



**HAL**  
open science

## Uric acid and sodium-glucose cotransporter-2 inhibition with empagliflozin in heart failure with reduced ejection fraction: the EMPEROR-reduced trial

Wolfram Doehner, Stefan D Anker, Javed Butler, Faiez Zannad, Gerasimos Filippatos, João Pedro Ferreira, Afshin Salsali, Carolyn Kaempfer, Martina Brueckmann, Stuart J Pocock, et al.

### ► To cite this version:

Wolfram Doehner, Stefan D Anker, Javed Butler, Faiez Zannad, Gerasimos Filippatos, et al.. Uric acid and sodium-glucose cotransporter-2 inhibition with empagliflozin in heart failure with reduced ejection fraction: the EMPEROR-reduced trial. *European Heart Journal*, 2022, 43 (36), pp.3435-3446. 10.1093/eurheartj/ehac320 . hal-03792414

**HAL Id: hal-03792414**

**<https://hal.univ-lorraine.fr/hal-03792414>**

Submitted on 30 Sep 2022






**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

# Uric acid and sodium-glucose cotransporter-2 inhibition with empagliflozin in heart failure with reduced ejection fraction: the EMPEROR-reduced trial

Wolfram Doehner <sup>1\*</sup>, Stefan D. Anker <sup>1</sup>, Javed Butler <sup>2,3</sup>, Faiez Zannad <sup>4</sup>, Gerasimos Filippatos<sup>5</sup>, João Pedro Ferreira<sup>4,6</sup>, Afshin Salsali<sup>7,8</sup>, Carolyn Kaempfer<sup>8,9</sup>, Martina Brueckmann<sup>10,11</sup>, Stuart J. Pocock<sup>12</sup>, James L. Januzzi<sup>13</sup>, and Milton Packer <sup>2,12,14</sup>

<sup>1</sup>Berlin Institute of Health Center for Regenerative Therapies, and Department of Cardiology (CVK), and German Centre for Cardiovascular Research Partner Site Berlin, and Center for Stroke Research Berlin, Charité Universitätsmedizin, Berlin, Germany; <sup>2</sup>Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, TX 75226 USA; <sup>3</sup>Department of Medicine, University of Mississippi School of Medicine, Jackson, MS 39216, USA; <sup>4</sup>Université de Lorraine, Inserm, Centre d'Investigation Clinique Plurithématique 1433, U1116, CHRU de Nancy, F-CRIN INI-CRCT, Nancy 54500, France; <sup>5</sup>National and Kapodistrian University of Athens School of Medicine, Athens University Hospital Attikon, 12461, Haidari Athens, Greece; <sup>6</sup>UnlC@RISE, Cardiovascular Research and Development Center, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, 4200-319 Porto, Portugal; <sup>7</sup>Heart Failure and Diabetes Global Development, Boehringer Ingelheim Pharmaceuticals, Inc, 900 Ridgebury Rd, Ridgefield, CT 06877, USA; <sup>8</sup>Faculty of Medicine, Rutgers University, New Brunswick, NJ 07103, USA; <sup>9</sup>mainanalytics GmbH, Sulzbach, Otto-Volger-Str. 3c, 65843 Sulzbach/Taunus, Germany; <sup>10</sup>Boehringer Ingelheim International, Binger Str. 173, 55218 Ingelheim, Germany; <sup>11</sup>First Department of Medicine, Faculty of Medicine Mannheim, University of Heidelberg, 68167 Mannheim, Germany; <sup>12</sup>Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK; <sup>13</sup>Division of Cardiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02115, USA; and <sup>14</sup>Imperial College, London SW7 2BX, UK

Received 2 December 2021; revised 10 May 2022; accepted 3 June 2022; online publish-ahead-of-print 5 July 2022

See the editorial comment for this article 'Serum uric acid lowering with empagliflozin in heart failure with reduced ejection fraction: a sweet added benefit?', by Isla S. Mackenzie and Thomas M. MacDonald, <https://doi.org/10.1093/eurheartj/ehac415>.

## Abstract

### Background

The sodium-glucose cotransporter-2 inhibitor empagliflozin decreases the risk of cardiovascular death or hospitalization for heart failure (HF) in patients with HF with reduced ejection fraction. Empagliflozin reduces serum uric acid (SUA), but the relevance of this effect in patients with HF is unclear. This study aimed to investigate the effect of empagliflozin on SUA levels and the therapeutic efficacy of empagliflozin in relation to SUA.

### Methods

The association between SUA and the composite primary outcome of cardiovascular death or hospitalization for worsening HF, its components, and all-cause mortality was investigated in 3676 patients of the EMPEROR-Reduced trial (98.6% of the study cohort). The treatment effect of empagliflozin was studied in relation to SUA as continuous variable, to clinical hyperuricaemia (SUA >5.7 mg/dL for women, >7.0 mg/dL for men) and in subgroups of patients of tertiles of SUA.

### Results

Hyperuricaemia was prevalent in 53% of patients with no sex differences. Elevated SUA (highest tertile, mean SUA 9.38 ± 1.49 mg/dL) was associated with advanced severity of HF and with worst outcome [composite outcome, hazard ratio (HR) 1.64 (95% confidence interval, CI 1.28–2.10); cardiovascular mortality, HR 1.98 (95% CI 1.35–2.91); all-cause mortality, HR 1.8 (95% CI 1.29–2.49), all  $P < 0.001$ ] in multivariate adjusted analyses, as compared with the lowest tertile. SUA was reduced following treatment with empagliflozin at 4 weeks (vs. placebo:  $-1.12 \pm 0.04$  mg/dL,  $P < 0.0001$ ) and remained lower throughout follow-up, with a similar reduction in all prespecified subgroups. Empagliflozin reduced events of clinically relevant hyperuricaemia (acute gout, gouty arthritis or initiation of anti-gout therapy) by 32% [HR 0.68 (95% CI 0.52–0.89),  $P = 0.004$ ].

\* Corresponding author. Berlin Institute of Health Center for Regenerative Therapies, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49 30 450 553 507, Email: [wolfram.doehner@charite.de](mailto:wolfram.doehner@charite.de)

© The Author(s) 2022. Published by Oxford University Press on behalf of European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

The beneficial effect of empagliflozin on the primary endpoint was independent of baseline SUA [HR 0.76 (95% CI 0.65–0.88),  $P < 0.001$ ] and of the change in SUA at 4 weeks [HR 0.81 (95% CI 0.69–0.95),  $P = 0.012$ ]. As a hypothesis-generating finding, an interaction between SUA and treatment effect suggested a benefit of empagliflozin on mortality (cardiovascular and all-cause mortality) in patients in elevated SUA ( $P$  for interaction = 0.005 and = 0.011, respectively).

**Conclusion**

Hyperuricaemia is common in HF and is an independent predictor of advanced disease severity and increased mortality. Empagliflozin induced a rapid and sustained reduction of SUA levels and of clinical events related to hyperuricaemia. The benefit of empagliflozin on the primary outcome was observed independently of SUA.

**Structured Graphical Abstract**

**Key Question**

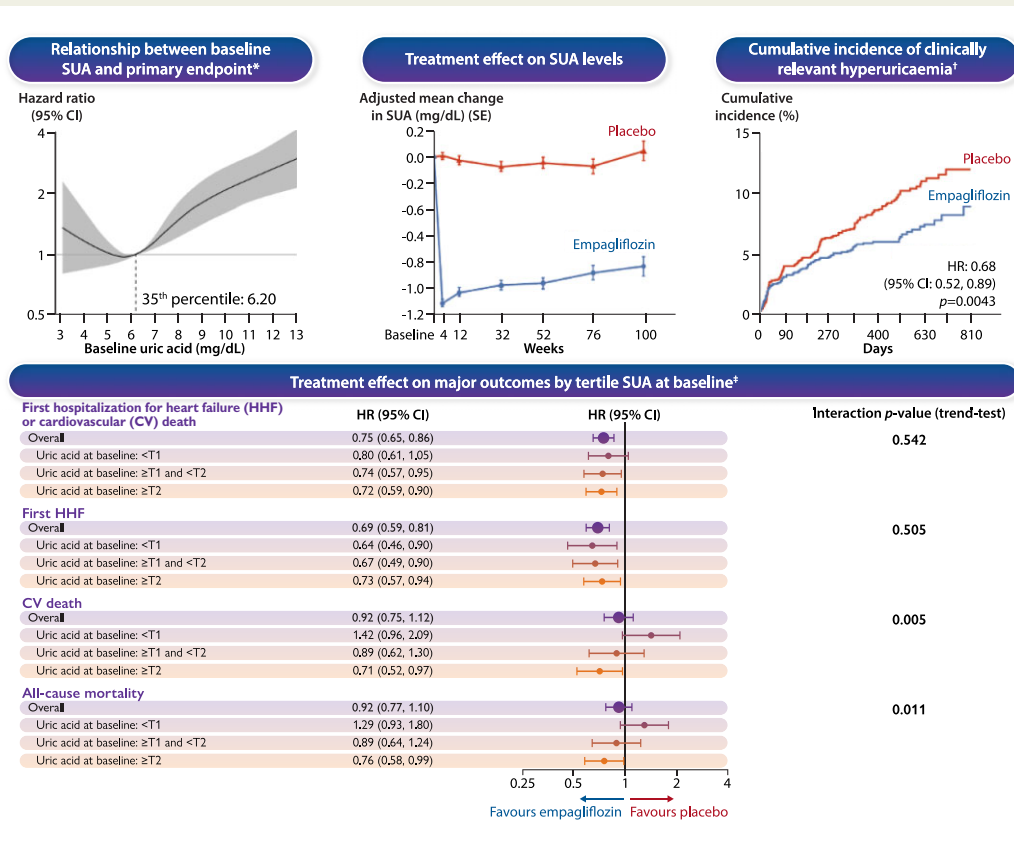
To assess the clinical relevance of the effect of empagliflozin to lower serum uric acid (SUA) in the EMPEROR-Reduced study cohort.

