









Dronedarone provides effective early rhythm control: post-hoc analysis of the ATHENA trial using EAST-AFNET 4 criteria

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Received 16 September 2024; accepted after revision 18 March 2025; online publish-ahead-of-print 29 April 2025

Aims

This post-hoc analysis of the ATHENA trial assessed whether dronedarone (400 mg twice daily) improved cardiovascular outcomes compared with placebo in patients with early atrial fibrillation/atrial flutter (AF) and cardiovascular comorbidities, based on EAST-AFNET 4 inclusion criteria and outcomes.

Methods and results

The co-primary outcomes were (i) a composite of cardiovascular death, stroke, or hospitalisation due to worsening of heart failure (HF) or acute coronary syndrome (ACS) and (ii) nights spent in hospital per year. Sinus rhythm (SR) at 12 months was a secondary outcome. The primary safety outcome was a composite of death, stroke, or pre-specified serious adverse events of special interest (AESIs) related to rhythm control therapy. 1810 patients with early AF were identified. Patients receiving dronedarone had fewer deaths from cardiovascular causes, strokes, or hospitalisations due to worsening of HF or ACS compared with patients receiving placebo [dronedarone ($n = 924$), 87 patients with ≥ 1 event; placebo ($n = 886$), 117 patients with ≥ 1 event; hazard ratio 0.71; 95% confidence interval 0.54–0.94; $P = 0.014$]. Number of nights spent in hospital did not differ between treatment groups. More patients receiving dronedarone (69.2%) were in SR at 12 months compared with placebo (60.8%). Primary safety events comprising death, stroke, or pre-specified serious AESIs related to rhythm control therapy were not different (dronedarone vs. placebo: 60 vs. 71 patients with ≥ 1 event).

Conclusion

These data support the use of dronedarone for early rhythm control therapy in selected patients with early AF.

Trial registration

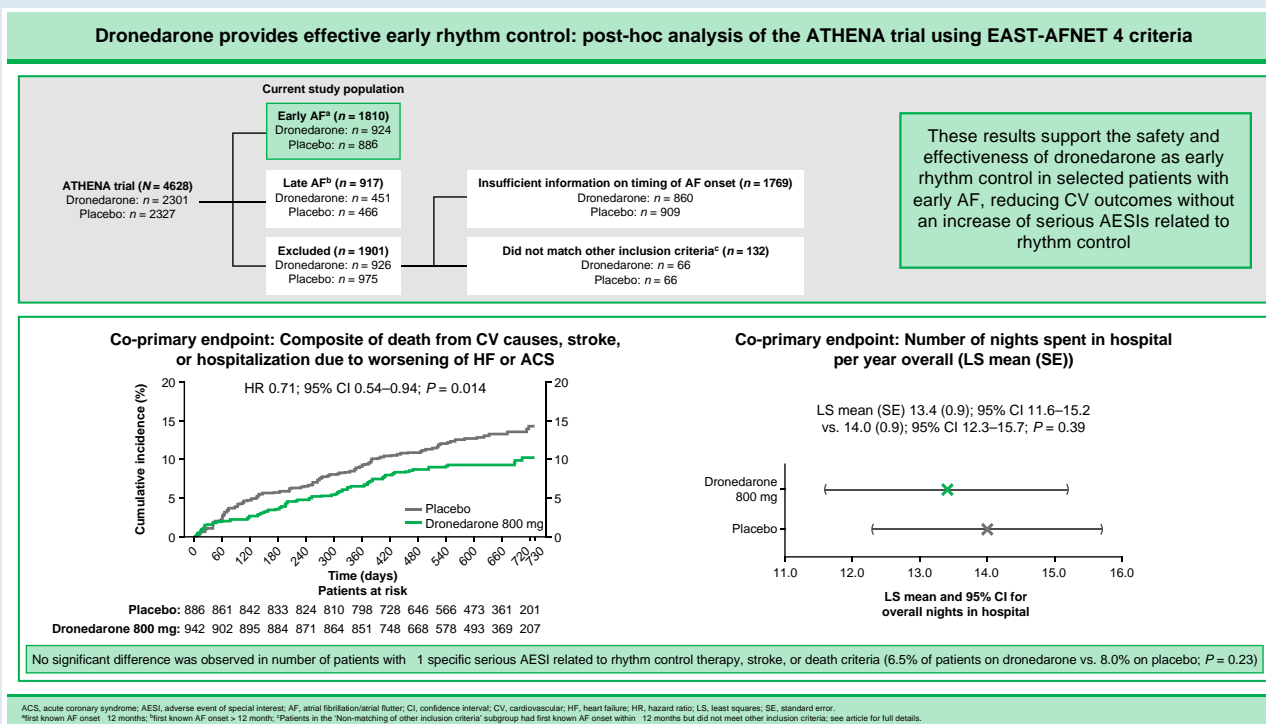
ATHENA: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00174785) identifier NCT00174785. EAST-AFNET 4: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01288352) identifier NCT01288352.

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Graphical Abstract



Keywords

Atrial fibrillation • Atrial flutter • Early rhythm control • Dronedaron

What's new?

