# Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group

Supplementary Appendix

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# Members of the EMPA-KIDNEY Collaborative Group

## Membership of the Executive Committee, Steering Committee and Independent Data Monitoring Committee

**Executive Committee**
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# Supplementary Methods

## Approach to Recording of Outcomes, Adjudication and Outcome Definitions

See next page

EMPA-KIDNEY
The study of heart and kidney protection with empagliflozin

# Approach to Recording of Outcomes, Adjudication and Outcome Definitions

## Standard Operating Procedure 9a
## EDMS 5452
## Version 1.1

| Version | Date | Comments |
|---|---|---|
| V1.0 | 11th January 2018 | First release |
| V1.1 | 7th September 2021 | Update to include serious genital infection definitions and refinements agreed with the Steering Committee (from SOP9b). |

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# 1 INTRODUCTION

This document describes the streamlined approach to outcome recording and adjudication and includes the primary, secondary and selected safety outcome definitions for the EMPA-KIDNEY trial. Where appropriate, the Cardiovascular and Stroke Endpoint Definitions for Clinical Trials developed by the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI) are incorporated.[1]

The existence of barriers to conducting sufficiently large clinical trials is well-recognized,[2] and there is a particular need for more large trials in nephrology.[3] The amount and type of data collected in a clinical trial affect the ability to recruit patients, follow their progress, and complete the trial. Inefficiencies in data collection also increase trial costs and the burden of participation for both patients and research teams. To date, trials in patients with kidney disease have tended to collect too many data fields in too few participants, leading to unnecessary complexity and limited power to assess hard clinical outcomes.[3]

The concept of trial "streamlining" requires design and conduct to focus on the main determinants of trial quality and avoid unnecessary elements that increase cost and complexity. For example, verification by central clinician review (often referred to as outcome adjudication) may have little effect on the relative risks reported by trials,[4] and a simplified approach could be considered in certain situations.

EMPA-KIDNEY aim is to assess the effect of empagliflozin 10 mg once daily versus matching placebo on a cardiorenal composite primary outcome in around 6000 participants with established chronic kidney disease (CKD) with or without diagnosed diabetes mellitus.

## *1.1 EMPA-KIDNEY primary and key secondary outcomes*

The EMPA-KIDNEY study's composite primary outcome is kidney disease progression or cardiovascular death. Kidney disease progression is defined as:

- End-stage kidney disease (ESKD)
- A sustained estimated glomerular filtration rate (eGFR) <10 mL/min/1.73m²
- Renal death, or
- A sustained decline of ≥40% in eGFR from randomization.

For the purposes of this trial, ESKD is defined as:

- Initiation of maintenance dialysis; or
- Receipt of a kidney transplant.

The key secondary outcomes include:

- Time to first hospitalization for heart failure or cardiovascular death
- Occurrences of all-cause hospitalizations (first and recurrent)
- Time to death from any cause.

The study's tertiary and safety outcomes are listed in Protocol Sections 2.3.1-2.3.2.

## *1.2 Principles of streamlined outcome recording in EMPA-KIDNEY*

### 1.2.1 Recording of outcomes based on clinical events

The study uses Quality-by-Design[5] approaches to prospectively build quality into the study design and operations rather than relying on retrospective monitoring. All study data are processed electronically using a set of custom-written applications developed to meet the requirements of the Protocol, ICH-Good Clinical Practice, and 21 CFR Part 11.

Information about clinical outcomes and adverse events are derived from regularly scheduled participant interviews performed by Local Clinical Centre (LCC) clinical staff at around 230 LCCs internationally. Those conducting the participant interviews are referred to as LCC Research Co-ordinators. They are usually qualified nurses, but in some cases may be medically qualified or have other relevant qualifications and experience. All individuals fulfilling this role receive study-specific training to perform interviews and code adverse events using MedDRA. Appropriate levels of Local Investigator support and oversight is provided. Information on clinical outcomes is collected, regardless of whether the participant continues to take study treatment or not and is entered in real-time directly into electronic case report forms.

The trial monitoring plan is tailored to the protocol and takes a risk-based approach.[6] It includes central monitoring of adverse event reporting. Wherever possible, on-site monitors observe a participant's study visit during a monitoring visit. This assesses the quality of participant interviews.

This large trial is event-driven, double-blind and placebo-controlled, so missing a small proportion of events (e.g. a participant forgets that they were admitted to hospital) would not bias the estimates of the relative effects of study treatment.[7] Therefore paper or electronic hospital notes are not routinely reviewed by LCC clinical staff nor by on-site monitors to identify outcomes or other adverse events. All locally reported clinical outcomes and adverse events entered by the LCC Research Co-ordinators are reviewed and electronically approved by a Local Investigator.

### 1.2.2 Recording of outcomes based on eGFR

Outcomes based on eGFR will be calculated using the CKD-EPI formula[8] from a single measurement of creatinine from each participant at their Randomization Visit and at each Follow-up visit. Follow-up visits are scheduled at 2 and 6 months after randomization and then 6-monthly. More than one baseline measurement is not required as this is a large trial and performing multiple baseline creatinine measurements to account for day-to-day variability (and any measurement error) adds considerable operational complexity without substantial improvement in statistical sensitivity (i.e. is not streamlined).

A single creatinine result from blood samples collected around the time of each scheduled visit will be used in assessments as this ensures bias is not

introduced by differences between treatment arms in the extent to which extra creatinine measurements are made outside of visits.

A *sustained* decline in eGFR to <10 mL/min/1.73m$^2$ and a *sustained* decline of ≥40% in eGFR are required to be:

i. Measured at two consecutive scheduled study follow-up visits; or
ii. Measured at the last scheduled study follow-up visit, or the last scheduled visit before death (or withdrawal of consent).

Outcomes (and components) purely based on laboratory values (e.g. sustained ≥40% decline in eGFR) will not be adjudicated and analyses will emphasize the results of measurements made at central laboratories.

## *1.3 Principles of streamlined adjudication in EMPA-KIDNEY*

### 1.3.1 Selected clinical outcomes and laboratory values will not be centrally adjudicated

This is a large streamlined clinical trial with a primary focus on hard outcomes which are readily identifiable at participant interview (e.g. starting dialysis or receipt of a kidney transplant) and centrally measured creatinine. Each such report is to be approved by a Local Investigator.

Initiation of maintenance dialysis and receipt of a kidney transplant have simple definitions (see Section 0) and so assessments are mainly based on investigator-approved local reports. Assessments of all-cause hospitalization are similarly be based on LCC reports and are not centrally adjudicated. eGFR outcomes are purely based on laboratory values with the definition of sustained is provided in Section 1.2.2 above.

### 1.3.2 Approach to clinical adjudication

Confirmation of outcomes by a centrally based clinician reviewing additional information collected from LCCs will focus on a limited set of key clinical outcomes where there are complex diagnostic criteria (e.g. hospitalization with heart failure or cause-specific mortality).

The list of outcomes selected for adjudication is provided in Section 3.7 of the Protocol. All review, processing and adjudication of outcomes selected for clinical adjudication is assessed blinded to study treatment allocation (empagliflozin or placebo). The complete process is set out in SOP 9b: Adjudication Procedures (EDMS #6062). In brief, LCC clinical staff seek additional information about outcomes and adverse events initially reported as death, heart failure, and selected tertiary (myocardial infarction and stroke) and safety outcome events. Such information may include copies of clinical records, investigations or treatments.

Blinded clinicians based at, or overseen by, the Central Co-ordinating Office provide the final adjudication. These clinicians may include, but will not necessarily be nephrologists or cardiologists and work under the guidance of senior clinical trialists with extensive experience of adjudicating many

thousands of such events (including ESKD, cardiovascular events, and death) in previous large-scale trials in similar populations.

In making their final decisions, clinicians review the additional information collected from the LCCs as well as other potentially relevant information recorded during study Follow-up visits. SOP 9b: Adjudication Procedures details a quality control process where an initial random sample of about 10% of the first 100 events assessed by each adjudicator.

Similar approaches to outcome recording and clinical adjudication have been successfully deployed in previous large studies which have demonstrated efficacy or serious hazard of medications. These include:

i. SHARP which demonstrated that, compared to placebo, allocation to simvastatin 20mg plus ezetimibe 10mg reduces major atherosclerotic events among patients with moderate-to-advanced CKD[9]; and
ii. THRIVE which demonstrated that compared to placebo, allocation to extended-release niacin–laropiprant does not significantly reduce the risk of major vascular events, but does increase the risk of serious gastrointestinal, skin, bleeding and infection-related adverse events among people at high risk of cardiovascular disease.[10]
iii. REVEAL which demonstrated that compared to placebo, allocation to anacetrapib 100mg reduces major coronary events in patients with prior cardiovascular disease.[11]

Clinical definitions of EMPA-KIDNEY primary, secondary and selected safety outcomes are provided below.

# 2 END-STAGE KIDNEY DISEASE

## *2.1 Definition*

According to the Protocol, the definition of ESKD includes:

i. Initiation of maintenance dialysis;
ii. Receipt of a kidney transplant.

### 2.1.1 Initiation of maintenance dialysis

At each scheduled follow-up appointment participants are asked about initiation of dialysis. When reporting dialysis, investigators are asked to provide the date dialysis started and:

i. Confirm whether dialysis is ongoing or was temporary (and if only temporary, the reason for stopping). In general, ongoing dialysis is considered as maintenance dialysis if it is required for ≥90 days. Note that death within 90 days of starting dialysis is a special situation.[a]
ii. Confirm the type of dialysis (peritoneal dialysis or haemodialysis).

### 2.1.2 Receipt of a kidney transplant

At each scheduled follow-up appointment participants are asked about kidney transplantation. When reporting receipt of a kidney transplant, investigators are asked to confirm the date of the procedure.

See Section 1.2.2 for the definition of kidney disease progression based on measurement of eGFR and see Section 3.3.1 for the definition of a renal death.

[a] During adjudication of a death, a central clinician adjudicator may note the start of dialysis therapy. The adjudicator is required to provide an opinion on whether the dialysis would have been likely to be required long-term (i.e. renal recovery to be independent of dialysis is unlikely) or only temporarily (i.e. dialysis was started for acute kidney injury and recovery would have been expected had the participant not died within 90 days of starting dialysis).

# 3 DEATH

## *3.1 Definition*

i. Review of all reports of death is required to adjudicate:
   a. The date of death
   b. The cause of death
ii. Deaths are to be coded using MedDRA Preferred Terms. They are categorized to facilitate the protocol-specified analyses as follows:

| | | |
|---|---|---|
| **Cardiovascular death** | | |
| Cardiac | Coronary heart disease | Myocardial infarction<br><br>Other coronary heart disease |
| | Other cardiac disease | Specific cardiac causes, including non-ischaemic heart failure<br><br>Sudden cardiac death |
| Stroke | Haemorrhagic<br><br>Ischaemic<br><br>Undetermined | <br><br>Ischaemic stroke (+/- haemorrhagic transformation) |
| Other cardiovascular | Specific other causes (not listed above) | (e.g. pulmonary embolism, ruptured aortic aneurysm) |
| Presumed cardiovascular | Unexplained death | |
| **Noncardiovascular death** | | |
| Medical | Renal | Death due to CKD stage 5 |
| | Infection (incl. COVID-19) | |
| | Cancer | |
| | Other medical | |
| Non-medical | External | Trauma |

## *3.2 Cardiovascular deaths*

Cardiovascular death includes deaths due to any of the following categories: cardiac, stroke, other cardiovascular and presumed cardiovascular (see table above).

### 3.2.1 Myocardial infarction death

Death due to acute myocardial infarction (MI) refers to a death within 30 days after a MI related to consequences seen immediately after the MI, such as progressive congestive heart failure, inadequate cardiac output, or recalcitrant arrhythmia. This includes:

i. Deaths due to either acute MI; and
ii. Deaths due to surgical and non-surgical investigations and procedures to treat acute MI or a complication thereof.

Deaths occurring within 30 days after a MI should be attributed to MI unless there was a clear alternative cause.

#### *3.2.1.1 Supporting evidence*

To confirm death from MI there should be evidence of myocardial necrosis plus at least one other piece of supporting information, and no other likely diagnosis:

**i. Evidence of myocardial necrosis from:**

a. Raised cardiac biomarker results compatible with acute myocardial necrosis (after taking into consideration the potential effects of CKD on such biomarkers); or
b. Autopsy with MI or coronary thrombus of an age consistent with the clinical presentation.

**ii. Other supporting information:**

a. Relevant presentation:
    1. Symptoms of ischaemia; or
    2. Death
b. ECG evidence of:
    1. New ischaemia; or
    2. Development of pathological Q waves
c. Cardiac imaging demonstrating new myocardial defect or evidence of acute coronary occlusion.

