Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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SUPPLEMENTARY APPENDIX

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Clinical Event Committee: Cardiology

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Section C. Definition of high risk of cardiovascular events

High risk of cardiovascular events was defined as the presence of ≥1 of the following:

- History of myocardial infarction >2 months prior to informed consent
- Evidence of multi-vessel coronary artery disease i.e. in ≥2 major coronary arteries or the left main coronary artery, documented by any of the following:
  - Presence of significant stenosis: ≥50% luminal narrowing during angiography (coronary or multi-slice computed tomography)
  - Previous revascularization (percutaneous transluminal coronary angioplasty ± stent or coronary artery bypass graft >2 months prior to consent
  - The combination of revascularization in one major coronary artery and significant stenosis (≥50% luminal narrowing) in another major coronary artery
- Evidence of single-vessel coronary artery disease, ≥50% luminal narrowing during angiography (coronary or multi-slice computed tomography) not subsequently successfully revascularized, with at least 1 of the following:
  - A positive non-invasive stress test for ischemia
  - Hospital discharge for unstable angina ≤12 months prior to consent
- Unstable angina >2 months prior to consent with evidence of single- or multi-vessel coronary artery disease
- History of stroke (ischemic or hemorrhagic) >2 months prior to consent
- Occlusive peripheral artery disease documented by any of the following:
  - Limb angioplasty, stenting, or bypass surgery
  - Limb or foot amputation due to circulatory insufficiency
  - Evidence of significant peripheral artery stenosis (>50% on angiography, or >50% or hemodynamically significant via non-invasive methods) in 1 limb
  - Ankle brachial index <0.9 in ≥1 ankle

Section D. Exclusion criteria

- Uncontrolled hyperglycemia with glucose >240 mg/dL after an overnight fast during placebo run-in and confirmed by a second measurement (not on the same day)
- Indication of liver disease, defined by serum levels of alanine amininotransferase, aspartate aminotransferase, or alkaline phosphatase above 3 x upper limit of normal during screening or run-in phase
- Planned cardiac surgery or angioplasty within 3 months
- Estimated glomerular filtration rate <30 ml/min/1.73 m^2 (according to the Modification of Diet in Renal Disease equation) at screening or during run-in phase
- Bariatric surgery within the past two years and other gastrointestinal surgeries that induce chronic malabsorption
- Blood dyscrasias or any disorders causing hemolysis or unstable red blood cells
- Medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 5 years
- Contraindications to background therapy according to the local label
- Treatment with anti-obesity drugs 3 months prior to informed consent or any other treatment at time of screening leading to unstable body weight
- Treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent
- Any uncontrolled endocrine disorder except type 2 diabetes
- Pre-menopausal women (last menstruation ≤1 year prior to informed consent) who were nursing, pregnant, or of child-bearing potential and were not practicing an acceptable method of birth control, or did not plan to continue using this method throughout the study, or did not agree to submit to periodic pregnancy testing during the trial
  - Acceptable methods of birth control include tubal ligation, transdermal patch, intrauterine devices/systems, oral, implantable or injectable contraceptives, sexual abstinence, double barrier method, vasectomy of partner
- Alcohol or drug abuse within 3 months of informed consent that would interfere with trial participation or any ongoing condition leading to decreased compliance with study procedures or study drug intake
- Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial or participating in another trial involving an investigational drug and/or follow-up

- Any clinical condition that would jeopardize patient safety while participating in this clinical trial (in Canada, this included current genito-urinal infection or genito-urinal infection within 2 weeks prior to informed consent)
- Acute coronary syndrome, stroke, or transient ischemic attack within 2 months prior to informed consent
- In South Africa: blood pressure >160/100 mmHg at screening

Section E. Definitions of major clinical outcomes

Cardiovascular death

The cause of death was determined by the principal condition that caused the death, not the immediate mode of death. Clinical Events Committee (CEC) members reviewed all available information and used their clinical expertise to adjudicate the cause of death. All deaths not attributed to the categories of CV death and not attributed to a non-CV cause were presumed CV deaths. Death certificates or summary, if possible, were provided for all patients who died, including date and details surrounding death. However, if a death certificate was the only information available for review besides the patient profile in the clinical trial database, the CEC may have decided not to use this information as cause of death if another etiology appeared more plausible. The following definitions were used for the adjudication of fatal cases:

Sudden cardiac death

Death that occurs unexpectedly in a previously stable patient and includes the following deaths:

- Witnessed and instantaneous without new or worsening symptoms
- Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms
- Witnessed and attributed to an identified arrhythmia (e.g., captured on ECG recording or witnessed on a monitor by either a medic or paramedic)
- Subjects unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology
- Unwitnessed death and there is no conclusive evidence of another, non-CV, cause of death (i.e. presumed CV death)

Sudden death due to acute MI (MI type 3)

Sudden death occurring up to 14 days after a documented acute MI (verified either by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombus) and where there is no conclusive evidence of another cause of death. If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

Death due to heart failure or cardiogenic shock

Death occurring in the context of clinically worsening symptoms and/or signs of congestive heart failure (CHF) without evidence of another cause of death.

New or worsening signs and/or symptoms of CHF include any of the following:

- New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
- Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration
- Confinement to bed predominantly due to heart failure symptoms
- Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
- Cardiogenic shock not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
    - Cardiogenic shock is defined as SBP <90 mmHg for more than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:
        - Cool, clammy skin
        - Oliguria (urine output < 30 mL/hour)

- Altered sensorium
- Cardiac index < 2.2 L/min/m^2

– Cardiogenic shock can also be defined in the presence of SBP ≥90 mmHg or for a time period <1 hour if the blood pressure measurement or the time period is influenced by the presence of positive inotropic or vasopressor agents alone and/or with mechanical support <1 hour. The outcome of cardiogenic shock will be based on CEC assessment and must occur after randomization. Episodes of cardiogenic shock occurring before and continuing after randomization will not be part of the study outcome. This category will include sudden death occurring during an admission for worsening heart failure

Death due to stroke, cerebrovascular event

Death occurring up to 30 days after a stroke that is either due to the stroke or caused by complication of the stroke.

Death due to other CV causes

Death must be due to a fully documented CV cause not included in the above categories (e.g. dysrythmia, pulmonary embolism, or CV intervention). Death due to a MI that occurs as a direct consequence of a CV investigation/procedure/ operation will be classified as death due to other CV cause.

Non-CV death

Non-CV death is defined as any death not covered by cardiac death or vascular death. The CEC will be asked to indicate the most likely cause of non-CV death. Examples of non-CV death are: pulmonary causes, renal causes, gastrointestinal causes, infection (including sepsis), non-infectious (e.g., systemic inflammatory response syndrome (SIRS)), malignancy (i.e., new malignancy, worsening of prior malignancy), hemorrhage (not intracranial), accidental/trauma, suicide, non-CV organ failure (e.g., hepatic failure) or non-CV surgery.

Myocardial infarction (MI) (non-fatal)

The term MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria A to C meets the diagnosis for myocardial infarction.

Criteria A: Spontaneous MI (type 1)

To identify a type 1 MI, patients should demonstrate spontaneous symptoms of myocardial ischemia unprovoked by supply/demand inequity, together with ≥1 of the following criteria:

- Cardiac biomarker elevation: Troponin is the preferred marker for use to adjudicate the presence of acute myocardial infarction. At least one value should show a rise and/or fall above the lowest cut-point providing 10% imprecision (typically the upper reference limit for the troponin run per standard of clinical care). Creatine kinase-MB is a secondary choice to troponin; a rise of CK-MB above the local upper reference limit would be consistent with myocardial injury

- ECG changes consistent with new ischemic changes

  – ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]) or ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy [LVH] and LBBB):

  – Development of pathological Q waves in the ECG

    - Any Q-wave in leads V2-V3 ≥0.02 seconds or QS complex in leads V2 and V3

    - Q-wave ≥ 0.03 seconds and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)

  – ST elevation: New ST elevation at the J-point in two contiguous leads with the cut-off points: ≥0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads

  – ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1

- Imaging evidence of new non-viable myocardium or new wall motion abnormality

Criteria B: "Demand" related (type 2) MI

- Patients with type 2 MI should be considered with similar diagnostic criteria as a type 1 MI, however type 2 MI should be considered present when myocardial ischemia and infarction are consequent to supply/demand inequity, rather than a spontaneous plaque rupture and coronary thrombosis.

Criteria C: Percutaneous Coronary Intervention (PCI)-related MI (type 4a/4b)

- For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL within 24 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers >3 x 99th percentile URL (troponin or CK-MB >3 x 99th percentile URL) are consistent with PCI-related MI.
- If the cardiac biomarker is elevated prior to PCI, a ≥20% increase of the value in the second cardiac biomarker sample within 24 hours of PCI and documentation that cardiac biomarker values were decreasing (two samples ≥6 hours apart) prior to the suspected recurrent MI is consistent with PCI-related MI.
- Symptoms of cardiac ischemia are not required.

Criteria D: Coronary Artery Bypass Grafting (CABG)-related MI (type 5)

- For CABG in patients with normal baseline troponin values, elevation of cardiac biomarkers above the 99th percentile URL within 72 hours of the procedure is indicative of peri-procedural myocardial necrosis. By convention, an increase of biomarkers >5 x 99th percentile URL (troponin or CK-MB >5 x 99th percentile URL) plus at least one of the following
    - New pathological Q waves in at least 2 contiguous leads on the electrocardiogram that persist through 30 days or new LBBB
    - Angiographically documented new graft or native coronary artery occlusion
    - Imaging evidence of new loss of viable myocardium is consistent with CABG-related MI
- If the cardiac biomarker is elevated prior to CABG, a ≥20% increase of the value in the second cardiac biomarker sample within 72 hours of CABG and documentation that cardiac

biomarker values were decreasing (two samples ≥6 hours apart) prior to the suspected recurrent MI plus new pathological Q waves in ≥2 contiguous leads on the electrocardiogram or new LBBB, angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium is consistent with a periprocedural MI after CABG. Symptoms of cardiac ischemia are not required.