**Key Finding**

Empagliflozin induced a fast and sustained lowering of SUA levels and reduced events of clinically relevant hyperuricaemia by 32%.

**Take Home Message**

- SUA, a marker of increased oxidative stress and gout-comorbidity in heart failure, is effectively reduced by empagliflozin treatment.
- An interaction of high SUA with treatment effect of empagliflozin on mortality is hypothesis-generating.



Elevated serum uric acid (SUA) relates to adverse outcome in HF with reduced ejection fraction (HFrEF), but empagliflozin significantly reduces SUA and clinically relevant hyperuricaemia. \*Hazard ratio shown for the primary composite endpoint using cubic splines (4 knots), multivariable adjusted analysis. †Clinically relevant hyperuricaemia is defined as the composite episodes of acute gout, gouty arthritis or the initiation of treatment with SUA lowering therapy (xanthine oxidase inhibitors, uricosuric agents or colchicine). ‡Tertiles of SUA: Male: T1 = 6.3 mg/dL, T2 = 8.0 mg/dL; Female: T1 = 5.5 mg/dL, T2 = 7.2 mg/dL. Cox regression models included age, sex, geographical region, diabetes status, left ventricular ejection fraction, and estimated glomerular filtration rate (CKD-EPI) and SUA subgroup and SUA subgroup\*treatment interaction for the subgroup analyses.

**Keywords**

Heart failure with reduced ejection fraction • Empagliflozin • Uric acid • Metabolism • Hospitalization • Outcome

## Introduction

Hyperuricaemia is a common finding in patients with heart failure (HF) that is related to advanced clinical status, to higher natriuretic peptides, lower peak oxygen uptake, higher ventricular filling pressure, and lower cardiac output.<sup>1,2</sup> Clinically overt gout is a common comorbidity in HF and a relevant clinical burden to the patients that accounts for a higher risk of hospitalization for HF<sup>3</sup> and increased mortality.<sup>4,5</sup> Consequently, serum uric acid (SUA) has been identified as an independent risk factor in prognostic scoring systems for HF.<sup>4,6,7</sup>

The uric acid generating enzyme xanthine oxidase (XO, EC 1.1.7.3.2) is activated in catabolic, hypoxic, or inflammatory conditions that are characteristic in HF pathophysiology<sup>8</sup> and is a potent source of reactive oxygen species (ROS).<sup>9</sup> Accordingly, elevated levels of SUA in HF have been recognized as a marker of catabolism and of increased oxidative stress independent of diuretic dose or impaired kidney function.<sup>1</sup> Other comorbidities of HF such as chronic kidney disease as well as treatments such as loop diuretics may further contribute to elevated SUA concentrations.

The potential role of SUA in HF beyond that of a marker of metabolic stress and impaired prognosis is not clear. Controlled clinical trials targeting the reduction of SUA either by inhibition of the synthesizing enzyme XO<sup>10,11</sup> or by uricosuric therapy<sup>12</sup> have not demonstrated a clinical benefit in patients with HF. In turn, several medical therapies in HF exert SUA lowering effects, but this effect has not been linked to the benefits of these therapies in HF. Angiotensin-converting enzyme (ACE) inhibitors and some angiotensin receptor blockers lower SUA levels via a mild uricosuric effects.<sup>13,14</sup> Nephilysin inhibitors lower SUA by an uricosuric effect combined with inhibited urate synthesis.<sup>15</sup> Beta-blockers produce inconsistent effects on SUA levels.<sup>16,17</sup> Diuretics and spironolactone increase SUA levels due to interference with renal uric acid clearance.<sup>18,19</sup>

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown a significant effect to lower SUA levels,<sup>20</sup> but the relevance of this observation for the overall beneficial effect of SGLT2 inhibitors in HF is not yet clear.<sup>21,22</sup> Here, we evaluated the relationship of SUA levels and SUA dynamics with the treatment effects of the SGLT2 inhibitor empagliflozin on hospitalization, mortality, and renal function in the EMPEROR-Reduced trial<sup>23</sup> in patients with HF with reduced ejection fraction (HFrEF). Further, the effect of empagliflozin on clinical events of hyperuricaemia was assessed.

## Methods

### EMPEROR-Reduced study design

The design, study methods, and endpoints of the EMPEROR-Reduced trial have been described previously in detail.<sup>24</sup> Briefly, the trial was a randomized, double-blind, parallel-group, placebo-controlled, and event-driven study that evaluated the effects of the SGLT2 inhibitor empagliflozin on the morbidity and mortality of patients with HFrEF. The study was approved by ethics committees and was registered at ClinicalTrials.gov (NCT03057977). This secondary analysis of the study data is part of a comprehensive analysis program for the EMPEROR-Reduced trial and follows a defined analysis plan based on prespecified hypotheses. At a later date, access to the full database will be provided in adherence with the transparency policy of the sponsor (available at [https://trials.boehringer-ingenheim.com/transparency\\_policy.html](https://trials.boehringer-ingenheim.com/transparency_policy.html)).

### Study patients, assessments, and follow-up

Eligible patients included those with chronic HF (functional class II, III, or IV) with reduced ejection fraction ( $EF \leq 40\%$ ) who were receiving all appropriate treatments for HF, including diuretics, inhibitors of the renin-angiotensin system and neprilysin, beta-blockers, mineralocorticoid receptor antagonists, and cardiac devices, as clinically indicated. The trial was designed to preferably enrol patients with an  $EF \leq 30\%$ . To achieve this goal, patients with left ventricular EF (LVEF)  $>30\text{--}40\%$  were required to have been hospitalized for HF within 12 months and/or have markedly elevated levels of *n*-terminal prohormone B-type natriuretic peptide (NT-proBNP), specifically,  $\geq 1000$  pg/mL for LVEF 31–35% and  $\geq 2500$  pg/mL for LVEF 36–40% as compared with  $\geq 600$  pg/mL in those with an LVEF  $\leq 30\%$ .<sup>24</sup> These thresholds were doubled for patients with atrial fibrillation.

Patients were randomly assigned (double-blind, in a 1:1 ratio) to treatment with empagliflozin 10 mg once daily or placebo in addition to their usual treatments for the diagnosis. During follow-up, all treatments for HF or for other medical conditions were provided and adjusted, as clinically indicated at the discretion of the treating physician. All randomized patients were followed at regularly planned visits throughout the duration of the trial for major outcomes and adverse events. SUA was measured (as mg/dL) in a central laboratory at baseline, at 4 and 12 weeks, and every 6 months for the duration of double-blind treatment. Hyperuricaemia was defined as SUA above the upper limit of normal as assessed in the central laboratory ( $>5.7$  mg/dL for women and  $>7.0$  mg/dL for men).

### Study outcomes

The primary endpoint was the composite of adjudicated cardiovascular death or hospitalization for HF, analysed as time to first event. The first secondary endpoint was the occurrence of all adjudicated hospitalizations for HF (first and recurrent events). Further outcomes were cardiovascular death, all-cause mortality, time to first hospitalization for HF, and a composite renal endpoint. The composite renal endpoint was defined as new onset of chronic dialysis, renal transplantation, or a sustained reduction in estimated glomerular filtration rate (eGFR) from baseline of  $\geq 40\%$  or to an  $eGFR < 15$  mL/min/1.73 m<sup>2</sup> for patients with baseline  $eGFR \geq 30$  mL/min/1.73 m<sup>2</sup> or  $eGFR < 10$  mL/min/1.73 m<sup>2</sup> for patients with baseline  $eGFR < 30$  mL/min/1.73 m<sup>2</sup>. The effect to lower SUA was assessed in prespecified subgroups as defined in the primary analysis.<sup>24</sup>

All hospitalizations for HF and all deaths were adjudicated by a clinical event committee in a blinded manner using prespecified criteria. Clinically relevant hyperuricaemia was identified according to the specified clinical event terms as defined in the MedDRA dictionary for standardized reporting of safety events and are presented as the composite of time to first event of investigator reported episodes of acute gout, gouty arthritis or the de-novo initiation SUA lowering medication (XO inhibitors, uricosuric agents, or colchicine).

### Statistical analyses

Baseline characteristics are presented as frequencies and percentages for categorical variables and means with standard deviation (SD) or medians with interquartile range for continuous variables. For descriptive and outcome analyses, the study population was grouped into tertiles of SUA, with thresholds defined separately for men and women. For men, the values used to define tertiles were 6.3 and 8.0 mg/dL; for women, the corresponding values were 5.5 and 7.2 mg/dL. Sex-specific tertiles were combined to present the analyses of tertiles for the entire population. Differences in baseline characteristics were evaluated using ordinal

regression likelihood ratio test. Incidence rates are presented as rates per 100 patient-years of follow-up.