### 3.2.2 Other coronary heart disease death

Death due to other coronary disease includes cardiac causes of death that are believed related to coronary atherosclerosis. This includes:

i. Deaths that are related to angina (e.g. death following admission with unstable angina), chronic ischaemia (including ischaemic cardiomyopathy), and late complications of MI (after 30 days);
ii. Deaths due to surgical and non-surgical investigations and procedures for coronary artery disease (other than as treatments for acute MI); and
iii. Deaths which are believed to be due to coronary atherosclerosis, with autopsy findings of coronary artery disease but without a lesion of an age corresponding to the clinical presentation.

In all cases, deaths due to MI as defined under 3.2.1 should be excluded.

### 3.2.3 Other cardiac disease death (including sudden cardiac death)

Death due to other cardiac disease includes:

i. Deaths that are likely to be due to specific cardiac disorders (e.g. valvular heart disease, non-ischaemic cardiomyopathy, primary arrhythmia); and
ii. Deaths due to surgical and non-surgical investigations and procedures for other cardiac disease (other than for coronary artery disease);
iii. Deaths that are sudden and believed likely to be due to cardiac disease, but no definite cardiac cause described above has been identified are sudden cardiac deaths (MedDRA Preferred Term: “Sudden cardiac death” [10049418]). These include witnessed sudden deaths with or without new or worsening of cardiac symptoms, and unwitnessed deaths in a participant who was seen to be alive and clinically well within 72 hours of being found

dead without any evidence of another cardiovascular or a non-cardiovascular cause.

Other cardiac death excludes deaths thought to be due to coronary heart disease (including MI). In some cases, there may be evidence of both coronary heart disease and other cardiac disease (e.g. coronary atherosclerosis in a patient with aortic stenosis). In such cases, the available evidence (e.g. clinical presentation, eye-witness reports, clinical investigations, autopsy findings) should be used to determine the pathology that most likely led to death.

### 3.2.4 Stroke death

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction. Death due to stroke refers to a death which results from:

i. An inexorable decline in the condition of the patient following stroke (typically, but not always within 30 days of the initial event); or
ii. A complication of the stroke (e.g. infection, complication of intervention or procedure); or
iii. Withdrawal of other therapies because of concerns relating to the poor prognosis associated with the stroke (e.g. withdrawal of dialysis).

Wherever possible, stroke subtype (e.g. haemorrhagic, ischaemic or undetermined) should be differentiated.

#### *3.2.4.1 Haemorrhagic stroke*

Haemorrhagic stroke is defined as a stroke caused by a non-traumatic intraparenchymal, intraventricular, or subarachnoid haemorrhage.

#### *3.2.4.2 Ischaemic stroke*

For the purposes of analysis, ischaemic stroke will include all of the following:

i. Ischaemic stroke, which is defined as a stroke caused by an infarction of central nervous system tissue; or
ii. Ischaemic stroke with haemorrhagic transformation, which is defined as ischaemic stroke with evidence of subsequent haemorrhage into an area of previous infarction.

#### *3.2.4.3 Undetermined stroke*

Undetermined stroke is defined as a stroke of unknown/unconfirmed pathological type, i.e. a stroke for which it is unclear whether there is an ischaemic or haemorrhagic cause because imaging was not performed or the result is not available.

#### *3.2.4.4 Exclusions*

The following conditions are not to be included in the definition of stroke:

i. Severe prolonged hypoglycaemia resulting in neurological deficits;
ii. Trauma;
iii. Any subdural or extradural haematoma;
iv. Findings on CT scans (done for any reason) that do not correlate with a clinical episode;

v. Transient ischaemic attacks and related syndromes (with symptoms lasting <24 hours and not leading to death, unless there is clear evidence of new infarction on cranial imaging); and
vi. Non-cardiovascular pathologies (e.g. tumour, degenerative disorders).

### 3.2.5 Other cardiovascular death

Other cardiovascular death includes:

i. Deaths due to other cardiovascular causes (e.g. pulmonary embolism, primary pulmonary hypertension, ruptured aortic aneurysm, limb ischaemia); and
ii. Deaths due to surgical and non-surgical investigations and procedures for other cardiovascular disease (including peripheral arterial revascularization procedures such as peripheral bypass grafting, endarterectomy, arterectomy, embolectomy, and angioplasty).

### 3.2.6 Unexplained death

i. Deaths for which no cause can be determined in a CKD population are often from cardiovascular causes, and are to be considered presumed cardiovascular deaths.[b]
ii. Deaths which are unexplained are those with no evidence of an alternative cardiovascular or non-cardiovascular cause of death (excluding sudden cardiac death – see Section 3.2.3). This would include deaths for which the cause of death is medically unclear (despite adequate supporting documentation) as well as those for which there is inadequate documentation (despite best efforts). [For example, a death for which there is no information beyond “found dead at home” or “patient died”, despite efforts to obtain further details (e.g. medical records, witness report) may be adjudicated as unexplained death.]

## *3.3 Noncardiovascular death*

Noncardiovascular death includes deaths due to any of the following categories: renal, infection, cancer, other medical and non-medical (see table in Section 3.1 for more details). Discussion with a Principal Investigator is encouraged for difficult cases. This may be particularly important if there is uncertainty as to whether a cardiovascular or a non-cardiovascular disease was the predominant cause of death.

### 3.3.1 Renal death

Evidence of renal death requires:

i. Evidence of CKD stage 5 (i.e. eGFR <15 mL/min/1.73m$^2$ [and usually <10 mL/min/1.73m$^2$] or ESKD); AND
ii. Evidence of:
    a. Conservative management of ESKD: the patient or their representatives had decided that, despite a clinical need, renal replacement therapy [RRT] was not to be provided. This includes progression to ESKD before RRT can be provided; OR

[b] As recommended by Standardized Data Collection for Cardiovascular Trials Initiative (SCTI) Cardiovascular and Stroke Endpoint Definitions for Clinical Trials.

b. Withdrawal from RRT: the patient or their representative has chosen to discontinue RRT (e.g. personal choice, intolerant of dialysis therapy); AND

No evidence that other major pathology led: (a) to death, or (b) to the decision to withdraw from RRT (e.g. cancer or stroke), or (c) made dialysis infeasible. Such deaths should be ascribed to the underlying condition.

### 3.3.2 Infection death

i. Infection should be coded as the cause of death if:
   - death results directly from the infection;
   - death results from a complication of the infection (e.g. acute kidney injury).

ii. Infection should not be coded as the cause of death if the criteria for renal death, cancer death or any type of cardiovascular death are met (e.g. death resulting from pneumonia occurring 2 weeks after a stroke would be coded as a stroke death).

### 3.3.3 Cancer death

The underlying cause of cancer should be coded as the cause of death if death results:

- Directly from the cancer; or
- From a complication of the cancer or its treatment (e.g. infection / surgery / chemotherapy / radiotherapy); or
- From withdrawal of other therapies (including dialysis) because of concerns relating to the poor prognosis associated with the cancer.

Cancer causes of death are to be categorized by site (e.g. primary organ of origin). Cancer deaths may arise from cancers that were present prior to randomization or which developed subsequently. These two scenarios are to be distinguished in the adjudication process, but if this distinction is not possible (e.g. due to lack of sufficiently detailed documentation) then the cancer will be assumed to have developed after randomization.

### 3.3.4 Other specific medical causes of death

i. The available evidence should be used to determine the most likely cause of death.

ii. Other medical causes of death should not be coded as the cause of death if the criteria for renal death, infection death, cancer death or any type of cardiovascular death are met.

iii. Acute kidney injury, ketoacidosis and liver causes of death should be adjudicated in line with the specific safety outcome definitions (see Section 5)

iv. Deaths due to surgical and non-surgical investigations and procedures for non-vascular diseases (e.g. bowel resection for Crohn's disease) should be attributed to the underlying disease for which the investigation or procedure was carried out.

### 3.3.5 Non-medical death

Non-medical death is defined as any death that is thought to be due to a non-medical ("external") cause. Not only are such deaths uncommon in most clinical

trials, but they are generally unlikely to be affected by study treatments. Examples include suicide, homicide, road traffic accident, house fire, electrocution, war and natural disaster.

# 4 HOSPITALIZATION FOR HEART FAILURE

## *4.1 Definition*

Hospitalization for heart failure is part of a composite key secondary outcome, combined with cardiovascular death. To confirm hospitalization for heart failure all of the following should generally be true:

i. Admission to inpatient care and staying at least one night in hospital;
ii. New or worsening symptoms of heart failure as a primary reason for hospitalization;
iii. Evidence of heart failure on examination or investigation;
iv. Treatment for heart failure during the admission.

Note: There should not be evidence that another non-cardiac diagnosis was the primary cause of hospitalization and symptoms. These other diagnoses include other specific cardiovascular disorders (e.g. primary pulmonary hypertension or pulmonary embolism), or non-cardiac diseases (e.g. chronic obstructive pulmonary disease, liver failure, severe anaemia, or fluid overload in an ESKD patient resulting from insufficient dialysis).

## *4.2 Supporting evidence*

### 4.2.1 Admission to inpatient care and staying at least one night in hospital

Evidence is required that a hospital discharge is at least one calendar day after admission.

### 4.2.2 New or worsening symptoms of heart failure

Evidence that heart failure is a primary cause of admission is required with presentations including:

i. New or worsening shortness of breath on exertion, lying down or paroxysmally at night; or
ii. Reduced exercise tolerance; or
iii. Increased fatigue; or
iv. Other symptoms which are considered to be caused by worsened end-organ perfusion such as dizziness, mental confusion or volume overload such as weight gain or lower extremity swelling.

### 4.2.3 Evidence of heart failure on physical examination or on investigations

Evidence of new or worsening of at least two physical examination findings; or of at least one physical examination finding and at least one investigational finding is required:

i. Examination findings:
    a. Pulmonary congestion, including bibasal inspiratory crepitations and/or pleural effusions;
    b. Peripheral oedema;
    c. Raised jugular venous pressure;
    d. Ascites (without primary liver disease);
    e. Rapid weight gain due to fluid retention;
    f. Gallop rhythm;

g. Cardiogenic shock (which is usually defined as a systolic blood pressure of <90 mmHg which is usually unresponsive to fluid resuscitation or heart rate correction and responds promptly to inotropic support).

ii. Investigational findings:
   a. Echocardiographic changes confirming heart failure;
   b. Radiological evidence of pulmonary congestion and/or pleural effusions;
   c. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). Note that in patients who might be expected to have chronically elevated natriuretic peptides (e.g. patients with a decreased eGFR or with chronic heart failure), a significant increase should be noted above a presumed or known historical level;
   d. Cardiac catheterization measurements confirming ventricular dysfunction.

### 4.2.4 Treatment for heart failure during the admission

Evidence is required of at least one of the following:

i. Initiation of new or substantial escalation of current diuretic therapy or vasodilators;
ii. Initiation of intravenous therapy, including diuretics, vasodilators or inotropic support (including vasopressors);
iii. Use of mechanical fluid removal such as ultrafiltration;
iv. Other methods to improve cardiac function, such as pacing, intra-aortic balloon pump, cardiac transplantation, etc.

# 5 SAFETY OUTCOMES

## *5.1 Ketoacidosis*

Non-ketotic raised anion-gap metabolic acidosis is common in advanced CKD. To clinically adjudicate and confirm ketoacidosis, evidence of all of the following criteria is generally required to confirm the occurrence of a ketoacidosis and distinguish it from renal acidosis:

i. Symptoms or relevant presentation (e.g. new confusion or drowsiness, dehydration, nausea/vomiting, abdominal pain, Kussmaul breathing, etc.) or relevant triggers, including missed insulin doses or intercurrent illness; AND
ii. Evidence of metabolic acidosis (i.e. serum bicarbonate levels <15 mmol/L); AND
iii. Evidence of ketones in blood or urine. A blood beta-hydroxybutrate level exceeding 1.5 mmol/L or urine ketones of at least

A raised blood glucose/sugar level is not required in the definition of ketoacidosis as “euglycaemic” presentations are reported in people taking SGLT-2 inhibitors.

## *5.2 Lower limb amputation*

i. Amputation is defined as resection of a limb through a bone, resection of a limb through a joint (i.e. disarticulation) and any auto-amputations (i.e. spontaneous separation of non-viable portion of the lower limb such as a digit).
ii. Debridement (removal of callus or dead tissue), procedures on an amputation stump (e.g. revision, drainage of an abscess, etc.) and traumatic amputation of a viable limb (or part thereof) are not considered amputation.

For each separately reported lower limb amputation, adjudicators should have sufficient evidence to confirm fact, date and level of amputation (e.g. toe, trans-metatarsal, ankle, below knee or above knee). Additionally, the presence of the following conditions preceding amputation will be recorded wherever mentioned in clinical notes: diagnosis or treatment for peripheral arterial disease, presence of peripheral neuropathy, recent diabetic foot ulceration, and recent lower limb infection or gangrene.