Clinical classification of acute MI

For every MI identified by the CEC, one of the following will be assigned:

- Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
- Type 2: MI secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension
- Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
- Type 4a: MI associated with PCI
- Type 4b: MI associated with stent thrombosis as documented by angiography or at autopsy
- Type 5: MI associated with CABG

Hospitalization for unstable angina

The date of this event is the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit. Unstable angina requiring hospitalization is defined as all of the following:

- No elevation in cardiac biomarkers (cardiac biomarkers are negative for myocardial necrosis) according to conventional assays or contemporary sensitive assays

- Clinical presentation: Cardiac symptoms lasting ≥10 minutes and considered to be myocardial ischemia on final diagnosis with one of the following:
  - Rest angina
  - New-onset (<2 months) severe angina (Canadian Cardiovascular Society [CCS] Grading Scale, or CCS classification system, classification severity ≥III)
  - Increasing angina (in intensity, duration, and/or frequency) with an increase in severity of >1 CCS class to CCS class >III
- Requiring an unscheduled visit to a healthcare facility and overnight admission
- At least one of the following:
  - New or worsening ST or T wave changes on ECG. ECG changes should satisfy the following criteria for acute myocardial ischemia in the absence of LVH and LBBB:
    - ST elevation: New transient (known to be <20 minutes) ST elevation at the J-point in two contiguous leads with the cut-off points - ≥0.2 mV in men or ≥0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads
    - ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1
  - Evidence of ischemia on stress testing with cardiac imaging
  - Evidence of ischemia on stress testing with angiographic evidence of ≥70% lesion and/or thrombus in an epicardial coronary artery or initiation/increased dosing of antianginal therapy
  - Angiographic evidence of ≥70% lesion and/or thrombus in an epicardial coronary artery

Stent thrombosis

Timing

Class	Description of stage
Class I	"Ordinary physical activity does not cause . . . angina," such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation
Class II	"Slight limitation of ordinary activity." Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and under normal conditions
Class III	"Marked limitations of ordinary physical activity." Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace
Class IV	"Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest"

Type		Timing
Early stent thrombosis	Acute stent thrombosis	0 to 24 hours after stent implantation
	Subacute stent thrombosis	>24 hours to 30 days after stent implantation
Late stent thrombosis*		>30 days to 1 year after stent implantation
Very late stent thrombosis*		>1 year after stent implantation

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified above. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheterization laboratory

*Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization

Definitions of definite, probable, and possible stent thrombosis

Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation:

- Angiographic confirmation of stent thrombosis: The presence of an intracoronary thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of ≥1 of the following criteria within a 48-hour time window:
  - Acute onset of ischemic symptoms at rest
  - New ischemic ECG changes that suggest acute ischemia
  - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI: troponin or CK-MB >99th percentile of URL, according to conventional assays or contemporary sensitive assays)
  - Non-occlusive thrombus Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream
  - Occlusive thrombus TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

NOTE: The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

- Pathological confirmation of stent thrombosis Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

Probable Stent Thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days

  - In ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis

- Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible Stent Thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

Heart failure (HF) requiring hospitalization

The date of this event is the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit. HF requiring hospitalization is defined as an event that meets all of the following criteria:

- Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12-hour stay (or a date change if the time of admission/discharge is not available)

- Clinical manifestations of heart failure (new or worsening) including at least one of the following:
  - Dyspnea
  - Orthopnea
  - Paroxysmal nocturnal dyspnea
  - Edema
  - Pulmonary basilar crackles
  - Jugular venous distension
  - Third heart sound or gallop rhythm
  - Radiological evidence of worsening heart failure

- Additional/increased therapy: at least one of the following:

- Initiation of oral diuretic, intravenous diuretic, inotrope, or vasodilator therapy
- Uptitration of oral diuretic or intravenous therapy, if already on therapy
- Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure

Changes in biomarker (e.g., brain natriuretic peptide) consistent with CHF will support this diagnosis.

Coronary revascularization procedure

Either CABG or PCI (e.g., angioplasty, coronary stenting).

- CABG: the successful placement of ≥1 conduit with either a proximal and distal anastomosis or a distal anastomosis only
- PCI: Successful balloon inflation with or without stenting and the achievement of a residual stenosis <50%. The balloon inflation and/or stenting could have been preceded by device activation (e.g., angiojet, directional coronary atherectomy, or rotational atherectomy)

In cases where the procedure leads to a MI (type 4a, 4b or 5) the event will be adjudicated as an MI.

Transient Ischemic Attack (TIA)

TIA: a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

Stroke

Stroke: the rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). Available neuroimaging studies are considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes are classified as ischemic, hemorrhagic, or unknown.

Diagnosis of stroke.

For the diagnosis of stroke, the following 4 criteria should be fulfilled:

- Rapid onset of a focal/global neurological deficit with at least one of the following:
  - Change in level of consciousness
  - Hemiplegia
  - Hemiparesis
  - Numbness or sensory loss affecting one side of the body
  - Dysphasia/aphasia
  - Hemianopia (loss of half of the field of vision of one or both eyes)
  - Other new neurological sign(s)/symptom(s) consistent with stroke

NOTE: If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation

- Duration of a focal/global neurological deficit ≥24 hours OR < 24 hours if this is because of at least one of the following therapeutic interventions:
  - Pharmacologic (i.e., thrombolytic drug administration)
  - Non-pharmacologic (i.e., neurointerventional procedure [e.g. intracranial angioplasty])

OR

  - Available brain imaging clearly documents a new hemorrhage or infarct

OR

  - The neurological deficit results in death

- No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion)
- Confirmation of the diagnosis by at least one of the following:*
  - Neurology or neurosurgical specialist

- Brain imaging procedure (at least one of the following):
  - CT scan
  - MRI scan
  - Cerebral vessel angiography
- Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

If a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event will be discussed at a full CEC meeting. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone, but full CEC consensus is mandatory.

If the acute focal signs represent a worsening of a previous deficit, these signs must have either

- Persisted for more than one week

OR

- Persisted for more than 24 hours and were accompanied by an appropriate new CT or MRI finding

Classification of stroke

Strokes are sub-classified as follows:

- Ischemic (non-hemorrhagic): A stroke caused by an arterial obstruction due to a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology. This category includes ischemic strokes with hemorrhagic transformation (i.e. no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan)
- Hemorrhagic: A stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category includes strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular) and primary subarachnoid hemorrhage
- Not assessable: The stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed

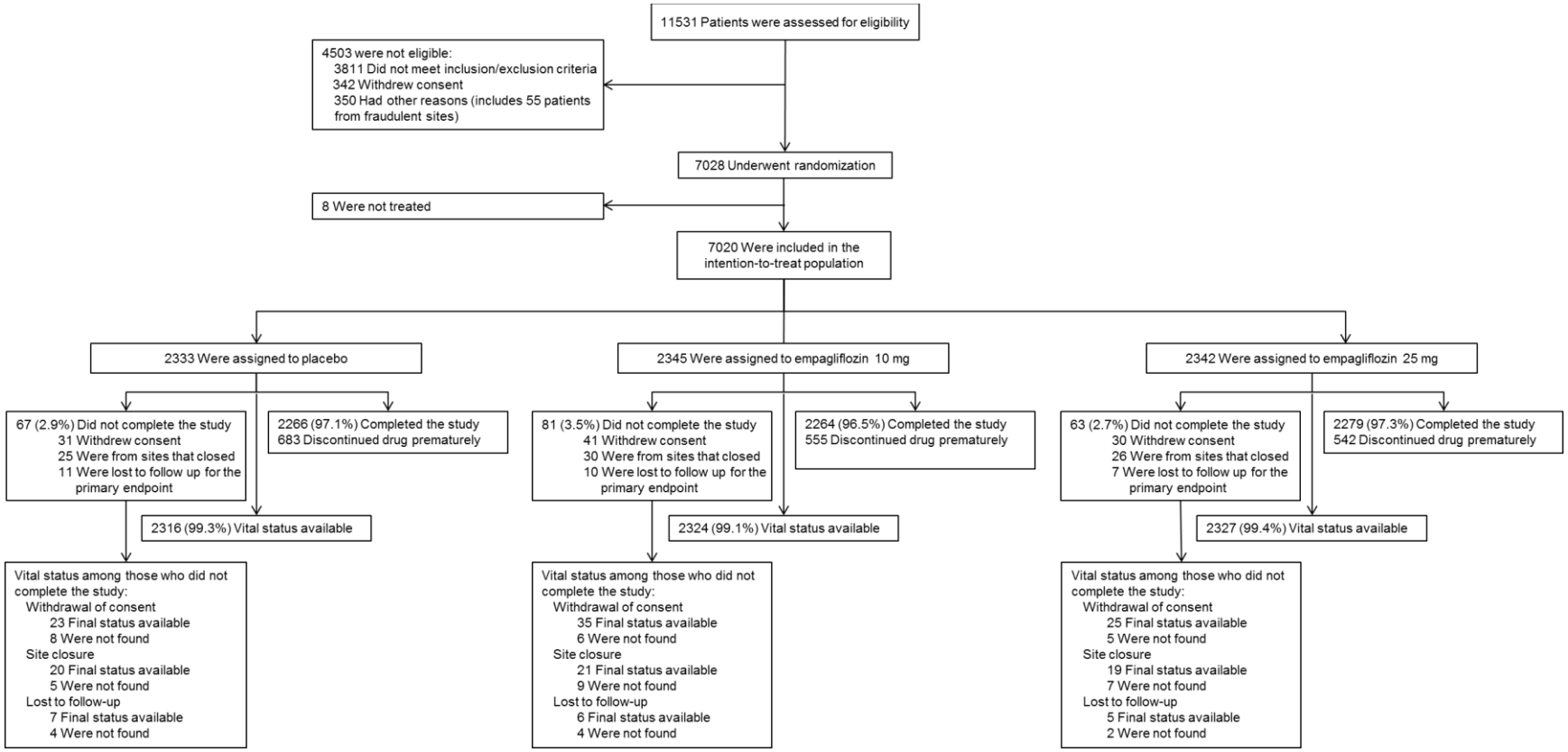
Section F. Sensitivity analyses and subgroup analyses (methodology)

Sensitivity analyses were conducted in patients who received ≥1 dose of study drug including only events observed ≤30 days after a patient's last intake of trial medication, in patients who received study drug for ≥30 days (cumulative) including only events that occurred ≤30 days after a patient's last intake of trial medication (on treatment set), and in patients treated with ≥1 dose of study drug who did not have important protocol violations (per-protocol set; for primary outcome only).

Subgroup analyses were performed in subgroups by baseline age, sex, race, ethnicity, region, glycated hemoglobin, body mass index, blood pressure control, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease equation, urine albumin-to-creatinine ratio, cardiovascular risk factors, use of glucose-lowering medication, use of statins/ezetimibe, use of anti-hypertensive therapy, and use of acetylsalicylic acid.

Section G. Patient disposition

Figure S1. Patient disposition.



Section H. Reasons for premature discontinuation from study medication

Table S1. Reasons for premature discontinuation from study medication

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Pooled empagliflozin
	no. (%)			
Treated	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)
Prematurely discontinued from trial medication	683 (29.3)	555 (23.7)	542 (23.1)	1097 (23.4)
Adverse event	303 (13.0)	267 (11.4)	273 (11.7)	540 (11.5)
Refusal to continue, not due to adverse event	172 (7.4)	118 (5.0)	122 (5.2)	240 (5.1)
Non-compliant with protocol	15 (0.6)	15 (0.6)	12 (0.5)	27 (0.6)
Lost to follow up	15 (0.6)	9 (0.4)	6 (0.3)	15 (0.3)
Lack of efficacy*	11 (0.5)	1 (<0.1)	0	1 (<0.1)
Other	162 (6.9)	142 (6.1)	125 (5.3)	267 (5.7)
Missing	5 (0.2)	3 (0.1)	4 (0.2)	7 (0.1)

*Hyperglycemia above the protocol-defined level despite intensification or addition of glucose-lowering therapy.

