Dronedarone for the Treatment of Atrial Fibrillation with Concomitant Heart Failure with Preserved and Mildly Reduced Ejection Fraction: Post-Hoc Analysis of the ATHENA Trial

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Abstract

Aims: Limited therapeutic options are available for the management of atrial fibrillation/flutter (AF/AFL) with concomitant heart failure with preserved and mildly reduced ejection fraction. (HFpEF and HFmrEF). Dronedarone reduces the risk of cardiovascular events in patients with AF, but sparse data are available examining its role in patients with AF complicated by HFpEF and HFmrEF.

Methods and Results: ATHENA was an international, multicenter trial that randomized 4,628 patients with paroxysmal or persistent AF/AFL and cardiovascular risk factors to dronedarone 400 mg twice daily versus placebo. We evaluated patients with 1) symptomatic HFpEF and HFmrEF (defined as LVEF>40%, evidence of structural heart disease, and New York Heart Association class II/III or diuretic use), 2) HF with reduced ejection fraction (HFrEF) or left ventricular dysfunction (LVEF≤40%), and 3) those without HF. We assessed effects of dronedarone vs placebo on death or cardiovascular hospitalization (primary endpoint), other key efficacy endpoints, and safety. Overall, 534 (12%) had HFpEF or HFmrEF, 422 (9%) had HFrEF or LV dysfunction, and 3,672 (79%) did not have HF. Patients with HFpEF and HFmrEF had a mean age of 73±9 years, 37% were women, and had a mean LVEF of 57±9%. Over 21±5 months mean follow-up, dronedarone consistently reduced risk of death or cardiovascular hospitalization (hazard ratio 0.76; 95% confidence interval 0.69-0.84) without heterogeneity based on HF status ($P_{interaction}$>0.10). This risk reduction in the primary endpoint was consistent across the range of LVEF (as a continuous function) in HF without heterogeneity ($P_{interaction}$=0.71). Rates of death, cardiovascular hospitalization, and HF hospitalization each directionally favored dronedarone vs. placebo in HFpEF and HFmrEF, but these treatment effects were not statistically significant.

Conclusions: Dronedarone is associated with reduced cardiovascular events in patients with paroxysmal or persistent AF/AFL and HF across the spectrum of LVEF, including among those with HFpEF and HFmrEF. These data support a rationale for a future dedicated and powered clinical trial to affirm the net clinical benefit of dronedarone in this population.

Key Words: antiarrhythmic drugs; atrial fibrillation; dronedarone; heart failure with preserved ejection fraction

Clinical Trial Registration: 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); ClinicalTrials.gov Identifier: NCT00174785

Introduction

Sustained atrial arrhythmias frequently complicate heart failure with preserved and mildly reduced ejection fraction (HFpEF and HFmrEF), in part related to rising rates of obesity and shared cardiometabolic risk factors. One in 2 patients enrolled in recent HFpEF clinical trials have a history of atrial fibrillation or flutter (AF/AFL)[1,2] and a substantial proportion of patients with AF with unexplained dyspnea may in fact have occult HFpEF.[3] Comorbid AF and HFpEF are independently associated with excess cardiovascular risks and adverse health status,[4] and may represent a distinct phenotype distinguished by marked left atrial mechanical dysfunction, congestion, mitral annular dilation often with atrial functional mitral regurgitation, and perturbed myocardial performance.[5-7] Indeed, increasing AF burden is closely correlated with progressive left atrial remodeling, elevated filling pressures, and clinical risk, and may represent a marker of disease progression in HFpEF.[8]

Despite this substantial clinical overlap and the recognition of AF as a potential therapeutic target in HFpEF, limited evidence-based strategies are available for its management. Designed as a non-iodinated congener of amiodarone with less tissue accumulation, dronedarone has been previously shown to increase mortality among hospitalized decompensated patients with HF and severe left ventricular (LV) dysfunction.[9] Whether its use in patients with HFpEF and AF in more stable settings can improve outcomes remains unknown. The recent 2020 European Society of Cardiology AF guideline provides a Class IA recommendation for dronedarone for long-term rhythm control in patients with AF and HFpEF.[10] This recommendation is based, in part, on its reassuring safety profile and effectiveness in real-world evaluation.[11-13] Given the limited evidence from randomized trial evaluating dronedarone in populations of HF with higher LV ejection fraction (LVEF), we examined the efficacy and safety

of dronedarone among patients with paroxysmal or persistent AF/AFL and HFpEF/HFmrEF in the 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) trial.

Methods

ATHENA Trial Population

The design[14] and primary results[15] of ATHENA have been previously published. In brief, ATHENA was a randomized, double-blind, placebo-controlled trial that randomized high-risk patients with paroxysmal or persistent AF/AFL to either dronedarone 400 mg twice daily or matching placebo. The pre-specified high-risk features for enrollment included at least one of the following: age ≥70 years, hypertension requiring 2 or more antihypertensive therapies, diabetes mellitus, prior stroke, transient ischemic attack, or systemic embolism, left atrial enlargement, or LVEF ≤40%. During the trial, an amendment allowed enrollment of patients aged ≥75 years (without additional risk factors) but required those aged ≥70 years to have one other risk factor and those younger than 70 years no longer met eligibility. Exclusion criteria included permanent AF, decompensated HF within 4 weeks, New York Heart Association (NYHA) class IV functional status, or life-limiting noncardiac illness. All participants provided written informed consent and the institutional review boards or local ethics committees at each participating site approved the study protocol.

