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Safety and efficacy of amiodarone and dronedarone for early rhythm control in EAST-AFNET 4

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Abstract

Aims Concerns exist about the safety of amiodarone and dronedarone. We assessed the long-term outcome of both drugs for early rhythm control (ERC) in the EAST-AFNET 4 trial.

Methods and Results Patients randomized for ERC and treated with amiodarone or dronedarone were compared to other ERC-therapies. Patients receiving amiodarone or dronedarone at initial therapy (n = 653/1395) were older with more comorbidities and less paroxysmal atrial fibrillation (AF, 29%) compared to patients never receiving amiodarone or dronedarone (Amiodarone/Dronedarone^{never}, 43% paroxysmal AF). Patients treated with amiodarone had more often heart failure (HF, 42%) and persistent AF (40%) compared to patients treated with dronedarone (16% HF, 15% persistent AF) and Amiodarone/Dronedarone^{never} (25% HF, 22% persistent AF). 115/398 amiodarone-treated patients (6.7/100 patient-years) and 51/255 dronedarone-treated patients (4.2/100 patient-years) experienced a primary efficacy outcome (cardiovascular death, stroke, HF-hospitalization or acute coronary syndrome), while 98/398 (5.3/100 patient-years) and 43/255 (3.4/100 patient-years) experienced a primary safety outcome (death, stroke or serious adverse events related to rhythm-control therapy). Serious adverse events related to drug therapy were similar for amiodarone (1.4/100 patient-years), dronedarone (1.2/100 patient-years), and other ERC (0.8/100 patient-years). Dronedarone (hazard ratio (HR) 0.5; CI 0.28–0.91), age (HR 1.05; CI 1.03–1.07), coronary artery disease (HR 1.84; CI 1.38–2.46) and stable HF (HR 1.66; CI 1.28–2.16) were associated with

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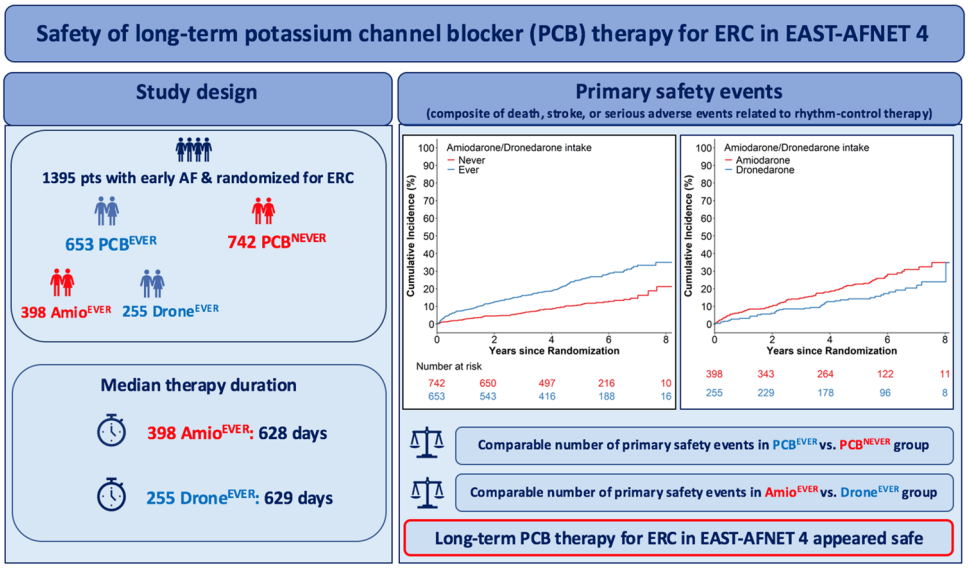
efficacy outcome upon multivariate Cox regression. Age (HR 1.07; CI 1.05–1.09) and left ventricular hypertrophy (HR 1.94; CI 1.13–3.32) were associated with safety outcome.

Conclusion Early rhythm control using amiodarone or dronedarone rarely led to drug-related serious adverse events in EAST-AFNET 4.

Clinical Trial Registration: ISRCTN04708680, NCT01288352, EudraCT2010-021258-20.

Graphical abstract

Central illustration



Keywords Atrial fibrillation · Anti-arrhythmic drug therapy · Amiodarone · Dronedarone · Safety

Introduction

Systematic use of early rhythm control therapy in the first year after diagnosing atrial fibrillation (AF) reduces cardiovascular events in patients with stroke risk factors compared to usual care in the EAST-AFNET 4 trial [1] and early rhythm control emerges as a new treatment paradigm in patients with AF[2, 3]. The positive effects have been observed in particular in patients with heart failure and in patients with a high comorbidity burden [4, 5]. These observations enhance the need for effective and safe rhythm control therapies in older patients with AF and multiple comorbidities. Access to AF ablation, the most effective rhythm control therapy [6], will remain limited to selected patients in the foreseeable future. Therefore, antiarrhythmic drugs (AADs) will remain necessary to deliver rhythm control therapy in patients with AF [1, 7]. Concerns regarding the efficacy of current AADs compared pulmonary vein ablation [6] and their safety, including serious proarrhythmic effect and increased rates of mortality [8, 9], remain common and slow the adoption of early rhythm control therapy.

Amiodarone is an iodinated benzofuran derivative and presently the most effective AAD [10, 11], inhibiting multiple ion channels (I_{Kr}, I_{Na}, I_{Ks}, I_{to}, I_{K1}, I_{Ca}, I_{KAch}) and the autonomic nervous system (α- and ß-adrenoreceptor). Amiodarone is recommended especially for rhythm control in symptomatic AF patients with structural heart disease. Unfortunately, toxic side effects limit its use [12, 13]. Dronedarone is a non-iodinated benzofuran derivative with a comparable ion channel-inhibiting profile similar to amiodarone, but with different relative effects on individual ion channels [14]. The structural change of dronedarone when compared to amiodarone decreases lipophilicity, resulting in a shortened half-life and reduced tissue accumulation. This pharmacodynamics profile and the lower iodine content of dronedarone can reduce toxicity compared to amiodarone [15, 16]. Dronedarone prevents recurrent AF [17, 18], is shown to prevent AF progression [19], and reduces a composite of hospitalization due to cardiovascular events or death in AF patients [20, 21] with positive effects on stroke identified in a post hoc analysis [22]. Dronedarone was shown to be improve clinical outcomes in particular among patients aged > / = 65 years and regardless of sex [23]. Dronedarone is associated with reduced cardiovascular events in patients with paroxysmal or persistent AF and heart failure [24]. However, dronedarone increased mortality

when used in patients with permanent AF and severe heart failure and without restoring sinus rhythm [8]. Nevertheless, dronedarone is less effective in maintaining sinus rhythm than amiodarone [25]. A Cochrane library review [26] about antiarrhythmic medication in AF confirms a lower efficacy (Mantel–Haenszel risk ratio (RR) for AF-recurrence; dronedarone RR 0.85, amiodarone RR 0.52 vs. placebo respectively), but also suggests lower adverse events (RR 1.58 and RR 6.70), lower all-cause-mortality (RR 0.86 vs. RR 1.66) and lower risk of stroke (RR 0.66 vs. RR 1.15) with dronedarone. Unfortunately, most of the trials were conducted in an era when anticoagulation was discontinued after "successful" restoration of sinus rhythm [27]. There are few data on use of amiodarone and dronedarone in combination with novel oral anticoagulants [28, 29]. Safety and efficacy of amiodarone and dronedarone to deliver early rhythm control therapy in a contemporary population are not known.

In this sub-analysis of the EAST-AFNET 4 trial, we therefore evaluated the long-term efficacy and safety of amiodarone and dronedarone initiated as early rhythm control therapy.

