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CLINICAL RESEARCH
Atrial fibrillation: diagnosis and pharmacological management

Effect of dronedarone vs. placebo on atrial fibrillation progression: a *post hoc* analysis from ATHENA trial

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Aims This *post hoc* analysis of the ATHENA trial (NCT00174785) assessed the effect of dronedarone on the estimated burden of atrial fibrillation (AF)/atrial flutter (AFL) progression to presumed permanent AF/AFL, and regression to sinus rhythm (SR), compared with placebo.

Methods and results The burden of AF/AFL was estimated by a modified Rosendaal method using available electrocardiograms (ECG). Cumulative incidence of permanent AF/AFL (defined as ≥6 months of AF/AFL until end of study) or permanent SR (defined as ≥6 months of SR until end of study) were calculated using Kaplan–Meier estimates. A log-rank test was used to assess statistical significance. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were estimated using a Cox model, adjusted for treatment group. Of the 4439 patients included in this analysis, 2208 received dronedarone, and 2231 placebo. Baseline and clinical characteristics were well balanced between groups. Overall, 304 (13.8%) dronedarone-treated patients progressed to permanent AF/AFL compared with 455 (20.4%) treated with placebo ($P < 0.0001$). Compared with those receiving placebo, patients receiving dronedarone had a lower cumulative incidence of permanent AF/AFL (log-rank $P < 0.001$; HR: 0.65; 95% CI: 0.56–0.75), a higher cumulative incidence of permanent SR (log-rank $P < 0.001$; HR: 1.19; 95% CI: 1.09–1.29), and a lower estimated AF/AFL burden over time ($P < 0.01$ from Day 14 to Month 21).

Conclusion These results suggest that dronedarone could be a useful antiarrhythmic drug for early rhythm control due to less AF/AFL progression and more regression to SR vs. placebo, potentially reflecting reverse remodeling.

Clinical trial registration NCT00174785

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Graphical Abstract

Effect of dronedarone vs. placebo on atrial fibrillation progression: a *post hoc* analysis from the ATHENA trial

Conclusion

These results suggest that dronedarone could be a useful antiarrhythmic drug for early rhythm control because there was less AF/AFL progression and more regression to SR versus placebo, potentially reflecting reverse remodeling

OBJECTIVE

To assess whether dronedarone vs placebo affects:

- Progression of AF/AFL to more persistent forms
- Regression of AF/AFL, measured by regression to permanent SR
- AF/AFL burden, defined as the amount of time in AF/AFL

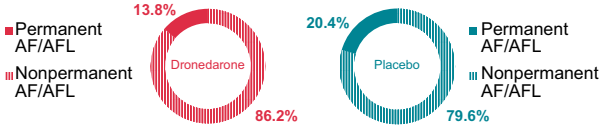
METHODS

Cumulative incidence of presumed permanent AF/AFL or permanent SR was calculated using the complement of Kaplan–Meier estimates, with statistical significance assessed by log-rank test

AF/AFL burden was estimated using a modified Rosendaal method, based on the presence or absence of AF/AFL assessed by ECG at each visit

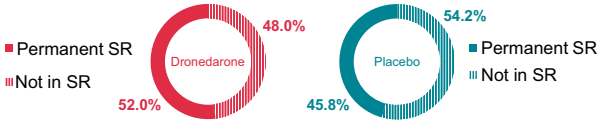
KEY RESULTS

Progressed to permanent AF/AFL



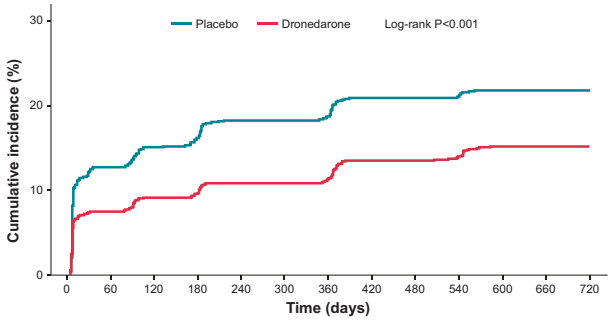
A total of 304 (13.8%) dronedarone-treated patients progressed to permanent AF/AFL compared with 455 (20.4%) who received placebo (P<0.0001)

Regression to permanent SR



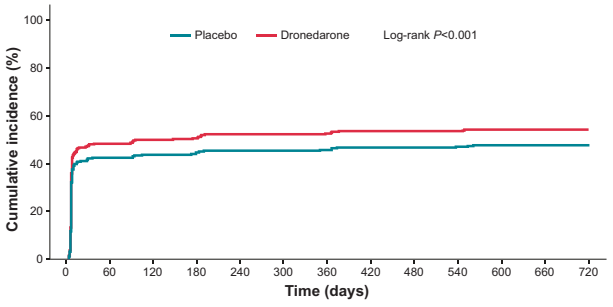
A total of 1149 (52.0%) dronedarone-treated patients achieved permanent SR compared with 1021 (45.8%) who received placebo (P=0.006)