Identifying HFpEF in ATHENA

Within the overall ATHENA study population, we evaluated patients with AF/AFL and 1) symptomatic HFpEF or HFmrEF, 2) HF with reduced ejection fraction (HFrEF) or LV

dysfunction (LVEF≤40%), and 3) those without HF. We adapted previously employed criteria from prior clinical trials[16,17] to define HFpEF/HFmrEF to require 1) LVEF >40%; 2) evidence of structural heart disease defined as left atrial enlargement (length on M-mode ≥50mm) or investigator-reported left ventricular cardiomyopathy; *and* 3) NYHA class II/III functional class or diuretic use (other than spironolactone) at baseline.

Efficacy and Safety Outcomes

Patients were followed at day 7, day 14, months 1, 3, 6, 9, and 12, and every 3 months thereafter. The primary endpoint of ATHENA was time to first occurrence of all-cause mortality or cardiovascular hospitalization. Other endpoints of interest for this analysis included components of the primary composite endpoint (which were both pre-specified secondary endpoints in ATHENA), stroke, HF hospitalization, and first AF/AFL recurrence. We additionally evaluated adverse events, including those that led to premature drug discontinuation, as key safety measures.

Statistical Analyses

All baseline characteristics were summarized as number (%) or mean (standard deviation) between study arms, stratified by HF status (HFpEF/HFmrEF, HFrEF/LV dysfunction, no HF). Kaplan Meier curves were generated by study arm for the primary composite endpoint for each of the groups. Cox proportional hazards models were used to evaluate time to first events among each of these groups with interaction testing between treatment effects with dronedarone and HF status (based on these 3 categorical groups). In addition, among patients with HF or LV dysfunction, the relationship between LVEF (as a continuous measure with restricted cubic splines) and treatment effect was evaluated. Additionally, a sensitivity analysis relaxing the criteria to define HFpEF/HFmrEF to remove the requirement for structural heart disease was

conducted. Two-tailed P-values <0.05 were considered statistically significant. No adjustment was made for multiple comparisons given the exploratory nature of this work.

Results

Baseline Characteristics

Across 551 sites in 37 countries, a total of 4,628 participants were enrolled in ATHENA. Overall, 534 (12%) had HFpEF or HFmrEF, 422 (9%) had HFrEF or LV dysfunction, and 3,672 (79%) did not have HF. Patients with HFpEF and HFmrEF had a mean age of 73±9 years, 37% were women, and had a mean LVEF of 57±9% (22% with LVEF 41-49%, 36% with LVEF 50-59%, and 42% with LVEF ≥60%). In those with HFpEF and HFmrEF, β-blockers were used in 77%, angiotensin converting enzyme inhibitors or angiotensin receptor blockers in 78%, spironolactone in 8%, digoxin in 18%, and oral anticoagulants in 72%. Baseline characteristics overall and in the HFpEF/HFmrEF subgroup were well balanced between study arms (**Table 1**).

Efficacy and Safety Outcomes

Over 21±5 months mean follow-up, 1,651 patients in ATHENA experienced a first primary endpoint (death or cardiovascular hospitalization), including 221 patients with HFpEF/HFmrEF. Placebo-treated patients with HFpEF or HFmrEF faced risks of death or cardiovascular hospitalization (57 [50-64] per 100 patient-years) comparable to those in HFrEF or LV dysfunction (54 [47-62] per 100 patient-years; $P = 0.37$) and higher than risks in those without HF (41 [39-44] per 100 patient-years; $P = 0.03$); **Supplemental Figure 1**.

Dronedarone consistently reduced risk of death or cardiovascular hospitalization (hazard ratio [HR] 0.76; 95% confidence interval [CI] 0.69-0.84) without heterogeneity based on HF status ($P_{interaction}>0.10$); **Figures 1 and 2**. In those with HFpEF and HFmrEF, dronedarone

was associated with a HR of 0.79 (95% CI 0.61-1.03) for the primary endpoint with an absolute risk difference of 13 per 100py. Risk reductions appeared relatively consistent across LVEF 41-49% (HR 0.81 [95% CI 0.44-1.48]), LVEF 50-59% (HR 0.94 [95% CI 0.59-1.49]), and LVEF ≥60% (HR 0.68 [95% CI 0.47-1.006]). The lower hazards with dronedarone for the primary endpoint were consistent across a range of LVEF (as a continuous function) in HF without heterogeneity ($P_{interaction}$=0.71); **Figure 3**.