## *5.3 Acute kidney injury*

Confirmation of acute kidney injury requires evidence of one of the following:

i. An increase in serum creatinine to 1.5-times a recent historical value (which is presumed to have increased within about a week); OR
ii. Initiation of RRT for acute kidney injury

At every scheduled Follow-Up visit, participants are asked about serious acute kidney injury (i.e. asked if they have been admitted to hospital because of a sudden change in their kidney function). Non-serious acute kidney injury should not be recorded, with the exception of when it results in study treatment discontinuation.

Participants also provide a blood sample for local analysis of creatinine at each scheduled Follow-up visit. Central study clinicians are trained to initiate contact

with the LCC clinical staff if there is a ≥50% increase in creatinine since the preceding Follow-up visit. Such increases need to be reported as adverse events if they result in hospitalization (or any of the other seriousness criteria are met) or lead to study treatment discontinuation.

All serious adverse events reported as acute kidney injury (or equivalent terms) are selected for clinical adjudication. Wherever possible, for each confirmed acute kidney injury event, the acute kidney injury stage (see below) and a single primary aetiology (pre-renal, renal, obstructive or unknown) are to be ascribed:

| Acute kidney injury stage | Serum creatinine increase |
|---|---|
| 1 | ≥1-5, <2.0-times historical value(s) |
| 2 | ≥2.0, <3.0-times historical value(s) |
| 3 | ≥3.0-times historical value(s) or initiation of RRT |

Note: Adapted from 2012 KDIGO Acute Kidney Injury staging guidance. Increase in serum creatinine of ≥27 µmol/L (or ≥0.3 mg/dL) within about 48 hours has been excluded from the definition of stage 1 as this is likely to occur simply due to natural variation in these participants with advanced CKD. Similarly, serum creatinine ≥353.6 µmol/L (or ≥4.0mg/dl) has been excluded from the definition of stage 3 as this may be less than their historical measurement(s).

### *5.4 Serious genital infections, including Fournier's gangrene*

i. A genital infection is any bacterial or fungal infection of the genitals or perineum, including vulvovaginitis, balanitis and infections of skin between the genital and anus.
ii. Necrotising fasciitis of the perineum (Fournier's gangrene) is a subset of all serious genital infections characterized by fulminant tissue destruction which may extend from a cellulitis to include fasciitis and myositis. In men, in which it is more common, it can affect the scrotum and penis. In both sexes, it can rapidly spread to involve the anterior abdominal wall and gluteal muscles.
iii. Necrotising fasciitis of the perineum is characterized by:
    a. Perineal inflammation (erythema and oedema) with or without evidence of necrosis, severe pain (out of proportion to examination findings), and crepitus or bullous changes (indicating gas gangrene, evident in perhaps a half of cases);
    b. Systemic features of infection;
    c. A need for rapid surgical debridement and intravenous antibiotics; and
    d. Histopathological evidence of extensive tissue destruction, inflammation with abundant bacteria along fascial planes and sometimes necrotising myositis.

To confirm a diagnosis of necrotising fasciitis of the perineum generally requires evidence of three of the four features listed above, and is specifically coded to differentiate it from other serious genital infections. Note that necrotising fasciitis of the lower limb and infections developing from primary ano-rectal disease are <u>not</u> considered a serious genital infection.

### *5.5 Liver-related outcomes*

Serious liver disease is defined biochemically as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5x Upper Limit of Normal (ULN) or the combination of ALT or AST ≥3x ULN with bilirubin ≥2x ULN measured in

the same blood sample at study follow-up or early recall visits. For each confirmed case of liver injury, an associated primary aetiology based on the most probable cause will be ascribed. Possible aetiologies include infections (e.g. hepatitis virus), alcohol, shock liver (e.g. severe hypotension/sepsis), drug hepatotoxicity (and the most likely causal medication, which may be study treatment, will be recorded), liver congestion, non-alcoholic fatty liver, autoimmune hepatitis, metabolic disorders, other or unknown.

### *5.6 Fractures*

i. A fracture is defined as a broken bone.
ii. Fracture reports will not be clinically adjudicated. Instead information on the site and aetiology will be recorded at the time of each fracture report.
iii. Aetiology is selected from one of the following at the time of reporting:

- High Trauma: fractures resulting from severe trauma such as motor vehicle crashes, being struck by a vehicle or other fast-moving projectile, or falls from greater than standing height (e.g. falls off a ladder or other raised surface, not including stairs)
- Low Trauma: fractures due to falls from standing height or less; falls on stairs, steps, or curbs; moderate trauma other than a fall (e.g. collisions with objects during normal activities); and minimal trauma other than a fall (e.g. turning over in bed)
- Pathological: fractures occurring in an area that is weakened by another disease process such as a tumour, metastatic cancer of the bone, infection, inherited bone disorders, etc.
- Stress: identifiable fractures caused by repetitive stress
- Other: fractures that cannot be attributable to the aetiological definitions above.

# 6 REFERENCES

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# Supplementary Methods

## Trial Adaptations due to Coronavirus-2019 Disease (COVID-19)

In 2020, EMPA-KIDNEY screening visits were temporarily stopped when regions/sites were particularly affected by the COVID-19 pandemic. The run-in window was temporarily extended to 6–15 weeks, where required. Follow-up of randomized participants unable to attend the study clinic remained possible using telephone follow-up and study treatment could be delivered by courier. Central sample collection was requested once in-person clinic visits were able to restart. Retrospective entries of any local measurements of creatinine were sought where central samples were missing.

## Laboratory Methods

Samples were processed and frozen at local sites before transfer to the Central Laboratories. Non-China samples were all analysed in Oxford. In Oxford, serum enzymatic creatinine was assayed using Beckman-Coulter AU680 clinical chemistry analysers and creatinine and albumin in urine were assayed using Beckman-Coulter DxC700 clinical chemistry analysers. Serum and urine assays used manufacturers' reagents, calibrators and settings (Beckman-Coulter, UK). Glomerular filtration rate was estimated using the CKD-EPI formula.[1] Glycated hemoglobin (HbA1c) analysis was performed by HPLC using ethylenediaminetetraacetic acid (EDTA) blood on an Arkray HA8180 analyser and reagents with a calibrator supplied by Menarini Diagnostics UK traceable to International Federation of Clinical Chemistry (IFCC) reference standards. N-terminal pro B-type natriuretic peptide (NT-proBNP) analysis was performed using Roche Cobas e601 system and manufacturers' reagents, calibrators and settings (Roche Diagnostics Ltd, UK). The Central Laboratory in Oxford is a UKAS-accredited testing laboratory, No. 2799 and with the exception of NT-proBNP, all assays are on scope of the Central Laboratory's accreditation.

The analysis for Chinese samples was performed by WuxiApptec in Shanghai, China with quality oversight by the Central Laboratory in Oxford. The Wuxi-Apptec Laboratory is a participant in the National Center for Clinical Laboratories External Quality Assessment (EQA) scheme and proficiency testing activities for serum and urine analytes. With the exception of HbA1c, WuxiApptec used the same methods as the central laboratory. HbA1c analysis on Chinese samples was performed using a Tosoh HLC-723G8 analyser and reagents with a calibrator supplied by Tosoh traceable to National Glycohemoglobin Standardization Program (NGSP) reference standards. A conversion factor was applied to convert results to IFCC; NGSP = [0.09148*IFCC] + 2.152).

[1] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604-12. (In eng). DOI: 10.7326/0003-4819-150-9-200905050-00006.

## Supplementary Statistical Methods

### Joint frailty models for analyses for all-cause hospitalization

The hazard ratio for the effect of allocation to empagliflozin versus placebo on all-cause hospitalizations (including first and subsequent hospitalizations) was estimated using a semi-parametric joint frailty model.[2] This approach accounts for the competing risk of death by jointly modelling: (a) the hazard function for all-cause hospitalizations conditional on the patient specific random frailty term; and (b) the hazard function for time to death conditional on the patient-specific random frailty term. To improve expected precision around effect size estimates, the model was adjusted for sex, prior diabetes and region (in the same categories used in the minimization process) as well as for age, estimated glomerular filtration rate (GFR) and log-transformed urinary albumin-to-creatinine ratio (ACR), each as continuous variables. Adjustment for baseline predictors as continuous variables where possible was done to improve expected convergence of the models.

### Shared parameter models for analyses of estimated GFR over time

Mean annual rates of change in estimated GFR from baseline to the final follow-up visit ("total slopes"), and from 2 months to the final follow-up visit ("chronic slopes") by treatment allocation were estimated using shared parameter models[3] adjusted for age, sex, prior diabetes, urinary ACR, and region (all in the categories used in the minimization process). Models estimating chronic slope were additionally adjusted for baseline estimated GFR (as a continuous variable) and the interaction between baseline estimated GFR and follow-up time. This approach jointly models: (a) the annual rate of change in estimated GFR using a linear mixed model (with random effects for each patient's slope and intercept); and (b) the time to event for end-stage kidney disease (ESKD) or death (using a Weibull survival model in which the scale parameter is assumed to be linearly related to the random effects from the linear mixed model).

Specifically, the linear mixed model component is

$$Y_{ij} = (\beta_0 + u_{0i}) + \beta_1 X_i + (\beta_2 + u_{1i}) t_{ij} + \beta_3 X_i t_{ij} + e_{ij}$$

and the Weibull model for time to ESKD or death has hazard function

$$h(t_{ij}) = \gamma \exp(\varphi + \eta_0 u_{0i} + \eta_1 u_{1i} + \alpha X_i)^{\gamma} {t_{ij}}^{\gamma - 1}$$

where $t_{ij}$ is the time (in years) of visit j for patient i, $Y_{ij}$ is the observed value of estimated GFR at visit j for patient i, $X_i$ is the treatment allocation for patient i, $\beta_0$ is the mean estimated GFR at baseline in the placebo arm, $\beta_1$ is the mean difference in baseline estimated GFR between treatment allocations, $\beta_2$ is the mean estimated GFR slope in the placebo arm, and $\beta_3$ is the mean difference in estimated GFR slopes between treatment allocations. $u_{1i}$ and $u_{0i}$ are the random effects for each patient's slope and intercept respectively, which are assumed to be independent multivariate normal random vectors with mean 0 and an unstructured covariance matrix. $e_{ij}$ is the random error at time $t_{ij}$, which are assumed to be independent and normally distributed with mean zero and constant variance.

[2] Rogers JK, Yaroshinsky A, Pocock SJ, Stokar D, Pogoda J. Analysis of recurrent events with an associated informative dropout time: Application of the joint frailty model. Statistics in Medicine 2016; **35**(13): 2195-205.

[3] Vonesh EF, Greene T, Schluchter MD. Shared parameter models for the joint analysis of longitudinal data and event times. Statistics in Medicine 2006; **25**(1): 143-63.