Cox proportional models were used to calculate incidence rates and hazard ratios (HRs) for prespecified outcomes in relation to SUA using the lowest SUA tertile as the reference. This analysis was restricted to the placebo group to exclude any potential effect of empagliflozin. A formal test of linearity vs. non-linear spline was conducted using the likelihood ratio test and due to the better fit of the cubical spline model the relationship between baseline SUA as continuous variable and outcomes are presented using a restricted cubic spline-regression model (using four knots). Time-to-event analyses for the effect of empagliflozin vs. placebo were performed using the Cox model, adjusted for age, sex, geographical region, diabetes status, LVEF, and eGFR (using the Chronic Kidney Disease Epidemiology Collaboration equation) and baseline SUA. We carried out an additional analysis of the Cox model, which included the change of SUA at 4 weeks post-randomization adjusted for baseline SUA as a covariate. Patients with missing SUA data at baseline or week 4 visit or patients with an event during the first 4 weeks were excluded from this analysis. For the analysis of HF events (first and repeated events), between-group differences were assessed using a joint frailty model, with cardiovascular death as competing risks and using the same covariates as for the primary endpoint.

Changes from baseline SUA laboratory measurements were assessed using a mixed model for repeated measures, which included age and baseline eGFR as linear covariates and sex, region, baseline LVEF, individual last projected visit based on dates of randomization and trial closure, and baseline diabetes status as fixed effects, along with interaction terms for baseline SUA tertile by visit and for baseline SUA tertile by visit by treatment. All *P*-values reported are two-sided, and *P*-values <0.05 were considered statistically significant; no adjustment was made for multiplicity of comparisons. All analyses were performed with SAS, version 9.4 (SAS Institute, Cary, NC).

## Results

### Baseline characteristics

Of the 3730 patients randomized in the EMPEROR-Reduced trial, 3676 patients (98.6%) with a baseline assessment of SUA were

included in this analysis. Mean SUA was  $7.29 \pm 2.06$  mg/dL in men and  $6.54 \pm 2.03$  mg/dL in women. SUA at baseline was slightly higher in the placebo group as compared to the empagliflozin group ( $7.18 \pm 2.11$  vs.  $7.04 \pm 2.04$  mg/dL, *P* = 0.04). The prevalence of hyperuricaemia at baseline was 51.6 vs. 55.3% (empagliflozin vs. placebo, *P* = 0.03).

Clinical characteristics of patients grouped in tertiles of SUA are shown in [Table 1](#). Black patients were somewhat overrepresented, and Asian patients were somewhat underrepresented in the patients with the highest SUA. Stepwise increments in SUA were associated with a greater severity of HF, as indicated by New York Heart Association (NYHA) functional class, LVEF, NT-proBNP concentration, or the frequency of hospitalization for HF in the last 12 months ([Table 1](#)). Certain comorbidities (i.e. atrial fibrillation, impaired renal function and obesity) were more prevalent among patients with elevated SUA. In turn, hypertension and diabetes, which are components of the metabolic syndrome, were not related to elevated SUA. The use of diuretics and mineralocorticoid receptor antagonists increased as SUA increased.

### Association of uric acid with clinical outcomes

In the placebo group, the risk of clinical outcomes increased in parallel with higher SUA levels for the primary endpoint, first or recurrent hospitalization, cardiovascular mortality, and all-cause mortality (all *P*-trend < 0.001, [Table 2](#)). The risks were 60–80% higher in patients in the highest tertile, as compared with the lowest tertile. Cumulative incidence curves for the composite primary endpoint and its individual components between SUA tertiles are shown in [Supplementary material online, Figure S1](#). When SUA was analysed as a continuous variable, a J-shaped relationship was observed with higher SUA levels being associated with worse outcomes ([Figure 1](#)). SUA did not predict the risk of the composite renal endpoint, but this analysis was based on 25 or fewer events in each tertile.

**Table 1** Clinical characteristics of patients according to serum uric acid tertiles

	Tertile 1	Tertile 2	Tertile 3	<i>P</i> -value for trend
Number of participants	1200	1247	1229	
Serum uric acid, mg/dL (mean $\pm$ SD)	4.99 $\pm$ 0.84	6.90 $\pm$ 0.60	9.38 $\pm$ 1.49	
Age, years, mean $\pm$ SD	67.3 $\pm$ 10.7	66.5 $\pm$ 10.8	66.7 $\pm$ 11.6	0.249
Female sex, <i>n</i> (%)	286 (23.8)	299 (24.0)	295 (24.0)	0.922
<b>Race, <i>n</i> (%)</b>				<0.001
White	851 (70.9)	882 (70.7)	855 (69.6)	
Black	62 (5.2)	77 (6.2)	111 (9.0)	
Asian	232 (19.3)	236 (18.9)	199 (16.2)	
Other including mixed races	40 (3.3)	35 (2.8)	38 (3.1)	
Missing	15 (1.3)	17 (1.4)	26 (2.1)	

Continued

**Table 1 Continued**

	<b>Tertile 1</b>	<b>Tertile 2</b>	<b>Tertile 3</b>	<b>P-value for trend</b>
<b>Region, n (%)</b>				<0.001
North America	120 (10.0)	133 (10.7)	165 (13.4)	
Latin America	439 (36.6)	428 (34.3)	403 (32.8)	
Europe	408 (34.0)	458 (36.7)	461 (37.5)	
Asia	161 (13.4)	173 (13.9)	156 (12.7)	
Other	72 (6.0)	55 (4.4)	44 (3.6)	
<b>NYHA Class, n (%)</b>				<0.001
II	943 (78.6)	953 (76.4)	865 (70.4)	
III	251 (20.9)	288 (23.1)	356 (29.0)	
IV	6 (0.5)	6 (0.5)	8 (0.7)	
Body mass index, kg/m <sup>2</sup> , mean ± SD	27.2 ± 5.3	28.1 ± 5.4	28.3 ± 5.4	<0.001
Heart rate, bpm, mean ± SD	70.5 ± 11.3	71.1 ± 11.7	72.2 ± 12.2	<0.001
Systolic blood pressure, mmHg, mean ± SD	123.3 ± 15.7	122.8 ± 15.9	119.7 ± 15.1	<0.001
Left ventricular ejection fraction, %, mean ± SD	27.9 ± 5.7	27.5 ± 5.9	27.0 ± 6.4	<0.001
NT-proBNP, pg/mL, median (IQR)	1684.5 (1014–2931.5)	1800 (1059–3220)	2301 (1335–4243)	<0.001 <sup>a</sup>
Hospitalization for HF in last 12 months, n (%)	304 (25.3)	375 (30.1)	458 (37.3)	<0.001
Atrial fibrillation <sup>b</sup> , n (%)	385 (32.1)	454 (36.4)	505 (41.1)	<0.001
Hypertension, n (%)	858 (71.5)	902 (72.3)	899 (73.1)	0.364
Diabetes, n (%)	578 (48.2)	624 (50.0)	627 (51.0)	0.161
<b>Estimated eGFR</b>				
<60 mL/min/1.73 m <sup>2</sup> , n (%)	427 (35.6)	578 (46.4)	765 (62.2)	<0.001
mL/min/1.73 m <sup>2</sup> , mean ± SD	68.2 ± 21.6	63.1 ± 20.3	54.9 ± 20.7	<0.001
<b>Device therapy, n (%)</b>				
Implantable cardioverter-defibrillator <sup>c</sup>	377 (31.4)	387 (31.0)	384 (31.2)	0.929
Cardiac resynchronization therapy <sup>d</sup>	138 (11.5)	140 (11.2)	156 (12.7)	0.355
<b>Heart failure medication, n (%)</b>				
Beta blocker	1129 (94.1)	1190 (95.4)	1164 (94.7)	0.490
ACE inhibitor	553 (46.1)	593 (47.6)	536 (43.6)	0.216
ARB without neprilysin inhibition	299 (24.9)	295 (23.7)	301 (24.5)	0.812
ARB with neprilysin inhibition	219 (18.3)	234 (18.8)	263 (21.4)	0.048
Loop diuretics	911 (75.9)	1051 (84.3)	1147 (93.3)	<0.001
Thiazides diuretics	81 (6.8)	83 (6.7)	118 (9.6)	0.007
Mineralocorticoid receptor antagonist	823 (68.6)	895 (71.8)	906 (73.7)	0.005

Tertiles [mg/dL]: male: T1: 6.3, T2:8.0; female: T1: 5.5, T2: 7.2.

<sup>a</sup>Based on log-transformed results.

<sup>b</sup>Defined as atrial fibrillation reported in any ECG before treatment intake or history of atrial fibrillation reported in medical history.

<sup>c</sup>Implantable cardioverter defibrillator with or without cardiac resynchronization therapy.

<sup>d</sup>Cardiac resynchronization therapy with or without a defibrillator.



