

## Analysis of Stroke in ATHENA: A Placebo-Controlled, Double-Blind, Parallel-Arm Trial to Assess the Efficacy of Dronedarone 400 mg BID for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter

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**Background**—Many patients with atrial fibrillation are at high risk for stroke and require antithrombotic therapy. Antiarrhythmic drugs have not previously been shown to reduce the risk of stroke in atrial fibrillation. The effect of dronedarone, a new multichannel-blocking antiarrhythmic drug, on stroke has been evaluated in a randomized, double-blind clinical trial, ATHENA (A placebo-controlled, double-blind, parallel-arm Trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter).

**Methods and Results**—Patients with persistent or paroxysmal atrial fibrillation and at least 1 risk factor for cardiovascular hospitalization were randomized to receive dronedarone (400 mg BID) or double-blind matching placebo and followed up for a minimum of 1 year to a common termination at 30 months. All strokes that occurred during the study were included in the present post hoc analysis. There were 4628 patients randomized to placebo or dronedarone. The baseline risk factors for stroke were well balanced between the 2 groups, and the baseline mean CHADS<sub>2</sub> score was 2. The baseline use of either oral anticoagulant therapy or antiplatelet agent alone was 60%. Dronedarone reduced the risk of stroke from 1.8% per year to 1.2% per year (hazard ratio 0.66, 95% confidence interval 0.46 to 0.96,  $P=0.027$ ). The effect of dronedarone was similar whether or not patients were receiving oral anticoagulant therapy, and there was a significantly greater effect of dronedarone in patients with higher CHADS<sub>2</sub> scores.

**Conclusions**—In this post hoc analysis, a reduction in stroke was observed in patients with atrial fibrillation who were receiving usual care, which included antithrombotic therapy and heart rate control, who were randomized to dronedarone. Further studies to investigate the effect of dronedarone and other antiarrhythmic agents on stroke are indicated. (*Circulation*. 2009;120:1174-1180.)

**Key Words:** stroke ■ arrhythmia ■ atrial fibrillation ■ antiarrhythmia agents

Stroke is one of the most serious potential consequences of atrial fibrillation (AF). A report from the Framingham study in 1988 clearly documented the increased risk of stroke in patients with nonrheumatic AF.<sup>1</sup> Subsequently, trials of oral anticoagulant (OAC) therapy and aspirin were conducted that demonstrated a substantial risk reduction with OAC therapy and a lesser benefit from aspirin.<sup>2</sup> OAC therapy is

now standard in higher-risk patients with AF, and aspirin is used in lower-risk patients.

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A more direct approach to preventing strokes related to AF would be suppression of AF itself. Ion channel-

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blocking antiarrhythmic drugs are clinically available that reduce or prevent AF recurrences in some patients; however, the use of these agents has not been shown to reduce the risk of stroke.<sup>3</sup>

Dronedaron is a new multichannel-blocking antiarrhythmic drug that is pharmacologically related to amiodaron but has different relative effects on individual ion channels and improved pharmacokinetic properties. Dronedaron has been shown to reduce the risk of recurrence of AF in 2 large phase III trials.<sup>4</sup> It has also been shown to slow the ventricular rate of AF by atrioventricular node blockade, both at rest and during exercise.<sup>5</sup> Recently, the ATHENA study (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedaron 400 mg BID for the prevention of cardiovascular Hospitalization or death from any cause in patiENTS with Atrial fibrillation/atrial flutter) demonstrated that in patients with persistent or paroxysmal AF and at least 1 risk factor for vascular events, dronedaron reduced the composite outcome of cardiovascular hospitalization or death.<sup>6</sup> Overall mortality was similar in both groups, but cardiovascular mortality and arrhythmic death were reduced. The dronedaron group had higher rates of bradycardia, QT-interval prolongation, nausea, diarrhea, and rash and an increased serum creatinine level compared with the placebo group. Rates of thyroid- and pulmonary-related adverse events were not significantly different between the 2 groups.<sup>6</sup> The purpose of the present post hoc analysis was to explore the effects of dronedaron against stroke in this patient population.

