ESC European Society of Cardiology

Europace (2024) **26**, euae121
https://doi.org/10.1093/europace/euae121

CLINICAL RESEARCH

Safety and efficacy of long-term sodium channel blocker therapy for early rhythm control: the EAST-AFNET 4 trial

Andreas Rillig [1,2†], Lars Eckardt [3,4†], Katrin Borof[1], A. John Camm [5], Harry J.G.M. Crijns [6], Andreas Goette [3,7,8], Günter Breithardt [3,4], Marc D. Lemoine [1,2], Andreas Metzner [1,2], Laura Rottner [1,2], Ulrich Schotten [9], Eik Vettorazzi [10], Karl Wegscheider [2,3,10], Antonia Zapf [10], Hein Heidbuchel [11,12,13], Stephan Willems [14], Larissa Fabritz [1,2,3,15,16], Renate B. Schnabel [1,2,3], Christina Magnussen [1,2], and Paulus Kirchhof [1,2,3,16]*

[1]Department of Cardiology, University Heart and Vascular Center, University Medical Center Hamburg–Eppendorf, Martinistraße 52, 20246 Hamburg, Germany; [2]German Center for Cardiovascular Research, Partner Site Hamburg/Luebeck/Kiel, Germany; [3]Atrial Fibrillation Network (AFNET), Mendelstraße 11, 48149 Münster, Germany; [4]Department of Cardiology II—Electrophysiology, University Hospital Münster, Münster, Germany; [5]Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St. George's University of London, London, UK; [6]Department of Cardiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht, Maastricht, The Netherlands; [7]St. Vincenz Hospital, Paderborn, Paderborn, Germany; [8]Working Group of Molecular Electrophysiology, University Hospital Magdeburg, Magdeburg, Germany; [9]Department of Physiology, Maastricht University, Maastricht, The Netherlands; [10]Institute of Medical Biometry and Epidemiology, University Medical Center Hamburg–Eppendorf, Hamburg, Germany; [11]Faculty of Medicine and Health Sciences, Department of Cardiology, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium; [12]Faculty of Medicine and Health Sciences, Cardiovascular Research, GENCOR, Antwerp University, Antwerp, Belgium; [13]Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium; [14]Asklepios Klinik St. Georg, Klinik für Kardiologie und internistische Intensivmedizin, Hamburg, Germany; [15]University Center of Cardiovascular Science, University Heart and Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; and [16]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK

Received 15 January 2024; accepted after revision 13 March 2024; online publish-ahead-of-print 4 May 2024

Aims Clinical concerns exist about the potential proarrhythmic effects of the sodium channel blockers (SCBs) flecainide and propafenone in patients with cardiovascular disease. Sodium channel blockers were used to deliver early rhythm control (ERC) therapy in EAST-AFNET 4.

Methods and results We analysed the primary safety outcome (death, stroke, or serious adverse events related to rhythm control therapy) and primary efficacy outcome (cardiovascular death, stroke, and hospitalization for worsening of heart failure (HF) or acute coronary syndrome) during SCB intake for patients with ERC ($n = 1395$) in EAST-AFNET 4. The protocol discouraged flecainide and propafenone in patients with reduced left ventricular ejection fraction and suggested stopping therapy upon QRS prolongation >25% on therapy. Flecainide or propafenone was given to 689 patients [age 69 (8) years; CHA_2DS_2-VASc 3.2 (1); 177 with HF; 41 with prior myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention; 26 with left ventricular hypertrophy >15 mm; median therapy duration 1153 [237, 1828] days]. The primary efficacy outcome occurred less often in patients treated with SCB [3/100 (99/3316) patient-years] than in patients who never received SCB [SCB^{never} 4.9/100 (150/3083) patient-years, $P < 0.001$]. There were numerically fewer primary safety outcomes in patients receiving SCB [2.9/100 (96/3359) patient-years] than in SCB^{never} patients [4.2/100 (135/3220) patient-years, adjusted $P = 0.015$]. Sinus rhythm at 2 years was similar between groups [SCB 537/610 (88); SCB^{never} 472/579 (82)].

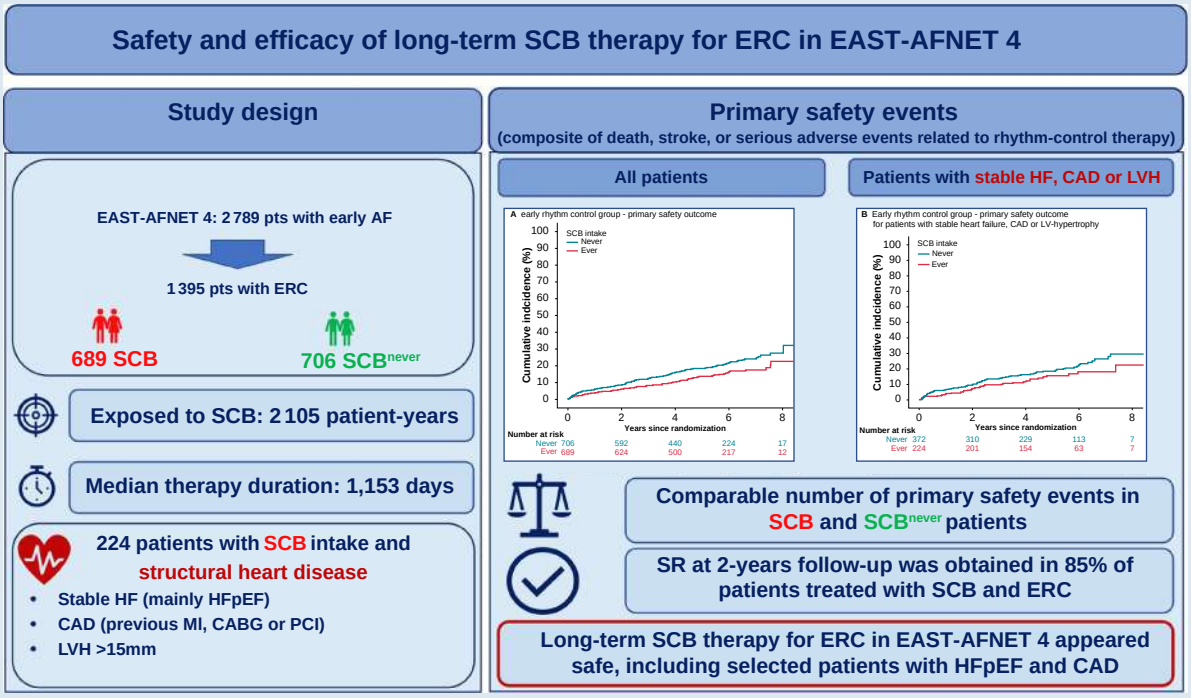
Conclusion Long-term therapy with flecainide or propafenone appeared to be safe in the EAST-AFNET 4 trial to deliver effective ERC therapy, including in selected patients with stable cardiovascular disease such as coronary artery disease and stable HF.

Clinical Trial Registration ISRCTN04708680, NCT01288352, EudraCT2010-021258-20, www.easttrial.org

* Corresponding author. Tel: +49 40 741053824. *E-mail address:* p.kirchhof@uke.de

† The first two authors contributed equally to the study.

Graphical Abstract



SCB, sodium channel blocker; ERC, early rhythm control; HF, heart failure; CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; LVH, left ventricular hypertrophy; SR, sinus rhythm.

Keywords Atrial fibrillation • Early rhythm control • Sodium channel blocker • Stable cardiovascular disease • Heart failure • Coronary artery disease

What's new?

- Flecainide and propafenone were used in patients without structural heart disease and in selected patients with left ventricular hypertrophy, heart failure with preserved ejection fraction, and with revascularized coronary artery disease.
- Patients treated with flecainide or propafenone to initiate early rhythm control in EAST-AFNET 4 had fewer outcome events than patients treated with other types of rhythm control over a 5-year follow-up.
- The results might encourage the use of flecainide and propafenone in similar patients when the protocol-mandated safety precautions are followed.

Introduction

Early rhythm control (ERC) therapy reduces cardiovascular events in patients with recently diagnosed atrial fibrillation (AF) in the EAST-AFNET 4 trial.[1] Beneficial effects have been observed in several subanalyses, including in patients with heart failure (HF) and in those with a high comorbidity burden.[2–8] Early rhythm control therapy in the EAST-AFNET 4 trial was initially delivered using antiarrhythmic drugs in 85% of the patients.[1] Sodium channel blockers play a major role in antiarrhythmic drug therapy based on their effectiveness[9] and their low risk of extracardiac side effects.[10] This is even more important, considering that in the past decade no novel antiarrhythmic agent became available.[11] Sodium channel blocker remains underutilized, even in patients without structural heart disease,[12,13] most likely due to fear of proarrhythmia.[14] The Cardiac Arrhythmia Suppression Trial (CAST) observed proarrhythmic effects of flecainide and encainide in patients with prior myocardial infarction, frequent ventricular premature beats, and HF with reduced ejection fraction.[10,15,16] These clear safety signals led to a restricted use of SCB. Whether patients with stable or revascularized coronary artery disease (CAD) and those with HF with preserved ejection fraction can be treated with SCB is not well evaluated, and current guidelines therefore slightly vary in their recommendations.[17] The potential underuse of SCB is specifically observed in older patients with comorbidities, patients that potentially have the most prognostic benefit from ERC therapy.[4,10,18,19]

To provide contemporary information on the efficacy and safety of SCB therapy, we analysed outcomes of long-term SCB therapy in the EAST-AFNET 4 patients with and without cardiovascular disease.

