-control and rhythm-control drugs) or for anticoagulation were included in the analysis. The use of other medications was similar in the 2 groups at baseline (10) and was not anticipated to differ materially between the 2 treatment groups during the course of the study. The duration of medication use was estimated to be the number of days between follow-up visits. Typical standardized doses used in practice, determined by consensus by the clinical authors, were applied to all medications for atrial fibrillation. If more than one antiarrhythmic medication was recorded at a follow-up visit, the duration of therapy for each drug was derived by dividing the number of days during the follow-up period evenly between them. Concurrent use of any combination of rate-control drugs except simultaneous use of diltiazem and verapamil was permitted. In addition, a single loading dose of 6 g was assumed the first time that the use of amiodarone was recorded for any patient. For patients taking antiarrhythmic drugs, the cost of anticoagulation with warfarin was also included at 2.5 mg of warfarin daily, with 5 mg of warfarin daily included for those who were not taking antiarrhythmic drugs.

For the base case, we determined the daily costs of medications from the Average Wholesale Prices for the least expensive generic drug available in the required dose with the fewest doses per day (27). We took the low estimate for the sensitivity analyses from the published prices from a widely used U.S. Internet pharmacy Web site that provides discount drug prices (28). The high estimate was taken as the average wholesale price for the most expensive drug in the class for the same drug regimen. When the average wholesale price was not available, an estimate was obtained from an alternative source (28). To reflect the costs of ongoing monitoring for warfarin therapy, the physician fee for one prothrombin time and international normalized ratio measurement (CPT 85610) was added for each month during the time period when warfarin use was recorded (22, 23, 29).

Cost-Effectiveness Analysis

Cost-effectiveness analysis evaluates and compares both costs and effects for alternative therapies. As described earlier, we first estimated effects (mean survival time) and the mean cost per patient for the rhythm-control and rate-control groups. We calculated the mean patient cost by multiplying each resource use component by the unit cost and summing the results for each patient; we then calculated the mean across all patients. Future costs and effects were discounted to their present value at a rate of 3% per annum (16, 30–32).

Then, the presence of dominance (when 1 strategy is both less costly and more effective than the other) is assessed by comparing the estimates for mean survival and mean cost for each group. If no dominance is present, the incremental cost-effectiveness ratio of rhythm control would be computed as the ratio of the difference (rhythm control minus rate control) in mean cost to the difference in mean survival (16, 33, 34).

Recent developments in economic methods emphasize the importance of quantifying uncertainty about the incremental cost-effectiveness ratio by examining the joint density of cost and effect differences (35–42). This is particularly relevant in the context of a negative trial, such as AFFIRM, in which differences in outcomes between rate control and rhythm control are either very small or not statistically different. In this situation, examining the economic implications of these alternative therapies is even more relevant. A sampling distribution of incremental costs and effects was estimated by the resampling technique of nonparametric bootstrapping with 10 000 replicates and was presented as a scatter plot. Bootstrapping is a simulation method for statistical inference. Each bootstrap sample is obtained by repeated random sampling with replacement from the original data points (43).

All analyses were performed by using SAS, version 8 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

The funding source had no role in the design, conduct, and reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

Survival

As reported in the main findings from AFFIRM (12), the survival distributions in the rhythm-control group and the rate-control group were similar. In this analysis, the within-study survival gain was approximately 0.08 year (95% CI, -0.02 to 0.17 year; *P* = 0.10) longer with rate control than with rhythm control, but this difference was not statistically significant (Table 1).

Costs

Patients in the rate-control group used fewer resources, as defined in the Methods, than those in the rhythm-control group (Table 2). The differences in resource use between rate control and rhythm control were most notable for the number of hospital days (3074 more days in the rhythm-control group), number of cardiovascular hospital days (117 more days in the rate-control group), number of all 3 types of cardioversions, and number of short-stay and emergency department visits (907 more visits in the rhythm-control group). The distribution of the number of hospital days was similar in the rate-control and rhythm-control groups. An increased rate of cardioversion is expected in the rhythm-control group, and an increased rate of ablations of the atrioventricular junction is expected in the rate-control group because each of these procedures is part of the treatment in each group.

The patterns of medication use reflected the randomized treatment assignment to the rhythm-control or rate-control group of AFFIRM (Table 3). The use of rate-control agents in the rhythm-control group was consistent with the study protocol and was representative of use in clinical practice. The drug cost per day was greater for all of the rhythm-control drugs compared with the rate-control drugs, with the exception of quinidine.

The incremental cost of rhythm control compared with rate control was \$5077 per person in the base case and ranged from \$2189 to \$5481 per person for the low-cost and high-cost scenarios, respectively.

