Type: Original article

Title: Empagliflozin and Cardiovascular and Kidney Outcomes Across KDIGO Risk Categories

Subtitle: *Post Hoc* Analysis of a Randomized, Double-Blind, Placebo-Controlled, Multinational Trial

Running title: Empagliflozin: KDIGO risk category cardiovascular/kidney outcomes

Adeera Levin, MD[1], Vlado Perkovic, MD[2], David C. Wheeler, MD[2,3], Stefan Hantel, PhD[4], Jyothis George, MD[5], Maximilian von Eynatten, MD[5], Audrey Koitka-Weber, PhD[5,6,7*], Christoph Wanner, MD[7*], on behalf of the EMPA-REG OUTCOME® Investigators

[1]Division of Nephrology, University of British Columbia, Vancouver, Canada;

[2]The George Institute for Global Health, University of New South Wales, Sydney, Australia;

[3]Centre for Nephrology, University College London, UK;

[4]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany;

[5]Boehringer Ingelheim International GmbH, Ingelheim, Germany;

[6]Department of Diabetes, Central Clinical School, Monash University, Melbourne, Australia;

[7]Department of Medicine, Würzburg University Clinic, Würzburg, Germany

*These authors contributed equally to this work as senior authors

Address for correspondence:

Dr. Adeera Levin, M.D., F.R.C.P.C; Division of Nephrology, St. Paul's Hospital, University of British Columbia, 1081 Burrard St., P-6010A, Vancouver, BC V6Z 1Y6, Canada

Phone +1 604 682 2344; Fax: +1 604 806 8120; e-mail: alevin@providencehealth.bc.ca.

Word count

Abstract (limit 300): **272**

Manuscript body (excluding references, figures and tables) (limit 3000): **3093**

Data were presented at the International Society of Nephrology's World Congress of Nephrology, April 21–25, 2017, Mexico City, Mexico.

ABSTRACT

Background and objectives In EMPA-REG OUTCOME®, empagliflozin, in addition to standard of care, significantly reduced risk of cardiovascular death by 38%, hospitalization for heart failure by 35%, and incident or worsening nephropathy by 39% compared with placebo in patients with type 2 diabetes and established cardiovascular disease. Using EMPA-REG OUTCOME® data, we assessed whether the Kidney Disease Improving Global Outcomes (KDIGO) chronic kidney disease (CKD) classification had an influence on the treatment effect of empagliflozin.

Design, setting, participants, & measurements Patients with type 2 diabetes, established atherosclerotic cardiovascular disease, and estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m^2 at screening were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to standard of care. *Post hoc*, we analyzed cardiovascular and kidney outcomes as well as safety using the two-dimensional KDIGO classification framework.

Results Of 6952 patients with baseline eGFR and urinary albumin-to-creatinine ratio (UACR) values, 47%, 29%, 15% and 8% were classified into low, moderately increased, high, and very high KDIGO risk categories, respectively. Empagliflozin showed consistent risk reductions across KDIGO categories for cardiovascular outcomes (*P* values for treatment by subgroup interactions ranged from 0.46 to 0.85) and kidney outcomes (*P* values for treatment by subgroup interactions ranged from 0.29 to 0.60). In all KDIGO risk categories, placebo and empagliflozin had similar adverse events rates, the notable exception being genital infection events, which were more common with empagliflozin for each category.

Conclusions The observed effects of empagliflozin versus placebo on cardiovascular and kidney outcomes were consistent across the KDIGO risk categories, indicating that the impact of treatment benefit of empagliflozin was unaffected by baseline CKD status.

Key words

Diabetic nephropathy, empagliflozin, glomerular filtration rate, KDIGO, kidney disease, SGLT2 inhibition

Clinical Trial Registration

EMPA-REG OUTCOME clinicaltrials.gov ID: NCT01131676

INTRODUCTION

Chronic kidney disease (CKD) occurs in approximately 40% of patients with type 2 diabetes mellitus (1) and leads to an increased risk of mortality and morbidity (2, 3). CKD is also a strong risk factor for cardiovascular disease (4). For example, in a large Canadian general population cohort of >900,000 individuals, the proportion of deaths from cardiovascular disease increased with decreasing estimated glomerular filtration rate (eGFR) from 28% in individuals with normal kidney function to 58% in patients with kidney failure (5). Therefore, the treatment of CKD can place a major burden on healthcare systems, both in terms of resources and costs (6, 7). As a result, there is a strong health and economic imperative to improve clinical outcomes in people with CKD and type 2 diabetes (8). Despite the introduction of novel and varied strategies to the management of type 2 diabetes in recent years, there remains uncertainty as to whether these approaches can impact positively on the course of cardiovascular and kidney disease in patients with type 2 diabetes (9).

Empagliflozin was approved by the FDA in 2014 as an adjunct to diet and exercise to improve glycemic control, or blood glucose levels, in adults with type 2 diabetes. It is a selective sodium-glucose cotransporter-2 (SGLT2) inhibitor that lowers kidney reabsorption of glucose, thereby increasing urinary glucose excretion (10). Empagliflozin has been shown to reduce glycated hemoglobin (HbA1c) levels in patients with type 2 diabetes with reductions in blood pressure and body weight (11-15). Subsequently, empagliflozin was additionally approved by the FDA in 2016 (16) to reduce the risk of cardiovascular death in patients with type 2 diabetes and established cardiovascular disease due to the fact that empagliflozin given in addition to standard of care, significantly reduced the risk of cardiovascular death by 38% in the EMPA-REG OUTCOME® trial, a large cardiovascular outcome study with those patients (17). In addition, empagliflozin also reduced the risk of

hospitalization for heart failure by 35% (17), the risk of incident or worsening nephropathy by 39% and decreased progression of kidney disease (18). Improvements in the urinary albumin-to-creatinine ratio (UACR) were also observed, irrespective of baseline UACR levels, although these improvements appeared to be of greatest clinical relevance in patients who had elevated UACR at baseline (19).

The Kidney Disease: Improving Global Outcomes (KDIGO) CKD classification system provides a two-dimensional framework for categorizing patients based on estimated glomerular filtration rate (eGFR) and UACR as markers of kidney function and damage (3). The current KDIGO CKD classification has its origins in the 2002 Kidney Disease Outcomes Quality Initiative guidelines on definition, classification and evaluation of CKD (20). These guidelines have evolved over the past 17 years to include an increasingly detailed description of the relationship between GFR, albuminuria and prognosis, which has, in turn, significantly improved our understanding of CKD in multiple populations (3). Patients with low eGFR levels and higher urinary albumin excretion rates are at higher risk of both adverse kidney and cardiovascular outcomes, allowing the KDIGO CKD classification system to be adapted into a risk "heat map" as used in this analysis.

