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RESEARCH ARTICLE

Empagliflozin in heart failure with preserved ejection fraction with and without atrial fibrillation

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Aims Atrial fibrillation/flutter (AF) is common in heart failure (HF) with preserved left ventricular ejection fraction (LVEF) and associated with worse outcomes. Empagliflozin reduces cardiovascular death or HF hospitalizations and slows estimated glomerular filtration rate (eGFR) decline in patients with HF and LVEF >40%. We aimed to assess the efficacy and safety of empagliflozin in improving outcomes in patients with HF and LVEF >40% with and without AF.

Methods and results In this pre-defined secondary analysis of EMPEROR-Preserved, we compared the effects of empagliflozin versus placebo on the primary and secondary endpoints and safety outcomes, stratified by baseline AF, defined as AF reported in any electrocardiogram before empagliflozin initiation or in medical history. Among 5988 patients randomized, 3135 (52%) had baseline AF; these patients were older, with worse functional class, more previous HF hospitalizations and higher natriuretic peptides compared to those without AF (all $p < 0.001$). After a median of 26 months, empagliflozin reduced cardiovascular death or HF hospitalization compared to placebo to a similar extent in patients with and without AF (hazard ratio [HR] 0.78 [95% confidence interval 0.66–0.93] vs. 0.78 [0.64–0.95], interaction $p = 0.96$). Empagliflozin also reduced total HF hospitalizations (HR 0.73 [0.57–0.94] vs. 0.72 [0.54–0.95], interaction $p = 0.94$) and annual eGFR decline (difference = 1.368 vs. 1.372 ml/min/1.73 m^2/year, interaction $p = 0.99$) consistently in patients with and without AF. There was no increase in serious adverse events with empagliflozin versus placebo in patients with and without AF.

Conclusions In patients with HF and ejection fraction >40%, empagliflozin reduced the risk of serious HF events and slowed the eGFR decline regardless of baseline AF.

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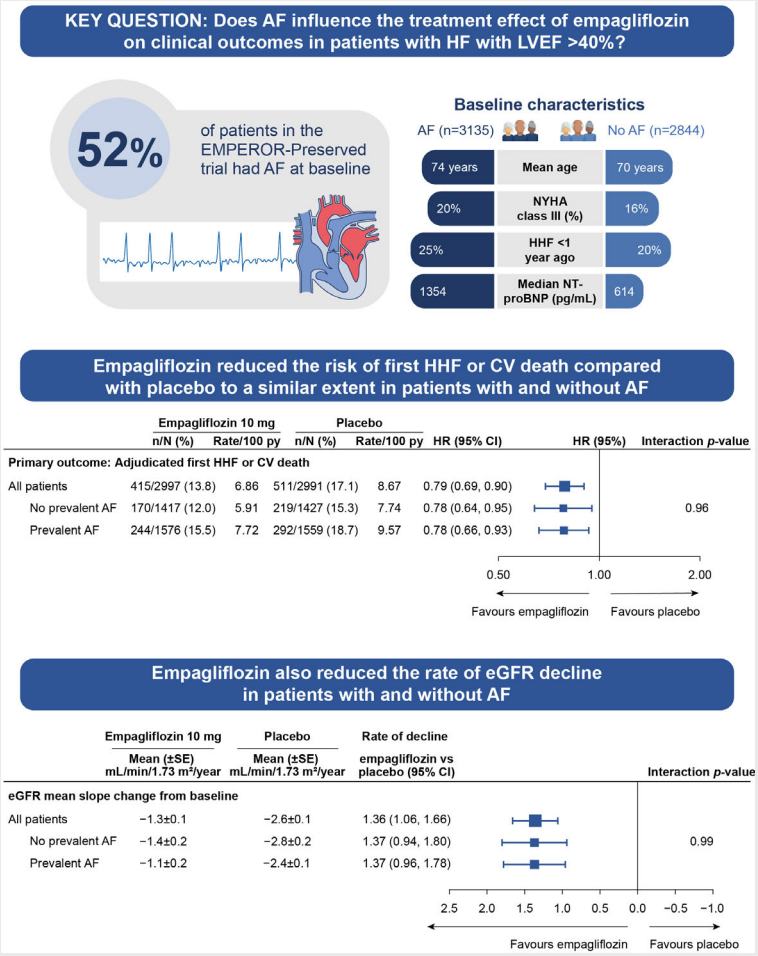
Graphical Abstract



Main results from the subanalysis by AF status in EMPEROR-Preserved: In patients with HF and EF >40% empagliflozin reduced the risk of serious HF events and slowed the eGFR decline regardless of baseline AF. AF, atrial fibrillation/flutter; CI, confidence interval; CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SE, standard error.

