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RESEARCH ARTICLE

Efficacy of empagliflozin on heart failure and renal outcomes in patients with atrial fibrillation: data from the EMPA-REG OUTCOME trial

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Aims Atrial fibrillation (AF) is common in patients with diabetes and heart failure (HF) and increases the future risk of adverse cardiovascular (CV) outcomes. This analysis from the EMPA-REG OUTCOME trial explores CV and renal outcomes in patients with vs. without AF at baseline and assesses the benefits of empagliflozin.

Methods and results Analyses were conducted on patients distinguished by the presence ($n = 389$) or absence ($n = 6631$) of AF at baseline. Outcome events were more frequent in patients with AF than those without AF. Empagliflozin compared to placebo reduced CV death or HF hospitalisation consistently in patients with AF [hazard ratio (HR) 0.58, 95% confidence interval (CI) 0.36–0.92] and without AF (HR 0.67, 95% CI 0.55–0.82, $P_{interaction} = 0.56$). Similar results were observed for the components of this endpoint, all-cause mortality, new or worsening nephropathy, first introduction of loop diuretics, or occurrence of oedema. The absolute number of prevented events was higher in patients with AF, resulting in larger absolute treatment effects of empagliflozin. New loop diuretics or oedema were associated with increased rates of subsequent events, and rates appeared lower in those randomised to empagliflozin.

Conclusions In patients with type 2 diabetes mellitus and established CV disease, those with AF at baseline had higher rates of adverse HF outcomes than those without AF. Irrespective of the presence of AF, empagliflozin reduced HF-related and renal events. The absolute number of prevented events is higher in patients with AF than without AF. Patients with diabetes, CV disease and AF may especially benefit from use of empagliflozin.

Keywords Diabetes • Empagliflozin • Heart failure • Mortality • Oedema • SGLT2 inhibitors

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Introduction

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia associated with both diabetes mellitus[1] and heart failure (HF).[2] Sodiumglucose co-transporter-2 (SGLT2) inhibitors, like empagliflozin, are anti-hyperglycaemic drugs that increase glucose excretion by the kidneys.[3] Empagliflozin has been shown to reduce cardiovascular (CV) and all-cause death,[4] HF hospitalisations, as well as slowing the progression of kidney disease[5] in type 2 diabetes mellitus (T2DM) at high CV risk. With the exception of mortality benefits, similar effects have been demonstrated with other SGLT2 inhibitors in T2DM at high CV risk including those with and without a history of HF.[6–8] AF is highly prevalent in the HF population and is associated with increased morbidity and mortality.[9] HF patients with AF might have different underlying mechanisms of disease progression compared to patients without AF as the risks associated with heart rate are different in AF.[10–12] Moreover, certain drugs, like beta-blockers, are effective in HF with sinus rhythms but do not reduce mortality when AF coexists.[12,13] This is supported by recent findings showing that the irregularity of the heart rhythm may exert paracrine effects to stimulate cardiac interstitial remodelling.[14]

This post-hoc analysis explored whether in the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial, AF compared with no AF is associated with more HF outcomes, whether the treatment effects of empagliflozin differ and whether extended investigator-reported events that could reflect early signs of HF, like first new-onset oedema or the need for first initiation of loop diuretics, have an impact on later outcomes and whether these incident events are sensitive to empagliflozin treatment.

Methods

Trial design

EMPA-REG OUTCOME was a randomised, double-blind, placebo-controlled trial assessing the efficacy of empagliflozin vs. placebo on CV outcomes in patients with T2DM on contemporary standard background therapy. The trial design,[15] main results on CV outcomes[4] and on renal outcomes[5] have been reported previously. Patients were treated in 42 countries at 590 sites. The trial continued until an adjudicated primary outcome event had occurred in at least 691 patients. The primary CV outcome was the composite of major adverse CV events defined as the first occurrence of death from CV causes, non-fatal myocardial infarction, or non-fatal stroke. The key secondary outcome was the composite of the primary outcome plus hospitalisation for unstable angina. HF hospitalisations were evaluated as exploratory outcomes. In this post-hoc analysis, patients were separated by AF and no AF at baseline. Herein, we focused on typical HF outcomes, including the composite of CV death (excluding fatal stroke) or HF hospitalisation, its components, HF hospitalisation and CV death, as well as all-cause death. Extended HF outcomes such as first introduction of loop diuretics or first onset of oedema were also evaluated, and incident or worsening nephropathy defined as new onset of macro-albuminuria or a doubling of serum creatinine accompanied by estimated glomerular filtration rate [eGFR, calculated by the Modification of Diet in Renal Disease (MDRD) formula] ≤ 45 mL/min/1.73 m^2, end-stage renal disease requiring renal replacement therapy, or death from renal disease. Furthermore, we explored the occurrence of subsequent CV death or HF hospitalisation as well as all-cause death following the occurrence of early signs of HF (new-onset oedema and first initiation of loop diuretics) in empagliflozin compared to placebo. For all analyses, patients receiving 10 mg or 25 mg of empagliflozin once daily were pooled because this was pre-specified for the primary analyses, and primary reports showed similar effects of both doses on CV,[4] renal[5] and HF outcomes.[6]

Study participants

Patients had established CV disease and an eGFR of ≥ 30 mL/min/1.73 m^2 of body surface area according to the four-variable MDRD formula. Of 7020 patients randomised and treated, 2333 patients were assigned to placebo and 4687 patients were assigned to either of the two doses of empagliflozin. A total of 389 patients had pre-existing AF at baseline as defined based on investigator reporting of medical history by use of the respective Medical Dictionary for Regulatory Activities preferred term, compared to 6631 patients without AF. The median duration of treatment was 2.6 years and the median observation time was 3.1 years. Overall, 97% of patients completed the study. Follow-up for vital status was complete in 99.2% of patients.