### Methods

The ATHENA design and the main ATHENA results were published previously.<sup>6,7</sup> Patients were eligible for inclusion in the ATHENA trial if they had either paroxysmal or persistent AF or flutter and at least 1 additional risk factor for cardiovascular events, including age ≥75 years or age 70 years with 1 or more of the following: Hypertension, diabetes mellitus, prior stroke or transient ischemic attack, left atrial enlargement (≥50 mm Hg), or depressed left ventricular ejection fraction (<0.40). Some patients younger than 70 years of age were enrolled in the study during the first year before a study protocol amendment. Patient exclusions included but were not limited to permanent AF, unstable hemodynamic situation, and New York Heart Association class IV heart failure. Patients were required to have had both sinus rhythm and AF or flutter documented in the 6 months before enrollment. The baseline risk of stroke was assessed with the CHADS<sub>2</sub> score, which is calculated by assigning 1 point each for the presence of congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and 2 points for history of stroke or transient ischemic attack.<sup>8</sup>

Patients were randomized to receive either dronedaron 400 mg twice daily or double-blind matching placebo. Patients were seen every 3 months and were followed up to a common termination point, with a minimum duration of follow-up of the last patient enrolled of 12 months.

The primary study outcome was the first occurrence of cardiovascular hospitalization or death due to any cause. The secondary outcomes were death, cardiovascular death, and cardiovascular hospitalization. Deaths were categorized by a blinded adjudication committee into 4 categories: Cardiac, arrhythmic; cardiac, nonarrhythmic; vascular, noncardiac; and nonvascular. Information on the occurrence of stroke was gathered from hospitalization reports and death reports, both of which included specific information on the occurrence of stroke. In addition, all adverse

**Table 1. Baseline Characteristics**

	Placebo (n=2327)	Dronedaron (n=2301)
Age, mean (SD), y	72 (9)	72 (9)
Female gender, n (%)	1038 (45)	1131 (49)
AF/atrial flutter at baseline, n (%)	586 (25)	569 (25)
Mean baseline systolic BP (SD), mm Hg	134 (18)	135 (18)
History of CHF, n (%)	693 (30)	672 (29)
Hypertension, n (%)	1996 (86)	1999 (87)
Age ≥75 y, n (%)	978 (42)	947 (41)
Diabetes mellitus, n (%)	463 (20)	482 (21)
Prior stroke or TIA, n (%)	300 (13)	316 (14)
Mean CHADS <sub>2</sub> score (SD)	2.0 (1.1)	2.1 (1.1)
CHADS <sub>2</sub> 0–1, n (%)	846 (36)	793 (35)
CHADS <sub>2</sub> 2–3, n (%)	1234 (53)	1263 (55)
CHADS <sub>2</sub> 4–6, n (%)	247 (11)	245 (11)
CHADS <sub>2</sub> ≥2, n (%)	1481 (64)	1508 (66)
Baseline antithrombotic therapy, n (%)		
OAC only	1050 (45)	1055 (46)
OAC plus antiplatelet	334 (14)	348 (15)
Antiplatelet only	765 (33)	723 (31)
Neither OAC nor antiplatelet	178 (8)	175 (8)

BP indicates blood pressure; CHF, congestive heart failure; and TIA, transient ischemic attack.

The CHADS<sub>2</sub> score is a risk-stratification scheme that gives a patient a score from 0 to 6, indicating an increasing risk of stroke.