The 2012 KDIGO classification framework has proven to be a useful tool for assessing the severity of kidney disease, and has been shown to be associated with the risk of various outcomes, including progression of CKD. However, it is not known whether this classification system might also be associated with treatment response. Here, we report a *post hoc* comparison of cardiovascular and kidney outcomes in participants in the EMPA-REG OUTCOME® trial, using the two-dimensional KDIGO classification framework to determine the impact of baseline KDIGO risk category on treatment effect.

MATERIALS AND METHODS

Study design

EMPA-REG OUTCOME® was a randomized, double-blind, placebo-controlled, multinational trial (NCT01131676, registration date May 27, 2010). Patients entered a 2-week, open-label, placebo run-in prior to randomization (1:1:1) to empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to standard of care for type 2 diabetes and cardiovascular risk management. Randomization was performed with the use of a computer-generated random-sequence and interactive voice- and Web-response system and was stratified according to the glycated hemoglobin level at screening (<8.5% or ≥8.5%), body mass index at randomization (<30 or ≥30), kidney function at screening (eGFR, 30 to 59 ml, 60 to 89 ml, or ≥90 ml per minute per 1.73 m^2), and geographic region. Investigators were encouraged to treat cardiovascular risk factors in order to achieve optimal standard of care according to local guidelines (17, 21).

The EMPA-REG OUTCOME® trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization 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 center. All the patients provided written informed consent before study entry.

Cardiovascular outcome events and deaths were prospectively adjudicated by Clinical Events Committees. Kidney events were reported by investigators, and were not adjudicated. The trial continued until at least 691 patients experienced an adjudicated event included in the primary composite outcome: first occurrence of 3-point major adverse cardiovascular events (3-point MACE: composite of cardiovascular death, nonfatal myocardial infarction [MI], or nonfatal stroke). Kidney function at baseline was assessed

using the creatinine-based GFR estimating equations, based on the Modification of Diet in Renal Disease (MDRD) formula.

Participants

Eligible patients were adults with type 2 diabetes (HbA1c ≥7.0% and ≤9.0% for treatment-naïve patients and HbA1c ≥7.0% and ≤10.0% for patients on background glucose-lowering therapy), a body-mass index of ≤45 kg/m^2, established cardiovascular disease, and eGFR (according to MDRD) ≥30 mL/min/1.73 m^2.

Outcomes and analyses

Prespecified cardiovascular outcomes included 3-point MACE and its individual components (i.e. myocardial infarction, stroke and cardiovascular death), hospitalization for heart failure, and all-cause mortality.

Prespecified kidney outcomes have been previously described in detail and included incident or worsening nephropathy (composite of progression to macroalbuminuria, doubling of serum creatinine accompanied by estimated eGFR of ≤45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from kidney disease) and progression to macroalbuminuria (18). Additionally, a *post hoc* analysis looked at the composite of doubling of serum creatinine, initiation of renal replacement therapy, or death from kidney disease.

Cardiovascular and kidney outcomes were analyzed in subgroups by baseline KDIGO risk category (3). For example, patients with an eGFR of <60 ml/min/1.73 m^2 and albumin excretion rates >300 mg/g, patients with an eGFR of <45 ml/min/1.73 m^2 and an albumin excretion rate >30 mg/g and all patients with an eGFR <30 ml/min/1.73 m^2 were classified as being at very high risk according to the KDIGO heat map (3).

Changes in eGFR values were assessed over time, alongside a prespecified eGFR slope analysis for three prespecified study periods (treatment-initiation effects from baseline to Week 4; chronic maintenance treatment effects from Week 4 to last value on treatment; and post-treatment effects from last value on treatment to follow-up) (22).

Analyses were performed in patients treated with at least one dose of study drug, and compared the placebo and pooled empagliflozin groups. A Cox proportional hazards model was used to investigate the consistency of treatment effect across subgroups. The model included terms for age, sex, baseline HbA1c category, baseline BMI category, geographical region, treatment, baseline KDIGO risk category and treatment-by-baseline KDIGO risk category interaction. All analyses were performed on a nominal two-sided α=0.05 without adjustment for multiplicity. Calculation of eGFR slopes within the three prespecified study periods was performed by applying a separate random coefficient model for each period allowing for random intercept random slope per patient (22).

Safety data were analyzed by KDIGO risk category for empagliflozin versus placebo. Incidence rates per 100 patient-years were calculated using MedDRA version 18.0 terms, from which incidence rate ratios and interaction *p*-values were calculated to assess differences between the empagliflozin and placebo groups and the effect of KDIGO risk category on this.

RESULTS

The EMPA-REG OUTCOME® trial has been described previously (17, 21). A total of 7042 patients were randomized to study treatment from September 2010 to April 2013; 7020 patients at 590 sites in 42 countries received ≥1 dose of study drug (placebo, *n*=2333; empagliflozin 10 mg, *n*=2345; empagliflozin 25 mg, *n*=2342) (18). The median duration of

183 treatment was 2.6 years and the median observation time was 3 years; 97% of patients
184 completed the trial.
185
186 **Baseline characteristics**
187 The distribution of patients across the KDIGO risk categories is shown in Table 1.
188 Among 7020 participants, baseline eGFR and UACR measurements were available for 6952
189 patients (99%; empagliflozin, *n*=4635; placebo, *n*=2317). Baseline characteristics and
190 concomitant medications were similar between the placebo and empagliflozin groups across
191 the KDIGO risk categories.
192 The proportions of patients by KDIGO risk category in the overall study population
193 are shown in Figure 1. As expected, randomization led to similar distributions of all patients
194 between placebo and treatment groups, within each KDIGO category (approximately 47%,
195 29%, 15% and 8% in each treatment group, for the low, moderately increased, high, and
196 very high KDIGO risk categories, respectively).
197
198 **Cardiovascular outcomes stratified by KDIGO risk status at baseline**
199 The event rates for all outcomes presented increased with higher KDIGO risk
200 category for both the empagliflozin- and placebo-treated groups (Figure 2). However, for
201 each of the cardiovascular outcomes (3-point MACE; fatal/nonfatal myocardial infarction
202 and fatal/nonfatal stroke cardiovascular death; hospitalization for heart failure; all-cause
203 mortality;), the reductions in risk with empagliflozin versus placebo were consistent for
204 patients with low, moderately increased, high, and very high KDIGO risk category at baseline
205 (the *P* values for treatment by subgroup interactions across all cardiovascular outcomes
206 ranged from 0.26 to 0.85) (Figure 2).