Statistical analysis

Analyses were performed in patients receiving at least one dose of the study drug in a modified intention-to-treat approach. Subgroup analyses by history of pre-existing AF vs. no AF at baseline were done using Cox proportional hazards models with factors for treatment, age, sex, baseline body mass index, baseline glycated haemoglobin, baseline eGFR and region, subgroup and interaction of treatment by subgroup. In addition, Kaplan–Meier estimates are presented. Data for patients who did not have an event were censored on the last day they were known to be free of the outcome. Heterogeneity of absolute risk differences across subgroups was assessed based on the Poisson regression model using the Delta method. Baseline characteristics were compared in patients with vs. without AF using the *t*-test for continuous data, and the Chi square test for categorical data. All analyses were performed on a nominal two sided $\alpha = 0.05$ without adjustment for multiplicity. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

Table 1 shows the baseline characteristics of patients with ($n = 389$) vs. without AF ($n = 6631$). Patients with AF were more often male, older and had a higher body mass index. Patients with AF tended to have more frequently a history of previous stroke, a higher prevalence of previous HF, a lower eGFR, more prevalent peripheral arterial disease and a higher CHA_2DS_2-VASc score indicating a generally higher risk in the AF group. Patients with AF were also more likely to be treated with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, or mineralocorticoid receptor antagonists (*Table 1*). The study flow and treatment allocation are shown in *Figure 1*. *Figure 2* shows that the event rates in patients with AF were generally higher than in those without AF. This applies to CV death alone (*Figure 2A*),

Table 1 Baseline characteristics

	AF at baseline		*P*-value
	No	Yes	
Patients (*n*)	6631 (100.0)	389 (100.0)	
Sex			
Male	4712 (71.1)	304 (78.1)	0.0026
Female	1919 (28.9)	85 (21.9)	
Age (years)	62.8 ± 8.6	68.4 ± 7.1	<0.0001
BMI (kg/m^2)	30.56 ± 5.25	31.69 ± 5.21	<0.0001
Mean systolic blood pressure (mmHg)	135.4 ± 17.0	135.9 ± 17.4	
Mean diastolic blood pressure (mmHg)	76.7 ± 9.9	76.8 ± 10.0	
eGFR (mL/min/1.73m^2)	74.44 ± 21.41 (*n* = 6629)	67.38 ± 20.28	<0.0001
History of ischaemic/haemorrhagic stroke	1532 (23.1)	105 (27.0)	0.0782
History of myocardial infarction	3080 (46.4)	193 (49.6)	0.2238
Prior cardiac failure	587 (8.9)	119 (30.6)	<0.0001
CHA_2DS_2-VASc score	2.9 ± 1.3	3.5 ± 1.4	<0.0001
Any CV high risk factor	6578 (99.2)	386 (99.2)	0.9518
Coronary artery disease	5004 (75.5)	304 (78.1)	0.2306
Coronary artery bypass graft	1614 (24.3)	124 (31.9)	0.0008
Multivessel coronary artery disease	3097 (46.7)	182 (46.8)	0.9749
Single vessel coronary artery disease	693 (10.5)	43 (11.1)	0.7067
Peripheral arterial disease	1358 (20.5)	103 (26.5)	0.0047
High CV risk			<0.0001
Only cerebrovascular disease	906 (13.7)	54 (13.9)	
Only coronary artery disease	3881 (58.5)	191 (49.1)	
Only peripheral arterial disease	577 (8.7)	26 (6.7)	
Two of the 3 CV high-risk categories	1112 (16.8)	104 (26.7)	
Antihypertensives			
Beta-blockers	4263 (64.3)	291 (74.8)	
ACE inhibitors/ARBs	5337 (80.5)	329 (84.6)	
Mineralocorticoid receptor antagonists	378 (5.7)	63 (16.2)	

Values are expressed as *n* (%), or mean ± standard deviation.
ACE angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate.
Note: Based on patients randomised and treated with at least one dose of study drug.

HF hospitalisation alone (*Figure 2B*), the composite of CV death or HF hospitalisation (*Figure 2C*), and all-cause death (*Figure 2D*). Empagliflozin consistently reduced these outcomes in patients with and without AF.

Figure 3 depicts the effects of empagliflozin on incident or worsening nephropathy in patients with and without AF. The event rates of nephropathy were similar in both groups. Empagliflozin also consistently reduced incident or worsening nephropathy in patients with AF vs. without AF.

Figure 4 summarises the incidence of early signs of HF, specifically of new initiation of loop diuretics (*Figure 4A*), new oedema (*Figure 4B*), and the composite of new initiation of loop diuretics or new oedema (*Figure 4C*). Again, the event rates were higher in those with vs. without AF. Empagliflozin consistently reduced these extended HF outcomes in both subgroups.

Figure 5 summarises hazard ratios and confidence intervals for all outcomes. Empagliflozin consistently reduced all outcomes in both those with and without AF [*P*-values for interaction were not significant (>0.05)].