Methods

The full methods of the EAST-AFNET 4 trial have been published [1]. All patients participating in the trial gave written informed consent. The trial was approved by an ethics committee at all institutions. EAST-AFNET 4 randomized 2789 patients in an international, investigator-initiated, parallel-group, randomized, open, blinded outcome assessment trial design. Patients included in the trial had AF diagnosed within 12 months prior to randomization and at least two risk factors approximating a CHA_2DS_2-VASc score of 2 or higher. Randomization was performed in a one-to-one fashion to either ERC therapy (ERC, n = 1395) or usual care (UC; n = 1394) [1]. ERC in the EAST-AFNET 4 trial consisted of AAD therapy, electrical cardioversion, or AF ablation. The initial therapy was selected by site investigators and followed local procedures. In patients assigned to usual care, rate control was the initial strategy and rhythm control was used to improve symptoms following guideline recommendations. The trial protocol provided clear guidance on dosing and loading of antiarrhythmic drugs, and suggestions for safe selection of antiarrhythmic drug therapy (available as a supplement to (1)). Dronedarone was used in its approved dosage (400 mg bid). The study protocol recommended amiodarone loading based on the schemes used in EMIAT (600 mg for 6 weeks, 400 mg for 4 weeks, then 200 mg per day [1]).

The underlying analysis focused on patients randomized to ERC. To assess safety and efficacy of these drugs, patients treated with amiodarone or dronedarone (Amiodarone/Dronedarone^{EVER}, n = 653) as initial therapy of ERC were compared to patients who never took amiodarone or dronedarone during the course of the study, but received other ERC therapies (Amiodarone/Dronedarone^{NEVER}, n = 742). In addition, efficacy and safety were further compared between amiodarone and dronedarone. Outcomes included the primary efficacy outcome (cardiovascular death, stroke and hospitalization for worsening of heart failure (HF) or acute coronary syndrome) and the safety outcome (death, stroke, or serious adverse events related to rhythm-control therapy) with a focus on therapy-related adverse events [1].

Safety events were systematically captured as required by the German drug trial regulator (BfArm) and all serious adverse events related to ERC were centrally adjudicated, including their relation to rhythm control therapy. Pre-specified serious adverse events related to antiarrhythmic drug therapy included drug- induced proarrhythmia (torsade de pointes, ventricular tachycardia or ventricular fibrillation), AV block, drug-induced atrial arrhythmias (e.g., atrial flutter), drug-induced bradycardia or syncope and strokes related to rhythm control procedures. Extracardiac side effects (e.g., thyroid, liver, pulmonary) were captured when they led to discontinuation of therapy or led to hospitalization [1]. Adverse events were considered to be serious when they resulted in death, were life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability, incapacity, a congenital anomaly or birth defect, or were judged a medically important event [1].

Statistical analyses

This analysis included all 2789 patients randomized in the EAST-AFNET 4 trial, and categorized patients to either Amiodarone/Dronedarone intake at baseline, Amiodarone/Dronedarone intake later during follow-up or never receiving amiodarone or dronedarone during the study period. Patients randomized to ERC (n = 1395) were used for further analysis. As no relevant differences were observed between patients with Amiodarone/Dronedarone intake at baseline and Amiodarone/Dronedarone intake later during follow-up (see supplementary tables), these two groups were combined into one group (Amiodarone/Dronedarone^{EVER}, n = 653) and compared to patients without any Amiodarone/Dronedarone intake during the study period (Amiodarone/Dronedarone^{NEVER}, n = 742).

Patients' baseline characteristics were summarized with descriptive statistical methods. Categorical data are summarized as absolute and relative frequencies and continuous variables were described by mean and standard deviation or median, 1st and 3rd quartiles. Duration of Amiodarone/Dronedarone intake was calculated as median according to

the starting date of drug intake at baseline. The p values shown are calculated from mixed linear regression models for continuous variables and mixed (ordinal) logistic regression models for categorical variables with sites included as random effect. For categorical variables with more than two categories (not ordinal), a random effect was not included.

The primary efficacy and safety outcomes of the EAST-AFNET 4 trial randomized to early rhythm control (n = 1395) were separately analyzed for patients with Amiodarone/Dronedarone intake (Amiodarone/Dronedarone^{EVER}, n = 653) or no Amiodarone/Dronedarone intake (Amiodarone/Dronedarone^{NEVER}, n = 742). For the primary efficacy outcomes and its individual components (death from cardiovascular causes, stroke, hospitalization with worsening of heart failure, hospitalization with acute coronary syndrome) as well as the primary safety outcomes (stroke, death and serious adverse event of special interest related to rhythm control therapy), we used Cox regression models with a time-dependent term for Amiodarone/Dronedarone intake for patients from the ERC group. Additionally, the models were expanded with adjustment for age, gender, CAD, LV hypertrophy and stable heart failure. The coefficients are expressed as hazard ratios with a 95% confidence interval.

Key secondary outcomes (LVEF, quality of life) as well as ECG parameters were analyzed using mixed linear models for repeated outcomes with a term indicating the initial intake of amiodarone vs. dronedarone vs. never and site and subject as a random effect.

Patients who were randomly assigned to ERC therapy were asked to transmit a patient-operated single-lead electrocardiogram (Vitaphone) twice per week and when symptomatic. All abnormal ECG recordings were forwarded to the study site. Documentation of recurrent atrial fibrillation triggered an in-person visit from the site team to escalate rhythm-control therapy as clinically indicated. Intra-individual changes in ECG parameters were calculated for each patient with an ECG available prior to therapy initiation and on therapy with amiodarone or dronedarone to quantify drug-related ECG changes independent of the inter-individual variability of ECG parameters. The ECG analysis was performed individually by each center, without restrictions to automated analysis or evaluation of a cardiologist.

Further, for the key secondary outcomes, a multiplied imputed dataset after 60 imputations of missing values for a set of variables based on suggestions by White, Royston, and Wood (see statistical analysis plan in the supplement of [1]) was used. Statistics software R version 4.1.0. was used for all analyses. All analyses reported were performed in the final, locked data set assigning patients to therapy group based on the randomization (intention-to-treat population). Data will be made available on reasonable request (contact: info@kompetenznetz-vorhofflimmern.de).

Results

Treatment with amiodarone and dronedarone in EAST-AFNET 4

A total of 653/1395 patients (47%) randomized to early rhythm control therapy received amiodarone or dronedarone during the course of the study (Amiodarone/Dronedarone^{EVER}), whereas 742/1395 patients never received amiodarone or dronedarone (Amiodarone/Dronedarone^{NEVER}, Fig. 1). Amiodarone therapy was given to 398 patients (Amio^{EVER}) and continued for a median of 628 (178; 1563) days. Dronedarone was administered to 255 patients (Drone^{EVER}) and continued for a median of 629 (124; 1674) days (Fig. 2). 428 patients of the ERC group started Amiodarone/Dronedarone intake at baseline and stayed on the same drug during the entire follow-up (amiodarone n = 264, dronedarone n = 164). The choice of amiodarone and dronedarone varied by country with clear national preferences of amiodarone or dronedarone (Supplementary Fig. 1). 6/11 (55%) of all participating countries prescribed amiodarone only.