- This post-hoc analysis of the ATHENA trial assessed whether dronedaron improved cardiovascular outcomes compared with placebo in patients with recently diagnosed (also known as 'early') atrial fibrillation/atrial flutter and cardiovascular comorbidities, applying EAST-AFNET 4 inclusion criteria and outcomes.
- Dronedaron was associated with fewer cardiovascular deaths, strokes, and hospitalisations due to worsening of heart failure or acute coronary syndrome (EAST-AFNET 4 primary outcome) compared with placebo in eligible ATHENA patients with early atrial fibrillation/atrial flutter and cardiovascular comorbidities.
- The safety profile of dronedaron was comparable to that of placebo, and nights spent in hospital were not different between treatment groups.
- These data support the use of dronedaron as early rhythm control therapy in selected patients with atrial fibrillation/atrial flutter.

Introduction

Despite improvements in the evaluation and management of atrial fibrillation over time, this condition remains associated with adverse clinical outcomes, including stroke, heart failure (HF), acute coronary syndrome (ACS), and death due to cardiovascular causes.^{1,2} Important aspects of atrial fibrillation therapy include anticoagulation, rate control therapy, rhythm control therapy, and identification/management of comorbid cardiovascular diseases and risk factors.^{3–6} Although antiarrhythmic drugs (AADs) are successful in maintaining sinus rhythm (SR), several AADs

have been associated with increased mortality and adverse effects, including long-term toxicity.⁵

Dronedaron is a multichannel blocking benzofuran that possesses class I–IV antiarrhythmic effects.⁷ The 2020 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guideline for the diagnosis and management of atrial fibrillation recommends dronedaron for long-term rhythm control in atrial fibrillation patients with normal/mildly impaired (but stable) left ventricular (LV) function or HF with preserved ejection fraction (HFpEF), ischaemic heart disease, or valvular heart disease (VHD).⁴ Similarly, the 2023 American College of Cardiology (ACC)/American Heart Association (AHA)/American College of Clinical Pharmacy (ACCP)/Heart Rhythm Society (HRS) guideline for the diagnosis and management of atrial fibrillation notes the use of dronedaron for long-term SR maintenance is reasonable in patients with atrial fibrillation without recent decompensated HF or severe LV dysfunction.⁸ In the randomized, placebo-controlled ATHENA trial (NCT00174785), dronedaron reduced the incidence of unplanned hospitalisation due to cardiovascular events or death in patients with paroxysmal or persistent atrial fibrillation/atrial flutter (henceforth referred to collectively as AF) and additional risk factors for death.⁹ The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4; NCT01288352) later demonstrated that initiating comprehensive early rhythm control (ERC) therapy with AADs or ablation in patients with early (i.e. diagnosed within ≤12 months) AF and cardiovascular risk was associated with a lower risk of cardiovascular outcomes than guideline-based usual care over a follow-up period of >5 years.¹⁰

The aim of this post-hoc analysis was to evaluate the effectiveness and safety of dronedaron for ERC in AF. To achieve this, outcomes were compared in all patients randomized in the ATHENA trial who fulfilled the enrolment criteria of the EAST-AFNET 4 trial.

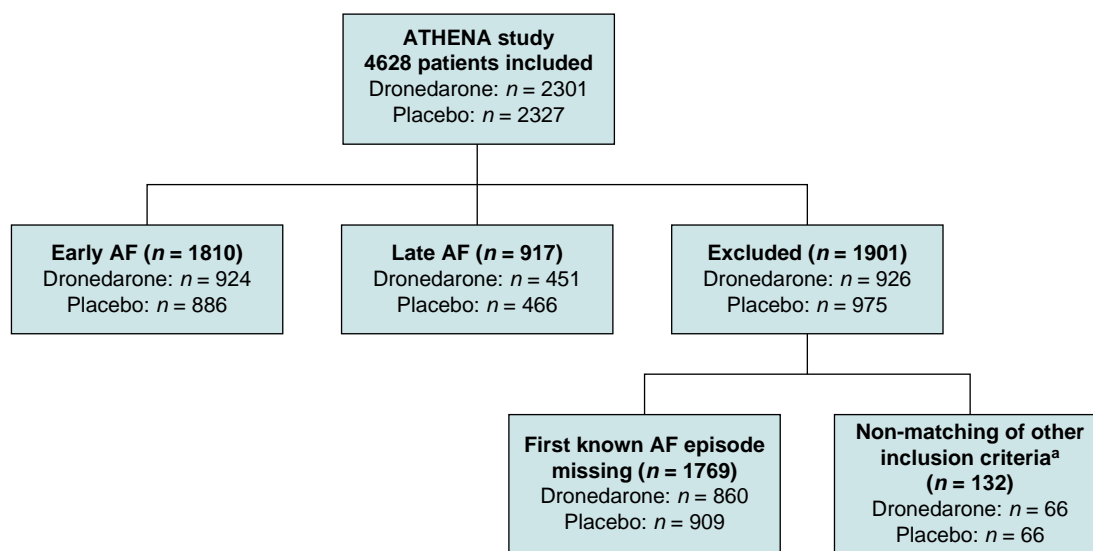


Figure 1 Patient disposition. Early AF defined as first known AF onset within ≤ 12 months. Late AF defined as first known AF onset > 12 months. ^aPatients in the 'Non-matching of other inclusion criteria' subgroup had first known AF onset within ≤ 12 months but did not meet other EAST-AFNET 4 inclusion criteria (see [Supplementary material online, Table S1](#) for details of these). AF, atrial fibrillation/atrial flutter.