Kidney outcomes stratified by KDIGO risk status at baseline

As observed with cardiovascular outcomes, the incidence of kidney outcome events was increased in higher KDIGO risk categories for both the empagliflozin and placebo groups (Figure 3). However, for each of the three kidney outcomes (incident or worsening nephropathy; progression to UACR >300 mg/g; and the composite of hard kidney end points [doubling of serum creatinine, initiation of renal replacement therapy, or death from kidney disease]), empagliflozin was associated with a consistent and lower relative risk versus placebo across the KDIGO risk categories (the *P* values for treatment by subgroup interactions across all kidney outcomes ranged from 0.29 to 0.60) (Figure 3).

eGFR slopes

The adjusted mean eGFR slopes for the three prespecified study periods are shown in Figure 4. Over the initial 4 weeks of treatment, the weekly mean adjusted eGFR decrease was numerically greater in the empagliflozin versus placebo groups for all KDIGO risk subgroups. During the chronic maintenance treatment period, however, the annual adjusted change in mean eGFR was stable in all empagliflozin subgroups but declined in the placebo subgroups. Finally, during the post-treatment follow-up the weekly adjusted mean eGFR in the empagliflozin subgroups increased and returned towards mean baseline eGFR levels, whereas little change was observed in eGFR levels in the placebo groups.

Safety

The effect of empagliflozin versus placebo on adverse events by baseline KDIGO risk category, as incidence rate ratios (based on rate per 100 patient-years), is shown in Figure 5.

The incidence rate ratios were similar for empagliflozin versus placebo across the adverse events assessed, with interaction p-values >0.05 for all except for the incidence of any adverse event and hyperkalemia. As reported in other trials of empagliflozin, and in trials of other SGLT2 inhibitors, the rates of adverse events consistent with genital infection were greater with empagliflozin than with placebo. This was seen across KDIGO risk categories, , with the 95% confidence interval for very high risk crossing unity (interaction p-value 0.2604) (Figure 5).

DISCUSSION

In this *post hoc* analysis of EMPA-REG OUTCOME®, the overall number of cardiovascular and kidney events increased with the degree of KDIGO risk categories in both empagliflozin and placebo groups, as reported previously in both diabetic and non-diabetic populations (23). Randomization to empagliflozin versus placebo (both given in addition to standard of care) resulted in a reduction in risk of cardiovascular outcomes (3-point MACE, cardiovascular death, hospitalization for heart failure, and all-cause mortality). This reduction in risk associated with active treatment was similar in relative terms, irrespective of baseline KDIGO risk category, and consistent with what have been previously observed in the overall trial population and across patients with or without prevalent kidney disease at baseline (17, 24).

In addition, empagliflozin, compared with placebo, also resulted in a reduction in risk of incident or worsening nephropathy, progression to UACR >300 mg/g and the composite of hard kidney end points (doubling of serum creatinine, initiation of renal replacement therapy, or death from kidney disease). These findings, which were seen across all baseline KDIGO risk categories, support previously reported kidney effects in the overall trial

population of EMPA-REG OUTCOME®, as well as across eGFR and albuminuria subgroups (18). The treatment effect of SGLT2 inhibitors on eGFR slopes has been shown to be a viable surrogate for clinical endpoints in CKD trials (25, 26). The acute and chronic eGFR slopes in the EMPA-REG OUTCOME trial have previously been published (22), and similar analyses have been reported from the CANVAS and CREDENCE trials (27, 28). Given the acute hemodynamic effect of SGLT2 inhibitors, the treatment effect of empagliflozin on eGFR slope by baseline KDIGO risk categories was investigated in this study. We showed that, over the initial 4 weeks of treatment, the weekly mean adjusted eGFR decrease was numerically greater in the empagliflozin versus placebo groups across all risk subgroups, but during chronic maintenance treatment the annual adjusted change in mean eGFR stabilized with empagliflozin but declined with placebo. In the post-treatment follow-up phase the weekly adjusted mean eGFR with empagliflozin returned towards mean baseline eGFR levels, while little change was seen with placebo.

The cardiovascular benefits in the current study are also in line with more recently reported outcomes from SGLT2 inhibitor trials (CANVAS and DECLARE-TIMI 58), that have shown reduction in the risk of cardiovascular outcomes in patients with high risk of cardiovascular events (27, 29). Kidney benefits of canagliflozin were suggested in the CANVAS trial and have been confirmed in the CREDENCE trial (28). In CREDENCE, improvement in a specified kidney outcome − end-stage kidney disease, doubling of serum creatinine, or kidney death − was shown to be consistent across eGFR and UACR subgroups with canagliflozin versus placebo (28). Furthermore, the positive effects of SGLT2 inhibition are seen in addition to the benefits of background therapy with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, and so are particularly important.

In the current analysis, the risk reductions seen with empagliflozin versus placebo were similar across the four risk category groups for each of the cardiovascular and kidney outcomes, with no attenuation of effect with higher KDIGO risk categories. The proposed mechanisms by which SGLT2 inhibition may lower the risk of cardiovascular and kidney outcomes is most likely multifactorial and may include improvements in blood pressure control, reduction in total body sodium and water, and weight loss, all of which are associated with improved outcomes in patients with type 2 diabetes. The restoration of tubuloglomerular feedback is likely to be an important contributor to the mechanism of action of the kidney-protective effect of SGLT2 inhibitors, thought this is not yet fully understood (30).. Other additional kidney mechanisms, such as tubular protection, reduced hypoxia and inflammation, or the long-term effects of natriuresis may also contribute to these kidney-protective effects (31).

In addition, it has been previously reported that the reduction in HbA1c from baseline with empagliflozin was smaller in patients with versus without CKD (24), consistent with results of other trials of empagliflozin (11, 33). Similar data are reported for canagliflozin (34) and dapagliflozin (35). However, the effects of empagliflozin on other cardiovascular parameters such as systolic blood pressure were similar regardless of kidney function (24). The attenuation of HbA1c lowering with empagliflozin in patients with CKD is not surprising, given its mechanism of action in the kidney (36). A similar finding was reported with canagliflozin (37). Additional research is required to explore the effects of SGLT2 inhibitors on cardiovascular and kidney outcomes in a broader population of patients with CKD. To this end clinical outcomes trials investigating these agents are underway. These include the DAPA-HF trial of patients with heart failure and reduced ejection fraction, with or without diabetes. The study included a renal function composite secondary

endpoint, for which no difference between dapagliflozin and placebo was reported (38); this finding was encouraging although the trial was relatively short (median follow-up 18.2 months). More recently, DAPA-CKD (NCT03036150) has investigated the effect of dapagliflozin on renal and cardiovascular events in a broad range of patients with CKD, importantly including those with and without diabetes (39). In this regard, DAPA-CKD differs from CREDENCE (28), which included only patients with type 2 diabetes. DAPA-CKD has been stopped early as the treatment benefits of dapagliflozin were occurring earlier than originally anticipated (40). A large clinical outcomes trial investigating empagliflozin for the heart and kidney protection in patients with CKD with or without diabetes, EMPA-KIDNEY, is underway, with plans to enroll approximately 6,000 people including those with and without albuminuria (ClinicalTrials.gov number, NCT03594110) (41). The results of these studies will help to further define the role of new treatment therapies in the management of patients with CKD, including the effects on cardiovascular disease and premature death.

