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## Rhythm Versus Rate Control Therapy and Subsequent Stroke or Transient Ischemic Attack in Patients With Atrial Fibrillation

Meytal Avgil Tsadok, PhD; Cynthia A. Jackevicius, PharmD, MSc; Vidal Essebag, MD, PhD; Mark J. Eisenberg, MD, MPH; Elham Rahme, PhD; Karin H. Humphries, DSc; Jack V. Tu, MD, PhD; Hassan Behloul, PhD; Louise Pilote, MD, PhD

**Background**—Stroke is a debilitating condition with an increased risk in patients with atrial fibrillation. Although data from clinical trials suggest that both rate and rhythm control are acceptable approaches with comparable rates of mortality in the short term, it is unclear whether stroke rates differ between patients who filled prescriptions for rhythm or rate control therapy.

**Methods and Results**—We conducted a population-based observational study of Quebec patients  $\geq 65$  years with a diagnosis of atrial fibrillation during the period 1999 to 2007 with the use of linked administrative data from hospital discharge and prescription drug claims databases. We compared rates of stroke or transient ischemic attack (TIA) among patients using rhythm (class Ia, Ic, and III antiarrhythmics), versus rate control ( $\beta$ -blockers, calcium channel blockers, and digoxin) treatment strategies (either current or new users). The cohort consisted of 16 325 patients who filled a prescription for rhythm control therapy (with or without rate control therapy) and 41 193 patients who filled a prescription for rate control therapy, with a mean follow-up of 2.8 years (maximum 8.2 years). A lower proportion of patients on rhythm control therapy than on rate control therapy had a CHADS<sub>2</sub> (congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, and previous stroke or TIA) score of  $\geq 2$  (58.1% versus 67.0%,  $P < 0.001$ ). Treatment with any antithrombotic drug was comparable in the 2 groups (76.8% in rhythm control versus 77.8% in rate control group). Crude stroke/TIA incidence rate was lower in patients treated with rhythm control in comparison with rate control therapy (1.74 versus 2.49, per 100 person-years,  $P < 0.001$ ). This association was more marked in patients in the moderate- and high-risk groups for stroke according to the CHADS<sub>2</sub> risk score. In multivariable Cox regression analysis, rhythm control therapy was associated with a lower risk of stroke/TIA in comparison with rate control therapy (adjusted hazard ratio, 0.80; 95% confidence interval, 0.74, 0.87). The lower stroke/TIA rate was confirmed in a propensity score-matched cohort.

**Conclusions**—In comparison with rate control therapy, the use of rhythm control therapy was associated with lower rates of stroke/TIA among patients with atrial fibrillation, in particular, among those with moderate and high risk of stroke. (*Circulation*. 2012;126:2680-2687.)

**Key Words:** atrial fibrillation ■ stroke ■ rate control ■ rhythm control

Atrial fibrillation (AF) is the most common type of chronic cardiac arrhythmia. It has been estimated that  $> 3$  million people in the United States and 4.5 million in the European Union have paroxysmal or persistent AF, and, as the population ages, the prevalence of AF is expected to increase considerably by 2050.<sup>1-4</sup>

### Clinical Perspective on p 2687

AF leads to detrimental consequences, reducing quality of life and increasing morbidities, and it also appears to be associated with increased mortality.<sup>5-7</sup> AF is also associated with a 5-fold increase in stroke risk.<sup>8</sup>

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Long-term pharmacological therapy is necessary in patients with AF to relieve symptoms and prevent stroke.<sup>9</sup> Antithrombotic therapy has been shown to be effective in these patients for the prevention of stroke and is usually guided stroke risk assessment using the CHADS<sub>2</sub> (congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus and previous stroke or transient ischemic attack [TIA]) score system.<sup>10,11</sup> The management of AF with rate ( $\beta$ -blockers, calcium channel blockers, and digoxin) or rhythm (class Ia, Ic, and III antiarrhythmics) control therapy is multifactorial and is individualized by patient characteristics and preferences.<sup>9</sup> Several clinical randomized trials have compared rate and rhythm control approaches in patients with AF and found no differences in short-term mortality,<sup>12–16</sup> with the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) trial being a landmark study. Further analyses of the AFFIRM trial have concluded that stroke rates did not differ according to the type of therapy.<sup>17</sup> To date, most trials comparing the 2 strategies had inadequate sample sizes to definitely assess their effect on stroke outcomes.

