ESC European Society of Cardiology

European Journal of Heart Failure (2022) **24**, 1094–1101
doi:10.1002/ejhf.2487

RESEARCH ARTICLE

Dronedarone for the treatment of atrial fibrillation with concomitant heart failure with preserved and mildly reduced ejection fraction: a post-hoc analysis of the ATHENA trial

Muthiah Vaduganathan[1]*, Jonathan P. Piccini[2], A. John Camm[3], Harry J.G.M. Crijns[4], Stefan D. Anker[5], Javed Butler[6], John Stewart[7], Rogelio Braceras[8], Alessandro P.A. Albuquerque[8], Mattias Wieloch[9,10], and Stefan H. Hohnloser[11]

[1]Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Duke University Medical Center and the Duke Clinical Research Institute, Durham, NC, USA; [3]Cardiology Clinical Academic Group Molecular & Clinical Sciences Institute, St George's University of London, London, UK; [4]Maastricht University Medical Center, Maastricht, The Netherlands; [5]Department of Cardiology (CVK); and Berlin Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Berlin, Germany; [6]Department of Medicine, University of Mississippi, Jackson, MS, USA; [7]Sanofi, Laval, Quebec, Canada; [8]Sanofi, Bridgewater, NJ, USA; [9]Sanofi, Paris, France; [10]Department of Coagulation Disorders, Skåne University Hospital, Lund University, Malmö, Sweden; and [11]Division of Clinical Electrophysiology, Department of Cardiology, J. W. Goethe University, Frankfurt, Germany

Received 20 January 2022; revised 15 February 2022; accepted 11 March 2022; online publish-ahead-of-print 10 April 2022

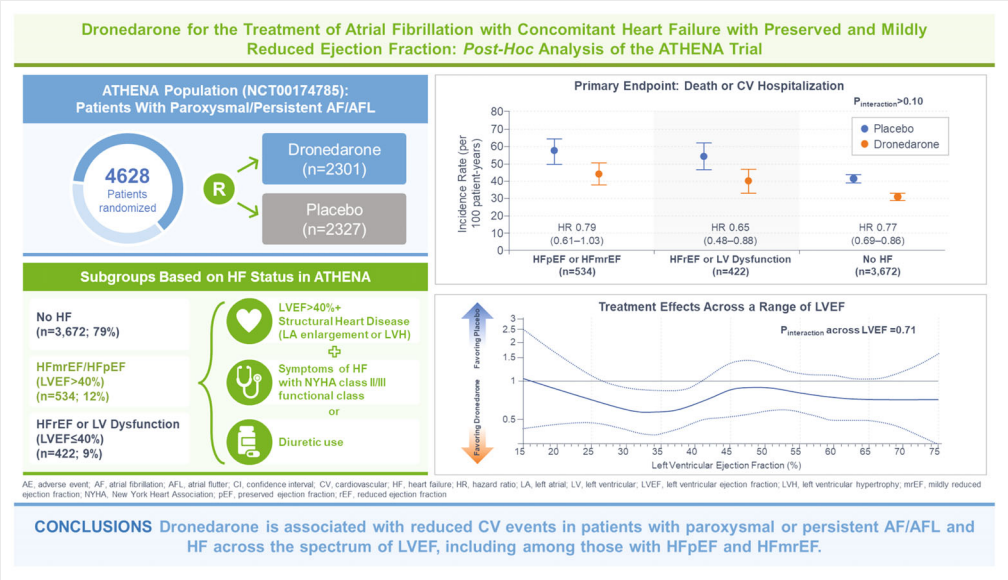
Aims Limited therapeutic options are available for the management of atrial fibrillation/flutter (AF/AFL) with concomitant heart failure (HF) with preserved (HFpEF) and mildly reduced ejection fraction (HFmrEF). Dronedarone reduces the risk of cardiovascular events in patients with AF, but sparse data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

Methods and results ATHENA was an international, multicentre trial that randomized 4628 patients with paroxysmal or persistent AF/AFL and cardiovascular risk factors to dronedarone 400 mg twice daily versus placebo. We evaluated patients with (i) symptomatic HFpEF and HFmrEF (defined as left ventricular ejection fraction [LVEF] >40%, evidence of structural heart disease, and New York Heart Association class II/III or diuretic use), (ii) HF with reduced ejection fraction (HFrEF) or left ventricular dysfunction (LVEF ≤40%), and (iii) those without HF. We assessed effects of dronedarone versus 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 left ventricular dysfunction, and 3672 (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 a mean follow-up of 21 ± 5 months, 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 favoured dronedarone versus placebo in HFpEF and HFmrEF, but these treatment effects were not statistically significant in this subgroup.