Keywords Heart failure with preserved ejection fraction • Empagliflozin • Sodium–glucose cotransporter 2 inhibitor • Atrial fibrillation • Atrial flutter • Prognosis

Introduction

Atrial fibrillation or flutter (AF) is encountered in up to two thirds of patients with heart failure (HF) and preserved ejection fraction (HFpEF).[1] Patients with both HFpEF and AF have worse symptoms and outcomes than those with either condition alone.[1,2] It has been proposed that HFpEF and AF are closely linked with a common pathogenetic background that is reflected as atrial disease, a preceding entity that may provide the 'common soil' for the development of both conditions.[3]

In HF with reduced ejection fraction (HFrEF), meta-analyses have shown that the coexistence of AF impairs the survival benefit of beta-blocker therapy.[4,5] Given the lack of effective therapies in HFpEF, it is not known whether the therapeutic response of these patients also varies according to the presence or absence of AF. The sodium–glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin was the first drug shown to improve cardiovascular (CV) outcomes and to slow renal function decline in HFpEF.[6]

In patients with type 2 diabetes mellitus and established CV disease, empagliflozin reduced HF-related and renal events

irrespective of the presence of AF.[7] Here we aim to assess whether the coexistence of AF modifies the beneficial effects of empagliflozin in patients with HFpEF.

Methods

This is a pre-defined secondary analysis of the EMPEROR-Preserved trial. The study design and main results have been described elsewhere.[6] In brief, EMPEROR-Preserved was a phase III, double-blind, parallel-group, placebo-controlled trial that enrolled 5988 patients with symptomatic HF, an ejection fraction >40%, elevated natriuretic peptide levels and evidence of structural cardiac disease or documented prior hospitalization for HF. Patients were randomized to empagliflozin 10 mg daily or placebo. The primary endpoint was the time to first hospitalization for HF or CV death. The key secondary endpoints included first and recurrent hospitalizations for HF and the rate of decline in the estimated glomerular filtration rate (eGFR) during double-blind treatment (eGFR slope). Other secondary endpoints included time to CV death, first hospitalization for HF, all-cause death, and time to a first composite renal endpoint [defined as time to first occurrence of (i) chronic dialysis; (ii) renal transplantation; (iii) sustained reduction of ≥40% in eGFR; or (iv) sustained eGFR <15 ml/min/1.73 m^2 for patients with baseline eGFR ≥30 ml/min/1.73 m^2 or <10 ml/min/1.73 m^2 for patients with baseline eGFR <30 ml/min/1.73 m^2]. The trial was approved by the institutional ethics committee at each site and all patients gave written informed consent.

In this analysis, we compared the effects of empagliflozin versus placebo on the primary and secondary endpoints between patients with and without AF at baseline. AF was defined as AF reported in any electrocardiogram (ECG) before study treatment intake or history of AF reported as medical history.

Statistical analysis

Baseline characteristics and differences between patients with and without AF were analysed using descriptive statistics. Categorical variables were compared using the chi-square test and continuous variables were compared using the *t*-test. For time-to-first-event analyses, differences between the placebo and empagliflozin groups were assessed for statistical significance using a Cox proportional hazards model, with pre-specified covariates of gender, geographical region, diabetes status at baseline, left ventricular ejection fraction, age and eGFR at baseline. In addition, for the primary endpoint of CV death or HF hospitalization, difference between patients with and without AF in the placebo arm are compared separately using a same Cox model. For the analysis of total (first and repeated) events, between-group differences were assessed using a joint frailty model, with CV death as a competing risk. Between-group difference in the slope of change in eGFR was analysed using a random intercept random slope model including baseline eGFR, baseline left ventricular ejection fraction and age as linear covariate and sex, region, baseline diabetes status, and baseline eGFR-by-time, treatment-by-AF group, and treatment-by-time-by-AF group as fixed effects; the model allows for randomly varying slope and intercept between patients. eGFR slope was analysed using on-treatment data. The mixed model for repeated measures and the joint frailty model included the same covariates as the Cox model. To assess the consistency of effects across subgroups, subgroup-by-treatment interaction terms were added in the models. In addition, time to new onset of atrial fibrillation was analysed using the same Cox model among patients who did not have history of AF. Analyses for safety were performed including all patients who had received at least one dose of empagliflozin or placebo. In addition, for the primary endpoint, total hospitalizations for HF and the slope of change in eGFR, subgroup analyses by type of atrial fibrillation (persistent/permanent vs. paroxysmal) were undertaken in patients with a history of atrial fibrillation. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). All *p*-values reported are two-sided, and $p < 0.05$ was considered as statistically significant. No adjustments for multiple testing were made.

