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Effect of dronedarone on clinical end points in patients with atrial fibrillation and coronary heart disease: insights from the ATHENA trial

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Aims This study aimed to assess safety and cardiovascular outcomes of dronedarone in patients with paroxysmal or persistent atrial fibrillation (AF) with coronary heart disease (CHD). Coronary heart disease is prevalent among AF patients and limits antiarrhythmic drug use because of their potentially life-threatening ventricular proarrhythmic effects.

Methods and results This *post hoc* analysis evaluated 1405 patients with paroxysmal or persistent AF and CHD from the ATHENA trial. Follow-up lasted 2.5 years, during which patients received either dronedarone (400 mg twice daily) or a double-blind matching placebo. Primary outcome was time to first cardiovascular hospitalization or death due to any cause. Secondary end points included first hospitalization due to cardiovascular events. The primary outcome occurred in 350 of 737 (47%) placebo patients vs. 252 of 668 (38%) dronedarone patients [hazard ratio (HR) = 0.73; 95% confidence interval (CI) = 0.62–0.86; $P = 0.0002$] without a significant increase in number of adverse events. In addition, 42 of 668 patients receiving dronedarone suffered from a first acute coronary syndrome compared with 67 of 737 patients from the placebo group (HR = 0.67; 95% CI = 0.46–0.99; $P = 0.04$).

Conclusion In this *post hoc* analysis, dronedarone on top of standard care in AF patients with CHD reduced cardiovascular hospitalization or death similar to that in the overall ATHENA population, and reduced a first acute coronary syndrome. Importantly, the safety profile in this subpopulation was also similar to that of the overall ATHENA population, with no excess in proarrhythmias. The mechanism of the cardiovascular protective effects is unclear and warrants further investigation.

Keywords Dronedarone • Atrial fibrillation • Coronary heart disease

Introduction

Coronary heart disease (CHD) is common among patients with atrial fibrillation (AF).[1] Atrial fibrillation symptoms that do not respond to rate control frequently require rhythm control. Besides increasing the risk of cardiovascular events, CHD facilitates ventricular proarrhythmia of most antiarrhythmic drugs. Subsequently, the therapeutic options for rhythm control in patients with AF and CHD are limited. Although the use of amiodarone is recommended in patients with AF and CHD,[2,3] the well-known extracardiac side effects associated with this drug create an important tradeoff.

Dronedarone is a multichannel-blocking antiarrhythmic drug pharmacologically related to amiodarone; however, structural modifications, i.e. removal of the iodine moiety and addition of a methanesulfonyl group have been made in order to reduce unwanted thyroid and other adverse effects associated with amiodarone use. In addition, these changes mean dronedarone is less lipophilic than amiodarone and thus, has a shorter half-life.[4–6] While the underlying mechanism of action is unclear, dronedarone appears to prevent the occurrence of microcirculatory abnormalities in the ventricles during AF.[7] The alleviation of these abnormalities, which appear to

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What's new?

- Application of Vaughan-Williams class Ic antiarrhythmic drugs in patients with atrial fibrillation suffering from coronary artery disease is limited due to severe side effects. In this *post hoc* analysis the new antiarrhythmic drug dronedarone appears safe and reduces cardiovascular hospitalization and death in patients with stable coronary artery disease and non-permanent atrial fibrillation.
- Dronedarone—and not placebo—reduces the pressure rate product thereby potentially limiting demand ischemia. This effect is most marked in patients with breakthrough atrial fibrillation.
- In patients with stable coronary artery disease and non-permanent atrial fibrillation, dronedarone reduces the incidence of acute coronary events. This effect is largest in patients with a decreased left ventricular ejection fraction.

represent early changes in the myocardial structure of AF patients, suggests that dronedarone might be particularly effective in the early stages of the disease.

In a study by Singh *et al.*,[8] dronedarone proved to be effective in preventing recurrence in patients with persistent or paroxysmal AF. More recently, in 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 atrial fibrillation/atrial flutter) study, dronedarone was shown to reduce the composite outcome of cardiovascular hospitalization or death in patients with persistent or paroxysmal AF and at least one risk factor for vascular events. Furthermore, the observed benefit of dronedarone was not offset by an increased number of serious adverse events.[9]

The current *post hoc* analysis from ATHENA therefore focuses on the safety and cardiovascular outcomes of dronedarone use in patients with AF and CHD.

