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► **To cite this version:**

Abhinav Sharma, Silvio E Inzucchi, Jeffrey M Testani, Anne Pernille Ofstad, David Fitchett, et al.. Kidney and heart failure events are bidirectionally associated in patients with type 2 diabetes and cardiovascular disease. *ESC Heart Failure*, 2023, 10.1002/ehf2.14601 . hal-04383282

HAL Id: hal-04383282

<https://hal.univ-lorraine.fr/hal-04383282v1>

Submitted on 9 Jan 2024

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Kidney and heart failure events are bidirectionally associated in patients with type 2 diabetes and cardiovascular disease

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Abstract

Aims This study aimed to evaluate the bidirectional relationship between kidney and cardiovascular (CV) events in trial participants with type 2 diabetes and CV disease.

Methods and results *Post hoc* analyses of EMPA-REG OUTCOME using Cox regression models were performed to assess the association of baseline factors with risk of a kidney event and bidirectional associations of incident kidney events and CV events. Among placebo-treated participants, baseline factors significantly associated with greater kidney event risk included lower baseline estimated glomerular filtration rate, albuminuria, higher uric acid, low-density lipoprotein cholesterol levels, and prior heart failure (HF). Coronary artery disease was not associated with increased risk. In placebo-treated participants, occurrence of an incident non-fatal kidney event increased the subsequent risk of hospitalization for HF (HHF) but not 3-point major adverse CV events (non-fatal stroke, non-fatal myocardial infarction, and CV death). Vice versa, HHF (but not myocardial infarction/stroke) increased the risk of subsequent kidney events. These associations were generally also seen in empagliflozin-treated participants and in the overall population. Interestingly, the risk of kidney events following HHF was not significantly increased in the relatively small number of placebo-treated participants already diagnosed with HF at baseline.

Conclusions These findings demonstrate a bidirectional inter-relationship between HHF and kidney events. Further exploration of this relationship and strategies to optimize the use of therapies to reduce both kidney and HF outcomes is warranted.

Keywords Heart failure; Kidney disease; Nephropathy; Type 2 diabetes

Received: 23 March 2023; Revised: 7 September 2023; Accepted: 31 October 2023

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Introduction

Heart function and kidney function are closely interrelated,^{1,2} and markers of kidney disease progression [such as low estimated glomerular filtration rate (eGFR) and albuminuria] are independently and additively associated with increases in risk of cardiovascular (CV) events and mortality^{2–4}; however the underlying pathophysiology of this association is still not fully understood.⁵

The association between kidney function and CV outcomes is well known in patients with type 2 diabetes (T2D). An observational study in patients with T2D observed that mortality rates were substantially higher in patients with chronic kidney disease (CKD) vs. those without (31% vs. 12%, respectively, for all-cause mortality, and 20% vs. 7%, respectively, for CV mortality).⁶ These observations indicate that kidney disease may be a contributing factor in the increased mortality observed in T2D patients.⁶

Kidney impairment is also common in patients with heart failure (HF),^{7,8} and poorer kidney function may predict left ventricular dysfunction,⁹ which supports the potential role of CKD as a risk factor for the development of HF. Indeed, it has been previously shown that kidney function is one of the strongest predictors of outcomes in HF.¹⁰ Treatment of HF, especially with regards to diuresis and adequate renin–angiotensin–aldosterone system (RAAS) blockade, is often limited by poor and deteriorating kidney function.¹¹ Randomized trials in the particularly vulnerable population that present with both HF and CKD are lacking. Currently, there is no clear understanding of how HF increases the decline in kidney function,¹² but altered renal perfusion and the effects of diuretics may play roles. There is also controversy about how kidney dysfunction may mediate HF outcomes.^{13,14} CKD and congestion are predictors of poor prognosis in patients with acute HF. It has been suggested that inflammatory cytokines, such as tumour necrosis factor- α (TNF- α), could be mediators of the association between CKD, congestion, and outcomes in acute HF.¹⁵ CKD may also mediate the response to medications and CV outcomes in patients with T2D.¹⁶ Indeed, inflammation is frequently associated with many cardio-metabolic comorbidities, such as T2D, obesity, and CKD, and may be a key driver of the development and progression of HF.¹⁷

The sodium–glucose cotransporter 2 (SGLT2) inhibitor, empagliflozin, has been shown to reduce the risk of hospitalization for HF (HHF) by 35% and risk of kidney events by 39% in patients with T2D and CV disease (CVD).^{18,19} Furthermore, empagliflozin has been shown to reduce HHF, CV death, and kidney outcomes and slow the rate of kidney function decline in patients with HF, regardless of the presence of T2D.^{20–22} SGLT2 inhibitors also reduce HHF and CV mortality in patients with HF and CKD.^{21,23} Thus, decreasing the occurrence or worsening of nephropathy with empagliflozin may represent a strategy to decrease the risk of subsequent CV outcomes.

In this *post hoc* analysis, we aimed to identify baseline factors associated with the occurrence of kidney events (new or worsening nephropathy) and to evaluate the bidirectional relationship of kidney and CV events in all participants and by HF at baseline in the EMPA-REG OUTCOME trial.

Methods

Study design

In EMPA-REG OUTCOME (NCT01131676), participants with T2D and established CVD were randomized 1:1:1 to empagliflozin 10 and 25 mg or placebo in addition to standard of care. The design and methods of this double-blind, placebo-controlled, multinational trial have been described previously.¹⁹

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines and was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol at each participating centre. All the patients provided written informed consent before study entry.