Results

Baseline atrial fibrillation or flutter prevalence

Among 5988 patients with HFpEF enrolled in the EMPEROR-Preserved trial, 3135 (52.4%) had AF at baseline, including 3132 (99.9%) with a history of AF reported as medical history and 2080 (66.3%) according to baseline ECG. Among patients with a history of AF, 1046 (33.4%) had sinus rhythm at baseline ECG. In contrast, 3 (0.05%) had newly diagnosed AF according to baseline ECG.

Baseline patient characteristics

Patients with AF were older, more likely having been hospitalized for HF in the past 12 months and less likely to have ischaemic HF aetiology and type 2 diabetes history compared to those without AF (*Table 1*). Patients with AF had worse New York Heart Association (NYHA) class, with more patients having NYHA class III and less patients having NYHA class II symptoms compared to patients without AF, higher heart rate, higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration and lower eGFR level. In terms of medical therapies, the use of neurohormonal blockers was generally high in both groups; patients with AF were more frequently treated with beta-blockers and diuretics and less frequently with angiotensin receptor blockers, compared to those without AF. Among patients with a history of AF, 2740 (87.4%) were using anticoagulant therapy at baseline; mean CHA_2DS_2-VASc score was 4.7 ± 1.4.

Impact of baseline atrial fibrillation or flutter status on patient outcomes

In the placebo group, the primary endpoint of CV death or HF hospitalization occurred in 292 (18.7%) patients with baseline AF compared to 219 (15.3%) patients without AF (hazard ratios [HR] 1.26 [95% confidence interval-CI 1.04−1.51]). Similarly, 318 hospitalizations for HF occurred among patients with AF, and 223 among patients without AF (HR 1.38 [95% CI 1.06−1.79]). In contrast, eGFR decline was comparable in patients with and without AF in the placebo arm (adjusted mean change from baseline to follow-up in eGFR slope, −2.4 and −2.8 ml/min/1.73 m^2, respectively; *p* for difference = 0.45).

Table 1 Baseline characteristics by atrial fibrillation or flutter status[a]