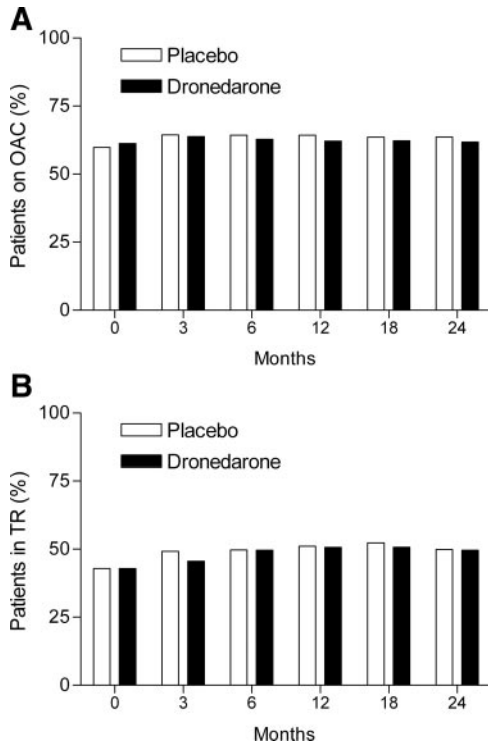
event reports were analyzed to determine the inclusion of pre-specified preferred terms associated with stroke or intracerebral hemorrhage. Information on occurrence of acute coronary syndrome was collected from hospitalization and death report forms. Major bleeding events were defined as bleeding that required 2 or more units of blood, any intracranial hemorrhage, or any bleeding that led to death, as reported on specific hospitalization or death report forms.<sup>9</sup> Strokes that did not lead to hospitalizations or death were reported as adverse events. These events were identified by a blinded review of the adverse events listings. All incidents of preferred terms for adverse events that contained the words “stroke,” “cerebrovascular accident,” or “cerebellar hemorrhage” were counted as strokes.

Analyses were performed in the intention-to-treat population, stratified by center, and the time to event was estimated according to the Kaplan–Meier method and compared by the log-rank test. The annual event rates (% per year) were calculated by dividing the actual number of events by the total follow-up years. All *P* values were 2-tailed. A multivariate logistic regression analysis was performed. The subgroup analysis was performed with a Cox proportional hazards model with no adjustment in *P* values for multiple analyses. The model included treatment group and several baseline patient variables that are known risk factors for stroke. The hypothesis tested was whether dronedaron treatment allocation would be a predictor of stroke after adjustment for other variables predictive of stroke.

The trial was sponsored by sanofi-aventis and designed by the steering committee in collaboration with the sponsor. Data management and statistical analysis were performed by the sponsor. The first draft of the report was written by the principal author, and subsequent drafts were revised and edited by all authors, who vouch for the accuracy and completeness of the data.

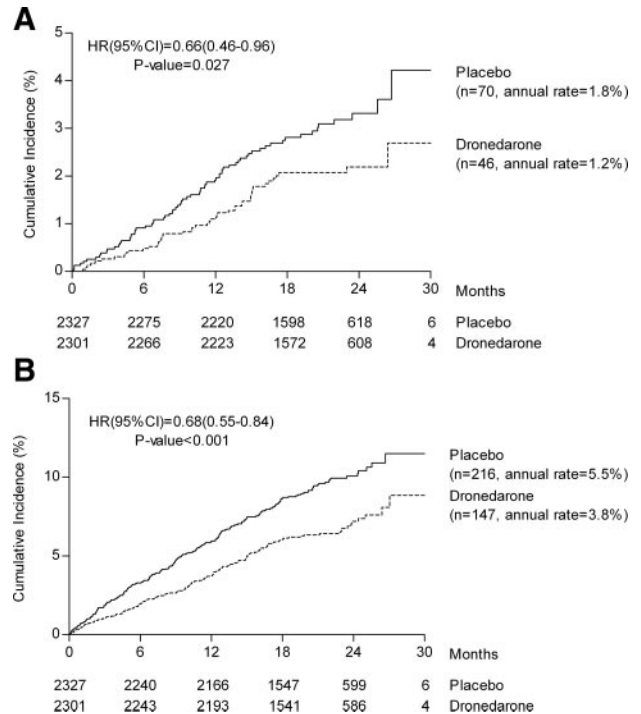
### Results

Patients were evenly randomized between placebo and dronedaron, with a mean age of 72 years; slightly less



**Figure 1.** OAC use (A) and international normalized ratio in range (B) at study visits. TR indicates therapeutic range, defined as international normalized ratio of 2 to 3 at the time of the visit.