Outcomes

In this *post hoc* analysis, we assessed: (i) the association of various baseline factors with time to first occurrence of an incident kidney event [new or worsening nephropathy, defined as progression to macroalbuminuria with urine albumin-to-creatinine ratio (UACR) >300 mg/g, doubling of serum creatinine from baseline with eGFR \leq 45 mL/min/1.73 m² (Modification of Diet in Renal Disease formula), initiation of renal replacement therapy, or death from kidney disease]; (ii) the association between an incident non-fatal kidney event (new or worsening nephropathy excluding death from kidney disease) and subsequent first CV event [CV death, HHF, 3-point major adverse CV event (3P-MACE; non-fatal stroke, non-fatal myocardial infarction, and CV death), and all-cause mortality]; and (iii) the association between an incident non-fatal CV event [HHF and a macrovascular composite of non-fatal myocardial infarction (MI) or non-fatal stroke] and subsequent first occurrence of a subsequent kidney event (new or worsening nephropathy).

Statistical analysis

All analyses were conducted following a modified intent-to-treat (ITT) approach in participants treated with at least one dose of study drug.

While all treated participants were considered at risk for CV events, new or worsening nephropathy was only analysed in treated participants who did not have macroalbuminuria at baseline, who had available measurements of serum creatinine at baseline and after baseline, and who had post-baseline measurements of the UACR (unless patients who did not fulfil these criteria had at least one of the other components of the composite renal outcome).¹⁸

To assess baseline factors that were prognostic for new or worsening nephropathy, analyses were performed using a multivariable Cox regression model with terms for baseline factors of age, sex, geographical region, time since diagnosis of T2D, glycated haemoglobin (HbA1c), systolic blood pressure (SBP), body mass index (BMI), smoking status, low-density lipoprotein (LDL) cholesterol, uric acid, eGFR, albuminuria, atrial fibrillation, coronary artery disease (CAD; defined as any of the components of history of MI, coronary

artery bypass graft, multivessel CAD, and single-vessel CAD), peripheral artery disease (PAD), stroke, and HF.

To explore the association between an incident non-fatal kidney event (new or worsening nephropathy excluding death from kidney disease) and subsequent CV event, we used Cox regression to analyse time to first CV event, with non-fatal kidney events as a time-varying covariate adjusted for the above-mentioned baseline factors, treatment, and treatment by non-fatal kidney event interaction. Each participant who did not have a CV event was censored on the last day they were known to be free of the outcome. For the time-varying covariate, the participant's status changed from non-exposed to exposed at the time of a kidney event until the first CV event or censoring. Similarly, we used Cox regression to analyse time to first kidney event with non-fatal CV event as a time-varying covariate, including the factors mentioned above and treatment by non-fatal CV event interaction.

Incidence rates for first CV event prior to/without or following a kidney event are shown as crude rates and are based on all participants available for the analysis. Incidence rates for first kidney event prior to/without or following a CV event were also assessed. The time at risk and count of events were restricted to the individual time prior to/without or following the kidney or CV event, respectively.

Analyses were performed in placebo and pooled empagliflozin (10 and 25 mg) treatment groups. For investigation of prognostic factors, defined as a measure of the natural history of the disease in the absence of therapy or with the application of standard of care, we focused on the placebo group. In addition, the bidirectional associations were assessed in placebo-treated participants with vs. without HF at baseline by including additional terms for subgroup and subgroup-by-time-varying covariate interaction.

All analyses were performed on a nominal two-sided $\alpha = 0.05$ without adjustment for multiplicity. Statistical analyses were performed using SAS® Version 9.4.

Results

The EMPA-REG OUTCOME trial included 7020 participants, of whom 2333 participants received placebo and 4687 received one of two doses of empagliflozin. Baseline characteristics were balanced between treatment groups.¹⁹

In the placebo group, baseline HF, absence of CAD, eGFR < 60 mL/min/1.73 m², presence of albuminuria, and higher uric acid and LDL cholesterol levels were associated with an increased risk for a kidney event. Also, the *P* value for time since T2D diagnosis was significant and suggested increased risk with duration >10 years but lower when duration was 5–10 years compared with <5 years, thus without a clear trend towards longer duration of T2D diagnosis increasing the risk for a kidney event (Figure 1). Baseline

factors not associated with increased risk for kidney event in the multivariable model are listed in Supporting Information, Figure S1.

Participants in the placebo group who experienced an incident kidney event were more likely to experience HHF, CV death, or all-cause mortality than those without a kidney event (Figures 2A and 3A). There was no significant association between an incident kidney event and subsequent first 3P-MACE (Figure 2A). Incident HHF was associated with an increased risk for subsequent kidney event, while incident non-fatal MI or stroke was not (Figures 2B and 3B).

In the subgroup of placebo participants without HF at baseline, a significant association was observed between a preceding kidney event and CV death, HHF, and all-cause mortality, but not 3P-MACE (Figure 4A). In patients with HF at baseline, there was no significant association between a preceding kidney event and subsequent CV events and mortality; however, it is important to mention that analyses were based on a small number of events (Figure 4A). The effect size for risk of subsequent first HHF appeared to be similar in participants with HF at baseline to those without HF at baseline (Figure 4A). The effect size was less for risk of subsequent CV death and all-cause mortality; however, confidence intervals for the hazard ratios in both subgroups overlap for all outcomes (Figure 4A). Similarly, a significant association between incident HHF and subsequent kidney event was identified in participants without HF at baseline (Figure 4B). There was no such association in participants with HF at baseline (*P* value for interaction 0.0174).