Cumulative Incidence Curves for Progression to Permanent AF/AFL



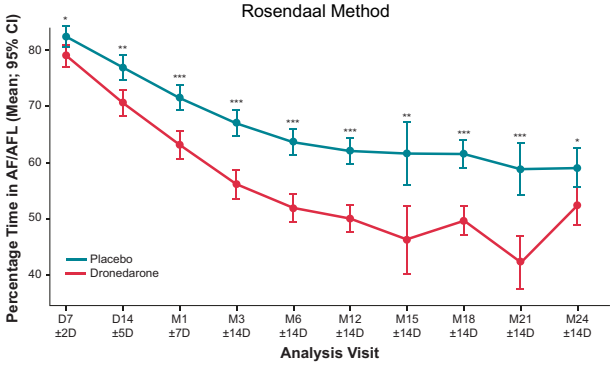
Cumulative incidence over time of permanent AF/AFL was significantly lower in dronedarone-treated patients (HR; 0.65; 95% CI 0.56-0.75); patients treated with dronedarone were 35% less likely to progress to permanent AF/AFL over time

Cumulative Incidence Curves for Regression to Permanent SR



Cumulative incidence of permanent SR over time was significantly higher in those receiving dronedarone vs placebo (HR; 1.19; 95% CI 1.09-1.29); patients treated with dronedarone were 19% more likely to improve to permanent SR over time

Mean Estimated AF/AFL Burden (%) Over Time Using Modified Rosendaal Method



*P < 0.05; **P < 0.001; ***P < 0.0001.

Estimated AF/AFL burden over time was lower in dronedarone- vs placebo-treated patients

AF, atrial fibrillation; AFL, atrial flutter; CI, confidence interval; D, day; ECG, electrocardiogram; HR, hazard ratio; M, month; SR, sinus rhythm.

Keywords Antiarrhythmic drug • Atrial fibrillation • Cardiovascular outcomes • Dronedarone • Progression

What's new?

- Progression to permanent AF/AFL was less frequent and regression to permanent sinus rhythm (SR) was more frequent among patients with atrial fibrillation (AF)/atrial flutter (AFL) who received dronedarone vs. placebo, potentially reflecting reverse remodeling
- Patients treated with dronedarone also had lower cumulative incidence of permanent AF/AFL, higher cumulative incidence of permanent SR, and lower estimated AF/AFL burden over time
- Progression to permanent AF/AFL occurred later with dronedarone vs. placebo
- To our knowledge, this *post hoc* analysis of the ATHENA trial is the first application of the Rosendaal method of linear interpolation to estimate AF/AFL burden

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with increased risk for stroke, heart failure, and cardiovascular death.[1–3] AF is a progressive arrhythmia that can advance from paroxysmal (duration ≤7 days) to persistent (duration >7 days without spontaneous conversion to sinus rhythm [SR]) or to permanent AF.[4,5] Results of a systematic review of use of AF ablation showed that in general population studies, progression to more persistent or permanent forms of AF occurred in 10%–20% of people with paroxysmal AF within 1 year of follow-up.[6] Progression over time to more persistent forms of AF is associated with increased disease burden, hospitalization rates, and increased mortality[4,7,8] and is related to structural and atrial electrical remodeling.[9,10] The findings of several studies support the use of rhythm control in people with AF to slow disease progression and improve cardiovascular outcomes.[11,12] Observational studies have shown that patients with non-permanent AF who received rhythm control were less likely to progress to permanent AF compared with those who received only rate control therapy,[13] and that early rhythm control is associated with a lower risk of adverse cardiovascular outcomes.[14] In the ATHENA trial, in which patients with paroxysmal or persistent AF were enrolled, treatment with dronedarone was associated with a significant reduction in the incidence of the primary composite endpoint of first cardiovascular hospitalization or death due to any cause compared with placebo.[15] Additionally, in a *post hoc* analysis of the ATHENA population, dronedarone demonstrated efficacy vs. placebo regardless of duration of AF/atrial flutter (AFL), but was more robust in those with short (<3 months) or intermediate (3 to <24 months) AF/AFL history compared with those with an AF/AFL history ≥24 months.[16] In the current *post hoc* analysis of ATHENA, we hypothesized that (i) there is a lower AF/AFL burden over time in patients receiving dronedarone compared with placebo, and (ii) there is less AF progression and more AF regression in dronedarone-treated vs. placebo-treated patients.

Methods

Overview of the ATHENA study

ATHENA was a double-blind, placebo-controlled randomized study (NCT00174785); design and primary results have been previously reported.[15,17] The study evaluated outcomes among 4628 patients with paroxysmal or persistent AF/AFL (enrolled between June 2005 and December 2006) who received dronedarone (400 mg twice daily) or placebo. The mean follow-up period was 21 ± 5 months with a minimum follow-up of 12 months. All patients in the ATHENA study provided written informed consent; the study was approved by independent review boards at participating sites and was conducted according to the Declaration of Helsinki.