Section I. Baseline characteristics

Table S2. Baseline characteristics

Characteristic*	Placebo (N = 2333)	Empagliflozin 10 mg (N = 2345)	Empagliflozin 25 mg (N = 2342)	Pooled empagliflozin (N = 4687)
Age – years	63.2 ± 8.8	63.0 ± 8.6)	63.2 ± 8.6)	63.1 ± 8.6
Male – no. (%)	1680 (72.0)	1653 (70.5)	1683 (71.9)	3336 (71.2)
Race – no. (%)				
White	1678 (71.9)	1707 (72.8)	1696 (72.4)	3403 (72.6)
Asian	511 (21.9)	505 (21.5)	501 (21.4)	1006 (21.5)
Black/African-American	120 (5.1)	119 (5.1)	118 (5.0)	237 (5.1)
Other/Missing	24 (1.0)	14 (0.6)	27 (1.2)	41 (0.9)
Ethnicity – no. (%)				
Not Hispanic or Latino	1912 (82.0)	1909 (81.4)	1926 (82.2)	3835 (81.8)
Hispanic or Latino	418 (17.9)	432 (18.4)	415 (17.7)	847 (18.1)
Missing	3 (0.1)	4 (0.2)	1 (<0.1)	5 (0.1)
Region – no. (%)				
Europe	959 (41.1)	966 (41.2)	960 (41.0)	1926 (41.1)
North America (plus Australia and New Zealand)	462 (19.8)	466 (19.9)	466 (19.9)	932 (19.9)
Asia	450 (19.3)	447 (19.1)	450 (19.2)	897 (19.1)
Latin America	360 (15.4)	359 (15.3)	362 (15.5)	721 (15.4)
Africa	102 (4.4)	107 (4.6)	104 (4.4)	211 (4.5)
Weight – kg	86.6 ± 19.1	85.9 ± 18.8	86.5 ± 19.0	86.2 ± 18.9
Body mass index – kg/m^2†	30.7 ± 5.2	30.6 ± 5.2	30.6 ± 5.3	30.6 ± 5.3
CV risk factor – no. (%)	2307 (98.9)	2333 (99.5)	2324 (99.2)	4657 (99.4)
Coronary artery disease	1763 (75.6)	1782 (76.0)	1763 (75.3)	3545 (75.6)
Multi-vessel coronary artery disease	1100 (47.1)	1078 (46.0)	1101 (47.0)	2179 (46.5)
History of myocardial infarction	1083 (46.4)	1107 (47.2)	1083 (46.2)	2190 (46.7)
Coronary artery bypass graft	563 (24.1)	594 (25.3)	581 (24.8)	1175 (25.1)
History of stroke‡	553 (23.7)	535 (22.8)	549 (23.4)	1084 (23.1)
Peripheral artery disease	479 (20.5)	465 (19.8)	517 (22.1)	982 (21.0)
Single vessel coronary artery disease‡	238 (10.2)	258 (11.0)	240 (10.2)	498 (10.6)
Cardiac failure§	244 (10.5)	240 (10.2)	222 (9.5)	462 (9.9)
Glycated hemoglobin – %¶	8.08 ± 0.84	8.07 ± 0.86	8.06 ± 0.84	8.07 ± 0.85
Time since diagnosis of type 2 diabetes – no. (%)				

≤1 years	52 (2.2)	68 (2.9)	60 (2.6)	128 (2.7)
>1 to 5 years	371 (15.9)	338 (14.4)	374 (16.0)	712 (15.2)
>5 to 10 years	571 (24.5)	585 (24.9)	590 (25.2)	1175 (25.1)
>10 years	1339 (57.4)	1354 (57.7)	1318 (56.3)	2672 (57.0)
Glucose-lowering therapy – no. (%)				
Medication taken alone or in combination				
Metformin	1734 (74.3)	1729 (73.7)	1730 (73.9)	3459 (73.8)
Insulin	1135 (48.6)	1132 (48.3)	1120 (47.8)	2252 (48.0)
Median daily dose – IU[‖]	52.0	52.5	54.0	54.0
Sulfonylurea	992 (42.5)	985 (42.0)	1029 (43.9)	2014 (43.0)
Dipeptidyl peptidase-4 inhibitor	267 (11.4)	282 (12.0)	247 (10.5)	529 (11.3)
Thiazolidinedione	101 (4.3)	96 (4.1)	102 (4.4)	198 (4.2)
Glucagon-like peptide-1 agonist	70 (3.0)	68 (2.9)	58 (2.5)	126 (2.7)
Monotherapy	691 (29.6)	704 (30.0)	676 (28.9)	1380 (29.4)
Dual therapy	1148 (49.2)	1110 (47.3)	1149 (49.1)	2259 (48.2)
Anti-hypertensive therapy – no. (%)	2221 (95.2)	2227 (95.0)	2219 (94.7)	4446 (94.9)
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	1868 (80.1)	1896 (80.9)	1902 (81.2)	3798 (81.0)
Beta-blockers	1498 (64.2)	1530 (65.2)	1526 (65.2)	3056 (65.2)
Diuretics	988 (42.3)	1036 (44.2)	1011 (43.2)	2047 (43.7)
Calcium channel blockers	788 (33.8)	781 (33.3)	748 (31.9)	1529 (32.6)
Mineralocorticoid receptor antagonists	136 (5.8)	157 (6.7)	148 (6.3)	305 (6.5)
Renin inhibitors	19 (0.8)	16 (0.7)	11 (0.5)	27 (0.6)
Other	191 (8.2)	193 (8.2)	190 (8.1)	383 (8.2)
Lipid-lowering therapy – no. (%)	1864 (79.9)	1926 (82.1)	1894 (80.9)	3820 (81.5)
Statins	1773 (76.0)	1827 (77.9)	1803 (77.0)	3630 (77.4)
Fibrates	199 (8.5)	214 (9.1)	217 (9.3)	431 (9.2)
Ezetimibe	81 (3.5)	95 (4.1)	94 (4.0)	189 (4.0)
Niacin	35 (1.5)	56 (2.4)	35 (1.5)	91 (1.9)
Other	175 (7.5)	172 (7.3)	193 (8.2)	365 (7.8)
Anti-coagulants – no. (%)	2090 (89.6)	2098 (89.5)	2064 (88.1)	4162 (88.8)
Acetylsalicylic acid	1927 (82.6)	1939 (82.7)	1937 (82.7)	3876 (82.7)

Clopidogrel	249 (10.7)	253 (10.8)	241 (10.3)	494 (10.5)
Vitamin K antagonists	156 (6.7)	141 (6.0)	125 (5.3)	266 (5.7)
Systolic blood pressure – mmHg	135.8 ± 17.2	134.9 ± 16.8	135.6 ± 17.0	135.3 ± 16.9
Diastolic blood pressure – mmHg	76.8 ± 10.1	76.6 ± 9.8	76.6 ± 9.7	76.6 ± 9.7
Total cholesterol – mg/dL**	161.9 ± 43.1	163.7 ± 45.2	163.3 ± 43.2	163.5 ± 44.2
Low density lipoprotein cholesterol – mg/dL††	84.9 ± 35.3	86.3 ± 36.7	85.5 ± 35.2	85.9 ± 36.0
High density lipoprotein cholesterol – mg/dL**	44.0 ± 11.3	44.7 ± 12.0	44.5 ± 11.8	44.6 ± 11.9
Triglycerides – mg/dL**	170.7 ± 121.2	168.4 ± 127.3	172.6 ± 132.0	170.5 ± 129.7
Estimated glomerular filtration rate – mL/min/1.73m^2‡‡	73.8 ± 21.1	74.3 ± 21.8	74.0 ± 21.4	74.2 ± 21.6
Estimated glomerular filtration rate – no. (%)‡‡				
≥90 mL/min/1.73m^2	488 (20.9)	519 (22.1)	531 (22.7)	1050 (22.4)
60 to <90 mL/min/1.73m^2	1238 (53.1)	1221 (52.1)	1202 (51.3)	2423 (51.7)
<60 mL/min/1.73m^2	607 (26.0)	605 (25.8)	607 (25.9)	1212 (25.9)
Urine albumin-to-creatinine ratio – no. (%)§§				
<30 mg/g	1382 (59.2)	1405 (59.9)	1384 (59.1)	2789 (59.5)
30 to 300 mg/g	675 (28.9)	645 (27.5)	693 (29.6)	1338 (28.5)
>300 mg/g	260 (11.1)	261 (11.1)	248 (10.6)	509 (10.9)

* Plus–minus values are means ± SD.

† Body mass index is the weight in kilograms divided by the square of the height in meters.

‡ Information was not available for one patient in the placebo group.

§ Based on the narrow standard MedDRA query 'cardiac failure'.

¶ Data were available for 2333 patients in the placebo group, 2344 patients in the empagliflozin 10 mg group, 2341 patients in the empagliflozin 25 mg group.

‖ Data were not available for 18 patients in the placebo group, 10 patients in the empagliflozin 10 mg group and 14 patients in the empagliflozin 25 mg group.

** Data were available for 2309 patients in the placebo group, 2318 patients in the empagliflozin 10 mg group, 2308 patients in the empagliflozin 25 mg group. Conversion factor: 1 mg/dL = 0.02586 mmol/L for cholesterol and 1 mg/dL = 0.01129 mmol/L for triglycerides.

†† Data were available for 2309 patients in the placebo group, 2317 patients in the empagliflozin 10 mg group, 2306 patients in the empagliflozin 25 mg group. 1 mg/dL = 0.02586 mmol/L.

‡‡ Data were not available for 2 patients in the empagliflozin 25 mg group. The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease formula.

§§ Data were not available for 16 patients in the placebo group, 34 patients in the empagliflozin 10 mg group, 17 patients in the empagliflozin 25 mg group.

There were no significant differences ($p<0.05$) between pooled empagliflozin and placebo based on Chi-square test for binary/categorical variables, t-test for continuous variables, and Wilcoxon rank sum test for insulin dose.

Section J. Treatment and observation times

Table S3. Treatment and observation times

	Placebo (N = 2333)	**Pooled empagliflozin (N = 4687)**
Treatment – years		
Median (interquartile range)	2.6 (1.8–3.4)	2.6 (2.0–3.4)
Mean	2.5	2.6
Observation – years		
Median (interquartile range)	3.1 (2.2–3.5)	3.2 (2.2–3.6)
Mean	2.9	3.0

Section K. Absolute reductions in incidence rates for cardiovascular outcomes.

Table S4. Absolute reductions in incidence rates for 3-point MACE, all-cause mortality, cardiovascular death, hospitalization for heart failure and heart failure hospitalization or cardiovascular death.

	Placebo (N = 2333)	**Empagliflozin (N = 4687)**	**Rate difference (95% CI)**	**p-value**
	Rate/1000 patient-years	***Rate/1000 patient-years***		
Cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (3-point MACE): primary outcome	43.9	37.4	-6.5 (-12.6, -0.4)	0.04
All-cause mortality	28.6	19.4	-9.1 (-13.8, -4.5)	<0.001
Cardiovascular death	20.2	12.4	-7.7 (-11.6, -3.9)	<0.001
Hospitalization for heart failure	14.5	9.4	-5.1 (-8.4, -1.8)	0.003
Heart failure hospitalization or cardiovascular death (excluding fatal stroke)	30.1	19.7	-10.5 (-15.3, -5.6)	<0.001

Section L. Categories of cardiovascular death

Table S5. Categories of cardiovascular death.