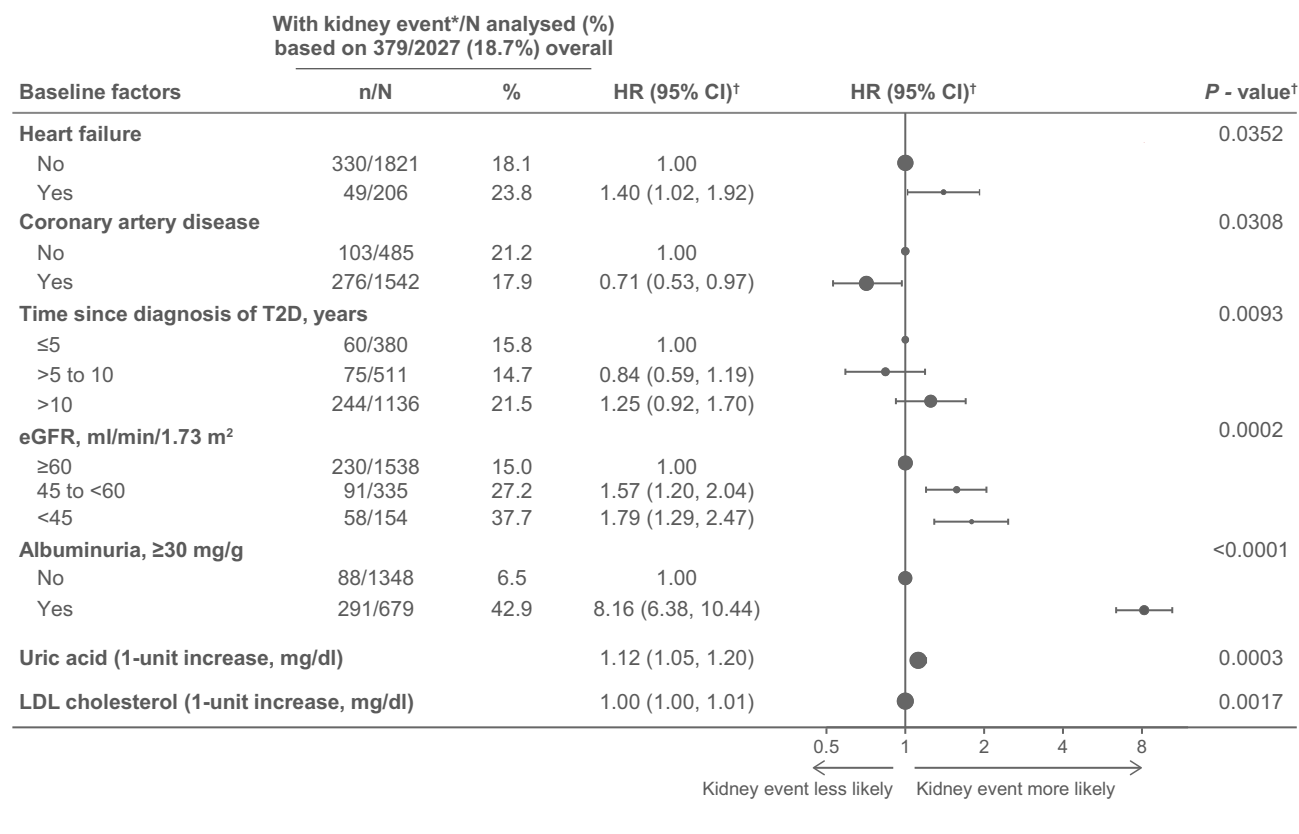
Generally, results were consistent in pooled empagliflozin (i.e. both doses) and overall analyses (Supporting Information, Figure S2) in terms of direction and size of effect. Risk of first 3P-MACE following a non-fatal kidney event, however, was shown to be significantly increased in the empagliflozin and overall groups but not in the placebo group, although confidence intervals overlapped (Supporting Information, Figure S3).

Discussion

In this *post hoc* analysis of EMPA-REG OUTCOME trial data, we focused on participants randomized to placebo treatment on top of standard of care, to identify prognostic factors for incident kidney outcomes and examine the bidirectional association between kidney events and CV events in participants with T2D and established CVD.

Measures of impaired kidney function (albuminuria and low eGFR) and HF at baseline were associated with an increased risk for a kidney event. Also, this risk was increased in participants with higher uric acid and higher LDL cholesterol levels at baseline and with non-coronary manifestation of CVD. Interestingly, in this multivariable analysis, age, blood

Figure 1 Baseline factors associated with the occurrence of a kidney event in the placebo group. *New or worsening nephropathy: progression to macroalbuminuria (urine albumin-to-creatinine ratio, >300 mg of albumin per gram of creatinine); a doubling of the serum creatinine level, accompanied by an estimated glomerular filtration rate (eGFR) of ≤ 45 mL/min/1.73 m² (Modification of Diet in Renal Disease); initiation of renal replacement therapy; or death from kidney disease. †Based on Cox regression model with terms for baseline factors of age, sex, geographical region, time since diagnosis of type 2 diabetes (T2D), glycated haemoglobin, systolic blood pressure, body mass index, smoking status, low-density lipoprotein (LDL) cholesterol, uric acid, eGFR, albuminuria, atrial fibrillation, coronary artery disease (defined as any of the components of history of myocardial infarction, coronary artery bypass graft, multivessel coronary artery disease, and single-vessel coronary artery disease), peripheral artery disease, stroke, and heart failure. CI, confidence interval; HR, hazard ratio.