Patients in the ERC group receiving amiodarone or dronedarone at initial therapy (Amiodarone/Dronedarone^{EVER}; n = 653) were older with more comorbidities and less paroxysmal AF (age 71 [8] years; CHA_2DS_2-VASc 3.6 (1.4); 32% HF; 29% paroxysmal AF) compared to patients never receiving amiodarone or dronedarone (Amiodarone/Dronedarone^{NEVER}, n = 742; age 69 [8] years; CHA_2DS_2-VASc 3.2 (1.2), 25% HF, 43% paroxysmal AF, Table 1). Patients treated with amiodarone more often had HF and more often suffered from persistent AF (40% persistent AF, 42% HF) compared to patients treated with dronedarone (15% persistent AF, 16% HF, Table 2), reflecting restrictions for the use of dronedarone in these patients. Amiodarone was preferred to dronedarone in patients with LVEF 40–50% (Supplementary Fig. 1). A bit more than half of the patients treated with amiodarone had conditions or co-medications that interact with amiodarone (8.4% COPD, 13% warfarin, 26% simvastatin, 3.9% QTc > 400 ms). Interacting conditions and medications were present in 11.8% of patients treated with dronedarone (1.4% LVEF < 40%; 6.1% dabigatran; 2.9% QTc > 500 ms, Table 2) (Table 3).

Primary efficacy and safety outcomes in patients receiving amiodarone or dronedarone

Of 398 patients treated with amiodarone, 115 (6.7/100 person-years) experienced a primary efficacy outcome and 98 (5.3/100 person-years) experienced a primary safety

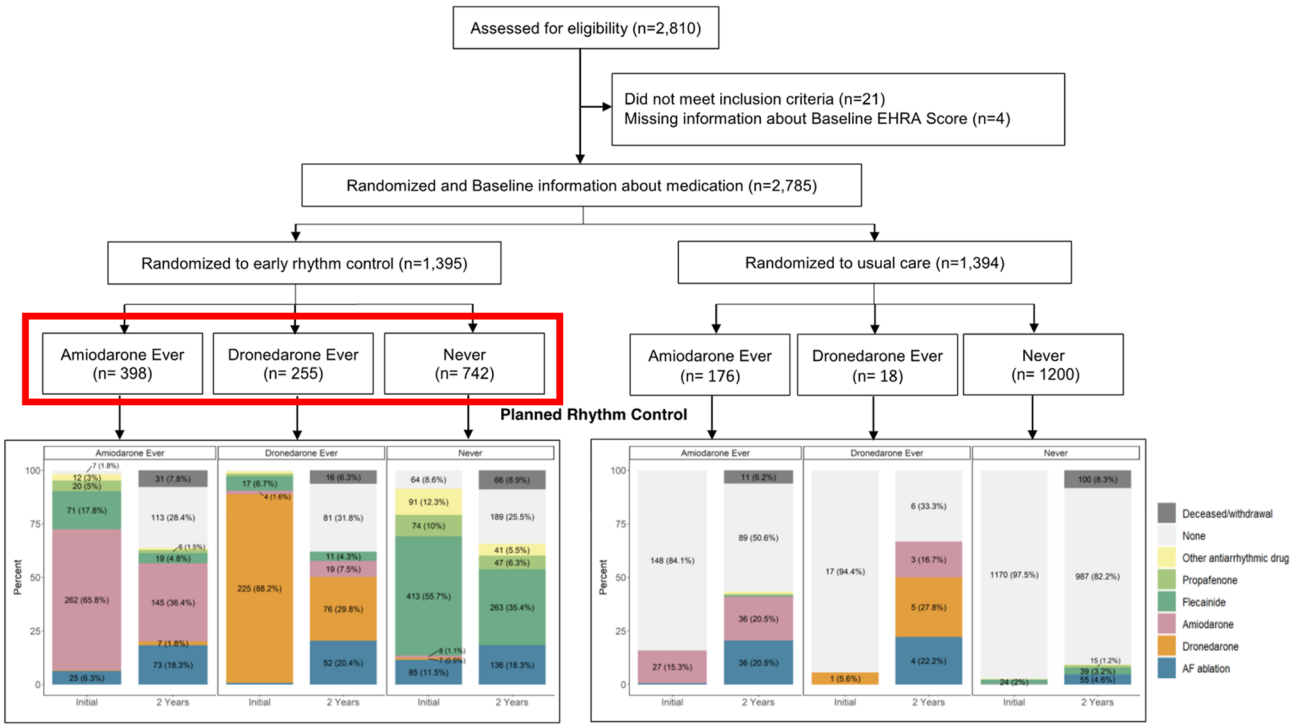


Fig. 1 CONSORT flow chart of the analysis

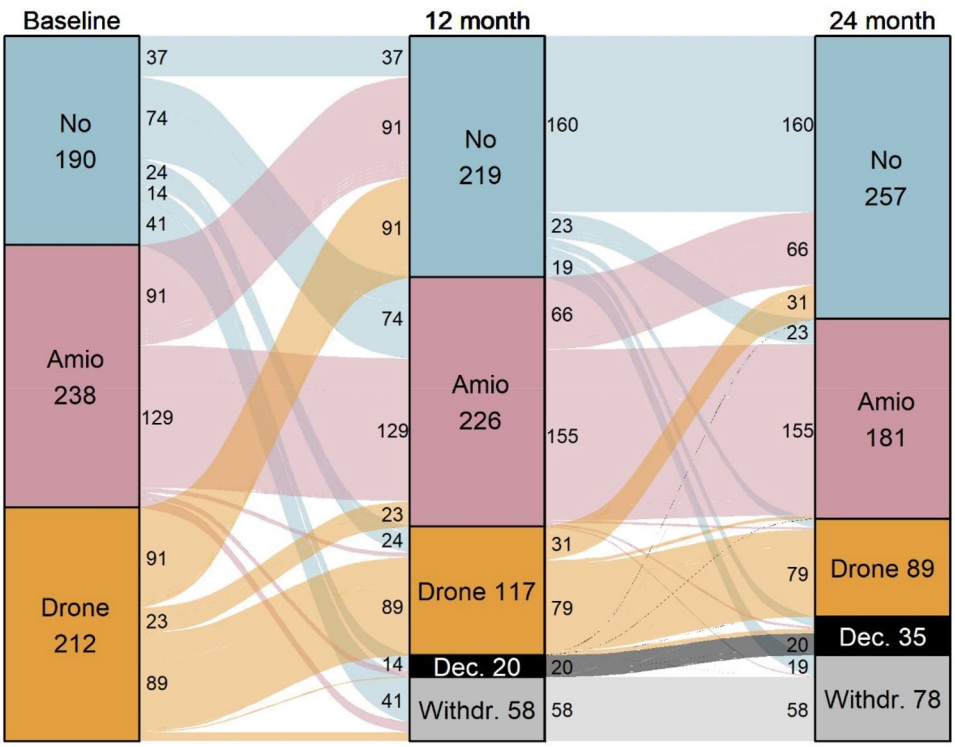


Fig. 2 Changes in drug agent, discontinuation of drug therapy (No), withdrawal (Withdr.) or deceased (Dec.) in ERC group with Amiodarone/Dronedarone intake as initial therapy

Table 1 Demographic and clinical characteristics of patients with and without potassium channel blocker (PCB) intake of patients treated with early rhythm control