Methods

Study design

The methods for the ATHENA and EAST-AFNET 4 trials have been described previously.^{9,10} ATHENA was a randomized, placebo-controlled, international, multicenter, double-blind, parallel-group trial conducted from 2005 to 2008 that assessed the efficacy of dronedarone for prevention of unplanned cardiovascular hospitalisation or death from any cause in patients with paroxysmal or persistent AF and additional cardiovascular risk factors.⁹ EAST-AFNET 4 was a randomized, European, multicenter, parallel-group, open-labelled treatment assignment, blinded-outcome-assessment trial (2011–2016) that assessed the efficacy of comprehensive ERC vs. guideline-based usual care in patients with early AF and additional cardiovascular risk factors.^{10,11} Detailed patient eligibility criteria for the ATHENA and EAST-AFNET 4 trials are shown in [Supplementary material online, Table S1](#). Patients randomized in ATHENA and fulfilling the inclusion criteria of EAST-AFNET 4 (namely first diagnosis of AF within ≤ 12 months and presence of ≥ 2 stroke risk factors) were identified and described as having early AF; patients randomized in ATHENA who had first known AF onset > 12 months were described as having late AF (presence/absence of other inclusion criteria was not assessed). The effectiveness and safety of dronedarone were compared with that of placebo.

Study outcomes

Outcomes were modelled on the primary outcomes of the EAST-AFNET 4 trial. The first co-primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalisation due to worsening of HF or ACS, while the second co-primary outcome was the number of nights spent in hospital per year (with nights in hospital due to cardiovascular causes as a secondary outcome). Other secondary outcomes were the individual components of the first co-primary outcome and SR at 12 months (SR at 24 months is not presented since relatively few ATHENA trial patients remained in the study at that time point). The primary safety outcome was a composite of death from any cause, stroke, or pre-specified serious adverse events of special interest (AESIs) related to rhythm control therapy. Specific details of study definitions and pre-specified AESIs for the ATHENA and EAST-AFNET 4 trials are shown in [Supplementary material online, Table S2](#).

Statistical analysis

Log-rank testing and Cox regression were used to compare the event and hazard rates between the treatment groups. The survival data were plotted as Aalen-Johansen curves (as done for the EAST-AFNET 4 trial)¹⁰ to estimate the cumulative probability of being alive and reaching an endpoint.¹² The individual components of the first co-primary outcome were assessed for statistical significance between treatment groups. An interaction test was performed by combining the ≤ 12 months and > 12 months strata to create a Cox regression model with strata and treatment as main effects and an interaction term of strata by treatment. Nights in hospital were presented as least squares mean, alongside standard error (SE). A landmark analysis was performed to show the cumulative incidence of the primary composite outcome in patients in SR at 12 months in both treatment groups, plotted as Kaplan–Meier curves. Safety data were presented using descriptive statistics, as presented in EAST-AFNET 4.

Results

Demographic and baseline characteristics

Of 2301 patients from the dronedarone arm and 2327 patients from the placebo arm, 1810 patients were categorized as having early AF (924 and 886, respectively) and 917 patients as having late AF (451 and 466, respectively) when entering the trial. A total of 1901 patients either had insufficient information on timing of AF onset (860 in the dronedarone arm and 909 in the placebo arm) or did not match other EAST-AFNET 4 inclusion criteria such as age (66 patients) or stroke risk (66 patients). Details of other inclusion criteria are shown in [Supplementary material online, Table S1](#). Patient disposition is shown in [Figure 1](#).

Median time from first known AF episode to randomisation was similar in both treatment groups (50.0 days for dronedarone and 50.5 days for placebo). Demographic and baseline characteristics in patients with early AF were similar between the treatment groups. Approximately half of all patients were male, and the majority were Caucasian ($> 85\%$ in both treatment groups). Over 85% were hypertensive with a mean CHA₂DS₂VASc score of 3.8 ([Table 1](#)). Approximately 26–29% of patients in each treatment group had a history of stable HF, and

Table 1 Demographic and baseline characteristics, cardiovascular history, and medication history of patients with early AF (onset ≤ 12 months)