Rates of death, cardiovascular hospitalization, and HF hospitalization each directionally favored dronedarone vs. placebo in HFpEF/HFmrEF, but these treatment effects were not statistically significant. In the HFpEF/HFmrEF subgroup, there were 45 death events in follow-up and dronedarone was associated with an HR of 0.59 (95% CI 0.33-1.09). In HFpEF/HFmrEF, any treatment-emergent adverse events (36% vs. 36%) or serious treatment-emergent adverse events (13% vs. 13%) were similar between arms, but dronedarone increased rates of permanent drug discontinuation due to treatment-emergent adverse events (7% vs. 4%); **Figure 4**. These consisted mainly of gastrointestinal adverse effects such as nausea or diarrhea.

Sensitivity Analysis with Broader HFpEF Selection Criteria

In a sensitivity analysis, we identified 2,353 individuals meeting less stringent criteria for HFpEF or HFmrEF by removing requirement for structural heart disease (**Supplemental Figure 2**). In this cohort, dronedarone was associated with a lower risk of the primary endpoint of death or cardiovascular hospitalization (HR 0.78; 95% CI 0.68-0.89) and a number of secondary endpoints including all-cause mortality (HR 0.65; 95% CI 0.45-0.95). There was no evidence of an increase in HF hospitalizations with dronedarone (HR 1.01; 95% CI 0.74-1.39).

Discussion

In this *post hoc* analysis of the ATHENA trial, dronedarone, when compared with placebo, was consistently associated with lower rates of death or cardiovascular hospitalization in patients with AF/AFL, including among patients with HFpEF and HFmrEF. Among patients with HF, clinical benefits of dronedarone were apparent across a spectrum of LVEF and extended to LVEF ≥60%. Dronedarone appeared safe in this HFpEF and HFmrEF subgroup without excess in mortality or HF hospitalizations. Taken together, these data support the safety and efficacy of dronedarone in paroxysmal or persistent AF/AFL and HF with higher LVEF (**Graphical Abstract**).

Despite recent ESC AF guideline Class IA recommendations for the use of dronedarone as a rhythm control strategy in AF with HFpEF, there has been limited randomized clinical trial evidence in this special population. A previous ATHENA secondary analysis focused on 209 participants with symptomatic HFrEF with NYHA class II or III symptoms.[18] We extended this assesment to patients with any LV systolic dysfunction (LVEF≤40%) irrespective of symptoms and evaluated patients at higher LVEF. ATHENA specifically enriched enrollment of older adults and those with abnormalities of myocardial structure or function and AF/AFL, and thus it was expected that many may have HFpEF. As HFpEF diagnoses were not prospectively assessed by investigators in ATHENA, we relied on retrospective application of established criteria. To improve specificity of this retrospective approach, we employed a rigorous definition similar to ones used in contemporary HFpEF clinical trials (requiring mildly reduced or preserved LV function, structural heart disease, *and* symptoms of HF or active diuretic use).[16,17] Consistent treatment effects were observed even at higher LVEFs (so called “true HFpEF”) in spline analyses without attenuation at LVEF ≥60% as has been seen with some HF therapies.[19]

Furthermore, sensitivity analyses with less stringent HFpEF diagnostic criteria yielded consistent benefits, including lower all-cause mortality in thos randomized to dronedarone. While this broader selection criteria may lessen the certainty of a HFpEF diagnosis, it has been demonstrated that majority of these patients with AF/AFL and preserved LV function with dyspnea may in fact have occult HFpEF when rigorously evaluated with invasive hemodynamics.[3]

In ATHENA, 68% of patients with known onset of their first AF/AFL episode were included <12 months of AF/AFL diagnosis[20] and this ATHENA analysis is also consistent with a pre-specificied secondary analysis of the HF subgroup of the EAST-AFNET4 trial (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial).[21] Among 798 patients with early AF (diagnosed within a year of enrollment) and HF in this trial (83% of whom had HF with mildly reduced or preserved LVEF), early rhythm control educed cardiovascular events compared with usual care (symptom-directed rhythm control).[22] Importantly, early rhythm control in HFpEF was mostly achieved with antiarrhythmic drugs (such as flecainide, amiodarone, and dronedarone) in EAST-AFNET4, while AF ablation was selected by investigators in a minority of individuals.[22] Rhythm control was also shown to be an effective strategy in reducing cardiovascular events, extending survival, and improving health-related quality of life in 778 participants with symptomatic HF in the CABANA trial (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation), the vast majority of whom had preserved or mildly reduced LVEF.[23] Observational studies too have suggested beneficial effects among those with HFpEF treated with rhythm control approaches (including dronedarone) in clinical practice,[24] but these may be subject to selection bias and unmeasured confounding.