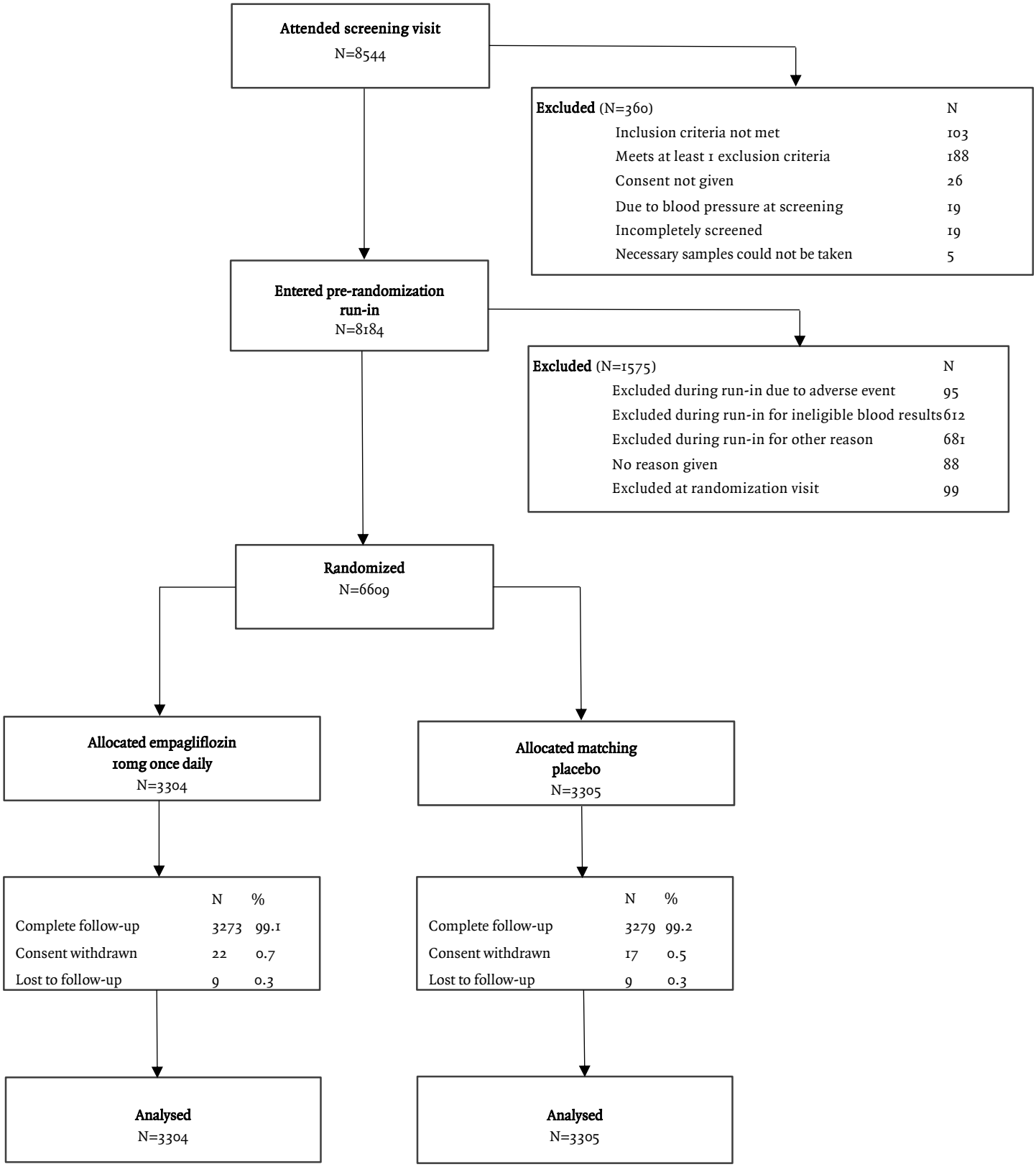
Analyses used all available central laboratory estimated GFR measurements prior to the development of ESKD. The advantage of the above modelling approach (over a standard linear mixed model) is that it additionally allows for the dependence between the annual rate of change in estimated GFR and the time to ESKD or death (which is important because those with faster rates of change in estimated GFR will generally have a shorter time to ESKD or death). The mean slopes provided by the shared parameter model (total or chronic) may be thought of as the average of the patient-specific slopes, conditional on the baseline covariates in the model, and in the hypothetical scenario where estimated GFR had continued to be measured beyond the time of ESKD or death. As with other methods, the estimates they provide merely reflect averages over the follow-up period of interest (and hence, in the context of a drug which has an initial acute effect, the "total slope" requires careful interpretation).

### Mixed model repeated measures (MMRM)

Linear mixed model repeated measures (MMRM) analyses were used to estimate mean estimated GFR by treatment allocation at each scheduled follow-up visit (and these values are shown in Figure 3). These models were adjusted for baseline estimated GFR (as a continuous variable), age, sex, prior diabetes, urinary ACR, and region (all in the same categories used in the minimization process), treatment allocation, follow-up time point and the interaction between baseline estimated GFR and follow-up time point. A further interaction term between treatment allocation and follow-up time point was then included in order to enable separate estimation of mean estimated GFR at each follow-up time point for each treatment arm, conditional on the other factors in the model. These models assume that any missing estimated GFR values can be predicted by the non-missing estimated GFR data for other individuals together with the other covariates in the model (i.e. that they are 'missing at random'). A similar approach was used for analyses of physical and laboratory measurements.

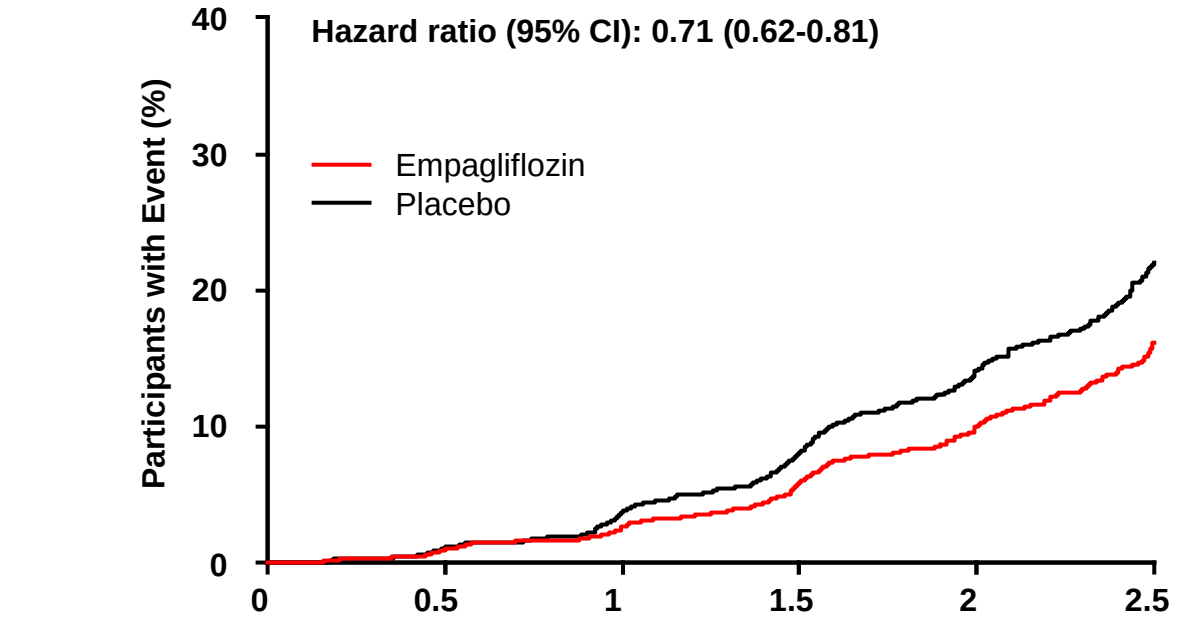
# Supplementary Figures

Figure S1. CONSORT Flow Diagram




Complete follow-up defined as death before April 01, 2022 (start of final follow-up window) or completed final follow-up with last known alive after April 01, 2022. More details of reasons for exclusion are provided in: EMPA-KIDNEY Collaborative Group. Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial. Nephrology Dialysis Transplantation 2022;37(7):1317-29.

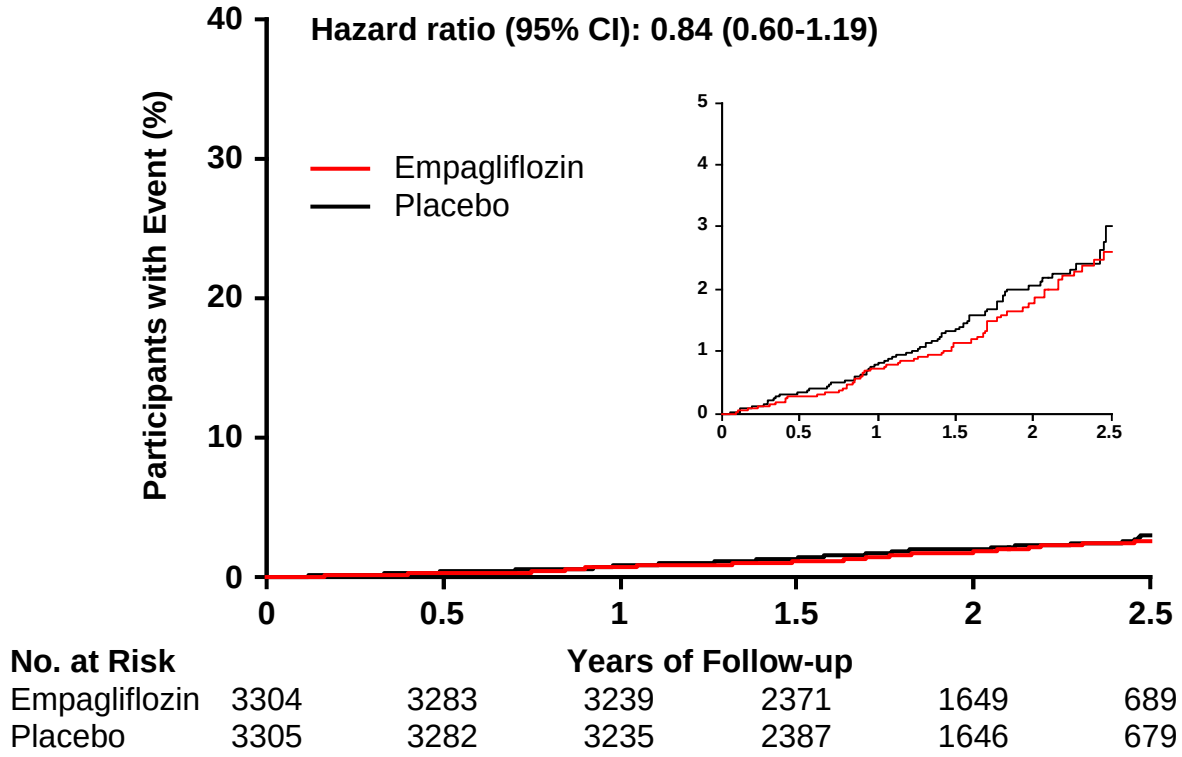
Figure S2a. Kidney Disease Progression




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Empagliflozin | 3304 | 3252 | 3163 | 2275 | 1538 | 624 |
| Placebo | 3305 | 3250 | 3129 | 2243 | 1496 | 592 |

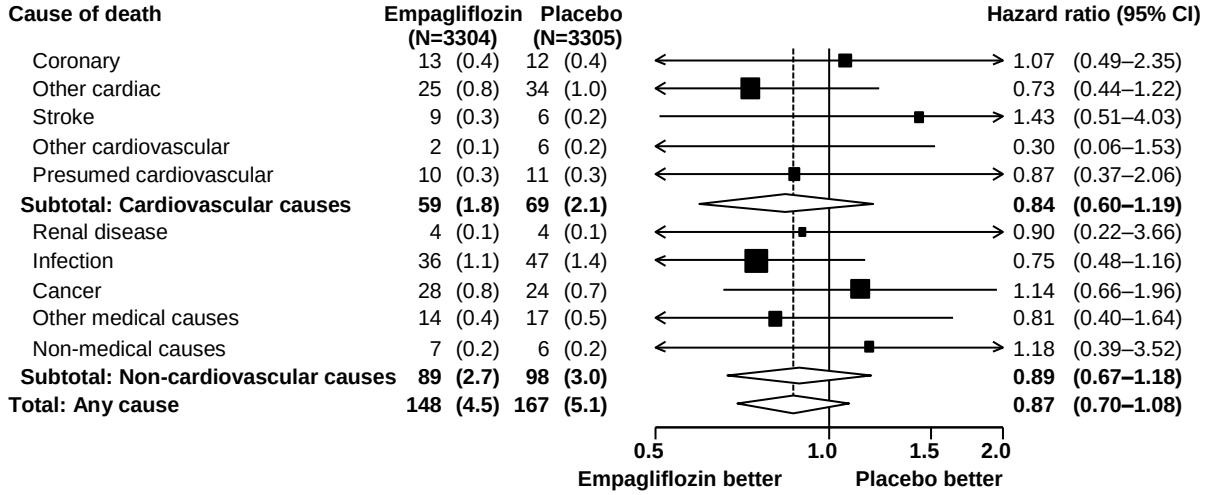
Kidney disease progression (end-stage kidney disease [maintenance dialysis or kidney transplant; sustained decline in estimated GFR to <10 ml per minute per 1.73 $m^2$; sustained decline in estimated GFR of ≥40% from randomization] or renal death) occurred in 384 participants (11.6%) in the empagliflozin group and 504 participants (15.2%) in the placebo group.

Figure S2b. Death from Cardiovascular Causes




Death from cardiovascular causes occurred in 59 participants (1.8%) in the empagliflozin group and 69 participants (2.1%) in the placebo group.

Figure S3. Death by Cause




Shown are forest plots of the hazard ratios for different causes of death (with the diamonds representing subtotals and total rows). Hazard ratios and confidence intervals were estimated with the use of Cox proportional hazards regression models, adjusted for age, sex, prior diabetes, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, and region.

