ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2022) **8**, 363–371
https://doi.org/10.1093/ehjcvp/pvab090

ORIGINAL ARTICLE

Dronedarone vs. placebo in patients with atrial fibrillation or atrial flutter across a range of renal function: a *post hoc* analysis of the ATHENA trial

Mate Vamos[1,*], Jonas Oldgren[2], Gi-Byoung Nam[3], Gregory Y.H. Lip[4], Hugh Calkins[5], Jun Zhu[6], Kwo-Chang Ueng[7], Ulf Ludwigs[8], Mattias Wieloch[9,10], John Stewart[11] and Stefan H. Hohnloser[12]

[1]Cardiac Electrophysiology Division, Department of Internal Medicine, University of Szeged, Szeged, Hungary; [2]Uppsala Clinical Research Center and Department of Medical Sciences, Uppsala University, Uppsala, Sweden; [3]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [4]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK; [5]Division of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA; [6]Fuwai Hospital, CAMS & PUMC, Beijing, China; [7]Division of Cardiology, Department of Internal Medicine, Chung-Shan Medical University Hospital, Taichung City, Taiwan; [8]Sanofi, Stockholm, Sweden; [9]Sanofi, Paris, France; [10]Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden; [11]Sanofi, Laval, Quebec, Canada; and [12]Department of Cardiology, J.W. Goethe University, Frankfurt, Germany

Received 23 August 2021; revised 3 December 2021; editorial decision 20 December 2021; accepted 22 December 2021; online publish-ahead-of-print 27 December 2021

Aims Use of antiarrhythmic drugs (AADs) in patients with chronic kidney disease (CKD) is challenging owing to issues with renal clearance, drug accumulation, and increased proarrhythmic risks. Because CKD is a common comorbidity in patients with atrial fibrillation/atrial flutter (AF/AFL), it is important to establish the efficacy and safety of AAD treatment in patients with CKD.

Methods and results Dronedarone efficacy and safety in individuals with AF/AFL and varying renal functionality [estimated glomerular filtration rate (eGFR): ≥60, ≥45 and <60, and <45 mL/min] was investigated in a *post hoc* analysis of ATHENA (NCT00174785), a randomized, double-blind trial of dronedarone vs. placebo in patients with paroxysmal or persistent AF/AFL plus additional cardiovascular (CV) risk factors. Log-rank testing and Cox regression were used to compare the incidence of endpoints between treatments. Overall, 4588 participants were enrolled from the trial. There was no interaction between treatment group and baseline eGFR assessed as a continuous variable ($P = 0.743$) for the first CV hospitalization or death from any cause (primary outcome). This outcome was lower with dronedarone vs. placebo across a wide range of renal function. First CV hospitalization and first AF/AFL recurrence were both lower in the two least renally impaired subgroups with dronedarone vs. placebo. Treatment emergent adverse events leading to treatment discontinuation were more frequent with dronedarone vs. placebo and occurred more often in patients with severe renal impairment.

Conclusion Dronedarone is an effective AAD in patients with AF/AFL and CV risk factors across a wide range of renal function.

* Corresponding author. Tel: +36 62 341 559, Fax: +36 62 342 538, Email: vamos.mate@gmail.com

© The Author(s) 2021. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Graphical Abstract

Post-hoc analysis of the ATHENA trial demonstrates the efficacy of dronedarone across a wide range of renal function

Keywords Dronedarone • Atrial fibrillation • Atrial flutter • Chronic kidney disease • ATHENA • Safety

Introduction

Atrial fibrillation (AF) and atrial flutter (AFL) are the most frequently encountered arrhythmias. AF-related symptoms and the risk of strokes are significantly improved with ventricular rate control and anticoagulation; controlling sinus rhythm can improve exercise capacity and quality of life in patients with AF.[1,2] As demonstrated in the recent EAST-AFNET 4 trial, early comprehensive rhythm control [such as antiarrhythmic drugs (AADs)] as part of a structured holistic management pathway is associated with a lower risk of cardiovascular (CV) outcomes in patients with newly diagnosed AF.[3]

AF/AFL is estimated to occur in 15–40% of patients with chronic kidney disease (CKD).[4] Additionally, mild CKD and moderate-to-severe CKD have been found to be independent risk factors for all-cause mortality in patients with AF/AFL.[5] However, the use of AADs in patients with CKD is challenging because of the increased proarrhythmic risks, especially in patients with CKD and concomitant structural heart disease.[4] A further concern is that administration of drugs that rely on kidney elimination can result in accumulation and drug toxicity,[6] especially as renal function deteriorates over time. Because CKD and AF are often coexisting[7] and increase with an advancing age, it is important to establish the efficacy and safety for AAD treatment in patients with AF and CKD. A *post hoc* analysis of the BALKAN-AF survey found that AF patients with CKD received less rhythm control than rate control; when they did receive rhythm control, it was almost exclusively amiodarone,[8] speaking to the need for increased awareness of the safety and efficacy of available alternative rhythm control therapies.

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; NCT00174785) was a randomized, double-blind, placebo-controlled trial to evaluate the use of dronedarone in patients with AF/AFL who had additional risk factors for death.[9] The study found that dronedarone reduced the incidence of CV hospitalization or death in patients with paroxysmal or persistent AF/AFL.[9]

The aim of this *post hoc* analysis of the ATHENA trial was to evaluate the impact of dronedarone on CV hospitalization or death from any cause and safety outcomes in patients enrolled in the trial across a range of renal function.

Methods

Study design

Details of the ATHENA trial have been described previously.[9,10] Briefly, ATHENA was a randomized, placebo-controlled, multicentre, double-blind, parallel-group trial that assessed the efficacy of dronedarone for the prevention of CV hospitalization or death from any cause in patients ≥70 years of age with paroxysmal or persistent AF/AFL and additional CV risk factors (arterial hypertension, previous stroke, transient ischaemic attack or systemic embolism, diabetes mellitus, left atrial diameter ≥50 mm, or left ventricular ejection fraction ≤40%). Patients with an estimated glomerular filtration rate (eGFR) of ≥10 mL/min (Cockcroft–Gault) were included in the study. Detailed patient eligibility and exclusion criteria can be found in the Supplementary material online. The study protocol was approved by the institutional review board at each participating institution.