Outcomes

In the present analysis, the outcomes of interest were estimated AF/AFL burden over time, cumulative incidence of presumed permanent AF/AFL (defined as AF progression) and presumed permanent SR (defined as AF regression). To be classified as having presumed permanent AF/AFL, patients were required to have a period of ≥6 months with all available electrocardiograms (ECGs) showing AF/AFL until the end of study. To be classified as having permanent SR, patients were required to have a period of ≥6 months with all available ECGs showing SR until the end of study.

Statistical analysis

Demographic characteristics, clinical characteristics, and safety data were summarized using descriptive statistics. Cumulative incidence functions were calculated using the complement of Kaplan–Meier estimates. Comparison between treatment groups was assessed using a log-rank test. Hazard ratios (HRs) with corresponding 95% confidence interval (CIs) were estimated using a Cox model adjusted for treatment group. AF/AFL burden was estimated using the modified Rosendaal method[18] to calculate percentage of time in AF/AFL assessed by available ECGs. The modified Rosendaal method[18] uses linear interpolation to estimate the time a patient spends in AF/AFL. This method was adapted to apply to qualitative outcomes and to calculate the percentage of time each patient spent in AF/AFL using available ECG assessments. All tests were two-sided, and *P*-values of <0.05 were considered statistically significant. *P*-values are displayed for descriptive purpose only. Data were analyzed using SAS version 9.4 (Cary, NC, USA).

Results

Of the 4628 patients randomized in the ATHENA study, 4439 were included in the analysis (2208 in the dronedarone arm and 2231 in the placebo arm). A total of 189 patients with missing ECGs or undefined assessment at baseline were excluded from the analysis. Baseline and clinical characteristics were well balanced between groups (*Table 1*), as was the use of baseline medications (*Table 2*).

AF progression and regression

Overall, at the end of follow-up, 304 of 2208 dronedarone-treated patients had progressed to permanent AF/AFL compared with 455 of 2231 patients who received placebo (13.8% vs. 20.4%, respectively; $P < 0.0001$). A total of 1149 dronedarone-treated patients had achieved permanent SR compared with 1021 patients who received placebo (52.0% vs. 45.8%, respectively; $P = 0.006$). Irrespective of treatment group, the proportions of patients progressing to permanent vs. non-permanent AF/AFL were higher for those who had left atrial diameters >40 mm (dronedarone 85.7% vs. 67.3%; placebo 80.4% vs. 66.5%), for those with left ventricular ejection <50% (dronedarone 22.6% vs. 16.6%; placebo 21.3% vs. 17.3%) (*Table 3*). The reverse was observed for those achieving permanent SR (*Table 3*).