These data affirming the safety of dronedarone in AF/AFL and HF with LVEF above 40% are in contrast to evidence of increased mortality in patients recently hospitalized with decompensated HFrEF in ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease).[9] What might explain these differences? ANDROMEDA evaluated a distinct patient population of whom only 38% had a history of AF/AFL and thus might not fully benefit from rhythm control like a population with AF/AFL and HFpEF. The safety of dronedarone may be more favorable in a stable, ambulatory population such as those evaluated in ATHENA and EAST-AFNET4. Use of dronedarone in a manner consistent with guideline recommendations, appropriate monitoring, and use of oral anticoagulation for stroke prevention, may be higher in these more recent studies. As dronedarone has class II anti-adrenergic and class IV vasodilatory properties, stable patients with HF might benefit while decompensated patients with severe LV dysfunction might be harmed by these effects. Additionally, as dronedarone is known to inhibit tubular transport of creatinine, thereby reducing creatinine clearance by 15-20% (without causing kidney injury), it may be hypothesized that this could have led to alteration of use or dosing of disease-modifying therapies in recently hospitalized patients with HFrEF leading to disease progression. In contrast, transient pertubations in creatinine clearance in otherwise stable patients and resultant short-term changes in HF therapies may be less impactful in HFpEF. Furthermore, dronedarone is known to increase digoxin concentrations via a P-glycoprotein interaction, which may have partially mediated adverse safety signals in prior trials.[24] Regulatory labeling recommends digoxin discontinuation or dose reduction when initiating dronedarone.[25,26] Digoxin use was notably less common in ATHENA (18% in HFpEF / HFmrEF subgroup) than in ANDROMEDA (31%)[9] or in PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of

Standard Therapy; 33%).[24] The efficacy of dronedarone among those with less severe forms of HF in ATHENA and early rhythm control in EAST-AFNET4 may also be necessary to disrupt early pathways of left atrial myopathy and adverse remodeling. As anti-arrhythmic drug therapy remains limited in contemporary HFpEF clinical practice,[27] these data suggest reconsideration of the role of dronedarone in current care pathways to manage AF/AFL in HF at higher LVEF.

Study Limitations

There are several limitations related to this work. This was a *post hoc* analysis with a modest number of patients identified with HFpEF or HFmrEF, and the original trial was not planned or powered to evaluate this subgroup. While ATHENA examined a global sample across more than 30 different countries, >90% were White which may limit the generalizability of our findings to other racial/ethnic groups. Elements that are useful in affirming HFpEF diagnoses including natriuretic peptide levels, detailed physical examination signs or symptom reporting, and prior HF hospitalization status were not available. ATHENA is an older trial with enrollment in 2005-2006 and thus does not reflect newer HFpEF advances. Similar to contemporary HFpEF clinical practice, however, renin-angiotensin-system inhibitor and β-blocker use approached 80% in ATHENA, but other therapies such as angiotensin receptor neprilysin inhibitors or sodium-glucose cotransporter-2 inhibitors were not used.

Conclusions

Dronedarone is associated with reduced cardiovascular events in patients with paroxysmal or persistent AF/AFL and HF across the spectrum of LVEF, including among those with HFpEF and HFmrEF. These data support a rationale for a future dedicated and powered clinical trial to affirm the net clinical benefit of dronedarone in patients with AF and HFpEF.

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Conflict of Interests

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Table 1. Baseline Characteristics in the ATHENA Trial by HF Status

	HFpEF or HFmrEF		HFrEF or LV Dysfunction		No HF	
	Dronedarone (n=266)	Placebo (n=268)	Dronedarone (n=201)	Placebo (n=221)	Dronedarone (n=1834)	Placebo (n=1838)
Age, mean (SD), years	71.6 (8.9)	72.5 (9.1)	71.3 (9.4)	72.5 (9.2)	71.6 (8.9)	71.5 (9.0)
Women	110 (41.4%)	99 (36.9%)	60 (29.9%)	66 (29.9%)	961 (52.4%)	873 (47.5%)
Race						
White	240 (90.2%)	246 (91.8%)	182 (90.5%)	200 (90.5%)	1643 (89.6%)	1626 (88.5%)
Asian	16 (6.0%)	10 (3.7%)	5 (2.5%)	8 (3.6%)	129 (7.0%)	136 (7.4%)
Black	5 (1.9%)	3 (1.1%)	3 (1.5%)	6 (2.7%)	11 (0.6%)	22 (1.2%)
Other	5 (1.9%)	9 (3.4%)	11 (5.5%)	7 (3.2%)	51 (2.8%)	54 (2.9%)
Body mass index≥30kg/m²	120 (45.1%)	120 (44.8%)	59 (29.4%)	64 (29.0%)	578 (31.5%)	549 (29.9%)
Coronary artery disease	100 (37.6%)	108 (40.3%)	99 (49.3%)	119 (53.8%)	462 (25.2%)	501 (27.3%)
Hypertension	242 (91.0%)	237 (88.4%)	148 (73.6%)	165 (74.7%)	1609 (87.7%)	1594 (86.7%)
Prior AF/AFL Ablation	17 (6.4%)	18 (6.7%)	8 (4.0%)	13 (5.9%)	65 (3.5%)	75 (4.1%)
CHA_2DS_2-VASc Score	2.9 (1.1)	3.0 (1.1)	2.9 (1.2)	2.9 (1.1)	2.9 (1.1)	2.8 (1.1)
LA diameter, mean (SD), mm	52.5 (5.5)	52.4 (5.8)	47.6 (7.1)	46.9 (7.7)	42.5 (5.8)	42.4 (6.1)
LVEF, mean (SD), %	57.6 (8.8)	57.3 (9.1)	33.3 (6.6)	33.7 (6.3)	60.0 (7.9)	60.2 (8.1)
Implanted cardioverter defibrillator	5 (1.9%)	5 (1.9%)	30 (14.9%)	28 (12.7%)	7 (0.4%)	10 (0.5%)
Pacemaker	30 (11.3%)	38 (14.2%)	38 (18.9%)	39 (17.6%)	146 (8.0%)	166 (9.0%)
Diuretics	240 (90.2%)	246 (91.8%)	123 (61.2%)	142 (64.3%)	824 (44.9%)	836 (45.5%)
β-blockers	196 (73.7%)	205 (76.5%)	151 (75.1%)	174 (78.7%)	1281 (69.8%)	1262 (68.7%)
Calcium channel blockers	39 (14.7%)	35 (13.1%)	21 (10.4%)	18 (8.1%)	271 (14.8%)	254 (13.8%)
Digoxin	47 (17.7%)	47 (17.5%)	56 (27.9%)	59 (26.7%)	218 (11.9%)	202 (11.0%)
ACEi/ARB	209 (78.6%)	210 (78.4%)	141 (70.1%)	157 (71.0%)	1264 (68.9%)	1235 (67.2%)
Spironolactone	29 (10.9%)	21 (7.8%)	38 (18.9%)	44 (19.9%)	81 (4.4%)	71 (3.9%)
Aspirin	89 (33.5%)	104 (38.8%)	91 (45.3%)	98 (44.3%)	838 (45.7%)	817 (44.5%)
Oral anticoagulant	202 (75.9%)	192 (71.6%)	149 (74.1%)	159 (71.9%)	1052 (57.4%)	1033 (56.2%)