Methods

The full methods of the EAST-AFNET 4 trial have been published previously.[1] The trial 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 and at least two stroke risk factors approximating a CHA_2DS_2-VASc score of 2 or higher. Randomization in a one-to-one fashion to either ERC therapy ($n = 1395$) or usual care (UC; $n = 1394$) was performed.[1] Early rhythm control was selected by the site teams and consisted of antiarrhythmic drug therapy, catheter ablation, or cardioversion. The protocol discouraged SCB therapy in patients with reduced left ventricular ejection fraction (LVEF) and recommended stopping SCB therapy in patients with a QRS prolongation >25% upon therapy initiation. In patients assigned to UC, rate control

was the initial strategy and rhythm control was only initiated in patients symptomatic on optimized rate control therapy.[1]

The first primary efficacy outcome was a composite of death from cardiovascular cause, stroke or hospitalization with worsening of HF or acute coronary syndrome. The primary safety outcome was defined as a composite of death, stroke, or serious adverse events related to rhythm control therapy.[1]

All serious adverse events were prospectively captured throughout the trial. Adverse events were considered to be serious in case 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]

All serious adverse events related to rhythm control therapy were centrally adjudicated as part of the primary safety outcome. The definition of 'proarrhythmia' was any arrhythmic event or an event with a potential arrhythmic background, judged as causally related to the therapeutic intervention, e.g. drug-induced proarrhythmia (torsade de pointes, ventricular tachycardia, or ventricular fibrillation), atrioventricular block, ablation-induced or drug-induced atrial arrhythmias (e.g. left atrial flutter), drug-induced bradycardia, or syncope.[1] Events that were judged as causally related to the therapies in the trial were considered for analysis such as drug toxicity of AF-related drug therapy, bleeding events caused by AF ablation or antithrombotic therapy, complications of ablation procedures, and others.[1]

Cardiovascular comorbidities were defined by the site teams at baseline and during regular follow-up visits following common clinical criteria as described in the EAST-AFNET 4 protocol (chapter 8[1]) In brief, stable HF was defined as presence of HF symptoms [New York Heart Association (NYHA)] class II or higher, or LVEF of <50%. Severe CAD was defined as previous myocardial infarction, coronary artery bypass graft (CABG) or percutaneous intervention (PCI); left ventricular hypertrophy (LVH) was defined as left ventricular (LV) wall thickness >15 mm (as defined via echocardiography).

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 are available on reasonable request (contact: info@kompetenznetz-vorhofflimmern.de).

The protocol was approved by the ethics review boards of all institutions involved. All patients participating in the trial gave written informed consent.

Statistics

This analysis included all 2789 patients randomized in the EAST-AFNET 4 trial and categorized patients into either SCB intake at baseline, SCB intake later during follow-up, or never SCB intake during the study period. Patients randomized to ERC ($n = 1395$) were used for further analysis. As no relevant differences were observed between patients with SCB intake at baseline and SCB intake later during follow-up (see Supplementary material online, *Table S1*), these two groups were summarized in one group (SCB group, $n = 689$) and compared to patients without any SCB intake during the study period (SCB^{never}, $n = 706$).

Patient's 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, first and third quartile.

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 ERC ($n = 1395$) were separately analysed for patients with SCB intake ($n = 689$) or no SCB intake (SCB^{never}, $n = 706$).

For the primary efficacy outcomes and its individual components (death from cardiovascular causes, stroke, hospitalization with worsening of HF, 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 multivariable Cox regression models with a time-dependent term for intake of SCB, site as a shared frailty term, for patients from the ERC group. Additionally, the models were expanded with adjustment for age, stable HF, CAD, and type of HF by LVEF (cut-off 35%). The coefficients are expressed as hazard ratios (HRs) with a 95% confidence interval.

Furthermore, we calculated the models for the safety outcomes in patients with stable cardiovascular disease (stable severe CAD including previous myocardial infarction, CABG or PCI), stable HF, and LVH >15 mm. Statistics software R version 4.1.0. was used for all analyses.

Results

Baseline characteristics

Of the randomized 2789 patients included in the EAST-AFNET 4 trial, 585 (21%) patients received SCB therapy at baseline (ERC: $n = 554$; UC: $n = 31$), whereas 2204 patients (79%) did not. Two hundred and fifty-three patients received SCB later during the study follow-up (ERC: $n = 135$; UC: $n = 118$) with baselines as described in Supplementary material online, *Tables S2 and S3*. Patients randomized to ERC ($n = 1395$) were included in the analysis. Finally, overall patients with SCB intake were defined as patients with ERC treated with SCB intake (SCB, $n = 689$) and compared to patients without SCB intake (SCB^{never}, $n = 706$; *Table 1*).

Patients with SCB intake were younger (age: 69 ± 8 years vs. 71 ± 9 years, $P = 0.002$), were more often female [354/689 (51%) vs. 291/706 (41%), $P < 0.001$], had less often stable structural heart disease such as stable HF [177/689 (26%) vs. 219/706 (31%), $P < 0.001$]and severe CAD [41/689 (6.0%) vs. 202/706 (29%), $P < 0.001$], and had lower CHA_2DS_2-VASc scores [3.2 (1.3) vs. 3.5 (1.3), $P < 0.001$] than patients without SCB intake with a similar rate of LVH [26/689 (3.8%) vs. 39/706 (5.5%), $P = 0.37$; *Table 1*]. Differences were also observed in AF type and the number of patients in sinus rhythm at the baseline (*Table 1*). Detailed baseline characteristics and patient characteristics as by randomized groups are shown in *Table 1* and Supplementary material online, *Tables S2 and S3*. Concomitant medical therapy showed no differences in oral anticoagulation [SCB: 625/689 (91%), SCB^{never}: 642/700 (92%), $P = 0.43$], but patients with SCB intake were less often treated with digoxin or digitoxin [16/689 (2.3%) vs. 30/700 (4.3%), $P = 0.021$], mineralocorticoid receptor antagonists [25/689 (3.6%) vs 65/700 (9.3%), $P < 0.001$], diuretics [240/689 (35%) vs. 319/700 (46%), $P < 0.001$], and platelet inhibitors [63/689 (9.1%) vs. 166/700 (24%), $P < 0.001$, *Table 1*].

Duration of sodium channel blocker intake and effectiveness

Duration of SCB intake was calculated as median according to the overall duration of drug intake during the course of the study. Median treatment with propafenone or flecainide duration was 2105 patient-years and median therapy duration 1153 [237, 1828] days (*Figure 1*, Supplementary material online, *Table S4*).

The number of patients in sinus rhythm at 12 months [$SCB^{baseline}$ 426 (88%); SCB^{later} 111 (87%); SCB^{never} 472 (82%)] and 24 months [$SCB^{baseline}$ 382 (85%); SCB^{later} 108 (86%); SCB^{never} 431 (79%)] was similar in patients with or without SCB intake (see Supplementary material online, *Table S5*).

A higher number of catheter ablations were performed in patients without SCB intake (see Supplementary material online, *Table S3*).

Impact of sodium channel blocker intake on left ventricular function and New York Heart Association class

Patients with SCB intake at baseline or later had more often a normal LV function at baseline as compared to patients without SCB intake

Table 1 Demographic and clinical characteristics of patients with and without SCB intake of patients treated with ERC