than half of the patients were female (Table 1). Lone AF was present in 6% of patients in both groups. Patients included in the study had an intermediate to high risk for stroke and other cardiovascular events, with a mean CHADS<sub>2</sub> score of 2 in both groups. Prior stroke or transient ischemic attack was present in 13% of placebo patients and 14% of dronedaron patients. At baseline, 60% of patients were receiving OAC therapy. Most of these patients were receiving only an OAC, but approximately one fourth of the patients taking an OAC also received an antiplatelet agent. Approximately one third of



**Figure 2.** Cumulative risk of stroke (A) and composite outcome of stroke, acute coronary syndrome, or cardiovascular death (B). HR indicates hazard ratio.

the patients were receiving only an antiplatelet agent, and 8% of the patients in both groups received neither an OAC nor an antiplatelet agent. The use of OAC therapy was relatively independent of the CHADS<sub>2</sub> risk score. The baseline use of OAC therapy was 60% and 63% in patients with CHADS<sub>2</sub> score ≤1 in the placebo and dronedaron groups, respectively, compared with 59% and 60%, respectively, in patients with CHADS<sub>2</sub> score ≥2. Figure 1A shows the percentage of patients receiving an OAC according to their treatment allocation at prespecified follow-up visits during the course of the study. As can be seen from Figure 1A, rates of use of OACs were similar between treatment groups and fairly consistent over time.

**Table 2. Summary of Annual Event Rates for Strokes and Treatment Effects**

	Placebo (n=2327), n (%)	Dronedaron (n=2301), n (%)	Hazard Ratio	95% CI	P
Total strokes	70 (1.8)	46 (1.2)	0.66	0.46–0.96	0.027
Stroke-related hospitalizations	55 (1.4)	38 (1.0)	0.69	0.46–1.05	0.082
Ischemic stroke	49 (1.3)	33 (0.9)	0.68	0.44–1.05	0.081
Hemorrhagic stroke	6 (0.2)	6 (0.2)	1.01	0.33–3.13	0.987
Other stroke*	9 (0.2)	5 (0.1)	0.56	0.19–1.67	0.292
Fatal stroke†	21 (0.5)	14 (0.4)	0.67	0.34–1.32	0.247
Stroke or TIA	90 (2.3)	63 (1.6)	0.70	0.51–0.97	0.031
Stroke, ACS, or CV death	216 (5.5)	147 (3.8)	0.68	0.55–0.84	<0.001
Stroke, ACS, or death	262 (6.7)	196 (5.1)	0.75	0.62–0.90	0.002

TIA indicates transient ischemic attack; ACS, acute coronary syndrome, including myocardial infarction and unstable angina; and CV, cardiovascular.

All percentage values refer to annual event rates.

\*Other stroke indicates strokes only reported as adverse events.

†Fatal stroke indicates main reason of death reported as stroke or intracerebral hemorrhage.

