Atrial Fibrillation and Congestive Heart Failure: A Cost Analysis of Rhythm-Control vs Rate-Control Strategies

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ABSTRACT

Background: Atrial fibrillation (AF) is common in patients with heart failure. Rhythm- and rate-control strategies are associated with similar efficacy outcomes. We compared the economic impact of the 2 treatment strategies in patients with AF and heart failure from the province of Québec, Canada.

Methods: In a substudy of the Atrial Fibrillation and Congestive Heart Failure trial, health care expenditures of patients from Québec randomized to rhythm and rate-control treatment strategies were compared from a single-payer perspective using a cost-minimization approach. In-trial resource utilization and unit costs were estimated from Québec Health Insurance Board databases supplemented by disease-specific costs from the Ontario Case Costing Initiative.

Results: In all, 304 patients were included, aged 68 ± 9 years; 86% male; ejection fraction, 26% ± 6%. Baseline characteristics were similar in rhythm-control (n = 149) and rate-control (n = 155) groups. Arrhythmia-related costs accounted for 45% of total expenditures. Rate-control patients had fewer cardiac procedures (146 vs 238, P < 0.001), driven by fewer cardioversions, and lower costs related to antiarrhythmic drugs (CAD$48 per patient [95% confidence interval (CI), $21-$96] vs $1319 per patient [95% CI, $1124-$1522]). However, these differences were offset by higher expenditures due to hospitalizations for noncardiovascular diagnoses, implantable cardiac arrhythmia devices, and noncardiovascular drugs in the rate-control group. The total cost per patient was not significantly different among the 2 treatment strategies.

RÉSUMÉ

Introduction : La fibrillation auriculaire (FA) est fréquente chez les patients ayant une insuffisance cardiaque. Les stratégies de la maîtrise du rythme et de la fréquence sont associées à des résultats d’efficacité similaires. Nous avons comparé les conséquences économiques des 2 stratégies de traitement chez les patients ayant une FA et une insuffisance cardiaque de la province de Québec, au Canada.

Méthodes : Dans une sous-étude de l’essai AF-CHF (Atrial Fibrillation and Congestive Heart Failure : fibrillation auriculaire et insuffisance cardiaque congestive), les dépenses en soins de santé des patients du Québec randomisés aux stratégies de traitement par la maîtrise du rythme et de la fréquence ont été comparées selon un modèle à payeur unique en utilisant une approche de minimitisation des coûts. L’utilisation des encours durant l’essai et les coûts unitaires ont été estimés à partir des bases de données de la Régie de l’assurance maladie du Québec complétées par les coûts spécifiques à la maladie de l’initiative ontarienne du coût par cas.

Résultats : En tout, 304 patients âgés de 68 ± 9 ans ont été inclus; 86 % d’hommes; une fraction d’éjection de 26 % ± 6 %. Les caractéristiques initiales étaient similaires dans les groupes de maîtrise du rythme (n = 149) et dans les groupes de maîtrise de la fréquence (n = 155). Les coûts liés à l’arythmie ont compté pour 45 % des dépenses totales. Les patients ayant une maîtrise de la fréquence ont subi moins d’interventions cardiaques (146 vs 238, P < 0.001) grâce à moins de cardioversions et à des coûts liés aux médicaments

Atrial fibrillation (AF) and heart failure are 2 of the most common cardiovascular diseases of the modern era. They are estimated to afflict 250,000 and 500,000 Canadians, respectively, with prevalence rates that are anticipated to dramatically increase during the next decades. Associated health care resource use is substantial.

The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial compared rhythm- and rate-control treatment strategies for AF in patients with CHF. After a mean follow-up of 37 months, no differences were found in primary and secondary efficacy end points, including cardiovascular death and all-cause mortality. Similar outcomes were observed despite the fact that the median proportion of time spent in
between rhythm-control ($72,764 [95% CI, $61,575-$85,145]) and rate-control ($78,767 [95% CI, $67,101-$92,139]) strategies.

**Conclusion:** In the study population, the therapeutic strategy used to manage AF in patients with severe heart failure appears to have little influence on the overall financial burden, which remains substantial.

sinus rhythm was 96% in the rhythm-control arm, compared with 9% in the rate-control arm. It has yet to be determined how cost considerations may influence management decisions. We, therefore, sought to compare the economic impact associated with rhythm- vs rate-control treatment strategies in patients with AF and CHF from the province of Québec, Canada.