**Table 2** Risk of endpoints according to serum uric acid levels in the placebo group

	No of patients	No of events (%)	Incidence/100 PY [95%CI]	HR	95%CI	P value	P-value (trend test)
<b>Primary endpoint</b>							<0.001
SUA tertile 1	573	112 (19.5)	16.1 [13.3, 19.3]				
SUA tertile 2	641	145 (22.6)	18.7 [15.8, 21.8]	1.14	(0.89, 1.46)	0.313	
SUA tertile 3	628	197 (31.4)	28.1 [24.3, 32.1]	1.64	(1.28, 2.10)	<0.001	
<b>Total number of HHF</b>							<0.001
SUA tertile 1	573	147					
SUA tertile 2	641	152		1.01	(0.73, 1.39)	0.954	
SUA tertile 3	628	249		1.81	(1.31, 2.51)	<0.001	
<b>First HHF</b>							<0.001
SUA tertile 1	573	80 (14.0)	11.5 [9.1, 14.2]				
SUA tertile 2	641	107 (16.7)	13.8 [11.3, 16.5]	1.18	(0.88, 1.58)	0.281	
SUA tertile 3	628	151 (24.0)	21.5 [18.2, 25.1]	1.75	(1.31, 2.33)	<0.001	
<b>CV death</b>							<0.001
SUA tertile 1	573	43 (7.5)	5.6 [4.1, 7.4]				
SUA tertile 2	641	60 (9.4)	7.0 [5.3, 8.9]	1.24	(0.84, 1.85)	0.282	
SUA tertile 3	628	94 (15.0)	11.4 [9.2, 13.8]	1.98	(1.35, 2.91)	<0.001	
<b>All cause death</b>							<0.001
SUA tertile 1	573	61 (10.6)	8.0 [6.1, 10.1]				
SUA tertile 2	641	77 (12.0)	9.0 [7.1, 11.1]	1.12	(0.79, 1.57)	0.523	
SUA tertile 3	628	122 (19.4)	14.8 [12.3, 17.5]	1.80	(1.29, 2.49)	<0.001	
<b>Composite kidney endpoint</b>							0.143
SUA tertile 1	573	12 (2.1)	2.0 [1.0, 3.3]				
SUA tertile 2	641	20 (3.1)	3.1 [1.9, 4.5]	1.42	(0.68, 2.94)	0.351	
SUA tertile 3	628	25 (4.0)	4.1 [2.6, 5.8]	1.73	(0.83, 3.60)	0.142	
<b>Incidence of clinically relevant hyperuricaemia</b>							<0.001
SUA tertile 1	445	8 (1.8)	1.47 [0.63, 2.64]				
SUA tertile 2	527	28 (5.3)	4.40 [2.92, 6.17]	2.74	(1.24, 6.05)	0.013	
SUA tertile 3	562	99 (17.6)	17.66 [14.35, 21.30]	9.86	(4.69, 20.75)	<0.001	

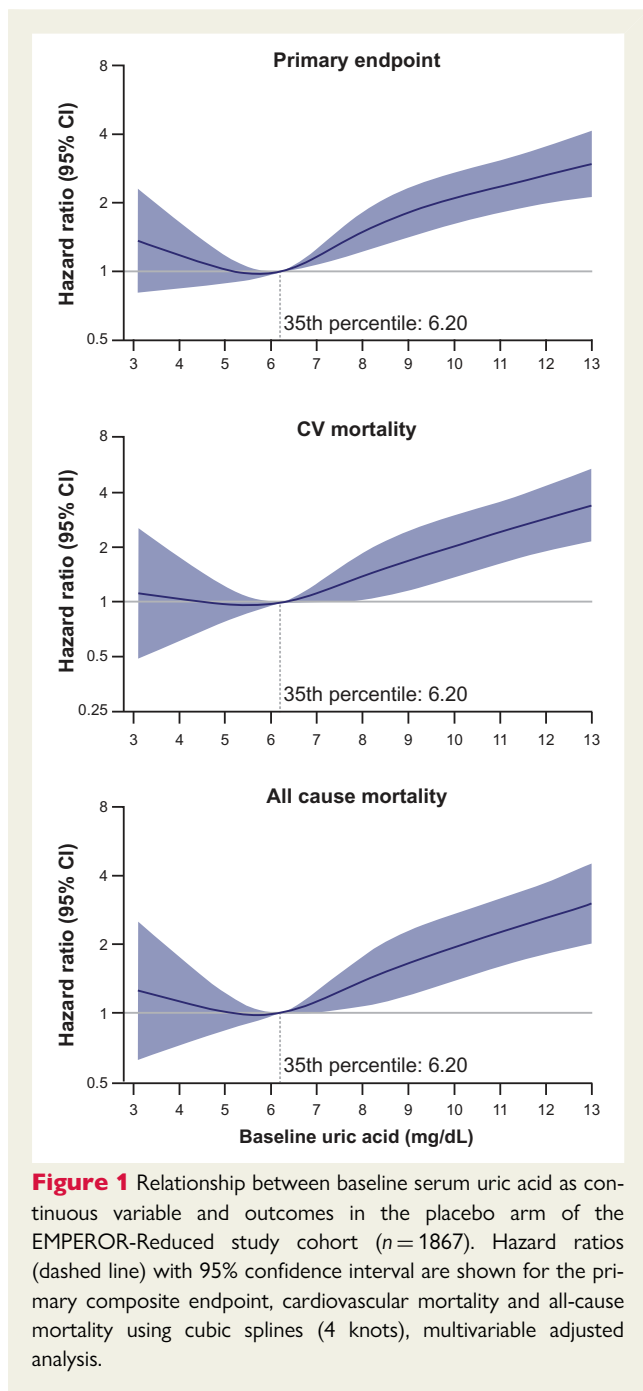
Based on a Cox regression model with terms for age, baseline eGFR as linear covariates and region, diabetes status, sex, baseline LVEF, and baseline uric acid.

In the placebo-treated patients, the rate of clinically relevant hyperuricaemic events was more than ten times higher in the highest SUA tertile, as compared to the lowest SUA tertile [incidence per 100 patient-years: 17.7 (14.4–21.3) vs. 1.5 (0.6–2.6) (Table 2)].

### Effect of empagliflozin on uric acid levels and clinical hyperuricaemic events

Treatment with empagliflozin resulted in a significant reduction of SUA within 4 weeks of therapy (mean change  $-1.11 \pm 0.03$  vs.  $0.01 \pm 0.03$  mg/dL, empagliflozin vs. placebo,  $P < 0.001$ , Figure 2),

and the magnitude of the treatment effect remained stable throughout the treatment period. The reduction of SUA levels at week 4 in patients treated with empagliflozin was most pronounced with highest baseline SUA (adjusted mean change from baseline  $\pm$  SE; tertile 1:  $-0.54 \pm 0.05$  mg/dL, tertile 2:  $-1.04 \pm 0.05$  mg/dL, tertile 3:  $-1.75 \pm 0.05$  mg/dL). The magnitude of the UA lowering effect of empagliflozin was consistent across prespecified subgroups (Table 3), including patients with severely impaired kidney function (see Supplementary material online, Figure S2). However, an interaction of study treatment was observed for diabetes and for race,



suggesting a greater effect to lower uric acid in patients without diabetes.

Events of clinically relevant hyperuricaemia occurred in 94 patients in the empagliflozin group vs. 135 patients in the placebo group. Treatment with empagliflozin reduced the risk of clinically relevant hyperuricaemic events by 32% (HR 0.68 [95%CI 0.52–0.89],  $P = 0.004$ , [Figure 3](#)). When analysing the components of clinically relevant hyperuricaemia separately, the risk reduction was comparable for both individual components (initiation of anti-hyperuricaemic medication: HR 0.69, 95%CI 0.52–0.91; gout events: HR 0.70, 95%CI 0.45–1.08, [Supplementary material online, Table S1](#)).

## Efficacy of empagliflozin in relation to serum uric acid levels and dynamics

The effect of empagliflozin on the primary composite endpoint and on the risk of hospitalization for HF was not influenced by SUA. The benefit of empagliflozin was similar in magnitude across the SUA tertiles (all interaction  $P > 0.1$ , [Figure 4](#)). When SUA at baseline was included in the Cox model as a continuous variable, the beneficial effect of empagliflozin on the primary composite outcome was independent of SUA (HR 0.76 [95%CI 0.65–0.88],  $P < 0.001$ ). The effect of empagliflozin on the composite outcome remained significant even after the percent change in SUA at 4 weeks was incorporated into the Cox model as a covariate (HR 0.81 [95%CI 0.69–0.95,  $P = 0.012$ ]).