	No ($n = 2844$)	Yes ($n = 3135$)	p-value
Age (years)	69.6 ± 10.2	74.0 ± 8.1	<0.01
Female sex, *n* (%)	1272 (44.7)	1399 (44.6)	0.94
Race, *n* (%)			<0.01
White	2009 (70.6)	2526 (80.6)	
Black/African American	183 (6.4)	74 (2.4)	
Asian	385 (13.5)	438 (14.0)	
Other including mixed races	266 (9.4)	96 (3.1)	
Missing	1 (<0.1)	1 (<0.1)	
Region, *n* (%)			<0.01
North America	306 (10.8)	412 (13.1)	
Latin America	1054 (37.1)	456 (14.5)	
Europe	1005 (35.3)	1682 (53.7)	
Asia	273 (9.6)	413 (13.2)	
Other	206 (7.2)	172 (5.5)	
NYHA class, *n* (%)			0.01
I	2 (0.1)	2 (0.1)	
II	2384 (83.8)	2492 (79.5)	
III	453 (15.9)	628 (20.0)	
IV	5 (0.2)	13 (0.4)	
CHA_2DS_2-VASc score	NA	4.7 ± 1.4	–
KCCQ-CSS	70.8 ± 21.4	70.1 ± 20.9	<0.01
Body mass index (kg/m^2)	29.7 ± 5.9	30.0 ± 5.9	0.02
Heart rate (bpm)	68.3 ± 10.4	72.2 ± 12.8	<0.01
Systolic blood pressure (mmHg)	133.1 ± 15.8	130.7 ± 15.4	<0.01
Diastolic blood pressure (mmHg)	75.1 ± 10.3	76.4 ± 10.7	<0.01
NT-proBNP (pg/ml), median (IQR)	614 (373–1129)	1354 (821–2118)	<0.01
Cause of heart failure, *n* (%)			
Ischaemic	1301 (45.7)	812 (25.9)	<0.01
Medical history, *n* (%)			
Diabetes mellitus	1555 (54.7)	1379 (44.0)	<0.01
Hypertension	2609 (91.7)	2807 (89.5)	<0.01
History of HHF in the last 12 months	573 (20.1)	793 (25.3)	<0.01
COPD	354 (12.4)	440 (14.0)	0.07
eGFR (ml/min/1.73 m^2)	63.0 ± 21.1	58.5 ± 18.3	<0.01
eGFR <60 ml/min/1.73 m^2, *n* (%)	1269 (44.6)	1714 (54.7)	<0.01
Heart failure medication, *n* (%)			
ACE inhibitor	1194 (42.0)	1215 (38.8)	0.01
ARB	1177 (41.4)	1132 (36.1)	<0.01
ARNi	68 (2.4)	65 (2.1)	0.41
Diuretic other than MRA	2146 (75.5)	2654 (84.7)	<0.01
MRA	1038 (36.5)	1202 (38.3)	0.14
Beta-blocker	2419 (85.1)	2740 (87.4)	<0.01
Anticoagulant	172 (6.0)	2740 (87.4)	<0.01
Antiplatelet	2117 (74.4)	709 (22.6)	<0.01

Data given as mean ± standard deviation unless otherwise stated.

ACE, angiotensin-converting enzyme; AF, atrial fibrillation/flutter; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; MRA, mineralocorticoid receptor antagonist; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

[a]AF status defined as AF reported in any ECG before treatment intake or history of AF reported as medical history.

Impact of atrial fibrillation type on patient outcomes

In patients with baseline atrial fibrillation in the placebo group, the risk of the primary endpoint or of HF hospitalizations did not differ by type of atrial fibrillation (persistent/permanent vs. paroxysmal; HR 0.94 [95% CI 0.73–1.21] for the primary endpoint; HR 1.00 [95% CI 0.71–1.41] for HF hospitalizations). The same was true for eGFR slope ($p = 0.31$).

Effects of empagliflozin versus placebo by baseline atrial fibrillation or flutter status

Compared with placebo, empagliflozin reduced the risk of CV death or HF hospitalization to a similar extent in patients with and without AF (HR 0.78 [95% CI 0.66–0.93] and HR 0.78 [95% CI 0.64–0.95], respectively; p for interaction = 0.96) (*Figure 1*). Empagliflozin also reduced the risk of first and recurrent HF hospitalizations compared with placebo consistently in patients with and without AF (HR 0.73 [95% CI 0.57–0.94] and HR 0.72 [95% CI 0.54–0.95], respectively; p for interaction = 0.94). Furthermore, empagliflozin slowed the yearly decline in eGFR similarly in patients with and without AF (slope difference, 1.37 ml/min/1.73 m^2 per year in both; p for interaction = 0.99) (*Figure 1*). The effect of empagliflozin versus placebo on CV death or all-cause death was consistent in patients with and without AF (p for interaction = 0.88 and = 0.39, respectively). Similarly, the effect on the composite renal outcome was consistent in patients with and without AF (p for interaction = 0.60) (*Figure 1*). There were no significant differences in the incidence of stroke between treatment arms in patients either with or without a history of AF (p for interaction = 0.11).

Incidence and impact of new-onset atrial fibrillation

During the study, 235 (8.0%) patients without history of atrial fibrillation developed new-onset atrial fibrillation (116 [8.0%] in empagliflozin and 119 [8.1%]) in placebo; HR 1.00 [95% CI 0.77, 1.29], ($p = 0.98$). There were no significant differences in the incidence of new-onset atrial fibrillation between the treatment arms in patients either with or without diabetes (online supplementary *Table Appendix S1*).

Safety of empagliflozin versus placebo by baseline atrial fibrillation/flutter status

The occurrence of serious adverse events tended to be lower in patients on empagliflozin than placebo; these results were consistent in patients with and without AF (*Table 2*). Whereas the occurrence of acute renal failure and hyperkalaemia was similar in empagliflozin and placebo, there were more patients in empagliflozin that reported adverse events consistent with hypotension and volume depletion, irrespective of AF status.