Although population-based studies are observational studies, they represent the risk profile and adherence of patients in the general population. They also usually provide a long-term follow-up and big sample size that enable the study of events with relatively low frequency such as stroke. With the use of a new user design, we previously demonstrated that in patients newly diagnosed as having AF, a strategy of rhythm control was associated with lower long-term mortality rates.<sup>18</sup> In this observational study, we compared the rates of stroke/TIA in patients treated with rate or rhythm control strategies (prevalent and new users) in a population-based cohort of admitted patients with recently diagnosed AF in the province of Quebec.

## Methods

### Study Design

An observational study with a population-based design was used to compare stroke/TIA rates in AF patients on rhythm versus rate control therapy by using linked administrative data. The study received institutional review board approval from McGill University Faculty of Medicine (study number A05-M79-08B).

### Data Sources

Patients with AF were identified by the use of the provincial hospital discharge database Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière, which provides inpatient data on diagnosis and clinical outcomes for hospitalized patients in Québec. To identify medications, drug identification numbers from the prescription claims database Régie de l'Assurance Maladie du Québec were used. Régie de l'Assurance Maladie du Québec contains information on prescription claims for patients aged  $\geq 65$  years in the outpatient setting. The Québec prescription claims database has been previously determined to be a reliable source of filled medication prescriptions.<sup>19</sup> Data from Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière was linked to data from Régie de l'Assurance Maladie du Québec by the use of encrypted provincial health insurance numbers. For the stroke/TIA outcome, we also used data from emergency department visit information in addition to information from the hospital discharge database.

### Study Population

The study population consisted of Quebec residents aged  $\geq 65$  years who were discharged alive from hospitalization with a primary or secondary diagnosis of AF from January 1, 1999 to March 31, 2007, as identified according to the *International Classification of Diseases, Ninth and Tenth Revisions* (ICD-9/10) codes (427.3, 427.31, or 427.32/148), and were treated with rhythm or rate control medications within 7 days postdischarge. Exclusion criteria for AF cases included age  $> 105$  years, AF coded as a complication postadmission, admission as a transfer from another institution that was already counted in the first facility, coronary artery bypass graft surgery or any cardiac surgery 30 days before AF index admission date, hyperthyroidism or thyrotoxicosis within 12 months before the index AF admission date, and  $> 1$  diagnostic code of AF (in which case, only the first event was counted). Additional exclusion criteria for the AF cohort were death before hospital discharge, residents of chronic care facilities, invalid health card number, and unavailable complete drug information. In this study, we used a prevalent user design, in which patients were not excluded on the basis of previous medication use for AF-related drugs to increase the sample size.

### Medication Use

Initial treatment was determined according to the first AF prescription dispensed within 7 days postdischarge. The 7-day time window for a prescription was selected so that we could capture the majority of patients with a prescription, while minimizing the potential for survival bias.<sup>20</sup>

Rate control drugs were  $\beta$ -blockers, calcium channel blockers (diltiazem, verapamil), and digoxin. Rhythm control drugs included class Ia antiarrhythmics (quinidine, procainamide, disopyramide), class Ic antiarrhythmics (propafenone, flecainide), and class III antiarrhythmic (amiodarone, sotalolol) medications. Patients simultaneously prescribed rhythm and rate control drugs were classified as rhythm control. We compared the group of patients who were on rhythm control (rhythm control alone or together with rate control medications) and rate control medications. We also obtained information on prescriptions filled for commonly used antithrombotic therapy (warfarin, acetylsalicylic acid, clopidogrel).

### Outcome and Covariates

The outcome of interest was first hospital admission or emergency department visit for stroke/TIA. Stroke/TIA was defined as ischemic cerebrovascular disease, with the inclusion of TIA and retinal infarct (ICD-9 codes 434, 435, 436, 362.3 or ICD-10 codes I63, I64, G45 [excluding G45.4], H34.1). Intracerebral hemorrhages were not included.

The Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière database was used to obtain information on patients' comorbidities within 1 year before AF admission (including time of admission) with the use of relevant ICD-9/10 diagnostic codes. For each patient, we calculated CHADS<sub>2</sub> score by assigning 1 point each for age  $\geq 75$  years, hypertension, diabetes mellitus, and heart failure and 2 points for previous stroke or TIA,<sup>21</sup> according to the presence within 1 year before admission with AF, including time of admission. Stratification was done into low (CHADS<sub>2</sub> score=0), moderate (CHADS<sub>2</sub> score=1), and high (CHADS<sub>2</sub> score  $\geq 2$ ) risk groups.<sup>22</sup>

### Statistical Analysis

Descriptive analyses were used to compare the demographics, comorbidities, and medication use of patients on rhythm or rate control therapy. Continuous variables are presented as mean  $\pm$  standard deviation or median and interquartile range as appropriate and were compared by using the Student *t* test or Mann-Whitney *U* test. Dichotomous variables are presented as percentages and were compared by using the  $\chi^2$  test.

Incidence rate of stroke/TIA was calculated as the number of events per 100 person-years of follow-up and was reported separately in the 2 treatment groups.

Adjusted stroke/TIA rates under the 2 treatments were compared with the Kaplan–Meier curves by using the inverse probability weights method.<sup>23</sup> The Kaplan–Meier curves were adjusted for comorbidities, sex, type of AF diagnosis (primary versus secondary), type of primary treating physician, CHADS<sub>2</sub> score components and filled prescription of any antithrombotic medication within 7 days postdischarge. Stroke/TIA events were constantly proportional over time, with no violation of the proportional hazards assumption.

To account for differences in baseline comorbidities and follow-up time and to adjust for the effects of potential confounders, we conducted multivariable analyses by using Cox proportional hazards models. All models were adjusted for comorbidities, sex, type of AF diagnosis (primary versus secondary), type of primary treating physician, CHADS<sub>2</sub> score components, and filled prescription of any antithrombotic medication within 7 days postdischarge. Follow-up started at the index discharge date, and the criteria to end a patient's follow-up were a first diagnosis of stroke/TIA, death, or end of study period, whichever came first. The analysis attempted to replicate an intention-to-treat analysis. Accordingly, treatment was modeled as a time-fixed binary variable (ie, patients were assigned to their initial treatment throughout follow-up, even if they later switched to the alternative treatment).

To account for potential confounding by stroke risk, we conducted a stratified analysis by low-, moderate-, and high-risk groups according to CHADS<sub>2</sub> score. To further control for potential residual confounding bias, we created a propensity-matched cohort by the use of the propensity score-matching technique, in which a propensity score is being calculated for each individual based on background covariates, and the rate control subjects are being matched with the rhythm control subjects on the basis of the propensity score. Variables that were included in the propensity score matching were warfarin prescription within 7 days postdischarge, sex, specific components of the CHADS<sub>2</sub> score (age  $\geq 75$  years, congestive heart failure, hypertension, diabetes mellitus, previous stroke/TIA), comorbidities 1 year before AF admission and at AF admission (coronary artery disease, hyperlipidemia, valvular disease, acute myocardial infarction, chronic kidney disease, bleeding events and complications, and liver disease), primary treating physician, and length of stay at the hospital during index admission. We created a propensity score-matched cohort by attempting to match each patient who received a rhythm control treatment with one who received a rate control treatment (a 1:1 match). We used the nearest available pair-matching method with a greedy algorithm.<sup>24</sup> In greedy matching, a patient with rhythm control treatment was selected and matching was attempted with the nearest patient with rate control treatment. This process was repeated until matches had been attempted for all patients with rhythm control treatment. We then conducted multivariable analyses by using a Cox proportional hazards regression model that stratified on matched pairs, in the propensity-matched cohort adjusting for comorbidities, sex, type of AF diagnosis (primary versus secondary), type of primary treating physician, CHADS<sub>2</sub> score components, and filled prescription of any antithrombotic medication within 7 days postdischarge.

Several sensitivity analyses were performed in additional models: in a first sensitivity analysis, we censored patients who switched to the other AF therapy (censored at the time of switch); in a second sensitivity analysis, we censored patients who discontinued their therapy; in another sensitivity analysis, to account for possible changes in the effect of initial treatment over time, we also performed a model in which treatment (rhythm versus rate) was treated as a time-dependent variable considering switches between treatments. Finally, we restricted our cohort to new users of AF-related drug prescriptions in the year before the admission (by excluding patients with medical records indicating rhythm control drug treatment, rate control drug treatment with an outpatient AF diagnosis, or warfarin medication not associated with valvular disease within 1 year before the index diagnosis of AF).

All statistical tests were 2-sided. Probability values of  $<0.05$  were considered to be statistically significant. All statistical analyses were performed with the use of the SAS statistical software (version 9.2; SAS Institute Inc, NC).