Methods

ATHENA's design, definitions, and main findings have been published previously.[9,10] In summary, patients with paroxysmal or persistent AF or atrial flutter who had both sinus rhythm and an arrhythmia documented in the previous 6 months and at least one additional risk factor for cardiovascular events, including age $\geq$75 years or 70 years with one or more risk factors [hypertension, diabetes mellitus, prior stroke or transient ischemic attack, left atrial enlargement ($\geq$50 mm), or depressed left ventricular ejection fraction ($\leq$0.40)], were recruited. Prior to a study protocol amendment in the first year of the trial, patients younger than 70 years were also eligible, if they also did not meet any exclusion criterion, of which unstable hemodynamic situation, New York Heart Association class IV heart failure, and permanent AF were key. Patients were randomly allocated to a regimen of dronedarone 400 mg twice daily or double-blind matching placebo, and followed up every 3 months until a common termination point assuring a minimum follow-up of at least 1 year for the patient enrolled last (maximum of 2.5 and mean of 1.7 years).

The primary study outcome was the first occurrence of cardiovascular hospitalization or death due to any cause. Any unplanned hospitalization (i.e. admission with an overnight stay in the hospital) was classified by the investigator as a hospitalization due to either cardiovascular or non-cardiovascular causes.[10] The secondary outcomes were death, cardiovascular death, and cardiovascular hospitalization. Deaths were categorized by a blinded adjudication committee into four categories: cardiac, arrhythmic; cardiac, nonarrhythmic; vascular, noncardiac; and nonvascular. Information on occurrence of acute coronary syndrome was collected from hospitalization and death report forms.

Coronary heart disease is defined as a documented history of either ischemic dilated cardiomyopathy, evidenced by clinically significant left ventricular dilatation secondary to coronary artery disease, or coronary artery disease, which was defined as acute myocardial infarction (MI) and/or the following: significant ($\geq$70%) coronary artery stenosis, history of revascularization procedure (percutaneous transluminal coronary angioplasty, stent implantation in a coronary artery, coronary artery bypass grafting, etc), positive exercise test, and positive nuclear scan of cardiac perfusion.

A treatment-emergent adverse event (TEAE) was defined as an adverse event occurring between first dose of the study drug and 10 days after the last dose. A serious TEAE was one that resulted in death, was life-threatening, required or prolonged hospitalization, was a medically important event, resulted in persistent, clinically significant disability or incapacity, or was a congenital anomaly or birth defect.

Statistics

Analyses were performed in the intention-to-treat population and the time to event was estimated according to the Kaplan–Meier method and compared using the log-rank test. Hazard ratio was calculated using Cox's proportional hazard model with treatment group as covariate. The *P* value for interaction between treatment and CHD status was tested based on Cox regression model. 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 two-tailed.

Results

Of the 1405/4628 (30%) patients in the entire ATHENA cohort with AF and CHD, 668 were randomized to receive dronedarone, and the remaining 737 to receive placebo. Apart from a similar prevalence of hypertension at baseline, in AF patients with CHD, cardiovascular diseases and associated medications were significantly more common compared with their non-CHD counterparts (*Table 1*).

In terms of the composite primary outcome, the risk of first cardiovascular hospitalization or death due to any cause was similar in the cohort of AF patients with CHD [hazard ratio (HR) = 0.73; 95% confidence interval (CI) = 0.62–0.86; $P = 0.0002$] and those without CHD (HR = 0.78; 95% CI = 0.69–0.88; $P < 0.0001$) (*Figure 1*). For the on-treatment analysis, a significantly greater proportion of AF patients with CHD were hospitalized due to a cardiovascular event (62.9% vs. 52.2) or died due to any cause (5.7 vs. 4.3) in the placebo group compared with the dronedarone group, respectively ($P < 0.01$). *Figure 2* shows that dronedarone significantly prevents the occurrence of a first acute coronary syndrome in AF patients with CHD (HR = 0.67; 95% CI = 0.46–0.99; $P = 0.04$). *Table 2* presents the comparison of the effect of dronedarone across the two subgroups, those with CHD and those without CHD. For both the primary and secondary outcomes, dronedarone is as effective in AF patients with CHD as in those without (*P* value for interaction = NS for all).