The adverse event profile of empagliflozin versus placebo was similar across KDIGO risk categories, with interaction p-values for incidence rate ratios >0.05 except for the incidence of any adverse event and hyperkalemia. Rates of adverse events consistent with genital infections, as reported in previous trials of empagliflozin and other SGLT2 inhibitors, were greater with empagliflozin than with placebo across risk categories, with the 95% confidence interval for very high risk crossing unity (interaction p-value 0.2604).

The limitations of our data include the *post hoc* exploratory nature of the analyses, and the relatively low number of patients with advanced CKD: only 8.0% (*n*=186) and 7.7% (*n*=359) of placebo and empagliflozin patients, respectively, were in the very high KDIGO risk category at baseline. Indeed, this analysis may be underpowered to detect differences in treatment effect across subgroups by virtue of the small proportions of patients in high and

very high-risk categories. In addition, the EMPA-REG OUTCOME trial was not powered or designed to robustly assess kidney outcomes, and these were not adjudicated. However, the consistency of effect size across various definitions of kidney outcomes, and across SGLT2 trials, suggests that this limitation may be inconsequential (42, 43).

Early detection of CKD and appropriate interventions are key to slowing disease progression and reducing the risk of adverse CV and kidney outcomes. For the small proportion of people with CKD and kidney failure who require dialysis and/or kidney transplantation, the economic impact of these interventions on healthcare budgets can be disproportionately high (3). Hence, identification of individuals at highest risk early in the course of their disease would enable earlier referral of those patients who will most likely gain benefit from specialist kidney services. This could lead to greater clinical and economic benefits (3). Furthermore, as CKD is a risk factor for CV disease, earlier intervention will also reduce the risk of CV and all-cause mortality. Evidence shows that the clinical presentation of CKD among adults with diabetes in the USA has evolved, with low eGFR (<60 ml/min/1.73 m^2) in the absence of albuminuria (UACR <30 mg/g) becoming the most common phenotype, with an associated increase in mortality (44). Therefore, any treatment strategies will also need to address the high mortality rates associated with this trend (44).

In conclusion, the overall number of cardiovascular and kidney events increased with increasing KDIGO risk category in both and empagliflozin and placebo groups. However, the observed cardiovascular and kidney benefits of empagliflozin versus placebo were consistent across the KDIGO risk categories, indicating that the treatment benefit of empagliflozin was unaffected by baseline CKD status.

ACKNOWLEDGMENTS

The EMPA-REG OUTCOME® trial was sponsored by the Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance. The authors thank the patients who participated in this trial, and Michaela Mattheus from Boehringer Ingelheim for her contribution to the statistical analyses. Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Charlie Bellinger and Sally Neath of Elevate Scientific Solutions, Horsham, UK, during the preparation of this article. The authors were fully responsible for all content and editorial decisions and were involved at all stages of manuscript development and have approved the final version.

Data sharing

The sponsor of the EMPA-REG OUTCOME Trial (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents, and patient level clinical study data. Researchers are invited to submit inquiries via the Clinical Study Data Request website (https://vivli.org).

DISCLOSURES

D.C.W. has received honoraria and consultancy fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Napp, Mundipharma, Mitsubishi, Ono, Pharmacosmos Reata and Vifor Fresenius.

A.L. has received research support from Amgen, Astra Zeneca, Janssen, Merck, Otsuka, Canadian Institute for Health Research, Kidney Foundation of Canada, Heart and Stroke Foundation of Canada, and the Michael Smith Health Research Foundation.

V.P. has reported grants and other from Janssen, during the conduct of the study; grants from Abbvie, grants from Astellas, other from Bayer, grants and other from GSK, other from

Bristol-Myers Squibb Company, other from Eli Lilly, grants and other from Pfizer, personal fees from Servier, other from Boehringer Ingelheim, other from AstraZeneca, other from Novo Nordisk, other from Pharmalink, grants from National Health and Medical Research Council, personal fees from National Health and Medical Research Council, other from Relypsa, grants from Baxter, other from Merck, other from Sanofi, other from Gilead, other from Novartis, other from Durect, outside the submitted work.

C.W. has reported honoraria from Boehringer Ingelheim and Janssen.

A.K.W. and JG are employees of Boehringer Ingelheim International GmbH.

S.H. is an employee of Boehringer Ingelheim Pharma GmbH & Co. KG.

M.v.E. was an employee of Boehringer Ingelheim International GmbH at the time of the study.

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TABLES AND FIGURES

Table 1. Baseline characteristics and concomitant medications of participants were similar between treatment groups across KDIGO risk categories.

	KDIGO Risk Category							
	Low		Moderately increased		High		Very high	
	Placebo (*n*=1099)	Empagliflozin* (*n*=2223)	Placebo (*n*=675)	Empagliflozin* (*n*=1343)	Placebo (*n*=357)	Empagliflozin* (*n*=710)	Placebo (*n*=186)	Empagliflozin* (*n*=359)
Male	787 (72)	1571 (71)	490 (73)	970 (72)	254 (71)	500 (70)	136 (73)	255 (71)
Age, years	62 ± 8.7	61 ± 8.3	64 ± 8.6	63 ± 8.5	66 ± 8.9	66 ± 8.3	66 ± 8.0	67 ± 8.0
BMI, kg/m^2	30.5 ± 5.2	30.5 ± 5.2	31.0 ± 5.2	30.7 ± 5.3	30.7 ± 5.4	30.6 ± 5.3	30.2 ± 5.3	30.6 ± 5.7
HbA1c, %	8.0 ± 0.81	8.0 ± 0.82	8.1 ± 0.85	8.1 ± 0.86	8.2 ± 0.86	8.2 ± 0.90	8.2 ± 0.94	8.1 ± 0.84
Systolic BP, mmHg	133.0 ± 15.6	132.2 ± 15.4	137.6 ± 17.4	136.6 ± 17.2	138.9 ± 19.5	139.4 ± 18.6	140.4 ± 18.8	140.5 ± 17.9
Diastolic BP, mmHg	76.8 ± 9.5	76.6 ± 9.2	77.6 ± 10.9	77.3 ± 10.1	76.1 ± 10.6	76.2 ± 10.0	75.7 ± 10.2	74.8 ± 10.4
LDLcholesterol, mg/dL	82.7 ± 33.8	85.1 ± 34.5	85.1 ± 34.2	85.3 ± 36.4	89.1 ± 39.1	87.5 ± 37.2	88.6 ± 39.1	89.8 ± 39.8
eGFR (MDRD), mL/min/1.73 m^2	83 ± 16.3	84 ± 16.9	74 ± 19.9	74 ± 20.2	60 ± 18.8	61 ± 19.6	44 ± 8.2	43 ± 8.6
≥60	1099 (100)	2223 (100)	470 (70)	926 (69)	145 (41)	286 (40)	0	0
<60	0	0	205 (30)	417 (31)	212 (59)	424 (60)	186 (100)	359 (100)
UACR, mg/g								
<30	1099 (100)	2223 (100)	205 (30)	417 (31)	76 (21)	139 (20)	2 (1)	10 (3)
30 to 300	0	0	470 (70)	926 (69)	136 (38)	285 (40)	69 (37)	126 (35)
>300	0	0	0	0	145 (41)	286 (40)	115 (62)	223 (62)
Background medications								