Characteristic	Overall N = 1.395[1]	ERC ONLY: Amiodarone/Dronedarone Intake		p-value[2]
		EVER N = 653 (47%)[1]	NEVER N = 742 (53%)[1]	
Age	70 (8)	71 (8)	69 (8)	< 0.001
Gender				0.075
Female	645/1.395 (46%)	291/653 (45%)	354/742 (48%)	
Male	750/1.395 (54%)	362/653 (55%)	388/742 (52%)	
Body Mass Index (calculated) [kg/m^2]	29.2 (5.4)	29.6 (5.4)	28.9 (5.4)	0.015
AF type				< 0.001
First episode	528/1.391 (38%)	269/653 (41%)	259/738 (35%)	
Paroxysmal	501/1,.391 (36%)	187/653 (29%)	314/738 (43%)	
(Long-standing) persistent	362/1.391 (26%)	197/653 (30%)	165/738 (22%)	
Sinus rhythm at baseline	762/1.389 (55%)	298/653 (46%)	464/736 (63%)	< 0.001
Median days since AF diagnosis (IQR)	36 (6, 114)	27 (5, 97)	43 (8,122)	< 0.001
Absence of atrial fibrillation symptoms	395/1.305 (30%)	194/623 (31%)	201/682 (29%)	0.41
Previous pharmacological or electrical cardioversion	546/1.364 (40%)	245/636 (39%)	301/728 (41%)	0.17
Previous stroke or transient ischemic attack	175/1.395 (13%)	91/653 (14%)	84/742 (11%)	< 0.001
At least mild cognitive impairment	582/1.326 (44%)	296/624 (47%)	286/702 (41%)	0.24
Arterial hypertension	1.230/1.395(88%)	580/653 (89%)	650/742 (88%)	0.70
Stable heart failure	396/1.395 (28%)	212/653 (32%)	184/742 (25%)	< 0.001
HFrEF	57/396 (14%)	42/212 (20%)	15/184 (8.2%)	0.051
HFmrEF	110/396 (28%)	68/212 (32%)	42/184 (23%)	0.37
HFpEF	224/396 (57%)	101/212 (48%)	123/184 (67%)	0.074
CHA_2DS_2-VASc score	3.36 (1.30)	3.56 (1.36)	3.18 (1.22)	< 0.001
Chronic kidney disease of MDRF stage 3 or 4	172/1.395 (12%)	91/653 (14%)	81/742 (11%)	0.041
Severe coronary artery disease (previous myocardial infarction, CABG or PCI)	243/1.395 (17%)	148/653 (23%)	95/742 (13%)	< 0.001
LV hypertrophy on echocardiography (> 15 mm wall thickness)	65/1.395 (4.7%)	41/653 (6.3%)	24/742 (3.2%)	0.14
Medication at discharge				
Oral anticoagulation with NOAC or VKA	1.267/1,389 (91%)	598/653 (92%)	669/736 (91%)	0.25
Digoxin or digitoxin	46/1.389 (3.3%)	23/653 (3.5%)	23/.736 (3.1%)	0.35
Beta blockers	1.058/1.389 (76%)	493/653 (75%)	565/736 (77%)	0.35
ACE inhibitors or angiotensin II receptor blocker	953/1.389 (69%)	457/653 (70%)	496/736 (67%)	0.38
Mineralocorticoid receptor antagonist	90/1.389 (6.5%)	54/653 (8.3%)	36/.736 (4.9%)	0.004
Diuretic	559/1.389 (40%)	306/653 (47%)	253/736 (34%)	< 0.001
Statin	628/1.389 (45%)	301/653 (46%)	327/736 (44%)	0.13
Platelet inhibitor	229/1.389 (16%)	135/653 (21%)	94/736 (13%)	< 0.001
Oral antidiabetics	228/1.389 (16%)	122/653 (19%)	106/736 (14%)	0.027

[1]Mean (SD) or Frequency with no./total no. (%)[2]

[2]p-values resulting from mixed linear or logistic regression models and Analysis of Deviance Table (Type II Wald chisquare tests). For categorical variables with more than two categories (not ordinal) random effect is not included (Pearson's Chi-squared test)

outcome. Serious adverse events related to amiodarone therapy occurred in 26 (1.4/100 patient-years) patients, mainly drug toxicity [6] and bradycardia [4]. Of 255 patients treated with dronedarone, 51 (4.2 incidence/100 patient-years) experienced a primary efficacy outcome and 43 (3.4/100 patient-years) experienced a primary safety outcome. Serious adverse events related to dronedarone therapy occurred in 15 patients (1.2/100 patient-years), mainly bradycardia [4] and drug toxicity (2, Fig. 3, Tables 4 and 5). Multivariate Cox regression analyses in all ERC patients identified dronedarone (Hazard Ratio (HR) 0.5; CI 0.28–0.91), age (HR 1.05; CI 1.03–1.07), coronary artery disease (HR 1.84, CI 1.38–2.46) and

Table 2 Demographic and clinical characteristics of patients ever and never receiving amiodarone or dronedarone during EAST-AFNET 4

Characteristic	Overall, N = 1.395[1]	ERC ONLY			p-value[2]
		Amio^{EVER} N = 398 (29%)[1]	Drone^{EVER} N = 255 (18%)[1]	Amio/Drone^{NEVER} N = 742 (53%)[1]	
Age	70 (8)	71 (8)	71 (8)	69 (8)	0.003
Gender					0.065
Female	645/1.395 (46%)	165/398 (41%)	126/255 (49%)	354/742 (48%)	
Male	750/1.395 (54%)	233/398 (59%)	129/255 (51%)	388/742 (52%)	
Body Mass Index (calculated) [kg/m^2]	29.2 (5.4)	29.7 (5.4)	29.4 (5.3)	28.9 (5.4)	0.037
AF type					< 0.001
First episode	528/1.391 (38%)	147/398 (37%)	122/255 (48%)	259/738 (35%)	
Paroxysmal	501 / 1,391 (36%)	92 / 398 (23%)	95 / 255 (37%)	314 / 738 (43%)	
(Long-standing) Persistent	362/1.391 (26%)	159 / 398 (40%)	38 / 255 (15%)	165 / 738 (22%)	
Sinus rhythm at baseline	762/1.389 (55%)	145/398 (36%)	153/255 (60%)	464/736 (63%)	< 0.001
Median days since AF diagnosis (IQR)	36 (6, 114)	34 (7, 108)	20 (3, 74)	43 (8, 122)	< 0.001
Absence of atrial fibrillation symptoms	395/1.305 (30%)	120/381 (31%)	74/242 (31%)	201/682 (29%)	0.68
Previous pharmacological or electrical cardioversion	546/1.364 (40%)	183/387 (47%)	62/249 (25%)	301/728 (41%)	< 0.001
Previous stroke or transient ischemic attack	175/1.395 (13%)	54/398 (14%)	37/255 (15%)	84/742 (11%)	< 0.001
At least mild cognitive impairment	582/1.326 (44%)	177/377 (47%)	119/247 (48%)	286/702 (41%)	0.49
Arterial hypertension	1.230/1.395 (88%)	348/398 (87%)	232/255 (91%)	650/742 (88%)	0.69
Stable heart failure	396/1.395 (28%)	165/398 (41%)	47/255 (18%)	184/742 (25%)	< 0.001
HFrEF	57/396 (14%)	38/165 (23%)	4/47 (8.5%)	15/184 (8.2%)	0.003
HFmrEF	110/396 (28%)	53/165 (32%)	15/47 (32%)	42/184 (23%)	0.62
HFpEF	224/396 (57%)	74/165 (45%)	27/47 (57%)	123/184 (67%)	0.049
CHA_2DS_2-VASc score	3.36 (1.30)	3.65 (1.38)	3.43 (1.30)	3.18 (1.22)	< 0.001
Chronic kidney disease of MDRF stage 3 or 4	172/1.395 (12%)	60/398 (15%)	31/255 (12%)	81/742 (11%)	0.090
Severe coronary artery disease (previous myocardial infarction, CABG or PCI)	243/1.395 (17%)	88/398 (22%)	60/255 (24%)	95/742 (13%)	< 0.001
LV hypertrophy on echocardiography (> 15 mm wall thickness)	65/1.395 (4.7%)	24/398 (6.0%)	17/255 (6.7%)	24/742 (3.2%)	0.33
Medication at discharge					
Oral anticoagulation with NOAC or VKA	1.267/1.389 (91%)	378/398 (95%)	220/255 (86%)	669/736 (91%)	0.067
Digoxin or digitoxin	46/1.389 (3.3%)	19/398 (4.8%)	4/255 (1.6%)	23/736 (3.1%)	0.12
Beta blockers	1.058/1.389 (76%)	298/398 (75%)	195/255 (76%)	565/736 (77%)	0.64
ACE inhibitors or angiotensin II receptor blocker	953/1.389 (69%)	285/398 (72%)	172/255 (67%)	496/736 (67%)	0.32
Mineralocorticoid receptor antagonist	90/1.389 (6.5%)	44/398 (11%)	10/255 (3.9%)	36/736 (4.9%)	< 0.001
Diuretic	559/1.389 (40%)	205/398 (52%)	101/255 (40%)	253/736 (34%)	< 0.001
Statin	628/1.389 (45%)	193/398 (48%)	108/255 (42%)	327/736 (44%)	0.25
Platelet inhibitor	229/1.389 (16%)	76/398 (19%)	59/255 (23%)	94/736 (13%)	< 0.001
Oral antidiabetics	228/1.389 (16%)	82/398 (21%)	40/255 (16%)	106/736 (14%)	0.034