Table 1 Baseline characteristics of patients with and without coronary heart disease[a]

	CHD		No CHD	
	Placebo (n = 737)	Dronedarone (n = 668)	Placebo (n = 1590)	Dronedarone (n = 1633)
Mean age, years (SD)	73.5 (8.2)	73.1 (7.7)	70.8 (9.3)	70.9 (9.3)
Male gender	485 (65.8%)	419 (62.7%)	804 (50.6%)	751 (46%)
Hypertension	639 (86.7%)	593 (88.8%)	1357 (85.3%)	1406 (86.1%)
Hypercholesterolemia	436 (59.2%)	416 (62.3%)	566 (35.6%)	618 (37.8%)
Diabetes mellitus	199 (27.0%)	166 (24.9%)	264 (16.6%)	316 (19.4%)
Chronic renal failure	38 (5.2%)	40 (6.0%)	45 (2.8%)	45 (2.8%)
Congestive heart failure	287 (38.9%)	261 (39.1%)	406 (25.5%)	411 (25.2%)
NYHA class III	67 (9.1%)	58 (8.7%)	42 (2.6%)	33 (2.0%)
LVEF <35%	58/723 (8.0%)	52/658 (7.9%)	29/1558 (1.9%)	40/1605 (2.5%)
Oral anticoagulant	436 (59.2%)	414 (62.0%)	948 (59.6%)	989 (60.6%)
Low dose of aspirin (≤365 mg)	413 (56.0%)	390 (58.4%)	606 (38.1%)	628 (38.5%)
Beta-blocking agents[b]	559 (75.8%)	534 (79.9%)	1082 (68.1%)	1094 (67.0%)
ARB or ACE inhibitor	551 (74.8%)	495 (74.1%)	1051 (66.1%)	1119 (68.5%)
Statins[c]	453 (1.5%)	429 (64.2%)	461 (29.0%)	449 (27.5%)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
[a]Data are numbers (%) unless otherwise specified.
[b]Not including sotalol.
[c]Statins are defined as 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors.

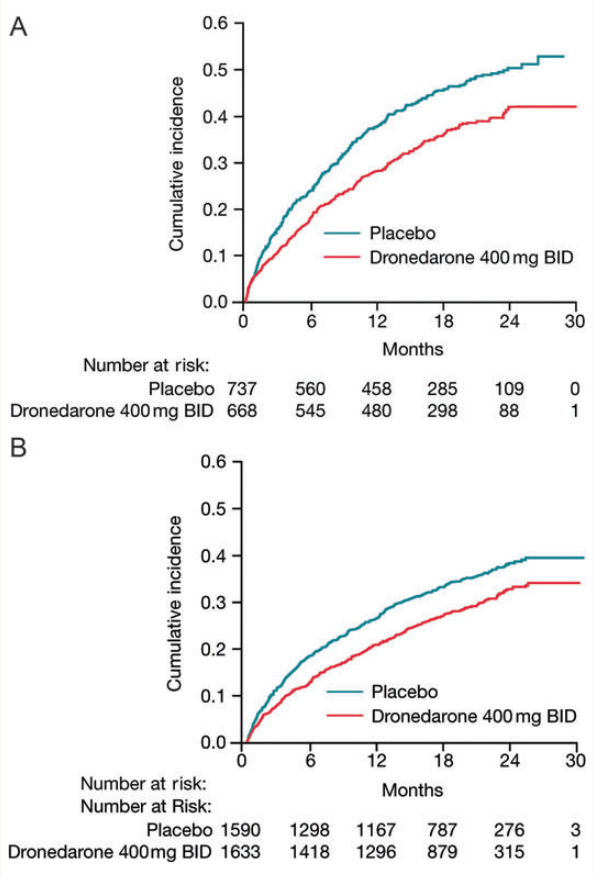

Figure 1 Cumulative risk of the composite outcome of first cardiovascular hospitalization or death from any cause in patients with (*A*) and without (*B*) coronary heart disease. BID, twice daily.

