Efficacy and Safety of Dronedarone in Patients Previously Treated With Other Antiarrhythmic Agents

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ABSTRACT

Background: Currently available antiarrhythmic drugs (AADs) for the prevention of atrial fibrillation (AF)/atrial flutter (AFL) suffer from incomplete efficacy and poor tolerability.

Hypothesis: Dronedarone could represent an effective and safe option in patients previously treated with AADs, especially class Ic AADs and sotalol.

Methods: Retrospective analysis of 2 double-blind, parallel-group trials (EURIDIS [European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm] and ADONIS [American–Australian–African Trial With Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm]) comparing the efficacy and safety of dronedarone with placebo over 12 months. The primary end point was AF/AFL recurrence in patients previously treated with another AAD that was discontinued for whatever reason prior to randomization.

Results: In patients previously treated with any AADs, dronedarone decreased the risk of AF recurrence by 30.4% vs placebo (hazard ratio [HR]: 0.70; 95% confidence interval [CI]: 0.59–0.82; $P < 0.001$). In patients previously treated with a class Ic agent, dronedarone decreased the risk of recurrence by 31.4% (HR: 0.69; 95% CI: 0.53–0.89; $P = 0.004$), whereas in patients previously treated with sotalol, dronedarone showed a trend toward a decrease of risk of recurrence (HR: 0.86; 95% CI: 0.67–1.11; $P = 0.244$). Dronedarone was equally effective irrespective of whether class Ic or sotalol were stopped for lack of efficacy or adverse events (AEs). Discontinuation rates were similar in the 2 groups (55.9% vs 43.1%), as were incidence of AEs and serious AEs.

Conclusions: Dronedarone seems to be effective in preventing AF recurrences in patients without permanent AF previously treated with other AADs, even if those were discontinued for lack of efficacy. Dronedarone appears to be well tolerated even in patients who already had tolerability issues with AADs.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with significant

morbidity, including stroke and tachycardia-induced cardiomyopathy,^{1,2} as well as high mortality rates.^{3–5} A growing public health problem, the prevalence of AF is expected to increase considerably over the next 40 to 50 years as the proportion of elderly individuals in the population grows and the prevalence of cardiovascular risk factors rises.^{6,7}

Currently available antiarrhythmic drugs (AADs) are associated with less than satisfactory efficacy in preventing AF.⁸ Patients treated with AADs, including class I agents, sotalol, and amiodarone, have an annual AF recurrence rate of 43% to 67%.⁹ The use of these drugs is also associated

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with serious side effects such as thyroid and pulmonary toxicity¹⁰ and proarrhythmic effects,¹¹ which together with poor tolerability profile, can lead to discontinuation rates as high as 46% for propafenone or sotalol and 34% with amiodarone during a 16-month follow-up.¹²

Therefore, the majority of patients who experience a recurrence of AF or have tolerability issues usually stop the drug to seek therapeutic alternatives.

More recently, dronedarone, a noniodinated benzofuran derivative related to amiodarone,¹³ has been shown to be an effective therapeutic option for the maintenance of sinus rhythm after AF.^{14–17} In addition, it has been shown to decrease the combined end point of cardiovascular hospitalization or death in patients with nonpermanent AF,¹⁸ but increased risks if given to patients with sinus rhythm and congestive heart failure or permanent atrial fibrillation.^{19,20} Therefore, dronedarone can be administered in patients with paroxysmal or persistent AF after sinus rhythm is reestablished, including some categories of patients in whom other agents have been discontinued due to a lack of efficacy or safety issues. However, there still is a lack of data regarding the possible efficacy of dronedarone in those patients who previously discontinued another AAD.

This post hoc analysis of data from the EURIDIS (European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm [NCT00259428]) and ADONIS (American–Australian–African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm [NCT00259376]) trials¹⁴ was conducted to evaluate whether dronedarone is superior to placebo for maintaining sinus rhythm after electrical, pharmacologic, or spontaneous conversion from AF or atrial flutter (AFL) in patients in whom other antiarrhythmic agents have been previously discontinued.

Methods

Study Design

Study designs for both EURIDIS and ADONIS have been previously described elsewhere.¹⁴

EURIDIS and ADONIS were identical, placebo-controlled, multicenter, double-blind, parallel-group trials. The study protocols were approved by the human research review boards at each participating institution. A single common steering committee designed the studies and the data analysis plans. An independent data and safety monitoring board oversaw the safety of patients. The academic investigators had independent access to the raw data.