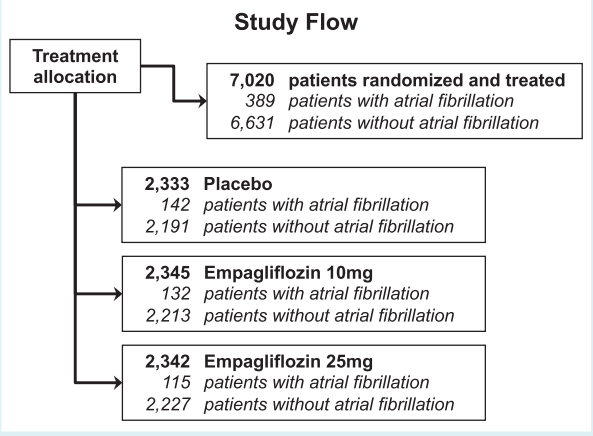

Figure 1 Diagram showing patient selection, treatment allocation and study flow of EMPA-REG OUTCOME.

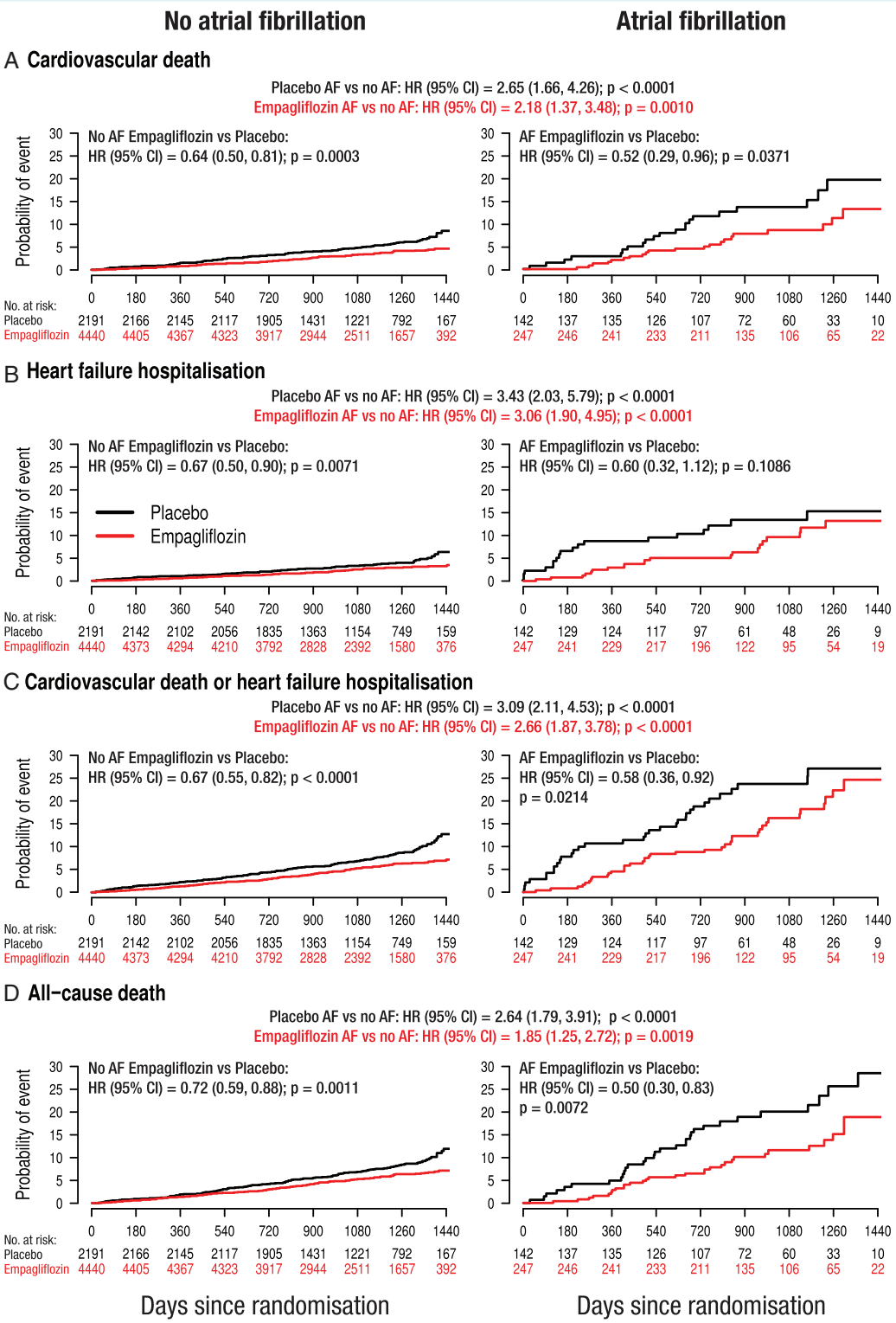

Figure 2 Kaplan–Meier estimates for cardiovascular death *(A)*, heart failure (HF) hospitalisation *(B)*, cardiovascular death (excluding fatal stroke) or HF hospitalisation *(C)*, and all-cause death *(D)* in patients without or with atrial fibrillation (AF) at baseline on empagliflozin or on placebo. *P*-values indicate differences for treatment within each subgroup (within subgroup without AF, or within subgroup with AF). CI, confidence interval; HR, hazard ratio.