Randomization and follow-up

Eligible patients were randomly assigned to either oral dronedarone 400 mg twice daily or a matching placebo (1:1 ratio). Assessment of vital signs and electrocardiography (ECG) were performed on Days 7 and 14 and at 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, and 30 months. Renal function was assessed by clearance of serum creatinine at each follow-up visit.

Study endpoints

The primary outcome of the ATHENA study[9,10] and this exploratory *post hoc* analysis was first CV hospitalization or death from any cause. Secondary endpoints were as follows: death from any cause, death from CV causes, first hospitalization due to CV events, and first documented recurrence of AF/AFL (assessed using standard ECG at follow-up visits). Safety outcomes including treatment-emergent adverse events (TEAEs), defined as an adverse event occurring between first dose of the study drug and 10 days after

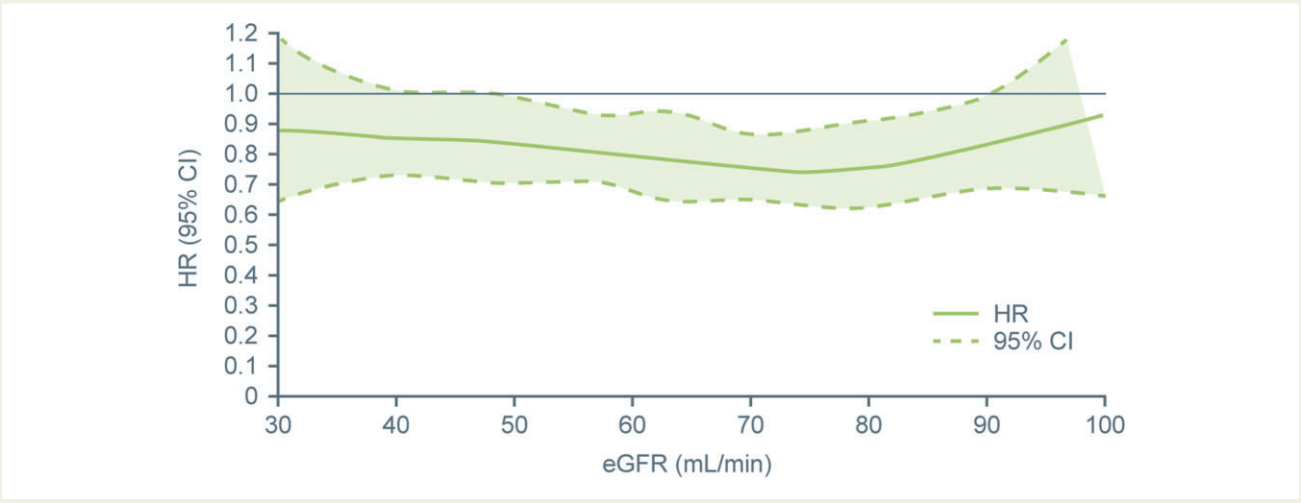

Figure 1 Hazard ratio (95% confidence interval) for first cardiovascular hospitalization or death from any cause related to treatment with dronedarone vs. placebo according to baseline estimated glomerular filtration rate. Hazard ratio and 95% confidence interval (dotted lines) shown. Test of interaction between treatment group and estimated glomerular filtration rate (Chronic Kidney Disease-Epidemiology Collaboration) as a continuous variable: *P*-value = 0.7434. CI, confidence interval; eGFR, estimated glomerular filtration rate; and HR, hazard ratio.

the last dose, and TEAE leading to discontinuation were also evaluated.

Statistical analysis

The original analysis of the ATHENA study used the Cockcroft–Gault formula.[10] In this exploratory subanalysis, renal function (eGFR) was assessed using the CKD-Epidemiology Collaboration (CKD-EPI) equation.[11] Patients were then grouped by eGFR strata in the following subgroups: ≥60, ≥45 and <60, and <45 mL/min. For confirmation purposes, outcomes were also analysed in eGFR strata classified according to the Modification of Diet in Renal Disease (MDRD) Study Group criteria and the Cockcroft–Gault formula.

Log-rank testing and Cox regression were used to compare time to events between treatment groups. Modelling was performed of time-to-event according to treatment, baseline CKD (eGFR assessed as a continuous variable), and its interaction, using restricted cubic spline for CKD. The restricted cubic spline analysis enabled the model to fit the non-linearity of the CKD effect by the addition of *k*-2 covariates of degree 3, with *k* being the number of knots. A Cox model with interaction was used to analyse time-to-event adjusted for treatment, CKD (CKD itself + three cubic terms = four covariates), and the four treatment-by-CKD interaction terms using SAS Proc PHREG.

Results

Baseline characteristics

The analysis included data from 4588 participants of the 4628 recruited for the ATHENA trial (*Table 1*). In total, 57% of patients had either no decrease or a mild decrease in eGFR (≥60 mL/min subgroup), 29% had a mild-to-moderate decrease in eGFR (≥45 and <60 mL/min subgroup), and the remaining 14% presented with moderate-to-severe decreases in eGFR (<45 mL/min subgroup). Median baseline eGFR for placebo and dronedarone were 74.1 and 73.2 mL/min, respectively, in the ≥60 mL/min subgroup, 53.4 and 53.5 mL/min, respectively, in the ≥45 and <60 mL/min subgroup, and 37.9 and 39.5 mL/min, respectively, in the <45 mL/min subgroup. The proportion of males in the subgroups decreased with worsening renal function. There was a trend towards increasing mean age and greater proportions with structural heart disease and coronary heart disease as renal function worsened. Mean CHA_2DS_2-VASc scores (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74, sex category [female]) also increased with decreasing renal function. In the ≥60 mL/min subgroup, ∼50% of participants had CHA_2DS_2-VASc scores >2, compared with ∼85% in the <45 mL/min subgroup.