**Table 1. Baseline Characteristics**

	Rate N=41 193	Rhythm N=16 325	P
<b>Demographics</b>			
Age, y, mean $\pm$ SD	79.5 $\pm$ 7.2	77.1 $\pm$ 6.7	$<0.001$
Sex (male), %	43.8	46.8	$<0.001$
<b>Comorbidities 1 y before AF admission, %</b>			
Coronary artery disease	46.4	48.7	$<0.001$
Hyperlipidemia	21.7	27.0	$<0.001$
Valvular disease	21.0	21.4	0.308
Acute myocardial infarction	17.7	20.2	$<0.001$
Chronic kidney disease	16.5	15.9	0.066
Bleeding events and complications	6.0	5.5	0.019
Liver disease	3.4	2.6	$<0.001$
<b>Specific components of CHADS<sub>2</sub> score, %</b>			
Congestive heart failure	32.9	28.5	$<0.001$
Hypertension	58.8	57.4	0.003
Age $\geq 75$ y	71.2	59.1	$<0.001$
Diabetes	24.4	21.9	$<0.001$
Previous stroke (including TIA and retinal infarction)	7.3	6.2	$<0.001$
<b>CHADS<sub>2</sub> score within 1 y before admission with AF, %</b>			
Mean CHADS <sub>2</sub> score ( $\pm$ SD)	2.0 $\pm$ 1.1	1.8 $\pm$ 1.1	$<0.001$
Low (CHADS <sub>2</sub> score=0)	7.2	11.7	$<0.001$
Moderate (CHADS <sub>2</sub> score=1)	25.8	30.2	$<0.001$
High (CHADS <sub>2</sub> score $\geq 2$ )	67.0	58.1	$<0.001$
Index admission with primary diagnosis of AF, %	27.6	42.9	$<0.001$
<b>Primary treating physician during hospitalization, %</b>			
General	52.0	45.2	$<0.001$
Internist	10.4	8.7	$<0.001$
Cardiologist	20.2	32.6	$<0.001$

SD indicates standard deviation; AF, atrial fibrillation; CHADS<sub>2</sub>, congestive heart failure, hypertension, age  $\geq 75$  y, diabetes, and previous stroke or transient ischemic attack; and TIA, transient ischemic attack.

## Results

### Study Population

The cohort consisted of 16 325 patients on rhythm control therapy (9091 rhythm control only and 7234 on both rhythm and rate control) and 41 193 patients on rate control-only therapy. Mean age was 77.1 $\pm$ 6.7 years for the rhythm control group and 79.5 $\pm$ 7.2 years for the rate control group ( $P<0.001$ ). The proportion of men was 46.8%, and 43.8%, respectively.

Burden of comorbidities within 1 year before admission was high but generally comparable between the 2 treatment strategies (Table 1). The specific components of the CHADS<sub>2</sub> score were less prevalent in the rhythm control group than in the rate control group. The proportion of patients with a CHADS<sub>2</sub> score  $\geq 2$  was lower among patients on rhythm control therapy (58.1% versus 67.0%,  $P<0.001$ ).



**Table 2. Baseline Characteristics in the Propensity Score-Matched Cohort**

	Rate N=16 325	Rhythm N=16 325	P
<b>Demographics</b>			
Age, y, mean±SD	78.0±7.3	77.1±6.7	<0.001
Sex (male), %	46.7	46.8	0.859
<b>Comorbidities 1 y before AF admission, %</b>			
Coronary artery disease	48.0	48.7	0.211
Hyperlipidemia	26.7	27.0	0.446
Valvular disease	22.4	21.4	0.021
Acute myocardial infarction	19.0	20.2	0.001
Chronic kidney disease	15.3	15.9	0.170
Bleeding events and complications	5.3	5.5	0.352
Liver disease	2.6	2.6	0.917
<b>Specific components of CHADS<sub>2</sub> score, %</b>			
Congestive heart failure	26.4	28.5	<0.001
Hypertension	58.1	57.4	0.258
Age ≥75 y	59.8	59.1	0.207
Diabetes	22.0	21.9	0.718
Previous stroke (including TIA and retinal infarction)	6.1	6.3	0.475
<b>CHADS<sub>2</sub> score within 1 y before admission with AF, %</b>			
Mean CHADS <sub>2</sub> score (±SD)	1.8±1.1	1.8±1.1	0.393
Low (CHADS <sub>2</sub> score=0)	11.7	11.7	0.863
Moderate (CHADS <sub>2</sub> score=1)	30.4	30.2	0.639
High (CHADS <sub>2</sub> score ≥2)	58.0	58.1	0.745
<b>Index admission with primary diagnosis of AF, %</b>	33.0	42.9	<0.001
<b>Primary treating physician during hospitalization, %</b>			
General	42.0	45.3	<0.001
Internist	10.1	8.7	<0.001
Cardiologist	32.8	32.6	0.715