[1]Mean (SD) or Frequency with no./total no. (%)

[2]p-values resulting from mixed linear or logistic regression models and Analysis of Deviance Table (Type II Wald chisquare tests). For categorical variables with more than two categories (not ordinal) random effect is not included (Pearson's Chi-squared test)

stable HF (HR 1.66; CI 1.28–2.16) as factors associated with the first primary efficacy outcome (Fig. 4A, Supplement Table 2), and age (HR 1.07; CI 1.05–1.09) and left ventricular hypertrophy (HR 1.07; CI 1.13–3.32) as factors associated with the primary safety outcomes (Fig. 4B, Supplement Table 3).

Effects of amiodarone and dronedarone on quality of life and left ventricular function

Regarding the key secondary efficacy outcomes comparing the 24-month FU to baseline (before initiation of ERC), amiodarone was associated with a decline of quality of life (EQ-5D: − 5.12 (− 7.38, − 2.86); p < 0.001), while dronedarone

Table 3 ECG parameter at baseline and during follow-up

ECG parameter [ms]	Amiodarone	Dronedarone	ΔAmiodarone to baseline	ΔDronedarone to baseline	P-value (ΔAmio vs. ΔDrone)
Baseline	N = 91 (38%)	N = 58 (27%)			
QRS duration	97 (19)	99 (23)			
PR interval	177 (28)	173 (33)			
QTc	428 (66)	431 (34)			
12 month FU	N = 91 (38%)	N = 58 (27%)	N = 91 (38%)	N = 58 (27%)	
QRS duration	105 (19)	101 (19)	8 (16)	5 (13)	0.200
PR interval*	195 (34)	177 (34)	11 (30)	5 (25)	0.110
QTc	443 (50)	430 (28)	16 (77)	1 (34)	0.037
24 month FU	N = 89 (37%)	N = 57 (27%)	N = 89 (37%)	N = 57 (27%)	
QRS duration	105 (18)	102 (20)	8 (14)	4 (10)	0.075
PR interval*	192 (26)	178 (32)	14 (20)	5 (23)	0.024
QTc	446 (43)	430 (28)	19 (70)	4 (39)	0.072

Mean (SD); n (%; fraction of amiodarone or dronedarone intake at study initiation, see sankey plot), FU (Follow-up)

*PR-value could not be measured due to atrial fibrillation at baseline (amiodarone: 57/89 (64%), dronedarone 18/57 (32%), at 12 month FU (amiodarone 19/89 (21%), dronedarone 6/57 (11%), and at 24 month FU (amiodarone 20/89 (22%), dronedarone (8/57 (14%)

(−1.58 (−4.35, 1.18) p = 0.262) and Amiodarone/Dronedarone^{NEVER} (−1.56 (−3.32, 0.2); p = 0.083) showed no difference. SF-12 mental score showed no difference in any group, while SF-12 physical score declined in patients treated with amiodarone (−1.04 (−1.97, −0.12), p = 0.027).

In patients with amiodarone and heart failure, 31/104 (30%) had HFrEF, 35/104 (34%) HFmrEF and 38/104 (37%) HFpEF. Patients with heart failure treated with dronedarone hardly had HFrEF (2/23 (9%)), while HFmrEF (8/23 (35%)) and HFpEF (12/23 (52%)) were common. Left ventricular function improved in patients receiving amiodarone or dronedarone. The absolute increase in LVEF was higher in patients treated with amiodarone (53 ± 12% at baseline vs. 58 ± 11% at 24-month follow-up; p = 0.002) than in patients treated with dronedarone (61 ± 8% at baseline vs. 62 ± 9% at 24-month follow-up, p = 0.005), probably reflecting the lower baseline ejection fraction in patients taking amiodarone.

Effects of amiodarone and dronedarone on ECG parameters

Comparison of ECGs at baseline, before initiation of antiarrhythmic drug therapy, and at 24 months identified electrophysiological changes with on-going amiodarone (n = 89) and dronedarone (n = 57). QRS duration was prolonged with amiodarone (8 ± 14 ms) and with dronedarone (4 ± 10 ms, mixed linear regression; p = 0.075), reflecting sodium channel inhibition. Amiodarone prolonged the PR interval (14 ± 20 ms) more than dronedarone (5 ± 23 ms, mixed linear regression; p = 0.024), reflecting inhibition of beta adrenoreceptors and calcium channels. QTc, mainly influenced by potassium channel inhibition, was prolonged more with amiodarone by 19 ± 70 ms than with dronedarone by 4 ± 39 ms (mixed linear regression; p = 0.072).

Discussion

This sub-analysis of the EAST-AFNET 4 trial investigated safety and efficacy outcomes of patients with atrial fibrillation (AF) receiving ERC by amiodarone or dronedarone.

Main findings of the present study are as follows:

(1) Long-term therapy with amiodarone and dronedarone was associated with a low incidence of drug-related serious adverse events.
(2) The overall positive effect of ERC therapy was replicated in patients treated with amiodarone or dronedarone.
(3) With regard to the key secondary efficacy outcome at two years of follow-up, dronedarone showed a benefit toward increased physical status and quality of life when compared to amiodarone in this non-randomized comparison.
(4) ECG parameter suggests a stronger IKr inhibition and beta adrenoreceptor inhibition by amiodarone than dronedarone, while the ECG-based effect on INa inhibition appeared similar.

This analysis suggests that both amiodarone and dronedarone are safe methods to deliver ERC therapy. The