Primary outcome: first cardiovascular hospitalization or death from any cause

In an analysis of all patients, rates of first CV hospitalization or death were 857/2621 (32.7%) patients in the ≥60 mL/min subgroup, 496/1332 (37.2%) in the ≥45 and <60 mL/min subgroup, and 279/635 (43.9%) in the <45 mL/min subgroup. The effect of treatment with dronedarone vs. placebo on first CV hospitalization or death from any cause vs. baseline eGFR assessed as a continuous variable is depicted in *Figure 1*, showing a relatively consistent hazard ratio (HR) for the effect of dronedarone vs. placebo across a wide range of renal function, with no significant interaction between the study treatment group and CKD ($P = 0.743$). The number of patients experiencing first CV hospitalization or death from any cause was also analysed according to assigned renal function group (eGFR) (*Figure 2*). Fewer patients experienced first CV hospitalization or death from any cause in the dronedarone vs. placebo groups, showing an HR ranging from 0.73 [95% confidence

Table 1 Demographic characteristics, cardiovascular disease history, and cardiovascular disease medication use

	eGFR ≥60 mL/min		eGFR ≥45 and <60 mL/min		eGFR <45 mL/min	
Characteristic, *n* (%)[a]	**Placebo (*n* = 1301)**	**Dronedarone (*n* = 1320)**	**Placebo (*n* = 683)**	**Dronedarone (*n* = 649)**	**Placebo (*n* = 322)**	**Dronedarone (*n* = 313)**
Age (years), mean ± SD	69.0 ± 9.4	69.2 ± 9.5	74.5 ± 7.2	73.6 ± 6.9	76.7 ± 6.6	77.1 ± 6.3
Sex, male	819 (63.0)	745 (56.4)	327 (47.9)	300 (46.2)	131 (40.7)	114 (36.4)
BMI ≥30 kg/m^2	435 (33.4)	410 (31.1)	193 (28.3)	222 (34.2)	99 (30.7)	119 (38.0)
eGFR (mL/min) at baseline, median (Q1, Q3)	74.1 (66.5, 84.7)	73.2 (66.5, 84.1)	53.4 (49.3, 56.6)	53.5 (49.9, 56.6)	37.9 (33.5, 42.0)	39.5 (33.7, 42.6)
Creatinine (μmol/L) at baseline, median (Q1, Q3)	80.0 (70.7, 94.0)	79.6 (70.7, 90.0)	104.0 (91.0, 114.9)	103.0 (92.0, 114.9)	132.6 (117.0, 150.3)	132.6 (114.9, 150.3)
Hypertension	1113 (85.5)	1124 (85.2)	585 (85.7)	575 (88.6)	280 (87.0)	285 (91.1)
Structural heart disease	723 (56.1)	708 (54.2)	438 (64.2)	391 (60.4)	233 (72.6)	221 (70.6)
Coronary heart disease	350 (26.9)	345 (26.1)	240 (35.1)	194 (29.9)	133 (41.3)	117 (37.4)
Any CHF	328 (25.2)	326 (24.7)	227 (33.2)	215 (33.1)	135 (41.9)	127 (40.6)
Ischaemic dilated cardiomyopathy	49 (3.8)	38 (2.9)	39 (5.7)	23 (3.5)	29 (9.0)	30 (9.6)
Non-ischaemic dilated cardiomyopathy	51 (3.9)	50 (3.8)	22 (3.2)	19 (2.9)	11 (3.4)	11 (3.5)
Rheumatic valvular heart disease	13 (1.0)	30 (2.3)	7 (1.0)	14 (2.2)	9 (2.8)	7 (2.2)
Non-rheumatic valvular heart disease	169 (13.0)	164 (12.4)	127 (18.6)	105 (16.2)	55 (17.1)	60 (19.2)
Hypertrophic cardiomyopathy	28 (2.2)	23 (1.7)	14 (2.0)	10 (1.5)	7 (2.2)	12 (3.8)
Congenital heart disease	9 (0.7)	14 (1.1)	4 (0.6)	3 (0.5)	3 (0.9)	4 (1.3)
CHA_2DS_2-VASc score, mean ± SD	2.5 ± 1.1	2.6 ± 1.1	3.1 ± 1.0	3.1 ± 1.0	3.5 ± 1.0	3.6 ± 1.0
CHA_2DS_2-VASc <2	228 (19.1)	224 (17.0)	43 (6.3)	32 (4.9)	8 (2.5)	7 (2.2)
CHA_2DS_2-VASc: 2	429 (33.0)	395 (29.9)	134 (19.6)	140 (21.6)	42 (13.0)	36 (11.5)
CHA_2DS_2-VASc >2	624 (48.0)	701 (53.1)	506 (74.1)	477 (73.5)	272 (84.5)	270 (86.3)
NYHA class						
Class 1	103 (7.9)	137 (10.4)	47 (6.9)	49 (7.6)	27 (8.4)	22 (7.0)
Class 2	186 (14.3)	155 (11.7)	136 (19.9)	134 (20.6)	82 (25.5)	81 (25.9)
Class 3	39 (3.0)	34 (2.6)	44 (6.4)	32 (4.9)	26 (8.1)	24 (7.7)
Left ventricular ejection fraction, mean ± SD	57.58 (10.50)	58.07 (10.36)	57.46 (11.74)	56.92 (11.23)	55.88 (12.81)	55.19 (12.48)
Pacemaker	98 (7.5)	91 (6.9)	96 (14.1)	66 (10.2)	46 (14.3)	54 (17.3)
Implanted cardioverter defibrillator	18 (1.4)	12 (0.9)	13 (1.9)	12 (1.8)	11 (3.4)	18 (5.8)
Left atrial diameter (mm), mean ± SD	43.91 (6.91)	43.90 (6.73)	43.91 (6.97)	44.11 (6.57)	44.72 (7.72)	44.69 (7.34)
CVD medication use						
Beta blockers (except sotalol)	921 (70.8)	919 (69.6)	476 (69.7)	483 (74.4)	237 (73.6)	219 (70.0)
ACE or AII inhibitor	886 (68.1)	906 (68.6)	484 (70.9)	478 (73.7)	226 (70.2)	226 (72.2)
Calcium channel blocker (rate lowering)	173 (13.3)	195 (14.8)	97 (14.2)	89 (13.7)	36 (11.2)	47 (15.0)
Diuretics other than spironolactone	622 (47.8)	619 (46.9)	382 (55.9)	366 (56.4)	217 (67.4)	198 (63.3)
Spironolactone	63 (4.8)	64 (4.8)	33 (4.8)	48 (7.4)	39 (12.1)	35 (11.2)
Vitamin K antagonists	812 (62.4)	827 (62.7)	381 (55.8)	376 (57.9)	184 (57.1)	196 (62.6)
Low-dose aspirin (≤365 mg)	535 (41.1)	568 (43.0)	322 (47.1)	310 (47.8)	162 (50.3)	137 (43.8)
Other chronic antiplatelet therapy	77 (5.9)	74 (5.6)	52 (7.6)	35 (5.4)	37 (11.5)	17 (5.4)
Statins (CYP3A4 metabolized)	400 (30.7)	407 (30.8)	224 (32.8)	216 (33.3)	129 (40.1)	111 (35.5)
Statins (not CYP3A4 metabolized)	103 (7.9)	83 (6.3)	39 (5.7)	41 (6.3)	24 (7.5)	22 (7.0)
Moderate inhibitors of CYP3A4	122 (9.4)	136 (10.3)	74 (10.8)	56 (8.6)	30 (9.3)	22 (7.0)
Digoxin	179 (13.8)	188 (14.2)	84 (12.3)	88 (13.6)	45 (14.0)	43 (13.7)
Drugs interacting with creatinine renal tubular secretion[b]	124 (9.5)	125 (9.5)	69 (10.1)	75 (11.6)	43 (13.4)	28 (8.9)
NSAID	60 (4.6)	69 (5.2)	34 (5.0)	31 (4.8)	29 (9.0)	14 (4.5)