Figure S4. Primary Outcome by Key and Other Prespecified Subgroups

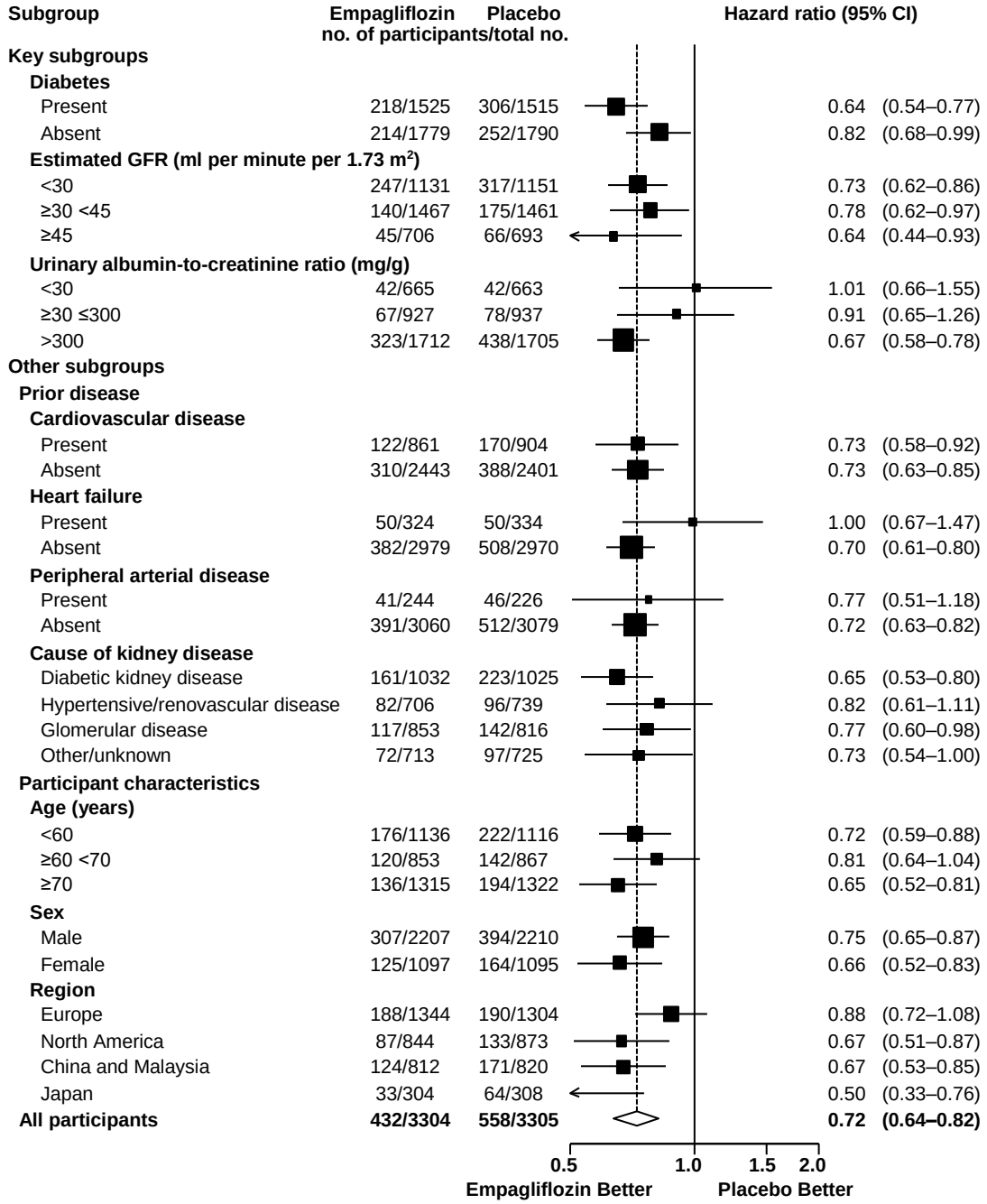



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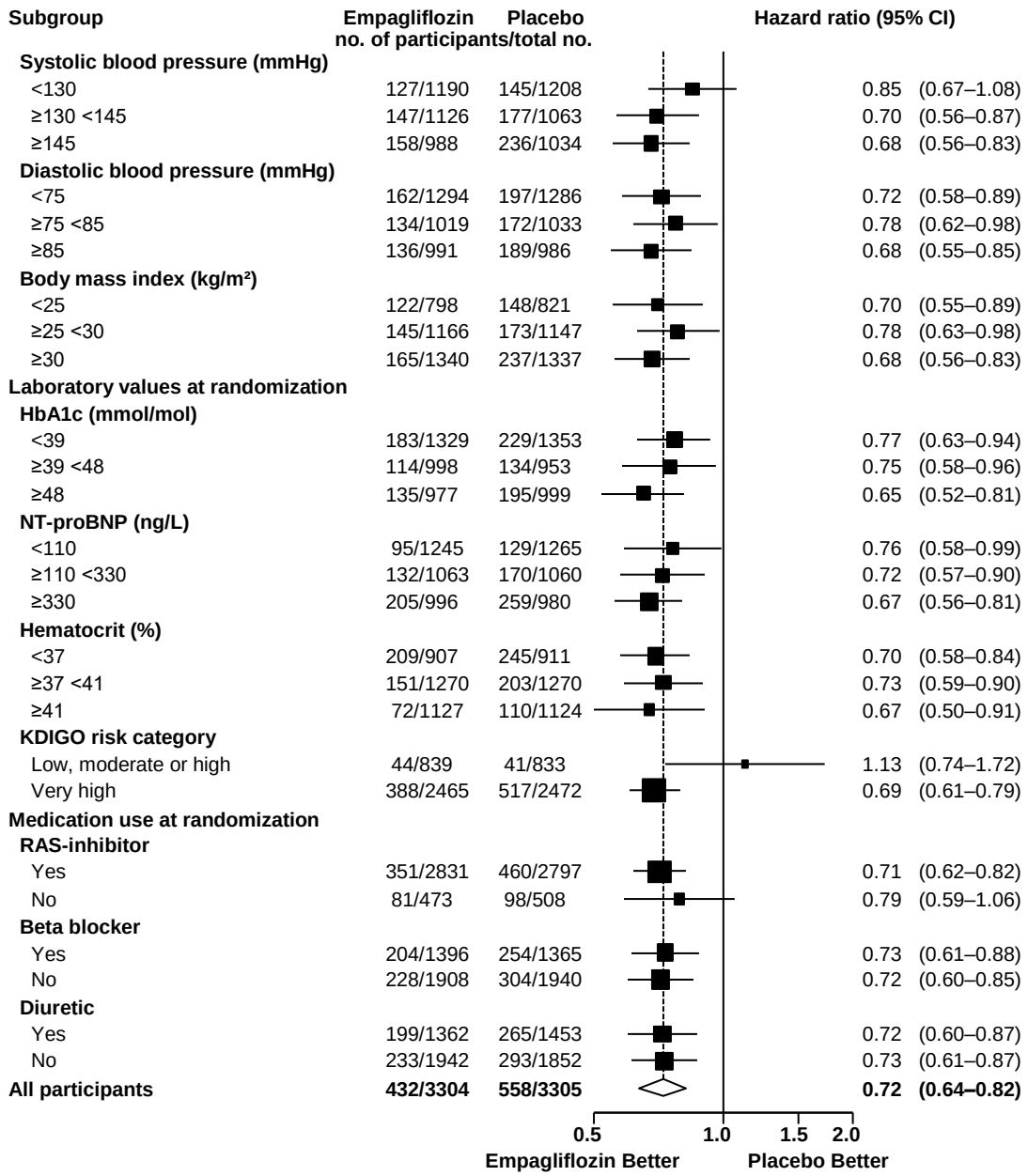
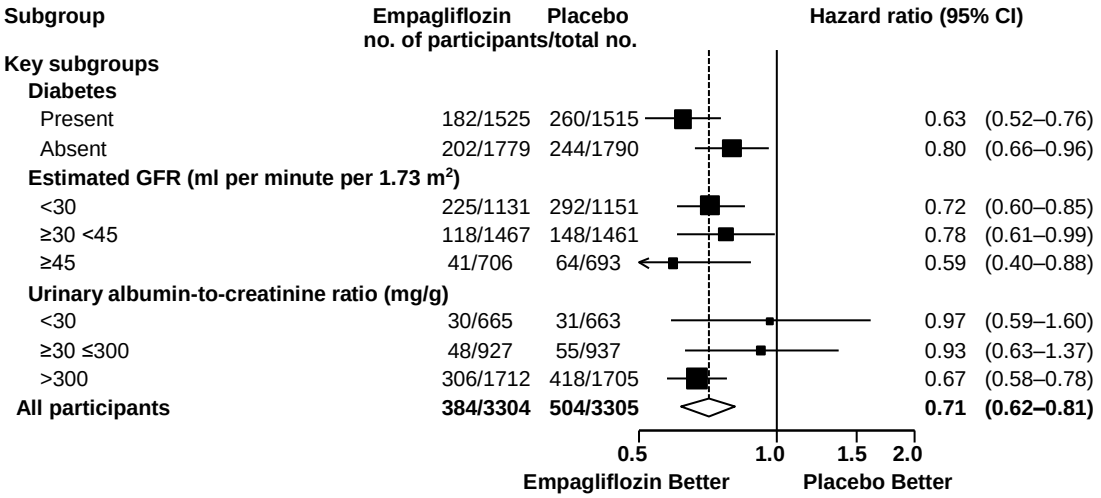
Figure S4. Primary Outcome by Key and Other Prespecified Subgroups (continued)



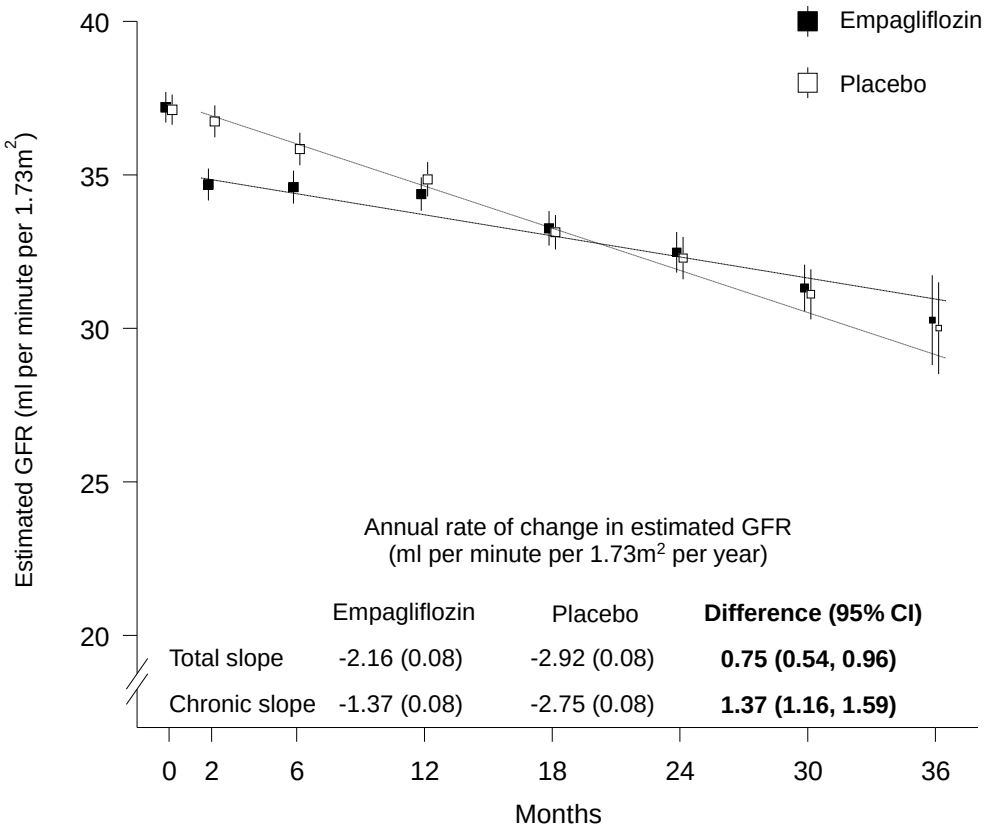

Shown are forest plots of the hazard ratios for the primary outcome according to key and other prespecified baseline subgroups. Hazard ratios and confidence intervals were estimated with the use of Cox proportional hazards regression models, adjusted for age, sex, prior diabetes, estimated GFR, urinary albumin-to-creatinine ratio, and region. Abbreviations: GFR = glomerular filtration rate; HbA1c = glycated hemoglobin; NT-proBNP = N-terminal pro B-type natriuretic peptide; KDIGO = Kidney Disease: Improving Global Outcomes; RAS = renin-angiotensin system.