Categorical variables are presented as n (%) and continuous variables as mean (SD)
Abbreviations: ACEi = angiotensin converting enzyme inhibitor; AF/AFL = atrial fibrillation/atrial flutter; ARB = angiotensin receptor blocker; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LA = left atrial; LVEF = left ventricular ejection fraction; SD = standard deviation

Figure 1. Kaplan Meier Analysis for Death or Cardiovascular (CV) Hospitalization in ATHENA by Heart Failure Status

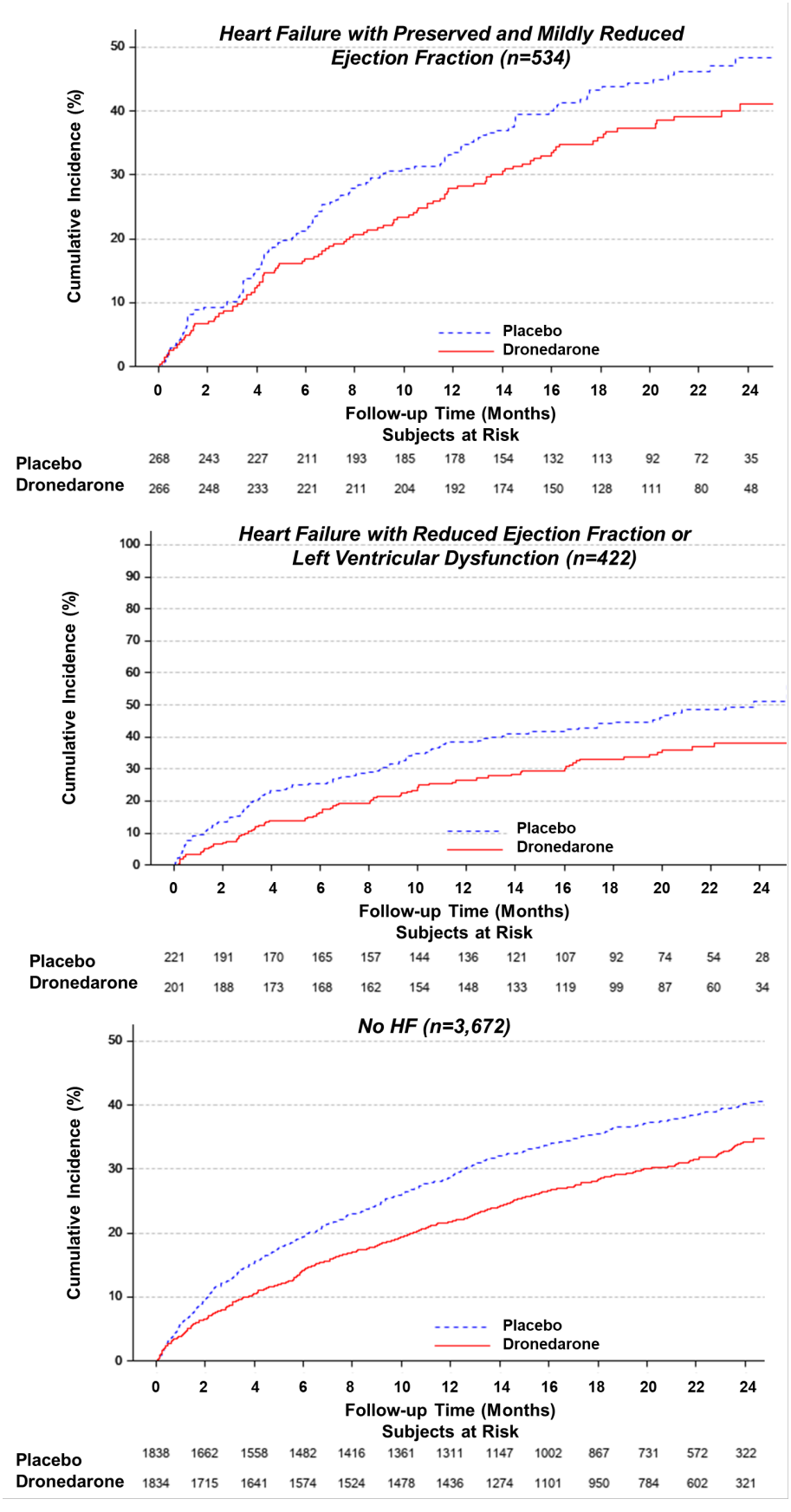


Figure 2. ATHENA Primary Endpoint (Death or Cardiovascular [CV] Hospitalization) by HF Status