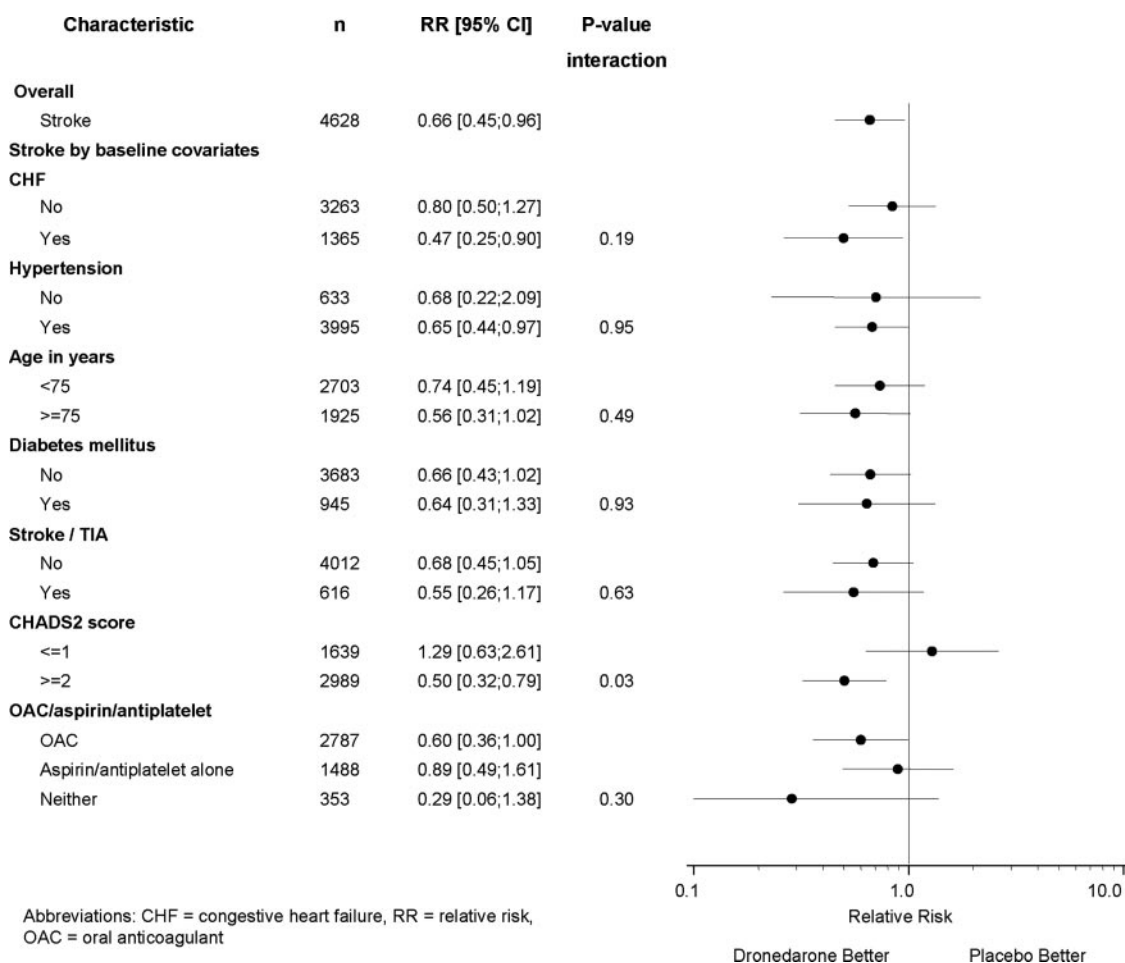


Figure 3. Specific subgroup analysis for stroke. RR indicates relative risk; CHF, congestive heart failure.

In patients taking an OAC, the international normalized ratio of the prothrombin time was measured at follow-up visits, and Figure 1B shows the percentage of patients with international normalized ratios in the therapeutic range (international normalized ratio 2 to 3) according to their treatment allocation at follow-up visits. The time spent in the therapeutic range was similar for the 2 treatment groups. The time in this range increased during the first 6 months and stabilized at close to 50%.

There was a significant reduction in the risk of stroke with dronedarone compared with placebo (Table 2). There were 70 strokes with placebo (annual rate 1.8%) compared with 46 strokes with dronedarone therapy (annual rate 1.2%), which provides a hazard ratio of 0.66 (95% confidence interval [CI] 0.46 to 0.96,  $P=0.027$ ). Strokes related to hospitalizations were reported as hemorrhagic or ischemic strokes. The number of hemorrhagic strokes was 6 (annual rate 0.2%) with placebo and 6 (annual rate 0.2%) with dronedarone therapy (hazard ratio 1.01, 95% CI 0.33 to 3.13,  $P=0.987$ ). The risk of ischemic stroke was 0.9% per year with dronedarone and 1.3% with placebo (hazard ratio 0.68, 95% CI 0.44 to 1.05,  $P=0.081$ ). Among the strokes, there were 21 fatal strokes in patients given placebo and 14 fatal strokes in those given dronedarone (hazard ratio 0.67, 95% CI 0.34 to 1.32,  $P=0.247$ ), which included 3 fatal hemorrhagic strokes in

each treatment group. Dronedaron also reduced the risk of the composite outcome of stroke, acute coronary syndrome, or cardiovascular death from 5.5% to 3.8% per year (hazard ratio 0.68, 95% CI 0.55 to 0.84,  $P<0.001$ ). Figure 2A shows the Kaplan–Meier curves for the outcome of stroke. The curves began to separate early and continued to separate throughout the course of the study. Figure 2B shows the Kaplan–Meier curves for the outcome of stroke, acute coronary syndrome, or cardiovascular death, with a similar pattern of an early and continued effect of dronedaron.