The effect of dronedarone on heart rate and systolic blood pressure is combined in *Figure 3*, which shows the pressure rate product (PRP): (heart rate × systolic blood pressure)/1000. Although the mean [standard deviation (SD)] baseline PRP was similar in patients randomized to receive dronedarone [9.3 (2.4)] or placebo [9.2 (2.4)], during follow-up a mean decrease in PRP compared with baseline was observed only in the dronedarone patients (−0.65 vs. +0.15 for dronedarone and placebo groups, respectively; difference of −0.8; 95% CI = −0.98 to −0.61). The effect was more pronounced in the dronedarone patients who were in AF during the on-treatment period, where their mean (SD) baseline PRP of 11.2 (3.0) dropped on average 1.5 points during follow-up, compared with those in sinus rhythm during the on-treatment period where the mean (SD) baseline PRP of 8.6 (1.7) was reduced on average 0.5 points ($P < 0.0001$).

A subgroup analysis was done to identify characteristics predictive of a reduced incidence of acute coronary syndromes in response to dronedarone treatment (*Figure 4*). The only significant interaction occurred in patients with a reduced left ventricular ejection fraction (<35%), meaning they had a significantly greater effect with dronedarone compared with those patients with a preserved ejection fraction ($P = 0.008$ for interaction).

In total, 510 (76.6%) of the patients with CHD randomized to receive dronedarone and 538 (73.4%) of the placebo patients experienced a TEAE; TEAEs resulted in premature discontinuation of study drug in 108 (16.2%) and 70 (9.5%) patients, respectively. In dronedarone patients the withdrawal was largely driven by gastrointestinal disorders (5.0%), such as diarrhea and nausea, and QT interval prolongation (2.7%). Serious TEAEs were reported in 22.7% of the dronedarone and 25.9% of the placebo patients. The occurrence and distribution of type of TEAEs are displayed in *Table 3*. Importantly, the expected increased occurrence of QTc interval prolongation >500 ms in patients randomized to receive dronedarone compared

with placebo did not lead to an increased number of serious (cardiac) TEAEs as shown in *Table 4*. Also, hepatic injury reported during treatment was similar between patients randomized to receive dronedarone (1.7%) and placebo (1.9%).

In patients with a history of CHD (or ischemic dilated cardiomyopathy) there were no clinically significant differences in the incidence of proarrhythmias in patients randomized to receive dronedarone compared with placebo. Overall 0.3 and 0.6% of patients in the placebo and dronedarone groups experienced a ventricular tachycardia (non-sustained and sustained VT) that resulted in hospitalization, respectively. In addition, ≤0.1% of patients in the two treatment groups experienced a proarrhythmic event (ventricular fibrillation/tachycardia) that resulted in death. In terms of congestive heart failure, 5.6 and 5.7% of patients were admitted to hospital due to worsening of congestive heart failure (CHF) in the placebo and dronedarone groups, respectively; 0.7% of patients in each treatment group, died as a result of CHF. Overall 0.7 and 0.4% of patients in the placebo and dronedarone treatment groups died as a result of a MI or unstable angina (including complications of MI, except arrhythmias), respectively.

Discussion

In this *post hoc* analysis of the ATHENA study, the use of the multichannel-blocking antiarrhythmic drug dronedarone in patients with AF and CHD reduced mortality or cardiovascular hospitalization, an observation that is in line with the results of the overall population in the ATHENA trial.[9] These findings are supported by the negative interaction test, which reinforces the concept that there was no heterogeneity of treatment effect in the CHD subgroup, relative to the overall population. Furthermore, in this subgroup, fewer patients randomized to receive dronedarone were admitted to the hospital because of an acute coronary syndrome during follow-up compared with the placebo arm. Of note, the reduced mortality and cardiovascular hospitalization associated with the use of dronedarone occurs in a subgroup of patients with more extensive cardiovascular disease and who already receive established (secondary) cardiovascular preventive drugs, i.e. β-blockers, statins, angiotensin-converting enzyme inhibitors, and antithrombotic therapy.