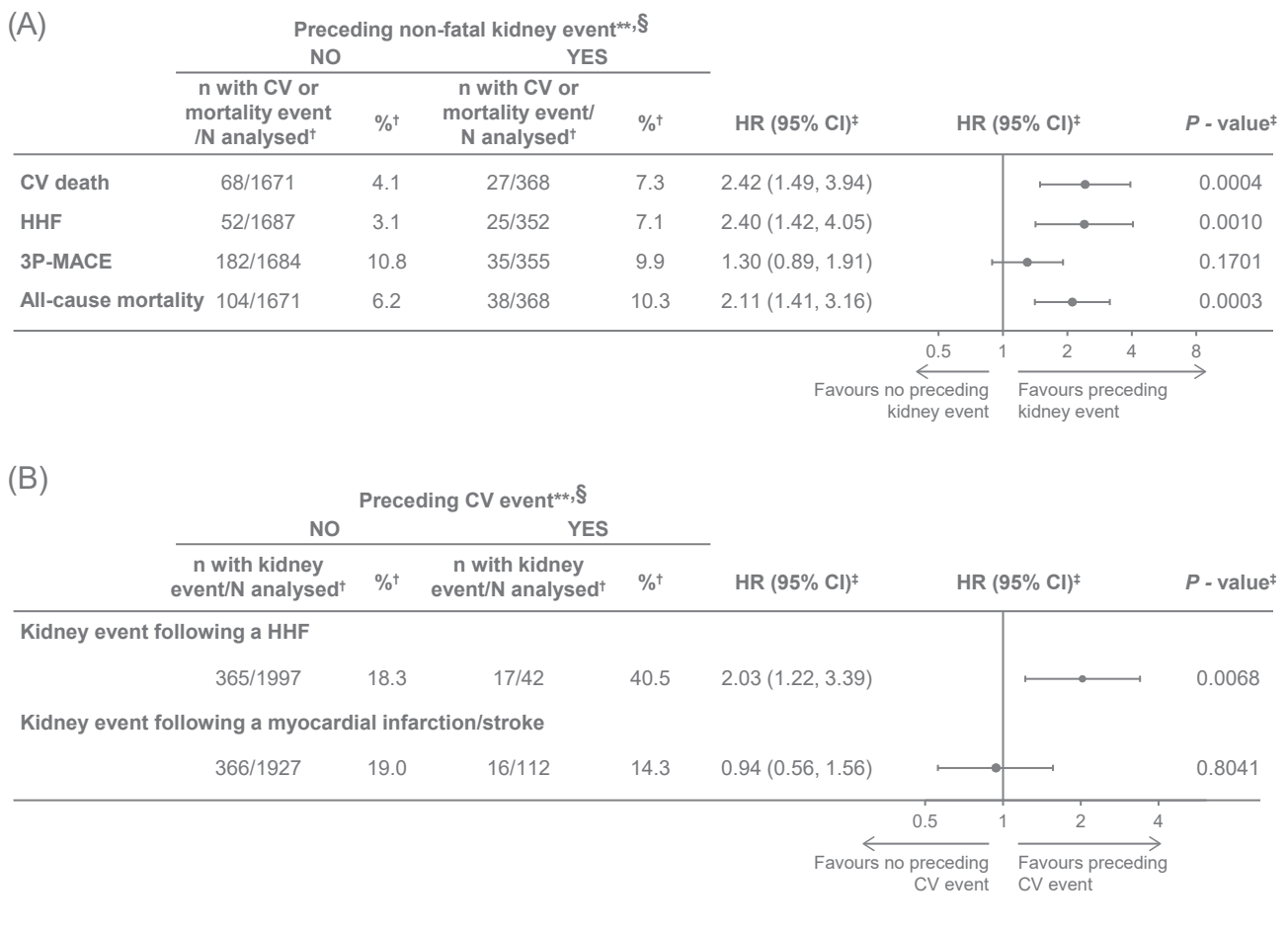
pressure, and HbA1c at baseline were not significantly associated with the risk of a kidney event. This finding seems to contrast with those of previous studies where decline in kidney function in patients with T2D was associated with increasing age, hypertension, and poor glycaemic control.^{24,25} It should be noted, however, that this was based on the multivariable model including the combination of all baseline factors presented. Impaired kidney function and HF diagnosis were identified as strong contributors, whereas the effect of other factors did not reach statistical significance.

Occurrence of an incident kidney event during the trial increased the risk of subsequent HHF, CV death, and all-cause mortality, but not 3-point MACE. These observations are consistent with other studies in patients with T2D⁶ and patients with HF.²⁶ The association with kidney events was bidirectional in terms of HHF. However, we found no association between macrovascular events (non-fatal MI or stroke) and subsequent kidney events, consistent with our observation that baseline CAD itself was not associated with a higher risk

of kidney events. As the risk for kidney events was increased by preceding HHF but not by non-fatal MI or stroke, the association may not solely reflect a more vulnerable population. Instead, this may be the result of plasma volume shifts due to aggressive diuretic therapy or may reflect common pathophysiological processes. These processes may include concurrent derangements in both cardiac and kidney haemodynamics, the effects of alterations in the renin-angiotensin-aldosterone axis, and other factors, including inflammation, oxidative stress, or sympathetic nervous system activation.^{1,27} The shared pathogenesis also suggests a potential beneficial interaction with the cardio-renal axis by SGLT2 inhibition, as observed with empagliflozin in patients with T2D and established CVD.^{18,19,28}

Congestion is a key clinical feature of HF, a major underlying cause of HHF²⁹ and also plays a pivotal role in cardio-renal dysfunction.³⁰ It has been recently reported that renal congestion is associated with worse outcomes in patients with HF, regardless of eGFR or UACR.³¹ Diuretics are