**Methods**

**AF-CHF study**

Efficacy data were derived from the AF-CHF trial. In short, 1,376 patients from 123 centres were randomized to rhythm- vs rate-control strategies. Randomization was performed with permuted blocks stratified according to the study centre. Inclusion criteria consisted of documented AF, left ventricular ejection fraction (LVEF) ≤ 35%, and New York Heart Association functional class II to IV symptoms within 6 months of randomization or class I symptoms if the LVEF was ≤ 25% or if the patient was hospitalized for heart failure in the preceding 6 months.

Rhythm control was attempted with electrical cardioversion combined with antiarrhythmic drug therapy (class III agents), and additional nonpharmacologic therapy (eg, catheter ablation) in refractory patients. Rate control was achieved primarily with atrioventricular nodal blocking drugs.

**Patient selection**

The cost analysis focused on the subgroup of patients from Québec, Canada. In Québec, all medical acts and hospitalizations are covered by a universal single payer health insurance plan. For medical services provided in hospitals or clinics, physicians are reimbursed by the Québec Health Insurance Board (Régie de l’assurance maladie du Québec [RAMQ]). The RAMQ administrative databases contain exhaustive health care services data on all patients who contacted the health care system as inpatients or outpatients. Diagnostic codes adhere to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). All patients aged 65 years and older are covered by the RAMQ medication insurance plan, and those younger than 65 years receive pharmaceutical coverage by RAMQ if they do not have access to a private plan. The reliability of the RAMQ database for pharmacoepidemiologic research has been validated previously.

For the current analysis, medical claims and pharmaceutical databases were obtained from 2001 through 2008 to encompass the AF-CHF study period (ending June 30, 2007). This cost analysis was a prespecified AF-CHF substudy approved by each participating centre’s institutional review board. All patients provided written informed consent.

**Economic evaluation**

The rationale to conduct a cost-minimization analysis as the primary analysis was based on equal effectiveness with regards to cardiovascular outcomes, all-cause mortality, quality of life, and functional capacity in patients with AF and CHF randomized to rhythm- vs rate-control strategies. The perspective adopted is that of a single payer agent, the Québec Ministry of Health. Direct medical costs included hospitalizations, cardiac procedures, emergency department visits, all other ambulatory medical encounters, and medications. Temporal horizon was limited to time spent by each patient while under observation. The 2 arms were compared by means of the intention-to-treat principle.

**Resource use and cost**

In-trial health care costs were inflated to 2009 Canadian values according to consumer price indices for health care. The costs of hospitalizations and cardiac procedures were estimated with 2006-2007 data from the Ontario Case Costing Initiative (OCCI). OCCI collects patient-level clinical and cost data from 47 Ontario hospitals classified by case mix group according to standardized case-costing methodology. It includes direct costs incurred, as well as hospital-related overhead expenses. Professional fees are typically not included. OCCI is considered representative of the Canadian health care system as a whole. Costs associated with physician services during hospitalizations, emergency department visits, other ambulatory medical encounters, and procedures were directly retrieved from the RAMQ database.

**Hospitalizations, emergency department visits, and other ambulatory medical encounters**

Number of hospitalizations and in-hospital length of stay were estimated from medical claims from RAMQ and
a previously validated algorithm. A hospitalization was considered “cardiovascular” if 1 of the following diagnostic categories was coded: arrhythmias (ICD-9-CM 426.x-427.x), embolism (ICD-9-CM 434.x-436.x), heart failure (ICD-9-CM 428.x), or other cardiovascular diagnoses (ICD-9-CM 390.x-425.x; 429.x). Emergency department visits associated with hospital admissions or additional claims on the following day were considered hospitalizations and costed as such.

Disease-specific hospitalization per diem costs were derived from OCCI data. Each emergency department visit was assigned a cost of CAD$308 based on the Montreal Heart Institute’s 2009 annual financial report and on estimated costs for routine tests (the Montreal Heart Institute was the AF-CHF coordinating centre). Physician claims not qualifying as emergency department visits or hospitalizations were considered “other ambulatory medical encounters.” Since it is not feasible to attribute a unit cost to the wide range of ambulatory noncardiac procedures and diagnostic acts, costs were limited to physician claims in the RAMQ database.