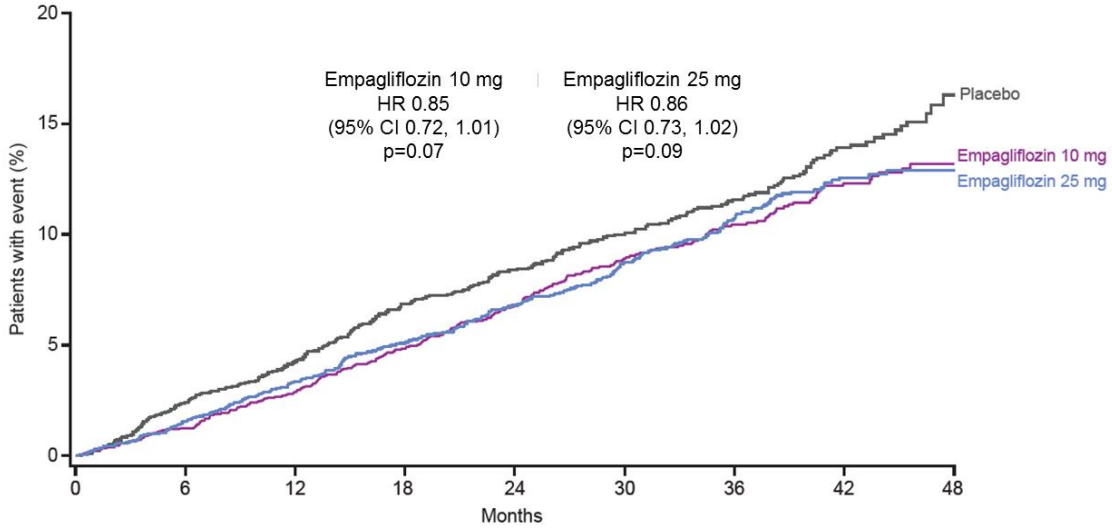
	Placebo (N = 2333)	**Empagliflozin 10 mg (N = 2345)**	**Empagliflozin 25 mg (N = 2342)**	**Pooled empagliflozin (N = 4687)**
	no. (%)			
Patients with cardiovascular death	137 (5.9)	90 (3.8)	82 (3.5)	172 (3.7)
Sudden death	38 (1.6)	30 (1.3)	23 (1.0)	53 (1.1)
Worsening of heart failure	19 (0.8)	7 (0.3)	4 (0.2)	11 (0.2)
Acute myocardial infarction	11 (0.5)	6 (0.3)	9 (0.4)	15 (0.3)
Stroke	11 (0.5)	9 (0.4)	7 (0.3)	16 (0.3)
Cardiogenic shock	3 (0.1)	1 (<0.1)	2 (0.1)	3 (0.1)
Other cardiovascular death*	55 (2.4)	37 (1.6)	37 (1.6)	74 (1.6)

*Includes fatal cases that were not assessable due to a lack of information and were presumed to be cardiovascular deaths as per conventional definition.

Section M. Cardiovascular outcomes with empagliflozin 10 mg and 25 mg

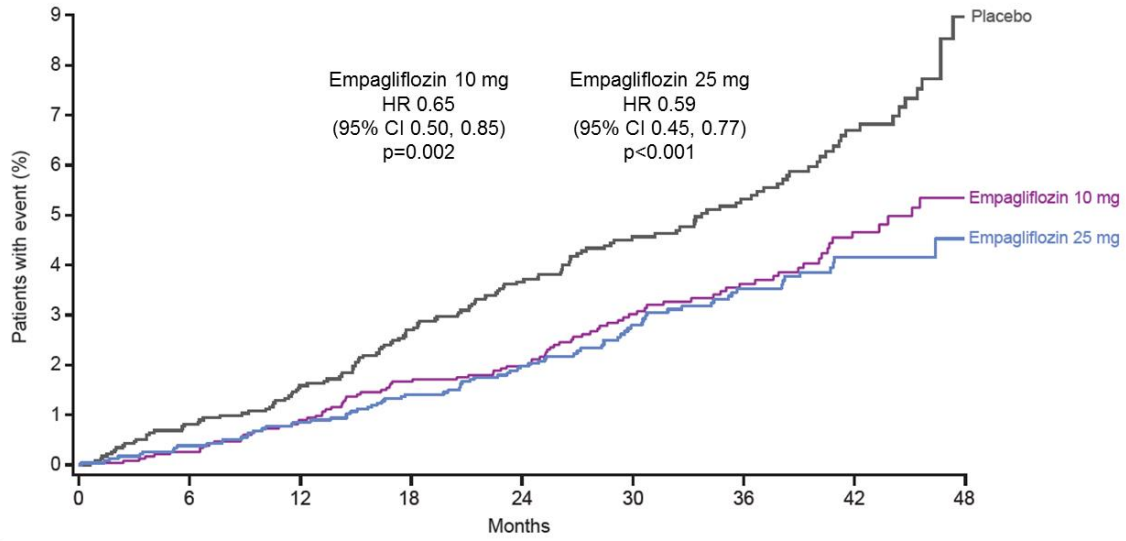
Figure S2. Time to first occurrence of cardiovascular outcomes and all-cause mortality. Cumulative incidence function for the primary outcome (Panel A), cumulative incidence function for cardiovascular death (Panel B), Kaplan-Meier estimate for all-cause mortality (Panel C) and cumulative incidence function for hospitalization for heart failure (Panel D) in the empagliflozin and placebo groups based on patients treated with ≥1 dose of study drug. Hazard ratios are based on Cox regression analyses.

A. Primary outcome (3-point MACE)



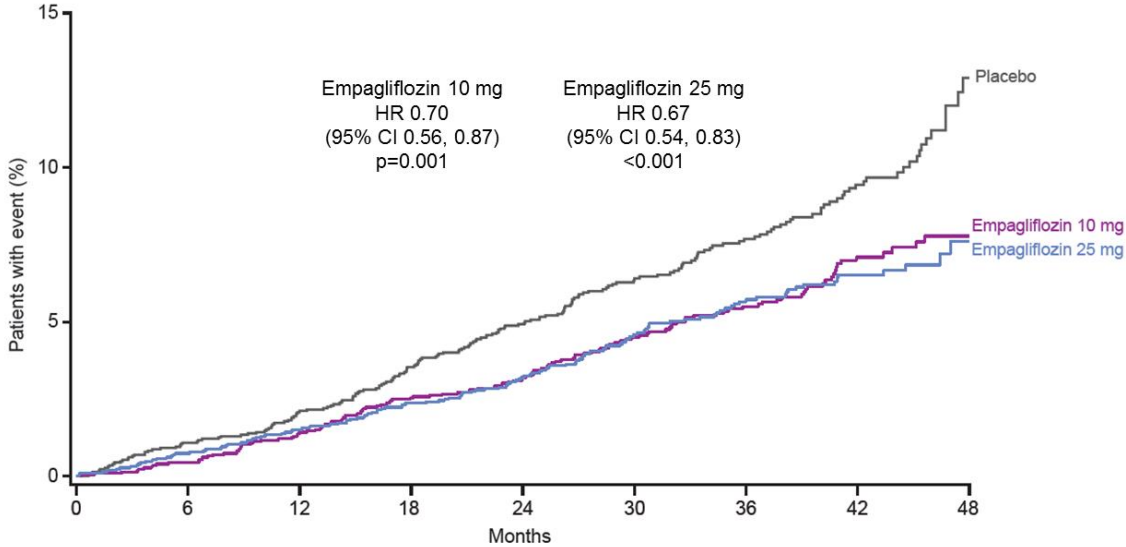
No. of patients									
Empagliflozin 10 mg	2345	2292	2233	2167	1918	1415	1177	753	178
Empagliflozin 25 mg	2342	2288	2222	2161	1933	1406	1182	781	192
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

B. Cardiovascular death



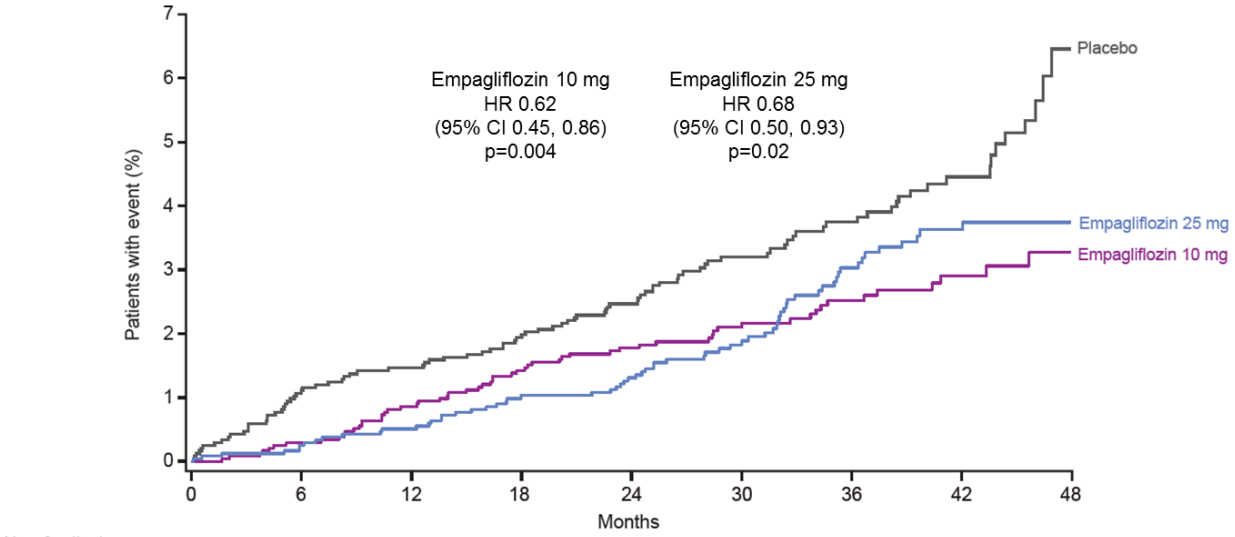
No. of patients									
Empagliflozin 10 mg	2345	2327	2305	2274	2055	1542	1303	847	201
Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

C. All-cause mortality



No. of patients									
Empagliflozin 10 mg	2345	2327	2305	2274	2055	1542	1303	847	201
Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

D. Hospitalization for heart failure



No. of patients									
Empagliflozin 10 mg	2345	2306	2256	2204	1981	1473	1240	804	188
Empagliflozin 25 mg	2342	2308	2267	2223	2007	1477	1247	830	207
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Table S6. Cardiovascular outcomes with empagliflozin 10 mg and empagliflozin 25 mg