The aim of this post hoc analysis was to evaluate the efficacy and safety of dronedarone in patients previously treated with AADs, with a specific focus on class Ic AADs or sotalol. Patients previously treated with amiodarone (29.8% of the total population) were included in the overall analysis and the primary end point analysis for completeness but not considered in the main subgroup analysis because of amiodarone's long half-life and possibility of carryover effect. Also, a post hoc analysis on this specific subpopulation has already been published.²¹

Therefore, only data regarding patients who were previously treated with class Ic AADs or sotalol and

who stopped treatment for whatever reason prior to randomization were included in the main subgroup analysis.

Patients

Male and female patients age ≥ 21 years, who had at least 1 episode of AF (or AFL) as seen on an electrocardiogram (ECG) in the preceding 3 months, and who were in sinus rhythm for at least 1 hour before randomization were eligible for inclusion. The following patients were excluded from the study: patients with AF duration ≥ 12 months; women who could become pregnant and who were not using birth control; patients who had had torsades de pointes; patients with persistent bradycardia < 50 bpm, a PR interval of ≥ 0.28 seconds on ECG, second-degree (or higher) atrioventricular block, and clinically significant sinus node disease without an implanted pacemaker; patients who were currently taking class I or III AADs; patients with New York Heart Association class III or IV congestive heart failure; and patients with a serum creatinine level of ≥ 1.7 mg/dL (≥ 150 μ mol/L), severe electrolyte abnormalities, and clinically significant hepatic, pulmonary, endocrine, or other disorders associated with AF. All patients were required to provide written informed consent.

After a 7-day screening period, eligible patients were randomly assigned in a 2:1 ratio to receive either 400 mg of oral dronedarone twice daily or matching placebo on top of standard treatment, excluding antiarrhythmics with class I and III properties other than the study drug. As per protocol, class I and III agents (including amiodarone and sotalol) were stopped prior to enrollment in the study, whereas class II and IV agents could have been coadministered with the study drug.

Follow-up visits included a review of symptoms, assessment of vital signs, and performance of electrocardiography on days 7, 14, and 21, and at 2, 4, 6, 9, and 12 months. All enrolled patients were given a transtelephonic electrocardiographic monitor (TTEM) and were instructed in its use. Patients transmitted ECGs on days 2, 3, and 5, at months 3, 5, 7, and 10, and whenever they had symptoms.

Prior Antiarrhythmic Therapy

To be able to provide data on the prior antiarrhythmic therapy, a specific case report form referred to as antiarrhythmic history for AF/AFL was used. This form collected information about previous treatment with an antiarrhythmic drug in a dichotomous fashion. The following categories were proposed in the case report form based on the Vaughan-Williams-Singh classification: class Ia, class Ib, class Ic, class II, class III, class IV, sotalol, amiodarone. These latter 2 agents were given a specific box because they combine more than 1 property of the classification. For each of these categories, the investigator had also to indicate if the reason for discontinuation was lack of efficacy, adverse event, patient's request, or other medical reasons.

Post Hoc Analysis End Points

The primary end point was AF or AFL recurrence over 12 months in patients previously treated with another

antiarrhythmic agent that was since discontinued for whatever reason prior to randomization. Recurrence was defined as an episode lasting ≥ 10 minutes and confirmed by 2 consecutive recordings taken 10 minutes apart on 12-lead electrocardiography or TTEM (and confirmed by the ECG central laboratory).

There were 2 secondary end points: the risk of AF recurrence over 12 months in patients previously treated with another antiarrhythmic agent discontinued for a lack of efficacy or adverse events (AEs) at any time, and heart rate at the time of first recurrence in patients previously treated with another antiarrhythmic agent discontinued for any reason at any time.

The safety analysis included an overview of treatment-emergent AEs (TEAEs): number of patients experiencing 1 or more TEAE, serious TEAE, TEAE leading to death, or AE leading to permanent treatment discontinuation.

Statistical Analysis

The efficacy population was based on the intention-to-treat population (defined as all randomized and treated patients). The primary efficacy variable was the time in days elapsed between randomization and the first documented AF recurrence within 12 months from randomization. Kaplan-Meier analysis was used to assess cumulative incidence of the primary end point. The hazard ratio with 95% confidence interval was estimated using a Cox model with treatment group as the only factor. Relative risk reductions were obtained by subtracting the hazard ratio from 1.