Figure 2 (A) Association of a non-fatal kidney event* with subsequent cardiovascular (CV) event and mortality in the placebo group. (B) Association of a non-fatal CV event with subsequent kidney event** in the placebo group. *Non-fatal kidney event defined as new or worsening nephropathy excluding death from kidney disease [progression to macroalbuminuria (urine albumin-to-creatinine ratio, >300 mg of albumin per gram of creatinine); a doubling of the serum creatinine level, accompanied by an estimated glomerular filtration rate (eGFR) of ≤ 45 mL/min/1.73 m², as calculated by the Modification of Diet in Renal Disease (MDRD) formula; and the initiation of renal replacement therapy]. †Only for presentation of numbers and frequency, categorization to with/without preceding non-fatal kidney event was determined at the time of first CV event/censoring (A) or categorization to with/without preceding CV event was determined at the time of first kidney event/censoring (B). ‡Based on Cox regression model with terms for age, sex, geographical region, time since diagnosis of type 2 diabetes, baseline glycated haemoglobin, systolic blood pressure, body mass index, smoking status, low-density lipoprotein cholesterol, uric acid, eGFR, albuminuria, atrial fibrillation, coronary artery disease [defined as any of the components of history of myocardial infarction (MI), coronary artery bypass graft, multivessel coronary artery disease, and single-vessel coronary artery disease] or peripheral artery disease, stroke, and heart failure, new or worsening nephropathy (without death from kidney disease) as a time-dependent covariate and treatment by new or worsening nephropathy (without death from kidney disease) covariate interaction (A), or respectively CV event as time-dependent covariate and treatment by CV event covariate interaction (B). **Kidney event defined as new or worsening nephropathy [progression to macroalbuminuria (urine albumin-to-creatinine ratio, >300 mg of albumin per gram of creatinine); a doubling of the serum creatinine level, accompanied by an eGFR of ≤ 45 mL/min/1.73 m², as calculated by the MDRD formula; the initiation of renal replacement therapy; or death from kidney disease]. ††CV event as indicated: hospitalization for heart failure (HHF) or non-fatal MI/stroke. 3P-MACE, 3-point major adverse cardiovascular event; CI, confidence interval; HR, hazard ratio.



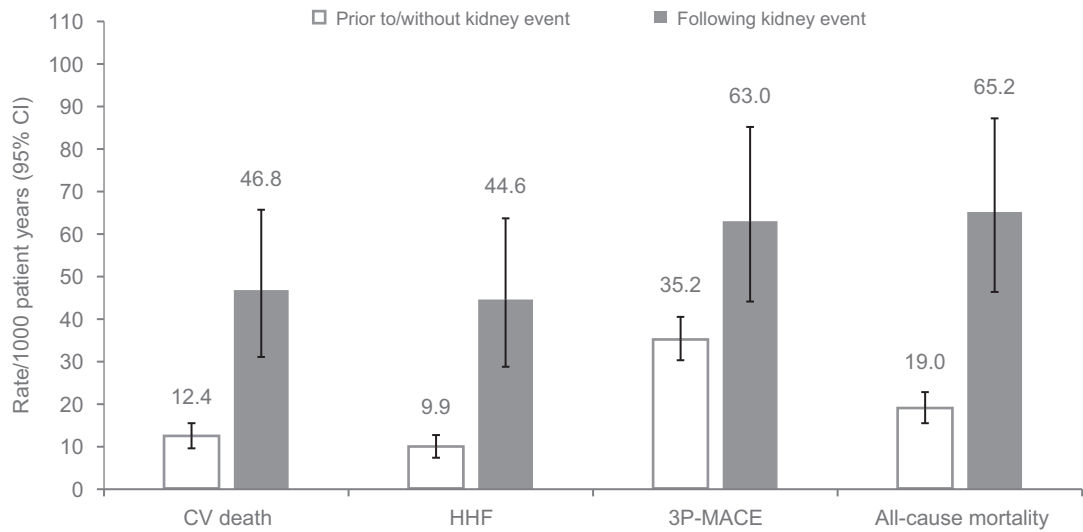
currently first-line therapy for the relief of congestion in patients with acute HF; however, their use may be inappropriate in the case of worsening renal function.³² Effective and safe decongestion remains a major goal for optimal therapeutic management of patients with acute HF. A *post hoc* analysis of the EMPULSE trial (NCT0415775) investigated the impact of empagliflozin on decongestion in patients hospitalized for acute HF. Initiation of empagliflozin resulted in an early,

effective, and sustained decongestion, which was associated with clinical benefit at Day 90.³³

The majority of studies to date have focused on the association between kidney events and CV events in general (i.e. not HF and vascular events independently). Although CKD and CVD share many conventional atherosclerotic risk factors, age-adjusted CV mortality is several times higher in patients with CKD than in the general population.³⁴ Recent

Figure 3 Incidence rates in the placebo group for (A) first cardiovascular (CV) event without prior kidney event (white bars) or following a kidney event (grey bars) and (B) first kidney event without prior CV event (white bars) or following a CV event (grey bars). Crude incidence rates, not adjusting for baseline factors, based on all participants available for the analysis. Thus, participant numbers may be slightly higher compared with those included in all analyses using the extended model that only includes participants with respective baseline factors available. (A) Until the first kidney event, patients contribute with time at risk to the phase ‘without prior kidney event’ for each CV/mortality outcome. After the first kidney event, patients contribute with time at risk and event occurrence (CV event yes/no) to the time to first CV event ‘following kidney event’. Patients without kidney event contribute with time at risk and event occurrence (CV event yes/no) only to the phase ‘without prior kidney event’. (B) Until the first CV event, patients contribute with time at risk to the phase ‘without prior CV event’ for kidney outcome. After the first CV event, patients contribute with time at risk and event occurrence (kidney event yes/no) to the time to first kidney event ‘following CV event’. Patients without CV event contribute with time at risk and event occurrence (kidney event yes/no) only to the phase ‘without prior CV event’. 3P-MACE, 3-point major adverse cardiovascular event; CI, confidence interval; HHF, hospitalization for heart failure; MI, myocardial infarction.