	Placebo (N = 2333)	**Empagliflozin 10 mg (N = 2345)**	**Empagliflozin 25 mg (N = 2342)**
	no. (%)		
Cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (3-point MACE): primary outcome	282 (12.1)	243 (10.4)	247 (10.5)
Hazard ratio (95% CI)		0.85 (0.72, 1.01)	0.86 (0.73, 1.02)
p-value		0.07	0.09
Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina (4-point MACE): key secondary outcome	333 (14.3)	300 (12.8)	299 (12.8)
Hazard ratio (95% CI)		0.89 (0.76, 1.04)	0.88 (0.76, 1.03)
p-value		0.15	0.12
Cardiovascular death	137 (5.9)	90 (3.8)	82 (3.5)
Hazard ratio (95% CI)		0.65 (0.50, 0.85)	0.59 (0.45, 0.77)
p-value		0.002	<0.001
All-cause mortality	194 (8.3)	137 (5.8)	132 (5.6)
Hazard ratio (95% CI)		0.70 (0.56, 0.87)	0.67 (0.54, 0.83)
p-value		0.001	<0.001
Fatal and non-fatal myocardial infarction (excluding silent myocardial infarction)	126 (5.4)	101 (4.3)	122 (5.2)
Hazard ratio (95% CI)		0.79 (0.61, 1.03)	0.95 (0.74, 1.22)
p-value		0.09	0.71
Silent myocardial infarction*	15 (1.2)	19 (1.6)	19 (1.6)
Hazard ratio (95% CI)		1.32 (0.67, 2.60)	1.24 (0.63, 2.45)
p-value		0.42	0.53
Non-fatal myocardial infarction	121 (5.2)	96 (4.1)	117 (5.0)
Hazard ratio (95% CI)		0.79 (0.60,1.03)	0.95 (0.74,1.23)
p-value		0.08	0.71
Hospitalization for unstable angina	66 (2.8)	69 (2.9)	64 (2.7)
Hazard ratio (95% CI)		1.03 (0.74, 1.45)	0.96 (0.68, 1.35)
p-value		0.85	0.80
Coronary revascularization procedure	186 (8.0)	154 (6.6)	175 (7.5)

Hazard ratio (95% CI)		0.81 (0.65, 1.00)	0.92 (0.75, 1.13)
p-value		0.05	0.42
Fatal and non-fatal stroke	69 (3.0)	85 (3.6)	79 (3.4)
Hazard ratio (95% CI)		1.22 (0.89, 1.68)	1.13 (0.82, 1.56)
p-value		0.21	0.46
Non-fatal stroke	60 (2.6)	77 (3.3)	73 (3.1)
Hazard ratio (95% CI)		1.27 (0.91, 1.79)	1.20 (0.85, 1.69)
p-value		0.16	0.30
Transient ischemic attack	23 (1.0)	19 (0.8)	20 (0.9)
Hazard ratio (95% CI)		0.83 (0.45, 1.53)	0.87 (0.48, 1.58)
p-value		0.56	0.64
Hospitalization for heart failure	95 (4.1)	60 (2.6)	66 (2.8)
Hazard ratio (95% CI)		0.62 (0.45, 0.86)	0.68 (0.50, 0.93)
p-value		0.004	0.02
Heart failure hospitalization or cardiovascular death (excluding fatal stroke)	198 (8.5)	133 (5.7)	132 (5.6)
Hazard ratio (95% CI)		0.66 (0.53, 0.83)	0.65 (0.52, 0.81)
p-value		<0.001	<0.001

Based on Cox regression analyses in patients treated with ≥1 dose of study drug.

* Analyzed in 1211 patients in the placebo group, 1174 patients in the empagliflozin 10 mg group and 1204 patients in the empagliflozin 25 mg group.

Section N. Subgroup analyses for the primary outcome and for cardiovascular death

Table S7. Hazard ratios for the primary outcome in subgroups.

	Patients with event/ patients analyzed		Hazard ratio	(95% CI)	p-value for interaction
	Empagliflozin	**Placebo**			
All patients	490/4687	282/2333	0.86	(0.74, 0.99)	
Age					0.01
<65 years	251/2596	121/1297	1.04	(0.84, 1.29)	
≥65 years	239/2091	161/1036	0.71	(0.59, 0.87)	
Sex					0.81
Male	367/3336	212/1680	0.87	(0.73, 1.02)	
Female	123/1351	70/653	0.83	(0.62, 1.11)	
Race					0.09
White	366/3403	205/1678	0.88	(0.74, 1.04)	
Asian	79/1006	58/511	0.68	(0.48, 0.95)	
Black/African-American	39/237	14/120	1.48	(0.80, 2.72)	
Ethnicity					0.07
Hispanic/Latino	70/847	52/418	0.63	(0.44, 0.90)	
Not Hispanic/Latino	420/3835	230/1912	0.91	(0.77, 1.07)	
Region					0.13
Europe	226/1926	112/959	1.02	(0.81, 1.28)	
North America	114/932	63/462	0.89	(0.65, 1.21)	
Latin America	53/721	43/360	0.58	(0.39, 0.86)	
Africa	26/211	14/102	0.86	(0.45, 1.65)	
Asia	71/897	50/450	0.70	(0.49, 1.01)	
Glycated hemoglobin					0.01
<8.5%	322/3212	209/1607	0.76	(0.64, 0.90)	
≥8.5%	168/1475	73/726	1.14	(0.86, 1.50)	
Body mass index					0.06
<30 kg/m^2	225/2279	148/1120	0.74	(0.60, 0.91)	
≥30 kg/m^2	265/2408	134/1213	0.98	(0.80, 1.21)	
Blood pressure control					0.65
SBP ≥140 mmHg and/or DBP ≥90 mmHg	214/1780	131/934	0.83	(0.66, 1.03)	
SBP <140 mmHg and DBP <90 mmHg	276/2907	151/1399	0.89	(0.73, 1.08)	
Estimated glomerular filtration rate					0.20
≥90 mL/min/1.73m^2	102/1050	44/488	1.10	(0.77, 1.57)	
60 to <90 mL/min/1.73m^2	212/2425	139/1238	0.76	(0.61, 0.94)	
<60 mL/min/1.73m^2	176/1212	99/607	0.88	(0.69, 1.13)	
Urine albumin-to-creatinine ratio					0.40
<30 mg/g	241/2789	134/1382	0.89	(0.72, 1.10)	
30 to 300 mg/g	158/1338	90/675	0.89	(0.69, 1.16)	
>300 mg/g	86/509	58/260	0.69	(0.49, 0.96)	
Cardiovascular risk					0.53
Only cerebrovascular disease	65/635	29/325	1.15	(0.74, 1.78)	

Only coronary artery disease	261/2732	152/1340	0.83	(0.68, 1.02)	
Only peripheral artery disease	25/412	12/191	0.94	(0.47, 1.88)	
2 or 3 high cardiovascular risk categories	137/878	87/451	0.79	(0.61, 1.04)	
Metformin					0.14
No	146/1228	93/599	0.72	(0.56, 0.94)	
Yes	344/3459	189/1734	0.92	(0.77, 1.10)	
Sulfonylurea					0.83
No	295/2673	173/1341	0.85	(0.70, 1.02)	
Yes	195/2014	109/992	0.87	(0.69, 1.11)	
Insulin					0.28
No	225/2435	140/1198	0.79	(0.64, 0.97)	
Yes	265/2252	142/1135	0.93	(0.75, 1.13)	
Thiazolidinediones					0.44
No	467/4489	271/2232	0.85	(0.73, 0.98)	
Yes	23/198	11/101	1.13	(0.55, 2.31)	
DPP-4 inhibitor					0.06
No	423/4158	254/2066	0.81	(0.70, 0.95)	
Yes	67/529	28/267	1.27	(0.82, 1.98)	
Statins/ezetimibe					0.54
No	106/1029	71/551	0.79	(0.59, 1.07)	
Yes	384/3658	211/1782	0.88	(0.74, 1.04)	
Antihypertensives					0.80
No	21/241	11/112	0.94	(0.45, 1.95)	
Yes	469/4446	271/2221	0.85	(0.73, 0.99)	
Angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers					0.49
No	91/889	61/465	0.77	(0.56, 1.07)	
Yes	399/3798	221/1868	0.88	(0.75, 1.04)	
Calcium channel blockers					0.71
No	321/3158	179/1545	0.87	(0.73, 1.05)	
Yes	169/1529	103/788	0.83	(0.65, 1.06)	
Beta blockers					0.61
No	159/1631	90/835	0.90	(0.70, 1.17)	
Yes	331/3056	192/1498	0.83	(0.70, 1.00)	
Diuretics					0.72
No	228/2640	138/1345	0.83	(0.67, 1.02)	
Yes	262/2047	144/988	0.88	(0.71, 1.07)	
Acetylsalicylic acid					0.66
No	88/811	53/406	0.80	(0.57, 1.12)	
Yes	402/3876	229/1927	0.87	(0.74, 1.02)	

Cox regression analysis in patients treated with ≥1 dose of study drug. Subgroup factors were pre-specified for the primary outcome.
p-value is for test of homogeneity of the treatment group difference among subgroups (test for group by covariate interaction) with no adjustment for multiple tests.

Table S8. Hazard ratios for cardiovascular death in subgroups.

	Patients with event/ patients analyzed		Hazard ratio	(95% CI)	p-value for interaction
	Empagliflozin	**Placebo**			
All patients	172/4687	137/2333	0.62	(0.49, 0.77)	
Age					0.21
<65 years	85/2596	59/1297	0.72	(0.52, 1.01)	
≥65 years	87/2091	78/1036	0.54	(0.40, 0.73)	
Sex					0.32
Male	125/3336	107/1680	0.58	(0.45, 0.75)	
Female	47/1351	30/653	0.76	(0.48, 1.20)	
Race					
White	134/3403	102/1678	0.64	(0.50, 0.83)	0.43
Asian	22/1006	25/511	0.44	(0.25, 0.78)	
Black/African-American	13/237	9/120	0.77	(0.33, 1.79)	
Ethnicity					0.49
Hispanic/Latino	31/847	28/418	0.53	(0.32, 0.88)	
Not Hispanic/Latino	141/3835	109/1912	0.64	(0.50, 0.83)	
Region					0.15
Europe	80/1926	56/959	0.72	(0.51, 1.01)	
North America plus Australia and New Zealand	40/932	25/462	0.81	(0.49, 1.33)	
Latin America	22/721	24/360	0.43	(0.24, 0.77)	
Africa	12/211	7/102	0.80	(0.31, 2.03)	
Asia	18/897	25/450	0.35	(0.19, 0.65)	
Glycated hemoglobin					0.51
<8.5%	114/3212	96/1607	0.59	(0.45, 0.77)	
≥8.5%	58/1475	41/726	0.69	(0.46, 1.03)	
Body mass index					0.05
<30 kg/m^2	80/2279	78/1120	0.50	(0.37, 0.68)	
≥30 kg/m^2	92/2408	59/1213	0.78	(0.56, 1.08)	
Blood pressure control					0.44
SBP ≥140 mmHg and/or DBP ≥90 mmHg	72/1780	65/934	0.56	(0.40, 0.79)	
SBP <140 mmHg and DBP <90 mmHg	100/2907	72/1399	0.67	(0.50, 0.91)	
Estimated glomerular filtration rate					0.15
≥90 mL/min/1.73m^2	28/1050	19/488	0.70	(0.39, 1.25)	
60 to <90 mL/min/1.73m^2	69/2425	70/1238	0.49	(0.35, 0.68)	
<60 mL/min/1.73m^2	75/1212	48/607	0.78	(0.54, 1.12)	
Urine albumin-to-creatinine ratio					0.22
<30 mg/g	81/2789	52/1382	0.77	(0.55, 1.10)	
≥30 to 300 mg/g	48/1338	49/675	0.49	(0.33, 0.74)	
>300 mg/g	42/509	36/260	0.55	(0.35, 0.86)	
Cardiovascular risk					0.39
Only cerebrovascular disease	21/635	15/325	0.72	(0.37, 1.39)	
Only coronary artery disease	90/2732	63/1340	0.69	(0.50, 0.95)	
Only peripheral artery	13/412	7/191	0.85	(0.34, 2.13)	