Discussion

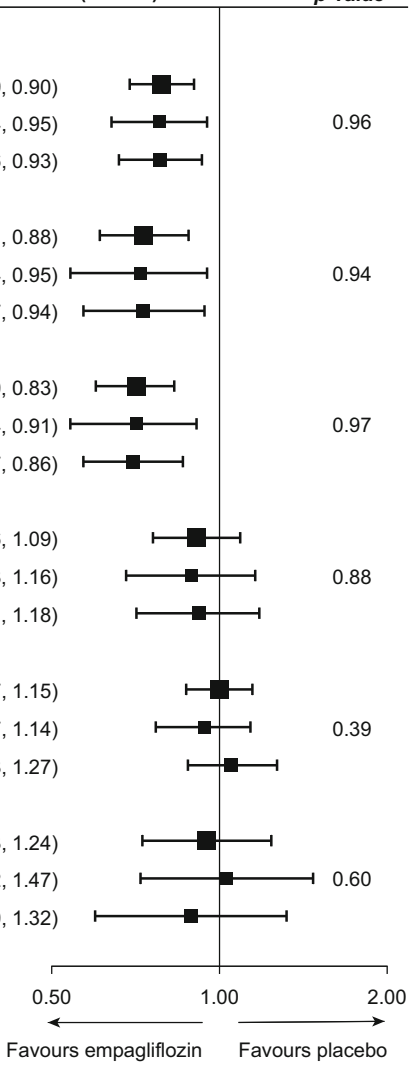
In the present pre-defined secondary analysis of the EMPEROR-Preserved trial, empagliflozin reduced the risk of CV death or HF hospitalization and the risk of total HF hospitalizations compared with placebo to a similar degree in patients with and without AF at baseline (*Graphical Abstract*). Empagliflozin also slowed renal function decline compared with placebo consistently in patients with and without AF. In addition, the safety profile of empagliflozin was confirmed in patients with and without AF.

The preserved benefit of empagliflozin on HF outcomes and renal function decline in patients with HF, an ejection fraction >40% and AF is an important finding given the fact that AF seems to be particularly common in this HF subgroup and associated with worse cardiac and renal function, as shown by the present and previous studies. AF, defined as either a history of AF or AF documentation by baseline ECG, was prevalent in approximately half of all patients enrolled in this study. Previous epidemiological studies have shown AF prevalence rises with increasing left ventricular ejection fraction in patients with HF.[1,2,8] In an analysis of the Swedish Heart Failure Registry on 41 446 patients, the prevalence of AF increased from 53% in HFrEF to 60% in HF with mildly reduced ejection fraction (HFmrEF) to 65% in HFpEF.[1] Similarly, in the European Society of Cardiology (ESC) Heart Failure Long-Term Registry, in 14 964 HF patients, AF prevalence ranged from 27% in HFrEF to 29% in HFmrEF, to 39% in HFpEF.[2] The higher age in patients with preserved versus reduced ejection fraction and the burden of comorbidities that also accumulate with time may account for the higher AF prevalence. It has been shown that increasing age and several cardiac and extra-cardiac comorbid conditions are associated with atrial anatomical and functional changes, collectively termed atrial disease, independently of the coexistence of HF.[3] Atrial disease further seems to provide the 'common soil' that links the pathophysiology of AF and HF.[3,9]

Patients with baseline AF enrolled in the present study had more severe HF features, including a higher rate of hospitalizations in the previous year, worse NYHA class and higher NT-proBNP concentration, along with worse renal function. This is consistent with previous reports having shown that patients with HFpEF and AF had worse exercise capacity with lower peak oxygen consumption and higher natriuretic peptide levels compared to those with HFpEF but in sinus rhythm.[10,11]

In accordance with the worse HF severity in the presence of AF, baseline AF was associated with worse outcomes as depicted by the higher placebo incidence rates in those with versus without baseline AF (9.57 vs. 7.74 per 100 patient-years, respectively). This is consistent with the findings of previous epidemiological studies. In the Swedish Heart Failure Registry, prevalent AF was associated with increased risk of death, HF hospitalization and stroke regardless of left ventricular ejection fraction.[1] In contrast, in the ESC registries, AF was associated with higher rates of all-cause death or HF hospitalization only in patients with HFpEF and HFmrEF, but not in those with HFrEF,[2] and similar findings were reported from the Korean registry, in which AF was associated with increased mortality only in patients with HFpEF.[8] Interestingly, in our study, kidney function decline was comparable in patients with