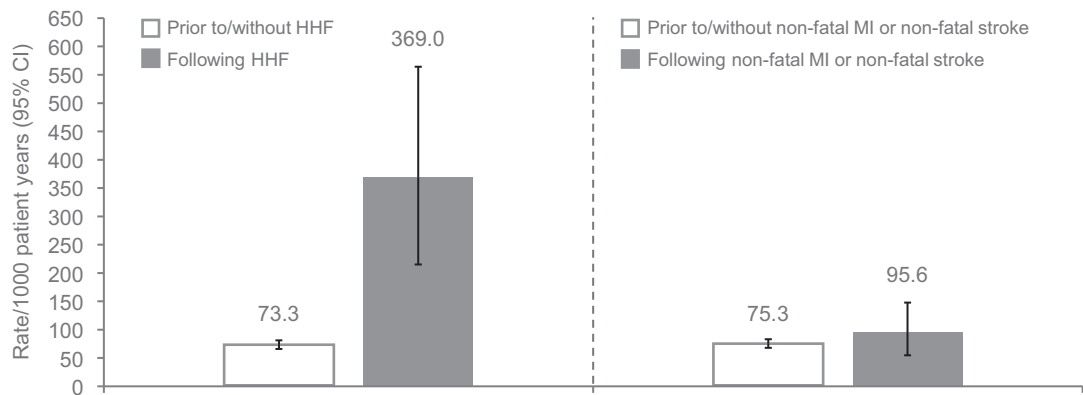
(A)



Participants, n

Prior to/without kidney event	2060	2060	2060	2060
Following kidney event	374	358	361	374

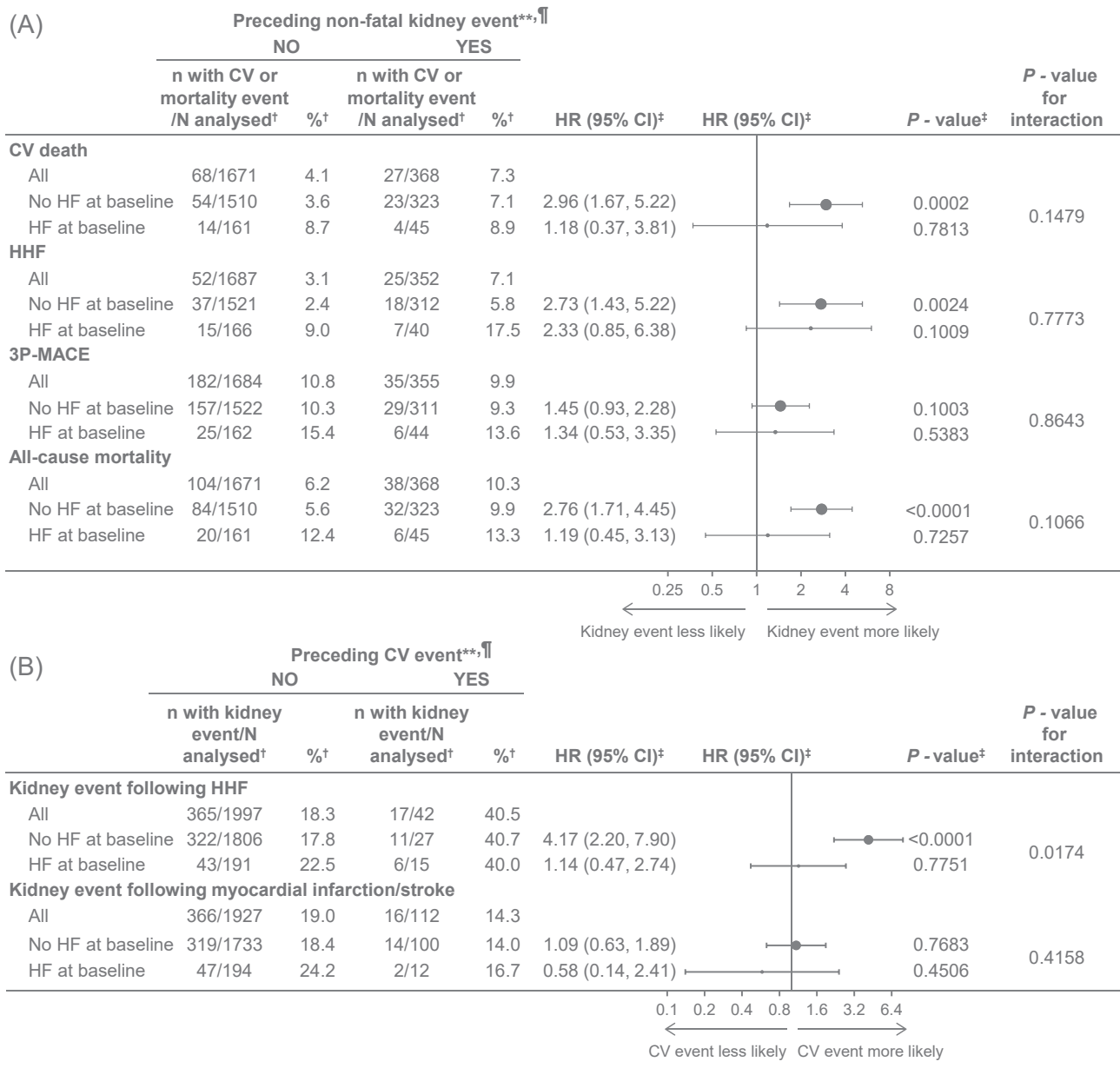
(B)