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.

*Corresponding author. Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA, USA. Tel: 1+ 617 525-7053, Email: mvaduganathan@bwh.harvard.edu

Graphical Abstract



Dronedarone for the treatment of atrial fibrillation with concomitant heart failure with preserved and mildly reduced ejection fraction: a post-hoc analysis of the ATHENA trial.

Keywords Antiarrhythmic drugs • Atrial fibrillation • Dronedarone • Heart failure with preserved ejection fraction

Introduction

Sustained atrial arrhythmias frequently complicate heart failure (HF) with preserved (HFpEF) and mildly reduced ejection fraction (HFmrEF), in part related to rising rates of obesity and shared cardiometabolic risk factors. One in two 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 dyspnoea 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 dilatation often with atrial functional mitral regurgitation, and perturbed myocardial performance.[5–7] Indeed, increasing AF burden is closely correlated with progressive left atrial remodelling, 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 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 trials evaluating dronedarone in populations of HF with higher left ventricular 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 (ClinicalTrials.gov Identifier: NCT00174785).

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 enrolment included at least one of the following: age ≥70 years, hypertension requiring two or more antihypertensive therapies, diabetes mellitus, prior stroke, transient ischaemic attack, or systemic embolism, left

atrial enlargement, or LVEF ≤40%. During the trial, an amendment allowed enrolment 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 non-cardiac 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 heart failure with preserved ejection fraction in ATHENA

Within the overall ATHENA study population, we evaluated patients with AF/AFL and (i) symptomatic HFpEF or HFmrEF, (ii) HF with reduced ejection fraction (HFrEF) or left ventricular dysfunction (LVEF≤40%), and (iii) those without HF. We adapted previously employed criteria from prior clinical trials[16,17] to define HFpEF/HFmrEF to require (i) LVEF >40%; (ii) evidence of structural heart disease defined as left atrial enlargement (length on M-mode ≥50 mm) or investigator-reported left ventricular cardiomyopathy; and (iii) NYHA functional class II/III 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/left ventricular 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 three categorical groups). In addition, among patients with HF or left ventricular 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 4628 participants were enrolled in ATHENA. Overall, 534 (12%) had HFpEF or HFmrEF, 422 (9%) had HFrEF or left ventricular dysfunction, and 3672 (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 a mean follow-up of 21 ± 5 months, 1651 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 left ventricular 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; $p = 0.03$) (online supplementary *Figure S1*.

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 100 patient-years. 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 favoured dronedarone versus 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 heart failure with preserved ejection fraction selection criteria

In a sensitivity analysis, we identified 2353 individuals meeting less stringent criteria for HFpEF or HFmrEF by removing requirement for structural heart disease (online supplementary *Figure S2*). In this cohort, dronedarone was associated with a lower risk of

Table 1 Baseline characteristics in the ATHENA trial by heart failure 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, years, mean (SD)	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 ≥30 kg/m^2	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, mm, mean (SD)	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)
Implantable 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%)

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AFL, 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; LV, left ventricular; LVEF, left ventricular ejection fraction; SD, standard deviation.

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 European Society of Cardiology 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 assessment to patients with any left ventricular systolic dysfunction (LVEF ≤40%) irrespective of symptoms and evaluated patients at higher LVEF. ATHENA specifically enriched enrolment 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 left ventricular 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 those randomized to dronedarone. While this broader selection criteria may lessen the certainty of a HFpEF diagnosis, it has been demonstrated that the majority of these patients with AF/AFL and preserved left ventricular function with dyspnoea may