	Empagliflozin 10 mg		Placebo			Interaction p-value
	n with event/ N analysed (%)	Rate per 100 patient-years	n with event/ N analysed (%)	Rate per 100 patient-years	HR (95% CI)	
Primary outcome:						
Adjudicated first HHF or CV death						
All patients	415/2997 (13.8)	6.86	511/2991 (17.1)	8.67	0.79 (0.69, 0.90)	
No prevalent AF	170/1417 (12.0)	5.91	219/1427 (15.3)	7.74	0.78 (0.64, 0.95)	0.96
Prevalent AF	244/1576 (15.5)	7.72	292/1559 (18.7)	9.57	0.78 (0.66, 0.93)	
First and recurrent HHF						
All patients	407/2997	-	541/2991	-	0.73 (0.61, 0.88)	
No prevalent AF	164/1417	-	223/1427	-	0.72 (0.54, 0.95)	0.94
Prevalent AF	243/1576	-	318/1559	-	0.73 (0.57, 0.94)	
Time to first HHF						
All patients	259/2997 (8.6)	4.28	352/2991 (11.8)	5.97	0.71 (0.60, 0.83)	
No prevalent AF	98/1417 (6.9)	3.41	141/1427 (9.9)	4.98	0.71 (0.54, 0.91)	0.97
Prevalent AF	161/1576 (10.2)	5.09	211/1559 (13.5)	6.92	0.70 (0.57, 0.86)	
Time to CV death						
All patients	219/2997 (7.3)	3.42	244/2991 (8.2)	3.81	0.91 (0.76, 1.09)	
No prevalent AF	103/1417 (7.3)	3.40	117/1427 (8.2)	3.85	0.89 (0.68, 1.16)	0.88
Prevalent AF	115/1576 (7.3)	3.42	127/1559 (8.1)	3.79	0.92 (0.71, 1.18)	
Time to all-cause mortality						
All patients	422/2997 (14.1)	6.60	427/2991 (14.3)	6.67	1.00 (0.87, 1.15)	
No prevalent AF	187/1417 (13.2)	6.18	202/1427 (14.2)	6.65	0.94 (0.77, 1.14)	0.39
Prevalent AF	234/1576 (14.8)	6.96	225/1559 (14.4)	6.71	1.05 (0.88, 1.27)	
Composite renal outcome						
All patients	108/2997 (3.6)	2.13	112/2991 (3.7)	2.23	0.95 (0.73, 1.24)	
No prevalent AF	61/1417 (4.3)	2.55	60/1427 (4.2)	2.56	1.03 (0.72, 1.47)	0.60
Prevalent AF	47/1576 (3.0)	1.75	51/1559 (3.3)	1.91	0.89 (0.60, 1.32)	



	Empagliflozin 10 mg	Placebo	Rate of decline	Interaction p-value
	Mean (±SE) mL/min/1.73 m²/year	Mean (±SE) mL/min/1.73 m²/year	empagliflozin vs placebo (95% CI)	
eGFR mean slope change from baseline				
All patients	−1.3±0.1	−2.6±0.1	1.36 (1.06, 1.66)	
No prevalent AF	−1.4±0.2	−2.8±0.2	1.37 (0.94, 1.80)	0.99
Prevalent AF	−1.1±0.2	−2.4±0.1	1.37 (0.96, 1.78)	

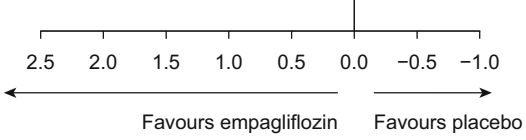


Figure 1 Clinical outcomes of empagliflozin versus placebo by atrial fibrillation or flutter (AF) status (defined as AF reported in any electrocardiogram before treatment intake or history of AF reported as medical history). CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio; SE, standard error.