SD indicates standard deviation; AF, atrial fibrillation; CHADS<sub>2</sub>, congestive heart failure, hypertension, age ≥75 y, diabetes, and previous stroke or transient ischemic attack; and TIA, transient ischemic attack.

After propensity score matching, there were 16 325 matched pairs of patients with rhythm and rate control treatment. Baseline characteristics and mean CHADS<sub>2</sub> scores of the 2 groups were comparable (Table 2).

### Medication Use

The most commonly used antiarrhythmic medication was the class III drug amiodarone (54.7%). Among rate control medications,  $\beta$ -blockers and digoxin were the most commonly used medications (Table 3). In both groups, initiation of treatment occurred immediately after hospital discharge. The majority of patients also used ≥1 antithrombotic drug. Warfarin was the most prescribed antithrombotic (59.3% in the rhythm control group and 58.8% in the rate control group), followed by acetylsalicylic acid and clopidogrel (Table 3).

**Table 3. Treatments in Patients With AF**

	Rate N=41 193	Rhythm N=16 325
<b>Medication use, %</b>		
$\beta$ -blockers	56.6	21.6
Digoxin	43.6	18.4
Calcium channel blockers	28.5	10.1
Amiodarone	...	54.7
Sotalol	...	27.2
Propafenone	...	14.4
Time between discharge and first filled prescription, median days (IQR)	0 (0, 0)	0 (0, 0)
<b>Any antithrombotic medication use, %</b>	77.8	76.8
Warfarin	58.8	59.3
ASA	27.8	26.4
Clopidogrel	3.2	3.0

AF indicates atrial fibrillation; IQR, interquartile range; and ASA, acetylsalicylic acid.

### Outcomes

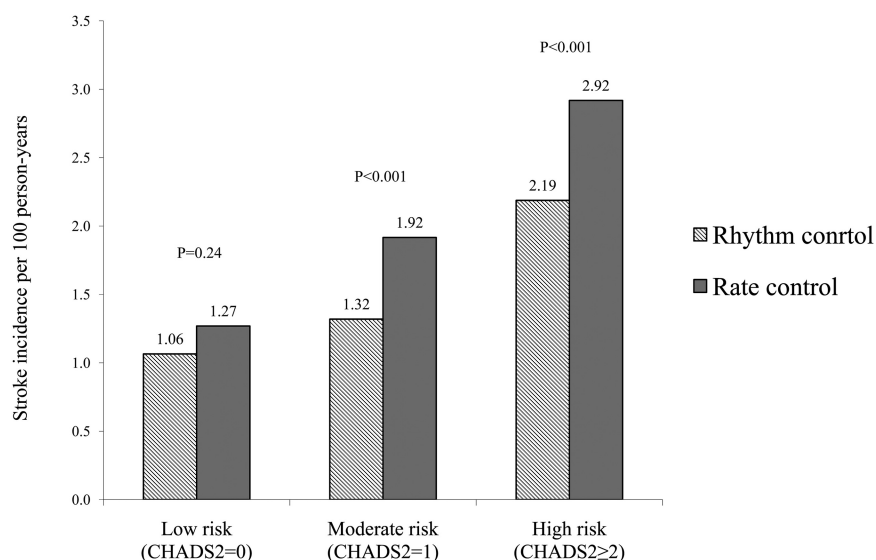
The mean follow-up times were 3.3 and 2.6 years in the rhythm control and rate control groups, respectively (maximum 8.2 years). Crude stroke/TIA incidence in the rhythm control group was 1.74 per 100 person-years in comparison with 2.49 in the rate control group ( $P<0.001$ ). Crude stroke/TIA incidence risk was statistically significantly lower in the rhythm control group in comparison with the rate control group only in the moderate and high CHADS<sub>2</sub> score risk groups (Figure 1).

The number of stroke/TIA events in each 1-year interval and the number of patients at risk at the end of each 1-year interval are presented in Figure 2.