Subgroup analysis was performed to investigate the baseline patient characteristics that were predictive of a response to dronedaron in reducing the incidence of stroke (Figure 3). The  $P$  values for interaction are shown, and the only statistically significant interaction was according to CHADS<sub>2</sub> score. Patients with a CHADS<sub>2</sub> score  $\geq 2$  had a significantly greater effect of dronedaron than those with a CHADS<sub>2</sub> score  $\leq 1$  ( $P=0.03$  for interaction). There were patients in whom all ECGs performed during the study (baseline and at each follow-up visit) showed AF or atrial flutter; 295 (12.7%) of these were given placebo, and 178 (7.7%) were given dronedaron. Conversely, there were 745 patients (32.0%) randomized to placebo who had sinus rhythm present on all ECGs compared with 904 (39.3%) who were given dronedaron.

**Table 3. Multivariable Analysis of Baseline Risk Factors for Stroke**

Prognostic Factors	Odds Ratio	95% CI	P
Prior stroke/TIA (yes/no)	2.19	1.43–3.35	<0.001
Age (per year; continuous parameter)	1.04	1.02–1.07	0.001
Treatment (dronedaron vs placebo)	0.64	0.44–0.93	0.020
Diabetes mellitus (yes/no)	1.41	0.92–2.15	0.112
Baseline OAC treatment (yes/no)	0.74	0.51–1.09	0.124
CHF (yes/no)	1.31	0.88–1.94	0.181
LVEF % (continuous parameter)	0.99	0.97–1.01	0.182
Hypertension (yes/no)	1.30	0.72–2.35	0.393
Systolic BP (mm Hg; continuous parameter)	1.00	0.99–1.01	0.730
Diastolic BP (mm Hg; continuous parameter)	1.00	0.98–1.03	0.739

TIA indicates transient ischemic attack; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; and BP, blood pressure.

rone. Among the patients with only AF or atrial flutter on all ECGs, there were 8 strokes in the placebo group and 2 in the dronedarone group (hazard ratio 0.41, 95% CI 0.09 to 1.91,  $P=0.24$ ).

A multivariate predictive model was used to determine the baseline clinical predictors of time to stroke and to address the hypothesis that randomization to placebo versus dronedarone would be an independent predictor of stroke (Table 3). In this model, there were 3 statistically significant factors that independently predicted an increased risk of stroke. Prior stroke or transient ischemic attack doubled the risk of stroke (hazard ratio 2.19, 95% CI 1.43 to 3.35,  $P<0.001$ ). Each year of advancing age increased the risk of stroke by 4% (hazard ratio 1.04, 95% CI 1.02 to 1.07,  $P=0.001$ ), and randomization to dronedarone reduced the risk of stroke by 36% (hazard ratio 0.64, 95% CI 0.44 to 0.93,  $P=0.02$ ). Baseline OAC use did not independently predict a reduced risk of stroke, although there was a trend toward this (hazard ratio 0.74, 95% CI 0.51 to 1.09,  $P=0.124$ ). Neither a history of hypertension nor measured blood pressure during the study independently predicted stroke in this analysis.

Blood pressure was recorded at follow-up visits. Compared with the baseline value, the mean decreases in systolic blood pressure at 1 month, 12 months, and the end of the study were 2.1, 1.6, and 1.9 mm Hg in the placebo group and 3.7, 2.6, and 2.8 mm Hg in the dronedarone group ( $P=0.062$ ), respectively. The mean decrease in diastolic blood pressure compared with the baseline value was 1.1, 0.8, and 0.9 mm Hg in the placebo group and 3.2, 2.3, and 2.3 mm Hg in the dronedarone group ( $P<0.001$ ) at 1 month, 12 months, and the end of the study, respectively.