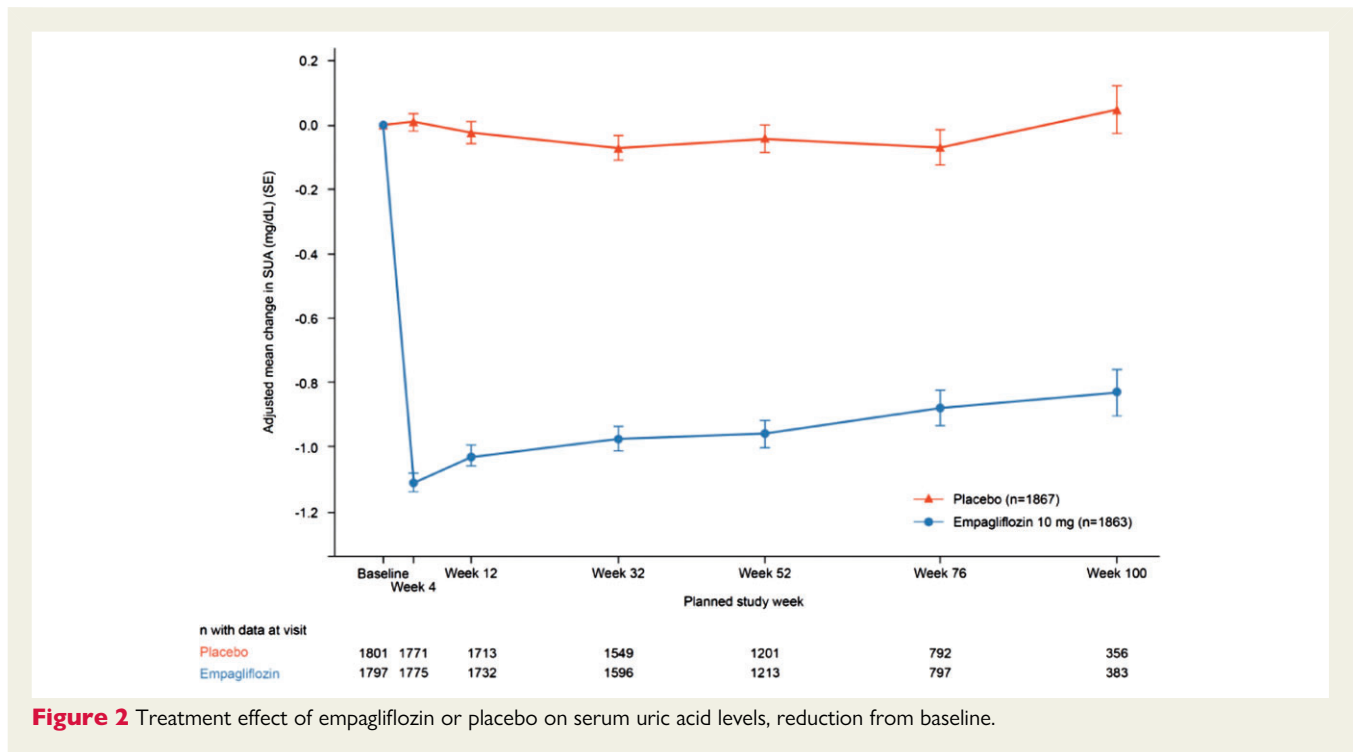
In contrast, we observed a significant interaction between the effect of empagliflozin treatment and baseline SUA levels for both cardiovascular mortality (interaction  $P = 0.005$ ) and for all-cause mortality (interaction  $P = 0.011$ , [Figure 4](#)). The HRs for empagliflozin vs. placebo were 0.71 [95%CI 0.52–0.97] for cardiovascular mortality and 0.76 [95%CI 0.58–0.99] for all-cause death in patients with the highest SUA tertile, whereas they were 1.42 [95%CI 0.96–2.09] and 1.29 [95%CI 0.93–1.80], respectively, for empagliflozin vs. placebo in patients with the lowest SUA tertile. When the multivariable model was further extended by inclusion of NT-proBNP and the level of loop diuretics, similar results were observed (see [Supplementary material online, Table S2](#)).

## Discussion

The main findings of this study are that (i) hyperuricaemia was very common in patients with HFrEF (prevalence of 53%) and was associated with more advanced disease state, as reflected by NYHA class, the risk of hospitalization for HF, NT-proBNP, and LVEF; (ii) elevated SUA was a strong and independent predictor of increased mortality (all-cause and cardiovascular mortality) and of hospitalization for HF; (iii) empagliflozin produced an early and sustained decrease in SUA that was maintained in all prespecified subgroups, and the drug reduced the incidence of clinically relevant hyperuricaemic events; and (iv) the effect of empagliflozin to reduce the risk of HF outcomes was independent of SUA levels ([Structured Graphical Abstract](#)).

Hyperuricaemia has previously been identified as a pathophysiological feature in HF and as a marker of increased oxidative stress in association with increased catabolism, inflammatory activation<sup>25</sup> and endothelial dysfunction.<sup>8</sup> In line with previous studies, we show that elevated SUA levels are associated with reduced functional capacity<sup>26</sup> and advanced HF disease severity and mortality.<sup>4,27,28</sup> We also show the direct clinical burden related to high SUA, i.e. the incidence of gout, gouty arthritis or the need for antihyperuricaemic therapy that is 10 times higher in the highest SUA tertile. In turn, empagliflozin reduced events of clinically relevant hyperuricaemia by 32%. While the SUA lowering effect of SGLT2 inhibitors has been reported in patients with type 2 diabetes mellitus,<sup>29,30</sup> we extend this knowledge to show the same clinical benefit of SGLT2 inhibition in patients with HF regardless of the presence of diabetes. Elevated levels of SUA and acute gout events are a relevant added clinical burden in patients with HF: they lead to increased risk of HF events, of hospital admissions and readmissions for HF, adverse outcome of





**Figure 2** Treatment effect of empagliflozin or placebo on serum uric acid levels, reduction from baseline.

acute HF events, and death.<sup>31,32</sup> Both uncontrolled SUA and gout events worsen health status and increase the incidence of acute HF events and cardiovascular death.<sup>33,34</sup> Anti-gout medication such as non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, steroids cause additional drug interactions including the risk for complications such as renal failure. Accordingly, current guidelines for the management of HF recommend to avoid such treatments in patients with HF.<sup>35</sup> Further, reducing antihyperuricaemic medications may reduce interactions with HF medications and last but not least may improve patient adherence due to less extensive multiple-drug regimen. Finally, episodes of gout may lead to difficult decisions regarding the reduction of use of diuretics in an effort to manage hyperuricaemia.<sup>36</sup>

Therefore, the pronounced and sustained uric acid lowering effect of empagliflozin presents a meaningful additional clinical benefit of empagliflozin in patients with HF. Notably, hyperuricaemia has classically been associated with the metabolic syndrome clustering with hypertension, diabetes mellitus and obesity,<sup>37</sup> but this clustering was not observed in our study. This suggests that elevated SUA in HF does not merely occur in the context of a metabolic syndrome but instead reflects metabolic derangements that are intrinsic to HF.

The beneficial effect of empagliflozin to reduce the composite risk of cardiovascular death or hospitalization for HF was confirmed independent of SUA levels and of SUA dynamics. However, an interaction was observed between SUA levels and treatment effect with empagliflozin on mortality. A significant reduction in cardiovascular mortality and all-cause mortality was observed in patients with elevated SUA (highest tertile), while this association was not seen in patients with lower SUA levels. This finding is hypothesis generating. The SUA lowering effect of empagliflozin was most pronounced in those patients with highest SUA levels at baseline which also have

shown the highest mortality risk. Hence, it is intriguing to speculate that empagliflozin's effect may be particularly relevant in patients with the highest pre-treatment oxidative stress, inflammatory activation, and endothelium dysfunction. Such a treatment effect would be well consistent with the concept of SUA as a marker of catabolism and increased oxidative stress in HF.<sup>1</sup> A reduced ROS accumulation could exert improved myocardial energetic efficacy and myocardial contractility as has comprehensively been reported.<sup>9,38</sup> Further, interaction of XO-derived ROS with nitric oxide contributes to endothelium dysfunction, another key characteristic in HF which would improve from reduced ROS accumulation.<sup>39</sup> In turn, in patients with lower SUA no increased oxidative stress is present which may explain the absence of treatment effect on mortality in the lower SUA tertile. Our observation is in line with previous studies in which mediation analyses have shown a statistical link between the reduction in SUA secondary to SGLT2 inhibitors with the beneficial effect on HF outcomes in patients with type 2 diabetes.<sup>40</sup> Notably, the finding of a significant trend for treatment effect on reduced mortality in the highest SUA tertile does not suggest an increased mortality risk for patients with low SUA. This observation warrants further investigation.