Figure S5. Kidney Disease Progression by Key Prespecified Subgroups (Prespecified Exploratory Outcome)



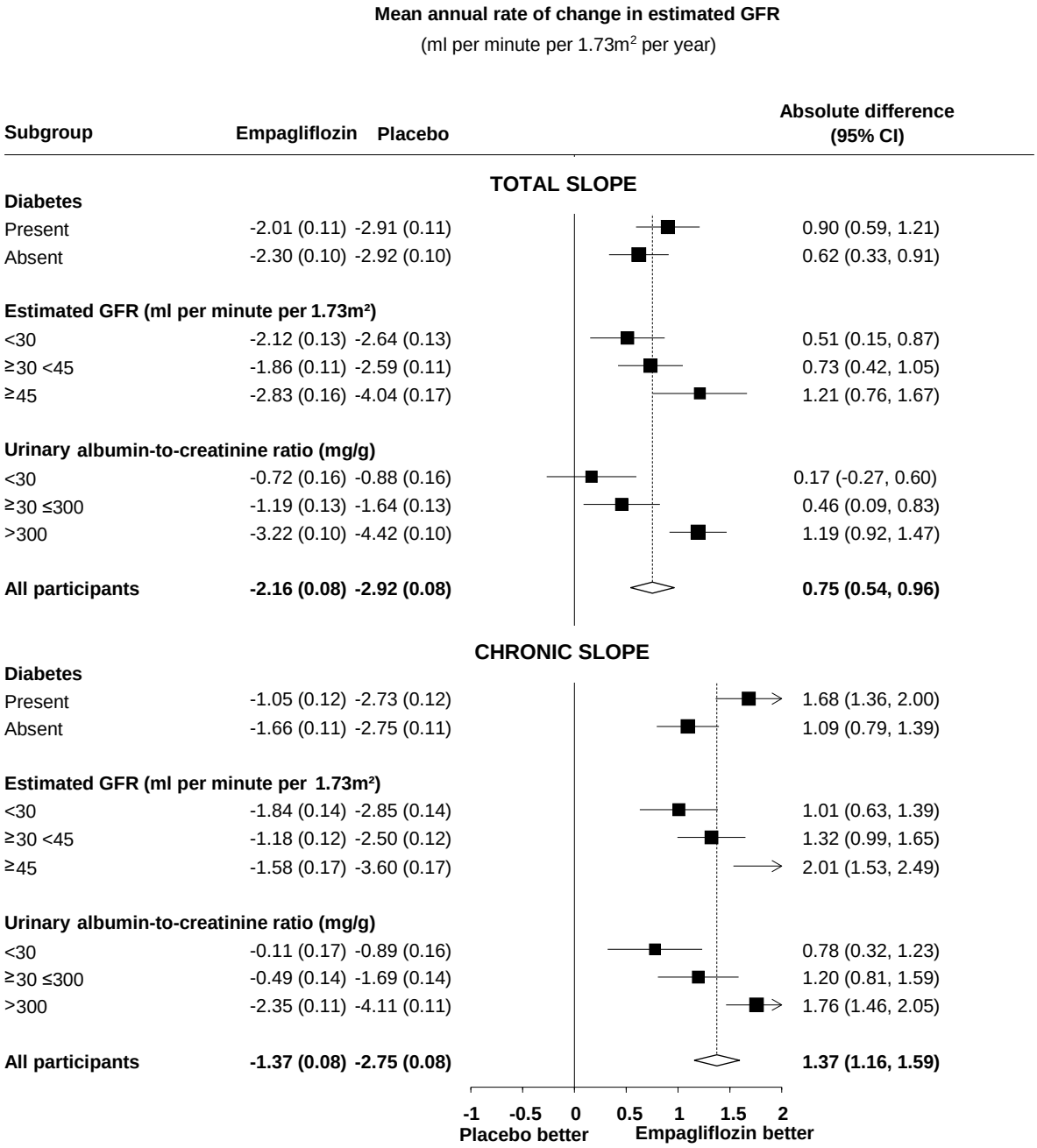

Shown are forest plots of the hazard ratios for the other secondary outcome of kidney disease progression according to key prespecified baseline subgroups (with the diamond representing the overall result). Hazard ratios, confidence intervals, and p values were estimated with the use of Cox proportional-hazards regression models, adjusted for age, sex, prior diabetes, estimated GFR, urinary albumin-to-creatinine ratio, and region. Tests for heterogeneity or trend in the hazard ratio for subgroups were estimated through the inclusion of relevant interaction terms. GFR = glomerular filtration rate.

Figure S6. Comparison of Estimated Chronic Slope with Mean Observed Estimated Glomerular Filtration Rate




Mean annual rates of change in estimated GFR in ml per minute per 1.73m$^2$ per year from baseline to the final follow–up visit ("total slopes"), and from 2 months to the final follow–up visit ("chronic slopes") by treatment allocation were estimated using shared parameter models (tertiary outcome). Observed mean estimated GFR by treatment allocation at each scheduled follow–up visit are plotted (which do not extrapolate missing estimated GFR values beyond the time of ESKD or death, unlike the shared parameter models or the model–based estimates presented in Figure 3). Error bars presented are 95%confidence intervals. X–coordinates of boxes shifted to avoid overlap. See Supplementary Statistical Methods for further details of statistical approaches.

Figure S7. Annual Rate of Change in Estimated GFR by Key Prespecified Subgroups (Prespecified Exploratory Outcome)




Mean annual rates of change in estimated GFR from baseline to the final follow−up visit ("total slopes"), and from 2 months to the final follow−up visit ("chronic slopes") by treatment allocation were estimated using shared parameter models. See Supplementary Statistical Methods section for more details of this approach. GFR = glomerular filtration rate.

# Supplementary Tables

Table S1. Representativeness of Study Participants

| Category | |
|---|---|
| Disease, problem, or condition under investigation | Chronic kidney disease (CKD) at risk of progression |
| Special considerations related to: | |
| Sex and gender | CKD affects men more than women, and the incidence (and prevalence) of end-stage kidney disease is greater in men than women. |
| Age | Prevalence of CKD increases steeply with age. |
| Race or ethnic group | The risks of developing CKD or its progression differ within countries by race and ethnicity. For example, black, Hispanic and Native American people in the USA, black and Asian people in the UK, and indigenous populations in Australia, Canada and South America are all at higher risk compared to the country's white population. |
| Geography | The crude prevalence of CKD varies globally from 2-15% although this may in part be due to differences in methods of ascertainment. The causes of kidney disease vary substantially between countries. Diabetes causes between 10-55% of CKD; chronic glomerulonephritis causes between 5-40% . However, the cause of kidney disease is frequently unknown. |
| Other considerations | Previous large placebo-controlled trials of sodium glucose cotransporter-2 (SGLT2) inhibitors mainly recruited patients with type 2 diabetes and proteinuric CKD. Relatively few patients with CKD without diabetes were studied. The CREDENCE and SCORED trials exclusively studied patients with CKD with type 2 diabetes, and the DAPA-CKD trial in patients with proteinuric CKD studied 1398 patients without diabetes at baseline. Globally the majority of people with CKD have low levels of albuminuria (i.e. a urinary albumin-to-creatinine ratio less than 300 milligrams per gram) and do not have diabetes. |
| Overall representativeness of this trial | Participants in EMPA-KIDNEY were selected to have CKD at risk of progression, so do not represent the larger population of all people with CKD. Patients with polycystic kidney disease were excluded. Nevertheless, EMPA-KIDNEY included a wide range of patients with CKD at risk of progression, and the proportional effects of treatment are likely to be generalizable.<br><br>Biologic sex (male or female) was reported by the participants and used to calculate estimate glomerular filtration rate. Gender was not reported. The participants in the present trial demonstrated an expected higher number of men than women. The proportion of Black patients who underwent randomization overall was 4%, but among patients enrolled in North America, 17% were Black and 17% were of Hispanic ethnicity. These are similar to the total population distribution of the United States.<br><br>Causes of CKD, including diabetic kidney disease, were otherwise consistent with registry data where these were available from participating countries. EMPA-KIDNEY recruited patients from centres in Europe, North America and Asia. No patients were enrolled in Africa or Oceania. |

Table S2. Other Characteristics of Participants at Randomization

| | Empagliflozin (N=3304) | | Placebo (N=3305) | |
|---|---|---|---|---|
| **DEMOGRAPHICS** | | | | |
| **Age at randomization (years)** | | | | |
| Mean (SD) | 63.9 | (13.9) | 63.8 | (13.9) |
| <60 | 1136 | (34%) | 1116 | (34%) |
| ≥60 <70 | 853 | (26%) | 867 | (26%) |
| ≥70 | 1315 | (40%) | 1322 | (40%) |
| **Region** | | | | |
| Europe (UK, Germany, Italy) | 1344 | (41%) | 1304 | (39%) |
| North America (USA, Canada) | 844 | (26%) | 873 | (26%) |
| China, Malaysia | 812 | (25%) | 820 | (25%) |
| Japan | 304 | (9%) | 308 | (9%) |
| **PRIOR DISEASE** | | | | |
| **History of heart failure** | | | | |
| Yes | 324 | (10%) | 334 | (10%) |
| No or missing | 2980 | (90%) | 2971 | (90%) |
| **History of peripheral arterial disease** | | | | |
| Yes | 244 | (7%) | 226 | (7%) |
| No | 3060 | (93%) | 3079 | (93%) |
| **CLINICAL MEASUREMENTS** | | | | |
| **Systolic blood pressure (mmHg)** | | | | |
| Mean (SD) | 136.4 | (18.1) | 136.7 | (18.4) |
| <130 | 1190 | (36%) | 1208 | (37%) |
| ≥130 <145 | 1126 | (34%) | 1063 | (32%) |
| ≥145 | 988 | (30%) | 1034 | (31%) |
| **Diastolic blood pressure (mmHg)** | | | | |
| Mean (SD) | 78.1 | (11.7) | 78.1 | (11.9) |
| <75 | 1294 | (39%) | 1286 | (39%) |
| ≥75 <85 | 1019 | (31%) | 1033 | (31%) |
| ≥85 | 991 | (30%) | 986 | (30%) |
| **Body mass index (kg/m$^2$)** | | | | |
| Mean (SD) | 29.7 | (6.7) | 29.8 | (6.8) |
| <25 | 798 | (24%) | 821 | (25%) |
| ≥25 <30 | 1157 | (35%) | 1140 | (34%) |
| ≥30 | 1340 | (41%) | 1337 | (40%) |
| Missing | 9 | (<1%) | 7 | (<1%) |
| **LABORATORY MEASUREMENTS** | | | | |
| **Glycated hemoglobin (mmol/mol)** | | | | |
| Mean (SD) | 45.0 | (13.5) | 45.0 | (13.7) |
| <39 | 1329 | (40%) | 1353 | (41%) |
| ≥39 <48 | 940 | (28%) | 897 | (27%) |
| ≥48 | 977 | (30%) | 999 | (30%) |
| Missing | 58 | (2%) | 56 | (2%) |

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Table S2. Other Characteristics of Participants at Recruitment (continued)

| | Empagliflozin (N=3304) | | Placebo (N=3305) | |
|---|---|---|---|---|
| **NT-proBNP (ng/L)** | | | | |
| Geometric mean (95% CI) | 172.3 | (164.0-180.9) | 167.1 | (159.2-175.5) |
| Median (Q1-Q3) | 162.0 | (70.0-421.2) | 158.5 | (67.7-417.4) |
| **Hematocrit (%)** | | | | |
| Mean (SD) | 39.1 | (5.1) | 39.1 | (5.1) |
| **KDIGO risk category** | | | | |
| Low, moderate or high | 839 | (25%) | 833 | (25%) |
| Very high | 2465 | (75%) | 2472 | (75%) |
| **Estimated GFR (ml per minute per 1.73m$^2$) and urinary ACR (mg/g)*** | | | | |
| Estimated GFR <45 and urinary ACR <200 | 1182 | (36%) | 1203 | (36%) |
| Estimated GFR <45 and urinary ACR ≥200 | 1416 | (43%) | 1409 | (43%) |
| Estimated GFR ≥45 | 706 | (21%) | 693 | (21%) |
| **CONCOMITANT MEDICATION USE** | | | | |
| Any diuretic | 1362 | (41%) | 1453 | (44%) |
| Loop diuretic | 851 | (26%) | 896 | (27%) |
| Thiazide diuretic | 547 | (17%) | 575 | (17%) |
| Mineralocorticoid receptor antagonist | 229 | (7%) | 246 | (7%) |
| Potassium sparing & other | 30 | (1%) | 8 | (<1%) |
| Beta blocker | 1396 | (42%) | 1365 | (41%) |
| Anticoagulant | 161 | (5%) | 155 | (5%) |
| Antiplatelet therapy | 1105 | (33%) | 1134 | (34%) |
| **Diabetes treatment** | | | | |
| Biguanide (e.g. metformin) | 332 | (10%) | 337 | (10%) |
| Sulphonylurea | 310 | (9%) | 275 | (8%) |
| Insulin | 823 | (25%) | 840 | (25%) |
| DPP-4 inhibitor | 446 | (13%) | 436 | (13%) |
| GLP-1 agonist | 173 | (5%) | 164 | (5%) |
| Other antidiabetic agent | 173 | (5%) | 141 | (4%) |

Figures are n (%) or mean (SD).
* Post-hoc category.
Abbreviations: NT-proBNP = N-terminal pro B-type natriuretic peptide; KDIGO = Kidney Disease: Improving Global Outcomes; GFR = glomerular filtration rate; ACR = albumin-to-creatinine ratio; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1. GFR = glomerular filtration rate.
Values are those from the randomization visit where available, otherwise from the screening visit.