The annual incidence of major bleeding events that led to hospitalization or death was similar in the placebo group ( $n=34$ , annual rate 0.9%) and the dronedarone group ( $n=39$ , annual rate 1.0%; hazard ratio 1.16, 95% CI 0.73 to 1.84,  $P=0.527$ ). Similar observations were made for any bleeding in the placebo group ( $n=249$ , annual rate 6.4%) and the

dronedaron group ( $n=245$ , annual rate 6.3%; hazard ratio 1.00, 95% CI 0.84 to 1.19,  $P=0.972$ ).

## Discussion

The results of the present study are important because they raise the possibility that a drug with antiarrhythmic activity could reduce the risk of stroke. It is generally accepted that the loss of atrial appendage contraction caused by AF is in part related to the high risk of stroke in this condition. Therefore, prevention of AF and restoration of atrial contraction as a way of preventing stroke is logical and appealing. However, this strategy has not been shown to reduce the risk of stroke. In AFFIRM (Atrial Fibrillation Follow-up Investigation of sinus Rhythm Management),<sup>10</sup> patients were randomized to receive either rate control or rhythm control treatment of their AF. Rate control patients only received drugs that slowed the rate of AF. Rhythm control patients could also receive rate control drugs but in addition received antiarrhythmic drugs that are effective for reducing the rate of recurrence of AF. Although the antiarrhythmic drugs did reduce the rate of recurrence of AF, there was no reduction of stroke. Underuse of anti-thrombotic drugs may be a partial explanation of the lack of effect; however, a recent meta-analysis of all of the rate control versus rhythm control randomized trials reported an increase in stroke in patients randomized to a rhythm control arm that was not statistically significant (odds ratio 0.50, 95% CI 0.14 to 1.83,  $P=0.30$ ).<sup>11</sup> The observation in the present study that an antiarrhythmic drug may have had an effect against stroke is therefore both novel and important, reopening the possibility that either pharmacological or nonpharmacological suppression of AF could have a beneficial effect on stroke.

There are several potential mechanisms by which dronedarone could reduce the risk of stroke. The most likely mechanism is by suppression of AF. Dronedaron has been clearly shown to reduce AF by 25% in previous studies and also reduced the frequency of AF in ATHENA.<sup>4</sup> However, there are other potential mechanisms that could play a role. There was a trend for reduction in stroke even in patients who appeared to be in AF throughout the study. Dronedaron was also associated with a modest reduction in blood pressure in ATHENA. Small reductions in blood pressure have been reported to have a significant impact on stroke.<sup>12,13</sup> Another potential mechanism of stroke reduction was heart rate slowing during AF with dronedaron. Recently, the ERATO (Efficacy and safety of dRonedARone for The cOntrol of ventricular rate during atrial fibrillation) trial<sup>5</sup> has shown, in a permanent AF population, a 12-bpm reduction in heart rate at rest with dronedaron and a 25-bpm reduction during exercise, and these rate-slowing effects were additive to those of other rate control agents. It is possible that a slower rate during AF recurrence could directly reduce the risk of stroke by preventing hypotension.

The use of antithrombotic agents in the present study was well documented. Rates of use of OAC therapy were

similar to rates reported in community practice.<sup>14,15</sup> The percentage of patients with an international normalized ratio in the therapeutic range was  $\approx 50\%$ . Although time in the therapeutic range has been reported to be higher in recent anticoagulation studies,<sup>16</sup> these results are probably fairly similar to contemporary practice. A recent study from an administrative database from Wales reported that 51% of patients with a CHADS<sub>2</sub> score of 2 or more had an international normalized ratio outside the therapeutic range more than 50% of time with warfarin therapy.<sup>17</sup> Even if dronedarone were only effective in patients not adequately treated with OAC, the observation that stroke was reduced would still be important in understanding the pathophysiology of stroke in AF and in the future development of antiarrhythmic and other therapy for stroke prevention.