The observed benefit : risk ratio of dronedarone in AF patients with CHD is of key importance for clinical practice. Ischemic heart disease

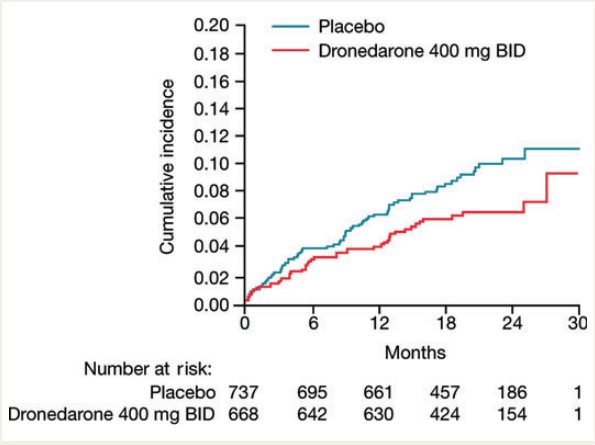

Figure 2 Cumulative risk of the occurrence of first acute coronary syndrome in patients with coronary heart disease. BID, twice daily.

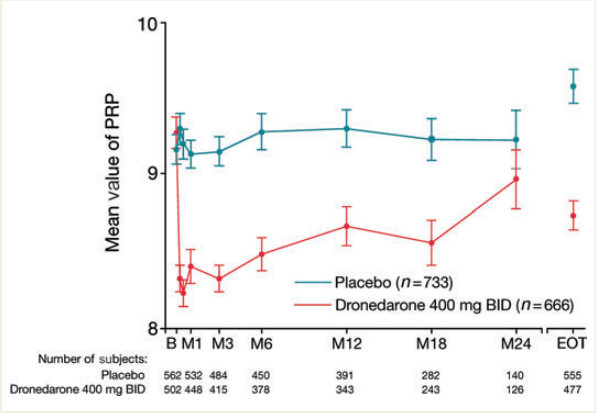

Figure 3 Pressure rate product over time in patients with coronary heart disease. B, baseline; EOT, end of treatment; M1, month 1; PRP, pressure rate product = (heart rate × systolic blood pressure)/1000.

Table 2 Comparison of the effect of dronedarone among patients with and without coronary heart disease

Outcome	CHD	Placebo, *n*/N (%)	Dronedarone, *n*/N (%)	HR for dronedarone (95% CI)	*P* value[a]
First cardiovascular hospitalization or death from any cause	Yes	350/737 (47.49)	252/668 (37.72)	0.733 (0.62–0.86)	0.535
	No	567/1590 (35.66)	482/1663 (29.52)	0.782 (0.69–0.88)	
Cardiovascular death	Yes	47/737 (6.38)	26/668 (3.89)	0.602 (0.37–0.97)	0.350
	No	47/1590 (2.96)	39/1663 (2.39)	0.814 (0.53–1.24)	
First ACS	Yes	67/737 (9.09)	42/668 (6.29)	0.671 (0.46–0.99)	0.429
	No	29/1590 (1.82)	26/1633 (1.59)	0.876 (0.52–1.49)	
First stroke, ACS or cardiovascular death	Yes	116/737 (15.74)	67/668 (10.03)	0.615 (0.46–0.83)	0.272
	No	101/1590 (6.35)	81/1633 (4.96)	0.778 (0.58–1.04)	

ACS, acute coronary syndrome; CHD, coronary heart disease; CI, confidence interval.
[a]*P* value of interaction between CHD status and treatment based on Cox regression model.