Table S3. Reasons for Discontinuing Randomized Treatment

| | Empagliflozin (N=3304) | | Placebo (N=3305) | |
|---|---|---|---|---|
| **Serious adverse event (SAE)** | | | | |
| Cardiac disorders | 5 | (0.2%) | 12 | (0.4%) |
| Eye disorders | 0 | (0.0%) | 2 | (0.1%) |
| Gastrointestinal disorders | 1 | (0.0%) | 2 | (0.1%) |
| General disorders and administration site conditions | 1 | (0.0%) | 0 | (0.0%) |
| Hepatobiliary disorders | 1 | (0.0%) | 3 | (0.1%) |
| Infections and infestations | 7 | (0.2%) | 8 | (0.2%) |
| Injury, poisoning and procedural complication | 1 | (0.0%) | 2 | (0.1%) |
| Investigations | 5 | (0.2%) | 6 | (0.2%) |
| Metabolism and nutrition disorders | 1 | (0.0%) | 2 | (0.1%) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | 7 | (0.2%) | 7 | (0.2%) |
| Nervous system disorders | 4 | (0.1%) | 1 | (0.0%) |
| Psychiatric disorders | 0 | (0.0%) | 1 | (0.0%) |
| Renal and urinary disorders | 16 | (0.5%) | 15 | (0.5%) |
| Respiratory, thoracic and mediastinal disorders | 0 | (0.0%) | 1 | (0.0%) |
| Skin and subcutaneous tissue disorders | 0 | (0.0%) | 1 | (0.0%) |
| Surgical and medical procedures | 5 | (0.2%) | 11 | (0.3%) |
| Vascular disorders | 5 | (0.2%) | 1 | (0.0%) |
| *Subtotal: Any SAE* | 59 | (1.8%) | 75 | (2.3%) |
| **Non-serious adverse event (NSAE)** | | | | |
| Ear and labyrinth disorders | 0 | (0.0%) | 1 | (0.0%) |
| Gastrointestinal disorders | 5 | (0.2%) | 2 | (0.1%) |
| General disorders and administration site conditions | 3 | (0.1%) | 2 | (0.1%) |
| Hepatobiliary disorders | 1 | (0.0%) | 1 | (0.0%) |
| Infections and infestations | 19 | (0.6%) | 7 | (0.2%) |
| Investigations | 11 | (0.3%) | 9 | (0.3%) |
| Metabolism and nutrition disorders | 4 | (0.1%) | 3 | (0.1%) |
| Nervous system disorders | 4 | (0.1%) | 6 | (0.2%) |
| Renal and urinary disorders | 3 | (0.1%) | 5 | (0.2%) |
| Reproductive system and breast disorders | 2 | (0.1%) | 1 | (0.0%) |
| Skin and subcutaneous tissue disorders | 6 | (0.2%) | 3 | (0.1%) |
| Vascular disorders | 0 | (0.0%) | 2 | (0.1%) |
| *Subtotal: Any NSAE* | 58 | (1.8%) | 42 | (1.3%) |
| **Other reasons** | | | | |
| In another trial or study | 1 | (0.0%) | 1 | (0.0%) |
| Trial administration problem | 1 | (0.0%) | 2 | (0.1%) |
| Relatives concerned about study treatment | 5 | (0.2%) | 4 | (0.1%) |
| Cannot attend clinic because of occupational problems | 1 | (0.0%) | 0 | (0.0%) |
| Cannot attend clinic because of transport problems | 7 | (0.2%) | 7 | (0.2%) |
| Cannot attend clinic because moving out of the area | 9 | (0.3%) | 15 | (0.5%) |
| Cannot attend clinic because of personal problems | 16 | (0.5%) | 8 | (0.2%) |
| Participant concerned about taking too many tablets | 4 | (0.1%) | 7 | (0.2%) |
| Participant concerned about study treatment | 28 | (0.8%) | 23 | (0.7%) |
| Undergoing investigations | 2 | (0.1%) | 7 | (0.2%) |
| Contraindicated drug started | 18 | (0.5%) | 31 | (0.9%) |
| Difficulty taking study medication | 4 | (0.1%) | 6 | (0.2%) |
| Doctor advice | 41 | (1.2%) | 39 | (1.2%) |
| Participant wishes | 68 | (2.1%) | 92 | (2.8%) |
| Convalescent | 0 | (0.0%) | 1 | (0.0%) |
| Death of relative | 1 | (0.0%) | 0 | (0.0%) |

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Table S3. Reasons for Discontinuing Randomized Treatment (continued)

| | Empagliflozin (N=3304) | | Placebo (N=3305) | |
|---|---|---|---|---|
| Disability | 2 | (0.1%) | 0 | (0.0%) |
| Family stress | 2 | (0.1%) | 4 | (0.1%) |
| Foreign travel | 1 | (0.0%) | 0 | (0.0%) |
| Immobile | 4 | (0.1%) | 2 | (0.1%) |
| Imprisonment | 0 | (0.0%) | 1 | (0.0%) |
| Job change | 0 | (0.0%) | 1 | (0.0%) |
| Living in residential institution | 0 | (0.0%) | 2 | (0.1%) |
| Marital problem | 1 | (0.0%) | 0 | (0.0%) |
| Sick relative | 0 | (0.0%) | 1 | (0.0%) |
| Stress at work | 1 | (0.0%) | 0 | (0.0%) |
| Refusal of treatment by relative | 1 | (0.0%) | 1 | (0.0%) |
| Refusal of treatment by patient | 8 | (0.2%) | 13 | (0.4%) |
| *Subtotal: Any other reason* | 226 | (6.8%) | 268 | (8.1%) |
| **Unknown reason** | 214 | (6.5%) | 255 | (7.7%) |
| **Any reason** | 557 | (16.9%) | 640 | (19.4%) |

Figures are number of participants (%).
Participants who died while on study treatment or who stopped study treatment within 7 days of their final follow-up visit are not included.

Table S4. All Hospitalizations Grouped By MedDRA System Organ Class

| | Empagliflozin (N=3304) | | Placebo (N=3305) | | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| Blood and lymphatic disorder | 19 | (0.6%) | 25 | (0.8%) | 0.76 (0.42-1.37) |
| Cardiac disorder† | 196 | (5.9%) | 215 | (6.5%) | 0.90 (0.74-1.09) |
| Congenital, familial and genetic disorders | 2 | (0.1%) | 4 | (0.1%) | |
| Ear and labyrinth disorder | 7 | (0.2%) | 3 | (0.1%) | 2.40 (0.61-9.40) |
| Endocrine disorder | 0 | (0.0%) | 2 | (0.1%) | |
| Eye disorder | 11 | (0.3%) | 8 | (0.2%) | 1.40 (0.56-3.49) |
| Gastrointestinal disorder | 76 | (2.3%) | 93 | (2.8%) | 0.81 (0.60-1.10) |
| General disorders and administration site conditions | 20 | (0.6%) | 35 | (1.1%) | 0.56 (0.32-0.97) |
| Hepatobiliary disorders | 25 | (0.8%) | 23 | (0.7%) | 1.08 (0.61-1.91) |
| Immune system disorders | 5 | (0.2%) | 0 | (0.0%) | |
| Infections and infestations | 258 | (7.8%) | 269 | (8.1%) | 0.95 (0.80-1.13) |
| Injury, poisoning and procedural complications | 96 | (2.9%) | 94 | (2.8%) | 1.01 (0.76-1.35) |
| Investigations | 114 | (3.5%) | 133 | (4.0%) | 0.85 (0.66-1.09) |
| Metabolism and nutrition disorders | 99 | (3.0%) | 109 | (3.3%) | 0.89 (0.68-1.17) |
| Musculoskeletal and connective tissue disorders | 31 | (0.9%) | 38 | (1.1%) | 0.82 (0.51-1.31) |
| Neoplasms benign, malignant and unspecified | 59 | (1.8%) | 75 | (2.3%) | 0.78 (0.56-1.10) |
| Nervous system disorders | 95 | (2.9%) | 103 | (3.1%) | 0.92 (0.69-1.21) |
| Pregnancy, puerperium and perinatal conditions | 1 | (0.0%) | 0 | (0.0%) | |
| Psychiatric disorders | 6 | (0.2%) | 15 | (0.5%) | 0.39 (0.15-1.01) |
| Renal and urinary disorders | 151 | (4.6%) | 184 | (5.6%) | 0.81 (0.65-1.01) |
| Reproductive system and breast disorders | 4 | (0.1%) | 5 | (0.2%) | |
| Respiratory, thoracic and mediastinal disorders | 44 | (1.3%) | 47 | (1.4%) | 0.93 (0.62-1.40) |
| Skin and subcutaneous tissue disorders | 9 | (0.3%) | 13 | (0.4%) | 0.68 (0.29-1.60) |
| Social circumstances | 2 | (0.1%) | 0 | (0.0%) | |
| Surgical and medical procedures | 237 | (7.2%) | 282 | (8.5%) | 0.83 (0.70-0.99) |
| Vascular disorders | 42 | (1.3%) | 55 | (1.7%) | 0.75 (0.50-1.12) |

Figures are number of participants (%). Hazard ratio estimates are derived from Cox proportional hazards regression models as described in the statistical methods section. Hazard ratios not shown when fewer than 10 events occurred.

* Hospitalization defined as the reason for the adverse event being serious is hospitalization.

† Cardiac disorders included hospitalization for heart failure. There were 88 (2.7%) first hospitalizations for heart failure in the empagliflozin group versus 107 (3.2%) in the placebo group: hazard ratio, 0.80, 95% CI 0.60-1.06.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

Table S5. Other Secondary and Tertiary Outcomes

| | Empagliflozin (N=3304) | | Placebo (N=3305) | | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| **Kidney disease progression overall and by components** | | | | | |
| ESKD† | 108 | (3.3%) | 158 | (4.8%) | 0.67 (0.52-0.85) |
| Sustained estimated GFR <10 ml per minute per 1.73 $m^2$‡ | 116 | (3.5%) | 167 | (5.1%) | 0.69 (0.54-0.87) |
| Death from renal causes | 4 | (0.1%) | 4 | (0.1%) | 0.90 (0.22-3.66) |
| ESKD, sustained estimated GFR <10 ml per minute per 1.73 $m^2$, or death from renal causes | 158 | (4.8%) | 221 | (6.7%) | 0.69 (0.56-0.85) |
| Sustained ≥40% decline in estimated GFR from randomization‡ | 359 | (10.9%) | 474 | (14.3%) | 0.70 (0.61-0.81) |
| Any kidney disease progression | 384 | (11.6%) | 504 | (15.2%) | 0.71 (0.62-0.81) |
| **Other tertiary outcomes** | | | | | |
| ESKD or death from any cause | 245 | (7.4%) | 299 | (9.0%) | 0.80 (0.67-0.94) |
| Kidney disease progression or death from any cause | 498 | (15.1%) | 625 | (18.9%) | 0.75 (0.67-0.84) |
| Major cardiovascular event§ | 200 | (6.1%) | 213 | (6.4%) | 0.93 (0.76-1.12) |
| Self-reported gout | 278 | (8.4%) | 317 | (9.6%) | 0.87 (0.74-1.02) |

Figures are number with event (%). Hazard ratio estimates are derived from Cox proportional hazards regression models as described in the statistical methods section.
† ESKD defined as start of maintenance dialysis or receipt of a kidney transplant.
‡ Sustained defined as present on two consecutive scheduled study follow-up visits or last scheduled follow-up visit prior to death or final follow-up (or withdrawal of consent). Estimated GFR measurements based on central laboratory measurements, wherever available.
§ Major cardiovascular event defined as the composite of cardiovascular death, myocardial infarction, stroke or hospitalization for heart failure.
Abbreviations: ESKD = end-stage kidney disease; GFR = glomerular filtration rate.

Table S6. New-Onset Diabetes

| | Empagliflozin (N=1779) | | Placebo (N=1790) | | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| Normoglycaemia (HbA1c <39 mmol/mol) | 6 / 1218 | (<0.1%) | 14 / 1254 | (<0.1%) | 0.43 (0.17-1.13) |
| Pre-diabetes (HbA1c ≥39 <48 mmol/mol) | 45 / 561 | (0.1%) | 47 / 536 | (0.1%) | 0.91 (0.60-1.37) |
| **All participants†** | 51 / 1779 | (<0.1%) | 61 / 1790 | (<0.1%) | 0.82 (0.56-1.19) |

Figures are number of participants (%). Hazard ratio estimates are derived from Cox proportional hazards regression models as described in the statistical methods section.
New-onset diabetes is defined as clinical diagnosis, commencement of glucose-lowering treatment, or HbA1c ≥48 mmol/mol measured by central laboratory on at least one occasion.
† Excludes participants with diabetes at baseline.
Abbreviations: HbA1c = glycated hemoglobin.