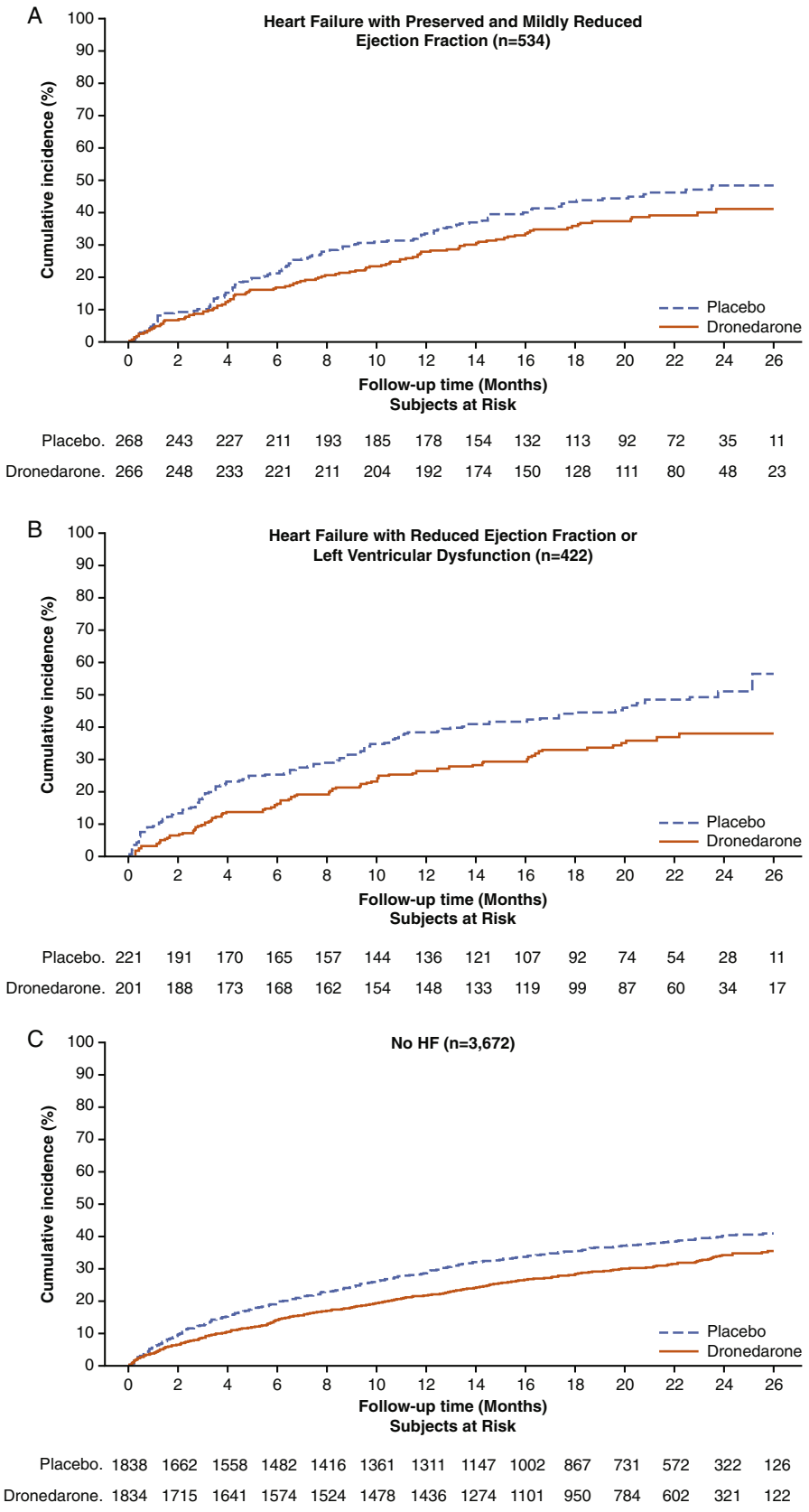


Figure 1 Kaplan–Meier analysis for death or cardiovascular hospitalization in ATHENA by heart failure (HF) status.

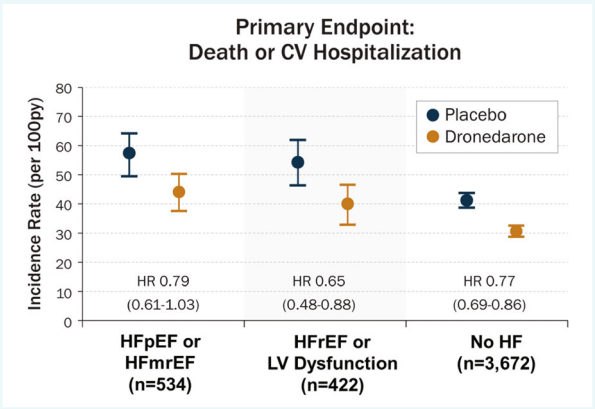


Figure 2 ATHENA primary endpoint (death or cardiovascular [CV] hospitalization) by heart failure (HF) status. HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LV, left ventricular.