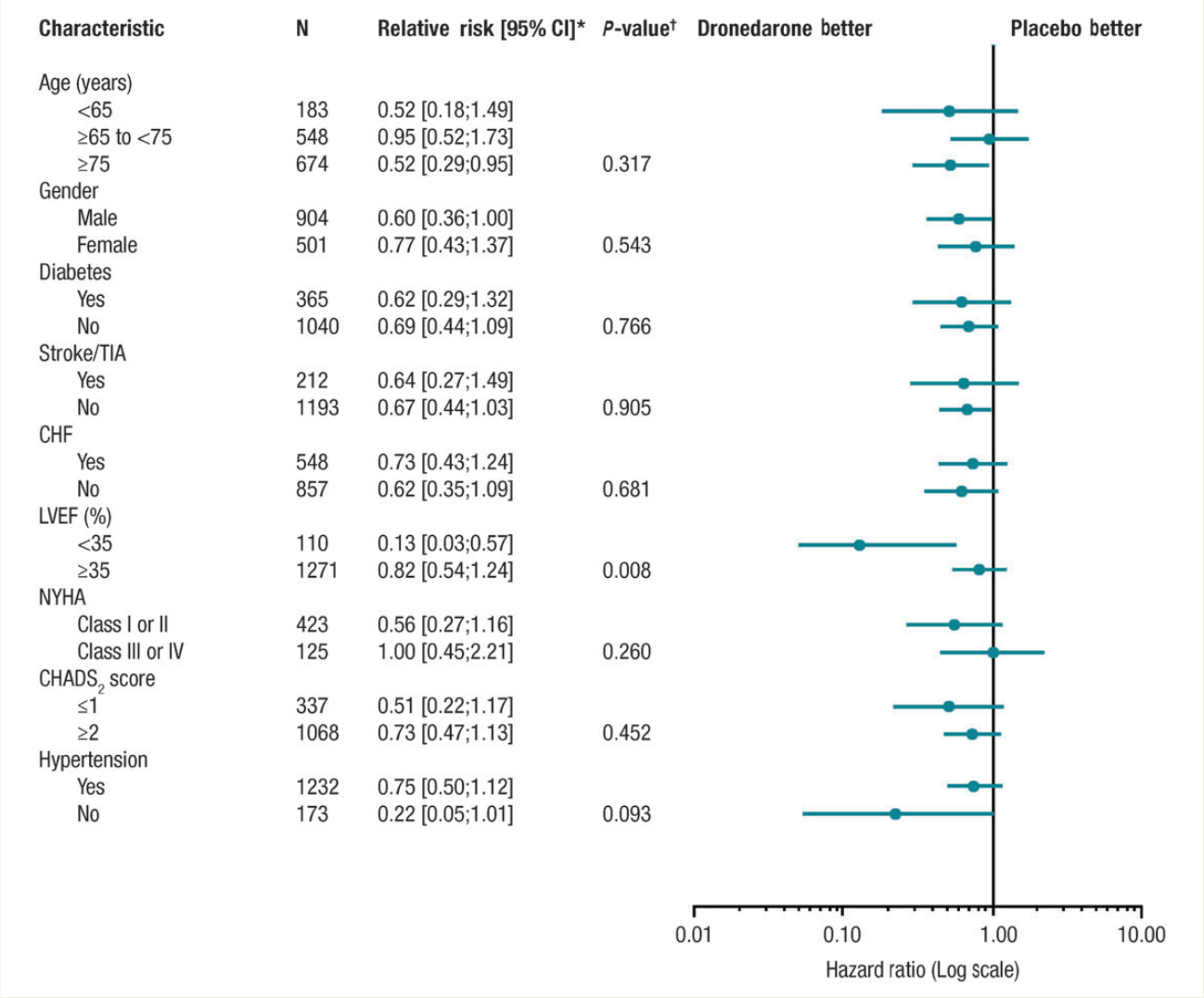

Figure 4 Specific subgroup analysis for acute coronary syndrome (ACS) in patients with coronary heart disease. The $CHADS_2$ score is a measure of the risk of stroke in patients with atrial fibrillation, with scores ranging from 0 to 6 and higher scores indicating a greater risk.[21] Congestive heart failure (CHF), hypertension, an age of 75 years or older, and diabetes are each assigned 1 point, and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient. CI, confidence interval; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; RR, relative risk. (*) Determined from Cox regression model. (†) *P*-value of interaction between baseline characteristic and treatment based on cox regression model.