Incremental Costs versus Incremental Effects

Point estimates of cost-effectiveness show that rhythm control was more costly and less effective than rate control for all 3 cost scenarios (base case, low, and high). This means that the incremental cost of rhythm control was greater than the cost of rate control, and the mean survival for rhythm control was lower (although only slightly) than for rate control.

The Figure is a scatter plot that illustrates the uncertainty in the expected incremental costs and life-years for rhythm control versus rate control for the base case. All bootstrap replicates lie above zero on the cost axis, indicating a high degree of certainty that rhythm control is more costly than rate control. Data points from bootstrapping that lie in the “northeast” quadrant of the cost-effectiveness plane represent a survival gain from rhythm control at an additional cost. Points that lie in the “northwest” quadrant represent lower survival from rhythm control at an additional cost. Rate control was associated with longer survival

Table 2. Number of Resource Events or Procedures in Each Group

Resource Events or Procedures	Overall (<i>n</i> = 4060), <i>n</i>	Rate-Control Group (<i>n</i> = 2027), <i>n</i>	Rhythm-Control Group (<i>n</i> = 2033), <i>n</i>	Difference in Events (Rate Control – Rhythm Control), <i>n</i>	Estimated Unit Costs, \$*		
					Base Case	Low Scenario	High Scenario
Hospital days	46 840	21 883	24 957	-3074			
Cardiovascular hospital days	6881	3499	3382	117	1627	606	1914
Noncardiovascular hospital days	39 729	18 233	21 496	-3263	1535	587	1746
Pacemaker procedures (single chamber)	177	130	47	83	9788	440	13 777
Pacemaker procedures (dual chamber)	265	103	162	-59	11 995	446	16 205
Implantable cardiac defibrillator procedures	30	14	16	-2	34 311	895	39 273
Percutaneous transluminal coronary angioplasties	177	92	85	7	848	691	5884
Coronary artery bypass graft procedures	135	72	63	9	2958	2451	19 378
Valve surgery procedures	87	45	42	3	3110	2575	14 881
Ablations	249	147	102	45	555	452	4559
Cardioversion recorded at follow-up							
Electrical	1341	262	1079	-817	150-633†	129-612†	645-1565†
Pharmacologic	810	176	634	-458	106	18	467
Combined (electrical and pharmacologic)	748	91	657	-566	256-739†	147-630†	1112-2032†
Short-stay or emergency department visits	5870	2618	3525	-907	569	382	1173

* 2002 U.S. dollars.

† Low end of range represents the unit cost when neither short-stay visit nor hospital days were recorded. The high end of the range represents the unit cost when either a short-stay visit or hospital days were recorded.

Table 3. Drugs Used at Any Time in the Rate-Control Group and Rhythm-Control Group

Study Drug	Rate-Control Group (n = 2027), n (%)	Rhythm-Control Group (n = 2033), n (%)	Difference (Rate Control – Rhythm Control), percentage points	Daily Dose*	Estimated Drug Cost per Day, \$†		
					Base Case	Low	High
Rate-control drugs							
Digoxin	1432 (70.6)	1106 (54.4)	16.2	0.25 mg	0.06	0.15	0.24
β-Blockers (atenolol, metoprolol, propranolol)	1380 (68.1)	1008 (49.6)	18.5	50, 100, or 120 mg	0.83	0.18	1.42
Diltiazem	935 (46.1)	610 (30.0)	16.1	240 mg	1.15	0.98	2.37
Verapamil	340 (16.8)	204 (10.0)	6.8	240 mg	1.37	0.26	2.16
Rhythm-control drugs							
Amiodarone	207 (10.2)	1277 (62.8)	–52.6	200 mg	3.53	1.44	3.92
Sotalol	84 (4.1)	841 (41.4)	–37.3	160 mg	4.69	2.28	5.62
Propafenone	45 (2.2)	294 (14.5)	–12.3	675 mg	6.99	3.94	7.79
Procainamide	30 (1.5)	173 (8.5)	–7	1000 mg	1.60	0.44	1.90
Quinidine	14 (0.7)	151 (7.4)	–6.7	900 mg	1.20	1.12	3.44
Flecainide	29 (1.4)	169 (8.3)	–6.9	200 mg	5.46	2.59	6.07
Disopyramide	7 (0.3)	87 (4.3)	–4	450 mg	2.46	1.68	2.46
Moricizine	2 (0.1)	35 (1.7)	–1.6	600 mg	3.28	2.85	3.92
Dofetilide	5 (0.2)	12 (0.6)	–0.4	500 μg	3.71	3.71	3.71
Nonstudy drugs							
Warfarin	1969 (97.1)	1967 (96.8)	0.3	5 mg (rate group) 2.5 mg (rhythm group)	0.61	0.39	0.71

* Standardized dose, as determined by the clinician authors.
† 2002 U.S. dollars.