In the multivariable Cox regression analysis, rhythm control treatment was associated with a lower risk of stroke/TIA in comparison with rate control therapy (adjusted hazard ratio [HR] 0.80; 95% confidence interval [CI], 0.74, 0.87; Table 4). In the propensity score-matched cohort, rhythm control remained associated with a lower stroke/TIA risk (adjusted HR, 0.77; 95% CI, 0.68, 0.87; Table 4).

Once stratified by CHADS<sub>2</sub> score, the rhythm control group had a lower stroke risk than the rate control group only for those with a high-risk CHADS<sub>2</sub> score (adjusted HR, 0.84; 95% CI, 0.77, 0.93) and with a moderate-risk CHADS<sub>2</sub> score (adjusted HR, 0.80; 95% CI, 0.68, 0.93).

Some patients switched between treatment strategies; 5124 (12.4%) of patients from rate control switched to rhythm control therapy, whereas 4845 (29.7%) patients switched from rhythm control to rate control therapy. When censoring patients who switched to the other drug regimen, the rhythm control therapy was still associated with a lower risk of stroke/TIA in comparison with the rate control strategy (adjusted HR, 0.75; 95% CI, 0.68, 0.83). In addition, rhythm control remained associated with a lower risk of stroke/TIA, after censoring patients who discontinued treatment (adjusted HR, 0.76; 95% CI, 0.69, 0.83) and when using a time-dependent analysis that considered switching of treatments (adjusted HR, 0.73; 95% CI, 0.66, 0.81).



**Figure 1.** Crude incidence rates of stroke/TIA by CHADS<sub>2</sub> score. Stroke/TIA crude incidence per 100 person-years among AF patients with filled prescription for rhythm or rate control treatment, according to CHADS<sub>2</sub> score risk assessment for stroke. TIA indicates transient ischemic attack; CHADS<sub>2</sub>, congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, and previous stroke or TIA; and AF, atrial fibrillation.

Once we restricted the cohort to new users of warfarin, rhythm or rate control drugs, and did not include prevalent users ( $n=26\,130$ ), rhythm control remained associated with a lower risk of stroke/TIA (adjusted HR, 0.78; 95% CI, 0.69, 0.89).

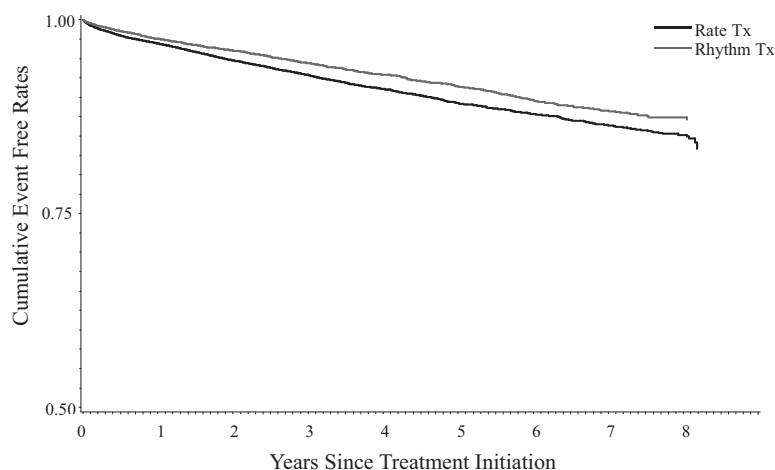
## Discussion

In this observational study of patients recently diagnosed with AF, we found that patients who filled a prescription for rhythm control therapy had a lower risk of stroke/TIA than those who filled a prescription for rate control therapy. This association was more marked in patients in the moderate- and high-risk groups for stroke according to CHADS<sub>2</sub> risk score.

Although, at baseline, patients receiving rhythm control therapy had fewer risk factors for stroke in comparison with patients receiving rate control strategy, the association be-

tween rhythm control treatment and lower stroke/TIA rates remained after multivariate analysis and propensity score-matched cohort analysis that balanced patient characteristics between groups.