Characteristic	Dronedaron (n = 924)	Placebo (n = 886)
Demographic and baseline characteristics/ cardiovascular history		
Age, mean (SD), years	73 (8.2)	73 (8.8)
Male	421 (45.6)	453 (51.1)
Race		
Caucasian	790 (85.5)	754 (85.1)
Asian	72 (7.8)	61 (6.9)
Black	13 (1.4)	21 (2.4)
Other	49 (5.3)	50 (5.6)
BMI ≥ 30 kg/m ²	291 (31.5)	278 (31.4)
Hypertension	815 (88.2)	760 (85.8)
Non-insulin-dependent diabetes mellitus	180 (19.5)	182 (20.5)
Insulin-dependent diabetes mellitus	30 (3.2)	35 (4.0)
eGFR MDRD, mean (SD), mL/min	66.6 (18.4)	66.3 (19.2)
Time since first AF, median (Q1, Q3), days	50.0 (14.5, 114.5)	50.5 (14.0, 122.0)
LVEF, mean (SD), %	58.2 (11.0)	57.1 (12.0)
LVEF, %		
<35%	29 (3.2)	44 (5.1)
$\leq 40\%$ (i.e. HFrEF) ^a	76 (8.3)	106 (12.2)
<45%	97 (10.6)	129 (14.9)
<50%	148 (16.2)	173 (20.0)
Left HF, NYHA class		
Class I	81 (8.8)	60 (6.8)
Class II	128 (13.9)	165 (18.6)
Class III	27 (2.9)	29 (3.3)
No HF	688 (74.5)	632 (71.3)
LAD >40 mm	593 (65.0)	569 (65.9)
CHA ₂ DS ₂ VASc score, mean (SD)	3.8 (1.4)	3.8 (1.4)
Structural heart disease	500 (54.4)	533 (60.7)
Coronary heart disease	260 (28.1)	276 (31.2)
Non-rheumatic valvular heart disease	118 (12.8)	139 (15.7)
Pacemaker	63 (6.8)	56 (6.3)
Ablation for AF	10 (1.1)	18 (2.0)
Medication use		
ACE inhibitors or angiotensin II receptor antagonist	638 (69.0)	596 (67.3)
Beta-blockers (except sotalol)	638 (69.0)	601 (67.8)
Calcium antagonists with HR-lowering effects	142 (15.4)	107 (12.1)
Oral anticoagulants	537 (58.1)	522 (58.9)
	473 (51.2)	469 (52.9)

Continued

Table 1 Continued

Characteristic	Dronedaron (n = 924)	Placebo (n = 886)
Diuretics (excluding spironolactone)		
Low-dose aspirin (≤ 365 mg)	441 (47.7)	386 (43.6)
Statins (CYP3A4 metabolized)	299 (32.4)	305 (34.4)
Digitalis	121 (13.1)	127 (14.3)

Data are n (%) unless otherwise stated and include the total number of patients in dronedarone and placebo groups. Early AF defined as first known AF onset within ≤ 12 months.

ACC, American College of Cardiology; ACE, angiotensin-converting enzyme; AF, atrial fibrillation/atrial flutter; AHA, American Heart Association; BMI, body mass index; CHA₂DS₂VASc, congestive heart failure, high blood pressure, age >75 years, diabetes, previous stroke or clot, vascular disease, age 65–74 years, sex; CYP3A4, cytochrome P450 3A4; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; HR, heart rate; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; MDRD, modification of diet in renal disease; NYHA, New York Heart Association; SD, standard deviation.

^aDefined per ACC/AHA/HFSA 2022 and ESC 2021 guidelines.¹³

76 (8.3%)/106 (12.2%) patients receiving dronedarone/placebo, respectively, had HF with reduced ejection fraction [HFrEF; defined per ACC/AHA/Heart Failure Society of America (HFSA) and ESC guidelines].¹³ The use of oral anticoagulants was similar at baseline in the dronedarone and placebo groups, with 58.1% and 58.9% of patients, respectively, using vitamin K antagonists (VKAs).

Co-primary outcomes

Patients randomized to dronedarone had fewer cardiovascular events than those randomized to placebo [dronedaron: 87 patients with ≥ 1 event, 8.64 events/100 patient-years; placebo: 117 patients with ≥ 1 event, 11.62 events/100 patient-years; unadjusted hazard ratio (HR) 0.71; 95% confidence interval (CI) 0.54–0.94; $P = 0.014$; Figure 2]. For the second co-primary outcome, patients in the dronedarone and placebo groups spent a similar number of nights in hospital overall [least squares mean (SE): 13.4 (0.9); 95% CI 11.6–15.2 vs. 14.0 (0.9); 95% CI 12.3–15.7; $P = 0.39$; Supplementary material online, Figure S1].

Safety

For the primary safety outcome, the number of patients with ≥ 1 pre-specified serious AESI related to rhythm control therapy, stroke, or all-cause death was 60 (6.5%) with dronedarone and 71 (8.0%) with placebo ($P = 0.23$; Table 2; Figure 3).