The most important limitation of the present analysis is that because it was not anticipated that dronedarone would reduce stroke, these outcomes were not prespecified or centrally adjudicated. Data on stroke, however, were collected carefully. There were detailed reports on the cause of every death and every hospitalization, including information about ischemic and hemorrhagic stroke. In addition, a prespecified and systematic approach was used to evaluate all reported adverse events for the occurrence of stroke by a defined analysis of preferred terms. Nonetheless, it is possible that some strokes were not included in the present analysis. Although there may have been underreporting of events, there should not be any bias in the analysis, because the study was blinded.

The results of the present study should not be interpreted to indicate that dronedarone might be a replacement for OAC therapy or a treatment for stroke prevention. The observations about stroke prevention in this report are of interest as a direction for future research. The main reasons to use dronedarone should be for reduction of the combined end point of cardiovascular hospitalization or death, the primary outcome of ATHENA,<sup>6</sup> and to reduce symptomatic and asymptomatic recurrences of AF as demonstrated in the ADONIS (American-Australian-African trial with DrONedaron In atrial fibrillation patients for the maintenance of Sinus rhythm) and EURIDIS (EURopean trial In atrial fibrillation patients receiving Dronedaron for the maIntenance of Sinus rhythm) trials.<sup>4</sup> The observation of a reduced rate of stroke in patients receiving dronedarone cannot be considered a definitive conclusion; rather, it is hypothesis generating and must be confirmed in future trials.

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The trial was sponsored by sanofi-aventis and designed by the steering committee in collaboration with the sponsor.

### Disclosures

Dr Hohnloser reports receiving consulting fees from sanofi-aventis, Cardiome, ARYx Therapeutics, and Bristol-Myers Squibb; research grants from sanofi-aventis and St Jude Medical; and lecture fees from sanofi-aventis, St Jude Medical, and Bristol-Myers Squibb. Dr Crijns reports receiving consulting fees from Medacorp,

AstraZeneca, sanofi-aventis, and Cardiome; research grants from AstraZeneca and St Jude Medical; and lecture fees from AstraZeneca, sanofi-aventis, and Chugai Pharmaceuticals. Dr van Eickels and Dr Gaudin report being employees of sanofi-aventis and owning shares in the company. Dr Page reports receiving consulting fees from sanofi-aventis, Astellas, and Pfizer; Dr Torp-Pedersen, consulting fees from sanofi-aventis and Cardiome, research grants from sanofi-aventis, and lecture fees from sanofi-aventis and Cardiome; and Dr Connolly, consulting fees and research grants from sanofi-aventis.

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### CLINICAL PERSPECTIVE

Dronedaron is a new antiarrhythmic drug developed for the management of atrial fibrillation that has been shown to reduce atrial fibrillation recurrence and to slow the rate of atrial fibrillation. To establish its efficacy and safety, a large, global, randomized clinical trial, ATHENA, was performed in patients with paroxysmal or persistent atrial fibrillation and risk factors for vascular events. Patients were randomized to receive dronedaron 400 mg BID or matching placebo and followed up for a minimum of 1 year. ATHENA reported a significant reduction in the primary end point of cardiovascular hospitalization or death. There were reductions in cardiovascular death and cardiovascular hospitalization, although there was no reduction in total mortality. The present report provides a post hoc exploratory analysis of stroke. In ATHENA, stroke was reduced from 1.8% per year to 1.2% per year with dronedaron, a 34% reduction that was statistically significant. The effect of dronedaron was similar whether or not patients were receiving oral anticoagulation, and there was a significantly greater effect of dronedaron in patients with higher CHADS<sub>2</sub> scores. The finding of stroke reduction was unexpected, and the analysis was exploratory, so the results should not be used to guide clinical decision making. However, this analysis does support the main finding of ATHENA, which is that dronedaron improves cardiovascular outcomes, and also provides a rationale for further research to explore whether dronedaron or other antiarrhythmic treatments can reduce stroke in patients with atrial fibrillation.