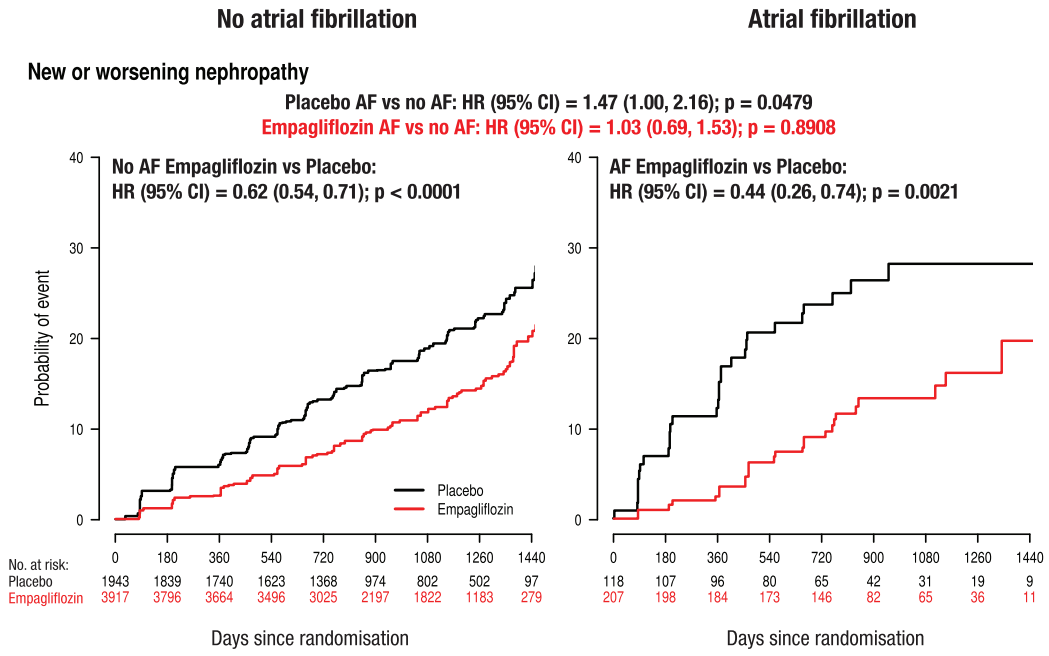

Figure 3 Kaplan–Meier estimates for new or worsening nephropathy in patients without or with atrial fibrillation (AF) at baseline on empagliflozin or on placebo. *P*-values indicate differences for treatment within each subgroup (within subgroup without AF, or within subgroup with AF). CI, confidence interval; HR, hazard ratio.

Next, we explored whether early signs of HF increased the risk of later CV events. In general, subsequent CV death or HF hospitalisation was more frequent following a first initiation of loop diuretics or a first onset of oedema (*Figure 6*). The same was observed for the components CV death and HF hospitalisation as well as for all-cause death. The incidence rates of those outcomes were lower with empagliflozin as compared to placebo before and after onset of oedema or first initiation of loop diuretics. The frequencies for new-onset AF based on the electrocardiogram were low (1.6% in placebo and 2.3% in empagliflozin) without relevant differences between placebo and empagliflozin.

Table 2 summarises the absolute treatment effect of empagliflozin or placebo in patients with or without AF by showing the event rates and prevented events per 1000 patient-years for both groups. In patients without AF, the event rates were generally lower for all outcomes compared to those with AF. However, in the AF group, the absolute number of prevented events by empagliflozin was greater for CV death or HF hospitalisation (38.0 vs. 8.8 prevented events per 1000 patient-years), CV death (25.3 compared to 6.6 prevented events per 1000 patient-years), and HF hospitalisation (20.2 compared to 4.2 prevented events per 1000 patient-years). The numerically higher absolute event reduction translated into a 4.3-, 3.8- and 4.8-fold, respectively, nominally greater absolute treatment difference in patients with AF than in those without AF, while relative treatment effects were similar. Nevertheless, the Poisson regression *P*-values for interaction showed only trends and were formally neutral due to the lower numbers of AF patients impacting the power of the Poisson regression (online supplementary *Table S1*). Similar trends were noted for all-cause death, new or worsening of nephropathy as well as the extended HF outcomes of new loop diuretics and new onset of oedema (*Table 2*). These data need to be considered descriptive.

Discussion

In the EMPA-REG OUTCOME trial, baseline AF was associated with a higher incidence of HF-related outcomes such as CV death, HF hospitalisation, all-cause death, and the first introduction of loop diuretics and development of oedema. The relative treatment benefits of empagliflozin were consistent in both patients with AF and without AF. However, with a higher event rate in patients with AF, the absolute number of events prevented by empagliflozin is greater than in patients with no AF. Early signs of HF, such as the development of oedema or symptoms necessitating new loop diuretic treatment are associated with an increased risk for CV death and HF hospitalisation, which also appear to be responsive to empagliflozin.