disease					
2 or 3 high cardiovascular risk categories	46/878	50/451	0.47	(0.31, 0.70)	
Metformin					0.07
No	54/1228	53/599	0.46	(0.32, 0.68)	
Yes	118/3459	84/1734	0.71	(0.54, 0.94)	
Sulfonylurea					0.85
No	105/2673	86/1341	0.61	(0.46, 0.81)	
Yes	67/2014	51/992	0.64	(0.44, 0.92)	
Insulin					0.92
No	79/2435	63/1198	0.61	(0.44, 0.85)	
Yes	93/2252	74/1135	0.63	(0.46, 0.85)	
Thiazolidinediones*					
No	165/4489	131/2232	NC	NC	–
Yes	7/198	6/101	NC	NC	–
DPP-4 inhibitor					
No	156/4158	130/2066	0.59	(0.46, 0.74)	0.11
Yes	16/529	7/267	1.23	(0.51, 2.99)	
Statins/ezetimibe					0.23
No	41/1029	43/551	0.50	(0.32, 0.76)	
Yes	131/3658	94/1782	0.68	(0.52, 0.88)	
Antihypertensives					0.41
No	10/241	5/112	0.97	(0.33, 2.83)	
Yes	162/4446	132/2221	0.61	(0.48, 0.76)	
Angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers					0.86
No	35/889	28/465	0.65	(0.39, 1.06)	
Yes	137/3798	109/1868	0.61	(0.48, 0.79)	
Calcium channel blockers					0.29
No	120/3158	87/1545	0.67	(0.51, 0.89)	
Yes	52/1529	50/788	0.52	(0.35, 0.77)	
Beta blockers					0.99
No	61/1631	49/835	0.62	(0.43, 0.90)	
Yes	111/3056	88/1498	0.62	(0.47, 0.82)	
Diuretics					0.46
No	76/2640	57/1345	0.68	(0.48, 0.95)	
Yes	96/2047	80/988	0.57	(0.42, 0.77)	
Acetylsalicylic acid					0.99
No	40/811	31/406	0.62	(0.39, 0.99)	
Yes	132/3876	106/1927	0.62	(0.48, 0.80)	

Cox regression analysis in patients treated with ≥1 dose of study drug. Subgroup analyses of cardiovascular death were conducted post-hoc.

*Hazard ratio and 95% CI were not analyzed as the total number of patients with an event was <14 in one subgroup.

p-value is for homogeneity of the treatment group difference among subgroups (test for group by covariate interaction) with no adjustment for multiple tests. p=0.054 for body mass index.

Section O. Sensitivity analyses

Table S9. Sensitivity analyses of the primary outcome

	Placebo	Empagliflozin
Cardiovascular death, non-fatal myocardial infarction (excluding silent myocardial infarction), or non-fatal stroke (3-point MACE): primary outcome		
Patients who received ≥1 dose of study drug including only events observed ≤30 days after a patient's last intake of trial medication		
N	2333	4687
Patients with events – no. (%)	229 (9.8)	412 (8.8)
Rate/1000 patient-years	39.8	34.4
Hazard ratio (95% CI)		0.87 (0.74, 1.02)
p-value		0.09
Patients who received study drug for ≥30 days (cumulative) including only events that occurred ≤30 days after a patient's last intake of trial medication (on treatment set)		
N	2308	4607
Patients with events – no. (%)	227 (9.8)	407 (8.8)
Rate/1000 patient-years	39.5	34.1
Hazard ratio (95% CI)		0.87 (0.74, 1.02)
p-value		0.08
Patients treated with ≥1 dose of study drug who did not have important protocol violations (per-protocol set)		
N	2316	4654
Patients with events – no. (%)	278 (12.0)	487 (10.5)
Rate/1000 patient-years	43.4	37.4
Hazard ratio (95% CI)		0.86 (0.75, 1.00)
p-value		0.05

Cox regression analysis.

Table S10. Sensitivity analyses of cardiovascular death, myocardial infarction and stroke

	Placebo	**Empagliflozin**
Cardiovascular death		
Patients who received ≥1 dose of study drug including only events observed ≤30 days after a patient's last intake of trial medication*		
N	2333	4687
Patients with events – no. (%)	92 (3.9)	114 (2.4)
Rate/1000 patient-years	15.5	9.2
Hazard ratio (95% CI)		0.59 (0.45, 0.78)
p-value		<0.001
Patients who received study drug for ≥30 days (cumulative) including only events that occurred ≤30 days after a patient's last intake of trial medication (on treatment set)		
N	2308	4607
Patients with events – no. (%)	90 (3.9)	112 (2.4)
Rate/1000 patient-years	15.2	9.1
Hazard ratio (95% CI)		0.60 (0.45, 0.79)
p-value		<0.001
Non-fatal myocardial infarction		
Patients who received ≥1 dose of study drug including only events observed ≤30 days after a patient's last intake of trial medication*		
N	2333	4687
Patients with events – no. (%)	103 (4.4)	193 (4.1)
Rate/1000 patient-years	17.7	15.9
Hazard ratio (95% CI)		0.90 (0.71, 1.15)
p-value		0.40
Patients who received study drug for ≥30 days (cumulative) including only events that occurred ≤30 days after a patient's last intake of trial medication (on treatment set)		
N	2308	4607
Patients with events – no. (%)	102 (4.4)	192 (4.2)
Rate/1000 patient-years	17.5	15.9
Hazard ratio (95% CI)		0.91 (0.71, 1.15)
p-value		0.43
Fatal and non-fatal myocardial infarction		
Patients who received ≥1 dose of study drug including only events observed ≤30 days after a		

patient's last intake of trial medication*		
N	2333	4687
Patients with events – no. (%)	108 (4.6)	202 (4.3)
Rate/1000 patient-years	18.6	16.7
Hazard ratio (95% CI)		0.90 (0.71, 1.14)
p-value		0.39
Patients who received study drug for ≥30 days (cumulative) including only events that occurred ≤30 days after a patient's last intake of trial medication (on treatment set)		
N	2308	4607
Patients with events – no. (%)	107 (4.6)	200 (4.3)
Rate/1000 patient-years	18.4	16.5
Hazard ratio (95% CI)		0.90 (0.71, 1.14)
p-value		0.39
Non-fatal stroke		
Patients who received ≥1 dose of study drug including only events observed ≤30 days after a patient's last intake of trial medication*		
N	2333	4687
Patients with events – no. (%)	58 (2.5)	133 (2.8)
Rate/1000 patient-years	9.9	10.9
Hazard ratio (95% CI)		1.12 (0.82, 1.52)
p-value		0.48
Patients who received study drug for ≥30 days (cumulative) including only events that occurred ≤30 days after a patient's last intake of trial medication (on treatment set)		
N	2308	4607
Patients with events – no. (%)	58 (2.5)	131 (2.8)
Rate/1000 patient-years	9.9	10.8
Hazard ratio (95% CI)		1.10 (0.81, 1.50)
p-value		0.54
Fatal and non-fatal stroke		
Patients who received ≥1 dose of study drug including only events observed ≤30 days after a patient's last intake of trial medication*		
N	2333	4687
Patients with events – no. (%)	66 (2.8)	143 (3.1)
Rate/1000 patient-years	11.3	11.7
Hazard ratio (95% CI)		1.06 (0.79, 1.41)
p-value		0.71

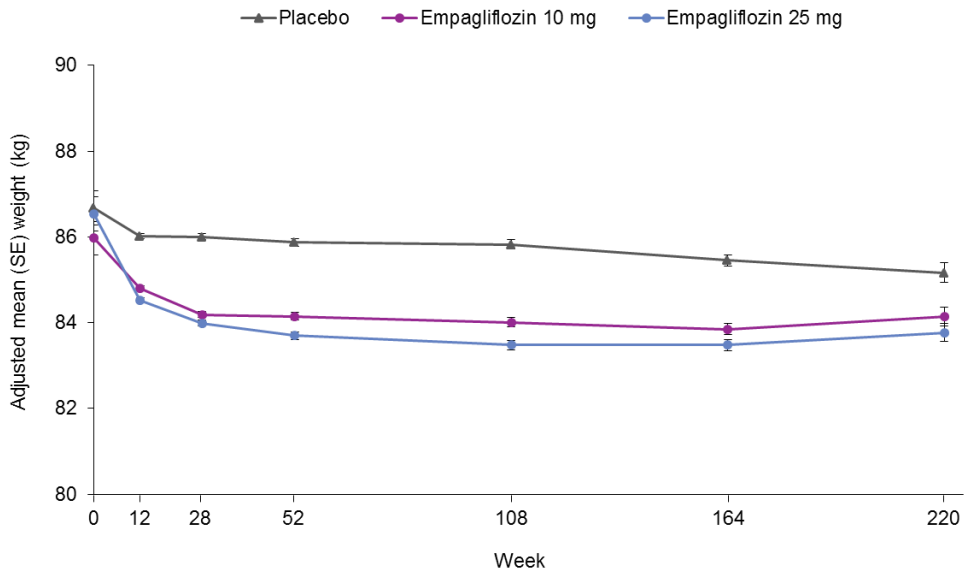
Patients who received study drug for ≥30 days (cumulative) including only events that occurred ≤30 days after a patient's last intake of trial medication (on treatment set)		
N	2308	4607
Patients with events – no. (%)	66 (2.9)	141 (3.1)
Rate/1000 patient-years	11.3	11.6
Hazard ratio (95% CI)		1.04 (0.78, 1.40)
p-value		0.78

Cox regression analysis. *Post-hoc analyses.

Section P. Weight, waist circumference, blood pressure, heart rate, low density and high density lipoprotein cholesterol, and uric acid over time.