in fact have occult HFpEF when rigorously evaluated with invasive haemodynamics.[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-specified secondary analysis of the HF subgroup of the EAST-AFNET 4 trial (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial).[21] Among 798 patients with early AF (diagnosed within a year of enrolment) and HF in this trial (83% of whom had HF with mildly reduced or preserved LVEF), early rhythm control reduced 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-AFNET 4, 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 favourable in a stable, ambulatory population such as those evaluated in ATHENA and EAST-AFNET 4. 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

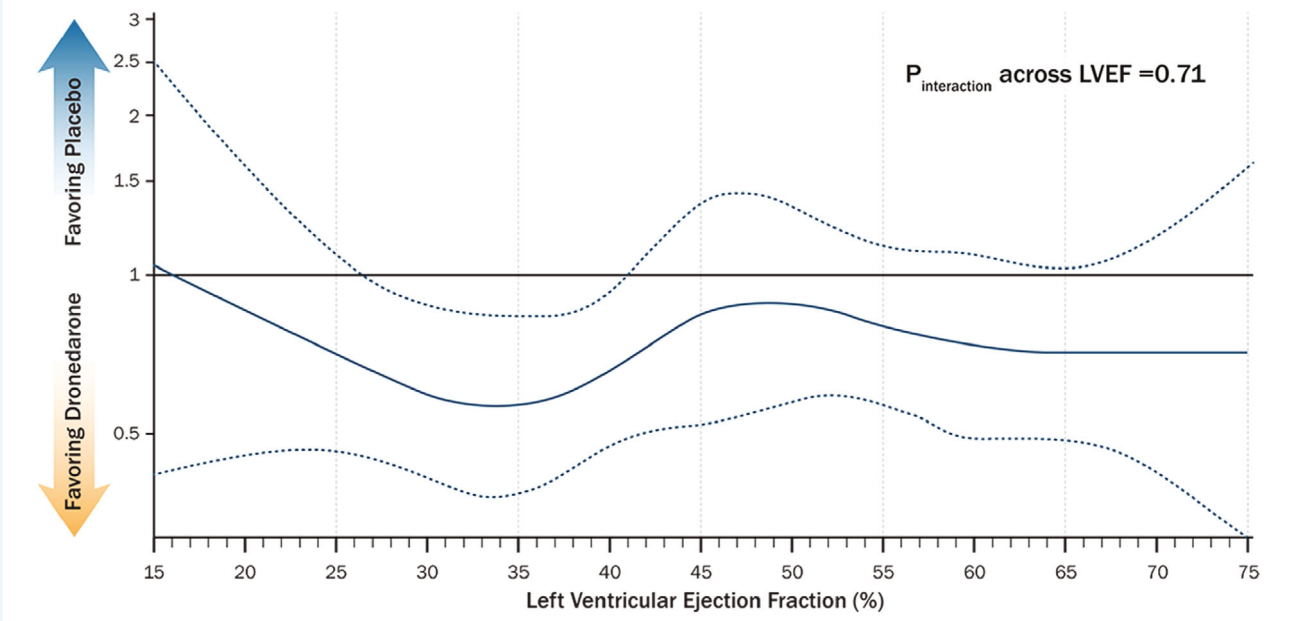
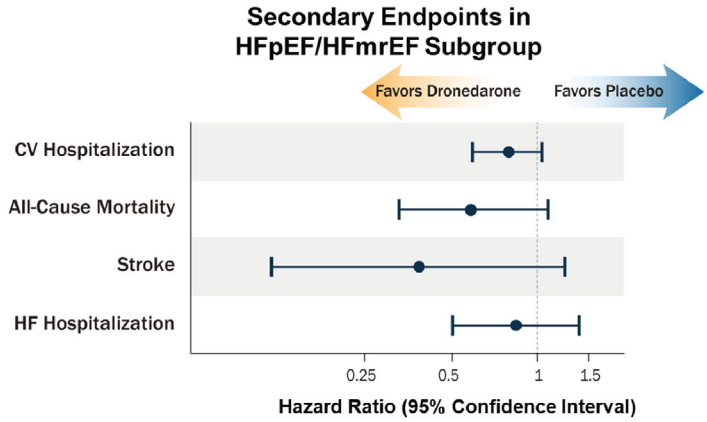


Figure 3 Treatment effects of dronedarone versus placebo in heart failure across a range of left ventricular ejection fraction (LVEF) for the primary endpoint (death or cardiovascular hospitalization). Estimated hazard ratios (solid lines) and 95% confidence intervals (dashed lines) are derived from Cox proportional hazards models with LVEF expressed as a continuous function via restricted cubic splines.