Characteristics	Overall, *N* = 1395[a]	Sodium channel blocker intake Ever		*P*-value*
		Yes, *N* = 689[a]	No, *N* = 706[a]	
Age				0.002
Mean ± SD	70 ± 8.4	69 ± 8.3	71 ± 8.5	
Median (IQR)	71 (65.0, 76)	70 (65.0, 75)	72 (66.0, 77)	
Gender				<0.001
Female	645/1395 (46%)	354/689 (51%)	291/706 (41%)	
Male	750/1395 (54%)	335/689 (49%)	415/706 (59%)	
Body mass index (calculated) (kg/m^2)				0.023
Mean ± SD	29.2 ± 5.4	28.9 ± 5.2	29.6 ± 5.5	
Median (IQR)	28.4 (25.5, 32.0)	28.2 (25.4, 31.5)	28.7 (25.8, 32.7)	
AF type				<0.001
First episode	528/1391 (38%)	244/689 (35%)	284/702 (40%)	
Paroxysmal	501/1391 (36%)	291/689 (42%)	210/702 (30%)	
Persistent or long-standing persistent	362/1391 (26%)	154/689 (22%)	208/702 (30%)	
Concomitant cardiovascular conditions				
Sinus rhythm at baseline	762/1389 (55%)	428/689 (62%)	334/700 (48%)	<0.001
Median days since AF diagnosis (IQR)				0.86
Mean ± SD	81.5 ± 172.5	79.0 ± 194.5	84.1 ± 148.0	
Median (IQR)	36.0 (6.0, 114.0)	36.0 (6.0, 104.0)	35.0 (6.0, 119.5)	
Absence of atrial fibrillation symptoms	395/1305 (30%)	180/644 (28%)	215/661 (33%)	0.047
Previous pharmacological or electrical cardioversion	546/1364 (40%)	288/681 (42%)	258/683 (38%)	0.83
Prior AF ablation				
No	1395/1395 (100%)	689/689 (100%)	706/706 (100%)	
Previous stroke or transient ischaemic attack	175/1395 (13%)	80/689 (12%)	95/706 (13%)	0.36
At least mild cognitive impairment	582/1326 (44%)	267/663 (40%)	315/663 (48%)	0.10
Arterial hypertension	1230/1395 (88%)	606/689 (88%)	624/706 (88%)	0.89
Systolic blood pressure (mmHg)				0.14
Mean ± SD	137 ± 19.4	136 ± 18.2	137 ± 20.5	
Median (IQR)	135 (122.0, 150)	135 (124.0, 145)	135 (120.0, 150)	
Diastolic blood pressure (mmHg)				0.79
Mean ± SD	81 ± 12.1	80 ± 11.3	81 ± 12.8	
Median (IQR)	80 (73.0, 90)	80 (72.0, 90)	80 (73.0, 90)	
Stable heart failure	396/1395 (28%)	177/689 (26%)	219/706 (31%)	<0.001
Medication at discharge				
HFrEF	57/396 (14%)	3/177 (1.7%)	54/219 (25%)	<0.001
HFmrEF	110/396 (28%)	37/177 (21%)	73/219 (33%)	0.28
HFpEF	224/396 (57%)	136/177 (77%)	88/219 (40%)	<0.001
CHA2DS2-VASc score				<0.001
Mean ± SD	3.4 ± 1.3	3.2 ± 1.3	3.5 ± 1.3	
Median (IQR)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (3.0, 4.0)	
Chronic kidney disease of MDRD stage 3 or 4	172/1395 (12%)	83/689 (12%)	89/706 (13%)	0.10
Severe coronary artery diseases (prev. MI, CABG or PCI)	243/1395 (17%)	41/689 (6.0%)	202/706 (29%)	<0.001
Left ventricular hypertrophy on echocardiography	65/1395 (4.7%)	26/689 (3.8%)	39/706 (5.5%)	0.37
LVEF at BL				<0.001
Abnormal	167/1364 (12%)	40/680 (5.9%)	127/684 (19%)	
Normal	1197/1364 (88%)	640/680 (94%)	557/684 (81%)	

Continued

Table 1 *Continued*

Characteristics	Overall, *N* = 1395[a]	Sodium channel blocker intake Ever		*P*-value*
		Yes, *N* = 689[a]	No, *N* = 706[a]	
Oral anticoagulation with NOAC or VKA	1267/1389 (91%)	625/689 (91%)	642/700 (92%)	0.43
Digoxin or digitoxin	46/1389 (3.3%)	16/689 (2.3%)	30/700 (4.3%)	0.021
Beta-blockers	1058/1389 (76%)	537/689 (78%)	521/700 (74%)	0.19
ACE inhibitors or angiotensin II receptor blocker	953/1389 (69%)	455/689 (66%)	498/700 (71%)	0.071
Mineralocorticoid receptor antagonist	90/1389 (6.5%)	25/689 (3.6%)	65/700 (9.3%)	<0.001
Diuretic	559/1389 (40%)	240/689 (35%)	319/700 (46%)	<0.001
Statin	628/1389 (45%)	279/689 (40%)	349/700 (50%)	<0.001
Platelet inhibitor	229/1389 (16%)	63/689 (9.1%)	166/700 (24%)	<0.001
Oral antidiabetics	228/1389 (16%)	102/689 (15%)	126/700 (18%)	0.078
Planned therapy for rhythm control at baseline				<0.001
AAD	1211/1395 (87%)	661/689 (96%)	550/706 (78%)	
Ablation	112/1395 (8.0%)	18/689 (2.6%)	94/706 (13%)	
None	72/1395 (5.2%)	10/689 (1.5%)	62/706 (8.8%)	

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; BL, baseline; CABG, coronary artery bypass graft; IQR, interquartile range; NOAC, novel oral anticoagulants; MDRD, modification of diet in renal disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; VKA, vitamin K antagonists.
[a]Mean (SD) or frequency with no./total no. (%)
**P*-values resulting from mixed linear regression models for metric variables and mixed (multinomial or ordinal) logistic regression models for categorical variables. For categorical variables with more than two categories (not ordinal), random effect is not included.

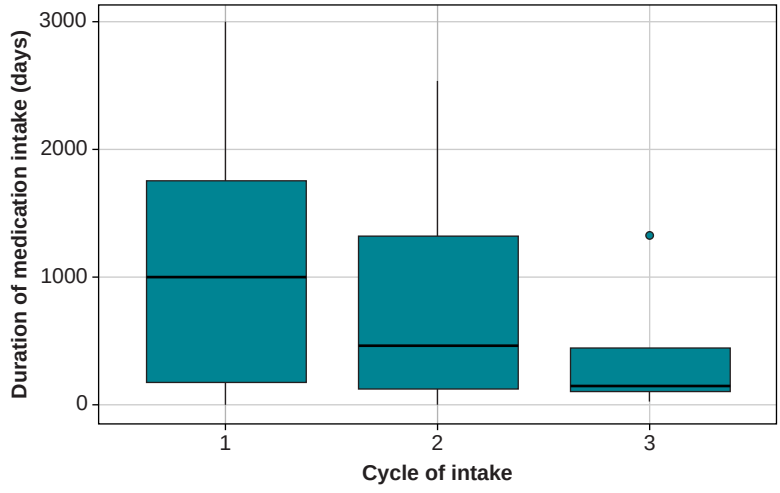


Figure 1 Details of Sodium channel blocker intake for patients with first intake later or at baseline and stratified for randomized groups. Cycle - Cycle of intake. Example: Cycle = 2 → patient took SCB for a while, then stopped and later started again. End of cycle can be end of follow-up, death, withdrawal or end of intake during follow-up on specific date.

[patients with SCB intake: 640/680 (94%) patients with normal LVEF; patients SCB^{never}: 557/684 (81%) patients with normal LVEF; *Table 1*].

Of the 177 patients with SCB intake and HF, 3/177 (1.7%) patients had heart failure with reduced ejection fraction (HFrEF), 37/177 (21%) patients had heart failure with mildly reduced ejection fraction (HFmrEF), and 136/177 (77%) had heart failure with preserved ejection fraction (HFpEF).

Within the follow-up period, no relevant changes in LV function were observed in patients with or without SCB intake (*Figure 2*). Similar findings were found for the NYHA class with no worsening of NYHA class in any group (*Figure 3*). The group of patients with SCB intake comprised a lower number of patients with stable HF [i.e. SCB intake: 177/689 (26%); SCB^{never} 219/706 (31%), *P*-value < 0.001], and changes in LV function or NYHA class were of similarity to those without SCB intake (*Table 1*, *Figures 2* and *3*).