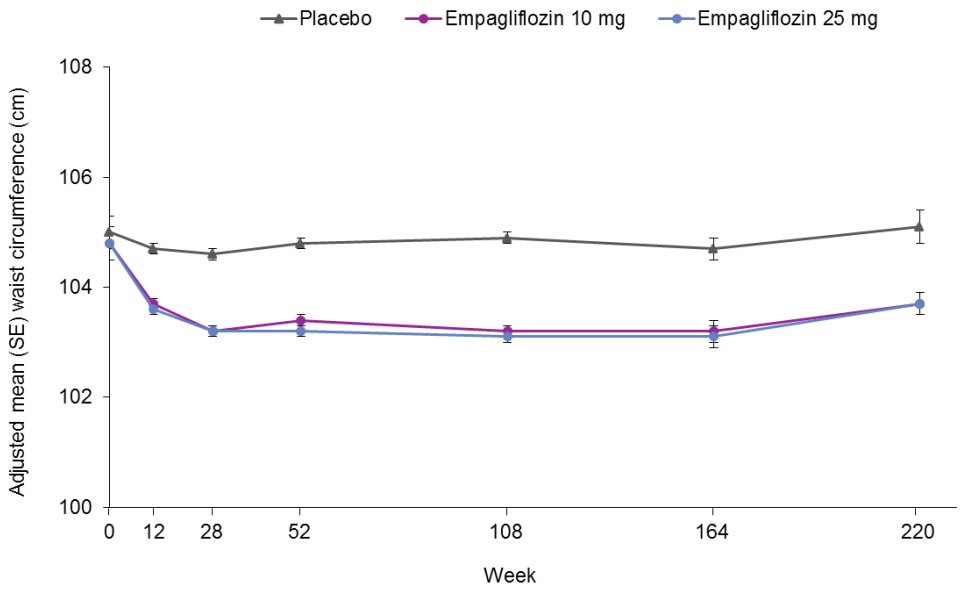
Figure S3. Weight (A), waist circumference (B), blood pressure (C and D), heart rate (E), low density and high density lipoprotein cholesterol (F and G), uric acid (H) over time.
Mixed model repeated measures analysis using all data up to individual trial completion in treated patients who had a baseline and post-baseline measurement for the respective outcome. The model included baseline glycated hemoglobin and baseline of the outcome in question as linear covariates and baseline eGFR, region, body mass index, the last week a patient could have had a measurement of the outcome in question, treatment, visit, visit by treatment interaction, baseline glycated hemoglobin by visit interaction and baseline of the outcome in question by visit interaction as fixed effects.

A. Weight



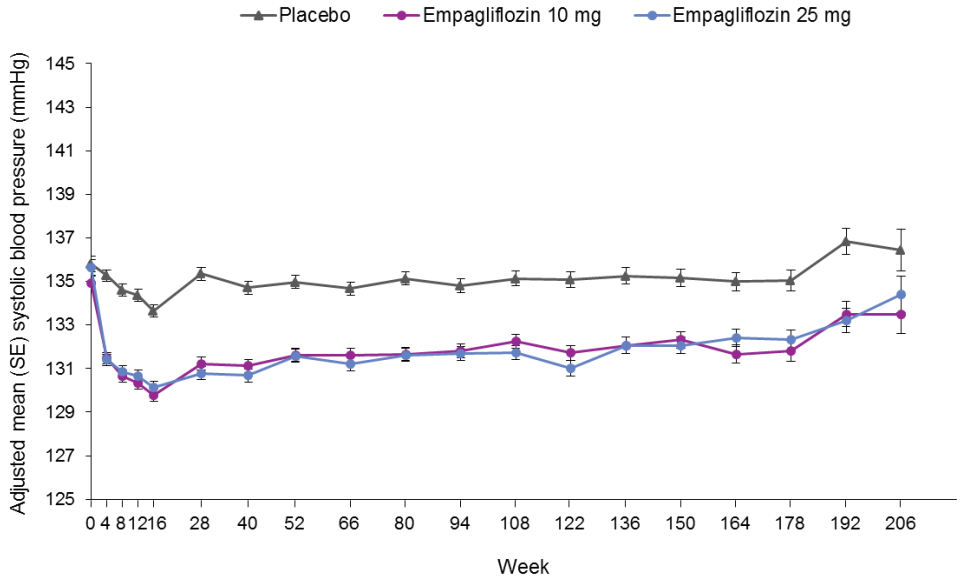
Placebo	2285	1915	2215	2138	1598	1239	425
Empagliflozin 10 mg	2290	1893	2238	2174	1673	1298	483
Empagliflozin 25 mg	2283	1891	2226	2178	1678	1335	489

B. Waist circumference.



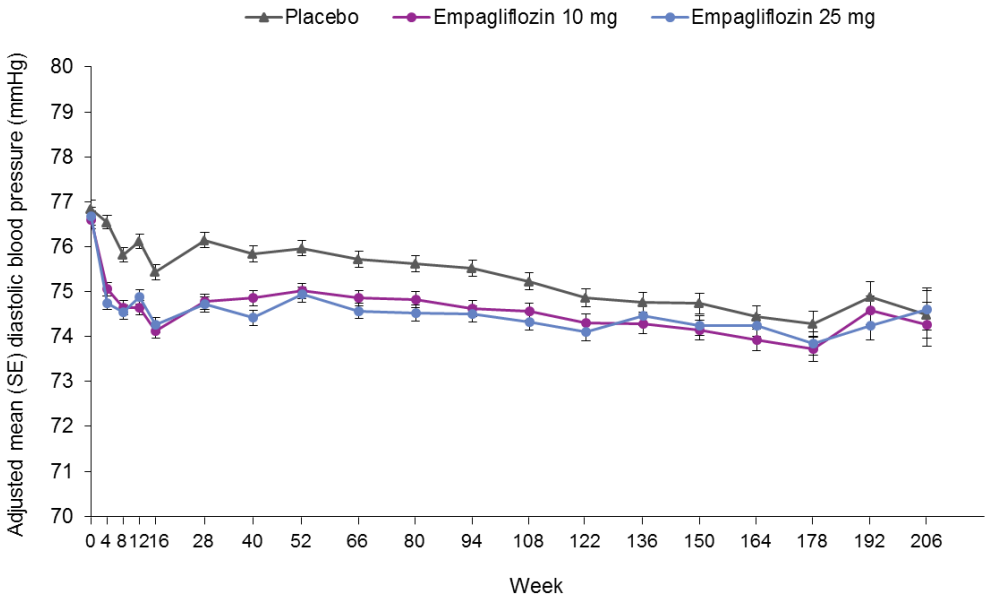
Placebo	2259	1869	2183	2110	1562	1220	418
Empagliflozin 10 mg	2272	1836	2219	2155	1644	1285	475
Empagliflozin 25 mg	2273	1857	2209	2157	1648	1329	486

C. Systolic blood pressure



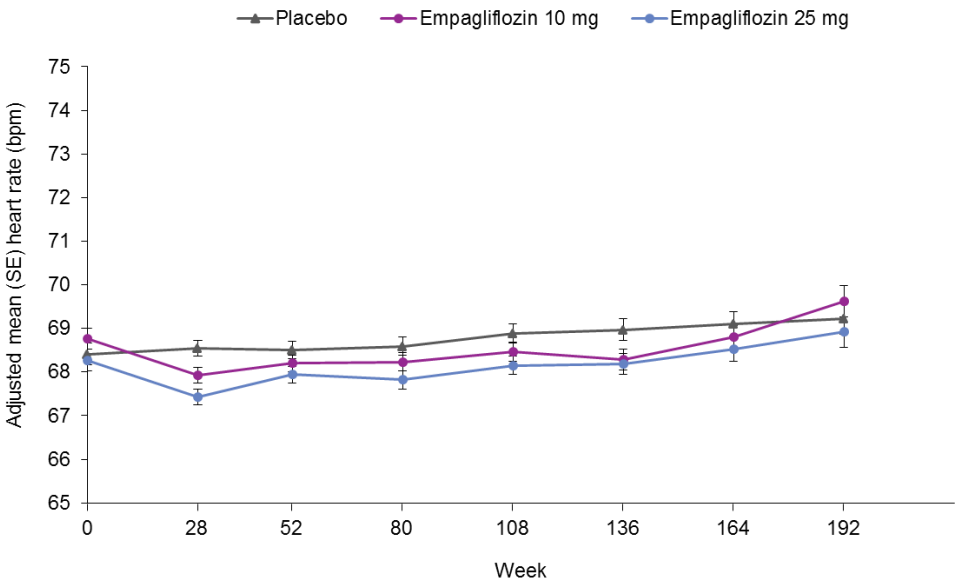
Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

D. Diastolic blood pressure



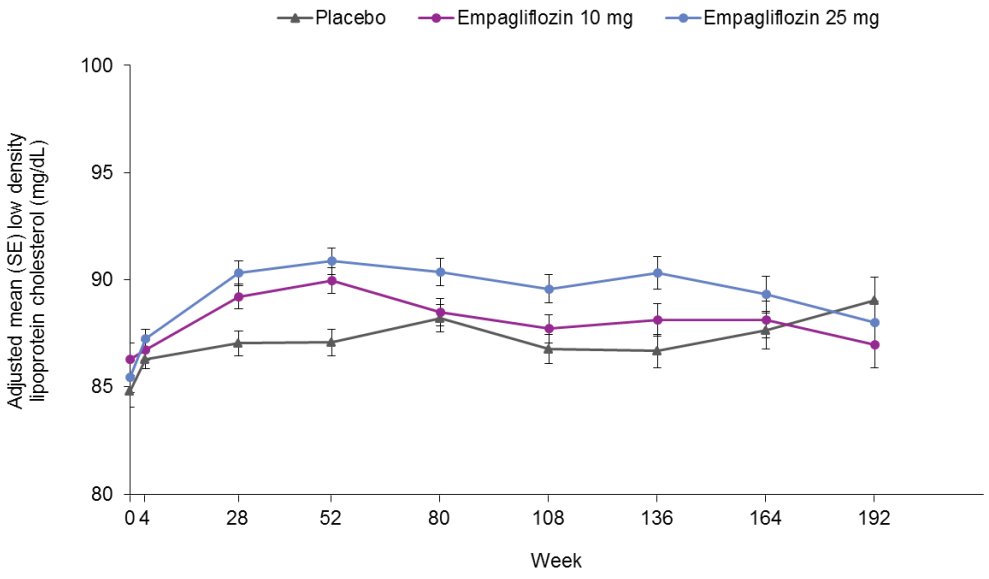
Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

E. Heart rate



Placebo	2174	2127	2032	1928	1796	1300	1002	552
Empagliflozin 10 mg	2205	2137	2064	2006	1877	1366	1045	597
Empagliflozin 25 mg	2192	2127	2066	2006	1907	1383	1086	633

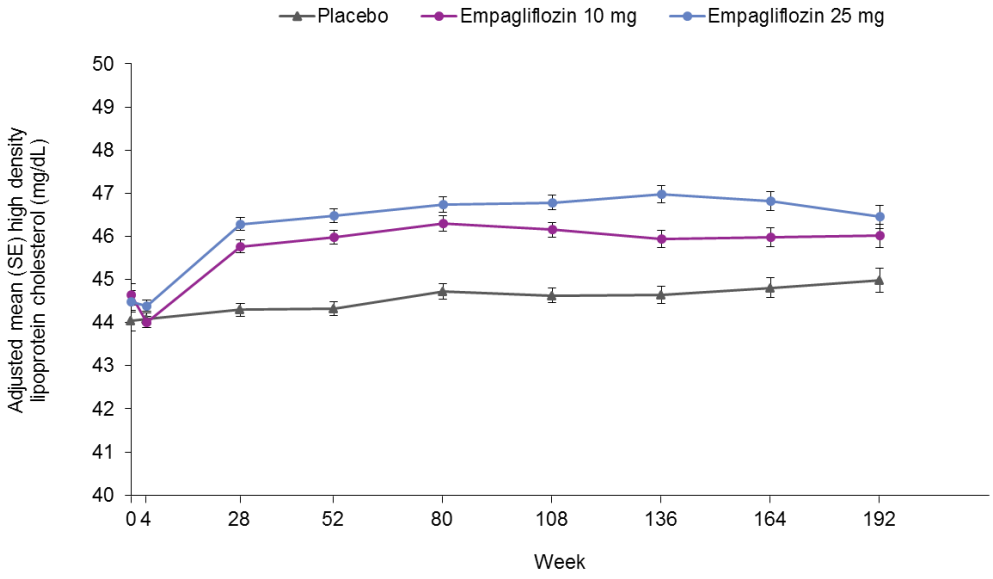
F. Low density lipoprotein cholesterol



Placebo	2297	2273	2179	2104	2006	1932	1419	1086	694
Empagliflozin 10 mg	2294	2269	2205	2143	2072	1998	1474	1133	740
Empagliflozin 25 mg	2287	2256	2188	2132	2060	2020	1503	1169	779