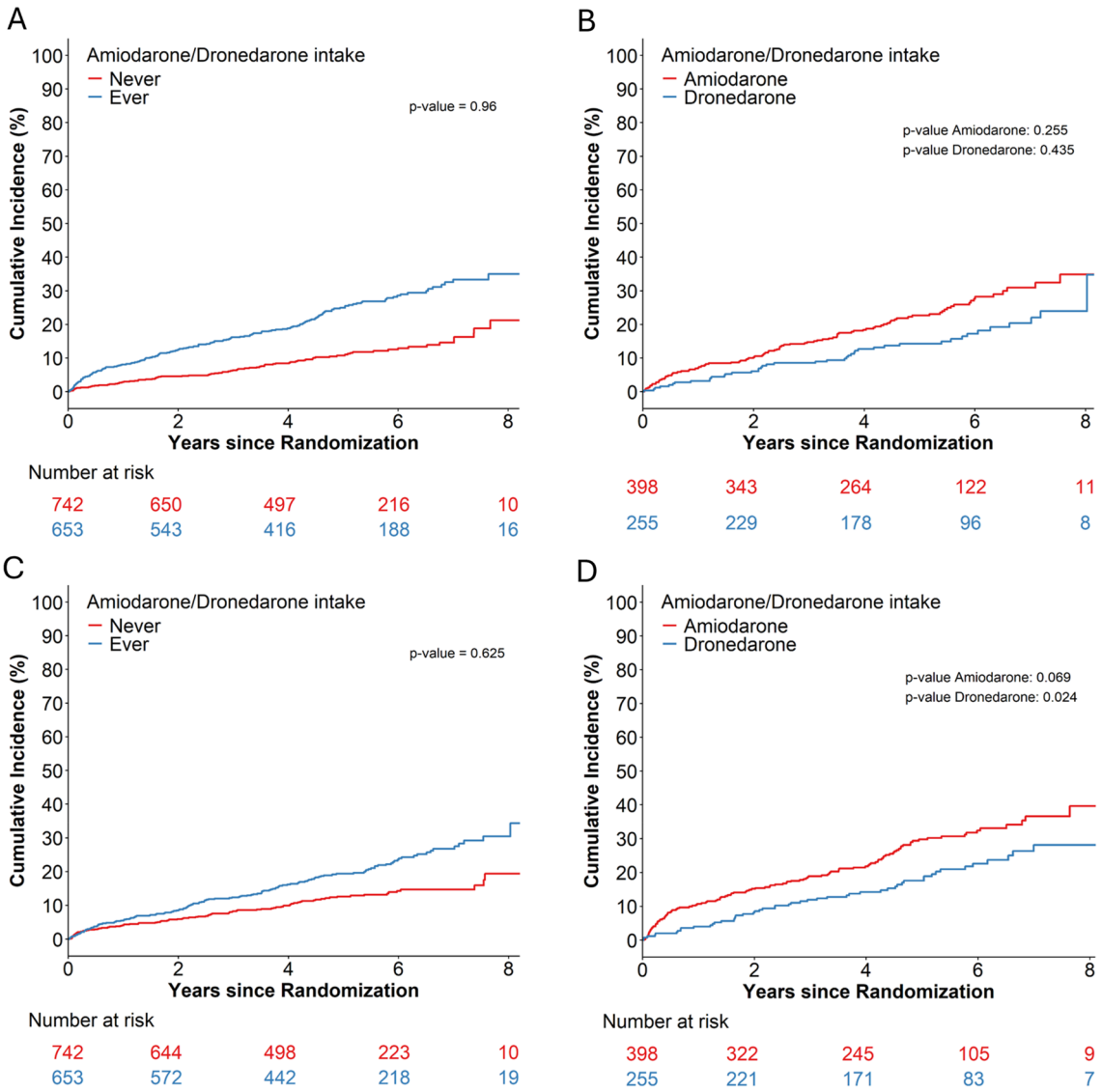


Fig. 3 Cumulative incidence of the primary safety outcome in all patients ever or never receiving amiodarone or dronedarone in the early rhythm control group (**A**) and in all patients receiving amiodarone vs. dronedarone (**B**) and cumulative incidence of the primary efficacy outcome in all patients ever or never receiving amiodarone or dronedarone in the early rhythm control group (**C**) and in all patients receiving amiodarone vs. dronedarone (**D**)

numerical differences in safety and efficacy outcomes observed here are probably related to different patient characteristics influencing the choice of antiarrhythmic drug therapy.

Baseline characteristics

In general, age and comorbidity burden of the trial population compare quite well to a population-based sample of patients with recently diagnosed AF [30]. Although the population studied is younger [31] than previously analyzed cohorts, it is, however, one of the oldest population studies ever investigated in a rhythm control trial and contains AF patients consenting to participate in a pragmatic trial with few exclusion criteria outside of definition of early AF at risk of stroke. The efficacy and the safety of ERC therapy using amiodarone or dronedarone in a contemporary AF population therefore provide important new aspects that will enable clinicians to choose antiarrhythmic drugs for early rhythm control.

Of note, patients initially receiving amiodarone or dronedarone were older with more comorbidities and less likely to have paroxysmal AF compared to those never receiving amiodarone or dronedarone. This reflects the approved and guideline-recommended use of dronedarone [32, 33] based on the phase III studies [20, 34]. Furthermore, patients

Table 4 Efficacy endpoints outcomes in patients with (EVER) or without (NEVER) Amiodarone/Dronedarone intake in patients with early rhythm control (ERC)

ERC ONLY	Amio^{EVER}	Drone^{EVER}	Amio/Drone^{NEVER}
First primary outcome—events/person-yr (incidence/100 person-yr)	115/1719 (6.7)	51/1219(4.2)	83/3461 (2.4)
Components of first primary outcome—events/person-yr (incidence/100 person-yr)			
Death from cardiovascular causes	33/1966 (1.7)	12/1336 (0.9)	22/3613 (0.6)
Stroke	17/1920 (0.9)	4/1329 (0.3)	19/3563 (0.5)
Hospitalization with worsening of HF	75/1807 (4.2)	29/1268 (2.3)	35/3546 (1)
Hospitalization with acs	22/1904 (1.2)	14/1293 (1.1)	17/3565 (0.5)
Second primary outcome—Nights spent in hospital/yr	9.03 ± 26.7	6.01 ± 16.9	4.03 ± 20.5
Key secondary outcomes at 2 years			
Change in LVEF	3.61 ± 11.6	0.89 ± 9.2	0.55 ± 8.6
Change in EQ-5D score	− 3.12 ± 24.2	1.63 ± 20.8	− 0.72 ± 19.8
Change in SF-12 Mental Score	0.9 ± 11.9	1.5 ± 9.8	0.3 ± 10.2
Change in SF-12 Physical Score	− 0.68 ± 8.8	1.52 ± 8.5	0.36 ± 8.3
Change in MoCA score	− 0.19 ± 3.4	− 0.12 ± 3.3	0.35 ± 3.2
Sinus rhythm	251/329 (76.3)	175/211 (82.9)	495/582 (85.1)
Asymptomatic	253/333 (76)	158/218 (72.5)	450/608 (74)

Continuous variables were presented as the mean and standard deviation. Note 2:EQ-5D: nonsurvivers were assigned value 0

receiving amiodarone had more often a reduced left ventricular function, in line with its recommended use [32, 33] and randomized trials evaluating amiodarone as a rhythm control agent [35]. Patients treated with other (mainly sodium channel blocking) antiarrhythmic drugs showed profound differences in baseline characteristic reflecting the restrictions of their use [36].

The choice of rhythm control drug therapy varied by country and center. In general, there were more centers with clear preference of amiodarone when compared to dronedarone. In addition to center preference [7], this analysis also identified country preferences for amiodarone and dronedarone, most likely reflecting national regulations regarding availability and reimbursement. Although dronedarone is approved for patients with heart failure and LVEF 40–50% [12], amiodarone was more frequently used for these patients. Switches between amiodarone and dronedarone or discontinuation of antiarrhythmic drug therapy were observed (for details, see Fig. 2). Some of these were due to recurrent AF, leading to escalation of antiarrhythmic therapy (either change to another agent or catheter ablation). Others were due to lack of recurrent episodes of AF, leading to 1/3 of patients being without rhythm control therapy at two years in the ERC arm [7].