Few studies have compared the effect of antiarrhythmic medications on stroke with the effect of placebo. In a post hoc analysis of the ATHENA (a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg twice daily for the prevention of cardiovascular hospitalization or death from any cause in patients with AF/atrial flutter) trial, it was found that the novel antiarrhythmic agent dronedarone was associated with a significant reduction in risk of ischemic and hemorrhagic stroke, independent of anticoagulant and rate control therapy (HR, 0.66; 95% CI, 0.45, 0.96).<sup>25</sup> The ATHENA study comprised patients with a higher risk of stroke in comparison with previous studies, and



**Figure 2.** Stroke/TIA rates in patients who filled prescriptions for rhythm versus rate control therapy: adjusted Kaplan-Meier curves. Stroke/TIA rates of patients with AF on rhythm versus rate control treatment. The stroke/TIA events underneath the graph are counted in the preceding 1-year interval. The numbers of patients at risk are counted at the end of each 1-year interval. TIA indicates transient ischemic attack; TX, treatment.

<b>Rate control</b>									
Stroke/TIA events	1133	584	376	263	185	85	55	20	4
At risk	41193	29105	21444	15231	10540	6919	4270	2132	415
<b>Rhythm control</b>									
Stroke/TIA events	327	164	142	106	82	67	29	10	1
At risk	16325	12473	10060	7984	6156	4528	2880	1489	282

**Table 4. Risk of Stroke/TIA in Patients Who Filled Prescriptions for Rhythm Versus Rate Control Therapy**

	Unadjusted		Adjusted*	
	HR (Rhythm vs Rate Control)	95% CI	HR (Rhythm vs Rate Control)	95% CI
All patients	0.72	0.67, 0.78	0.80	0.74, 0.87
According to levels of CHADS <sub>2</sub> score†				
Low (CHADS <sub>2</sub> score=0, n=4876)	0.86	0.65, 1.13	0.93	0.70, 1.24
Moderate (CHADS <sub>2</sub> score=1, n=15 551)	0.71	0.61, 0.83	0.80	0.68, 0.93
High (CHADS <sub>2</sub> score ≥2, n=37 091)	0.77	0.70, 0.84	0.84	0.77, 0.93
Propensity score–matched cohort	0.75	0.67, 0.85	0.77	0.68, 0.87

TIA indicates transient ischemic attack; HR, hazard ratio; CI, confidence interval; AF, atrial fibrillation; CHADS<sub>2</sub>, congestive heart failure, hypertension, age ≥75 y, diabetes, and previous stroke or transient ischemic attack.

\*Adjusted for sex, baseline comorbidities, type of AF diagnosis (primary versus secondary), primary treating physician, CHADS<sub>2</sub> components, and any antithrombotic treatment within 7 days postdischarge.

†Adjusted for sex, baseline comorbidities, type of AF diagnosis (primary versus secondary), primary treating physician, patients' age at index admission, and any antithrombotic treatment within 7 days postdischarge.

a greater reduction in stroke risk was observed among patients with CHADS<sub>2</sub> score ≥2. This was the first indication that an antiarrhythmic drug might have a beneficial effect on stroke risk reduction. Later, the results of the Permanent Atrial fibrillation outcome Study (PALLAS) using dronedarone on top of standard therapy<sup>26</sup> indicated that, among patients with permanent AF and risk factors for major vascular events, dronedarone increased the risk of stroke by >2-fold in comparison with placebo (HR, 2.32; 95% CI, 1.11, 4.88). It is important to mention, however, that dronedarone was not one of the antiarrhythmic drugs prescribed in our study.

In previous studies comparing rhythm and rate control therapies, stroke rates were found to be similar among the 2 groups.<sup>13,16,17</sup> In addition, 3 of 4 meta-analyses have shown similar thromboembolic outcomes in the rate and rhythm control strategies, whereas 1 meta-analysis (that had moderate heterogeneity) showed that rate control strategy was associated with a strikingly lower risk of thromboembolic stroke in studies with a mean follow-up of <20 months (odds ratio, 0.18; 95% CI, 0.04, 0.82).<sup>27–30</sup> This is in contrast with our finding in the current population-based observational study indicating that rhythm control therapy is associated with lower risk for stroke/TIA in comparison with rate control strategy.