Atrial fibrillation is the most common arrhythmia associated with diabetes[1] and is more prevalent with the development of HF.[16] While it is unclear whether AF independently predicts adverse outcomes,[17,18] the presence of AF regardless whether paroxysmal, persistent or of new onset, is associated with adverse outcomes in HF.[19] These observations are consistent with the present findings that indicate AF is associated with more frequent adverse HF outcomes in a diabetic population and is predictive of a worse prognosis. The present findings also show that in patients with

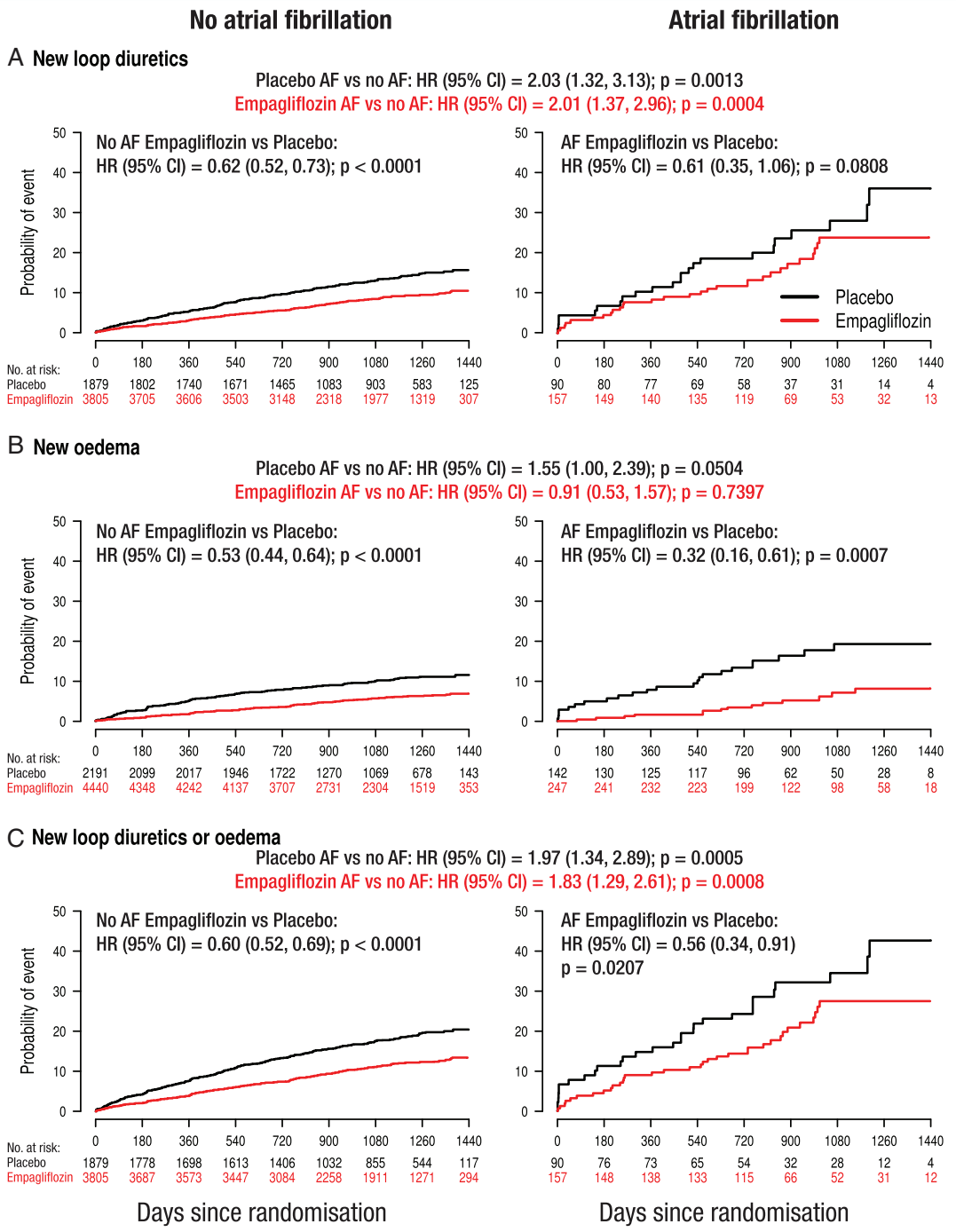

Figure 4 Kaplan–Meier estimates for new loop diuretics *(A)*, new oedema *(B)*, or new loop diuretics or oedema *(C)*, in patients without or with atrial fibrillation (AF) at baseline on empagliflozin or on placebo. *P*-values indicate differences for treatment within each subgroup (within subgroup without AF, or within subgroup with AF). CI, confidence interval; HR, hazard ratio.

diabetes, progressive nephropathy occurred more often in patients with AF and was improved by empagliflozin treatment. The rate of new-onset AF during the trial was low, and there was no difference between empagliflozin and placebo. It is emphasised that the present analysis has been done in a population with T2DM and high CV risk and not in a dedicated HF population. In future HF trials with SGLT2 inhibitors, the possibility of AF prevention needs to be revisited.