Table 1 Baseline and clinical characteristics

Patient characteristics	Progression to permanent AF/AFL				Regression to permanent SR			
	Dronedarone		Placebo		Dronedarone		Placebo	
	Permanent AF/AFL ($n = 304$)	Non-permanent AF/AFL ($n = 1904$)	Permanent AF/AFL ($n = 455$)	Non-permanent AF/AFL ($n = 1776$)	Permanent SR ($n = 1149$)	Not permanent SR ($n = 1059$)	Permanent SR ($n = 1021$)	Not permanent SR ($n = 1210$)
Age, years *mean (SD)*	70.2 (9.3)	71.7 (8.8)	71.7 (8.8)	71.6 (9.0)	71.5 (8.5)	71.6 (9.3)	70.8 (9.1)	72.2 (8.8)
Male *n* (%)	175 (57.6)	942 (49.5)	256 (56.3)	979 (55.1)	555 (48.3)	562 (53.1)	544 (53.3)	691 (57.1)
Race *n* (%)								
White	269 (88.5)	1713 (90.0)	388 (85.3)	1598 (90.0)	1028 (89.5)	954 (90.1)	912 (89.3)	1074 (88.8)
Asian	28 (9.2)	117 (6.1)	46 (10.1)	103 (5.8)	70 (6.1)	75 (7.1)	58 (5.7)	91 (7.5)
Black	0 (0.0)	18 (0.9)	5 (1.1)	24 (1.4)	8 (0.7)	10 (0.9)	11 (1.1)	18 (1.5)
Other	7 (2.3)	56 (2.9)	16 (3.5)	51 (2.9)	43 (3.7)	20 (1.9)	40 (3.9)	27 (2.2)
Weight, mean (SD), kg	82.7 (17.5)	80.1 (17.2)	82.0 (18.9)	80.2 (17.5)	79.7 (16.9)	81.2 (17.6)	79.5 (16.1)	81.4 (19.0)
CHA_2DS_2-VASc score *mean (SD)*								
Male, *n*	175	942	256	979	555	562	544	691
Mean (SD)	3.0 (1.5)	3.1 (1.4)	3.0 (1.4)	3.1 (1.5)	3.1 (1.4)	3.1 (1.5)	3.0 (1.4)	3.1 (1.5)
Female, *n*	129	962	199	797	594	497	477	519
Mean (SD)	4.5 (1.5)	4.3 (1.4)	4.5 (1.4)	4.3 (1.4)	4.3 (1.4)	4.4 (1.4)	4.2 (1.4)	4.4 (1.5)
Cardiovascular comorbidities *n (%)*								
Structural heart disease	186 (61.4)	1086 (57.5)	270 (59.6)	1074 (60.9)	644 (56.6)	628 (59.5)	588 (58.0)	756 (62.8)
Coronary heart disease	92 (30.3)	534 (28.0)	117 (25.7)	574 (32.3)	319 (27.8)	307 (29.0)	312 (30.6)	379 (31.3)
Hypertrophic cardiomyopathy	6 (2.0)	38 (2.0)	10 (2.2)	36 (2.0)	18 (1.6)	26 (2.5)	18 (1.8)	28 (2.3)
Non-ischaemic dilated cardiomyopathy	12 (3.9)	64 (3.4)	21 (4.6)	58 (3.3)	30 (2.6)	46 (4.3)	26 (2.5)	53 (4.4)
Ischaemic dilated cardiomyopathy	10 (3.3)	75 (3.9)	24 (5.3)	87 (4.9)	37 (3.2)	48 (4.5)	36 (3.5)	75 (6.2)
Hypertension	261 (85.9)	1656 (87.0)	397 (87.3)	1521 (85.6)	1007 (87.6)	910 (85.9)	895 (87.7)	1023 (84.5)
Ablation for AF/AFL	11 (3.6)	67 (3.5)	20 (4.4)	78 (4.4)	33 (2.9)	45 (4.2)	34 (3.3)	64 (5.3)
Pacemaker	16 (5.3)	142 (7.5)	41 (9.0)	147 (8.3)	32 (2.8)	126 (11.9)	39 (3.8)	149 (12.3)
Implanted cardioverter defibrillator	4 (1.3)	32 (1.7)	5 (1.1)	30 (1.7)	6 (0.5)	30 (2.8)	12 (1.2)	23 (1.9)
Lone atrial fibrillation	17 (5.6)	120 (6.3)	19 (4.2)	115 (6.5)	74 (6.5)	63 (6.0)	62 (6.1)	72 (6.0)
CHF symptoms *n (%)*	91 (29.9)	562 (29.5)	132 (29.0)	538 (30.3)	342 (29.8)	311 (29.4)	311 (30.5)	359 (29.7)
NYHA class *n (%)*								
I	24 (7.9)	180 (9.5)	36 (7.9)	135 (7.6)	110 (9.6)	94 (8.9)	87 (8.5)	84 (6.9)
II	54 (17.8)	310 (16.3)	75 (16.5)	319 (18.0)	189 (16.4)	175 (16.5)	190 (18.6)	204 (16.9)
III	13 (4.3)	72 (3.8)	21 (4.6)	84 (4.7)	43 (3.7)	42 (4.0)	34 (3.3)	71 (5.9)
NA	213 (70.1)	1342 (70.5)	323 (71.0)	1238 (69.7)	807 (70.2)	748 (70.6)	710 (69.5)	851 (70.3)

Continued

Table 1 *Continued*

Patient characteristics	Progression to permanent AF/AFL				Regression to permanent SR			
	Dronedarone		Placebo		Dronedarone		Placebo	
	Permanent AF/AFL (*n* = 304)	Non-permanent AF/AFL (*n* = 1904)	Permanent AF/AFL (*n* = 455)	Non-permanent AF/AFL (*n* = 1776)	Permanent SR (*n* = 1149)	Not permanent SR (*n* = 1059)	Permanent SR (*n* = 1021)	Not permanent SR (*n* = 1210)
LVEF < 35% or NYHA class > 1 *n*	302	1885	451	1757	1135	1052	1010	1198
n (%)	96 (31.8)	578 (30.7)	138 (30.6)	561 (31.9)	348 (30.7)	326 (31.0)	321 (31.8)	378 (31.6)
Received concomitant oral anticoagulants *n (%)*	280 (92.1)	1257 (66.0)	403 (88.6)	1175 (66.2)	650 (56.6)	887 (83.8)	570 (55.8)	1008 (83.3)
eGFR category (CKD-EPI), *n*	303	1898	453	1775	1146	1055	1021	1207
<45 mL/min, *n* (%)	35 (11.6)	268 (14.1)	63 (13.9)	251 (14.1)	134 (11.7)	169 (16.0)	138 (13.5)	176 (14.6)
≥45 to <60 mL/min *n* (%)	88 (29.0)	536 (28.2)	140 (30.9)	510 (28.7)	320 (27.9)	304 (28.8)	288 (28.2)	362 (30.0)
≥60 mL/min *n* (%)	180 (59.4)	1094 (57.6)	250 (55.2)	1014 (57.1)	692 (60.4)	582 (55.2)	595 (58.3)	669 (55.4)
Time since first known AF/AFL episode *n* (%)[a]								
<12 months	92 (51.4)	868 (71.7)	160 (58.6)	759 (69.4)	574 (76.3)	386 (60.5)	488 (73.9)	431 (61.2)
≥12 months	87 (48.6)	344 (28.4)	113 (41.4)	334 (30.6)	179 (23.7)	252 (39.5)	173 (26.1)	274 (38.8)
Cardioversion *n* (%)								
≥ 1 cardioversion	39 (12.8)	282 (14.8)	77 (16.9)	392 (22.1)	95 (8.3)	226 (21.3)	129 (12.6)	340 (28.1)
≥ 1 successful cardioversion	20 (6.6)	268 (14.1)	47 (10.3)	372 (20.9)	95 (8.3)	193 (18.2)	126 (12.3)	293 (24.2)