Secondary outcomes, comparison to late AF

Statistical analyses of the individual components of the primary composite outcome are described in Table 3. Numerically fewer patients assigned to dronedarone experienced any individual component of the primary composite outcome compared with patients assigned to placebo. At 12 months of follow-up, 69.2% ($n/N = 639/924$) of patients assigned to dronedarone were in SR, a higher proportion than the 60.8% ($n/N = 539/886$) of patients assigned to placebo. For nights in hospital due to cardiovascular causes, patients on dronedarone spent 10.3 (1.0; 95% CI 8.2–12.3) nights in hospital compared with

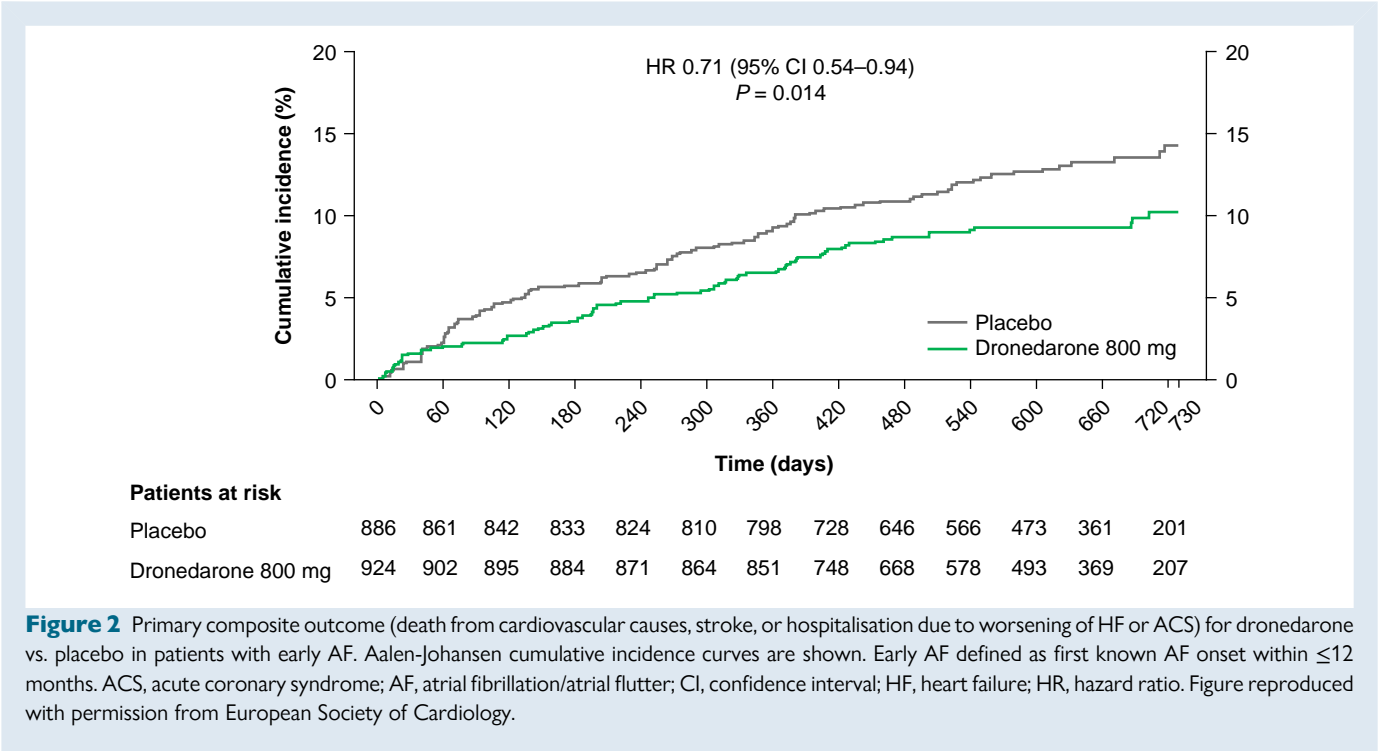


Figure 2 Primary composite outcome (death from cardiovascular causes, stroke, or hospitalisation due to worsening of HF or ACS) for dronedarone vs. placebo in patients with early AF. Aalen-Johansen cumulative incidence curves are shown. Early AF defined as first known AF onset within ≤12 months. ACS, acute coronary syndrome; AF, atrial fibrillation/atrial flutter; CI, confidence interval; HF, heart failure; HR, hazard ratio. Figure reproduced with permission from European Society of Cardiology.

Table 2 Outcomes for the primary safety endpoint in patients with early AF

	Dronedaron (n = 924)	Placebo (n = 886)
Total number of patients with first composite among any death, stroke, or pre-specified serious AESIs related to rhythm control therapy ^a	60 (6.5)	71 (8.0)
Death	53 (5.7)	59 (6.7)
Stroke	10 (1.1)	11 (1.2)
Pre-specified serious AESIs related to rhythm control therapy	2 (0.2)	4 (0.5)
Total number of events among any death, stroke, or pre-specified serious AESIs related to rhythm control therapy/number of patients with events (ratio)	85/60 (1.4)	99/71 (1.4)

Data are n (%) and include the total number of patients in dronedaron and placebo groups. Early AF defined as first known AF onset within ≤12 months. Patients were included in one category only, in the following order of priority: death, stroke, pre-specified AESIs related to rhythm control therapy.
AESI, adverse event of special interest; AF, atrial fibrillation/atrial flutter.
^aPre-specified AESIs related to rhythm control therapy are listed in [Supplementary material online, Table S2](#), aligned with the EAST-AFNET 4 primary safety composite endpoint.

primary composite outcome compared with patients treated with placebo (see [Supplementary material online, Figure S2A](#)). Conversely, patients who were not in SR at 12 months (i.e. still experiencing AF) who were treated with placebo were numerically less likely to experience the primary composite outcome compared with patients treated with dronedaron (see [Supplementary material online, Figure S2B](#)).