ACE inhibitors/ARBs	846 (77)	1754 (79)	556 (82)	1119 (83)	305 (85)	585 (82)	147 (79)	299 (83)
Diuretics	405 (37)	841 (38)	295 (44)	605 (45)	172 (48)	360 (51)	110 (59)	216 (60)
History of heart failure	95 (8.6)	181 (8.1)	77 (11.4)	146 (10.9)	48 (13.4)	84 (11.8)	23 (12.4)	50 (13.9)
Smoking status								
Never smoked	464 (42.2)	902 (40.6)	260 (38.5)	556 (41.4)	144 (40.3)	288 (40.6)	80 (43.0)	164 (45.7)
Ex-smoker	489 (44.5)	967 (43.5)	326 (48.3)	623 (46.4)	169 (47.3)	353 (49.7)	85 (45.7)	164 (45.7)
Currently smokes	146 (13.3)	354 (15.9)	89 (13.2)	164 (12.2)	44 (12.3)	69 (9.7)	21 (11.3)	31 (8.6)
Duration of diabetes (years)								
≤1	35 (3.2)	78 (3.5)	11 (1.6)	31 (2.3)	2 (0.6)	14 (2.0)	4 (2.2)	5 (1.4)
>1 to 5	216 (19.7)	424 (19.1)	103 (15.3)	189 (14.1)	41 (11.5)	65 (9.2)	10 (5.4)	25 (7.0)
>5 to 10	301 (27.4)	597 (26.9)	159 (23.6)	344 (25.6)	69 (19.3)	156 (22.0)	35 (18.8)	64 (17.8)
>10	547 (49.8)	1124 (50.6)	402 (59.6)	779 (58.0)	245 (68.6)	475 (66.9)	137 (73.7)	265 (73.8)
Metformin use	885 (80.5)	1752 (78.8)	514 (76.1)	1022 (76.1)	219 (61.3)	476 (67.0)	104 (55.9)	172 (47.9)
Insulin use	447 (40.7)	933 (42.0)	338 (50.1)	648 (48.3)	211 (59.1)	412 (58.0)	130 (69.9)	232 (64.6)

582 *Pooled. Data are n (%) unless otherwise indicated.

583 ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration

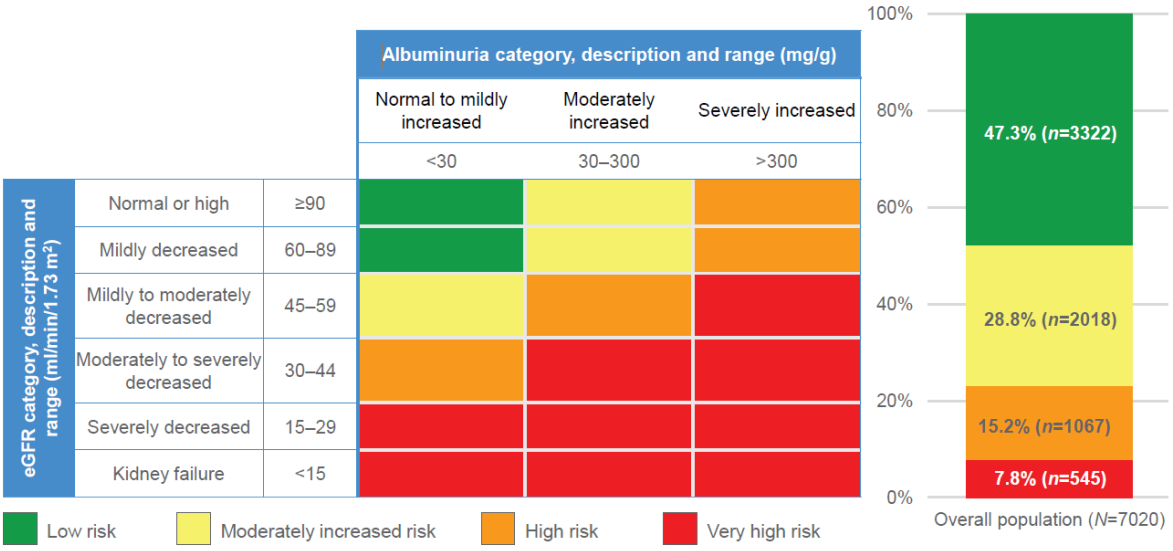
584 rate; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease; UACR, urinary albumin-to-creatinine ratio.

585

586 **Figure 1.** | Proportions of patients by KDIGO risk category in the overall trial population. The

587 KDIGO 'heat map' showing prognosis of CKD by GFR and albuminuria category is shown for

588 reference (3).



Of all treated patients, baseline eGFR and UACR measurements were available for 4635 empagliflozin (98.9%) and 2317 placebo (99.3%) patients. eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urine albumin-to-creatinine ratio. *Reprinted from Kidney International Supplements, Vol 3, Issue 1, The Kidney Disease: Improving Global Outcomes (KDIGO) CKD Working Group, 'KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease,' Pages 1–150, Copyright (2013), with permission from Elsevier.*