[a]Percentages calculated on patients with known AF/AFL episode before study entry.

AF, atrial fibrillation; AFL, atrial flutter; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and sex category (female); CHF, congestive heart failure; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtrate rate; LVEF; left ventral ejection fraction; NYHA, New York Heart Association; SD, standard deviation; SR, sinus rhythm; TEAE, treatment-emergent adverse-event.

Table 2 Baseline cardiovascular medications

Baseline medications *n* (%)	Progression to permanent AF/AFL				Regression to permanent SR			
	Dronedarone		Placebo		Dronedarone		Placebo	
	Permanent AF/AFL (*n* = 304)	Non-permanent AF/AFL (*n* = 1904)	Permanent AF/AFL (*n* = 455)	Non-permanent AF/AFL (*n* = 1776)	Permanent SR (*n* = 1149)	Not permanent SR (*n* = 1059)	Permanent SR (*n* = 1021)	Not permanent SR (*n* = 1210)
Beta blocking agents (not including sotalol)	215 (70.7)	1348 (70.8)	315 (69.2)	1267 (71.3)	836 (72.8)	727 (68.6)	724 (70.9)	858 (70.9)
ACE inhibitors or AII receptor antagonist	209 (68.8)	1352 (71.0)	321 (70.5)	1228 (69.1)	846 (73.6)	715 (67.5)	721 (70.6)	828 (68.4)
Oral anticoagulant	250 (82.2)	1098 (57.7)	351 (77.1)	975 (54.9)	564 (49.1)	784 (74.0)	461 (45.2)	865 (71.5)
Diuretics								
Other than spironolactone	162 (53.3)	979 (51.4)	245 (53.8)	929 (52.3)	580 (50.5)	561 (53.0)	521 (51.0)	653 (54.0)
Spironolactone	26 (8.6)	113 (5.9)	29 (6.4)	101 (5.7)	52 (4.5)	87 (8.2)	52 (5.1)	78 (6.4)
Aspirin (<365 mg)	96 (31.6)	882 (46.3)	138 (30.3)	846 (47.6)	581 (50.6)	397 (37.5)	558 (54.7)	426 (35.2)
Statins								
Metabolized by CYP3A4	99 (32.6)	600 (31.5)	148 (32.5)	578 (32.5)	343 (29.9)	356 (33.6)	320 (31.3)	406 (33.6)
Not metabolized by CYP3A4	22 (7.2)	122 (6.4)	27 (5.9)	133 (7.5)	73 (6.4)	71 (6.7)	64 (6.3)	96 (7.9)
Calcium antagonist (with heart rate lowering effects)	46 (15.1)	274 (14.4)	58 (12.7)	232 (13.1)	140 (12.2)	180 (17.0)	112 (11.0)	178 (14.7)
Digitalis	56 (18.4)	252 (13.2)	82 (18.0)	211 (11.9)	109 (9.5)	199 (18.8)	89 (8.7)	204 (16.9)

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; AFL, atrial flutter.

Progression of AF/AFL, as defined by the cumulative incidence of permanent AF/AFL over time, was lower in patients who received dronedarone vs. placebo (log-rank $P < 0.001$; HR: 0.65; 95% CI: 0.56–0.75; *Figure 1*). Regression of AF/AFL, as defined by the cumulative incidence of permanent SR over time, was higher in dronedarone-treated vs. placebo-treated patients (log-rank $P < 0.001$; HR: 1.19; 95% CI: 1.09–1.29; *Figure 2*). Estimated AF/AFL burden was significantly lower at each planned visit in patients who received dronedarone compared with those who received placebo (*Figure 3*).

Safety

A summary of treatment-emergent adverse events (TEAEs) is included in *Table 4*. Rates of TEAEs leading to permanent discontinuation of study drug were higher with dronedarone vs. placebo in all comparison groups (*Table 4*), in line with the findings in the main ATHENA trial.[15] Overall rates of discontinuation for dronedarone vs. placebo were 12.7% vs. 8.1%, respectively, with events of diarrhoea, nausea, prolongation of QT on ECG, and increased levels of serum creatinine contributing to the imbalance.