Abbreviations: HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; LV = left ventricular

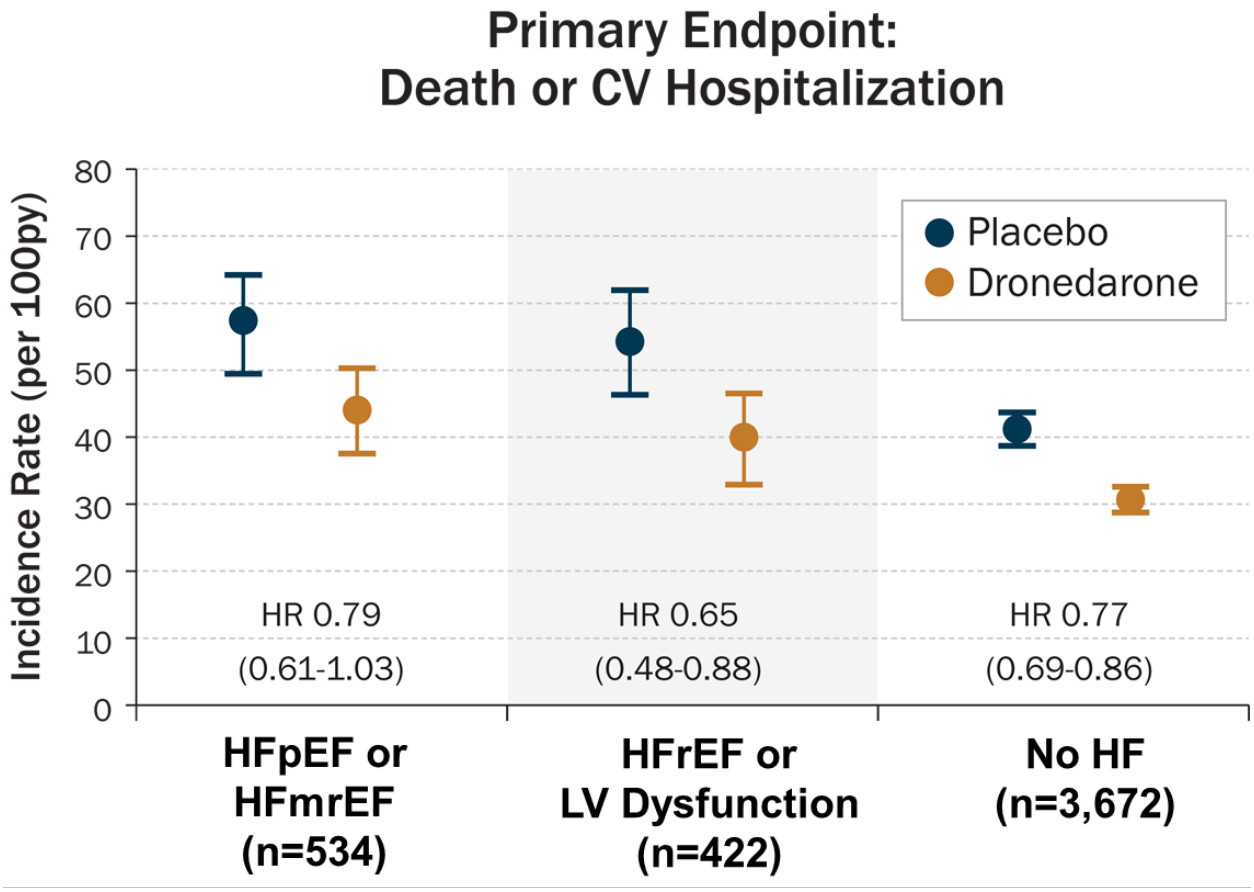


Figure 3. Treatment Effects of Dronedarone vs. Placebo in Heart Failure across a Range of Left Ventricular Ejection Fraction (LVEF) for the Primary Endpoint (Death or Cardiovascular Hospitalization)

Estimated hazard ratios (solid lines) and 95% confidence intervals (dashed lines) are derived from Cox proportional hazards models with LVEF expressed as a continuous function via restricted cubic splines.