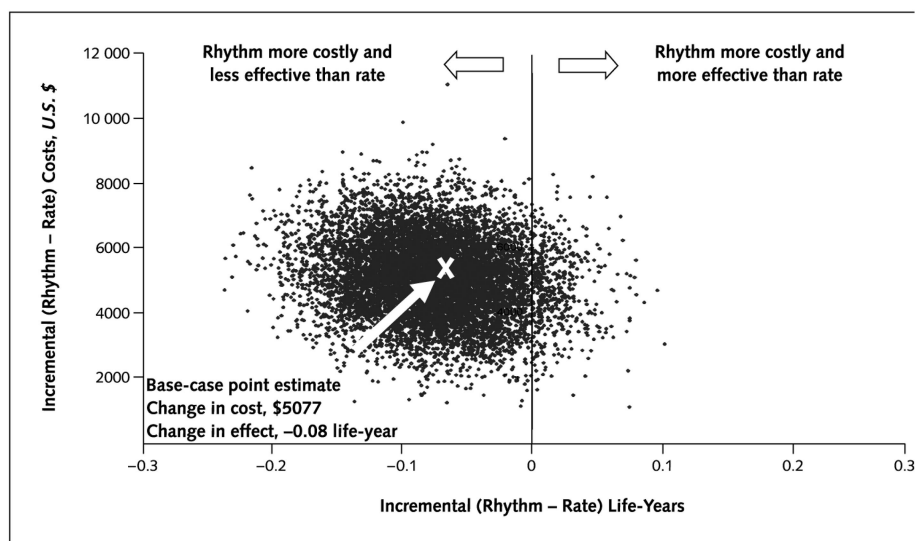
and lower cost than rhythm control in 95% of the bootstrap replicates in all cost scenarios (Figure and Table 1).

DISCUSSION

This economic analysis of AFFIRM demonstrates that on the basis of conventional decision criteria (44), rhythm control is not cost-effective compared with rate control. AFFIRM demonstrated a nonsignificant trend toward re-

duced survival in patients with atrial fibrillation who attempt rhythm control compared with rate control. The present analysis demonstrated that rhythm control is consistently more expensive than rate control in such patients, and, consequently, rate control is the preferred alternative (rhythm control was dominated by rate control) on the basis of cost. An intervention that is less effective and more costly than its comparator is considered to be “dominated

Figure. Scatter plot of estimated joint density of incremental costs and incremental effects of rhythm control versus rate control by bootstrap resampling (base case).



by” the alternative (16). These results were insensitive to changes in the cost estimates explored in the sensitivity analyses.

In AFFIRM-eligible patients, a rate-control strategy is acceptable. Because other trials showed that anticoagulation to reduce embolic complications significantly reduces mortality in patients with atrial fibrillation, clinicians should initiate and maintain anticoagulation regardless of whether rate control or rhythm control is attempted (45–48).

Other authors have examined the incremental cost-effectiveness of rhythm-control and rate-control strategies for treating atrial fibrillation by using decision analytic models. Catherwood and colleagues (15) concluded that strategies involving cardioversion with or without antiarrhythmic agents were more effective and less costly than rate control plus warfarin or aspirin. Eckman and colleagues (14) found that cardioversion followed by the use of amiodarone and warfarin was the most effective strategy among several competing antithrombotic and antiarrhythmic treatment strategies. The results of these modeling studies were limited by the lack of randomized data on efficacy and resource use, which required several assumptions about the model parameters.

In this economic analysis from the results of AFFIRM, we found nonsignificant differences in mean survival time, but the costs of treatment were always higher in the rhythm-control group. The incremental cost of rhythm control was \$5077 per person, and the mean survival for the rhythm-control group was lower (difference, 0.08 year [CI, –0.02 to 0.17 year]; $P = 0.10$) than for the rate-control group. Rhythm control was dominated by rate control in 95% of the bootstrap replicates. To examine the robustness of the results, we included 2 alternative cost estimates in a sensitivity analysis. The low and high cost estimates represent the lowest and highest cost for each component of resource use, respectively. Regardless of which cost scenario was used, rhythm control was dominated by rate control (rhythm control was both less effective and more costly than rate control).