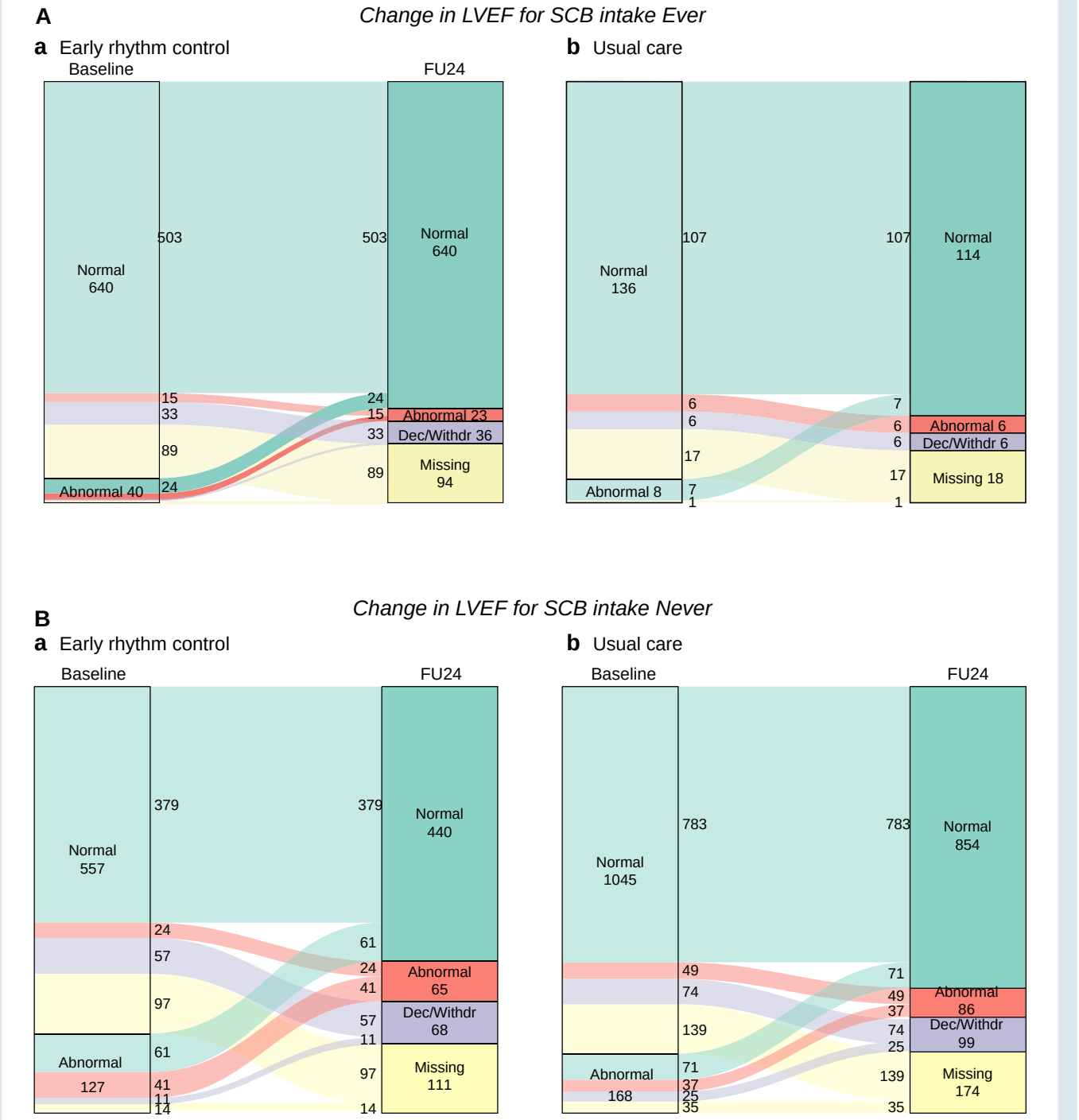


Figure 2 (*A*) Changes in left ventricular function in patients of the ERC group with SCB intake. (*B*) Changes in LV function in patients without SCB intake in the ERC group. LVEF, left ventricular ejection fraction; SCB, sodium channel blocker.

Efficacy and safety outcomes in patients with sodium channel blocker intake

The effect on the primary efficacy endpoint differed in patients with and without SCB intake. Patients with ERC on SCB had less outcomes of cardiovascular death, stroke, or hospitalization with worsening of HF or acute coronary syndrome [HR 0.55 (0.39–0.77); SCB intake: 3/100 (99/3316) patient-years; SCB^{never} (4.9/100 (150/3083) patient-years, multivariable Cox model $P < 0.001$, *Table 2*, Supplementary material online, Tables *S6A* and *S6B*, Supplementary material online, *Figure S2*) as well as for the secondary endpoints (see Supplementary material online, Table *S6B*).

Incidence rate ratios for the second primary outcome parameter (nights spent in hospital) were lower in patients with SCB intake as compared to patients without SCB intake (see Supplementary material online, *Table S7* and Supplementary material online, *Figure S2*).

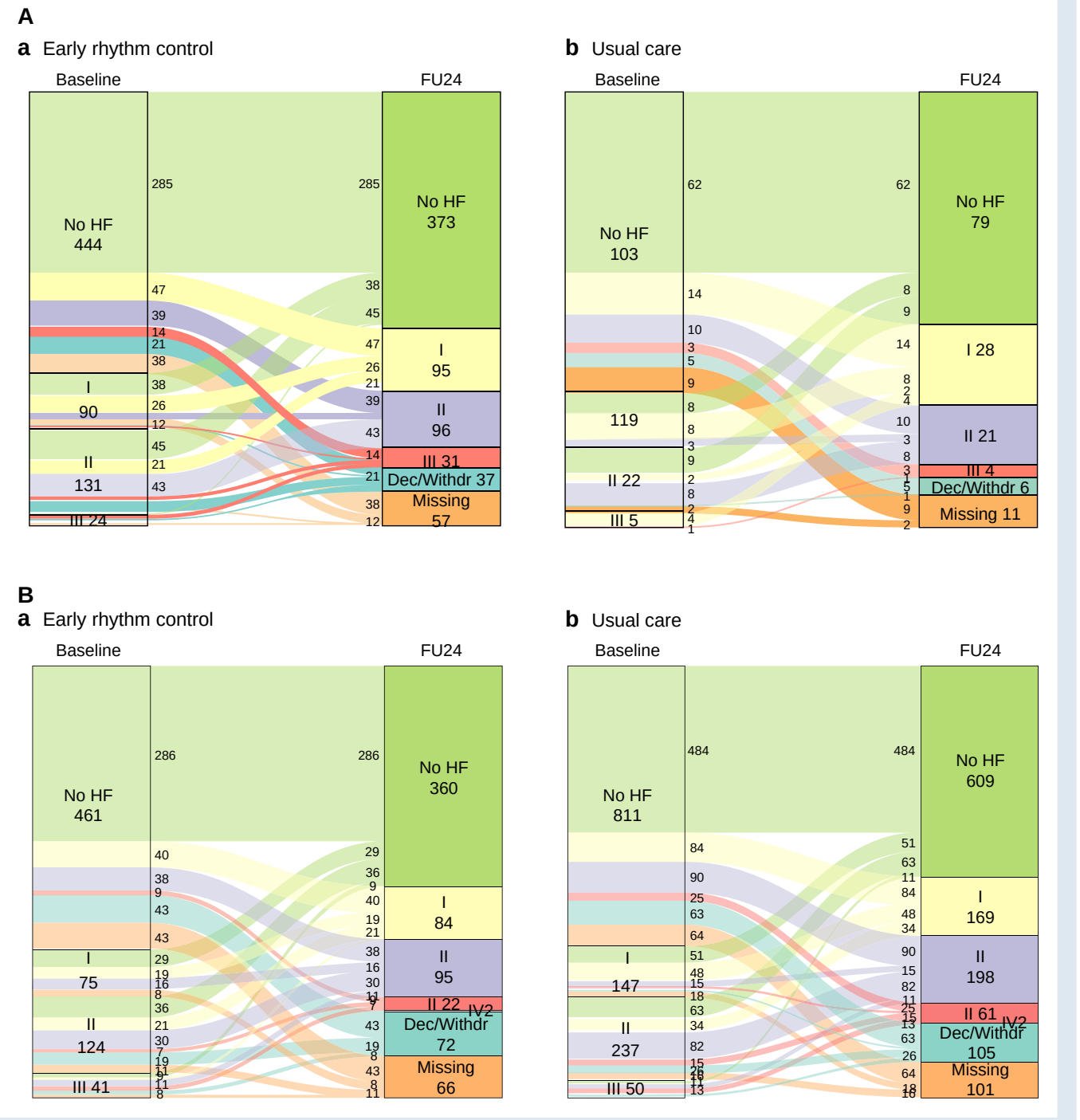


Figure 3 Changes in the NYHA class in patients with and without SCB intake. (*A*) Changes in the NYHA class in patients of the ERC group with SCB intake. (*B*) Changes in the NYHA class in patients without SCB intake in the ERC group. HF, heart failure.

The primary safety endpoint was numerically less often observed in patients with SCB intake as compared to SCB^{never} patients [SCB 2.9/100 (96/3359) patient-years vs. SCB^{never} 4.2/100 (135/3220 patient-years, $P = 0.027$, adjusted $P = 0.11$) *Table 3*, *Figure 4A*]. When in multivariable Cox models, treatments were adjusted for age, male gender, CAD, LVH on ECG, and stable HF the primary safety endpoint and its components were observed less frequently in patients with ERC [HR 0.62 (0.45–0.86), $P = 0.004$; *Table 4*]. Serious adverse events related to rhythm control therapy in the ERC group were observed with similar frequency in SCB and SCB never patients [HR 0.89 (0.52–1.53), $P = 0.685$)].

Changes in ECG parameters during sodium channel blocker intake

Resting ECGs at baseline were compared to resting ECGs at 12 and 24 months, and compared between patients with SCB intake and SCB^{never} patients (baseline ECG characteristics of patients with or without SCB

Table 2 Cox models with time-dependent SCB intake for patients with ERC—first primary outcome and its components

Predictors	First primary outcome		Death from cv causes		Stroke		Hospitalization worsening HF		Hospitalization acute coronary syndrome	
	HR (CI)	*P*-value	HR (CI)	*P*-value	HR (CI)	*P*-value	HR (CI)	*P*-value	HR (CI)	*P*-value
Time-dependent SCB intake	0.55 (0.39–0.77)	**<0.001**	0.37 (0.18–0.79)	**0.010**	0.70 (0.33–1.50)	0.346	0.34 (0.21–0.58)	**<0.001**	0.95 (0.48–1.88)	0.885
Age	1.05 (1.03–1.07)	**<0.001**	1.08 (1.05–1.12)	**<0.001**	1.06 (1.02–1.11)	**0.003**	1.06 (1.03–1.08)	**<0.001**	1.01 (0.97–1.04)	0.586
Male gender	1.18 (0.91–1.53)	0.218	1.10 (0.67–1.83)	0.707	1.36 (0.71–2.61)	0.362	0.98 (0.69–1.38)	0.890	1.27 (0.70–2.30)	0.421
CAD	1.61 (1.20–2.15)	**0.001**	1.15 (0.64–2.05)	0.620	1.01 (0.45–2.27)	0.983	1.27 (0.85–1.88)	0.265	3.74 (2.07–6.76)	**<0.001**
LVH on ECG	1.43 (0.81–2.52)	0.237	2.33 (0.91–5.93)	0.078	1.23 (0.29–5.21)	0.799	1.02 (0.41–2.53)	0.960	1.89 (0.66–5.37)	0.244
Stable HF	1.74 (1.35–2.26)	**<0.001**	1.80 (1.10–2.96)	**0.017**	0.71 (0.33–1.55)	0.392	2.65 (1.89–3.71)	**<0.001**	0.99 (0.54–1.81)	0.974

CAD, coronary artery disease; CI, confidence interval; ECG, electrocardiogram; HF, heart failure; HR, hazard ratio; LV, left ventricular; SCB, sodium channel blocker.
Values reaching statistical significance are shown in bold characters.

intake at baseline are shown in Supplementary material online, *Table S8*). QRS duration in baseline ECGs was slightly shorter in patients with SCB intake [SCB: 95 (17) ms, SCB^{never}: 97 (21) ms; $P < 0.001$]. No clinically relevant changes in baseline ECG characteristics at 12 and 24 months were observed (see Supplementary material online, *Table S9*).