In EMPA-REG OUTCOME, HF-related outcomes were reduced by empagliflozin consistently in patients with or without a HF

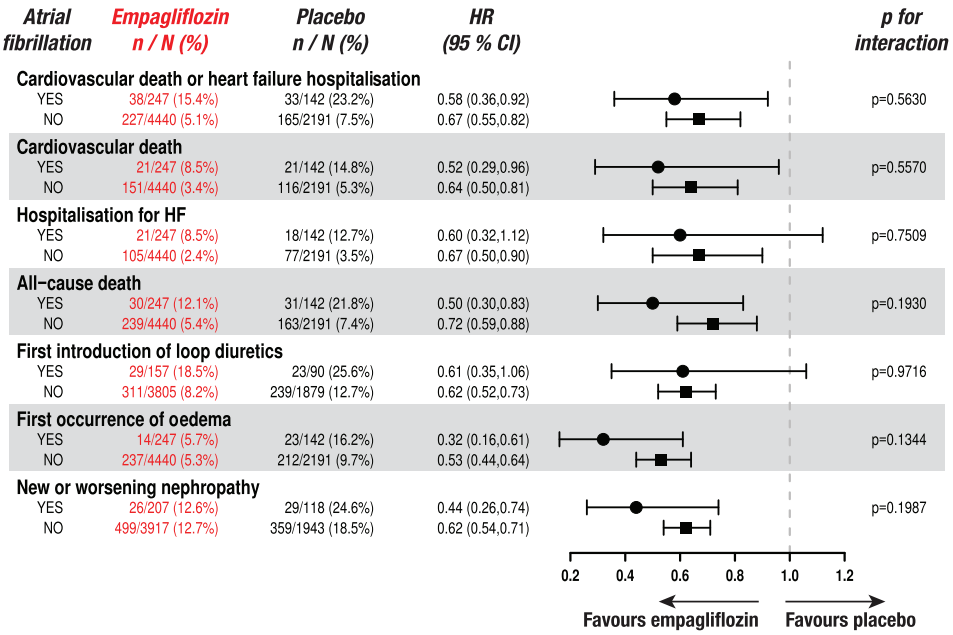

Figure 5 Hazard ratios (HR) with 95% confidence intervals (CI) for patients with atrial fibrillation (yes) or no atrial fibrillation (no) for the composite of heart failure hospitalisation for heart failure (HF) or cardiovascular death (excluding fatal stroke), its individual components, all-cause death, new or worsening nephropathy, first introduction of loop diuretics, and first occurrence of oedema. The HRs were obtained from a Cox regression with factors for age, sex, baseline body mass index, baseline glycated haemoglobin, baseline estimated glomerular filtration rate, region, subgroup and subgroup-by-treatment interaction.

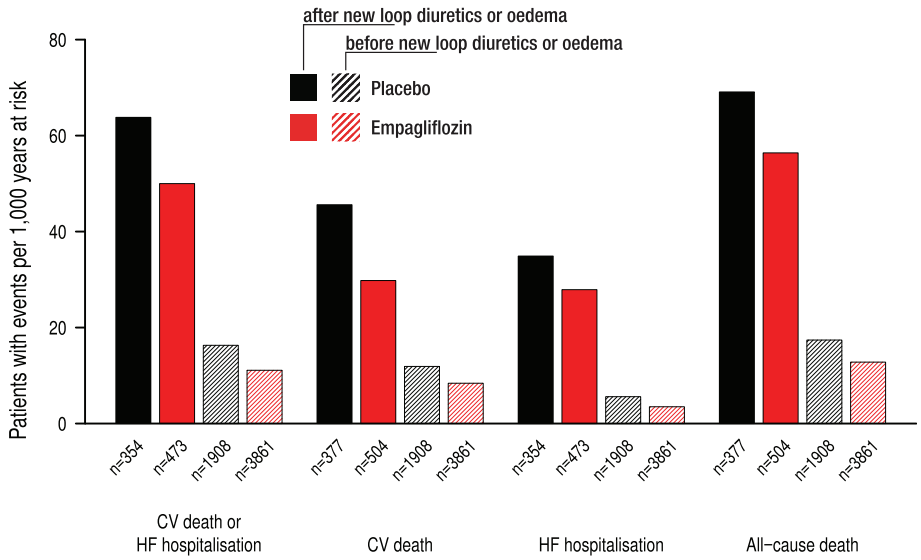

Figure 6 Incidence rates for cardiovascular (CV) death or heart failure (HF) hospitalisation, CV death, HF hospitalisation, or all-cause death after or before the occurrence of an early sign of HF (initiation of new loop diuretics, or new onset of oedema) on placebo or empagliflozin. Number of patients within each category of the time-dependent variable (of an early sign of HF) are based on any time in the study prior to a HF or CV event/censoring and patients can be counted in more than one category. Number of patients with an event within each category refers to the last category recorded prior to the event.

Table 2 Incidence rates, prevented events and treatment effects

	No AF at baseline					AF at baseline					
	Incidence rates[a] (95% CI)				Prevented events/ 1000 py[b]	Incidence rates[a] (95% CI)				Prevented events/ 1000 py[b]	Fold treatment effect, empagliflozin vs. placebo in AF vs. no AF
	Placebo		Empagliflozin			Placebo		Empagliflozin			
CV death or HF hospitalisation[c]	26.5	(22.6–30.7)	17.7	(15.5–20.1)	8.8	97.6	(67.2–133.6)	59.6	(42.2–80.0)	38.0	4.3
CV death	18.1	(14.9–21.5)	11.5	(9.7–13.4)	6.6	56.2	(34.8–82.6)	30.9	(19.1–45.4)	25.3	3.8
HF hospitalisation	12.4	(9.8–15.3)	8.2	(6.7–9.8)	4.2	53.2	(31.6–80.5)	33.0	(20.4–48.5)	20.2	4.8
All-cause death	25.4	(21.6–29.4)	18.2	(15.9–20.5)	7.2	82.9	(56.3–114.6)	44.1	(29.8–61.3)	38.8	5.4
New loop diuretics	47.1	(41.3–53.3)	29.1	(25.9–32.4)	18.0	111.7	(708.–161.8)	75.1	(50.3–104.8)	36.6	2.0
New oedema	35.8	(31.1–40.8)	18.9	(16.5–21.3)	16.9	67.6	(42.8–97.8)	21.7	(11.8–34.4)	45.9	2.7
New or worsening nephropathy	73.9	(66.5–81.8)	47.5	(43.4–51.8)	26.4	117.0	(78.4–163.3)	53.1	(34.7–75.4)	63.9	2.4