Primary efficacy and safety outcomes

In general, there were few serious adverse events over a median of almost two years of therapy with amiodarone and dronedarone. The incidence rate of serious drug-related adverse effects (1.5%/year for amiodarone and 1.2%/year for dronedarone) is lower than in previous studies [20, 37, 38] despite systematic capture of these events and central adjudication of all potential drug-related adverse events. The two key drug-associated serious adverse events were drug toxicity and bradycardia. Drug toxicity was more frequently found with amiodarone (Table 5), which is not surprising as amiodarone is known to be associated with hyperthyroidism/hypothyroidism and occasional skin, eye, lung, and liver toxicities [37]. Within the randomized DIONYSOS trial, which prospectively compared amiodarone and dronedarone for the treatment of AF patients in term of efficacy and safety, the incidence of main safety events was 39.3% and 44.5% at 12 months for dronedarone and amiodarone. The reduced incidence of the main safety events in the dronedarone group versus the amiodarone group was mainly driven by fewer thyroid events. On the other hand, DIONYSOS reported on more gastrointestinal (GI) events for dronedarone, mainly diarrhea [37]. In our study, GI events play no role, while bradycardia was more often found with dronedarone, which is in line with the main safety outcomes in ATHENA, where bradycardia was the most common treatment-emergent adverse event, and more commonly reported in patients receiving dronedarone compared to placebo (3.5% vs. 1.2%, $p < 0.001$ [20]). However, within the EFFECT-AF cohort study, no significant differences in safety or liver toxicity were found with the use of dronedarone compared to other AADs under real-world circumstances [29]. Importantly, there were no serious adverse events related to ventricular arrhythmias in this analysis, potentially due to the advice

Table 5 Primary safety endpoint of patients with (EVER) or without (NEVER) Amiodarone/Dronedarone intake in patients with early rhythm control (ERC)

ERC ONLY—events (incidence/100 patient years)	Amio^{EVER}	Drone^{EVER}	Amio/Drone^{NEVER}	p-value*	p-value adj**
n	398	255	742		
Primary composite safety outcome	98 (5.3)	43 (3.4)	90 (2.6)	< 0.001	< 0.001
Stroke	17 (0.9)	4 (0.3)	19 (0.5)	0.194	0.173
Death	64 (3.3)	30 (2.2.)	44 (1.2)	< 0.001	< 0.001
Serious adverse event of special interest related to rhythm control therapy	26 (1.4)	15 (1.2)	27 (0.8)	0.097	0.125
Serious adverse event related to antiarrhythmic drug therapy – events (%)					
Nonfatal cardiac arrest	0 (0.0)	0 (0.0)	1 (0.1)	1	1
Drug toxicity of AF related drug therapy	6 (1.5)	2 (0.8)	2 (0.3)	0.102	0.09
Drug induced bradycardia	4 (1.0)	4 (1.6)	6 (0.8)	0.585	0.524
Atrioventricular block	2 (0.5)	0 (0.0)	0 (0.0)	1	1
Torsade de pointes tachycardia	1 (0.3)	0 (0.0)	0 (0.0)	1	
Serious adverse event related to AF ablation—events (%)					
Pericardial tamponade	0 (0.0)	0 (0.0)	3 (0.4)	1	1
Major bleeding related to AF ablation	1 (0.3)	3 (1.2)	2 (0.3)	0.967	0.871
Nonmajor bleeding related to AF ablation	1 (0.3)	0 (0.0)	0 (0.0)	1	1
Serious adverse event of special interest related to RC therapy—events (%)					
Blood pressure related event	0 (0.0)	0 (0.0)	1 (0.1)	1	0.998
Hospitalization for AF	7 (1.8)	3 (1.2)	1 (0.1)	< 0.001	0.098
Other cardiovascular event	1 (0.3)	0 (0.0)	4 (0.5)	0.485	0.427
Other event	0 (0.0)	0 (0.0)	1 (0.1)	1	1
Syncope	2 (0.5)	0 (0.0)	2 (0.3)	0.568	0.961
Hospitalization for worsening of HF with decomp HF	2 (0.5)	1 (0.4)	0 (0.0)	< 0.001	
Implantation of a pacemaker defi or other	0 (0.0)	2 (0.8)	6 (0.8)	0.989	0.984

*Mixed logistic-regression models with a random effect for site were used for comparision of Ever VS Never for patients with ERC treatment. p-values resulting from Analysis of Deviance Table (Type II Wald chisquare tests)

**Mixed logistic-regression models with a random effect for site were used for comparision of Ever VS Never for patients with ERC treatment adjusted for Age, Stable Heart failure, CAD and type of heart failure by LVEF (cut-off 35). p-values resulting from Analysis of Deviance Table (Type II Wald chisquare tests)

on ECG monitoring of antiarrhythmic drug effects in the protocol of the EAST-AFNET 4 trial but may also related to drug-specific cellular characteristics in particular in chronic heart failure [39].

It is known that side effects of medication are often dependent on respective serum drug levels. Our analysis did not separately consider serum concentrations of antiarrhythmic drugs or metabolism types and a specific analysis of outcomes depending on serum concentrations is not available.

The main driver of more primary efficacy outcomes in the amiodarone group was the hospitalization due to HF (Table 4), which might be explained by the higher fraction of patients with HF in the amiodarone group. Main driver of the primary safety outcomes in the amiodarone group was stroke and death, which, also at least additionally, might be explained by an elderly patient cohort with high comorbidity burden within the amiodarone group (Table 2).

Multivariate Cox regression analyses identified dronedarone, age, coronary artery disease, and stable HF as factors associated with the first primary efficacy outcome. Age and left ventricular hypertrophy were associated with primary safety outcomes. The low rate of stroke in patients taking dronedarone is in line with the Cochrane analysis [26]. The conditions associated with cardiovascular events are known conditions associated with stroke, heart failure, cardiovascular death, and all-cause death [12, 40]. In addition, dronedarone therapy at baseline was associated with primary outcome events. It is likely that dronedarone was given to patients who were deemed to be sicker and therefore at higher risk of stroke, death, and heart failure than patients receiving sodium channel blockers. These non-measured confounders are the most likely explanation that dronedarone was associated with primary outcome events in this analysis.

Interestingly, in the analysis of key secondary efficacy outcomes, amiodarone showed a significant worsening in quality of life (EQ-5D) and SF-12 physical scores after 24 months of treatment compared to only non-significant