creates a hazardous (electrical) milieu in which administration of most antiarrhythmic drugs is prohibited or not recommended due to their potential life-threatening ventricular proarrhythmic effects.[11] As a result, the number of antiarrhythmic drugs that can be safely used to treat symptomatic AF patients with CHD is limited.[2,3] Because the use of dofetilide, a pure class III antiarrhythmic with a high proarrhythmic profile, is restricted to the United States, and sotalol may be contraindicated in AF patients with CHD (due to left ventricular hypertrophy), amiodarone is often the only option based on its multichannel properties, leading to a very low proarrhythmic profile.[2,3] While amiodarone appears to have a superior antiarrhythmic efficacy profile compared with dronedarone,[12] due to its very long half-life, in conjunction with the well-known extracardiac side effects and important interactions associated with its use, it is not the ideal drug to prescribe to such a large group of patients. From this perspective, dronedarone could be an ideal alternative because its use minimizes the excess risk of the abovementioned serious side effects compared with amiodarone. In addition, in light of the recently raised concerns of hepatic toxicity associated with dronedarone use,[13] it is important to note that the occurrence of hepatic events was similar in patients randomized to receive dronedarone and those who received placebo in this subgroup of patients with CHD as well as in the entire ATHENA cohort. However, this does not negate the recommendation to perform careful, systematic follow-up of the liver enzymes. A meta-analysis on the benefits and risks of amiodarone showed that the pooled reduction in all-cause death with the use of amiodarone was limited to an

Table 3 Occurrence and distribution of treatment-emergent adverse events according to history of coronary heart disease[a]

Prognostic factor		Placebo[b]			Dronedarone 400 mg BID[b]			Relative risk[a] Dronedarone/placebo		
	Category	*n*	*N*	%	*N*	*N*	%	Relative risk	95% CI	*P* value[c]
TEAE	Overall	1603	2313	69.3	1649	2291	72	1.138	1.06–1.22	
	CHD[d]	538	733	73.4	510	666	76.6	1.197	1.06–1.35	
	No CHD	1065	1580	67.4	1139	1625	70.1	1.123	1.03–1.22	0.38
Serious TEAE	Overall	489	2313	21.1	456	2291	19.9	0.937	0.82–1.06	
	CHD[d]	190	733	25.9	151	666	22.7	0.900	0.73–1.11	
	No CHD	299	1580	18.9	305	1625	18.8	0.977	0.83–1.15	0.54
AE leading to drug discontinuation	Overall	187	2313	8.1	290	2291	12.7	1.590	1.32–1.91	
	CHD[d]	70	733	9.6	108	666	16.2	1.772	1.31–2.39	
	No CHD	117	1580	7.4	182	1625	11.2	1.519	1.20–1.92	0.43

AE, adverse event; CHD, coronary heart disease; CI, confidence interval; TEAE, treatment-emergent AE.
[a]Determined from Cox regression model.
[b]*n*, Number of patients with endpoint; N, number of patients, %, $(n/N) \times 100$.
[c]*P* value of interaction between CHD at baseline and treatment based on Cox regression model.
[d]Patients with CHD are defined as patients with history of coronary heart disease or ischemic dilated cardiomyopathy.

Table 4 Treatment-emergent adverse events in AF patients with CHD treated with dronedarone or placebo

	Placebo ($n = 733$)	Dronedarone ($n = 666$)	*P* value
Any TEAE	538 (73.4%)	510 (76.6%)	
Any cardiac events	92 (12.6%)	83 (12.5%)	NS
Bradycardia	13 (1.8%)	29 (4.4%)	0.007
QT interval prolongation	5 (0.7%)	21 (3.2%)	<0.001
Any respiratory events	129 (17.6%)	117 (17.6%)	NS
Any gastrointestinal events	183 (25.0%)	203 (30.5%)	0.023
Diarrhea	52 (7.1%)	78 (11.7%)	0.003
Any serious TEAE	190 (25.9%)	151 (22.7%)	
Cardiac events	6 (0.8%)	6 (0.9%)	NS
Other events of interest			
Hepatic events	14 (1.9%)	11 (1.7%)	NS
Serum creatinine increase	10 (1.4%)	34 (5.1%)	<0.001
INR increase	15 (2.0%)	18 (2.7%)	NS

TEAE, treatment-emergent adverse event; INR, international normalized ratio.