AF, atrial fibrillation; CI, confidence interval; CV, cardiovascular; HF, heart failure; py, patient-years.
[a]Based on patients with events per 1000 py at risk.
[b]Derived as difference in incidence rates between empagliflozin and placebo.
[c]Excluding fatal stroke.
Note: Based on patients randomised and treated with at least one dose of study drug. The following number of patients for adjudicated CV/all-cause death endpoints and new oedema were included: 247 patients with AF on empagliflozin, 142 patients on placebo; 4440 patients without AF on empagliflozin, 2191 on placebo. For new loop diuretics: 157 patients with AF on empagliflozin, 90 patients on placebo; 3805 patients without AF on empagliflozin, 1879 on placebo. For new or worsening nephropathy: 207 patients with AF on empagliflozin, 118 patients on placebo; 3917 patients without AF on empagliflozin, 1943 on placebo.

history at baseline.[6] The present findings extend those results showing that the relative risk reduction of HF outcomes was similar in patients with and without AF. Since events were more frequent in patients with AF than in patients without AF, the absolute number of events prevented by empagliflozin was larger in patients with AF. Empagliflozin reduced HF-related endpoints, including early signs of HF, nephropathy and all-cause death in patients with and without AF. The absolute treatment benefit of empagliflozin was more pronounced over a wide range of endpoints that included the introduction of loop diuretics (2.0-fold), incident or worsening nephropathy (2.4-fold), new oedema (2.7-fold), CV death (3.8-fold), the composite of CV death or HF hospitalisation (4.3-fold), HF hospitalisation alone (4.8-fold), and all-cause death (5.4-fold) in patients with and without AF.

Beyond classical endpoints, such as CV death, HF hospitalisation and all-cause mortality, other more frequent and clinically relevant signs and symptoms of HF, such as the development of oedema or the need for loop diuretic treatment are usually not captured in clinical trials. These extended HF outcomes, especially when associated with emergency room visits and intensification of HF therapy, are associated with a similar increased risk of subsequent death as HF.[20,21] In the present study, incidence rates for subsequent HF outcomes following the initiation of a loop diuretic, or development of new oedema, as a first sign of HF, were increased, and empagliflozin reduced the incidence of these important HF outcomes.

There are attractive speculations on the mechanisms of SGLT2 inhibitors such as reducing plasma volume and off-loading the ventricles and/or improving cardiac energy dynamics by enhancing ketone oxidation and cardio-myocyte Na–H exchange.[22] Enhancement of sodium and fluid excretion[23] might be involved in the reduction of first diuretic application and first onset of oedema reported here. A recent meta-analysis of SLGT2 inhibitor trials and real-world studies provided a consistent reduction of the composite of HF hospitalisation and CV death.[24] HF studies in appropriate HF populations with reduced ejection fraction[25,26] or preserved ejection fraction[27] are ongoing.

Limitations

This is a retrospective, post-hoc analysis of a randomised, placebo-controlled trial, and thus hypothesis generating by nature. The number of patients with AF is lower than that in the no AF group and the number of outcome events within this subgroup is limited. However, the high event rates and clear treatment effects are robust and consistent through the whole spectrum of studied outcomes. With the acknowledgment that this is not a dedicated HF study, this analysis examines HF-related outcomes in a diabetes population at high CV risk. HF patients were under-represented in EMPA-REG OUTCOME (approximately 10%) and detailed information, in particular on ejection fraction, atrial size or strain, characterisation of diastolic function, duration or burden of AF and anti-arrhythmic therapies, is not available. Nevertheless, HF-related outcomes are observed frequently and the mechanisms of action are plausible for the observed treatment effects. This study did not aim to evaluate statistical differences between treatments within subgroups, and between the different subgroups for absolute treatment effects or numbers of prevented events, because tests were underpowered and cannot assure significant difference with sufficient confidence. Thus, these parts of the study are exploratory and need to be further scrutinized in the ongoing HF trials of this drug category.

Conclusion

In the EMPA-REG OUTCOME trial of patients with T2DM at high CV risk, those who had concomitant AF experienced HF-related

outcomes more frequently than those without AF. In this population, the benefits from use of the SGLT2 inhibitor empagliflozin, including early signs or symptoms of HF, were greater in absolute terms than if AF was absent, while relative effects were consistent. Findings were similar for the significant co-morbidity of incident or worsening nephropathy. Early evidence of possible HF (first oedema or the introduction of new loop diuretics) was associated with significant increases in events thereafter, which were sensitive to treatment with the SLGT2 inhibitor empagliflozin. These outpatient signs of cardiac deterioration identify patients at particular high risk, who deserve early treatments with evidenced-based drugs.

Supplementary Information

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

Table S1. *P*-values for interaction subgroup treatment on additive (original scale), i.e. based on incidence rate differences.