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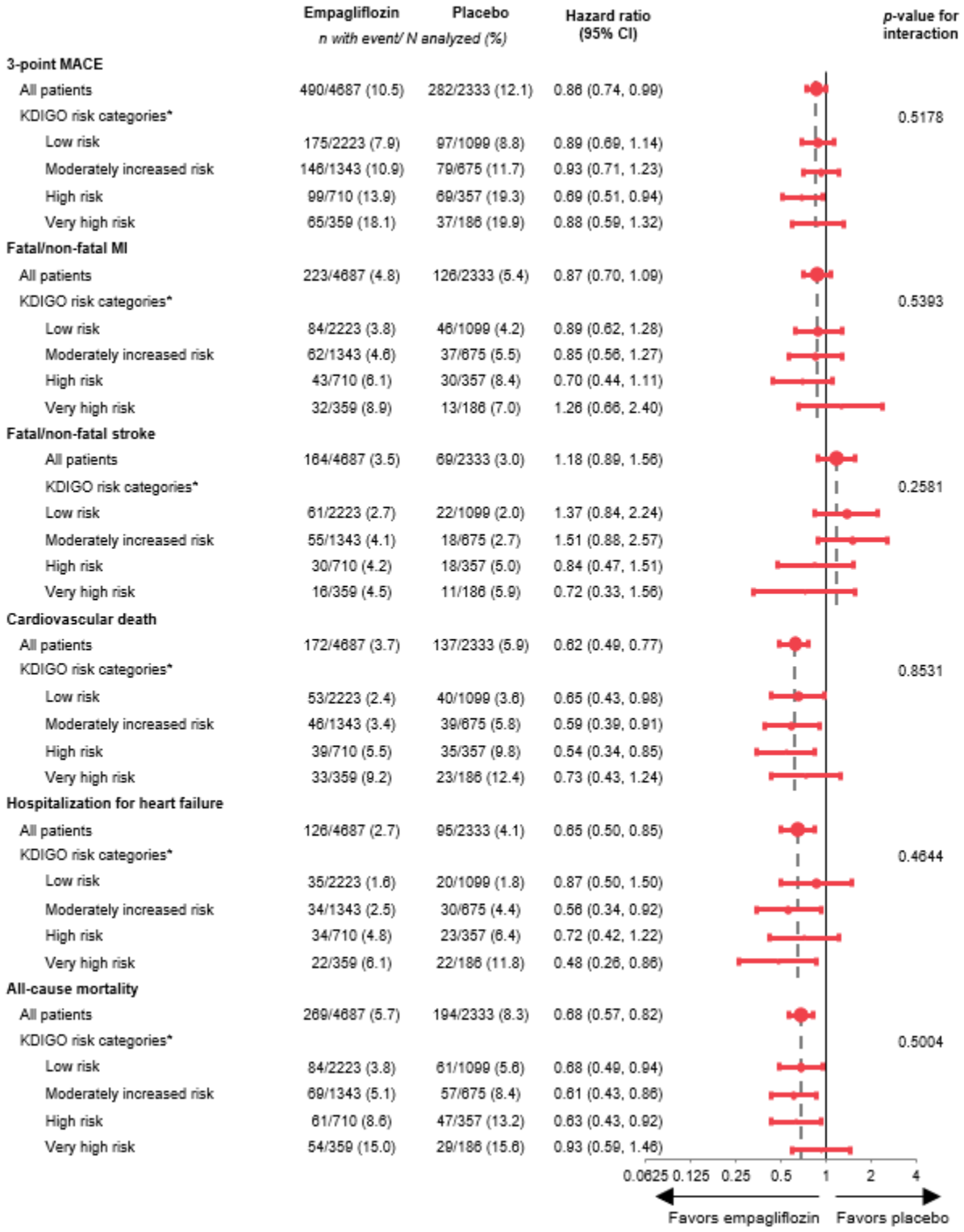
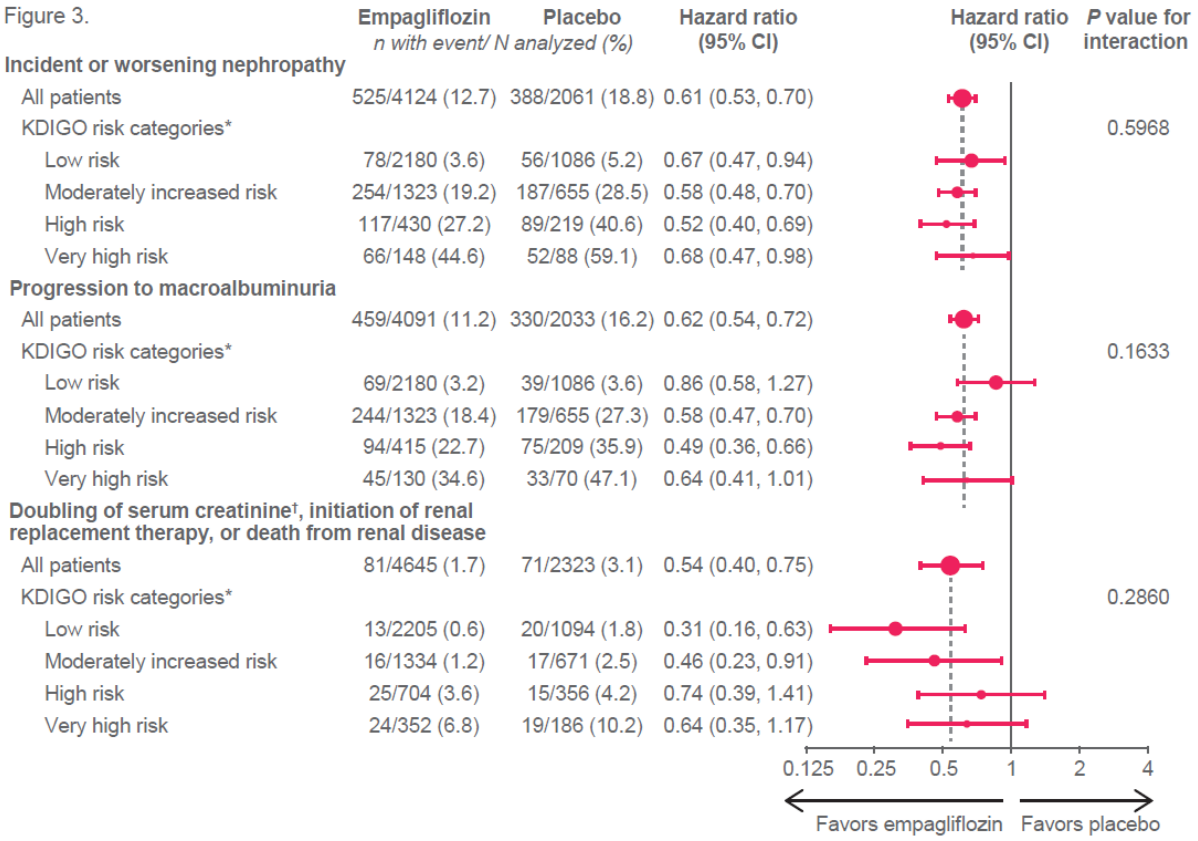
Figure 2. | Forest plot showing that the risk reduction of cardiovascular outcomes with empagliflozin versus placebo are consistent across KDIGO risk categories.