Twelve-lead ECG parameters (heart rate and corrected QT interval according to Bazett's formula) and their changes from baseline were summarized using means, standard deviations, medians, and ranges at each protocol time point and for the last measure assessed before the last study drug intake. Mean changes from baseline and its corresponding standard error were plotted. Only patients with baseline values for the parameter considered were included in the analyses.

Results

Patients

The vast majority of patients included in the EURIDIS and ADONIS trials¹⁴ (73%) were treated with an antiarrhythmic agent prior to randomization. According to the inclusion criteria explained above, 298 patients treated with placebo and 605 patients treated with dronedarone were included in the present analysis.

There were no differences in terms of baseline demographic and clinical characteristics between patients randomized to dronedarone or placebo, even after subdividing the population according to previous antiarrhythmic therapy (Table 1).

Treatment

Three hundred sixty-nine patients were treated with amiodarone (40.9%), 298 (33.0%) were treated with a class Ic agent, and 326 (36.1%) with sotalol. Each patient was allowed to receive more than 1 treatment.

Table 1. Baseline Characteristics of the Population

	Class Ic Before Randomization		No Class Ic Before Randomization		Sotalol Before Randomization		No Sotalol Before Randomization	
	Placebo, n = 108	Dronedarone 400 mg BID, n = 190	Placebo, n = 301	Dronedarone 400 mg BID, n = 638	Placebo, n = 112	Dronedarone 400 mg BID, n = 214	Placebo, n = 297	Dronedarone 400 mg BID, n = 614
Age, y	59.6 $\pm$ 11.4	61.8 $\pm$ 10.6	63.1 $\pm$ 10.9	64.0 $\pm$ 10.7	59.4 (11.6)	63.2 (10.3)	63.2 (10.8)	63.6 (10.9)
Height, cm	173.4 $\pm$ 9.2	172.3 $\pm$ 9.6	173.7 $\pm$ 10.3	173.2 $\pm$ 10.6	174.7 (9.8)	174.0 (9.7)	173.2 (10.1)	172.6 (10.7)
Weight, kg	85.37 $\pm$ 14.67	83.78 $\pm$ 15.71	87.77 $\pm$ 18.03	86.99 $\pm$ 17.99	87.80 (16.46)	84.78 (15.32)	86.88 (17.52)	86.77 (18.23)
Male gender	73 (67.6%)	124 (65.3%)	207 (68.8%)	454 (71.2%)	78 (69.6%)	159 (74.3%)	202 (68.0%)	419 (68.2%)
Hypertension	47 (43.5%)	101 (53.2%)	58 (52.5%)	396 (62.1%)	53 (47.3%)	114 (53.3%)	152 (51.2%)	383 (62.4%)
Structural heart disease	36 (33.6%)	62 (33.0%)	123 (41.8%)	286 (45.3%)	38 (33.9%)	79 (37.1%)	121 (41.9%)	269 (44.3%)
Coronary heart disease	15 (13.9%)	38 (20.0%)	60 (19.9%)	157 (24.6%)	15 (13.4%)	53 (24.8%)	60 (20.2%)	142 (23.1%)
Valvular heart disease	18 (16.7%)	21 (11.1%)	43 (14.3%)	115 (18.0%)	15 (13.4%)	28 (13.1%)	46 (15.5%)	108 (17.6%)
Lone AF	43 (39.8%)	64 (33.9%)	87 (29.2%)	141 (22.2%)	42 (37.5%)	73 (34.3%)	88 (29.9%)	132 (21.6%)
β -blockers ^a	46 (42.6%)	84 (44.2%)	132 (43.9%)	287 (45.0%)	42 (37.5%)	88 (41.1%)	136 (45.8%)	283 (46.1%)
ACE inhibitors	33 (30.6%)	52 (27.4%)	111 (36.9%)	243 (38.1%)	37 (33.0%)	68 (31.8%)	107 (36.0%)	227 (37.0%)
ARBs	6 (5.6%)	11 (5.8%)	21 (7.0%)	63 (9.9%)	5 (4.5%)	19 (8.9%)	22 (7.4%)	55 (9.0%)
Diuretics	22 (20.4%)	31 (16.3%)	77 (25.6%)	185 (29.0%)	33 (29.5%)	30 (14.0%)	66 (22.2%)	186 (30.3%)

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; BID, twice daily.