Discussion

ATHENA is the largest clinical trial to date assessing clinical outcomes in AF patients using an antiarrhythmic drug (AAD). In this *post hoc* analysis, the effect of dronedarone on the progression of AF/AFL was evaluated using the cumulative incidence of presumed permanent AF/AFL and estimated AF/AFL burden using the modified Rosendaal method.[18] To our knowledge, this is the first study to apply this methodology in the context of estimating AF/AFL burden.

A lower proportion of patients treated with dronedarone as compared with placebo progressed to permanent AF/AFL over time; a higher proportion of patients had AF regression to SR and, overall, had a lower estimated AF/AFL burden. At any time point during the study period, patients treated with dronedarone were 35% less likely to progress to permanent AF/AFL and 19% more likely to improve to permanent SR compared with patients who received placebo. The positive effects on progression, regression, and AF/AFL burden suggest that dronedarone may reverse atrial and ventricular remodeling. This suggestion is supported by results from animal studies of structural heart disease in which dronedarone was found to decrease remodeling through increased bioavailability of nitric oxide[19] and to cause regression of myocardial remodeling.[20–22] Moreover, dronedarone has previously been shown in the HESTIA study to reduce AF burden in patients with pacemakers who had paroxysmal or persistent AF.[23] The protective effect of dronedarone in preventing recurrence of AF has also been recorded in a real world observational study (EFFECT-AF), with dronedarone having similar efficacy to other AADs (mainly amiodarone [46.5%], Class Ic drugs [42.1%], or sotalol [10.8%]) in preventing first AF recurrence.[24] The positive effects on AF/AFL burden, and on AF

Table 3 Baseline cardiovascular examinations

Patient characteristics	Progression to permanent AF/AFL				Regression to permanent SR			
	Dronedarone		Placebo		Dronedarone		Placebo	
	Permanent AF/AFL ($n = 304$)	Non-permanent AF/AFL ($n = 1904$)	Permanent AF/AFL ($n = 455$)	Non-permanent AF/AFL ($n = 1776$)	Permanent SR ($n = 1149$)	Not permanent SR ($n = 1059$)	Permanent SR ($n = 1021$)	Not permanent SR ($n = 1210$)
Baseline cardiovascular examination								
Left atrium diameter *n*	300	1883	450	1748	1132	1051	1009	1189
Mean (SD)	46.53 (6.14)	43.65 (6.77)	46.35 (6.75)	43.39 (7.01)	42.88 (6.44)	45.30 (6.87)	42.37 (6.72)	45.38 (7.04)
> 40 mm *n* (%)	257 (85.7)	1267 (67.3)	362 (80.4)	1162 (66.5)	726 (64.1)	798 (75.9)	619 (61.3)	905 (76.1)
Left ventricular ejection fraction % *n*	301	1879	451	1748	1130	1050	1007	1192
Mean (SD)	56.01 (11.19)	57.66 (10.82)	56.70 (11.26)	57.60 (11.20)	58.33 (9.98)	56.47 (11.71)	58.68 (10.62)	56.35 (11.59)
< 50% *n* (%)	68 (22.6)	312 (16.6)	96 (21.3)	303 (17.3)	158 (14.0)	222 (21.1)	135 (13.4)	264 (22.1)

AF, atrial fibrillation; AFL, atrial flutter; SD, standard deviation.

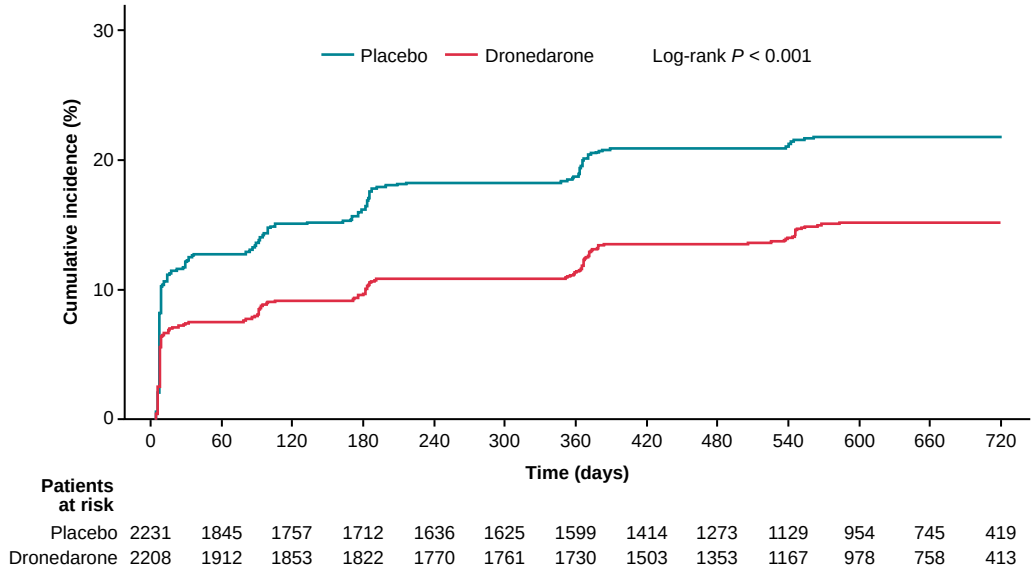


Figure 1 Cumulative incidence curves for progression to permanent AF/AFL. AF, atrial fibrillation; AFL, atrial flutter; CI, confidence interval; HR, hazard ratio.