Safety Endpoints in HFpEF/HFmrEF Subgroup

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

Figure 4 Secondary and safety endpoints in ATHENA subgroup with heart failure (HF) and left ventricular ejection fraction >40%. AE, adverse event; CV, cardiovascular; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

class II anti-adrenergic and class IV vasodilatory properties, stable patients with HF might benefit while decompensated patients with severe left ventricular 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 perturbations 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 labelling recommends digoxin discontinuation or dose reduction when initiating dronedarone.[25,26] Digoxin use was notably less common in ATHENA (18% in the 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-AFNET 4 may also be necessary to disrupt early pathways of left atrial myopathy and adverse remodelling. 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 enrolment 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.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

The original analysis was performed by the sponsor. Complete individual participant-level data from the ATHENA trial were then shared with Brigham and Women's Hospital (Boston, MA) for independent data analytic validation. The manuscript was drafted by the first author and revised with input from all coauthors. Editorial support was provided by Hanna Mourad-Agha of Fishawack Communications Ltd, and was limited to formatting and collating co-author feedback and approvals. This support was funded by Sanofi.

Funding

The original ATHENA trial and this *post-hoc* analysis were sponsored by Sanofi.

Conflict of interest: M.V. has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacosmos, Relypsa, Roche Diagnostics, and Sanofi, speaker engagements with Novartis and Roche Diagnostics, and participates in clinical trial committees for studies sponsored by Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. J.P.P. is supported by R01HL128595 from the National Heart, Lung and Blood Institute and R01AG074185 from the National Institutes of Aging; he also receives grants for clinical research from Abbott, American Heart Association, the Association for the Advancement of Medical Instrumentation, Bayer, Boston Scientific, iRhythm, and Philips and serves as a consultant to Abbott, Abbvie, Ablacon, Altathera, ARCA Biopharma, Biotronik, Boston Scientific, Bristol Myers Squibb, LivaNova, Medtronic, Milestone, ElectroPhysiology Frontiers, Pfizer, Sanofi, Philips, and Up-to-Date. A.J.C. reports grants and personal fees from Boehringer Ingelheim, Bayer, Pfizer,/BMS, Daiichi Sankyo, personal fees from Medtronic, Boston Scientific, Menarini, and Biotronik, and support from Anthos, Sanofi, St. Jude (now Abbott), Glaxo Smith Kline, Abbott, Johnson and Johnson, The Atrial Fibrillation Association, The Arrhythmia Alliance, The European Hearth Rhythm Association, and The World Society of Arrhythmia. H.J.G.M.C. reports support from the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation, CVON 2014–9 (RACE V); he also acts as consultant/advisor/speaker to Acesion, Incarda, Sanofi, Roche, Ksyos, Corsano Health, and DZHK; support for educational activities from Medtronic, Abbott and Boston Scientific. S.D.A. reports grants and personal fees from Vifor Int. and Abbott Vascular and personal fees from AstraZeneca, Bayer, Brahms, Boehringer Ingelheim, Cardiac Dimensions, Novartis, Occlutech, Servier and Vifor Int. J.B. reports consulting fees from BI, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave Ltd, and Vifor. J.S., R.B., A.P.A.A. and M.W. are employees of Sanofi and may hold shares and/or stock options in the company. S.H.H. reports personal fees from Bayer Healthcare, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Pfizer, and Sanofi.