[a] Data are *n* (%) unless otherwise stated.
[b] Presence of drugs that compete with creatinine for renal tubular secretion may result in reduced estimated glomerular filtration rate values, despite no change in renal functionality measured by other parameters.
ACE, angiotensin converting enzyme; AII, angiotensin II; BMI, body mass index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74, sex category (female); CHF, chronic heart failure; CVD, cardiovascular disease; CYP3A4, cytochrome P450 3A4; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug; Q1, quartile 1; Q3, quartile 3; and SD, standard deviation.
Placebo group: *n* = 2306; dronedarone group: *n* = 2282.

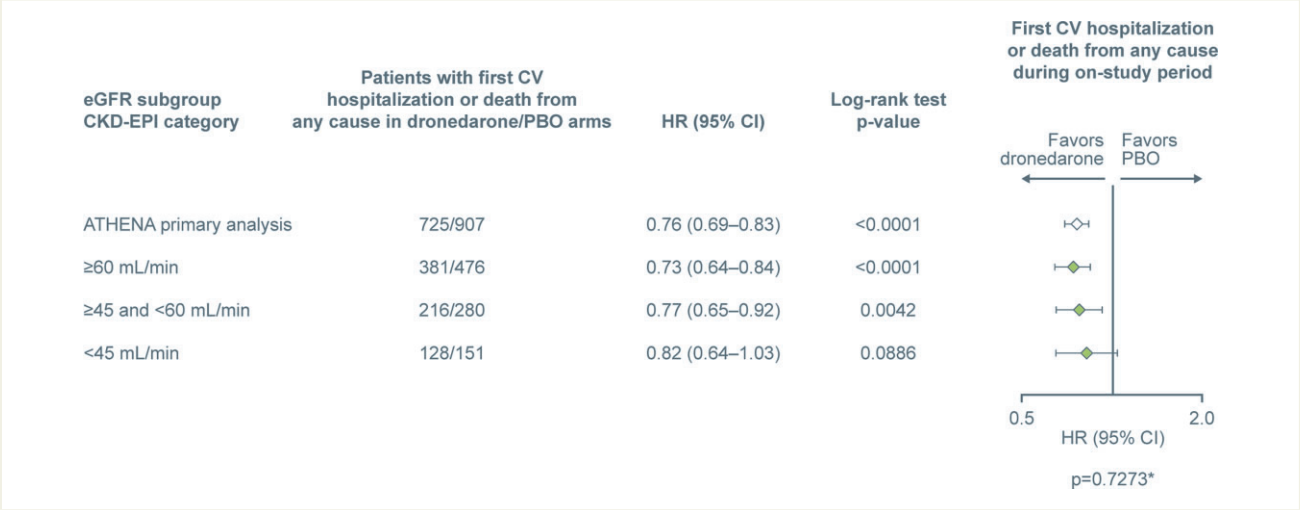

Figure 2 Number of patients experiencing first cardiovascular hospitalization or death from any cause. The 'ATHENA primary analysis' data are from Hohnloser *et al.*[9]
*Probability of interaction between the treatment group and the subgroup. Total patients in dronedarone and placebo subgroups—≥60 mL/min: 1320 and 1301; ≥45 and <60 mL/min: 649 and 683; <45 mL/min: 313 and 322. CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; and PBO, placebo.

interval (CI) 0.64–0.84] to 0.82 (95% CI 0.65–1.03) across the renal function groups, with no interaction effect of treatment group and CKD subgroup ($P = 0.727$). In a subanalysis of patients with severe renal impairment, similar results were observed [HR 0.77 (0.43–1.39) for eGFR ≥10 and <30 mL/min; HR 0.83 (0.64–1.08) for eGFR ≥30 and <45 mL/min; Supplementary material online, *Figure S1*].

