Supplementary Appendix

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

Supplement to: Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;379:347-57. DOI: 10.1056/NEJMoa1812389

Supplementary Appendix for the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58) Trial

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

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Section B - SUPPLEMENTARY METHODS

ADDITIONAL STATISTICAL METHODS – Update to analysis and effect on statistical power

The trial was initially sized and powered for a single primary efficacy endpoint of MACE. The main manuscript provides extensive discussion of the timing and rationale of the change in primary endpoint. At the time of the change, the trial was fully enrolled, and it was elected to not update the sample size. Since the primary safety objective was unchanged there was no effect on the power for this outcome. As reported in the design paper, we calculated that approximately 770 CVD/HHF events would correspond to the planned 1390 MACE events. These 770 events with the alpha split would provide 80% power for a 20% RRR in CVD/HHF. For a 15% reduction in MACE, the power without alpha recycling the power was approximately 78%, but with alpha recycling increased to >85%.

Timeline of decision making and actions regarding change in analysis:

- EMPA-REG reporting date: Results presented at EASD 2015, Stockholm, Sweden: 17 September 2015
- Executive committee (EC) teleconference meeting to discuss results and implications of results from EMPA-REG for DECLARE: 9 October 2015.
- Memo informed investigators of the results of EMPA-REG and included a white paper: 2 December 2015
- EC teleconference meeting to review and confirm plan for endpoint change: 10 December 2015
- Date of revised protocol for update of primary endpoint: amendment 5, revised draft CSP version 5: 18 December 2015
- Date of update of clinicaltrials.gov to reflect the change in PEP: 21 December 2016
- Revised Protocol and SAP version 6 sent to FDA: 23 December 2015
- DMC chairman was informed of planned change: 21 January 2016 (included a copy of the draft protocol submitted to the FDA)
- First DMC MACE review (33% of planned events) – 8 February 2016

ADDITIONAL STUDY PROCEDURES – Safety Data Collection

Serious adverse events (SAE) and adverse events leading to discontinuation of study drug (DAE) were collected comprehensively. Case record forms for clarifying questions were used to analyze specific safety events including all neoplasms (except non-melanoma skin cancers), major hypoglycemia and hepatic events. In addition, prespecified AEs of special interest were fractures, symptoms of volume depletion, renal events (including acute kidney injury) and SAE/DAE of genital infections, urinary infections and hypersensitivity reactions. Due to external events during the trial, both amputations and events of potential diabetic ketoacidosis were collected retro- and prospectively with specific case record forms introduced during the study to collect additional relevant information. Study sites were asked to review all subjects for events occurring prior to initiation of the collection forms and report those events. The TIMI clinical events committee, consisting of content experts in the medical area of interest and whose members were unaware of treatment assignment, adjudicated all primary and key components of other safety and efficacy outcomes including MACE, CVD/HHF, malignancies, and diabetic ketoacidosis. Hepatic events were adjudicated with evaluation of causality to study drug and reported events are those adjudicated. Analyses were performed using the on-treatment analysis set; patients who had a safety outcome while they were on treatment or within 7 days (AEs) or 30 days (SAEs) after discontinuation of the drug or placebo, except for amputation, fracture and malignancies outcomes, which included all events after first dose in all patients who underwent randomization and received at least one dose of dapagliflozin or placebo and have any data observed after first dose. Additional details can be found in the clinical study protocol, section 6.4.4.

For Table 2 in the main paper, the data source for the events listed is:

- CEC Adjudicated: Diabetic ketoacidosis (definite or probable) and neoplasm adjudicated to be malignancy
- Hepatic events that were triggered for adjudication for evaluation of causality to study drug
- Major hypoglycemia defined as symptomatic events requiring external assistance due to severe impairment of conciseness with prompt recovery after glucose or glucagon administration
- MedDRA preferred terms (PT) for AE/SAE : *Acute kidney injury* and pre-defined PT-lists for AE/SAE of symptoms of volume depletion and fractures
- MedDRA PT-lists for SAE/DAE: Genital infections, urinary tract infections and hypersensitivity reactions

Section C - STUDY ELIGIBILITY CRITERIA

INCLUSION CRITERIA

1. Provision of informed consent prior to any study specific procedures (including run-in)
2. Female or male aged ≥ 40 years
3. Diagnosed with T2DM, defined as:
    - Prior documentation of type 2 diabetes AND/OR
    - Treatment with anti-hyperglycemic medications and/or diet AND/OR
    - ADA criteria: fasting >126 mg/dl (7.0 mmol/L) or HbA1C ≥6.5% or 2-h plasma glucose≥200 mg/dl (11.1 mmol/L) during an oral glucose tolerance test, or a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) in patients with classic symptoms of hyperglycemia or hyperglycemic crisis. In the absence of unequival hyperglycemia, results should be confirmed by repeat testing.
4. High Risk for CV event defined as having either established CV disease and/or multiple risk factors:
    - Established CV Disease, defined as any of the following:
        - Ischemic heart disease (any of the following):
            - Documented Myocardial Infarction
            - Percutaneous Coronary Intervention
            - Coronary Artery Bypass Grafting
            - Objective Findings of Coronary Stenosis (≥ 50%) in at least 2 coronary artery territories (ie, left anterior descending, ramus intermedius, left circumflex, right coronary artery) involving the main vessel, a major branch, or a bypass graft
        - Cerebrovascular disease (any of the following):
            - Documented ischemic Stroke
              (Known transient ischemic attack, primary intracerebral haemorrhage or sub-arachnoid hemorrhage do not qualify.)
            - Carotid stenting or endarterectomy
        - Peripheral Arterial Disease (any of the following):
            - peripheral arterial intervention, stenting or surgical revascularization
            - lower extremity amputation as a result of peripheral arterial obstructive disease
            - Current symptoms of intermittent claudication AND ankle/brachial index (ABI) < 0.90 documented within last 12 months