References

1. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al.; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;**385**:1451–61.
2. Solomon SD, Vaduganathan M, Claggett BL, de Boer RA, DeMets D, Hernandez AF, et al. Baseline characteristics of patients with HF with mildly reduced and preserved ejection fraction: DELIVER trial. *JACC Heart Fail*. 2022;**10**: 184–97.
3. Reddy YNV, Obokata M, Gersh BJ, Borlaug BA. High prevalence of occult heart failure with preserved ejection fraction among patients with atrial fibrillation and dyspnea. *Circulation*. 2018;**137**:534–5.
4. Cikes M, Claggett B, Shah AM, Desai AS, Lewis EF, Shah SJ, et al. Atrial fibrillation in heart failure with preserved ejection fraction: the TOPCAT trial. *JACC Heart Fail*. 2018;**6**:689–97.
5. Freed BH, Daruwalla V, Cheng JY, Aguilar FG, Beussink L, Choi A, et al. Prognostic utility and clinical significance of cardiac mechanics in heart failure with preserved ejection fraction: importance of left atrial strain. *Circ Cardiovasc Imaging*. 2016;**9**: e003754.
6. Deferm S, Bertrand PB, Verbrugge FH, Verhaert D, Rega F, Thomas JD, et al. Atrial functional mitral regurgitation: JACC review topic of the week. *J Am Coll Cardiol*. 2019;**73**:2465–76.
7. Patel RB, Shah SJ. Therapeutic targeting of left atrial myopathy in atrial fibrillation and heart failure with preserved ejection fraction. *JAMA Cardiol*. 2020;**5**: 497–9.
8. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. *J Am Coll Cardiol*. 2020;**76**:1051–64.
9. Køber L, Torp-Pedersen C, McMurray JJ, Gøtzsche O, Lévy S, Crijns H, et al.; Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med*. 2008;**358**:2678–87.
10. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC). Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;**42**:373–498.
11. Friberg L. Safety of dronedarone in routine clinical care. *J Am Coll Cardiol*. 2014;**63**:2376–84.
12. Friberg L. Ventricular arrhythmia and death among atrial fibrillation patients using anti-arrhythmic drugs. *Am Heart J*. 2018;**205**:118–27.
13. Ehrlich JR, Look C, Kostev K, Israel CW, Goette A. Impact of dronedarone on the risk of myocardial infarction and stroke in atrial fibrillation patients followed in general practices in Germany. *Int J Cardiol*. 2019;**278**:126–32.
14. Hohnloser SH, Connolly SJ, Crijns HJ, Page RL, Seiz W, Torp-Petersen C. Rationale and design of 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. *J Cardiovasc Electrophysiol*. 2008;**19**:69–73.
15. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, et al.; ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009;**360**:668–78.
16. Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. *Eur J Heart Fail*. 2021;**23**:1217–25.
17. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al.; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;**381**:1609–20.
18. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, et al.; ATHENA Investigators. Dronedarone in patients with congestive heart failure: insights from ATHENA. *Eur Heart J*. 2010;**31**:1717–21.
19. Kondo T, McMurray JJV. Re-emergence of heart failure with a normal ejection fraction? *Eur Heart J*. 2022;**43**:427–9.
20. Blomström-Lundqvist C, Marrouche N, Connolly S, Corp Dit Genti V, Wieloch M, Koren A, et al. Efficacy and safety of dronedarone by atrial fibrillation history duration: insights from the ATHENA study. *Clin Cardiol*. 2020;**43**:1469–77.
21. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, et al.; EAST-AFNET 4 Trial Investigators. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med*. 2020;**383**:1305–16.
22. Rillig A, Magnussen C, Ozga AK, Suling A, Brandes A, Breithardt G, et al. Early rhythm control therapy in patients with atrial fibrillation and heart failure. *Circulation*. 2021;**144**:845–58.
23. Packer DL, Piccini JP, Monahan KH, Al-Khalidi HR, Silverstein AP, Noseworthy PA, et al.; CABANA Investigators. Ablation versus drug therapy for atrial fibrillation in heart failure. *Circulation*. 2021;**143**:1377–90.
24. Hohnloser SH, Halperin JL, Camm AJ, Gao P, Radzik D, Connolly SJ; PALLAS Investigators. Interaction between digoxin and dronedarone in the PALLAS trial. *Circ Arrhythm Electrophysiol*. 2014;**7**:1019–25.
25. US Food and Drug Administration Product Labeling for Dronedarone. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022425s010lbl.pdf (accessed 14 February 2022).
26. European Medicines Agency Product Labeling for Dronedarone. Available from: https://www.ema.europa.eu/en/documents/product-information/multaq-epar-product-information_en.pdf (accessed 14 February 2022).
27. Kelly JP, DeVore AD, Wu J, Hammill BG, Sharma A, Cooper LB, et al. Rhythm control versus rate control in patients with atrial fibrillation and heart failure with preserved ejection fraction: insights from Get With The Guidelines-Heart Failure. *J Am Heart Assoc*. 2019;**8**:e011560.