The number of patients who experienced a first CV hospitalization was lower with dronedarone compared with placebo, with an HR of 0.72 to 0.84 ($P < 0.01$ in the ≥60 mL/min and ≥45 and <60 mL/min groups; $P > 0.05$ in the <45 mL/min group) (*Figure 3A*). There was no interaction effect of treatment group and CKD subgroup ($P = 0.573$). The number of patients who experienced death from any cause was numerically lower with dronedarone compared with placebo in the ≥60 and <45 mL/min subgroups, and similar in the ≥45 and <60 mL/min subgroup (*Figure 3B*). However, log-rank test *P*-values were all >0.05, likely due to the smaller patient populations following stratification. There was no interaction effect of treatment group and CKD subgroup ($P = 0.576$).

First recurrence of atrial fibrillation/atrial flutter

Median time (in days) from randomization until first documented recurrence of AF/AFL was longer with dronedarone vs. placebo in all three subgroups [≥60 mL/min, 533 (386–552) vs. 197 (178–312); ≥45 and <60 mL/min, 534 (378–593) vs. 187 (153–290); and <45 mL/min, 363 (95% CI 191–555) vs. 183 (89–305)]. There was also a difference in the number of patients experiencing first recurrence of AF/AFL between the dronedarone and placebo groups favouring dronedarone (HR 0.78 and 0.76, $P < 0.01$ for both, for the ≥60 mL/min and ≥45 and <60 mL/min subgroups, respectively). The <45 mL/min subgroup showed an HR of 0.85, $P > 0.05$ (*Figure 3C*). There was no interaction effect of treatment group and CKD subgroup ($P = 0.724$). Patients with severe renal impairment (≥30 and <45 mL/min and ≥10 and <30 mL/min) showed HRs of 0.82 and 0.97, respectively ($P > 0.05$ for both groups).

Change in creatinine

Following dronedarone treatment, creatinine levels initially increased in all eGFR subgroups but appeared to plateau after the first measurement (performed at Week 1) (*Figure 4*). In the more renally impaired subgroups, values returned close to baseline at later time points.

Safety

There was a general trend towards more TEAEs, serious TEAEs, and TEAEs leading to discontinuation in patients with more impaired renal function (*Table 2*). Differences between the dronedarone and placebo groups were small with regard to TEAEs and serious TEAEs. TEAEs leading to treatment discontinuation were more frequent in the dronedarone vs. placebo arm and were more prevalent in patients with poor renal function (ranging from 10.3% to 21.4% for dronedarone and from 7.8% to 9.6% for placebo). TEAEs leading to treatment discontinuation were primarily of gastrointestinal origin in both groups (*Table 2*); these gastrointestinal TEAEs were mostly attributable to diarrhoea and nausea. Few patients in either treatment group reported QT prolongation as a serious TEAE leading to treatment discontinuation [placebo: one patient (0.04%); dronedarone: four patients (0.2%)].

TEAEs in a subanalysis of patients with severe renal impairment are presented in the Supplementary material online, *Table S1*. A higher proportion of patients receiving dronedarone reported TEAEs leading to treatment discontinuation compared with patients receiving placebo in all renal function groups; again, gastrointestinal TEAEs (primarily diarrhoea and nausea) leading to discontinuation were most commonly observed.