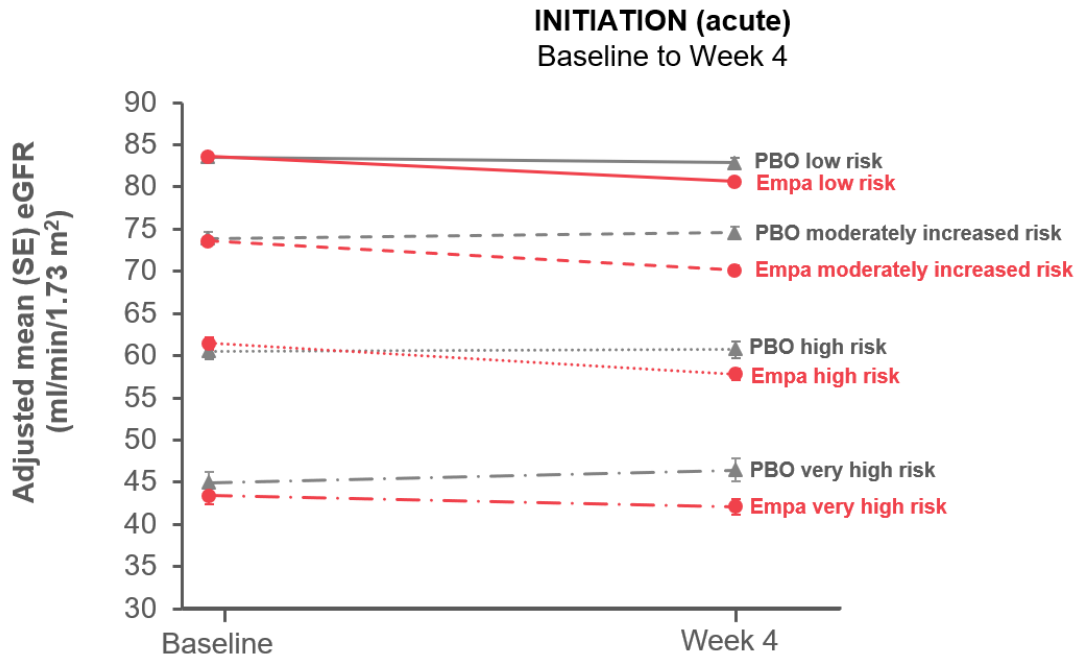
MACE, major adverse cardiovascular events; MI, myocardial infarction.

Figure 3. | Forest plot showing that the risk reduction of kidney outcomes with empagliflozin versus placebo are consistent across KDIGO risk categories.



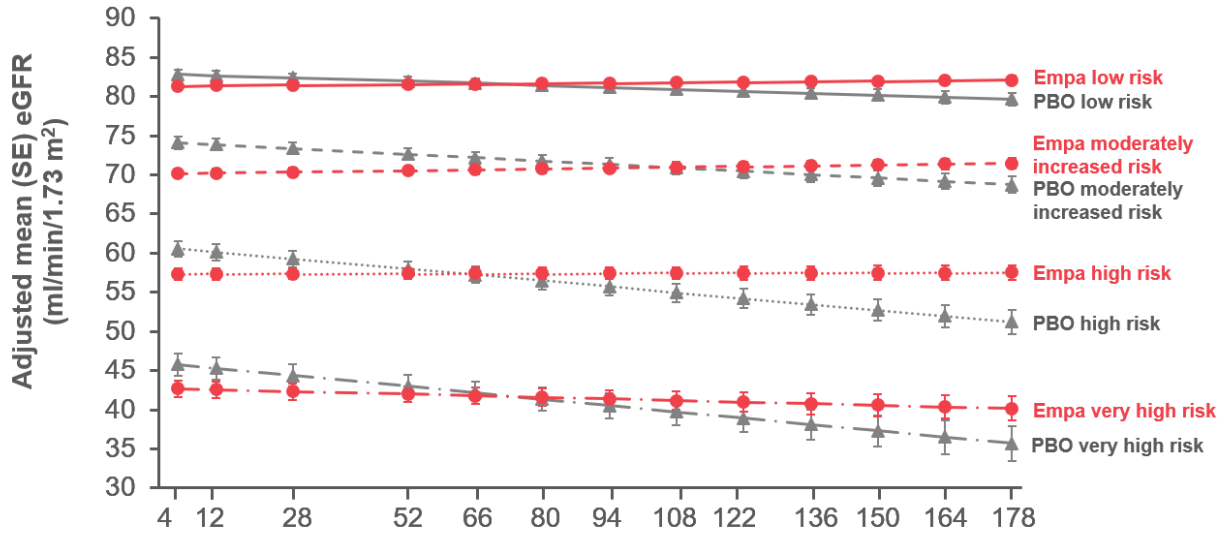
Cox regression analysis in patients treated with ≥1 dose of study drug. *68 patients were excluded as subgroup variable was missing.
†Accompanied by eGFR ≤45 mL/min/1.73 m². Macroalbuminuria: UACR >300 mg/g.
CI, confidence interval; CV, cardiovascular; KDIGO, Kidney Disease: Improving Global Outcomes; MACE, major adverse CV events.

Figure 4. | Empagliflozin consistently slowed the long-term annual decline in eGFR across all patient subgroups regardless of KDIGO risk category, as assessed by mean eGFR (MDRD) slopes based on random-intercept/random-coefficient models.



No. of patients (low risk)		
Placebo	1051	1051
Empagliflozin	2124	2124
No. of patients (moderately increased risk)		
Placebo	646	646
Empagliflozin	1271	1271
No. of patients (high risk)		
Placebo	339	339
Empagliflozin	662	662
No. of patients (very high risk)		
Placebo	173	173
Empagliflozin	337	337

LONG-TERM (chronic)
Week 4 to last value on treatment



No. of patients (low risk)													
Placebo	941	943	756	561	492	417	384	303	237	187	155	128	88
Empagliflozin	1926	1934	1690	1371	1267	1120	1070	894	690	576	488	428	304
No. of patients (moderately increased risk)													
Placebo	560	559	422	318	270	218	199	163	130	106	90	73	47
Empagliflozin	1144	1151	1002	828	729	644	607	533	419	343	291	252	183
No. of patients (high risk)													
Placebo	294	295	216	154	125	102	93	70	54	43	31	25	15
Empagliflozin	562	567	481	370	340	286	283	215	176	135	116	104	71
No. of patients (very high risk)													
Placebo	151	153	118	66	51	43	37	30	22	17	11	8	4
Empagliflozin	279	277	218	152	119	97	87	58	45	37	25	19	17