In patients with late AF (for whom demographic and baseline characteristics are shown in [Supplementary material online, Table S3](#)), similar, albeit non-significant, results were observed for the primary composite outcome (unadjusted HR 0.79; 95% CI 0.54–1.14; P = 0.206; [Supplementary material online, Figure S3](#)) and for secondary outcomes (see [Supplementary material online, Table S4](#)). There was no interaction between treatment group and early or late AF presentation (P = 0.641). Percentages of safety outcomes were at the same levels in patients with late AF receiving either dronedaron or placebo (see [Supplementary material online, Table S5](#)).

Discussion

Results from this post-hoc analysis of the ATHENA trial show that dronedaron improved cardiovascular outcomes compared with placebo in patients with recently diagnosed AF and cardiovascular risk factors. These results replicate the main findings from the EAST-AFNET 4 trial¹⁰ and support the use of dronedaron as ERC therapy.

Subanalyses of the EAST-AFNET 4 trial showed a consistent effect extended to patients with HF with reduced, mid-range, or preserved ejection fraction (n = 798) and also to asymptomatic patients (n = 801).^{11,14} Dronedaron was not evaluated independently in EAST-AFNET 4, but was one of the most common AADs used to initiate ERC in that trial; 16.7% of patients randomized to ERC were initially treated with dronedaron.¹⁰ A mediator analysis of the EAST-AFNET 4 trial demonstrated that achieving SR was the key mediator of effective ERC; the type of rhythm control therapy, including AF ablation, had a lesser effect. In EAST-AFNET 4, ERC was commonly started with an AAD.^{10,15}

12.0 (0.9; 95% CI 10.1–13.8) nights for patients on placebo [least squares mean (SE)]. Patients in SR at 12 months who were treated with dronedaron were numerically less likely to experience the

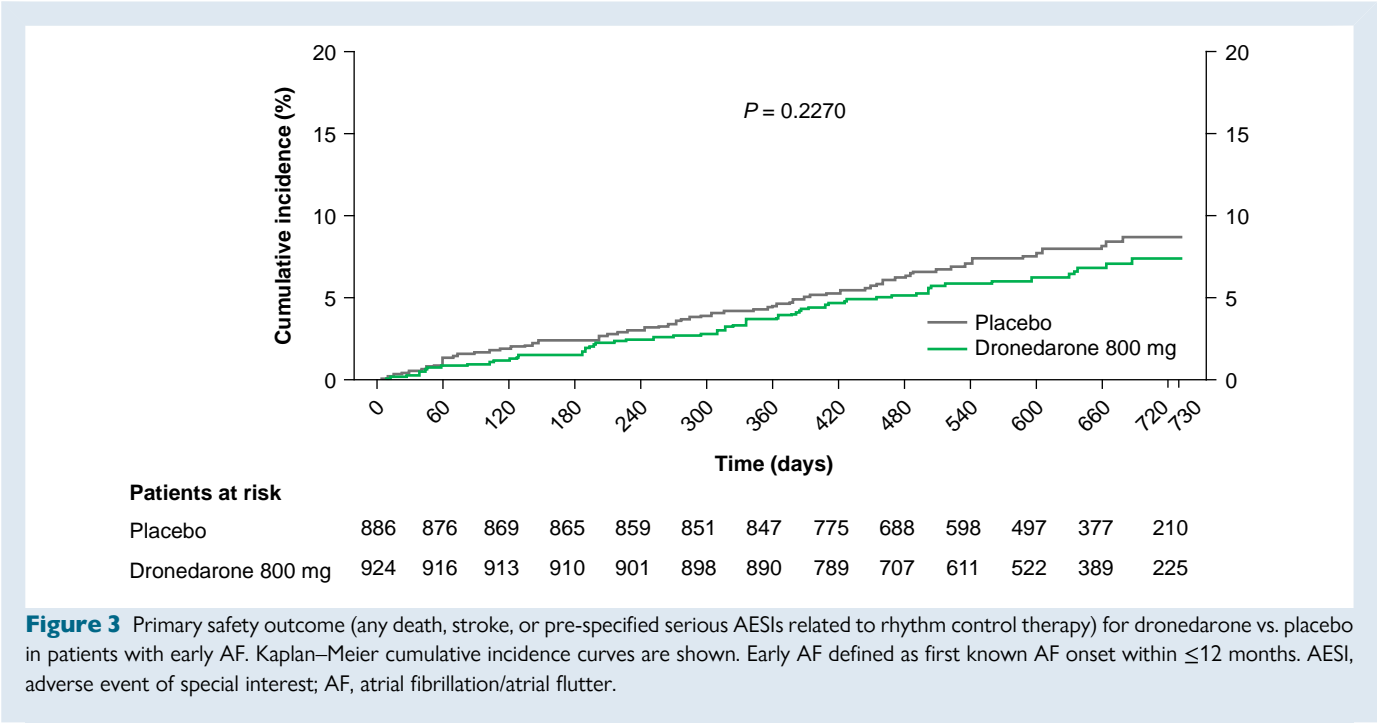


Table 3 Outcomes of the individual components of the primary composite endpoint for patients with early AF