progression and regression by dronedarone in the current study suggest dronedarone may be a preferred treatment option early in the course of AF, particularly given its low pro-arrhythmic risk.[15] In a previous *post hoc* analysis of ATHENA that categorized patients into groups according to time since first-known AF/AFL episode (<3 months, 3 to <24 months, and ≥24 months),[16] dronedarone was shown to be associated with improved primary outcome of cardiovascular hospitalization and death from any cause at all time points. The effects were, however, more pronounced in those with shorter vs. longer AF/AFL histories,[16] suggesting that dronedarone should be used at an early stage of the AF disease, whereas factors such as age or sex do not impact the efficacy of dronedarone.[25] Recently, the

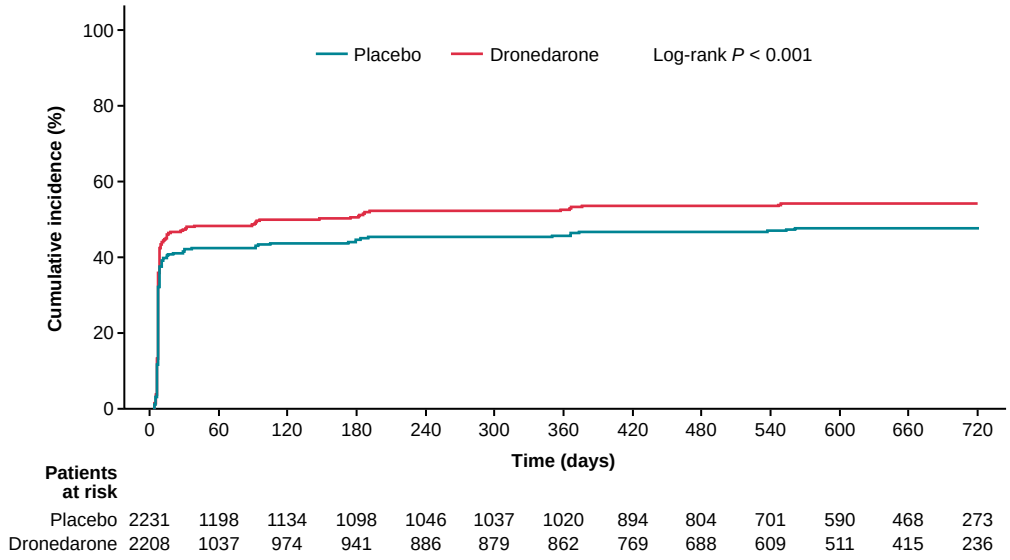


Figure 2 Cumulative incidence curves for AF/AFL regression to permanent SR. AF, atrial fibrillation; AFL, atrial flutter; CI, confidence interval; HR, hazard ratio; SR, sinus rhythm.

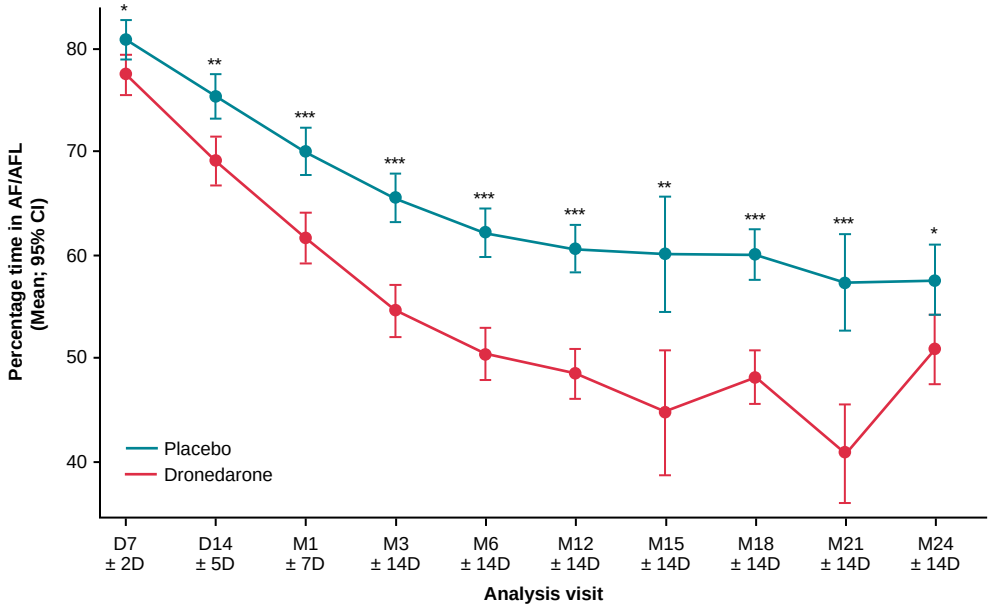


Figure 3 Estimated mean AF/AFL burden (%) calculated using modified Rosendaal method.[18] AF, atrial fibrillation; AFL, atrial flutter; CI, confidence interval; D, day; M, month. Analysis performed using Student's *t*-test: * $P < 0.05$; ** $P < 0.001$; *** $P < 0.0001$.