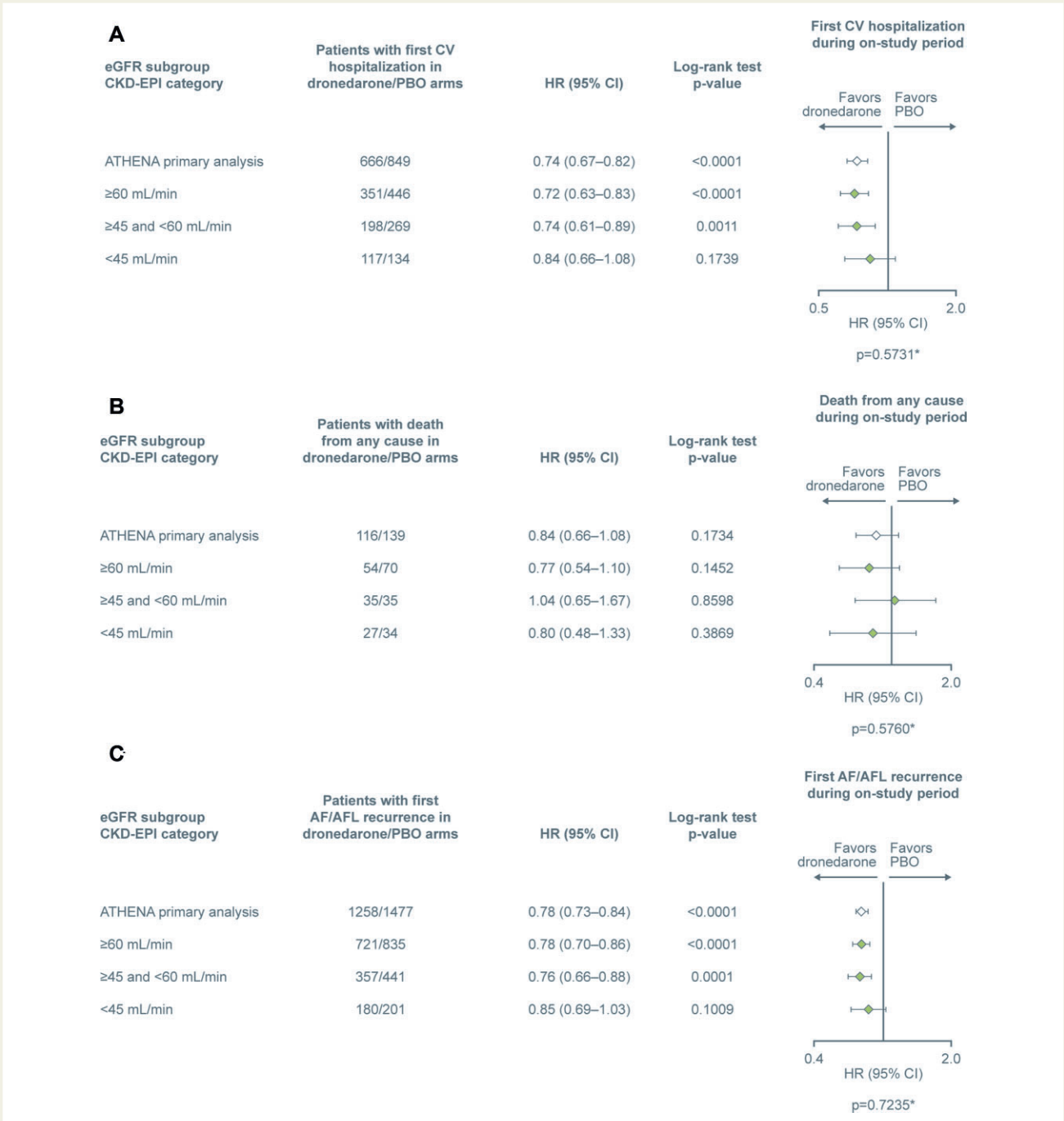

Figure 3 Number of patients with (*A*) first cardiovascular hospitalization, (*B*) death from any cause, and (*C*) first atrial fibrillation / atrial flutter recurrence. The 'ATHENA primary analysis' data are from Hohnloser *et al.*[9] *Probability of interaction between the treatment group and the subgroup. Total patients in dronedarone and placebo subgroups—≥60 mL/min: 1320 and 1301; ≥45 and <60 mL/min: 649 and 683; <45 mL/min: 313 and 322. AF, atrial fibrillation; AFL, atrial flutter; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; and PBO, placebo.

Modification of Diet in Renal Disease Study Group criteria and Cockcroft–Gault formula

As a sensitivity analysis, outcomes were also analysed in eGFR strata classified according to the MDRD Study Group criteria and the Cockcroft–Gault formula, used in the original ATHENA analysis.[10] The findings were unchanged and these data are not presented herein.

Discussion

This exploratory *post hoc* analysis of the ATHENA trial aimed to determine the efficacy and safety of dronedarone in relation to

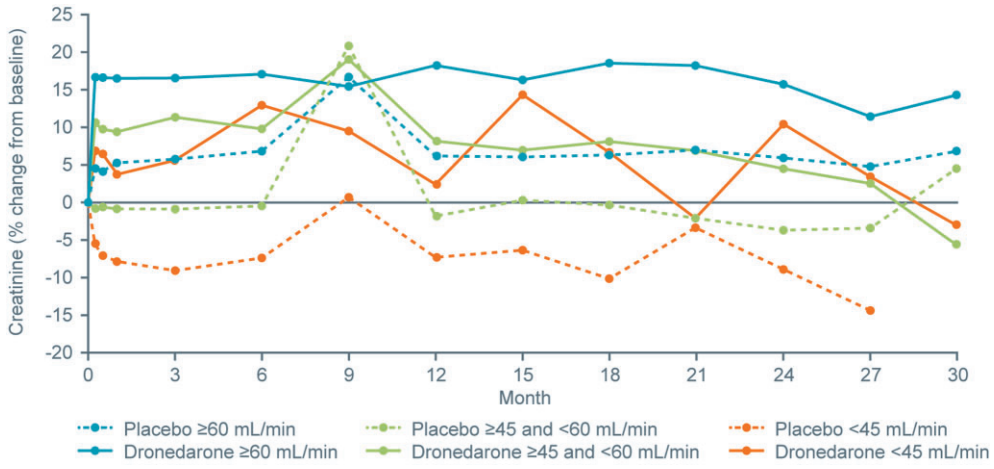

Figure 4 Percentage change from baseline in creatinine by estimated glomerular filtration rate category, with study time displayed on the *x*-axis.

Table 2 Summary of treatment-emergent adverse events by treatment and estimated glomerular filtration rate subgroup (≥60, ≥45 and <60, and <45 mL/min)

	eGFR ≥60 mL/min		eGFR ≥45 and <60 mL/min		eGFR <45 mL/min	
***n* (%)**	**Placebo (*n* = 1301)**	**Dronedarone (*n* = 1320)**	**Placebo (*n* = 683)**	**Dronedarone (*n* = 649)**	**Placebo (*n* = 322)**	**Dronedarone (*n* = 313)**
Any TEAE	886 (68.1)	921 (69.8)	479 (70.1)	478 (73.7)	233 (72.4)	243 (77.6)
Any serious TEAE	267 (20.5)	243 (18.4)	137 (20.1)	132 (20.3)	84 (26.1)	77 (24.6)
Any TEAE leading to discontinuation	102 (7.8)	136 (10.3)	55 (8.1)	90 (13.9)	31 (9.6)	67 (21.4)
Cardiac disorders	14 (1.1)	21 (1.6)	7 (1.0)	12 (1.8)	8 (2.5)	11 (3.5)
Gastrointestinal disorders	46 (3.5)	67 (5.1)	15 (2.2)	35 (5.4)	11 (3.4)	24 (7.7)
General disorders and administration site conditions	28 (2.2)	28 (2.1)	14 (2.0)	16 (2.5)	8 (2.5)	18 (5.8)
Infections and infestations	19 (1.5)	23 (1.7)	9 (1.3)	17 (2.6)	9 (2.8)	10 (3.2)
Investigations	15 (1.2)	36 (2.7)	9 (1.3)	32 (4.9)	5 (1.6)	23 (7.3)
Metabolism and nutrition disorders	9 (0.7)	15 (1.1)	5 (0.7)	7 (1.1)	3 (0.9)	13 (4.2)
Musculoskeletal and connective tissue disorders	18 (1.4)	26 (2.0)	9 (1.3)	10 (1.5)	7 (2.2)	7 (2.2)
Nervous system disorders	25 (1.9)	33 (2.5)	9 (1.3)	14 (2.2)	9 (2.8)	10 (3.2)
Psychiatric disorders	7 (0.5)	15 (1.1)	5 (0.7)	3 (0.5)	8 (2.5)	2 (0.6)
Renal and urinary disorders	5 (0.4)	6 (0.5)	1 (0.1)	6 (0.9)	5 (1.6)	10 (3.2)
Respiratory, thoracic and mediastinal disorders	18 (1.4)	21 (1.6)	11 (1.6)	11 (1.7)	8 (2.5)	9 (2.9)
Skin and subcutaneous tissue disorders	17 (1.3)	27 (2.0)	4 (0.6)	11 (1.7)	6 (1.9)	9 (2.9)