	Number of patients with ≥1 event (%)		HR (95% CI)	P value
	Dronedarone (n = 924)	Placebo (n = 886)		
Cardiovascular death	29 (1.6)	41 (2.3)	0.68 (0.42–1.09)	0.110
Stroke	10 (0.6)	11 (0.6)	0.88 (0.37–2.07)	0.768
HF hospitalisation	48 (2.7)	55 (3.0)	0.84 (0.57–1.24)	0.377
ACS hospitalisation	16 (0.9)	35 (1.9)	0.44 (0.24–0.79)	0.005

Early AF defined as first known AF onset within ≤12 months.
ACS, acute coronary syndrome; AF, atrial fibrillation/atrial flutter; CI, confidence interval; HF, heart failure; HR, hazard ratio.

Patients in the ATHENA post-hoc analysis were slightly older than patients in the EAST-AFNET 4 trial, more likely to be female and had higher CHA₂DS₂-VASc scores; the proportion of patients with BMI ≥30 kg/m² was also slightly higher.¹⁰ Furthermore, a lower proportion of patients in the ATHENA post-hoc analysis had HF, while a higher proportion had pacemakers installed compared with the EAST-AFNET 4 trial population.¹⁰ Median time since first AF was longer in ATHENA post-hoc analysis (by ~2 weeks) than in the EAST AFNET-4 trial.¹⁰ Approximately 90% of patients in EAST-AFNET 4 received anticoagulation at baseline [either direct oral anticoagulants (DOACs) or VKAs]¹⁰ compared with ~60% of patients in this ATHENA post-hoc analysis (VKAs only); this is explained by the non-availability of DOACs when the ATHENA trial was conducted, less awareness about the benefits of anticoagulation vs. risk of bleeding, and changes in the recommendations for stroke prevention during this time frame compared with current guidelines. Although there were differences in their use, anticoagulant treatment was balanced between treatment groups in this analysis, unlike the withdrawal of oral anticoagulation in the AFFIRM trial that probably contributed to the

neutral outcome of that trial,¹⁶ even in patients with recently diagnosed atrial fibrillation.¹⁷ Nights spent in hospital did not differ between treatment groups in this analysis, similar to the neutral effect of ERC on the same outcome in the EAST-AFNET 4 trial.¹⁰ Study drug was initiated as outpatient treatment in ATHENA,⁹ similar to the outpatient initiation of AADs in most centres in the EAST-AFNET 4 trial.¹⁵ A recent subanalysis of the EAST-AFNET 4 trial found that SR at 12 months was the most relevant mediator of ERC effectiveness and was responsible for 81% of treatment effect vs. usual care during the 4.1-year follow-up period.¹⁸ In the current analysis, a greater proportion of patients receiving dronedarone were in SR at 12 months compared with patients receiving placebo (69.2% vs. 60.8%), and patients on dronedarone who were in SR at 12 months were less likely than those on placebo to subsequently experience the primary composite outcome. It appears that surviving patients who were in SR at 12 months benefitted significantly from dronedarone in terms of event-free survival. This may possibly relate to better prevention of atrial fibrillation recurrence with

dronedarone vs. placebo. In contrast, patients who received dronedarone and were experiencing atrial fibrillation at 12 months displayed a higher incidence of the primary composite outcome vs. placebo. Dronedarone has a well-documented rhythm-controlling effect in patients with atrial fibrillation.^{19–22} While the findings of this analysis suggest that attaining SR mediates in part the effect of ERC, precise data on recurrent atrial fibrillation are not available in ATHENA, and so these findings are to be considered hypothesis-generating in nature.

It should be noted that the majority of patients (85.3%) were Caucasian, which may limit generalizability of these results. However, the efficacy and tolerability of dronedarone in the Asian population of ATHENA (7.3% of patients) were previously assessed and found to be consistent with results observed in the non-Asian population,²³ suggesting the results of the current analysis may be relevant to other populations. In other ATHENA subanalyses, dronedarone has been associated with reduced progression to permanent AF and increased regression to SR vs. placebo.²⁴ Risk of cardiovascular hospitalisation or death due to any cause was similarly reduced with dronedarone vs. placebo independent of sex and was also reduced with dronedarone vs. placebo in patients aged <65 or ≥65 years, with a greater effect in the latter group (although incidence of treatment-emergent adverse events was also higher in the older patient population).²⁵ Additionally, real-world data shows that dronedarone is as effective as other AADs (i.e. amiodarone, flecainide, propafenone, and sotalol) in patients with atrial fibrillation²⁶ and has been suggested as a potentially safer/more effective post-ablation treatment option vs. sotalol based on a comparative analysis of the two agents.²⁷