Participants, n

Prior to/without CV event	2061	2061
Following CV event	43	114

Figure 4 (A) Placebo group with and without heart failure (HF) at baseline: association of non-fatal kidney events* with subsequent cardiovascular (CV) events and mortality. (B) Placebo group with and without HF at baseline: association of non-fatal CV events with subsequent kidney events**. *Non-fatal kidney event defined as new or worsening nephropathy excluding death from kidney disease [progression to macroalbuminuria (urine albumin-to-creatinine ratio, >300 mg of albumin per gram of creatinine); a doubling of the serum creatinine level, accompanied by an estimated glomerular filtration rate (eGFR) of ≤ 45 mL/min/1.73 m², as calculated by the Modification of Diet in Renal Disease (MDRD) formula; and the initiation of renal replacement therapy]. †Only for presentation of participant numbers and frequency, categorization to with/without CV event was determined at the time of kidney event/censoring (A) or categorization to with/without CV event determined at the time of kidney event/censoring (B). ‡Based on Cox regression model with terms for age, sex, geographical region, time since diagnosis of type 2 diabetes, baseline glycated haemoglobin, systolic blood pressure, body mass index, smoking status, low-density lipoprotein cholesterol, uric acid, eGFR, albuminuria, atrial fibrillation, coronary artery disease [defined as any of the components of history of myocardial infarction (MI), coronary artery bypass graft, multivessel coronary artery disease, and single-vessel coronary artery disease], peripheral artery disease, stroke, and HF, treatment, new or worsening nephropathy (without death from kidney disease) as time-dependent covariate and treatment by new or worsening nephropathy (without death from kidney disease) covariate interaction (A), or respectively CV event as time-dependent covariate and treatment by CV event covariate interaction (B). **Kidney event defined as new or worsening nephropathy [progression to macroalbuminuria (urine albumin-to-creatinine ratio, >300 mg of albumin per gram of creatinine); a doubling of the serum creatinine level, accompanied by an eGFR of ≤ 45 mL/min/1.73 m², as calculated by the MDRD formula; the initiation of renal replacement therapy; or death from kidney disease]. ††CV event as indicated: hospitalization for heart failure (HHF) or MI/stroke. 3P-MACE, 3-point major adverse cardiovascular event; CI, confidence interval; HR, hazard ratio.



research suggests that coronary microvascular dysfunction may contribute to the transition to pathological left ventricle remodelling and subsequently an increased risk of HF in patients with CKD.³⁵

In the present analysis, we observed that incident HHF was associated with an increased risk of a subsequent kidney event. However, this association was not observed in the small subgroup of participants with HF at baseline. This may be due to the fact that 'first' HHF patients present with significant haemodynamic derangements and are subsequently introduced to interventional HF medications (e.g. RAAS inhibitors and diuretics) to control them. In comparison, following subsequent HHF, patients may experience less significant haemodynamic changes and fewer modifications to their treatment regimens.¹ While a unique observation, it is important to note that the number of events in these analyses was low. Therefore, further investigation on the potential association of kidney events with subsequent HHF in participants with existing HF is warranted. Although these analyses concentrated on placebo-treated participants, we found that results in the empagliflozin group were generally comparable with the placebo group.

Due to the *post hoc* nature of these analyses, our findings should be considered exploratory, with prospective studies being required to confirm them. While this analysis is based on adjudication-confirmed CV events following randomization, baseline HF was investigator reported, and there were no baseline investigations (i.e. natriuretic peptides or ejection fraction) confirmed to establish a definitive HF diagnosis or its type and aetiology.

It is important to note that effects on risk of subsequent kidney events may have been confounded by risk factor control,²⁸ concomitant use of medications such as RAAS inhibitors, particularly in participants with baseline CAD, and changes in patient medication regimens, including diuretics.³⁶ Similar results were noted in an observational study with suspected ischaemic heart disease, which observed an association between impaired kidney function and MACE, mortality, and HF, but not MI.³⁵ One study also found an association between acute kidney injury and risk of HF with no association with MACE.³⁷

In conclusion, we observed that presence of HF and impaired kidney function were associated with increased risk of kidney events. Vice versa, the occurrence of an incident kidney event increased the risk of subsequent CV death, HHF, and all-cause mortality. The observation that the risk for kidney events was increased by preceding HHF but not MI or stroke possibly reflects a common pathophysiology involving abnormal cardiac and kidney haemodynamics. Further investigation is warranted to elucidate the association between kidney events and subsequent HHF with particular focus on participants with existing HF. Overall, these data demonstrate the close interrelation of HF and CKD, uncovering this interaction as a topic of further investigation in the cardio-renal risk reduction with SGLT2 inhibition.

Acknowledgements

The authors would like to thank the study investigators and all participants who took part in the studies. Editorial assistance was provided by Katarina Kolaric of Elevate Scientific Solutions, which was contracted and compensated by Boehringer Ingelheim. To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the International Committee of Medical Journal Editors (ICMJE) criteria, Boehringer Ingelheim grants all external authors access to clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data when it becomes available on <https://vivli.org/> and earliest after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete, and other criteria are met. Please visit <https://www.mystudywindow.com/msw/datasharing> for further information. The authors meet criteria for authorship as recommended by the ICMJE and were fully responsible for all content and editorial decisions and were involved at all stages of manuscript development.