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References

1. Pallisgaard JL, Lindhardt TB, Olesen JB, Hansen ML, Carlson N, Gislason GH. Management and prognosis of atrial fibrillation in the diabetic patient. *Expert Rev Cardiovasc Ther* 2015;**13**:643–651.
2. Benjamin E, Wolf P, D'Agostino R, Silbershatz H, Kannel W, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;**98**:946–952.
3. Grempler R, Thomas L, Eckhardt M, Himmelsbach F, Sauer A, Sharp DE, Bakker RA, Mark M, Klein T, Eickelmann P. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. *Diabetes Obes Metab* 2012;**14**:83–90.
4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128.
5. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;**375**:323–334.
6. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Trial Investigators. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME trial. *Eur Heart J* 2016;**37**:1526–1534.
7. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, DK MG, JPH W, Ruff CT, IAM G-N, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–357.
8. Mahaffey KW, Neal B, Perkovic V, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Fabbrini E, Sun T, Li Q, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2018;**137**:323–334.
9. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail* 2009;**11**:676–683.
10. Sartipy U, Savarese G, Dahlström U, Fu M, Lund LH. Association of heart rate with mortality in sinus rhythm and atrial fibrillation in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2019;**21**:471–479.
11. Böhm M, Perez AC, Jhund PS, Reil JC, Komajda M, Zile MR, McKelvie RS, Anand IS, Massie BM, Carson PE, McMurray JJ; I-Preserve Committees and Investigators. Relationship between heart rate and mortality and morbidity in the irbesartan patients with heart failure and preserved systolic function trial (I-Preserve). *Eur J Heart Fail* 2014;**16**:778–787.
12. Kotecha D, Flather MD, Altman DG, Holmes J, Rosano G, Wikstrand J, Packer M, Coats AJ, Manzano L, Böhm M, van Veldhuisen DJ, Andersson B, Wedel H, von Lueder TG, Rigby AS, Hjalmarson Å, Kjekshus J, JG C; Beta-Blockers in Heart Failure Collaborative Group. Heart rate and rhythm and the benefit of beta-blockers in patients with heart failure. *J Am Coll Cardiol* 2017;**69**:2885–2896.
13. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD; Beta-Blockers in Heart Failure Collaborative Group. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet* 2014;**384**:2235–2243.
14. Slawik J, Adrian L, Hohl M, Lothschütz S, Laufs U, Böhm M. Irregular pacing of ventricular cardiomyocytes induces pro-fibrotic signalling involving paracrine effects of transforming growth factor beta and connective tissue growth factor. *Eur J Heart Fail* 2019;**21**:482–491.
15. Zinman B, Inzucchi SE, Lachin JM, Wanner C, Ferrari R, Fitchett D, Bluhmk E, Hantel S, Kempthorne-Rawson J, Newman J, Johansen OE, Woerle HJ, Broedl UC. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME™). *Cardiovasc Diabetol* 2014;**13**:102.
16. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 2003;**91**:2–8.

17. Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, Metra M, Torp-Pedersen C, Poole-Wilson P. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *Eur Heart J* 2005;**26**:1303–1308.
18. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. *Circulation* 2009;**119**:2516–2525.
19. Mogensen UM, Jhund PS, Abraham WT, Desai AS, Dickstein K, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Køber L, McMurray JJ; PARADIGM-HF and ATMOSPHERE Investigators and Committees. Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol* 2017;**70**:2490–2500.
20. Böhm M, Young R, Jhund PS, Solomon SD, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Packer M, McMurray JJ. Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF. *Eur Heart J* 2017;**38**:1132–1143.
21. Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD, Packer M, McMurray JJ; PARADIGM-HF Investigators and Committees. Importance of clinical worsening of heart failure treated in the outpatient setting: evidence from the Prospective Comparison of ARNI with ACEI to Determine Impact on global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF). *Circulation* 2016;**133**:2254–2262.
22. Verma S, Rawat S, Ho KL, Wagg CS, Zhang L, Teoh H, Dyck JE, Uddin GM, Oudit GY, Mayoux E, Lehrke M, Marx N, Lopaschuk GD. Empagliflozin increases cardiac energy production in diabetes: novel translational insights into the heart failure benefits of SGLT2 inhibitors. *JACC Basic Transl Sci* 2018;**3**:575–587.
23. Verma S, McMurray JJ, Cherney DZ. The metabolodiuretic promise of sodium-dependent glucose cotransporter 2 inhibition: the search for the sweet spot in heart failure. *JAMA Cardiol* 2017;**2**:939–940.
24. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RH, Bhatt DL, Leiter LA, McGuire DK, Wilding JP, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019;**393**:31–39.
25. McMurray JJ, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD; DAPA-HF Committees and Investigators. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail* 2019;**21**:665–675.
26. Zannad F, Filippatos G, Butler J, Salsali A, Kimura K, Schnee J, Zeller C, Pocock S, George J, Brueckmann M, Anker SD, Packer M. Design and rationale of the Empagliflozin outcome trial in patients with chronic heart failure (EMPEROR-Reduced). *Eur J Heart Fail* 2018;**20**:441 (abstr).
27. Butler J, Packer M, Filippatos G, Zannad F, Salsali A, Kimura K, Schnee J, Zeller C, Pocock S, George J, Brueckmann M, Anker SD. Design and rationale of the Empagliflozin outcome trial in patients with chronic heart failure (EMPEROR-Preserved). *Eur J Heart Fail* 2018;**20**:232 (abstr).