Table S7. Additional Safety Outcomes

| | Empagliflozin (N=3304) | | Placebo (N=3305) | | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| **Serious urinary tract infection, by sex** | | | | | |
| Male | 30 / 2207 | (1.4%) | 32 / 2210 | (1.4%) | |
| Female | 22 / 1097 | (2.0%) | 22 / 1095 | (2.0%) | |
| Total: serious urinary tract infection | 52 | (1.6%) | 54 | (1.6%) | 0.94 (0.64-1.37) |
| **Serious genital infection, by sex** | | | | | |
| Male | 0 / 2207 | (0.0%) | 1 / 2210 | (<0.1%) | |
| Female | 1 / 1097 | (0.1%) | 0 / 1095 | (0.0%) | |
| Total: serious genital infection* | 1 | (<0.1%) | 1 | (<0.1%) | |
| **Liver injury, by cause†** | | | | | |
| Infection | 1 | (<0.1%) | 2 | (0.1%) | |
| Alcohol | 1 | (<0.1%) | 0 | (0.0%) | |
| Drug toxicity | 1 | (<0.1%) | 4 | (0.1%) | |
| Obstruction/cholestasis | 1 | (<0.1%) | 2 | (0.1%) | |
| Hepatic congestion | 0 | (0.0%) | 1 | (<0.1%) | |
| Non-alcoholic fatty liver disease | 1 | (<0.1%) | 1 | (<0.1%) | |
| Other cause | 2 | (0.1%) | 1 | (<0.1%) | |
| Unknown cause | 6 | (0.2%) | 1 | (<0.1%) | |
| Total: all liver injury | 13 | (0.4%) | 12 | (0.4%) | 1.09 (0.50-2.38) |
| **Ketoacidosis, by diabetes status†** | | | | | |
| Prior diabetes | 5 / 1525 | (0.3%) | 1 / 1515 | (0.1%) | |
| No prior diabetes | 1 / 1779 | (0.1%) | 0 / 1790 | (0.0%) | |
| Total: all ketoacidosis | 6 | (0.2%) | 1 | (<0.1%) | |
| **Lower limb amputation, by level†** | | | | | |
| Toe | 20 | (0.6%) | 14 | (0.4%) | |
| Forefoot | 7 | (0.2%) | 1 | (<0.1%) | |
| Foot | 0 | (<0.1%) | 0 | (<0.1%) | |
| Below knee | 5 | (0.2%) | 4 | (0.1%) | |
| Above knee | 2 | (0.1%) | 1 | (<0.1%) | |
| Total: lower limb amputation | 28 | (0.8%) | 19 | (0.6%) | 1.43 (0.80-2.57) |
| **Bone fracture, by site and by aetiology** | | | | | |
| By site | | | | | |
| Long bone fracture | 57 | (1.7%) | 65 | (2.0%) | |
| Non-long bone fracture | 77 | (2.3%) | 63 | (1.9%) | |
| By aetiology | | | | | |
| High impact fracture | 21 | (0.6%) | 10 | (0.3%) | |
| Low impact fracture | 95 | (2.9%) | 89 | (2.7%) | |
| Other cause | 20 | (0.6%) | 28 | (0.8%) | |
| Total: bone fracture | 133 | (4.0%) | 123 | (3.7%) | 1.08 (0.84-1.38) |

Figures are number of participants (%). Hazard ratio estimates are derived from Cox proportional hazards regression models as described in the statistical methods section.

* Serious genital infections were defined as any bacterial or fungal infection of the genitals or perineum, including vulvovaginitis, balanitis and infections of skin between the genital and anus which met standard ICH-GCP criteria for seriousness. There were no cases of necrotising fasciitis of the perineum (Fournier's gangrene).

† Includes both serious and non-serious adverse events.

Table S8. All Serious Adverse Events Grouped By MedDRA System Organ Class

| | Empagliflozin (N=3304) | | Placebo (N=3305) | | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| Blood and lymphatic disorder | 19 | (0.6%) | 27 | (0.8%) | 0.70 (0.39-1.26) |
| Cardiac disorder | 209 | (6.3%) | 228 | (6.9%) | 0.90 (0.75-1.09) |
| Congenital, familial and genetic disorders | 2 | (0.1%) | 5 | (0.2%) | |
| Ear and labyrinth disorder | 7 | (0.2%) | 6 | (0.2%) | 1.16 (0.39-3.46) |
| Endocrine disorder | 1 | (0.0%) | 3 | (0.1%) | |
| Eye disorder | 18 | (0.5%) | 16 | (0.5%) | 1.13 (0.58-2.22) |
| Gastrointestinal disorder | 76 | (2.3%) | 96 | (2.9%) | 0.78 (0.58-1.06) |
| General disorders and administration site conditions | 45 | (1.4%) | 64 | (1.9%) | 0.69 (0.47-1.01) |
| Hepatobiliary disorders | 30 | (0.9%) | 27 | (0.8%) | 1.10 (0.66-1.86) |
| Immune system disorders | 5 | (0.2%) | 0 | (0.0%) | |
| Infections and infestations | 319 | (9.7%) | 332 | (10.0%) | 0.95 (0.82-1.11) |
| Injury, poisoning and procedural complications | 114 | (3.5%) | 108 | (3.3%) | 1.05 (0.81-1.37) |
| Investigations | 182 | (5.5%) | 214 | (6.5%) | 0.84 (0.69-1.02) |
| Metabolism and nutrition disorders | 127 | (3.8%) | 137 | (4.1%) | 0.92 (0.72-1.17) |
| Musculoskeletal and connective tissue disorders | 41 | (1.2%) | 44 | (1.3%) | 0.93 (0.61-1.42) |
| Neoplasms benign, malignant and unspecified | 117 | (3.5%) | 126 | (3.8%) | 0.92 (0.72-1.19) |
| Nervous system disorders | 111 | (3.4%) | 118 | (3.6%) | 0.93 (0.72-1.21) |
| Pregnancy, puerperium and perinatal conditions | 1 | (0.0%) | 0 | (0.0%) | |
| Psychiatric disorders | 7 | (0.2%) | 16 | (0.5%) | 0.43 (0.18-1.05) |
| Renal and urinary disorders | 180 | (5.4%) | 211 | (6.4%) | 0.85 (0.69-1.03) |
| Reproductive system and breast disorders | 4 | (0.1%) | 5 | (0.2%) | |
| Respiratory, thoracic and mediastinal disorders | 48 | (1.5%) | 57 | (1.7%) | 0.84 (0.57-1.23) |
| Skin and subcutaneous tissue disorders | 10 | (0.3%) | 16 | (0.5%) | 0.60 (0.27-1.33) |
| Social circumstances | 2 | (0.1%) | 0 | (0.0%) | |
| Surgical and medical procedures | 255 | (7.7%) | 304 | (9.2%) | 0.83 (0.70-0.98) |
| Vascular disorders | 47 | (1.4%) | 68 | (2.1%) | 0.68 (0.47-0.99) |
| **Total: Any Serious Adverse Event** | **1164** | **(35.2%)** | **1245** | **(37.7%)** | **0.92 (0.85-0.99)** |

Figures are number of participants (%). Hazard ratio estimates are derived from Cox proportional hazards regression models as described in the statistical methods section. Hazard ratios not shown when fewer than 10 events occurred.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

Table S9a. Physical and Laboratory Assessments

| | Empagliflozin (N=3273) | | Placebo (N=3265) | | Difference | |
|---|---|---|---|---|---|---|
| | | | | | **Absolute Difference (SE)** | |
| **Physical measurements** | | | | | | |
| Weight (kg)* | 82.3 | (0.1) | 83.2 | (0.1) | -0.9 | (0.1) |
| Systolic blood pressure (mmHg)* | 132.8 | (0.2) | 135.3 | (0.2) | -2.6 | (0.3) |
| Diastolic blood pressure (mmHg)* | 76.3 | (0.1) | 76.8 | (0.1) | -0.5 | (0.2) |
| **Laboratory measurements** | | | | | | |
| | | | | | **Absolute Difference (95% CI)** | |
| HbA1c (mmol/mol)* | | | | | | |
| Prior diabetes | 53.44 | (0.28) | 54.30 | (0.28) | -0.86 | (-1.63, 0.09) |
| No prior diabetes | 36.88 | (0.07) | 36.91 | (0.07) | -0.03 | (-0.22, 0.17) |
| All | 44.52 | (0.14) | 44.90 | (0.14) | -0.39 | (-0.77, -0.01) |
| Potassium (mmol/L)* | 4.52 | (0.01) | 4.55 | (0.01) | -0.04 | (-0.05, -0.02) |
| | | | | | **Relative Difference (SE)** | |
| Liver function tests | | | | | | |
| ALT or AST ≥5x ULN‡ | 13 | (0.4%) | 12 | (0.4%) | 0.03% | (0.15%) |
| ALT or AST ≥3x ULN and bilirubin ≥2x ULN‡ | 2 | (0.1%) | 4 | (0.1%) | -0.06% | (0.07%) |
| | | | | | **Relative Difference (95% CI)** | |
| Urinary albumin-to-creatinine ratio (mg/g)† | 202 | (4) | 250 | (5) | -19% | (-23%, -15%) |

All analyses (with the exception of liver function tests) use a linear mixed model repeated measures (MMRM) approach including fixed, categorical effects of treatment allocation, time point, treatment-by-time point interaction, and the prognostic variables used in the minimization algorithm (in the same categories used in the minimization process) along with continuous effects of baseline (randomization) measurement and baseline-by-time point interaction. Mean follow-up values averaged over all time points at which measurements were scheduled are presented (see protocol and DAP for further details). For analyses of HbA1c by diabetes status, models were fitted separately among participants with and without diabetes.

* Mean (standard error [SE]).

† Geometric mean (SE).

‡ Number of participants (%).

Abbreviations: HbA1c = glycated hemoglobin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Table S9b. Liver Function Test Assessments, by Time

| | Empagliflozin (N=3037) | | Placebo (N=3054) | |
|---|---|---|---|---|
| **Laboratory measurements** | | | | |
| ALT or AST ≥5x ULN | | | | |
| 2 months | 3 | (0.1%) | 2 | (0.1%) |
| 6 months | 1 | (0.0%) | 1 | (0.0%) |
| 12 months | 4 | (0.1%) | 1 | (0.0%) |
| 18 months | 2 | (0.1%) | 4 | (0.1%) |
| 24 months | 3 | (0.2%) | 2 | (0.1%) |
| 30 months | 0 | (0.0%) | 3 | (0.2%) |
| 36 months | 0 | (0.0%) | 0 | (0.0%) |
| ALT or AST ≥3x ULN and bilirubin ≥2x ULN | | | | |
| 2 months | 0 | (0.0%) | 0 | (0.0%) |
| 6 months | 0 | (0.0%) | 0 | (0.0%) |
| 12 months | 2 | (0.1%) | 1 | (0.0%) |
| 18 months | 0 | (0.0%) | 1 | (0.0%) |
| 24 months | 0 | (0.0%) | 0 | (0.0%) |
| 30 months | 0 | (0.0%) | 2 | (0.2%) |
| 36 months | 0 | (0.0%) | 0 | (0.0%) |

Figures are number of participants (%).
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Table S10. Local Laboratory Blood Assessments at 18 Months, in a Subset from the United Kingdom

| | Empagliflozin (N=442) | | Placebo (N=395) | | Difference (SE) | |
|---|---|---|---|---|---|---|
| Sodium (mmol/L) | 139.3 | (0.1) | 138.8 | (0.1) | 0.5 | (0.2) |
| Corrected calcium (mmol/L) | 2.36 | (0.01) | 2.35 | (0.01) | 0.01 | (0.01) |
| Phosphate (mmol/L) | 1.17 | (0.01) | 1.13 | (0.01) | 0.04 | (0.02) |
| Hematocrit (%) | 40.4 | (0.2) | 38.2 | (0.2) | 2.2 | (0.3) |
| Hemoglobin (g/L) | 135.3 | (0.6) | 127.8 | (0.6) | 7.5 | (0.8) |

Figures are mean (SE). For sodium, corrected calcium, and phosphate, mean follow-up values and their differences are presented. For haematocrit and haemoglobin, baseline-adjusted mean follow-up values (estimated using ANCOVA adjusted for each patient's value at randomization) and their differences are presented.