Safety of sodium channel blocker intake in patients with coronary heart disease, stable heart failure, and left ventricular hypertrophy

Stable HF, prior myocardial infarction, PCI, or CABG, and LVH > 15 mm were observed in 596 patients of the ERC group (SCB: $n = 224$; SCB^{never}: $n = 372$; *Table 1*). In those 224 patients with SCB intake, stable HF was observed in 177 patients, prior myocardial infarction, PCI, or CABG in 41 patients, and LVH >15 mm in 26 patients (*Table 1*). There were numerically similar primary safety outcomes in patients receiving SCB with previous myocardial infarction, CABG, or PCI and stable HF or LVH [34 (15.2%)] than in patients not receiving SCB [74 (19.9%), *Table 4*]. However, as outlined above, when assessed in multivariable Cox models the primary safety endpoint and its components were observed in fewer frequency in patients with ERC [HR 0.62 (0.45–0.86), $P = 0.004$; *Table 5*]. To substantiate the safety of SCB therapy, we performed a separate safety analysis including all patients who received SCB including those who received SCB as part of UC. The overall safety was comparable (see Supplementary material online, *Tables* S10 and S11).

Discussion

This analysis provides information on the long-term safety and effectiveness of the SCBs flecainide and propafenone as part of ERC therapy in patients with AF and stroke risk factors. These findings include safety information in selected patients with HFpEF and with stable or revascularizedCAD. The study provides an increase in information on the safety of flecainide and propafenone, substances that have mainly been used in patients with no or only a few cardiovascular diseases.[9,16,20] The results might encourage the use of flecainide and propafenone in similar patients when safety precautions are followed, including assessment of QRS duration with swift action to halt drug therapy in the case of extensive QRS prolongation upon therapy.

Long-term sodium channel blocker treatment in clinical practice

Although SCB has shown high efficacy in reducing AF burden and maintaining sinus rhythm, precautions still exist to prescribe antiarrhythmic drugs (AADs), especially in patients with higher age and higher comorbidity burden.[12,18] The reservations against using SCB mainly originate from the CAST and CAST II, where SCB intake (flecainide, moricizine, and encainide) was associated with a 2.5-fold excess mortality in patients with previous myocardial infarction and a high burden of premature ventricular contractions. Mortality was significantly higher in patients with non-Q-wave infarction as compared to patients with Q-wave infarction with a 5-time higher relative risk of mortality. Further analysis in CAST revealed that acute ischaemia served as one of the main triggers for lethal tachyarrhythmias.[15,21] The findings of CAST have led to an Food and Drug Administration (FDA) recommendation that labels flecainide use to be contraindicated in all patients with structural heart disease of any aetiology.[16] However, patients with (untreated or treated) stable CAD or HF with preserved ejection fraction or mildly reduced ejection fraction without prior myocardial infarction were not studied in CAST.[15,21] There are also few data on the safety of

Table 3 Primary safety endpoint of patients with (ever) or without (never) SCB intake in patients with ERC or UC

	ERC				UC	
	Ever	Never	*P*-value*	*P*-value adj**	Ever	Never
n	689	706			149	1245
Primary composite safety outcome	96 (13.9)	135 (19.1)	0.027	0.11	20 (13.4)	203 (16.3)
Stroke	17 (2.5)	23 (3.3)	0.438	0.496	7 (4.7)	55 (4.4)
Death	45 (6.5)	93 (13.2)	< 0.001	0.001	9 (6.0)	155 (12.4)
Serious adverse event of special interest related to rhythm control therapy	34 (4.9)	34 (4.8)	0.783	0.587	6 (4.0)	13 (1.0)
Serious adverse event related to antiarrhythmic drug therapy						
Non-fatal cardiac arrest	1 (0.1)	0 (0.0)	0.851	1	0 (0.0)	1 (0.1)
Drug toxicity of AF-related drug therapy	5 (0.7)	5 (0.7)	0.969	0.835	2 (1.3)	1 (0.1)
Drug-induced bradycardia	8 (1.2)	6 (0.8)	0.561	0.525	1 (0.7)	4 (0.3)
Atrioventricular block	1 (0.1)	1 (0.1)	0.968	0.477	0 (0.0)	0 (0.0)
Torsade de pointes tachycardia	1 (0.1)	0 (0.0)	1	1	0 (0.0)	0 (0.0)
Serious adverse event related to AF ablation						
Pericardial tamponade	1 (0.1)	2 (0.3)	0.585	0.36	0 (0.0)	0 (0.0)
Major bleeding related to AF ablation	1 (0.1)	5 (0.7)	< 0.001	0.88	0 (0.0)	0 (0.0)
Non-major bleeding related to AF ablation	1 (0.1)	0 (0.0)	0.9	1	1 (0.7)	1 (0.1)
Serious adverse event of special interest related to RC therapy						
Blood pressure-related event	0 (0.0)	1 (0.1)	1	0.95	0 (0.0)	0 (0.0)
Hospitalization for AF	4 (0.6)	7 (1.0)	0.432	0.896	1 (0.7)	2 (0.2)
Other cardiovascular event	1 (0.1)	4 (0.6)	0.222	0.349	1 (0.7)	0 (0.0)
Other event	1 (0.1)	0 (0.0)	0.831	0.993	1 (0.7)	2 (0.2)
Syncope	3 (0.4)	1 (0.1)	0.23	0.264	0 (0.0)	1 (0.1)
Hospitalization for worsening of HF with Decomp HF	2 (0.3)	1 (0.1)	0.22		0 (0.0)	0 (0.0)
Implantation of a pacemaker, defibrillator, or other	5 (0.7)	3 (0.4)	0.614	0.789	0 (0.0)	4 (0.3)

AF, atrial fibrillation; HF, heart failure; RC, rhythm control; UC, usual care.
*Mixed logistic regression models with a random effect for site were used for comparison of intake at ever vs. never for patients with ERC treatment.
**Mixed logistic regression models with a random effect for site were used for comparison of intake at 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).

SCBs in patients with LVH or in those with HF with preserved ejection fraction.[10,16,22,23] The recommendations of the current ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death provide more flexibility for SCB treatment also in patients with structural heart disease, when no myocardial infarction has been reported.[24,25]

Considerations for the safety of long-term sodium channel blocker intake in patients with structural heart disease

The Flec-SL trial has shown that long-term use of flecainide is more effective as compared to short-term use after electrical cardioversion with a comparable safety profile.[9] However, long-term SCB use in the Flec-SL trial was defined as an intake of no longer than 6 months and patients with a reduced LV function <40% were excluded.[9] This underlines the need for additional data from large prospective patient cohorts for long-term safety of SCB use in patients with and without stable cardiac comorbidities. Recent analyses, obtained from non-randomized cohorts, have shown that flecainide does not show an increased rate of proarrhythmia or HF events in patients with stable or revascularized CAD when compared to the treatment with class III AADs.[26] In addition, experimental data have demonstrated only limited impact of flecainide and propafenone on voltage-gated potassium channels.[27]

Specific trials have shown that antiarrhythmic drugs remain effective after AF ablation.[28] The original trials of propafenone and flecainide tested their use in patients not undergoing AF ablation. Of note, in the POWDER-AF trial patients treated with antiarrhythmic drugs, mainly based on SCBs, after catheter ablation did not show a higher number of adverse events related to antiarrhythmic drug therapy during a 1-year follow-up period.[28]

In the EAST-AFNET 4 trial, rhythm control was obtained using AADs in the majority of patients (>85%), although SCB therapy considered as the primary initial treatment in patients randomized to ERC in the EAST-AFNET 4 trial was higher (>40%)[1] than the final treatment with SCB (21% of patients at baseline, *Table 1*). The present subanalyses provide detailed insights into the safety and efficacy of long-term SCB intake in the EAST-AFNET 4 population. Several primary safety events were reported in patients treated with SCB in the present subanalyses, but events potentially related to AAD treatment such as bradycardia, torsade de pointes tachycardia or sudden cardiac death as well as life-threatening events were rarely seen in both groups (*Table 2*). Remarkably, similar event rates of the primary safety endpoint were observed in patients with and without stable structural heart disease, which suggests that patients with stable heart disease including stable