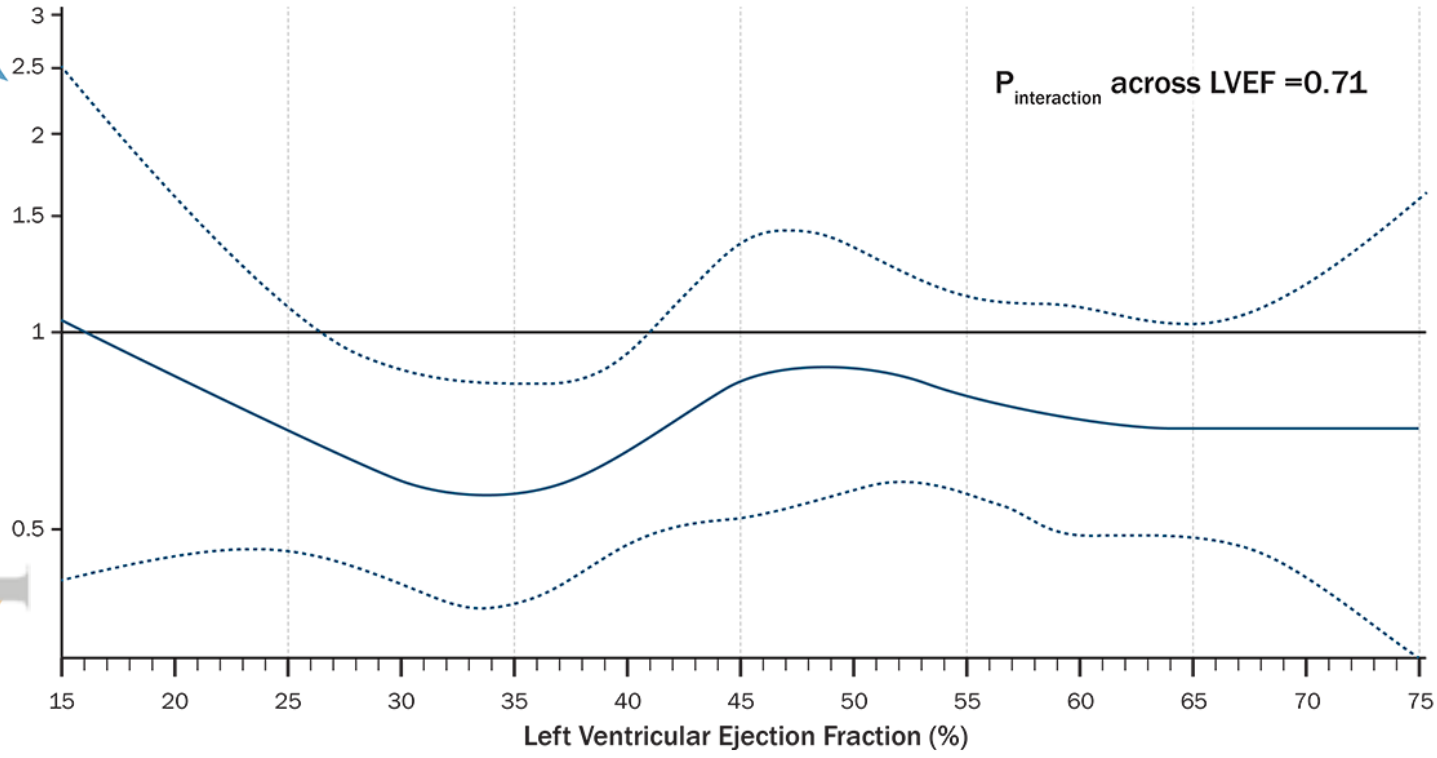
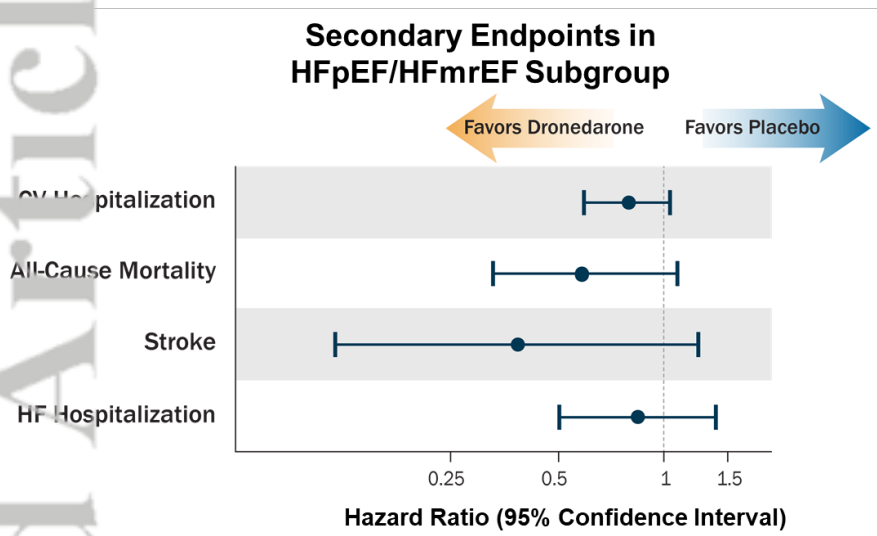