^aExcept sotalol.

Figure 1. Kaplan-Meier analysis of time from randomization to first AF/AFL recurrence within 12 months. All randomized and treated patients with any antiarrhythmic drugs stopped for whatever reasons before randomization. Abbreviations: BID, twice daily.

The main reason for the discontinuation of both class Ic agents and sotalol was lack of efficacy (57.0% and 49.1%, respectively) in preventing AF recurrences. Of those patients previously treated with class Ic antiarrhythmic agents, approximately 50% had been receiving flecainide, and 50% had been receiving propafenone.

Primary End Point

In patients previously treated with another antiarrhythmic agent that was discontinued for whatever reason at any time prior to randomization, dronedarone decreased the risk of AF or AFL recurrence by 30.4% in comparison to placebo ($P < 0.001$) (see Supporting Table 1 in the online version of this article). In patients who experienced a recurrence, associated symptoms were present in 62.2% of the placebo group and 61.2% of the dronedarone group. Kaplan-Meier estimates of cumulative incidence of AF/AFL recurrence during the 1-year follow-up are shown in Figure 1.

Regarding specific treatment, in the subgroup of patients previously treated with a class Ic agent, dronedarone significantly decreased the risk of AF/AFL recurrence by 31.4% in comparison to placebo ($P = 0.004$). In the subgroup of patients previously treated with sotalol, dronedarone showed a nonsignificant decrease of risk of AF/AFL recurrence by 13.8% in comparison to placebo ($P = 0.244$). Kaplan-Meier estimates of cumulative incidence of AF/AFL recurrence during the 1-year follow-up according to previous treatment with either class Ic AADs or sotalol are shown in Figure 2A,B.

Secondary End Points

In patients previously treated with another antiarrhythmic agent that was discontinued for lack of efficacy at any time prior to randomization, dronedarone decreased the risk of AF/AFL recurrence by 22.9% in comparison to placebo ($P = 0.023$) (see Supporting Table 1 in the online version of this article). When only the patients previously treated with a class Ic agent were taken into account, dronedarone showed a risk reduction of AF/AFL recurrence by 22% in comparison to placebo, but without reaching statistical significance ($P = 0.140$). Similar results were found in patients previously treated with sotalol, in whom dronedarone was associated with a nonsignificant decreased risk of AF/AFL recurrence by 21.1% in comparison to placebo ($P = 0.169$).

In patients previously treated with another antiarrhythmic agent that was discontinued for an AE at any time prior to randomization, dronedarone decreased the risk of AF/AFL recurrence by 38.9% in comparison to placebo ($P = 0.006$) (see Supporting Table 1 in the online version of this article). Again, when only those patients previously treated with a class Ic agent were taken into account, dronedarone showed a nonsignificant risk reduction of AF/AFL recurrence by 37.7% in comparison to placebo ($P = 0.308$). A similar trend was also found in patients previously treated with sotalol, in whom a nonsignificant decrease in the risk of AF/AFL recurrence by 39.8% was observed with dronedarone in comparison to placebo ($P = 0.172$).

Among all patients who experienced AF/AFL recurrence, patients in the dronedarone group had a lower mean ventricular rate at the time of recurrence, regardless of

Figure 2. (A) Kaplan-Meier analysis of time from randomization to first AF/AFL recurrence within 12 months. All randomized and treated patients previously treated with class IC AADs stopped for whatever reasons before randomization. (B) Kaplan-Meier analysis of time from randomization to first AF/AFL recurrence within 12 months. All randomized and treated patients with sotalol stopped for whatever reasons before randomization. Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; AFL, atrial flutter; BID, twice daily.

Table 2. Overview of Adverse Events, Excluding AF/AFL Events, According to Class Ic or Sotalol Before Randomization

	Class Ic or Sotalol Before Randomization			No Class Ic or Sotalol Before Randomization		
	Placebo, n = 179	Dronedaronе, 400 mg BID, n = 332	RR [95% CI] ^a	Placebo, n = 230	Dronedaronе, 400 mg BID, n = 496	RR [95% CI] ^a
TEAE ^b	102 (57.0%)	200 (60.2%)	1.06 [0.91-1.23]	155 (67.4%)	358 (72.2%)	1.07 [0.96-1.19]
Serious TEAE	23 (12.8%)	31 (9.3%)	0.73 [0.44-1.21]	41 (17.8%)	87 (17.5%)	0.98 [0.70-1.38]
AE leading to premature study drug discontinuation ^b	8 (4.5%)	27 (8.1%)	1.82 [0.84-3.92]	17 (7.4%)	53 (10.7%)	1.45 [0.86-2.44]
Serious TEAE leading to hospitalization	22 (12.3%)	29 (8.7%)	0.71 [0.42-1.20]	38 (16.5%)	79 (15.9%)	0.96 [0.68-1.37]
Serious TEAE leading to death	0	2 (0.6%)	NA	4 (1.7%)	7 (1.4%)	0.81 [0.24-2.74]