Cardiac procedures. Cardiac procedures were identified by their ICD-9-CM codes in the RAMQ database. Case report forms completed by local investigators were used to validate codes for biventricular pacemakers, implantable cardioverter-defibrillators, and ablation procedures. The OCCI unit cost was used for each cardiovascular procedure. Unlike other procedures, OCCI data for coronary artery bypass graft surgery, valve surgery, and cardiac transplantation provide an average total cost per case for an average hospital length of stay, merging procedural and hospitalization costs. In order to avoid duplication of hospitalization costs, admissions involving 1 of these 3 procedures were exclusively assigned the OCCI unit cost, with no separate costing for the hospitalization. For example, the cost attributed to coronary artery bypass graft surgery was $20,865, which includes a mean inpatient stay of 9 days. When the actual length of stay for an individual hospitalization was different from the mean OCCI value, costs were adjusted by adding or subtracting corresponding cardiovascular per diem costs. Costs associated with biventricular pacemakers and catheter ablation for pulmonary vein isolation were derived from the OCCI supplemented by 2 Ontario Health Technology analyses.

Medications. The RAMQ pharmaceutical services database served as the primary data source for all publically insured patients. The pharmaceutical consumption of privately insured patients was assumed to be equivalent to that of RAMQ-insured patients. RAMQ payments include the pharmacist’s professional fee and the authorized medication cost.

Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables are summarized by mean ± standard deviation or median and interquartile range (25th, 75th percentile), depending on normality of distribution. Comparisons between rhythm- and rate-control groups were analyzed with Pearson’s \( \chi^2 \) tests for categorical variables and the Student’s t test for continuous data. Freedom from cardiovascular death was estimated by the Kaplan-Meier method and compared by the log-rank test. Mean per-patient costs are presented, along with corresponding 95% confidence intervals (CIs). Because of the nonnormality of data distribution, the bootstrap resampling method (10,000 samples) was used to compare health care resource use and costs. The bias-corrected and accelerated method was used to generate CIs. A level of significance of 0.05 was set for all analyses. All statistical analyses were conducted with SAS version 9.2 (SAS Institute Inc, Cary, NC).

In addition, 1-way and 2-way sensitivity analyses were performed by varying the hospitalization rates within plausible estimates. In addition, the relationship between difference in costs and effectiveness by the bootstrap resampling method was plotted (Fig. 1).

Results

Baseline characteristics

Among the 1376 patients enrolled in the AF-CHF trial, 310 were from Québec. Six patients were excluded because of expired RAMQ files (eg, out-of-province relocation). The study population consisted of the remaining 304 patients, 149 of whom were randomized to rhythm control and 155 to rate control. The patients were well matched with respect to baseline characteristics (see Supplemental Table S1) and were generally representative of the Canadian patients enrolled in the AF-CHF study (Supplemental Table S2). Patients randomized to rhythm control and rate control were followed for 523 and 508 patient-years, respectively. Consistent with the main trial results, death from cardiovascular causes occurred in 37 (25%) and 49 (32%) patients in rhythm- and rate-control groups (log-rank \( P = 0.17 \)).

Health care resource utilization and costs

Table 1 summarizes health care resource utilization by treatment group and associated unit costs. During the course of the study, there were 1070 hospitalizations, 506 in the rhythm-control group and 564 in the rate-control group, resulting in 4414 and 5213 hospitalization days, respectively.
(\(P = 0.36\)). Cardiovascular diagnoses accounted for 84% and 80% of hospitalization days in the rhythm- and rate-control groups, respectively (\(P < 0.001\)). Cardiovascular procedures were more frequently performed in the rhythm-control group, driven by a higher number of electrical cardioversions (0.8 ± 1.2 vs 0.1 ± 0.5 per patient; \(P < 0.001\)). Pulmonary vein isolation was performed in only 3 patients in the rhythm-control group. Single-chamber pacemakers were more commonly implanted in the rate-control group. A nonsignificant trend also suggested more biventricular pacemakers and implantable cardioverter-defibrillators in the rate-control group. The number of emergency department visits was likewise similar between the 2 groups. Atrial fibrillation was responsible for nearly half of these claims (50% vs 48% in rhythm- vs rate-control groups, respectively (\(P = 0.46\)). Other ambulatory medical encounters were likewise evenly distributed between the 2 groups. A cardiovascular diagnosis was responsible for nearly half of these claims (50% vs 48% in rhythm- vs rate-control groups, respectively).

As summarized in Table 2, pharmaceutical expenditures were similar for the 277 publicly insured patients in the rhythm- and rate-control groups. Patients assigned rhythm control had significantly higher costs related to antiarrhythmic drugs. Amiodarone was the drug of choice for maintenance of sinus rhythm.