The reduction of SUA after initiating therapy with empagliflozin was observed rapidly (i.e. at 4 weeks), and was maintained throughout the follow-up period. This durable effect is consistent with previous studies.<sup>41</sup> Our earliest measurement of uric acid was at 4 weeks; an even faster reduction of SUA has been previously reported after 5 days of treatment with empagliflozin.<sup>42</sup> One mechanism to explain the SUA lowering by SGLT2 inhibitors is postulated to be an uricosuric effect secondary to glucosuria, which leads to a competitive decrease in renal urate re-absorption in the proximal convoluted tubule *via* GLUT9b.<sup>43,44</sup> However, we observed a significant

**Table 3** The treatment effect of empagliflozin to lower serum uric acid in patient subgroups

	Empagliflozin 10 mg		Placebo		Adjusted mean difference (95%CI) <sup>b</sup>	Interaction P-value
	Baseline	Change at week 4 <sup>a</sup>	Baseline	Change at week 4 <sup>a</sup>		
<b>History of hypertension</b>						0.985
Yes	7.02 (0.06)	-1.11 (0.03)	7.18 (0.06)	0.01 (0.03)	-1.12 (-1.26, -0.97)	
No	7.05 (0.09)	-1.12 (0.05)	7.09 (0.09)	0.00 (0.05)	-1.12 (-1.21, -1.03)	
<b>Diabetes</b>						<0.001
Diabetic	7.11 (0.07)	-0.91 (0.04)	7.27 (0.07)	0.08 (0.04)	-0.99 (-1.09, -0.88)	
Not diabetic	6.95 (0.06)	-1.31 (0.04)	7.05 (0.07)	-0.06 (0.04)	-1.25 (-1.36, -1.14)	
<b>Age</b>						0.256
<65 years	6.96 (0.08)	-1.08 (0.05)	7.31 (0.08)	-0.02 (0.04)	-1.06 (-1.19, -0.94)	
≥65 years	7.07 (0.06)	-1.13 (0.03)	7.06 (0.06)	0.02 (0.049)	-1.15 (-1.25, -1.06)	
<b>Sex</b>						0.596
Male	7.24 (0.05)	-1.15 (0.03)	7.32 (0.06)	-0.02 (0.03)	-1.13 (-1.22, -1.04)	
Female	6.36 (0.09)	-1.00 (0.06)	6.66 (0.10)	0.08 (0.06)	-1.08 (-1.24, -0.92)	
<b>Race</b>						0.023
White	7.06 (0.06)	-1.16 (0.04)	7.11 (0.06)	-0.04 (0.04)	-1.12 (-1.22, -1.03)	
Black	7.41 (0.22)	-1.02 (0.11)	7.48 (0.19)	-0.11 (0.11)	-0.91 (-1.20, -0.61)	
Asian	6.81 (0.10)	-1.03 (0.13)	7.20 (0.12)	0.24 (0.13)	-1.27 (-1.45, -1.09)	
Other incl. mixed race	6.56 (0.26)	-0.75 (0.17)	6.76 (0.25)	-0.13 (0.15)	-0.62 (-1.07, -0.18)	
<b>BMI</b>						0.354
<30 kg/m <sup>2</sup>	6.94 (0.06)	-1.10 (0.03)	7.07 (0.06)	-0.01 (0.03)	-1.10 (-1.19, -1.00)	
≥30 kg/m <sup>2</sup>	7.21 (0.09)	-1.13 (0.05)	7.36 (0.09)	0.04 (0.05)	-1.17 (-1.31, -1.04)	
<b>Cause of HF</b>						0.827
Ischaemic	7.08 (0.07)	-1.14 (0.04)	7.18 (0.07)	-0.03 (0.04)	-1.11 (-1.22, -1.00)	
Non-ischaemic	6.97 (0.07)	-1.08 (0.04)	7.14 (0.07)	0.05 (0.04)	-1.13 (-1.24, -1.02)	
<b>Baseline NYHA class</b>						0.697 <sup>c</sup>
II	6.92 (0.05)	-1.10 (0.03)	7.08 (0.05)	0.01 (0.03)	-1.11 (-1.20, -1.03)	
III	7.37 (0.11)	-1.11 (0.06)	7.42 (0.11)	0.01 (0.06)	-1.13 (-1.28, -0.97)	
IV	6.77 (0.64)	-0.87 (0.39)	6.62 (0.63)	0.75 (0.38)	-1.62 (-2.69, -0.56)	
<b>Baseline HF physiology</b>						0.603
LVEF ≤30% and NT-proBNP < median	6.79 (0.07)	-1.14 (0.04)	6.82 (0.07)	-0.01 (0.04)	-1.14 (-1.26, -1.01)	
LVEF ≤30% and NT-proBNP ≥ median	7.36 (0.09)	-1.17 (0.05)	7.57 (0.09)	-0.03 (0.05)	-1.14 (-1.27, -1.01)	
LVEF > 30%	6.96 (0.09)	-0.98 (0.05)	7.10 (0.09)	0.07 (0.05)	-1.05 (-1.20, -0.90)	
<b>Baseline use of MRA</b>						0.459
No	6.92 (0.09)	-1.04 (0.05)	7.10 (0.10)	0.03 (0.05)	-1.07 (-1.22, -0.93)	
Yes	7.08 (0.06)	-1.14 (0.03)	7.18 (0.06)	0.00 (0.03)	-1.14 (-1.23, -1.05)	

Continued

**Table 3 Continued**

	Empagliflozin 10 mg		Placebo		Adjusted mean difference (95%CI) <sup>b</sup>	Interaction P-value
	Baseline	Change at week 4 <sup>a</sup>	Baseline	Change at week 4 <sup>a</sup>		
<b>Baseline use of ARNi</b>						0.525
No	7.03 (0.05)	-1.11 (0.03)	7.12 (0.05)	0.00 (0.03)	-1.11 (-1.19, -1.02)	
Yes	7.04 (0.11)	-1.12 (0.06)	7.30 (0.11)	0.05 (0.06)	-1.17 (-1.34, -1.00)	

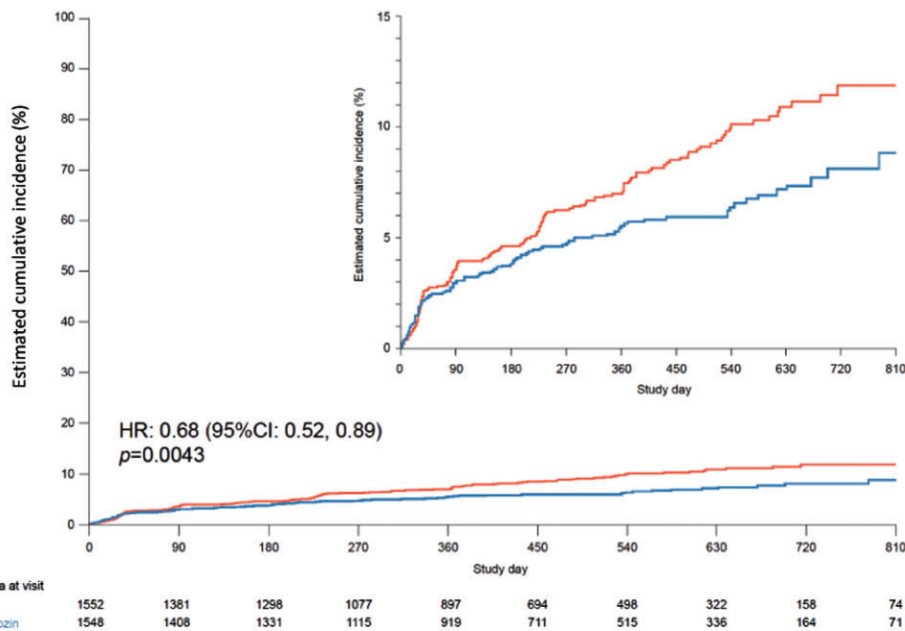
All values are mean (SE).

<sup>a</sup>Models of adjusted mean change (SE) include age and baseline eGFR as linear covariates and region, diabetes status<sup>d</sup>, sex<sup>d</sup>, baseline LVEF, week reachable, visit by treatment by subgroup interaction, and baseline uric acid by visit interaction as fixed effects.

<sup>b</sup>Treatment comparison all <0.001 except for race (other, P=0.006) and NYHA (class IV, P=0.003).

<sup>c</sup>P for trend.

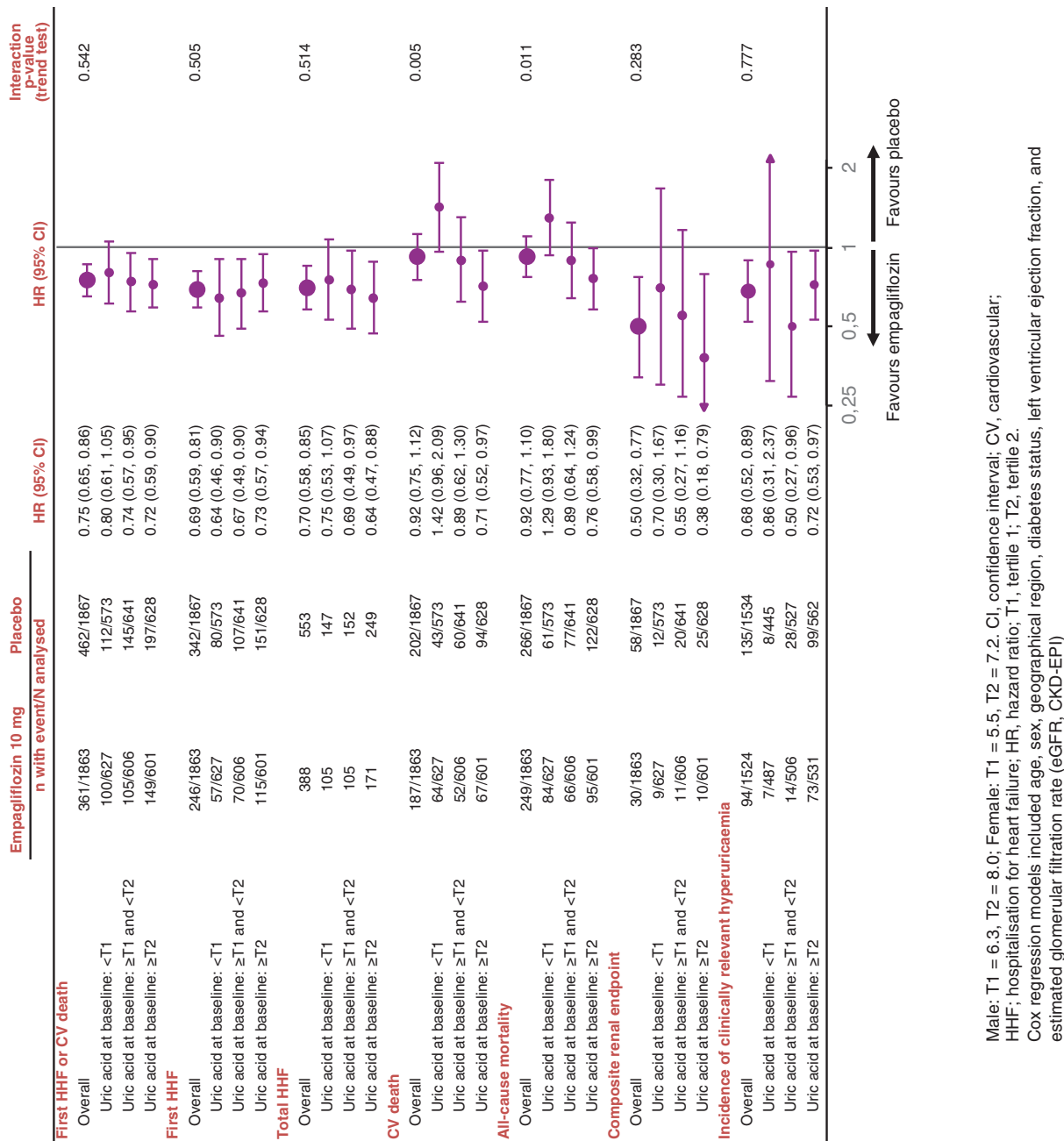
<sup>d</sup>Omitted as factor if considered as subgroup.