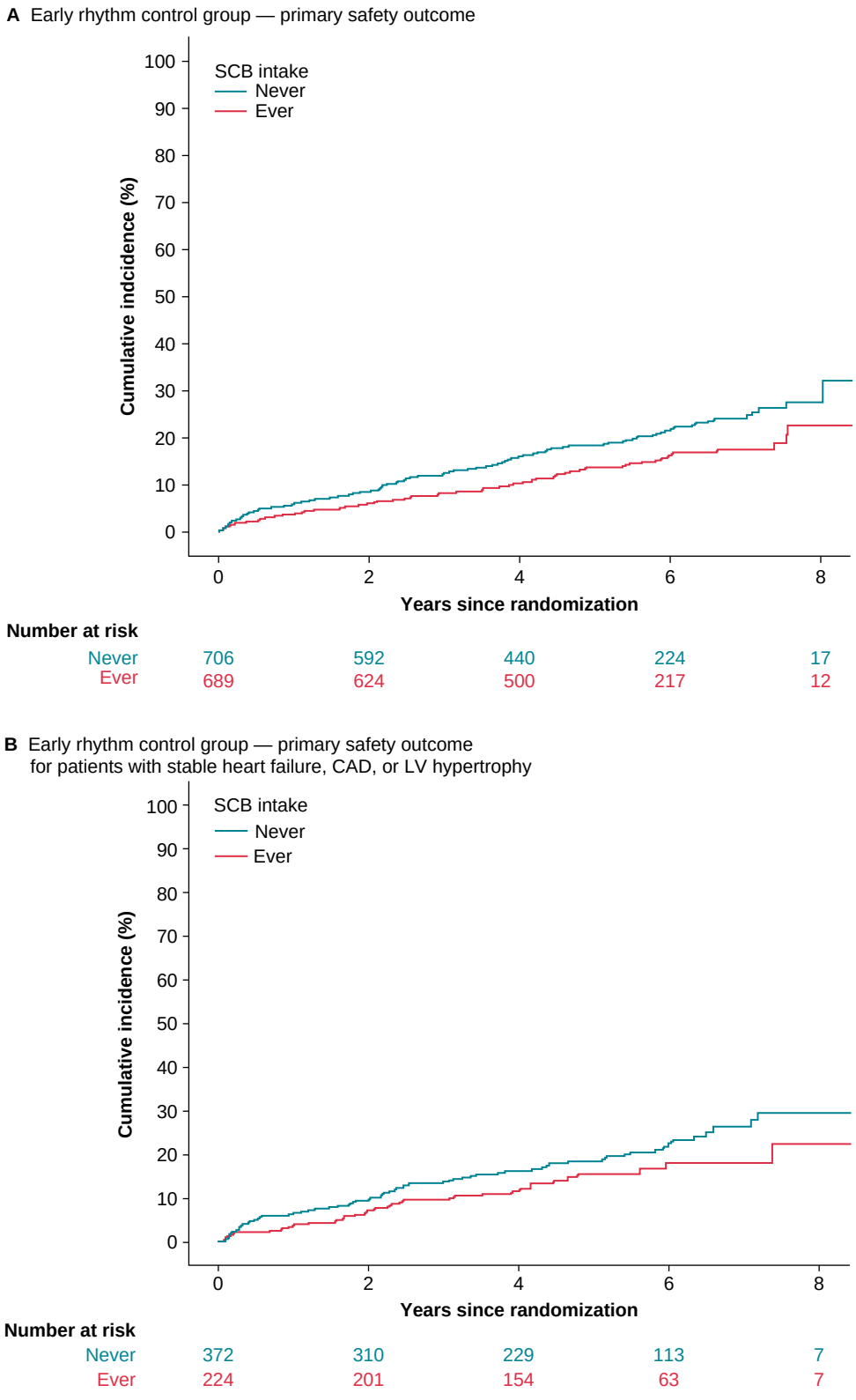


Figure 4 Cumulative incidence of the primary safety outcome in all patients with SCB intake (*A*) and patients with stable cardiovascular disease (severe CAD, HF, and LV hypertrophy) (*B*) in the ERC group. CAD, coronary artery disease; LV, left ventricular; SCB, sodium channel blocker.

Table 4 Cox models with time-dependent SCB intake for patients with ERC—safety outcomes

Predictors	Primary composite safety outcome		Death		SAE of special interest related to RC therapy	
	HR (CI)	*P*	HR (CI)	*P*	HR (CI)	*P*
Time-dependent SCB intake	0.62 (0.45–0.86)	**0.004**	0.40 (0.24–0.68)	**0.001**	0.89 (0.52–1.53)	0.685
Age	1.07 (1.05–1.09)	**<0.001**	1.09 (1.07–1.12)	**<0.001**	1.03 (1.00–1.06)	0.055
Male gender	1.10 (0.84–1.44)	0.483	1.39 (0.97–1.98)	0.074	0.74 (0.45–1.22)	0.243
CAD	1.05 (0.76–1.46)	0.760	0.99 (0.65–1.50)	0.961	1.14 (0.60–2.17)	0.683
LVH on ECG	1.85 (1.08–3.16)	**0.022**	2.20 (1.13–4.25)	**0.017**	1.56 (0.56–4.36)	0.401
Stable HF	1.26 (0.95–1.66)	0.112	1.52 (1.06–2.16)	**0.022**	1.15 (0.68–1.95)	0.595

CAD, coronary artery disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; LVH, left ventricular hypertrophy; RC, rhythm control; SAE, serious adverse event; SCB, sodium channel blocker.
Values reaching statistical significance are shown in bold characters.

Table 5 Primary safety outcomes in patients with stable cardiovascular comorbidities (stable CAD, stable HF, LVH >15 mm) stratified for SCB intake at baseline, later SCB intake, and no SCB intake

	Early rhythm control				Usual care	
	Ever	Never	*P*-value*	*P*-value adj**	Ever	Never
n	224	372			42	550
Primary composite safety outcome	34 (15.2)	74 (19.9)	0.557	0.622	6 (14.3)	109 (19.8)
Stroke	4 (1.8)	13 (3.5)	0.233	0.401	4 (9.5)	22 (4.0)
Death	18 (8.0)	51 (13.7)	0.121	0.166	1 (2.4)	86 (15.6)
Serious adverse event of special interest related to rhythm control therapy	12 (5.4)	18 (4.8)	0.604	< 0.001	1 (2.4)	10 (1.8)
Serious adverse event related to antiarrhythmic drug therapy						
Non-fatal cardiac arrest	0 (0.0)	0 (0.0)			0 (0.0)	1 (0.2)
Drug toxicity of AF-related drug therapy	1 (0.4)	3 (0.8)	0.607	0.348	0 (0.0)	1 (0.2)
Drug-induced bradycardia	4 (1.8)	3 (0.8)	0.295	0.342	0 (0.0)	3 (0.5)
Atrioventricular block	1 (0.4)	0 (0.0)	0.996	0.996	0 (0.0)	0 (0.0)
Torsade de pointes tachycardia	1 (0.4)	0 (0.0)	< 0.001	1	0 (0.0)	0 (0.0)
Serious adverse event related to AF ablation						
Pericardial tamponade	1 (0.4)	0 (0.0)	0.865		0 (0.0)	0 (0.0)
Major bleeding related to AF ablation	1 (0.4)	3 (0.8)	0.607	0.927	0 (0.0)	0 (0.0)
Non-major bleeding related to AF ablation	1 (0.4)	0 (0.0)	0.926	1	1 (2.4)	0 (0.0)
Serious adverse event of special interest related to RC therapy						
Blood pressure-related event	0 (0)	0 (0)			0 (0)	0 (0)
Hospitalization for AF	1 (0.4)	5 (1.3)	0.312		0 (0.0)	2 (0.4)
Other cardiovascular event	1 (0.4)	2 (0.5)	0.45	0.588	0 (0.0)	0 (0.0)
Other event	0 (0.0)	0 (0.0)			0 (0.0)	2 (0.4)
Syncope	0 (0.0)	1 (0.3)	1	1	0 (0.0)	1 (0.2)
Hospitalization for worsening of HF with Decomp HF	0 (0.0)	1 (0.3)	1		0 (0.0)	0 (0.0)
Implantation of a pacemaker, defibrillator, or other	1 (0.4)	2 (0.5)	0.268	0.198	0 (0.0)	3 (0.5)

AF, atrial fibrillation; HF, heart failure.
*Mixed logistic regression models with a random effect for site were used for comparison of intake at BL vs. never for patients with ERC treatment.
**Mixed logistic regression models with a random effect for site were used for comparison of intake at BL vs. never for patients with ERC treatment adjusted for age, stable HF, CAD, and type of HF by LVEF (cut-off 35).

or revascularized CAD were safely treated with SCB therapy in the EAST-AFNET 4 trial unless otherwise contraindicated. Sinus rhythm at the 12- and 24-month follow-up was similar in patients with or without SCB use in the ERC group. However, patients not treated with SCB were often treated with other effective antiarrhythmic drugs such as amiodarone or dronedarone.

Safety of long-term sodium channel blocker intake in patients with coronary artery disease, left ventricular hypertrophy, and heart failure

In the EAST-AFNET 4 trial, patients with unstable angina, untreated CAD, or unstable HF were excluded, but a relevant number of patients with stable CAD were randomized. According to the findings of these subanalyses, SCBs were safely applied in this patient population of the EAST-AFNET 4 trial as safety events were observed only in a minority of these patients and lethal complications such as cardiovascular death and life-threatening arrhythmias were rare (*Table 5*).