The present analysis does have limitations. First, this is a post-hoc analysis, and as mentioned, the ATHENA trial did not primarily evaluate rhythm control with dronedarone vs. placebo, nor ERC *per se*. Hence, a significant number of patients in the ATHENA trial did not fit the EAST-AFNET 4 inclusion criteria (most commonly due to lack of information regarding timing of AF onset) and were therefore excluded from this analysis. However, the sample size is still one of the largest seen in a placebo-controlled trial of an AAD. Furthermore, some adverse safety events of interest in EAST-AFNET 4, like hospitalisation for atrial fibrillation (pro-arrhythmia) or HF (worsening after AAD initiation), could not be validated in this analysis and have hence been excluded. Second, the nature of the control group varied between ATHENA and EAST-AFNET 4; in ATHENA, dronedarone was compared with placebo, whilst in EAST-AFNET 4, ERC was compared with usual care including symptom-directed therapy with AADs and AF ablation. Third, as previously mentioned, the proportion of patients treated with VKAs (e.g. warfarin) in ATHENA was lower than that of more recent trials such as EAST-AFNET 4, which also included anticoagulation with DOACs. Changes in the management of atrial fibrillation (and the rise in OAC use with the advent of DOACs) since the ATHENA trial was conducted may mean that dronedarone could have a different effect in contemporary patients with atrial fibrillation compared with the ATHENA population. Furthermore, this analysis cannot answer the question of whether dronedarone, or other types of rhythm control therapy, are effective when initiated late after a first diagnosis of AF. While no interaction was observed between randomized treatment and early or late AF diagnosis, this analysis was underpowered as only 917 patients had late AF. Finally, the definitions of the outcomes evaluated in this analysis differ from those specified in the ATHENA trial (details available in [Supplementary material online, Table S2](#)), and thus, the interpretation of these results may vary across different patient subgroups.

Overall, the results from this post-hoc analysis of the ATHENA trial using EAST-AFNET 4 inclusion criteria and outcomes support the effectiveness and safety of dronedarone compared with placebo for ERC in patients with early AF, reducing cardiovascular outcomes without an increase in serious AESIs related to rhythm control therapy

according to EAST-AFNET 4 criteria. Further data are needed to evaluate the outcome-reducing effect of rhythm control therapy in patients with longer durations of AF.

Supplementary material

[Supplementary material](#) is available at *Europace* online.

Author contributions

All authors had access to relevant data, contributed critically to the development of the manuscript, and approved it for submission. All authors were equally involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical review of the manuscript for important intellectual content.

Acknowledgements

Coordination of the development of this manuscript, facilitation of author discussion, and critical review were provided by Charlotte Singh, MD, CMPP and Karen Finnegan, PhD, CMPP at Sanofi. The authors acknowledge medical writing and editorial assistance provided by Hanna Mourad-Agha, PhD, CMPP, of Fishawack Communications Ltd, part of Avalere Health, funded by Sanofi. The authors were responsible for all content and editorial decisions and received no honoraria related to the development of this publication.

Funding

This analysis was funded by Sanofi.

Conflict of interest: P.K.: Grants and non-financial support from BMBF (German Ministry of Education and Research) and EHRA (European Heart Rhythm Association); grants from Sanofi, Abbott, German Heart Foundation, DZHK (German Centre for Cardiovascular Research) during the conduct of the study; grants from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK); non-financial support from German Centre for Heart Research outside the submitted work. P.K. also has a patent Atrial Fibrillation Therapy WO 2015140571 issued to University of Birmingham and a patent Markers for Atrial Fibrillation WO 2016012783 issued to University of Birmingham. A.J.C.: Consulting fees from Abbott, Allergan, Acesion Pharma, Bayer, Boston Scientific, Daiichi-Sankyo, HUYABIO, InCarda, Johnson and Johnson, Medtronic, Menarini, Milestone, Pfizer, Sanofi; institutional grants from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Pfizer/Bristol Myers Squibb. H.J.G.M.C.: Advisor/speaker for AtriCure, Cardialis, InCarda Therapeutics, Roche Diagnostics, Medtronic, Sanofi, Acesion Pharma. J.P.P.: Supported by R01AG074185 from the National Institutes of Aging; grants for clinical research from Abbott, American Heart Association, Bayer, Boston Scientific, iRhythm, Philips. Consultant to Abbott, AbbVie, Abbacon, AltaThera, ARCA biopharma, Bayer, Biotronik, Boston Scientific, Bristol Myers Squibb/MyoKardia, Element Science, Medtronic, Milestone, ElectroPhysiology Frontiers, ReCor, Sanofi, Philips, UpToDate. C.T.-P.: Grants for studies from Bayer and Novo Nordisk. D.S.M., M.W.: Employees of Sanofi and may hold shares and/or stock options in the company. S.H.H.: Consulting fees from Bayer Healthcare, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Johnson & Johnson, Pfizer, Sanofi-Aventis, Servier, Zoli; lecture fees from Abbott, Bayer Healthcare, Boehringer Ingelheim, Bristol Myers Squibb, Medtronic, Pfizer, Sanofi-Aventis.

Data availability

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

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