**Figure 3** Cumulative incidence of clinically relevant hyperuricaemic events\* for patients treated with empagliflozin vs. placebo.\*Clinically relevant hyperuricemia is defined as the composite episodes of acute gout, gouty arthritis or the initiation of treatment with serum uric acid lowering therapy (xanthine oxidase inhibitors, uricosuric agents or colchicine).

reduction of SUA in all patients subgroups, including patients with severely impaired kidney function (see [Supplementary material online, Figure S1C](#)), even though SGLT2 inhibitor-induced glycosuria is known to be attenuated in these patients.<sup>45</sup> Moreover, the glycosuric effect of empagliflozin is smaller in non-diabetic individuals,<sup>46</sup> and hence, an effect on SUA reduction mediated by glucose-competitive renal extraction would be expected to be smaller in non-diabetics. Yet, in our study, empagliflozin exerts a greater SUA lowering effect in patients without diabetes. These findings suggest that other mechanisms (beside increased renal excretion) contribute to the uric acid-lowering effect of empagliflozin; these may include reduced production of pro-inflammatory cytokines.<sup>47</sup> and oxidative stress.<sup>48</sup>

Our study is a post hoc analysis of a large clinical trial database and should be considered in light of certain strengths and limitations. Despite multivariate adjustments, we could not adjust for baseline differences for unmeasured variables. Some previous studies in patients with HF<sup>49</sup> or diabetes mellitus<sup>23</sup> have observed a higher prevalence of high SUA levels in men, but we observed no difference in sex distribution among tertiles of SUA. Notably, these earlier studies reported on SUA subgroups combining male and female patients and ignored the fact that SUA levels are physiologically lower in women than in men. In our study, we identified tertile cut points separately for men and women based on sex-dependent distribution of SUA. Using this approach, the prevalence of hyperuricaemia was not



**Figure 4** The effect of empagliflozin vs. placebo on major outcomes by tertile serum uric acid levels at baseline.

Male: T1 = 6.3, T2 = 8.0; Female: T1 = 5.5, T2 = 7.2. CI, confidence interval; CV, cardiovascular; HHF; hospitalisation for heart failure; HR, hazard ratio; T1, tertile 1; T2, tertile 2. Cox regression models included age, sex, geographical region, diabetes status, left ventricular ejection fraction, and estimated glomerular filtration rate (eGFR, CKD-EPI)

dependent on sex, a finding in accord with other studies using a similar approach.<sup>16</sup>

In conclusion, hyperuricaemia was shown to be as a common comorbidity in patients with HF and reduced EF and elevated SUA was an independent predictor of advanced disease and poor prognosis. Treatment with empagliflozin induced a rapid and sustained reduction of SUA and decreased the risk of clinically relevant hyperuricemic events, which is a newly reported and clinically meaningful effect of SGLT2 inhibitor treatment in HF. The effect of empagliflozin to lower SUA was observed in all patient subgroups, and the benefit of empagliflozin on HF outcomes was observed independent of SUA and of SUA dynamics.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

## Funding

This study was funded by Boehringer Ingelheim and Eli Lilly. Graphical assistance was provided by 7.4 Ltd and was funded by Boehringer Ingelheim.

**Conflict of interest:** W.D. reports consulting fees from Boehringer Ingelheim (BI) related to work on clinical events committee during the conduct of the study and personal fees from Aimeriq, Bayer, BI, Medtronic, Pfizer, Sanofi-Aventis, Sphingotec, Vifor Pharma and research support from EU (Horizon2020), German ministry of Education and Research, German Center for Cardiovascular Research, Vifor Pharma, and ZS Pharma. S.D.A. reports grants from Abbott Vascular and Vifor (International) Ltd; consulting fees from Abbott Vascular; consulting fees from Bayer, Brahms GmbH, Cardiac Dimensions, Cordio, Novartis, Servier, and Vifor (International) Ltd and is a Trial Executive Committee member of BI and Eli Lilly and Company (ELC) Diabetes Alliance (trial sponsor). J.B. reports payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Abbott, Adrenomed, Amgen, Applied Therapeutics, Array, AstraZeneca (AZ), Bayer, BerlinCures, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana Medical, Occlutech, and Vifor and is a Trial Executive Committee member of BI and ELC Diabetes Alliance (trial sponsor). F.Z. reports payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from BI, Amgen, CVRx, AZ, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, Merck, and Bayer; other financial or nonfinancial interests in CVCT and Cardiorenal; and is a Trial Executive Committee member of BI and ELC Diabetes Alliance (trial sponsor). G.F. reports payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from BI, Medtronic, Vifor, Servier, and Novartis; research grants from the European Commission, and is a Trial Executive Committee member of BI and ELC Diabetes Alliance (trial sponsor). J.P.F. reports consulting fees from BI; grants from AZ, Bayer and Novartis; honoraria payments from BI and AZ. and is a Trial Executive Committee member of BI and ELC Diabetes Alliance (trial sponsor). A.S. and M.B. are employees of BI. C.C. is an employee of main-analytics GmbH, Sulzbach, contracted by Boehringer Ingelheim. S.P. reports consulting fees and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from BI and is a Trial Executive Committee member of BI and ELC Diabetes Alliance (trial sponsor). J.L.J. is a Trustee of the American College of Cardiology, a Board member of Imbria

Pharmaceuticals, has received grant support from Applied Therapeutics, Innolife, Novartis Pharmaceuticals and Abbott Diagnostics, consulting income from Abbott, Janssen, Novartis, and Roche Diagnostics, and participates in clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Amgen, Bayer, CVRx, Janssen, MyoKardia, and Takeda. M.P. reports consulting fees from Abbvie, Actavis, Amgen, Amarin, AZ, BI, Bristol Myers Squibb, Casana, CSL Behring, Cytokinetics, Johnson & Johnson, ELC, Moderna, Novartis, ParatusRx, Pfizer, Relypsa, Salamandra, Synthetic Biologics, and Theravance and is a Trial Executive Committee member of BI and ELC Diabetes Alliance (trial sponsor).