clinical importance of early rhythm control has been emphasized in a number of studies.[11,12,26–28] The EAST-AFNET 4 trial demonstrated that early comprehensive rhythm control (using AADs and/or catheter ablation) was associated with a significant reduction in risk of adverse cardiovascular outcomes compared with the guideline-recommended standard of care, which was limited to the guideline-based management of AF-related symptoms.[26,27] Additionally, the STOP AF First and EARLY AF trials support the use of ablation over AADs as initial early rhythm control therapy (dronedarone was used by 12% and 8.1% of patients included in the AAD groups in these studies, respectively).[11,12]

Patients with AF/AFL progression in this analysis tended to have larger left atrial diameters and lower left ventricular ejection fractions irrespective of treatment group, which is consistent with other reports.[29] Additionally, in the dronedarone (as opposed to placebo) arm, patients who progressed to permanent AF/AFL were also more likely to have structural heart disease or coronary heart disease—all

Table 4 Treatment-emergent adverse events (TEAEs)

	Analyses by progression to presumed permanent AF/AFL				Analyses by regression to permanent SR			
	Dronedarone		Placebo		Dronedarone		Placebo	
	Permanent AF/AFL (*n* = 304)	Non-permanent AF/AFL (*n* = 1906)	Permanent AF/AFL (*n* = 455)	Non-permanent AF/AFL (*n* = 1774)	Permanent SR (*n* = 1150)	Not permanent SR (*n* = 1060)	Permanent SR (*n* = 1020)	Not permanent SR (*n* = 1209)
Any TEAE *n* (%)	231 (76.0)	1356 (71.1)	349 (76.7)	1193 (67.2)	779 (67.7)	808 (76.2)	663 (65.0)	879 (72.7)
Serious TEAE[a] *n* (%)	67 (22.0)	373 (19.6)	105 (23.1)	369 (20.8)	197 (17.1)	243 (22.9)	203 (19.9)	271 (22.4)
Deaths[b] *n* (%)	5 (1.6)	32 (1.7)	8 (1.8)	35 (2.0)	8 (0.7)	29 (2.7)	7 (0.7)	36 (3.0)
Permanently discontinued study drug for TEAE *n* (%)	44 (14.5)	236 (12.4)	32 (7.0)	147 (8.3)	109 (9.5)	171 (16.1)	57 (5.6)	122 (10.1)

[a]Including serious AEs leading to death.
[b]Patients who died from first study drug intake up to last study drug intake plus 10 days.

known factors related to the progression of atrial cardiomyopathy and to more persistent forms of AF.[4,29] Although these differences were small, this *post hoc* analysis provides the incentive to further investigate whether treatment with the multi-channel blocker dronedarone can protect against atrial disease progression and promote AF regression in patients at different stages/durations of AF.

Limitations

This was a *post hoc* analysis, and as such, the results of this analysis should be considered hypothesis-generating. It was not known whether patients had paroxysmal or persistent forms of AF/AFL upon randomization or follow-up in the ATHENA trial. While the Rosendaal method has been previously used to estimate the percentage of time a continuous outcome remains within a therapeutic range, in this *post hoc* analysis, this method was adapted to estimate the percentage of time a patient remains in AF/AFL, a categorical outcome. ECG evaluations in this study were infrequent, as they were assessed at specific time points as per study protocol, limiting the accuracy of assessment of estimated AF/AFL burden, and AF/AFL progression and regression.

Conclusions

In this *post hoc* analysis of the ATHENA trial, the observation of a lower estimated AF/AFL burden, lower AF progression, and more AF regression to SR over time in patients receiving dronedarone compared with those receiving placebo suggests that dronedarone may potentially reverse cardiac remodeling and thereby be a useful early treatment for patients with AF.

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Conflict of interest: C.B.L. receives honoraria from Medtronic AB, Boston Sci, Octopus, Bayer, Organon, Sanofi, BMS, Philips, Johnson and Johnson, and Cathprint. G.V.N. is a consultant for Sanofi, Acesion, Milestone, Incarda Therapeutics, and Glaxo Smith Kline. D.S.M. and M.W. are employees of Sanofi. G.B. is an employee of IVIDATA Life Sciences. S.H.H. receives honoraria from Pfizer, BMS, BI, Daiichi and Zoll.

Data availability

Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and data set specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.vivli.org/.

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