Abbreviations: AE, adverse event; AF, atrial fibrillation; AFL, atrial flutter; BID, twice daily; CI, confidence interval; NA, not applicable; RR, relative risk; SAEs, serious adverse events; TEAE, treatment-emergent adverse event.

^aRR estimates with 95% CI: dronedarone 400 mg BID vs placebo. ^b Including SAEs.

previous treatment with class Ic agents and/or sotalol (see Supporting Table 2 in the online version of this article). Mean heart rate at recurrence was 12.3 bpm lower if previous treatment with either class Ic or sotalol was present ($P < 0.001$) and 15.1 bpm lower if class Ic or sotalol had not been administered prior to randomization in the dronedarone group when compared to placebo ($P < 0.001$). This effect on heart rate is similar to that seen in the overall population.¹⁴

Safety

The proportion of patients with ≥ 1 AE was comparable in the placebo and dronedarone groups, with the exception of mild gastrointestinal disorders such as diarrhea, nausea, and vomiting. In patients previously treated with a class Ic agent, diarrhea was observed in 6.8% and 4.6% of dronedarone and placebo patients, respectively ($P = 0.44$), whereas nausea and vomiting was observed in 3.2% and 1.9% ($P = 0.5$), respectively.

In terms of those patients previously treated with sotalol, again there were no significant differences in the proportion of patients who experienced diarrhea (7.0% vs 8.0%; $P = 0.74$) or nausea and vomiting (5.1% vs 5.4%; $P = 0.93$) between the dronedarone and placebo groups. However, serious AEs were slightly higher in the placebo group than in the dronedarone group (Table 2).

The incidence of AEs in patients previously treated with a class Ic AADs or sotalol compared to those patients without previous treatment is presented in Table 2. The relative risk of AEs in patients treated with dronedarone was similar to the relative risk of patients randomized to placebo, irrespective of previous treatment with class Ic or sotalol, as shown by the confidence intervals.

In patients who previously suspended 1 or more other antiarrhythmic drug prior to randomization, there were no significant differences in discontinuation rates between dronedarone and placebo in both trials (55.9% vs 43.1%), even for reasons other than lack of efficacy and/or end point (12.8% vs 15.7%) (Table 3). The main reason for premature discontinuation of the study drug was a lack of efficacy and/or occurrence of the primary end point of

the study—AF recurrence—observed more frequently in the placebo group compared to the dronedarone group. In addition, the proportion of patients discontinuing for AEs was similar in the placebo and dronedarone groups, although numerically slightly higher in the latter.

For ECG parameters, no particular trend was seen in patients with previous class Ic vs no previous class Ic or for patients with previous sotalol vs no previous sotalol.

Discussion

The EURIDIS and ADONIS studies demonstrated that dronedarone was superior to placebo in prolonging time to first AF recurrence.¹⁴ The findings of this post hoc analysis of 73% of the total population from the EURIDIS and ADONIS studies confirms the efficacy of dronedarone in patients previously treated with a class Ic antiarrhythmic agent and/or sotalol for rhythm control.

Switching antiarrhythmic therapy is relatively common in AF patients; the majority does so for a documented lack of efficacy (35%–63%, according to different study drugs and populations).^{9,22} In addition, most of the AADs currently recommended for rhythm control are burdened by poor tolerability and a plethora of side effects.²³ A recent meta-analysis⁹ showed that class Ic AADs and sotalol were often withdrawn due to AEs, with a number needed to harm (NNH) of 17 to 36; whereas all AADs, except amiodarone and propafenone, had clinical proarrhythmic effects (NNH, 17–19).