Conversion factor: 1 mg/dL = 0.02586 mmol/L

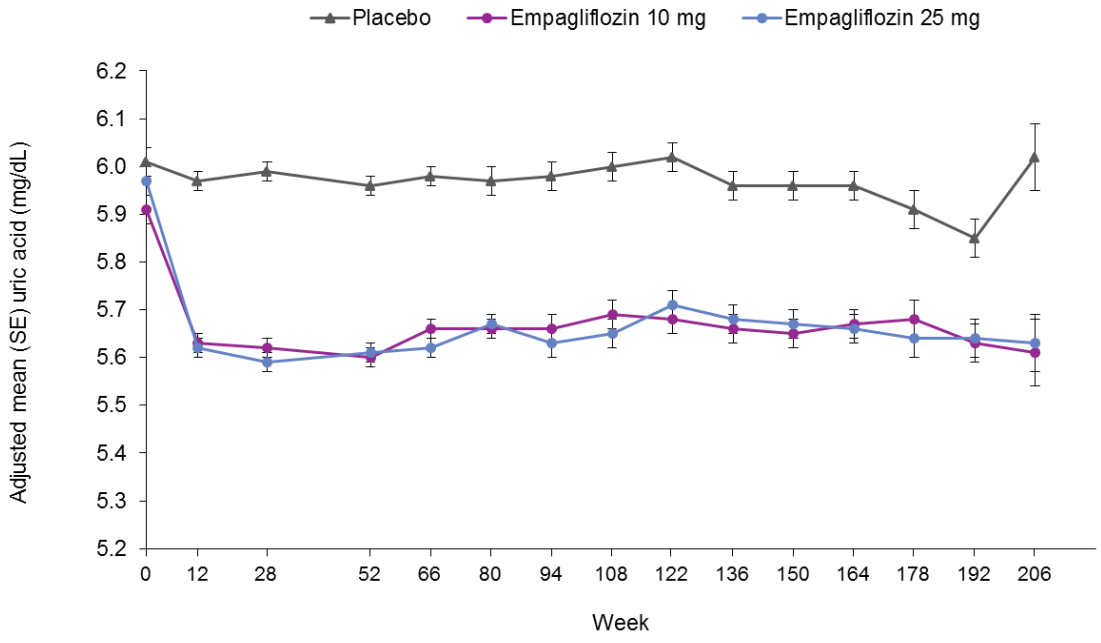
G. High density lipoprotein cholesterol



Placebo	2297	2273	2181	2104	2007	1932	1419	1087	694
Empagliflozin 10 mg	2295	2270	2209	2144	2074	2001	1475	1134	741
Empagliflozin 25 mg	2289	2259	2191	2135	2064	2022	1507	1170	779

Conversion factor: 1 mg/dL = 0.02586 mmol/L

H. Uric acid



Placebo	2292	2271	2202	2117	2062	2009	1968	1760	1476	1261	1121	976	729	447	170
Empagliflozin 10 mg	2299	2272	2233	2161	2114	2086	2058	1838	1540	1318	1177	1024	784	513	193
Empagliflozin 25 mg	2298	2279	2217	2159	2111	2086	2056	1871	1563	1341	1208	1060	834	524	213

Conversion factor: 1 mg/dL = 59.485 µmol/L

Section Q. Glucose-lowering and cardiovascular medications introduced post-baseline

Table S11. Glucose-lowering medications introduced post-baseline

	Placebo (N = 2333)	Empagliflozin (N = 4687)
	no. (%)	
Any glucose-lowering therapy	736 (31.5)	913 (19.5)
Insulin	268 (11.5)	272 (5.8)
Dipeptidyl peptidase-4 inhibitor	193 (8.3)	263 (5.6)
Sulfonylurea	164 (7.0)	176 (3.8)
Metformin	112 (4.8)	172 (3.7)
Thiazolidinedione	68 (2.9)	56 (1.2)
Glucagon-like peptide-1 agonist	57 (2.4)	65 (1.4)

Data are from patients treated with ≥1 dose of study drug.

Table S12. Cardiovascular medications introduced post-baseline

	Placebo (N = 2333)	Empagliflozin (N = 4687)
	no. (%)	
Anti-hypertensive therapy	1106 (47.4)	1903 (40.6)
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	640 (27.4)	1108 (23.6)
Diuretics	530 (22.7)	760 (16.2)
Beta blockers	420 (18.0)	745 (15.9)
Calcium channel blockers	427 (18.3)	592 (12.6)
Mineralocorticoid receptor antagonists	110 (4.7)	135 (2.9)
Renin inhibitors	6 (0.3)	8 (0.2)
Other	138 (5.9)	234 (5.0)
Lipid-lowering drugs	643 (27.6)	1245 (26.6)
Statins	529 (22.7)	1040 (22.2)
Fibrates	118 (5.1)	188 (4.0)
Ezetimibe	44 (1.9)	87 (1.9)
Niacin	12 (0.5)	23 (0.5)
Other	64 (2.7)	92 (2.0)
Anticoagulants	623 (26.7)	1179 (25.2)
Acetylsalicylic acid	402 (17.2)	736 (15.7)
Clopidogrel	112 (4.8)	224 (4.8)
Vitamin K antagonists	89 (3.8)	136 (2.9)

Data are from patients treated with ≥1 dose of study drug. Restricted to medications introduced while patients were on study medication.

Section R. Complicated urinary tract infections

Table S13. Breakdown of complicated urinary tract infections by MedDRA preferred term

	Placebo (N = 2333)	Empagliflozin 10 mg (N = 2345)	Empagliflozin 25 mg (N = 2342)	Pooled empagliflozin (N = 4687)
	no. (%) with one or more event			
Complicated urinary tract infection	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Urinary tract infection	16 (0.7)	13 (0.6)	16 (0.7)	29 (0.6)
Urosepsis	3 (0.1)	6 (0.3)	11 (0.5)	17 (0.4)
Pyelonephritis	4 (0.2)	3 (0.1)	10 (0.4)	13 (0.3)
Pyelonephritis chronic	10 (0.4)	4 (0.2)	6 (0.3)	10 (0.2)
Pyelonephritis acute	6 (0.3)	7 (0.3)	1 (<0.1)	8 (0.2)
Cystitis	2 (0.1)	0	0	0
Kidney infection	2 (0.1)	1 (<0.1)	3 (0.1)	4 (0.1)
Urinary tract infection fungal	0	0	3 (0.1)	3 (0.1)
Cystitis bacterial	1 (<0.1)	0	0	0
Escherichia urinary tract infection	1 (<0.1)	0	0	0
Urinary tract infection pseudomonal	0	0	1 (<0.1)	1 (<0.1)
Cystitis glandularis	0	0	1 (<0.1)	1 (<0.1)
Cystitis hemorrhagic	1 (<0.1)	0	0	0
Nephritis	0	1 (<0.1)	0	1 (<0.1)

Data are from patients treated with ≥1 dose of study drug based on events that occurred on treatment or ≤7 days after the last intake of study medication. Complicated urinary tract infection defined as pyelonephritis, urosepsis or serious adverse event consistent with urinary tract infection. There were no significant differences ($p<0.05$) between pooled empagliflozin and placebo.

Section S. Clinical laboratory data.

Table S14. Changes in clinical laboratory parameters.

	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg	
	Baseline	**Change from baseline**	**Baseline**	**Change from baseline**	**Baseline**	**Change from baseline**
Hematocrit, %	41.1 ± 5.7	0.9 ± 4.7	41.2 ± 5.6	4.8 ± 5.5	41.3 ± 5.7	5.0 ± 5.3
Hemoglobin, g/dL	13.4 ± 1.5	-0.1 ± 1.2	13.4 ± 1.5	0.8 ± 1.3	13.5 ± 1.5	0.8 ± 1.3
Serum creatinine, mg/dL	1.03 ± 0.29	0.03 ± 0.22	1.02 ± 0.28	0.04 ± 0.18	1.03 ± 0.30	0.05 ± 0.18
Estimated glomerular filtration rate, mL/min/1.73m^2	74.0 ± 21.1	-2.0 ± 11.5	74.4 ± 21.8	-2.3 ± 12.1	74.3 ± 21.1	-2.9 ± 11.8
Aspartate aminotransferase, U/L	14 ± 12	0 ± 24	13 ± 10	0 ± 15	14 ± 11	0 ± 26
Alanine aminotransferase, U/L	18 ± 14	0 ± 32	17 ± 11	-1 ± 17	18 ± 12	-2 ± 22
Alkaline phosphatase, U/L	64 ±32	5 ± 33	65 ± 32	3 ± 33	64 ± 33	3 ± 26
Electrolytes						
Sodium, mEq/L	141 ± 2	0 ± 2	141 ± 2	0 ± 2	141 ± 2	0 ± 2
Potassium, mEq/L	4.3 ± 0.4	0.0 ± 0.4	4.3 ± 0.4	0.0 ± 0.4	4.3 ± 0.4	0.0 ± 0.4
Calcium, mg/dL	9.7 ± 0.5	0.0 ± 0.5	9.7 ± 0.4	0.0 ± 0.5	9.7 ± 0.4	0.0 ± 0.5
Magnesium, mEq/L	1.7 ±0.2	0.0 ± 0.2	1.7 ± 0.2	0.1 ± 0.2	1.7 ± 0.2	0.1 ± 0.2
Chloride, mEq/L	102 ± 2	-1 ± 2	102 ± 2	-1 ± 2	102 ± 2	-1 ± 2
Phosphate, mg/dL	3.7 ± 0.3	0.0 ± 0.3	3.7 ± 0.3	0.1 ± 0.3	3.7 ± 0.3	0.1 ± 0.3

Plus-minus values are means ± SD and data are normalized to a standard reference range. Changes from baseline are the last measurement ≤3 days after the last intake of study medication. Data are from patients treated with ≥1 dose of study drug with a baseline and on-treatment measurement.

Conversion factors: serum creatinine: 1 mg/dL = 88.4 µmol/L; sodium, potassium, chloride and phosphate: 1 mEq/L = 1 mmol/L; calcium: 1 mg/dL = 0.25 mmol/L; magnesium: 1 mEq/L = 0.5 mmol/L