Table 2 Adverse events by atrial fibrillation or flutter status

	Empagliflozin ($n = 2996$)		Placebo ($n = 2989$)	
	n/N (%)	Rate/100 py	*n/N* (%)	Rate/100 py
Patients with any SAE				
No AF	628/1417 (44.3)	30.40	694/1426 (48.7)	35.91
AF	807/1575 (51.2)	38.25	847/1558 (54.4)	42.42
Patients with AEs leading to discontinuation				
No AF	245 (17.3)	9.11	270 (18.9)	10.26
AF	325 (20.6)	11.17	280 (18.0)	9.51
Patients with AEs				
No AF	1200 (84.7)	126.27	1224 (85.8)	142.44
AF	1370 (87.0)	144.99	1356 (87.0)	153.83
Hypotension				
No AF	129/1417 (9.1)	5.07	86/1426 (6.0)	3.35
AF	182/1575 (11.6)	6.66	170/1558 (10.9)	6.13
Volume depletion				
No AF	144/1417 (10.2)	5.68	97/1426 (6.8)	3.79
AF	212/1575 (13.5)	7.84	188/1558 (12.1)	6.83
Acute renal failure				
No AF	169/1417 (11.9)	6.67	177/1426 (12.4)	7.08
AF	194/1575 (12.3)	7.08	206/1558 (13.2)	7.41
Hyperkalaemia				
No AF	106/1417 (7.5)	4.10	120/1426 (8.4)	4.80
AF	80/1575 (5.1)	2.82	100/1558 (6.4)	3.51

AEs are shown up to 7 days after discontinuation of study medication. Search for specified AEs of interest was based on the pre-defined list of preferred terms.
AE, adverse event; AF, atrial fibrillation/flutter; py, patient-years; SAE, serious adverse event.

and without AF with no indication of a more rapid progression in those with AF.

The beneficial effects of empagliflozin on time to first hospitalization for HF or CV death and on first and recurrent hospitalizations for HF were consistent in patients with and without baseline AF. Moreover, empagliflozin slowed kidney function decline similarly in patients with or without AF. This is an important and clinically relevant finding, given the limited treatment options in HFpEF, the increasing prevalence of both AF and HFpEF and the fact that AF confers a worse prognosis in HFpEF.

New-onset atrial fibrillation occurred in 8% of patients without atrial fibrillation at baseline over a median follow-up period of 26 months, yielding an event rate of four per 100 patient-years. This rate is higher than that observed in the TOPCAT trial, also in patients with HFpEF, that reported an incidence rate of 1.8 per 100 patient-years over a median follow-up of 3.3 years.[12] Empagliflozin did not lower the risk of new-onset atrial fibrillation. Similar findings have been reported in patients with HFrEF, in whom dapagliflozin did not reduce the risk of incident atrial fibrillation in patients in sinus rhythm at baseline.[13] In contrast, previous reports have indicated a beneficial effect of empagliflozin on atrial remodelling, the anatomical substrate for AF development. Indeed, empagliflozin has been shown to reduce left atrial volume index in patients with HFrEF, patients with type 2 diabetes at high CV risk and patients with type 2 diabetes and recent acute coronary syndrome.[14–16] In addition, in a meta-analysis of 22 trials with a total of 52 115 patients with type 2 diabetes, chronic kidney disease or HF, SGLT2i were associated with a lower risk of AF.[17] The lack of an effect of empagliflozin on new-onset atrial fibrillation in the present study could be related to the small number of new atrial fibrillation events and the relatively short follow-up period. Indeed, in the aforementioned study on newly diagnosed HFpEF, the incidence of new-onset atrial fibrillation in patients in sinus rhythm at diagnosis was 32% over a follow-up of nearly 4 years.[11] Since atrial disease provides an earlier form of atrial derangement and a window of opportunity for preventive interventions, it would be interesting to see whether targeting patients with atrial disease with SGLT2i would reduce the risk of AF development.

The present study represents a secondary analysis of a randomized controlled trial and as such, its findings should be interpreted with caution. However, it should be stressed that the results observed in the subgroups of patients with and without AF were in accordance with those in the whole study population. Although ECG was recorded at baseline, there was no active search for AF by, for example, ECG monitoring, thus, some patients may still have undetected AF even though categorized as not having AF in our analyses.

In conclusion, in patients with HF and an ejection fraction >40%, empagliflozin reduced the risk of serious HF events and slowed the eGFR decline compared with placebo regardless of the presence or absence of AF at baseline.

Supplementary Information

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

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