Placebo group (overall): *n* = 2306; dronedarone group (overall): *n* = 2282. Treatment-emergent adverse event types leading to discontinuation in ≥2% of patients in any treatment group/estimated glomerular filtration rate subgroup are listed. eGFR, estimated glomerular filtration rate; TEAE, treatment-emergent adverse event.

renal function. Dronedarone was associated with a lower incidence of first CV hospitalization or death from any cause vs. placebo across a wide spectrum of renal function, consistent with the outcomes of the primary ATHENA trial.[9] These findings are supported by modelling of treatment by baseline eGFR as a continuous variable, rather than choosing the specific cut-off points dividing patients into subgroups. The failure to achieve statistical significance separately in the <45 mL/min subgroup was most likely a reflection of the smaller population size resulting in reduced statistical power.

Secondary endpoints, including CV hospitalization and first recurrence of AF/AFL, showed improved or similar outcomes with dronedarone vs. placebo, with the ≥60 mL/min and ≥45 and <60 mL/min subgroups showing improvements that were statistically significant, but because of the *post hoc* nature of our analyses,

further studies are needed to corroborate these findings. As expected, in ATHENA the risk for first CV hospitalization or death from any cause was higher in patients with renal impairment, in line with similar findings on the increased risk for all-cause and CV mortality with worsening renal impairment.[12]

Dronedarone competes with creatinine for the renal tubular cation transport pathway, inhibiting tubular secretion of creatinine by ~18% and subsequently increasing serum creatinine.[13] Although this increase in serum creatinine was also described for dronedarone in the ANDROMEDA, EURIDIS-ADONIS, and PALLAS trials,[9,14–16] it does not represent a decrease in glomerular filtration rate (GFR).[13] In this analysis, the increase in creatinine in the dronedarone groups was maintained until the end of the study in the ≥60 mL/min subgroup, but returned close to baseline in the subgroups with greater renal impairment.

Although the study was not powered to detect differences between the treatment arms in subgroups based on renal function, the results did not show any signs of unfavourable individual outcomes with dronedarone across a wide spectrum of renal function. No significant difference in deaths from any cause was observed between dronedarone and placebo in any eGFR subgroup. Serious TEAEs and deaths did not differ notably between dronedarone and placebo in each group, although TEAEs leading to discontinuation were numerically higher in patients with an eGFR of <45 mL/min receiving dronedarone vs. placebo. Another analysis of the ATHENA study has linked older age with a higher discontinuation rate;[17] since older age was associated with worse renal function in the current analysis, this may explain the observed high rate of discontinuation in patients with severe renal impairment. CHA_2DS_2-VASc scores, a prognostic marker of increased risk for stroke or thromboembolic events and well recognized as a 'frailty index',[18] were also higher in patients with more severe renal impairment, possibly reflecting a more fragile population of older age, with more comorbidities and medications with which possible drug–drug interactions and adverse effects are more common. While the higher medication burden in elderly vs. younger populations may increase the potential for adverse interaction, results from this analysis indicate that the rate of treatment discontinuation due to serious TEAEs involving bleeding/thrombotic events, QT prolongation, or heart failure was generally low, which may provide reassurance of the acceptable safety profile of dronedarone in this population.

Limitations

This was a *post hoc* analysis of a prospective randomized controlled trial, and patients were not stratified according to renal function in the main trial. Splitting the overall trial population into eGFR categories meant that the number of participants in each subgroup was reduced compared with the overall study population in the original trial.[9] This resulted in a loss of power, particularly in the most renally impaired <45 mL/min subgroup [which constituted only 14% (n = 635) of included patients], although there was no interaction when studying eGFR as a continuous variable. The majority of patients had mild to moderate renal impairment, limiting the generalizability to patients with severe renal impairment. Finally, direct oral anticoagulants (DOACs) were not approved for atrial fibrillation at the time of the ATHENA study[19] and so are not represented in the trial population; therefore, it is not possible to make any assessment of the safety/efficacy of dronedarone in conjunction with DOAC administration based on the current analysis.

Conclusions

Our findings demonstrate that dronedarone reduced first CV hospitalization or death from any cause in individuals with AF/AFL and additional risk factors across a wide range of renal function. Although dronedarone is an effective treatment in patients with structural heart disease and renal impairment compared with other AADs, which have limitations in their use or require dose reduction,[4] further assessment of safety will be required in larger populations of patients with severe CKD.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

Acknowledgements

Editorial assistance was provided by Alex van der Wateren (PhD), of Fishawack Communications Ltd, and was funded by Sanofi. We thank Wanda Stipek, PharmD, BCPS (Sanofi), for coordination of the development, facilitating author discussions, and critical review of this manuscript.

Funding

Sanofi.