      OR
    - No known cardiovascular disease AND at least two cardiovascular risk factors in addition to T2DM, defined as:
        - Age ≥ 55 years in men and ≥ 60 in women

      AND
        - presence of at least 1 of the following additional risk factors

- Dyslipidemia (at least one of the following)
    - Low-density lipoprotein cholesterol (LDL-C) >130 mg/dl (3.36 mmol/L) within last 12 months
    - On lipid lowering therapy prescribed by a physician for hypercholesterolemia (ie LDL-C > 130 mg/dl (3.36 mmol/L)) for greater than 12 months. This should be verified by documentation of lab value LDL-C > 130 mg/dl (3.36 mmol/L).
- Hypertension (at least one of the following)
    - BP >140/90 mm/Hg at enrollment visit. The patient must have both an elevated systolic BP (> 140 mmHg) and an elevated diastolic BP (> 90 mmHg) on both measurements
    - On anti-hypertensive therapy prescribed by a physician for blood pressure lowering
- Current Tobacco use (5 cigarettes/day or more for at least 1 year at randomization)

5. WOCBP must take precautions to avoid pregnancy throughout the study and for 4 weeks after intake of the last dose.

- WOCBP must have a negative urine pregnancy test. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal.
- WOCBP must be willing to use a medically accepted method of contraception that is considered reliable in the judgment of the Investigator.

EXCLUSION CRITERIA

1. Use of the following excluded medications:

- Current or recent (within 24 months) treatment with pioglitazone and/or use of pioglitazone for a total of 2 years or more during lifetime
- Current or recent (within 12 months) treatment with rosiglitazone
- Previous treatment with any SGLT2 inhibitor
- Any patient currently receiving chronic (>30 consecutive days) treatment with an oral steroid at a dose equivalent to oral prednisolone ≥10 mg (e.g., betamethasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day

2. Acute cardiovascular event [e.g., acute coronary syndrome (ACS), transient ischemic attack (TIA), stroke, any revascularization, decompensated HF, sustained ventricular tachycardia <8 weeks prior to randomization. Patients with acute cardiovascular events can be enrolled in the run-in period as long as randomization does not occur within 8 weeks of the event.

3. Systolic BP >180 or diastolic BP >100 mmHg at randomization. Patient should be excluded if either the systolic BP is elevated (> 180 mmHg) or the diastolic BP is elevated (> 100 mmHg) on both measurements

4. Diagnosis of Type 1 diabetes mellitus, MODY, or secondary diabetes mellitus
5. History of bladder cancer or history of radiation therapy to the lower abdomen or pelvis at any time
6. History of any other malignancy within 5 years (with the exception of successfully treated non-melanoma skin cancers)
7. Chronic cystitis and/or recurrent urinary tract infections (3 or more in the last year)
8. Any conditions that, in the opinion of the Investigator, may render the patient unable to complete the study including but not limited to cardiovascular (NYHA class IV CHF, recurrent ventricular arrhythmias) or non-cardiovascular disease (e.g., active malignancy with the exception of basal cell carcinoma, cirrhosis, chronic lung disease, severe autoimmune disease) and/or a likely fatal outcome within 5 years
9. Pregnant or breast-feeding patients
10. Involvement in the planning and/or conduct of the study or other dapagliflozin studies (applies to AZ, BMS, Hadassah and Thrombolysis in Myocardial Infarction [TIMI] or representative staff and/or staff at the study site)
11. Previous enrollment or randomization in the present study
12. Active participation in another clinical study with IP and/or investigational device
13. Individuals at risk for poor protocol or medication compliance during run-in period (reasonable compliance defined as 80 – 120%, unless a reason for non-compliance is judged acceptable by the Investigator). If for any reason, the Investigator believes that the patient will not tolerate or be compliant with IP or study procedures, the patient should not be randomized and considered a run-in failure.
14. HbA1c ≥12% or HbA1c<6.5% from the central laboratory (nb, the proportion of subjects with an HbA1c between 6.5 % and < 7.0 % will be capped at approximately 5 % of the study)
15. AST or ALT >3x ULN or Total bilirubin >2.5 x ULN
16. CrCl < 60 ml/min (based on the Cockroft-Gault equation)
17. Hematuria (confirmed by microscopy at Visit 1) with no explanation as judged by the Investigator up to randomization. If bladder cancer is identified, patients are not eligible to participate.
18. Any reason the Investigator believes the patient is not likely to be compliant with the study medication and protocol.