Conflict of interest

A.S. has received support from Roche Diagnostics, Boehringer Ingelheim, Novartis, AstraZeneca, Bayer, Janssen, Servier, and Takeda. S.E.I. has consulted and/or served on Clinical Trial Steering/Executive/Publication Committees for Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Lexicon Pharmaceuticals, Merck, Pfizer, Abbott, Esperion, and vTv Therapeutics and has given lectures for Boehringer Ingelheim and AstraZeneca. J.M.T. reports grants and/or personal fees from 3ive Labs, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, AstraZeneca, Novartis, Cardionomic, MagentaMed, Reprise Inc., FIRE1, W. L. Gore, Sanofi, Sequana Medical, Otsuka, Abbott, Merck, Windtree Therapeutics, Lexicon Pharmaceuticals, preCARDIA, Relypsa, Regeneron, BD, Edwards Lifesciences, and Lilly. In addition, J.M.T. has a patent treatment of diuretic resistance issued to Yale and Corvidia Therapeutics Inc., a patent method for measuring renalase issued to Yale, and a patent treatment of diuretic resistance pending with Reprise Inc. A.P.O. is an employee of Boehringer Ingelheim. D.F. has received honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck & Co., and Sanofi. M.M. is an employee of Boehringer Ingelheim. S.V. holds a Tier 1 Canada Research Chair in Cardiovascular Surgery and reports receiving research grants and/or speaking honoraria from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, EOCI Pharmacomm Ltd, HLS Therapeutics, Janssen, Merck,

Novartis, Novo Nordisk, Sanofi, Sun Pharmaceutical, PhaseBio, and the Toronto Knowledge Translation Working Group. He is a member of the scientific excellence committee of the EMPEROR-Reduced trial and served as a national lead investigator of the DAPA-HF and EMPEROR-Reduced trials. He is the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. F.Z. has received personal fees from Boehringer Ingelheim during the conduct of the study; personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, Merck, Bayer, and CellProthera outside the submitted work; and other support from CVCT and Cardiorenal outside the submitted work. C.W. has received personal fees from Akebia, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Gilead, MSD, Mundipharma, Sanofi, and Vifor Fresenius outside the submitted work. B.J.K. is an employee of Boehringer Ingelheim and University Hospital Würzburg and has received grant support from the IZKF Würzburg and honoraria from Boehringer Ingelheim.

Funding

This analysis was funded by Boehringer Ingelheim. The EMPA-REG OUTCOME trial was funded by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance. A.S. has received support from the Canadian Institutes of Health Research (Grant No. 175095) and Fonds de Recherche Santé Quebec (FRSQ) Junior 1 clinician scholars' programme.

Supporting information

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

Figure S1. Baseline factors not associated ($p > 0.05$) with the occurrence of a kidney event* in the placebo group (multivariable model) *New or worsening nephropathy: progression to macroalbuminuria (urinary albumin-to-creatinine ratio, >300 mg of albumin per gram of creatinine); a doubling of the serum creatinine level, accompanied by an eGFR of ≤ 45 ml/min/1.73 m², as calculated by the MDRD formula; the initiation of renal replacement therapy; or death from kidney disease. †Based on Cox regression model with terms for baseline factors of age, sex, geographical region, time since diagnosis of T2D, HbA1c, SBP, BMI, smoking status, LDL cholesterol, uric acid, eGFR, albuminuria, atrial fibrillation, CAD (defined as any of the components of history of MI, coronary artery bypass graft, multivessel coronary artery disease, single vessel coronary artery disease), PAD, stroke, or

heart failure. BMI, body mass index; CAD, coronary artery disease; CI, confidence intervals; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HR, hazard ratio; LDL, low density lipoprotein; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; PAD, peripheral artery disease; SBP, systolic blood pressure; T2D, type 2 diabetes.

Figure S2. Bidirectional association of non-fatal kidney events with subsequent CV events *Non-fatal kidney event defined as new or worsening nephropathy excluding death from kidney disease (progression to macroalbuminuria [urine albumin-to-creatinine ratio, >300 mg of albumin per gram of creatinine]; a doubling of the serum creatinine level, accompanied by an eGFR of ≤ 45 ml per minute per 1.73 m², as calculated by the MDRD formula; the initiation of renal replacement therapy). †Only for presentation of participant numbers, those with/without kidney event were determined at the time of cardiovascular event/censoring (panel A) or those with/without CV event determined at time of kidney event/censoring (panel B). ‡Based on Cox regression model with terms for age, sex, geographical region, time since diagnosis of T2D, baseline HbA1c, SBP, BMI, smoking status, LDL cholesterol, uric acid, eGFR, albuminuria, atrial fibrillation, prior CAD (defined as any of the components of history of MI, coronary artery bypass graft, multivessel coronary artery disease, single vessel coronary artery disease), or PAD, stroke, and heart cardiac failure, treatment, new or worsening nephropathy (without death from kidney disease) as time dependent variable and treatment by new or worsening nephropathy (without death from kidney disease) interaction (panel A) or respective CV event as time dependent variable (panel B). ** CV event as indicated: HHF or MI/stroke. BMI, body mass index; CAD, coronary artery disease; CI, confidence intervals; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HHF, hospitalisation for heart failure; HR, hazard ratio; LDL, low density lipoproteins; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; PAD, peripheral artery disease; SBP, systolic blood pressure; T2D, type 2 diabetes; PY, patient-years; 3P-MACE, 3-point major adverse cardiovascular event.

Figure S3. Incidence rates in the empagliflozin group for (A) first CV event prior to/without kidney event or following a kidney event and (B) first kidney event prior to/without CV event or following a CV event. Crude incidence rates, not adjusting for baseline factors, based on all participants available for the analysis. Thus, participant numbers may be slightly higher compared to those included in all analyses using the extended model that only include participants with respective baseline factors available. CI, confidence intervals; CV, cardiovascular; HHF, hospitalisation for heart failure; MI, myocardial infarction; 3P-MACE, 3-point major adverse cardiovascular event.

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