We propose several reasons to suggest why we obtained results different from these studies. First, these studies were randomized controlled trials,<sup>12–16</sup> whereas our study was a population-based observational study. In comparison with randomized, controlled trials, our study population was larger and consisted of older patients, more female patients, and patients with a larger burden of comorbidities and a higher risk of stroke. These differences in study population and the larger sample size could account for our ability to detect a difference for the stroke risk outcome. In addition, observational studies are designed to identify associations rather than causality; therefore, our results can only infer an association between rhythm control therapy and a lower risk of stroke/TIA. Second, we had a median follow-up of ≈3 years, with a maximum of 8.2 years, whereas the trials had shorter

follow-ups, ranging from 1 to 3.5 years, giving more follow-up time to assess stroke rate differences.<sup>12–16</sup> Third, in our population-based study, the rate of warfarin prescription was comparable between the patients treated with rhythm and rate control therapy and was filled among ≈60% of our population. In the AFFIRM study, the use of warfarin therapy was high in comparison with other studies in the literature,<sup>6,31</sup> and differed between the 2 treatment strategies with >85% of patients in the rate-control group taking warfarin in comparison with only 70% in the rhythm control group.<sup>17</sup> We believe that the nature of our population-based study reflects in a better way the use pattern of warfarin in the real-world setting, where warfarin use is not as frequent and is more equalized between comparison groups.

Our study has potential limitations that should be considered. The main limitation of our study is the possible residual confounding from unknown, unavailable, or unmeasurable factors. Although we were able to establish a large and well-balanced cohort of patients treated with rhythm and rate control therapies matched on the basis of the propensity score, there may be still unmeasured confounding factors that may contribute to our findings, such as quality of anticoagulation. Another potential limitation is that the database used for this study does not allow for quantification of AF burden, which may differ between patients selected for rhythm versus rate control therapy; however, previous data have failed to show a difference in stroke risk between paroxysmal (lower burden) AF and persistent or permanent AF.<sup>32</sup> In this study, prevalent and new users of therapy were analyzed. There are advantages and disadvantages of both designs, but the concern for sufficient power factored in our choice of the former design in the current study, whereas a more restricted cohort was studied in our previously published study looking at mortality as an outcome.<sup>18</sup> Nevertheless, in a sensitivity analysis, we conducted the comparison in both the larger and smaller cohorts for both studies and found consistent results.

Finally, as an observational cohort build on administrative data, our database may not contain information on some clinically relevant patient characteristics such as international normalized ratio levels or severity of stroke. Nonetheless, the

current study is at the population level, consists of a large sample size, and, therefore, may provide a good estimation of the possible effect of rhythm versus rate control strategies on stroke/TIA risk in patients with AF and forms the basis for larger and more representative future randomized controlled trials.

To date, there is a lack of information about the possible effect of rhythm versus rate control strategies in relation to stroke outcome in the real-world setting. In this unique population-based observational study, rhythm control therapy in comparison with rate control therapy was associated with a significantly lower risk of stroke/TIA in patients with AF, principally among those at moderate and high risk for stroke. Further population-based investigation and clinical trials of AF management strategies may help clarify whether rhythm control or rate control therapy is more advantageous for stroke prevention.

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### Disclosures

None.

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### CLINICAL PERSPECTIVE

Despite anticoagulation, stroke remains a complication of atrial fibrillation. Several randomized controlled trials have compared rate and rhythm control approaches in patients with atrial fibrillation and demonstrated a similar impact on mortality, but most trials had inadequate sample size to assess their relative effect on stroke outcome. In the current observational study, we compared the rates of stroke/transient ischemic attack in patients treated with rhythm ( $n=16\,325$ ) or rate ( $n=41\,193$ ) control strategies in a large population-based cohort of patients with recently diagnosed atrial fibrillation. Crude stroke/ transient ischemic attack incidence in the rhythm control group was 1.74 per 100 person-years in comparison with 2.49 in the rate control group ( $P<0.001$ ). Although at baseline, patients receiving rhythm control therapy had fewer risk factors for stroke in comparison with patients receiving rate control therapy, the association between rhythm control treatment and lower stroke rates remained after multivariate analysis (adjusted hazard ratio, 0.80; 95% confidence interval, 0.74, 0.87) and propensity score analysis (adjusted hazard ratio, 0.77; 95% confidence interval, 0.68, 0.87), which balanced patients' characteristics between groups. Once stratified by CHADS<sub>2</sub> (congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, and previous stroke or transient ischemic attack) score, the rhythm control group had a lower stroke risk than the rate control group only for patients with high- and moderate-risk CHADS<sub>2</sub> scores. The results of this study provide additional information to guide clinicians' choice of treatment strategy by considering the outcome of stroke. This study may stimulate future large randomized trials comparing the effectiveness of rhythm versus rate control strategies on the risk of stroke and emphasizes the need for the development of new therapies for atrial fibrillation.

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