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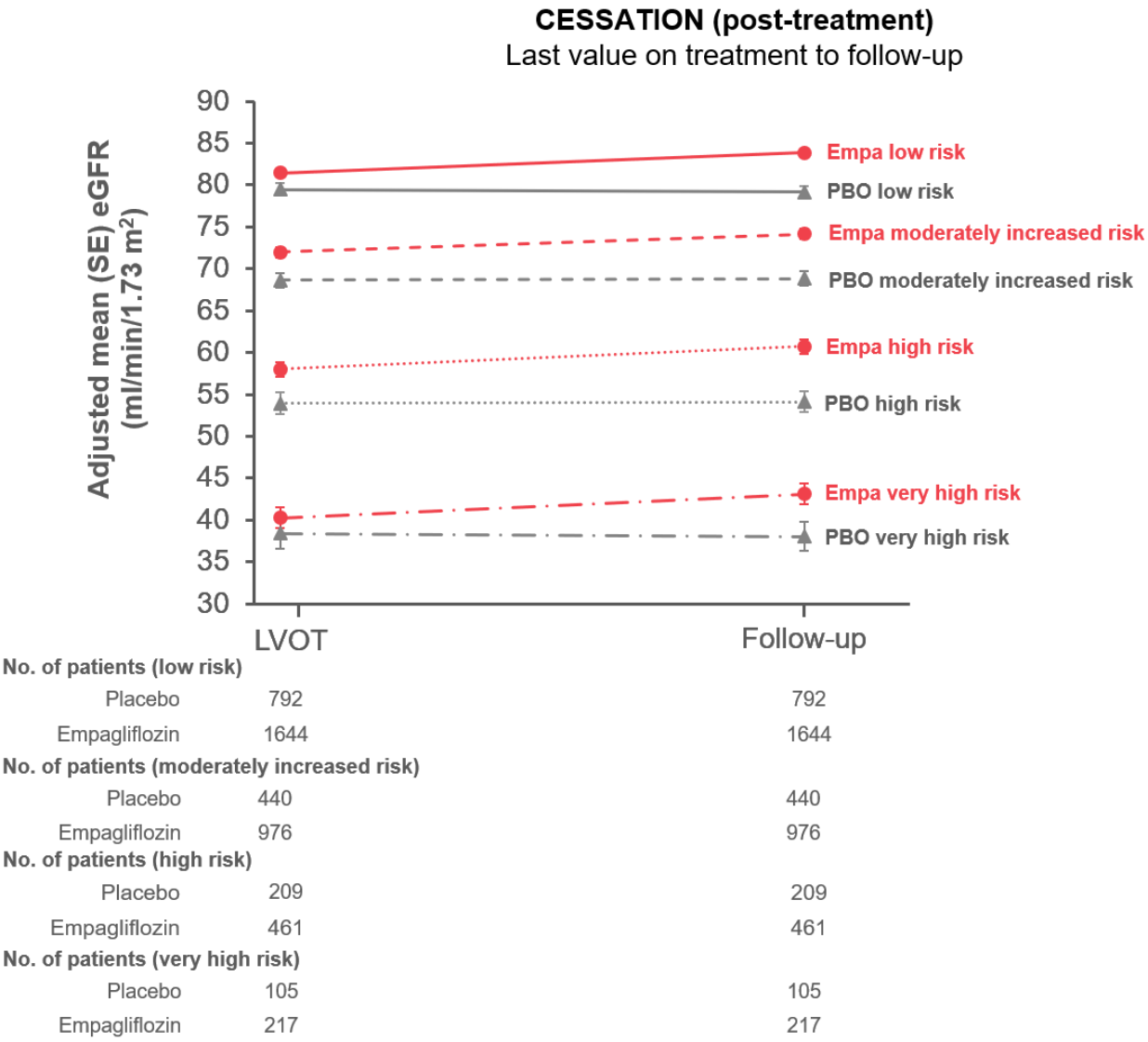

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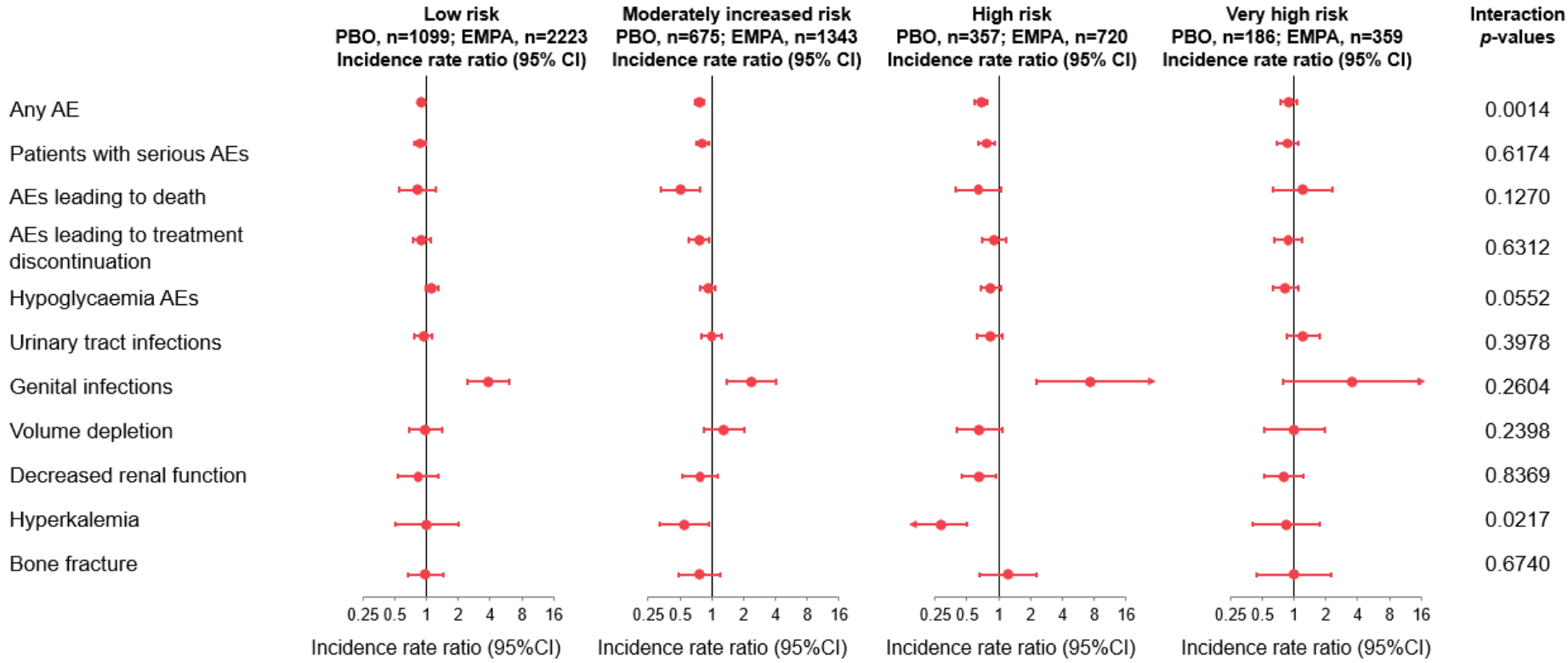
609 Adjusted mean eGFR across subgroups of KDIGO risk category. eGFR, estimated glomerular
610 filtration rate; Empa, empagliflozin; LVOT, last value on treatment; MDRD, Modification of
611 Diet in Renal Disease; PBO, placebo.

Figure 5. | Adverse events. Incidence rate ratios (based on rate per 100 patient-years) for empagliflozin compared with placebo. Data are from patients treated with ≥1 dose of study drug.



MedDRA version used for reporting: 18.0. AE, adverse event; CI, confidence interval; Empa, empagliflozin; MedDRA, Medical Dictionary for Drug Regulatory Activities; PBO, placebo.