Apparently, in our subanalyses, primary safety events were not more often observed in patients with stable HF as compared to patients without. Furthermore, LV function and NYHA class remained stable in the majority of patients and did less often worsen during follow-up when compared with patients without structural heart disease (*Figures 2* and *3*); neither relevant impairment of systolic LV function nor an increase of the NYHA class was observed in any of the subgroups with SCB intake. The observations mainly apply to patients with preserved LV function. These findings show that patients with stable cardiac comorbidities receiving SCB therapy did not have more safety events than patients treated with other AADs in the EAST-AFNET 4 trial supporting early medical rhythm control in these patients with high efficacy and a low risk of harm. Of note, patients in the EAST-AFNET 4 trial were treated with the recommended SCB dose (200 mg flecainide/day, 600 mg propafenone/day), whereas clinical practice tends to prescribe lower doses.[29]

Strengths and limitations

This is a post hoc subgroup analysis of the prospective randomized EAST-AFNET 4 trial, and therefore, although obtained from a large international randomized multicentre cohort, the results remain hypothesis-generating. Sodium channel blocker intake varied during study participation resulting in some patients with continuous SCB intake and others with on/off SCB therapy. The term severe CAD was defined as previous myocardial infarction, CABG, or PCI; however, detailed information about the severity of the disease (single-/multivessel disease as well as presence of untreated stenoses of the coronary arteries) was not available for analysis. Although the available information, especially the normal global LV function, suggests that only patients with small myocardial infarctions were treated with SCBs in the EAST-AFNET 4, no information on exercise testing and no information on the type, size, or location of previous myocardial infarction were available. The suitability for SCB therapy was assessed by the local study team. The main outcome of this analysis is the safety of SCB therapy in the trial without mandated exercise testing or routine angiography. A majority of patients with HF had HFpEF; the definition of HF in patients with ejection fraction <50% was based on symptoms and therefore provides limited granularity. Similarly, the definition that the authors use for LVH does not consider the underlying aetiology.

As flecainide therapy alone might accelerate ventricular conduction during AF and could result in 1:1 flutter with high ventricular rates, concomitant β-blocker therapy is recommended due to its AV node slowing effects. In the EAST-AFNET 4 trial, 1:1 atrial flutter was rarely observed. The high use of concomitant β-blocker therapy in the SCB group (flecainide-only-treated patients 78% and propafenone-only-treated patients 80%) might have contributed to the encouraging results for a safe and effective long-term use of flecainide in the present subanalyses. The low overall number of safety events precluded a meaningful analysis of specific patient features that may be associated with safety events with and without SCB therapy. Much larger data bases, e.g. stemming from merged electronic health records and prescribing information, may address this topic.

No information to the actual dosage of the medications can be provided. However, recommended dosing of SCBs was defined in the study protocol according to the AF guidelines (flecainide daily dose 200–300 mg, propafenone daily dose 450–600 mg).[1,10]

Of note, the results have to be interpreted with caution due to differences in age and cardiovascular comorbidities of the SCB therapy group with other patients, making comparison more difficult. The main finding of this analysis is the long-term safety of therapy with flecainide and propafenone, including in selected patients deemed unsuitable for these drugs. In addition, patients in the SCB group were less often treated with digoxin which may have contributed to the observed safety profile.[30–32]

Nonetheless, patients in this analysis were treated for a long time period with a median SCB intake of 2105 patient-years (median therapy duration 1153 [237, 1828] days), providing robust information on the long-term effectiveness and safety of SCB in ERC therapy in patients with AF with and without stable structural heart disease so far.

Although sensitivity analyses were performed considering age, stable HF, CAD, and type of HF as stratified by LVEF, we cannot exclude other confounders in the cohort of non-SCB intake, as patients in the SCB group had a higher comorbidity burden. This might at least in part explain why the primary safety endpoint in patients with SCB intake was less often observed than in patients not treated with SCB. Some patients initiated SCB later in the trial, but the overall findings mainly apply to patients with relatively recently diagnosed AF.

Conclusion

The findings of this subanalysis in selected patients of the EAST-AFNET 4 trial show that no safety signals were observed during SCB therapy for ERC therapy in patients with AF with or without stable cardiovascular disease such as CAD, LVH, or stable HF (mainly patients with HFpEF) in the EAST-AFNET 4 trial.

Supplementary material

Supplementary material is available at *Europace* online.

Funding

EAST-AFNET 4 was supported by a grant from the German Ministry of Education and Research (01 GI 0204), the German Center for Cardiovascular Research (DZHK), the Atrial Fibrillation Network (AFNET), the European Heart Rhythm Association, St. Jude Medical—Abbott, Sanofi, and the German Heart Foundation. These analyses received additional support from the European Union [grant agreement 633196 (CATCH ME) to P.K., L.F., and AFNET; grant agreement EU IMI 116074 [BigData@Heart] to P.K.; and [grant agreement 965286 (MAESTRIA) to L.F., U.S., A.G., and AFNET], the British Heart Foundation (FS/13/43/30324, PG/17/30/32961, PG/20/22/35093, and AA/18/2/34218, to P.K. and L.F.), and the Leducq Foundation (to P.K.).

Conflict of interest: A.R.: Consultant fees, travel grants or lecture fees from Medtronic, Biosense Webster, Abbott, Boston Scientific, Ablamap, Philips, Cardiofocus, Bayer, Pfizer and Novartis, Edwards and Lifetech. Committee: German Society of Cardiology (Select-chair of EP community). L.E.: Grants/contracts: research support by the German heart foundation. Consulting fees Boston Scientific, lecture fees for various medical companies. Society, committee: German Society of Cardiology; European Society of Cardiology; European Heart Rhythm Society. K.B.: no COIs. J.C.: Participation on a data safety monitoring board: Anthos, Johnson and Johnson, Enso, Bayer, Charité. H.C.: Grants/contracts: ZonMw grant no. 104021005 RACE 9 Device-based rate vs. rhythm control treatment in patients with symptomatic recent-onset atrial fibrillation in the emergency department (RACE 9). Consulting fees: InCarda Therapeutics, Roche, Sanofi, Atricure. Payment or Honoraria: Medtronic. Participation on a data safety monitoring board or advisory board: Chair DSMB Decision trial. Committee/society: DZHK, German Centre for Cardiovascular research. A.G.: Grants/contracts: Maestria Grant EU 965286. Consulting fees:

Sanofi-Aventis, Bayer, Astra Zeneca, Daiichi Sankyo, BMS/Pfizer, Viofor, Boston Scientific, Medtronic, Menarini. G.B.: Chair, advisory board to AFNET e.V., no payment. M.L.: No COIs. A.M.: Consulting fees: Medtronic, Johnson and Johnson, Boston Scientific, LifeTech. Lecture honoraria: Medtronic, Johnson and Johnson, Lifetech, Pfizer, Boston Scientific, Bayer, Bristol Meyer Squibb. L.R.: No COIs. U.S.: Grants/contracts: EU: CATCH ME, MAESTRIA, Personalize AF, REPAIR, Dutch Heart foundation, RACE V Embrace. Consulting fees: Roche advisory board, YourRhythmics BV. Payment or honoraria: Johnson and Johnson. Patents: non-invasive classification of AF with ECG. Society/Committee: Board of directors of AFNET. Stock or stock options: YourRhythmics BV. E.V.: Support for present manuscript: AFNET: payments made to my institution. Outside this work: Biotronik: payments made to my institution. K.W.: All support payment for manuscript: AFNET. Grants/contracts: Biotronik, Resmed. Payment/honoraria: Boston scientific, Novartis. A.Z.: Support for present manuscript: AFNET: payments made to my institution. Outside this work: Biotronik: payments made to my institution. Grants/contracts: Biotronik, Resmed. Payment/honoraria: Boston scientific. H.H.: Unconditional Research Grants through the University of Hassels and Antwerp: Abbott, Medtronic, Biotronik, Boston scientific, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Pfizer–BMS. Payment or honoraria: Bayer, Biotronik, Bristol Myers Squibb, Daiichi Sankyo, Milestone Pharmaceuticals, Centrix India, CTI Germany, European Society of Cardiology, Medscape, Springer healthcare. Participation on a data safety monitoring board or advisory board: Member, DSBM Prestige-AF. S.W.: Grants: Boston Scientific, Consulting fees: Boston Scientific, Abbott. Speakers Bureau: BSCI; Abbott, BMS, Medtronic. L.F.: Institutional government or charity research support: European Union Horizon 2020 MAESTRIA [grant agreement number 965286 (MAESTRIA)] European Union Horizon 2020 CATCH ME, [grant agreement number 633196 (CATCH ME), European Union Horizon 2020 AFFECT-EU, grant agreement number 847770 (AFFECT-EU)] Institutional governmental support, National Institute for Health and Care Research NIHR, Medical Research Council (UK), German Centre for Cardiovascular Research DZHK. Support for attending meetings: ESC, EHRA, and ESC working groups, ARVC patient organization (charity). Patents planned issued or pending: L.F. is listed as inventor of two patents (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). Society/committee: BHF project grant committee (charity). BHF chair committee visits (charity), AFNET steering committee (charity), ARVC patient organization (charity). Equipment and analytics to AFNET for AFNET 9: Preventicus, Trial costs to AFNET for AFNET 9: Daiichi Sankyo. R.S. has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme under the grant agreement No 648131, from the European Union's Horizon 2020 research and innovation programme under the grant agreement no. 847770 (AFFECT-EU) and German Center for Cardiovascular Research (DZHK e.V.) (81Z1710103 and 81Z0710114); German Ministry of Research and Education (BMBF 01ZX1408A) and ERACoSysMed3 (031L0239). Wolfgang Seefried project funding German Heart Foundation. Lecture fees and advisory board fees from BMS/Pfizer and Bayer. Society/committee: ESC stroke council nucleus member. C.M.: Grants or contracts: Research funding from German Center for Cardiovascular Research (Promotion of women scientists programme; *FKZ 81X3710112*); *Deutsche Stiftung für Herzforschung*; *Dr. Rolf M. Schwiete Stiftung*; NDD; Loewenstein Medical. Payment or honoraria: AstraZeneca, Novartis, Boehringer Ingelheim/Lilly, Bayer, Pfizer, Sanofi, Aventis, Apontis, Abbott. Support for attending meetings: AstraZeneca, Novartis, Boehringer Ingelheim/Lilly, Novo Nordisk. Participation on a data safety monitoring board or advisory board: Boehringer Ingelheim/Lilly; Novo Nordisk. P.K.: P.K. was partially supported by European Union AFFECT-AF (grant agreement 847770), and MAESTRIA (grant agreement 965286), British Heart Foundation (PG/17/30/32961; PG/20/22/35093; AA/18/2/34218), German Center for Cardiovascular Research supported by the German Ministry of Education and Research (DZHK, grant numbers DZHK FKZ 81X2800182, 81Z0710116, and 81Z0710110), German Research Foundation (Ki 509167694), and Leducq Foundation. P.K. receives research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research, from several drug and device companies active in atrial fibrillation. P.K. is listed as inventor on two issued patents held by University of Hamburg (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). P.K. receives research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Center for Cardiovascular Research, from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies in the past, but not in the last 3 years. P.K. is board member of the ESC and speaker of the board AFNET.