The mean total direct medical cost per patient during the trial, shown in Table 3, was estimated at $72,764 (95% CI, $61,575-$85,145) with rhythm control vs $78,767 (95% CI, $67,101-$92,139) with rate control, representing a nonsignificant reduction of $6,004 (95% CI, $23,577 to $11,193) with the rhythm-control strategy. The mean follow-up duration was 42 months in the rhythm-control group vs 39 months in the rate-control group (\(P = 0.22\)), yielding a mean annualized cost per patient of $28,185 (95% CI, $22,331-$36,011) vs $36,898 (95% CI, $28,869-$47,620), respectively. This represents a nonsignificant annualized reduction of $8,713 (95% CI, $20,448 to $2,594) with rhythm control. Figure 1 displays the distribution of incremental cost and survival using bootstrap simulation on a cost-effectiveness plane.

### Arrhythmia- and heart failure-related costs

The proportion of hospitalizations that included an arrhythmia diagnosis was 35% with rhythm and 31% with rate control, respectively (\(P = 0.21\)). Considering only arrhythmia-related costs, differences in expenses remained nonsignificant ($34,620 [95% CI, $27,459-$42,782] vs $34,538 [95% CI, $27,968-$42,481] per patient with rhythm vs rate control; cost difference, $82 [95% CI, $-10,277 to $10,695]). Costs related to hospitalizations for arrhythmias were similar ($20,738 [95% CI, $15,889-$26,429] vs $19,684 [95% CI, $15,676-$24,347] per patient with rhythm vs rate control; cost difference, $105 [95% CI, $-5,624 to $8,065]). Costs related to hospitalizations for heart failure were likewise similar in the 2 groups ($18,358 [95% CI, $13,554-$23,817] vs $19,989 [95% CI, $14,757-$26,409] per patient with rhythm vs rate control; cost difference, $-1632 [95% CI, $-9615 to $5864]).

### One-way and 2-way sensitivity analyses

Six scenarios were generated by varying hospitalization rates by ± 25% independently in 1 treatment group at a time and simultaneously in the 2 treatment arms. In 4 scenarios, the results remained consistent with the base-case analysis showing no statistically significant difference in total cost per
Table 2. Pharmaceutical costs for publicly insured patients

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Rhythm control (n = 108)</th>
<th>Rate control (n = 119)</th>
<th>Cost difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sum of costs, $</td>
<td>Mean per patient, (95% CI)</td>
<td>Sum of costs, $</td>
</tr>
<tr>
<td>Antiarrhythmic agents</td>
<td>142,419</td>
<td>(1124-1522)</td>
<td>5723</td>
</tr>
<tr>
<td>β-blockers</td>
<td>74,587</td>
<td>(495-951)</td>
<td>97,475</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>16,786</td>
<td>(79-255)</td>
<td>22,469</td>
</tr>
<tr>
<td>Digoxin</td>
<td>22,114</td>
<td>(156-260)</td>
<td>40,707</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>149,090</td>
<td>(1146-1643)</td>
<td>136,534</td>
</tr>
<tr>
<td>Diuretics</td>
<td>36,632</td>
<td>(338-392)</td>
<td>38,188</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>9683</td>
<td>(62-121)</td>
<td>14,082</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>12,550</td>
<td>(33-248)</td>
<td>4950</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>47,049</td>
<td>(309-613)</td>
<td>56,197</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>139,926</td>
<td>(1032-1522)</td>
<td>169,927</td>
</tr>
<tr>
<td>Other cardiovascular drugs*</td>
<td>48,151</td>
<td>(1124-1522)</td>
<td>49,091</td>
</tr>
<tr>
<td>Thyroid hormone replacement</td>
<td>12,952</td>
<td>(80-165)</td>
<td>6711</td>
</tr>
<tr>
<td>Total</td>
<td>1,131,215</td>
<td>(8819-12,037)</td>
<td>1,152,095</td>
</tr>
</tbody>
</table>

All costs are listed in Canadian dollars.

* Hydralazine, long-acting nitrates, and aldactone.

patient. In 2 scenarios, rate control led to significantly higher medical costs than did rhythm control. Differences between rhythm- and rate-control groups ranged from −$6,504 to $18,511 per patient. Rhythm control was never associated with significantly higher costs than rate control.

**Discussion**

Our results indicate that total health care and arrhythmia-related costs associated with rhythm- and rate-control treatment strategies for AF in the setting of heart failure do not differ significantly. The trend toward higher costs associated with rate control ($6,000) and the results of our bootstrap replication analysis challenge the common belief that rhythm control is a more costly treatment strategy in this patient population. Strengths of the current study include the comprehensive RAMQ database, which covers the full continuum of medical services and captures all encounters with the health care system, including those not included in case report forms. Moreover, actual professional fees billed to third-party payers are measured directly. Similarly, pharmaceutical service costs are limited to actual prescriptions dispensed to patients by the pharmacist as opposed to any prescription, whether or not received.