estimated 13% [odds ratio = 0.87; (95% CI = 0.78–0.99); $P = 0.030$] based on classic fixed-effects meta-analysis, and to a nonsignificant 15% reduction [0.85 (0.71–1.02), $P = 0.081$] using the more conservative random-effects approach.[14] Furthermore, a recent mixed treatment comparison analysis by Freemantle *et al.*[15] even suggests potential increased mortality associated with amiodarone use in contrast to a potential reduction of serious adverse events and proarrhythmia by dronedarone.[15]

The reduced number of acute coronary syndromes in patients with AF and CHD who were randomized to dronedarone is probably not unexpected based on the observed decrease in the number of strokes reported by Connolly *et al.*[16] The precise mechanism(s) of the cardiovascular protective effects associated with the use of dronedarone in these patients are unclear. Hypothetically, in the setting of fixed coronary artery stenosis, a partial explanation could be the observed reduced rate pressure product in dronedarone patients, which relates to a decreased myocardial oxygen demand. This potential mechanism would mainly be driven by a decrease in heart rate, given the modest reduction in systolic blood pressure by dronedarone,[9] but the clear prevention of AF[9] and reduction of ventricular rate seen in patients with permanent AF on top of other rate-controlling drugs in the Efficacy and safety of dRonedArone for

The cOntrol (ERATO) trial.[17] The available data from the recent Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient vs. Strict Rate Control (RACE) II study, however, do not support this. RACE II showed that after a 2 year follow-up period, the occurrence of the primary outcome (a composite of cardiovascular death and hospitalization for heart failure, and stroke systemic embolism, bleeding, and life-threatening arrhythmic events) was similar in permanent AF patients randomized to a strict rate-control target (resting heart rate <80 beats per minute and a heart rate <110 beats per minute during moderate exercise) compared with a more lenient one (resting heart rate <110 beats per minute).[18] Also considering amiodarone does not reduce stroke risk,[19–21] it would be interesting to investigate any potential cardiovascular protective effect that antiarrhythmic drugs could harbor in future research.

Recently the results of the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) trial showed an increased cardiovascular event rate in permanent AF patients randomized to dronedarone.[22] As such, both the European Medicines Agency and the American Food and Drugs Administration have added new warnings to the dronedarone label stating that dronedarone should not be used in patients with permanent AF. According to the European label, dronedarone is now contraindicated in patients with permanent AF (AF duration $\geq$6 months or unknown, and attempts to restore sinus rhythm no longer considered by the physician). The US label states that dronedarone should not be used in patients who will not or cannot be converted into normal sinus rhythm (permanent AF). In addition, the US label states that people taking dronedarone should undergo monitoring of cardiac rhythm at least once every 3 months and that dronedarone should be stopped if a patient is found to be in AF (or patient cardioverted).

Whether and to what extend the permanent nature of the arrhythmia, older age, inclusion of more severe NYHA class heart failure patients and drug interactions by dronedarone (e.g. vitamin K antagonists) explains the important discrepancies between ATHENA and PALLAS remains to be seen.

Limitations

Potential limitations of this study are that it was retrospective, exploratory, and based on a small number of patients. The results of this *post hoc* analysis were not fully protected by randomization, but at the same time the double-blind study design minimizes bias and therefore strengthens the current analysis. Information on acute coronary syndromes was carefully collected as it was part of the primary end point (cardiovascular hospitalization and death due to any cause), but these were not prespecified or centrally adjudicated, or reported as adverse events using a prespecified and systematic approach.

Conclusions

The reduced mortality and cardiovascular hospitalization associated with dronedarone use, and the safety profile of dronedarone, are consistent with the results of the main ATHENA trial. Altogether, this makes dronedarone a welcome addition to the antiarrhythmic drug arsenal for patients with paroxysmal or persistent AF and CHD and a possible alternative to amiodarone therapy in this subgroup. The observed reduced number of acute coronary syndromes is interesting, and should therefore spark our thoughts on the underlying (preventive) mechanisms (i.e. hypothesis-generating), rather than to guide prescription of dronedarone. However, in order to comprehend the apparent controversy with the results from PALLAS additional analyses are warranted.

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