For comparison, we consider the results for life-years gained from previously published cost-effectiveness results of interventions for cardiac patients. In the Scandinavian Simvastatin Survival Study (49, 50), the cost-effectiveness of cholesterol lowering in 59-year-old men with a history of heart disease was estimated at approximately \$5500 per life-year gained (using a conversion rate of 1.72 U.S. dollars/British pound). The Oxford health check study estimated the cost-effectiveness of advice on lifestyle to 50-year-old men to reduce cardiovascular risk to be approximately \$16 500 per life-year gained (50, 51). The Bypass Angioplasty Revascularization Investigation demonstrated that in patients with multivessel coronary disease, coronary bypass surgery had a cost-effectiveness ratio of

\$26 117 per life-year gained compared with angioplasty (52).

Our study has several limitations. The data on resource use collected in AFFIRM were limited; they included only medications, hospital visits, cardiac procedures, and short-stay and emergency department visits. Because details on the quantities and doses of dispensed medications and adherence to prescribed medications were not available, we made assumptions about medication use on the basis of routine clinical practice. In addition, data on the use of medications for atrial fibrillation were obtained from reports at each follow-up visit, and duration was assumed to be the number of days between follow-up visits. Standardized medication doses were assumed. Misclassification of medication exposure was probably nondifferential and almost certainly small with respect to treatment assignment. Any misclassification would probably result in an underestimate of the true difference in the cost of medications for rhythm control versus rate control.

Hospital stays constituted a large proportion of total health care resource use for this patient sample, but information about hospital stays was limited to the total number of days hospitalized since the previous follow-up visit and whether the hospitalization that accounted for the most days in a given follow-up period was for cardiovascular or noncardiovascular reasons. We assumed that all hospitalization days during a follow-up period were for the reason indicated as the main reason for hospitalization. Although there is little information to validate this assumption, the absolute difference in unit costs between cardiovascular and noncardiovascular hospital days was small (<\$100 for the base case [Table 2]). It is unlikely that even an extreme misclassification of hospital day types would change the interpretation of the results because the total number of hospital days for rhythm control was greater than rate control.

Costs were assigned to resource use estimates from various sources, mostly representing Medicare reimbursement rates. Although base-case costs could have been estimated from 1 or all of the participating centers in AFFIRM, this study was conducted at 213 clinical sites across the United States and Canada. Therefore, for the base-case scenario, we applied unit costs that are publicly available and more generally representative of standard estimates for a broad range of centers.

The generalizability of these economic results is limited to patients similar to those enrolled in AFFIRM (that is, those with atrial fibrillation who were at least 65 years of age or who had other risk factors for stroke or death) and given similar treatment protocols. The results apply to many patients with atrial fibrillation but probably cannot be generalized to younger patients without risk factors for stroke or death.

In addition, the AFFIRM protocol permitted the use of several drugs and nonpharmacologic therapy, and high crossover rates (14.9% from rate control to rhythm control

and 37.5% from rhythm control to rate control after 5 years) were observed. Use of a single drug treatment may have yielded a different result. Furthermore, the mean length of follow-up was 3.5 years, and the cost-effectiveness analysis is a within-study analysis, confined to this time period.

Further considerations in this analysis are the assumptions regarding costs. We assumed that costs were evenly distributed over the study follow-up period for the purpose of discounting. Although we could account for censoring in the estimation of survival, this analysis does not address the joint problem of estimating CIs for cost-effectiveness with censored cost and outcomes data (19).

Finally, the cost-effectiveness estimate reported here is based on survival as the outcome, without accounting for differences in quality of life between the 2 treatment strategies. The cost-effectiveness of rhythm control could become more favorable if the quality of life were lower in the rate-control group. Given the side effect profile of rhythm control, this is unlikely. Furthermore, no difference in quality of life was found between the rhythm-control and rate-control strategies in either a subset of the patients enrolled in AFFIRM (53), in a European study (54), or in the RACE study (55).

Despite these limitations, this analysis has several strengths. First, to our knowledge, it is the only economic analysis of antiarrhythmic therapy for atrial fibrillation that is based on effects and major resource use data collected concurrently from a large randomized trial. The results of such an analysis are less susceptible to bias or confounding than previous analyses that combined effects data from multiple sources. Second, the analysis evaluated the point estimate and variation in incremental costs and effects. Third, the sensitivity analyses demonstrated that results are robust to reasonable changes in costs.

This analysis of AFFIRM shows that, over a wide range of assumptions, rhythm control was both more costly and less effective than rate control. The probability that rhythm control is cost-effective relative to rate control for the base-case scenario remains less than 0.01, even at a value of \$100 000 per life-year gained. In general, for patients with atrial fibrillation similar to those enrolled in AFFIRM, rate control is a cost-effective approach to the management of atrial fibrillation when compared with maintenance of sinus rhythm.

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