Data availability

Data are available on reasonable request (contact: info@kompetenznetz-vorhofflimmern.de).

References

1. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A *et al.* Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;**383**:1305–16.
2. Metzner A, Suling A, Brandes A, Breithardt G, Camm AJ, Crijns H *et al.* Anticoagulation, therapy of concomitant conditions, and early rhythm control therapy: a detailed analysis of treatment patterns in the EAST-AFNET 4 trial. *Europace* 2021;**23**:ii34–9.
3. Rillig A, Magnussen C, Ozga AK, Suling A, Brandes A, Breithardt G *et al.* Early rhythm control therapy in patients with atrial fibrillation and heart failure. *Circulation* 2021;**144**:845–58.
4. Rillig A, Borof K, Breithardt G, Camm AJ, Crijns HJGM, Goette A *et al.* Early rhythm control in patients with atrial fibrillation and high comorbidity burden. *Circulation* 2022;**146**:836–47.
5. Willems S, Borof K, Brandes A, Breithardt G, Camm AJ, Crijns H *et al.* Systematic, early rhythm control strategy for atrial fibrillation in patients with or without symptoms: the EAST-AFNET 4 trial. *Eur Heart J* 2022;**43**:1219–30.
6. Eckardt L, Sehner S, Suling A, Borof K, Breithardt G, Crijns H *et al.* Attaining sinus rhythm mediates improved outcome with early rhythm control therapy of atrial fibrillation: the EAST-AFNET 4 trial. *Eur Heart J* 2022;**43**:4127–44.
7. Jensen M, Suling A, Metzner A, Schnabel RB, Borof K, Goette A *et al.* Early rhythm-control therapy for atrial fibrillation in patients with a history of stroke: a subgroup analysis of the EAST-AFNET 4 trial. *Lancet Neurol* 2023;**22**:45–54.
8. Dickow J, Kany S, Roth Cardoso V, Ellinor PT, Gkoutos GV, Van Houten HK *et al.* Outcomes of early rhythm control therapy in patients with atrial fibrillation and a high comorbidity burden in large real-world cohorts. *Circ Arrhythm Electrophysiol* 2023;**16**:e011585.
9. Kirchhof P, Andresen D, Bosch R, Borggrefe M, Meinertz T, Parade U *et al.* Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label, blinded endpoint assessment trial. *Lancet* 2012;**380**:238–46.
10. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C *et al.* 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498.
11. Remme CA, Heijman J, Gomez AM, Zaza A, Odening KE. 25 years of basic and translational science in EP Europace: novel insights into arrhythmia mechanisms and therapeutic strategies. *Europace* 2023;**25**:euad210.
12. Allen LaPointe NM, Dai D, Thomas L, Piccini JP, Peterson ED, Al-Khatib SM. Comparisons of hospitalization rates among younger atrial fibrillation patients receiving different antiarrhythmic drugs. *Circ Cardiovasc Qual Outcomes* 2015;**8**:292–300.
13. Aliot E, Capucci A, Crijns HJ, Goette A, Tamargo J. Twenty-five years in the making: flecainide is safe and effective for the management of atrial fibrillation. *Europace* 2011;**13**:161–73.
14. Frommeyer G, Eckardt L. Drug-induced proarrhythmia: risk factors and electrophysiological mechanisms. *Nat Rev Cardiol* 2016;**13**:36–47.
15. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH *et al.* Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;**324**:781–8.
16. Echt DS, Ruskin JN. Use of flecainide for the treatment of atrial fibrillation. *Am J Cardiol* 2020;**125**:1123–33.
17. Wolfes J, Ellermann C, Frommeyer G, Eckardt L. Evidence-based treatment of atrial fibrillation around the globe: comparison of the latest ESC, AHA/ACC/HRS, and CCS guidelines on the management of atrial fibrillation. *Rev Cardiovasc Med* 2022;**23**:56.
18. Klamer TA, Bots SH, Neefs J, Tulevski II, Ruijter HMD, Somsen GA *et al.* Rate and rhythm control treatment in the elderly and very elderly patients with atrial fibrillation: an observational cohort study of 1497 patients. *Curr Probl Cardiol* 2022;**47**:100996.
19. Eckardt L, Wolfes J, Frommeyer G. Benefits of early rhythm control of atrial fibrillation. *Trends Cardiovasc Med* 2023. doi:10.1016/j.tcm.2023.04.001
20. Nielsen JC, Lin YJ, de Oliveira Figueiredo MJ, Sepehri Shamloo A, Alfie A, Boveda S *et al.* European heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on risk assessment in cardiac arrhythmias: use the right tool for the right outcome, in the right population. *Europace* 2020;**22**:1147–8.
21. Cardiac Arrhythmia Suppression Trial III. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992;**327**:227–33.

22. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;**130**:2071–104.
23. Eckardt L, Haverkamp W, Gottker U, Madeja M, Johna R, Borggrefe M et al. Divergent effect of acute ventricular dilatation on the electrophysiologic characteristics of d,l-sotalol and flecainide in the isolated rabbit heart. *J Cardiovasc Electrophysiol* 1998;**9**:366–83.
24. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;**43**:3997–4126.
25. Konemann H, Dagres N, Merino JL, Sticherling C, Zeppenfeld K, Tfelt-Hansen J et al. Spotlight on the 2022 ESC guideline management of ventricular arrhythmias and prevention of sudden cardiac death: 10 novel key aspects. *Europace* 2023;**25**:euad091.
26. Burnham TS, May HT, Bair TL, Anderson JA, Crandall BG, Cutler MJ et al. Long-term outcomes in patients treated with flecainide for atrial fibrillation with stable coronary artery disease. *Am Heart J* 2022;**243**:127–39.
27. Rolf S, Haverkamp W, Borggrefe M, Musshoff U, Eckardt L, Mergenthaler J et al. Effects of antiarrhythmic drugs on cloned cardiac voltage-gated potassium channels expressed in Xenopus oocytes. *Naunyn Schmiedebergs Arch Pharmacol* 2000;**362**:22–31.
28. Duytschaever M, Demolder A, Phlips T, Sarkozy A, El Haddad M, Taghji P et al. PulmOnary vein isolation With vs. without continued antiarrhythmic Drug trEatment in subjects with Recurrent Atrial Fibrillation (POWDER AF): results from a multicentre randomized trial. *Eur Heart J* 2018;**39**:1429–37.
29. Andrade JG, Wells GA, Deyell MW, Bennett M, Essebag V, Champagne J et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. *N Engl J Med* 2021;**384**:305–15.
30. Kirchhof P, Engelen M, Franz MR, Ribbing M, Wasmer K, Breithardt G et al. Electrophysiological effects of flecainide and sotalol in the human atrium during persistent atrial fibrillation. *Basic Res Cardiol* 2005;**100**:112–21.
31. Ellermann C, Wolfes J, Puckhaber D, Bögeholz N, Leitz P, Lange PS et al. Digitalis promotes ventricular arrhythmias in flecainide- and ranolazine-pretreated hearts. *Cardiovasc Toxicol* 2019;**19**:237–43.
32. Milberg P, Frommeyer G, Ghezelbash S, Rajamani S, Osada N, Razvan R et al. Sodium channel block by ranolazine in an experimental model of stretch-related atrial fibrillation: prolongation of interatrial conduction time and increase in post-repolarization refractoriness. *Europace* 2013;**15**:761–9.