Conflict of interest: M.V. reports receiving consulting fees and/or non-financial support from Abbott, Biotronik, Medtronic, Minimal Invasive Technology, Pfizer, and Sanofi-Aventis, outside the submitted work. S.H.H. reports receiving consulting fees from Bayer Healthcare, BI, BMS, Boston Scientific, Daiichi Sankyo, Gilead, Johnson & Johnson, Medtronic, Pfizer, Sanofi-Aventis, Servier, and Zoll and lecture fees from Bayer Healthcare, BI, BMS, Daiichi Sankyo, Pfizer, Sanofi-Aventis, and Medtronic. G.B.N. has no conflicts to declare. J.O. reports fees to his institution from AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Novartis, Pfizer, Roche Diagnostics, and Sanofi, outside the present work. G.Y.H.L. is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi Sankyo. No fees are received personally. H.C. is a consultant to Medtronic, Atricure, Abbott Medical, and Ablacon and reports honoraria from Medtronic and Ablacon. J.Z. reports receiving speaker fees from Boehringer Ingelheim, Bayer, and Novartis. K.C.U. reports no conflict of interest. M.W., U.L., and J.S. are employees of Sanofi and may hold shares and/or stock options in the company.

References

1. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD, Jr, Raisch DW, Ezekowitz MD. Sotalol Amiodarone Atrial Fibrillation Efficacy Trial I. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med* 2005;**352**:1861–1872.

2. The National Institute for Health and Care Excellence (NICE). https://www.nice.org.uk/guidance/cg180 (November 2021).
3. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, Hamann F, Heidbüchel H, Hindricks G, Kautzner J, Kuck K-H, Mont L, Ng GA, Rekosz J, Schoen N, Schotten U, Suling A, Taggeselle J, Themistoclakis S, Vettorazzi E, Vardas P, Wegscheider K, Willems S, Crijns HJGM, Breithardt G. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;**383**:1305–1316.
4. Turakhia MP, Blankestijn PJ, Carrero JJ, Clase CM, Deo R, Herzog CA, Kasner SE, Passman RS, Pecoits-Filho R, Reinecke H, Shroff GR, Zareba W, Cheung M, Wheeler DC, Winkelmayer WC, Wanner C, Conference Participants. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Eur Heart J* 2018;**39**:2314–2325.
5. Goto S, Angchaisuksiri P, Bassand JP, Camm AJ, Dominguez H, Illingworth L, Gibbs H, Goldhaber SZ, Goto S, Jing ZC, Haas S, Kayani G, Koretsune Y, Lim TW, Oh S, Sawhney JPS, Turpie AGG, van Eickels M, Verheugt FWA, Kakkar AK, GARFIELD-AF Investigators. Management and 1-year outcomes of patients with newly diagnosed atrial fibrillation and chronic kidney disease: results from the prospective GARFIELD-AF registry. *J Am Heart Assoc* 2019;**8**:e010510.
6. Lea-Henry TN, Carland JE, Stocker SL, Sevastos J, Roberts DM. Clinical pharmacokinetics in kidney disease: fundamental principles. *Clin J Am Soc Nephrol* 2018;**13**:1085–1095.
7. Jonsson KM, Wieloch M, Sterner G, Nyman U, Elmstahl S, Engstrom G, Svensson PJ. Glomerular filtration rate in patients with atrial fibrillation on warfarin treatment: a subgroup analysis from the AURICULA registry in Sweden. *Thromb Res* 2011;**128**:341–345.
8. Koziel M, Simovic S, Pavlovic N, Nedeljkovic M, Kocijancic A, Paparisto V, Music L, Trendafilova E, Dan AR, Manola S, Kusljugic Z, Dan GA, Lip GYH, Potpara TS, Balkan-AF Investigators. Treatment implications of renal disease in patients with atrial fibrillation: the BALKAN-AF survey. *J Arrhythm* 2020;**36**:863–873.
9. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ, ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;**360**:668–678.
10. 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.
11. Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. *Am J Kidney Dis* 2014;**63**:820–834.
12. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006;**17**:2034–2047.
13. Tschuppert Y, Buclin T, Rothuizen LE, Decosterd LA, Galleyrand J, Gaud C, Biollaz J. Effect of dronedarone on renal function in healthy subjects. *Br J Clin Pharmacol* 2007;**64**:785–791.
14. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, Atar D, Avezum A, Blomstrom P, Borggrefe M, Budaj A, Chen SA, Ching CK, Commerford P, Dans A, Davy JM, Delacretaz E, Di Pasquale G, Diaz R, Dorian P, Flaker G, Golitsyn S, Gonzalez-Hermosillo A, Granger CB, Heidbuchel H, Kautzner J, Kim JS, Lanas F, Lewis BS, Merino JL, Morillo C, Murin J, Narasimhan C, Paolasso E, Parkhomenko A, Peters NS, Sim KH, Stiles MK, Tanomsup S, Toivonen L, Tomcsanyi J, Torp-Pedersen C, Tse HF, Vardas P, Vinereanu D, Xavier D, Zhu J, Zhu JR, Baret-Cormel L, Weinling E, Staiger C, Yusuf S, Chrolavicius S, Afzal R, Hohnloser SH, PALLAS Investigators. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011;**365**:2268–2276.
15. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H, Amlie J, Carlsen J, Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;**358**:2678–2687.
16. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, Radzik D, Aliot EM, Hohnloser SH, Euridis ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007;**357**:987–999.
17. Curtis AB, Zeitler EP, Malik A, Bogard A, Bhattacharyya N, Stewart J, Hohnloser SH. Efficacy and safety of dronedarone across age and sex subgroups: a *post hoc* analysis of the ATHENA study among patients with non-permanent atrial fibrillation/flutter. *Europace* 2021;1–9.
18. Philippart R, Brunet-Bernard A, Clementy N, Bourguignon T, Mirza A, Babuty D, Angoulvant D, Lip GY, Fauchier L. Prognostic value of CHA_2DS_2-VASc score in patients with 'non-valvular atrial fibrillation' and valvular heart disease: the Loire Valley Atrial Fibrillation Project. *Eur Heart J* 2015;**36**:1822–1830.
19. Chen A, Stecker E, AW B. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *J Am Heart Assoc* 2020;**9**:e017559.