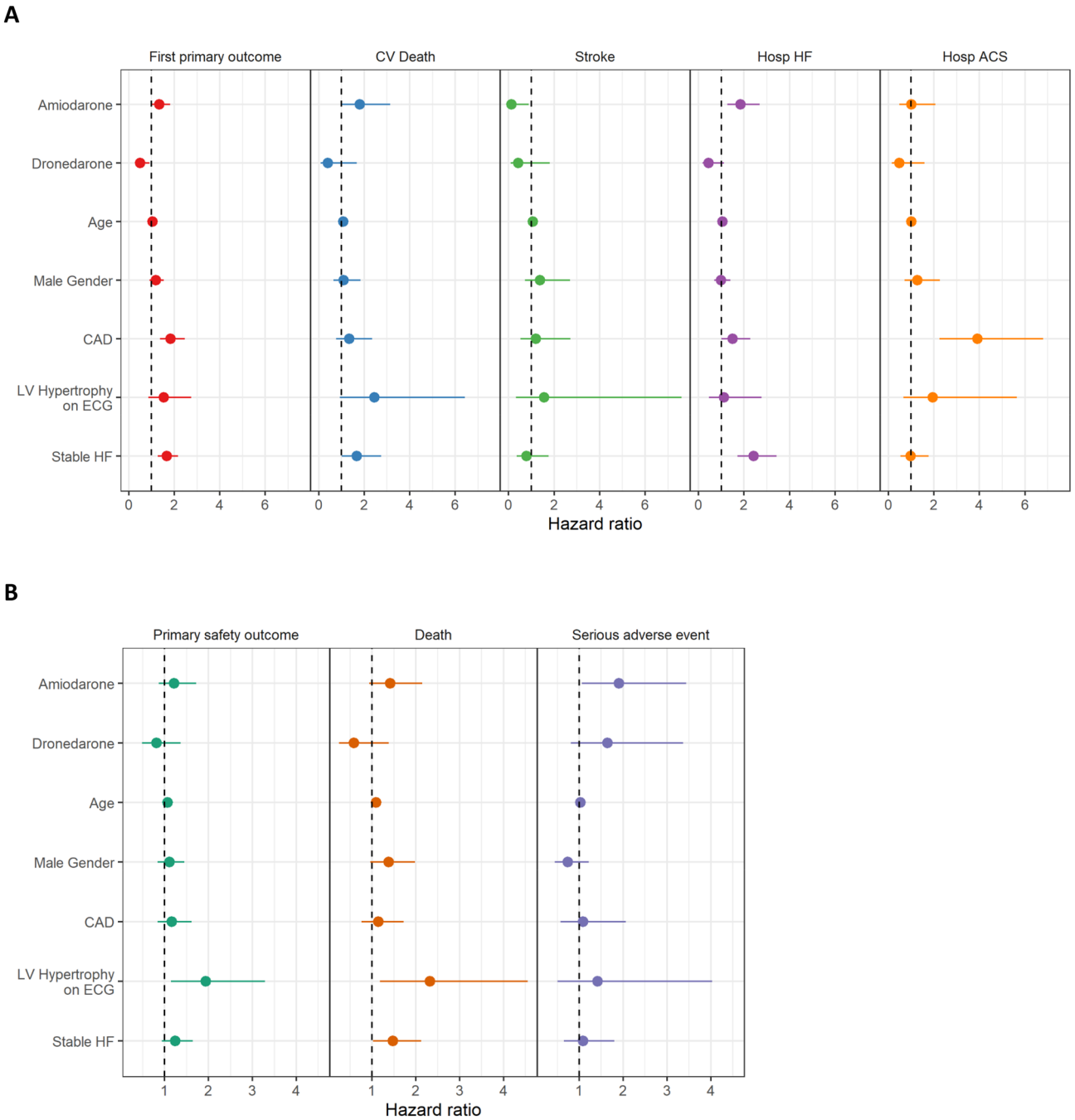


Fig. 4 **A** Cox models with time-dependent Amiodarone/Dronedarone intake for ERC patients—First primary outcome and its components, illustrated by hazard ratio and confidence intervals. **B** Cox models with time-dependent Amiodarone/Dronedarone intake for ERC patients—Safety outcomes. Please note that the confidence interval of age is to small to be shown in the graph

changes in dronedarone or Amiodarone/Dronedarone^{NEVER} group, which is in line with previous studies [38]. Reasons for this difference are multifactorial and will include higher comorbidity burden in patients treated with amiodarone (more to gain), leading to a higher increase EQ-5D on early rhythm control [4]. Neurological side effects like tremor or sleep disorder [37] might interfere with quality of life. Furthermore, the effect of early rhythm control on quality of life could be more pronounced in patients with comorbidities that lead to a reversible reduction in quality of life, e.g., heart failure, while other comorbidities, e.g., a prior stroke, may cause a fix reduction in quality of life that cannot be altered by rhythm control therapy. Whether early AF ablation conveys similar benefits as the intervention tested in

EAST-AFNET 4, mainly relying on antiarrhythmic drugs, will be studied in the recently initiated EASThigh-AFNET 11 trial (NCT06324188).

CASTLE-AF and CASTLE-HTX investigated rhythm control therapy of AF patients with reduced ejection fraction and showed an improvement of LVEF by ~ 8% [41, 42]. In EAST-AFNET4 trial, patients receiving amiodarone showed more often a reduced left ventricular function at baseline which improved at 2 years [5], probably explaining the highest increase in LVEF at 2-year FU of 5%.

Amiodarone and dronedarone are weak inhibitors of cytochrome P450 (CYP2D6) and may increase plasma levels of CYP2D6 dependent drugs, such as metoprolol [43]. Since 298/398 (75%) patients with $Amio^{EVER}$ and 195/255 (76%) with $Drone^{EVER}$ had coadministration with betablocker, there is a relevant number of patient with potential interaction. However, drug-induced bradycardia was not more often in patients with amiodarone and metoprolol (0.6%) than in patients with amiodarone without metoprolol (1.3%).

Amiodarone- and dronedarone-induced ECG changes

Amiodarone inhibits multiple ion channels (I_{Kr}, I_{Na}, I_{Ks}, I_{to}, I_{K1}, I_{Ca}, I_{KAch}) and the autonomic nervous system (α- and ß-adrenoreceptor), similar to dronedarone with small differences of relative effects on individual ion channels [14]. Experimental data in dogs suggest that chronic dronedarone treatment has only little effect on I_{Na} and I_{Kr}, but more effect on I_{Ca} [14]. Treatment with amiodarone and dronedarone prolonged the PR interval, QRS duration, and QTc as expected from a multi-channel blocker. Amiodarone therapy led to more pronounced PR and QTc prolongation, reflecting more extensive inhibition of AV nodal conduction (possibly by stronger inhibition of ß-adrenoreceptors and I_{Ca}) and more intensive I_{Kr} inhibition compared to dronedarone, whereas I_{Na} inhibition seems to be similar. Whether this differential effect in ECG parameter can be translated to stronger negative inotropic effect of dronedarone compared to amiodarone cannot be solved with our data.

Strengths and limitations

This is a post hoc subgroup analysis of the prospective randomized EAST-AFNET 4 trial. Strengths are the systematic follow-up in a controlled clinical trial and the long observation period. The choice of antiarrhythmic drug was non-randomized, rendering all comparisons between individual drugs subject to confounding. Furthermore, patients agreed to participate in EAST-AFNET 4, creating potential selection biases. Amiodarone/Dronedarone intake varied during study participation resulting in some patients with continuous Amiodarone/Dronedarone intake and others with on/off Amiodarone/Dronedarone therapy. Nonetheless, patients in this analysis were treated for a long time with Amiodarone or Dronedarone, providing robust information on the long-term effectiveness and safety of amiodarone and dronedarone for early rhythm control therapy in patients with AF. Although sensitivity analyses were performed considering age, stable heart failure, coronary artery disease, and type of heart failure as stratified by left ventricular ejection fraction, comparisons between antiarrhythmic treatment options will be influenced by residual confounders, e.g., chronic obstructive lung disease [44] or chronic kidney disease [45] that could not be systematically included in this analysis. Some patients initiated amiodarone or dronedarone later in the trial, but the overall findings mainly apply to patients with relatively recently diagnosed AF. Serum concentrations of antiarrhythmic drugs and drug metabolism were not analyzed. Systematic capture of severe side effects of antiarrhythmic drugs is a strength of the data set. While the event rates were comparable to recent observational data sets [29], more analyses, ideally in nationwide electronic records, are desirable and side effects that did not lead to drug discontinuation or to serious adverse events were not systematically captured. Drug-related side effects were only included in analysis when they led to therapy cessation or therapy change. The design of EAST-AFNET 4 as a therapy strategy trial precludes a reliable analysis of recurrent AF. This information could only be inferred from therapy changes and discontinuations, and from rhythm at 12 and 24 months, in this analysis. The field is moving away from recurrent AF and toward considering AF burden [46]. The data presented here suggest that patients changed therapy with dronedarone or amiodarone during the follow-up time after a median of around 21 months with a sufficiently low AF burden to maintain the effect of early rhythm control on outcomes. Future analyses integrating the telemetric ECG data that are not yet analyzed may shed more light onto this area of growing interest.

Conclusion

This analysis suggests that both amiodarone and dronedarone are safe methods to deliver ERC therapy. Further research and clinical exploration are warranted to refine the selection criteria for optimal amiodarone and dronedarone therapy in patients with AF.

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Data availability Data are available on reasonable request (contact: info@kompetenznetzvorhofflimmern.de).

Declarations

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