Our findings refute the hypothesis that rhythm control is associated with greater costs as a result of antiarrhythmic drug therapy and more numerous hospital admissions for recurrent AF and cardioversions. These potential additional costs were offset by factors such as increased costs for noncardiovascular hospitalizations, additional implantable cardiac arrhythmia devices, and noncardiovascular drugs in the rate-control group. We hypothesize that the more common use of pacemakers and cardioverter-defibrillators in the rate-control group during the study resulted from the more aggressive use of negative chronotropic agents in this group. In this context, it is plausible that depressed LVEF and poor functional class influenced the selection of device therapy (eg, biventricular pacemaker and implantable cardioverter-defibrillators).

Our patient population was characterized by substantial morbidities, as 75% of patients had New York Heart Association class III or IV symptoms within the preceding 6 months, the LVEF averaged 26%, coronary artery disease was present in 63%, and prior stroke in 12%. As a result, the overall economic burden was primarily driven by non–arrhythmia-related costs. Nevertheless, when only arrhythmia-related expenditures were considered, costs remained comparable between the 2 strategies. The sensitivity analyses showed that the data are robust when hospitalization rates, a major driver of cost in this population, were varied within large boundaries.

Prior economic research efforts assessing the cost-effectiveness of therapies for AF have been based largely on decision-analytical techniques.19,20 In the Atrial Fibrillation
Follow-up Investigation of Sinus Rhythm Management (AFFIRM) trial, the largest randomized study to compare rate- vs rhythm-control strategies in patients with predominantly normal heart function, rate control was associated with fewer hospital days, electrical cardioversions, short-stay visits, and emergency department visits, when compared with rhythm control.11 Since rate control was associated with a trend toward longer survival and lower costs, it was considered the preferred alternative. However, information regarding hospital stays and medications was limited. In addition, follow-up visit reports used to quantify resource use were potentially subject to recall biases and misclassification errors. Our current analysis, which relies on more extensive costing methodology, suggests that these results may not be generalized to a population with more advanced forms of heart disease and greater comorbidities.

Limitations

Any economic analysis performed alongside a clinical trial may be subject to protocol-driven costs. However, the AF-CHF trial was designed to reflect usual care and to capture rather than mandate approaches used to achieve rhythm or rate control. While few patients in our study had catheter ablation for AF, the potential impact of more widespread use of this procedure was not modelled in our analysis. Second, skewed cost distribution data, as encountered in most economic analyses, may pose particular challenges. Methods to address resulting issues, such as the use of standard nonparametric statistical tests or data truncation, reduce the impact of outliers but may produce misleading results. We preferred the nonparametric bootstrap test, which, unlike alternative methods, takes into account the impact of large costs without making any assumption regarding normality of data.17 Third, RAMQ pharmaceutical information was lacking in 25% of the study cohort because of private insurance plans. Since baseline patient characteristics and concomitant drug therapy between those with (n = 227) and without (n = 77) public health insurance were comparable, pharmaceutical costs were assumed to be similar. This assumption is unlikely to substantially bias our overall findings, considering that pharmaceutical expenditures accounted for only 13% of overall costs and that misclassification errors are likely to be nondifferential. In addition, the study population was relatively small, such that analyses were underpowered to assess cost equivalency (ie, possibility of a type II error). However, given the nonsignificantly lower costs associated with rhythm-control therapy, it is unlikely that a larger sample size would reverse this trend to favour rate control. Furthermore, health resource use may reflect local practices in Québec, which may not be generalizable to other health care systems. Nevertheless, the Québec population was generally representative of Canadian patients enrolled in the AF-CHF study, as reflected by similar characteristics with respect to associated comorbidities, previous hospitalizations, functional class, LVEF, primary classification of AF, and prior cardioversions.

Conclusion

Our cost analysis of rhythm- vs rate-control strategies in patients with AF and CHF indicates that the overall financial burden is substantial. The patient population is characterized by considerable comorbidities such that arrhythmia-related costs accounted for less than half of the total economic burden. The rhythm-control strategy was associated with a greater number of electrical cardioversions and higher anti-arrhythmic drug-related expenses. However, these costs were counterbalanced by other expenditures such that arrhythmia-related and total costs were not significantly different from rate-control therapy. These findings challenge the popular belief that rhythm control is more costly than rate control and provide further justification for tailored therapy according to the clinical scenario.

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Disclosures

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References


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