## References

- Packer M. Uric acid is a biomarker of oxidative stress in the failing heart: lessons learned from trials with allopurinol and SGLT2 inhibitors. *J Card Fail* 2020;**26**: 977–984.
- Cicero AF, Rosticci M, Parini A, Baronio C, D'Addato S, Borghi C. Serum uric acid is inversely proportional to estimated stroke volume and cardiac output in a large sample of pharmacologically untreated subjects: data from the brisighella heart study. *Intern Emerg Med* 2014;**9**:655–660.
- Vaduganathan M, Greene SJ, Ambrosy AP, Mentz RJ, Subacius HP, Chioncel O et al. Relation of serum uric acid levels and outcomes among patients hospitalized for worsening heart failure with reduced ejection fraction (from the efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan trial). *Am J Cardiol* 2014;**114**:1713–1721.
- Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. *Circulation* 2003;**107**:1991–1997.
- Huang H, Huang B, Li Y, Huang Y, Li J, Yao H et al. Uric acid and risk of heart failure: a systematic review and metaanalysis. *Eur J Heart Fail* 2014;**16**:15–24.
- Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle heart failure model: prediction of survival in heart failure. *Circulation* 2006;**113**:1424–1433.
- L1 M, Babalis D, Roughton M, Shibata M, Anker SD, Ghio S et al. Predictors of clinical outcomes in elderly patients with heart failure. *Eur J Heart Fail* 2011;**13**: 528–536.
- Doehner W, Frenneaux M, Anker SD. Metabolic impairment in heart failure. The myocardial and systemic perspective. *J Am Coll Cardiol* 2014;**64**:1388–1400.
- Doehner W, Landmesser U. Xanthine oxidase and uric acid in cardiovascular disease: clinical impact and therapeutic options. *Semin Nephrol* 2011;**31**: 433–440.
- Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation* 2002;**105**:2619–2624.
- Givertz MM, Anstrom KJ, Redfield MM, Deswal A, Haddad H, Butler J, et al. Effects of Xanthine oxidase inhibition in hyperuricemic heart failure patients: the xanthine oxidase inhibition for hyperuricemic heart failure patients (EXACT-HF) study. *Circulation* 2015;**131**:1763–1771.
- Ogino K, Kato M, Furuse Y, Kinugasa Y, Ishida K, Doehner W et al. Uric acid-lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. *Circ Heart Fail* 2010;**3**:73–81.
- Leary WP, Reyes AJ, Van der Byl K. Effects of angiotensin-converting enzyme inhibitors on urinary excretions: interactions with diuretics. *Am J Med* 1992;**92**: 64S–68S.
- Kim HS, Kim H, Lee SH, Kim JH. Comparative analysis of the efficacy of angiotensin II receptor blockers for uric acid level change in asymptomatic hyperuricaemia. *J Clin Pharm Ther* 2020;**45**:1264–1270.
- Selvaraj S, Claggett BL, Pfeffer MA, Desai AS, Mc Causland FR, McGrath MM et al. Serum uric acid, influence of sacubitril-valsartan, and cardiovascular outcomes in heart failure with preserved ejection fraction: PARAGON-HF. *Eur J Heart Fail* 2020;**22**:2093–2101.
- Reyes AJ. Cardiovascular drugs and serum uric acid. *Cardiovasc Drugs Ther* 2003;**17**: 397–414.
- Karabacak M, Dogan A, Tayyar S, Bas HA. The effects of carvedilol and nebivolol on oxidative stress status in patients with non-ischaemic heart failure. *Kardiol Pol* 2015;**73**:201–206.
- Sica DA, Carter B, Cushman W, Hamm L. Thiazide and loop diuretics. *J Clin Hypertens (Greenwich)* 2011;**13**:639–643.
- Schrijver G, Weinberger MH. Hydrochlorothiazide and spironolactone in hypertension. *Clin Pharmacol Ther* 1979;**25**:33–42.

20. Ouchi M, Oba K, Kaku K, Suganami H, Yoshida A, Fukunaka Y *et al.* Uric acid lowering in relation to HbA1c reductions with the SGLT2 inhibitor tofogliflozin. *Diabetes Obes Metab* 2018;**20**:1061–1065.
21. Li J, Woodward M, Perkovic V, Figtree GA, Heerspink HJL, Mahaffey KW, *et al.* Mediators of the effects of canagliflozin on heart failure in patients with type 2 diabetes. *JACC Heart Fail* 2020;**8**:57–66.
22. Verma S, Ji Q, Bhatt DL, Mazer CD, Al-Omran M, Inzucchi SE *et al.* Association between uric acid levels and cardio-renal outcomes and death in patients with type 2 diabetes: a subanalysis of EMPA-REG OUTCOME. *Diabetes Obes Metab* 2020;**22**:1207–1214.
23. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, *et al.* Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424.
24. Packer M, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J *et al.* Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-reduced trial. *Eur J Heart Fail* 2019;**21**:1270–1278.
25. Leyva F, Anker SD, Godsland IF, Teixeira M, Hellewell PG, Kox WJ, *et al.* Uric acid in chronic heart failure: a marker of chronic inflammation. *Eur Heart J* 1998;**19**:1814–1822.
26. Leyva F, Anker SD, Swan JW, Godsland IF, Wingrove CS, Chua TP, *et al.* Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure. *Eur Heart J* 1997;**18**:858–865.
27. Mantovani A, Targher G, Temporelli PL, Lucci D, Gonzini L, Nicolosi GL *et al.* Prognostic impact of elevated serum uric acid levels on long-term outcomes in patients with chronic heart failure: a post-hoc analysis of the GISSI-HF (gruppo italiano per lo studio della sopravvivenza nella insufficienza Cardiaca-heart failure) trial. *Metabolism* 2018;**83**:205–215.
28. Huang G, Qin J, Deng X, Luo G, Yu D, Zhang M, *et al.* Prognostic value of serum uric acid in patients with acute heart failure: a meta-analysis. *Medicine (Baltimore)* 2019;**98**:e14525.
29. Hu X, Yang Y, Hu X, Jia X, Liu H, Wei M *et al.* Effects of sodium-glucose cotransporter 2 inhibitors on serum uric acid in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. *Diabetes Obes Metab* 2022;**24**:228–238.
30. Ferreira JP, Inzucchi SE, Mattheus M, Meinicke T, Steubl D, Wanner C, *et al.* Empagliflozin and uric acid metabolism in diabetes: a post hoc analysis of the EMPA-REG OUTCOME trial. *Diabetes Obes Metab* 2022;**24**:135–141.
31. Thanassoulis G, Brophy JM, Richard H, Pilote L. Gout, allopurinol use, and heart failure outcomes. *Arch Intern Med* 2010;**170**:1358–1364.
32. Stamp LK, Frampton C, Drake J, Doughty RN, Troughton RW, Richards AM. Associations of gout and baseline serum urate level with cardiovascular outcomes: analysis of the coronary disease cohort study. *Arthritis Rheumatol* 2019;**71**:1733–1738.
33. Krishnan E. Gout and the risk for incident heart failure and systolic dysfunction. *BMJ Open* 2012;**2**:e000282.
34. Francis-Sedlak M, LaMoreaux B, Padnick-Silver L, Holt RJ, Bello AE. Characteristics, comorbidities, and potential consequences of uncontrolled gout: an insurance-claims database study. *Rheumatol Ther* 2021;**8**:183–197.
35. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M *et al.* 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726.
36. Evans PL, Prior JA, Belcher J, Mallen CD, Hay CA, Roddy E. Obesity, hypertension and diuretic use as risk factors for incident gout: a systematic review and meta-analysis of cohort studies. *Arthritis Res Ther* 2018;**20**:136.
37. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 2008;**359**:1811–1821.
38. Baldus S, Müllerleile K, Chumley P, Steven D, Rudolph V, Lund GK *et al.* Inhibition of xanthine oxidase improves myocardial contractility in patients with ischemic cardiomyopathy. *Free Radic Biol Med* 2006;**41**:1282–1288.
39. Maxwell AJ, Bruinsma KA. Uric acid is closely linked to vascular nitric oxide activity. Evidence for mechanism of association with cardiovascular disease. *J Am Coll Cardiol* 2001;**38**:1850–1858.
40. Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, Schumacher M *et al.* How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care* 2018;**41**:356–363.
41. Zanchi A, Burnier M, Muller ME, Ghajarzadeh-Wurzner A, Maillard M, Loncle N, *et al.* Acute and chronic effects of SGLT2 inhibitor empagliflozin on renal oxygenation and blood pressure control in nondiabetic normotensive subjects: a randomized, placebo-controlled trial. *J Am Heart Assoc* 2020;**9**:e016173.
42. Heise T, Jordan J, Wanner C, Heer M, Macha S, Mattheus M *et al.* Acute pharmacodynamic effects of empagliflozin with and without diuretic agents in patients with type 2 diabetes Mellitus. *Clin Ther* 2016;**38**:2248–2264.
43. Chino Y, Samukawa Y, Sakai S, Nakai Y, Yamaguchi J, Nakanishi T, *et al.* SGLT2 Inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. *Biopharm Drug Dispos* 2014;**35**:391–404.
44. Bailey CJ. Uric acid and the cardio-renal effects of SGLT2 inhibitors. *Diabetes Obes Metab* 2019;**21**:1291–1298.
45. Kasichayanula S, Liu X, Pe Benito M, Yao M, Pfister M, LaCreta FP *et al.* The influence of kidney function on dapagliflozin exposure, metabolism and pharmacodynamics in healthy subjects and in patients with type 2 diabetes mellitus. *Br J Clin Pharmacol* 2013;**76**:432–444.
46. Ferrannini E, Baldi S, Frascerra S, Astiarraga B, Heise T, Bizzotto R, *et al.* Shift to fatty substrate utilization in response to sodium-glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. *Diabetes* 2016;**65**:1190–1195.
47. Díaz-Rodríguez E, Agra RM, Fernández ÁL, Adrio B, García-Caballero T, González-Juanatey JR *et al.* Effects of dapagliflozin on human epicardial adipose tissue: modulation of insulin resistance, inflammatory chemokine production, and differentiation ability. *Cardiovasc Res* 2018;**114**:336–346.
48. Hasan R, Lasker S, Hasan A, Zerin F, Zamila M, Chowdhury FI, *et al.* Canagliflozin attenuates isoprenaline-induced cardiac oxidative stress by stimulating multiple anti-oxidant and anti-inflammatory signaling pathways. *Sci Rep* 2020;**10**:14459.
49. Mogensen UM, Køber L, Jhund PS, Desai AS, Senni M, Kristensen SL *et al.* Sacubitril/valsartan reduces serum uric acid concentration, an independent predictor of adverse outcomes in PARADIGM-HF. *Eur J Heart Fail* 2018;**20**:514–522.