In this post hoc analysis, dronedarone was shown to be effective in maintaining sinus rhythm in patients who suspended other AADs, irrespective of reason (including tolerability issues or lack of efficacy). As AF patients frequently switch antiarrhythmic agents for rhythm control, the present benefit/risk data provide further evidence to suggest that dronedarone is an important therapeutic option also in non-naïve patients. This crucial last point underlines the role of dronedarone as a possible therapeutic option even in eligible patients who had already experienced a recurrence with another antiarrhythmic drug, whether amiodarone, sotalol, or class Ic agents.

As previously described, the safety profile of dronedarone is highly dependent on the study population,²⁴ being

Table 3. Randomized and Treated Patients With Sotalol and/or Vaughan Williams Class Ic Stopped for All Reasons Before Randomization

	Placebo, n = 179	Dronedaron 400 mg BID, n = 332	Total, N = 511
Patients who discontinued the study drug prematurely, n (%)	100 (55.9%)	143 (43.1%)	243 (47.6%)
Patients who discontinued the study drug prematurely for reason other than "lack of efficacy and/or end point" confirmed by the adjudication committee as primary end point, n (%)	23 (12.8%)	52 (15.7%)	75 (14.7%)
Main reason for premature discontinuation, n (%)			
Lack of efficacy and/or end point confirmed by adjudication committee, n (%)	77 (43.0%)	91 (27.4%)	168 (32.9%)
Lack of efficacy and/or end point not confirmed by adjudication committee, n (%)	1 (0.6%)	0	1 (0.2%)
Adverse event, n (%)	11 (6.1%)	27 (8.1%)	38 (7.4%)
Poor compliance with protocol, n (%)	2 (1.1%)	0	2 (0.4%)
Patient's request, n (%)	6 (3.4%)	20 (6.0%)	26 (5.1%)
Lost to follow-up, n (%)	0	0	0
Other reason, n (%)	3 (1.7%)	5 (1.5%)	8 (1.6%)

Abbreviations: BID, twice daily.
Missing data on reasons for discontinuation were not taken into account.

satisfactory in patients with no left ventricular dysfunction and paroxysmal AF,¹⁸ but poor in patients with severe heart failure¹⁹ or permanent AF.²⁰ In our study, dronedarone was shown to have a good tolerability and safety profile, even in patients who stopped previous antiarrhythmic agents for tolerability issues. Even with the limitations associated with a small sample size, patients treated with dronedarone and placebo-matched controls had a similar incidence of AEs, serious AEs, hospitalization, and death. Compared with placebo, the lower incidence of AEs leading to hospitalization, even if not statistically significant, can be at least partially explained by the lower prevalence of AF recurrences in patients treated with dronedarone, and by the heart rate-lowering effect of dronedarone at the time of first AF recurrence, a finding previously observed in the 2 main trials.¹⁴ Furthermore, the lack of any difference between the dronedarone and placebo groups in terms of proportion of patients discontinuing the study drug supports the optimal tolerability profile in patients without permanent AF.

Among the population of patients with a history of previous treatment with an antiarrhythmic agent, and who reached the primary end point, recurrence of AF was symptomatic in about two-thirds. This proportion was similar in the placebo and the dronedarone group, in patients previously treated with a class Ic agent, and in those previously treated with sotalol; however, as in the overall population,¹⁴ fewer patients reached the primary end point in the dronedarone compared to the placebo group, resulting in fewer symptomatic recurrences.

Limitations

Limitations of this study include its retrospective, exploratory nature. Given the study design, which was

based on planned visits and remotely transmitted tracings, it is unlikely that every AF recurrence in our study patients was detected. Follow-up ECGs were obtained at prespecified intervals and in the case of symptoms, which could also explain the high prevalence of symptomatic recurrences in our study.

With regard to the efficacy of dronedarone in patients previously treated with another antiarrhythmic agent and classified according to different types of underlying heart disease, the small number of patients does not allow us to draw any firm conclusions from between-group comparisons. In addition, specific data on patients who never failed an antiarrhythmic treatment are not available, because this subgroup was not defined in the protocol and therefore the information was not collected.

Conclusion

This retrospective analysis suggests that dronedarone could be effective for the prevention of AF in patients previously treated with another antiarrhythmic agent, even if the drug was discontinued for lack of efficacy. Our data support the notion that dronedarone could be a valuable treatment option to preserve sinus rhythm in patients for whom class Ic or sotalol AADs have failed. In a similar manner, dronedarone appears to be well tolerated and has a discontinuation rate similar to placebo, even in patients who already had tolerability issues with either class Ic AADs or sotalol.

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