Figure 4. Secondary and Safety Endpoints in ATHENA Subgroup with HF and LVEF >40%

Abbreviations: HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction



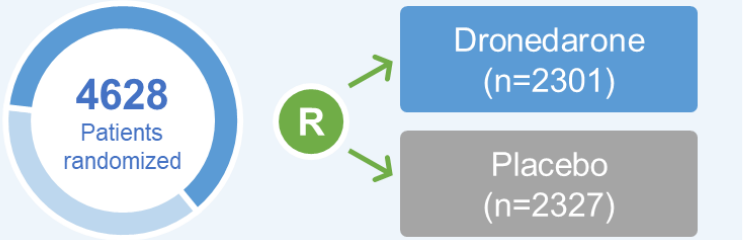
Safety Endpoints in HFpEF/HFmrEF Subgroup

	Dronedarone	Placebo
Treatment-Emergent AE	36%	36%
Serious AE	13%	13%
Permanent Drug Discontinuation	7%	4%

Graphical Abstract.

Dronedarone for the Treatment of Atrial Fibrillation with Concomitant Heart Failure with Preserved and Mildly Reduced Ejection Fraction: *Post-Hoc* Analysis of the ATHENA Trial

ATHENA Population (NCT00174785): Patients With Paroxysmal/Persistent AF/AFL



Subgroups Based on HF Status in ATHENA

- No HF (n=3,672; 79%)
- HFmrEF/HFpEF (LVEF>40%) (n=534; 12%)
- HFrEF or LV Dysfunction (LVEF≤40%) (n=422; 9%)

LVEF>40%+ Structural Heart Disease (LA enlargement or LVH)

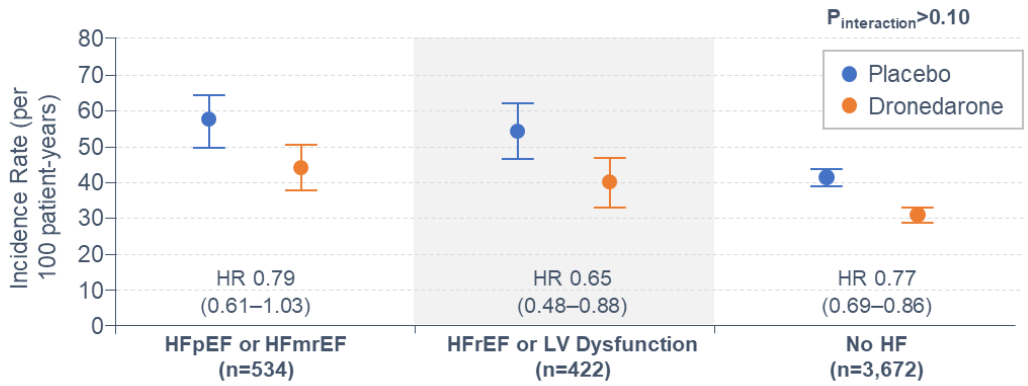
+

Symptoms of HF with NYHA class II/III functional class

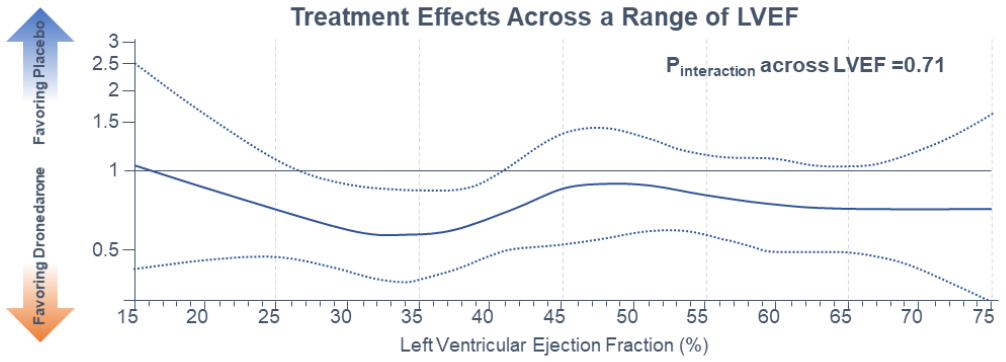
or

Diuretic use

Primary Endpoint: Death or CV Hospitalization



Treatment Effects Across a Range of LVEF



AE, adverse event; AF, atrial fibrillation; AFL, atrial flutter; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; mrEF, mildly reduced ejection fraction; NYHA, New York Heart Association; pEF, preserved ejection fraction; rEF, reduced ejection fraction

CONCLUSIONS Dronedarone is associated with reduced CV events in patients with paroxysmal or persistent AF/AFL and HF across the spectrum of LVEF, including among those with HFpEF and HFmrEF.