Section D – ENDPOINT AND EVENT DEFINITIONS

PRIMARY AND SECONDARY ENDPOINT DEFINITIONS

CARDIOVASCULAR DEATH

Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

1. **Death due to Acute Myocardial Infarction** refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days (the 30 day cut-off is arbitrary) after a MI related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. There may be assessable mechanisms of cardiovascular death during this time period, but for simplicity, if the cardiovascular death occurs ≤ 30 days of the MI, it will be considered a death due to myocardial infarction.

   Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis.

   Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)), or to treat a complication resulting from MI, should also be considered death due to acute MI.

2. **Sudden Cardiac Death** refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:
   - **a.** Death witnessed and occurring without new or worsening symptoms
   - **b.** Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
   - **c.** Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
   - **d.** Death after unsuccessful resuscitation from cardiac arrest
   - **e.** Death 30 days after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
   - **f.** Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

- Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is seen alive ≤ 24 hours of being found dead, sudden cardiac death (criterion **2**f) should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed, but who had not been seen by family for several days).

3. **Death due to Heart Failure** refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology (see Heart Failure Event Definition). Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions (unless ≤30 days after an MI, see definition for Death due to Acute MI above), ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

4. **Death due to Stroke** refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke (see Cerebrovascular Event Definition).

5. **Death due to Cardiovascular Procedures** refers to death caused by the immediate complications of a cardiac procedure unless procedure is to treat a myocardial infarction.

6. **Death due to Cardiovascular Hemorrhage** refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (see Cerebrovascular Event Definition), non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

7. **Death due to Other Cardiovascular Causes** refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

NON-CARDIOVASCULAR DEATH

Non-cardiovascular Death is defined as any death without a specific cause that is not thought to be cardiovascular in nature. The following is a suggested list of non-CV causes of death:

- Pulmonary
- Renal - *defined as death occurring after a patient refuses or a physician withholds renal replacement therapy (i.e., initiation of chronic dialysis or renal transplantation) or in cases where dialysis is unavailable. Deaths due to another primary process and/or when another cause is adjudicated (e.g., sepsis, end-stage heart failure, malignancy) will be*

adjudicated as death resulting from the primary process and will not be considered renal death.

- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Inflammatory (e.g. Systemic Inflammatory Response Syndrome (SIRS)/Immune (including autoimmune)
- Hemorrhage that is neither cardiovascular bleeding nor a stroke
- Non-CV procedure or surgery
- Trauma
- Suicide
- Non-prescription drug reaction or overdose
- Prescription drug reaction or overdose
- Neurological (non-cardiovascular)
- Malignancy
- Other non-CV, specify: _____

UNDETERMINED CAUSE OF DEATH

Undetermined Cause of Death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV.

CARDIAC ISCHEMIC / ACUTE CORONARY SYNDROMES

1. General Considerations

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.
In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and

trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

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

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
    - Symptoms of ischemia
    - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB).
    - Development of pathological Q waves in the ECG.
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
    - Identification of an intracoronary thrombus by angiography or autopsy

2. Criteria for Myocardial Infarction

a. Clinical Presentation

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, heart failure, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

b. Biomarker Elevations

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. *In general, troponins are preferred. CK-MB should be used if*

troponins are not available, and total CK may be used in the absence of CK-MB and troponin.

For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be required. The specific criteria will be referenced to the URL.

c. Electrocardiogram (ECG) Changes

Electrocardiographic changes can be used to support or confirm a diagnosis of MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

- **ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):**

    - ST elevation
      New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women.

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

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

- **Criteria for pathological Q-wave**

    - 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; V1-V6; II, III, and aVF)[a]

    [a]The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

- **ECG changes associated with prior myocardial infarction**

    - Pathological Q-waves, as defined above
    - R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

- **Criteria for prior myocardial infarction**

  Any one of the following criteria meets the diagnosis for prior MI:
  - Pathological Q waves with or without symptoms in the absence of non-ischemic causes
  - Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
  - Pathological findings of a prior myocardial infarction

Criteria for universal classification of myocardial infarction

Type 1: Spontaneous myocardial infarction

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Myocardial infarction secondary to an ischemic imbalance

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 4c: Myocardial infarction related to restenosis
Restenosis is defined as ≥50% stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTn values .99th percentile URL and no other significant obstructive CAD of greater severity following: (i) initially successful stent deployment or (ii) dilatation of a coronary artery stenosis with balloon angioplasty (<50%).

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Note: As noted in criterion 2b, although language states troponin, CKMB can be used with similar cut points.

ST-Segment Elevation MI versus Non-ST-segment Elevation MI
All events meeting criteria for MI will also be classified as either ST-segment elevation MI (STEMI), non-ST-segment elevation MI (NSTEMI), or unknown.

- **STEMI** – To be classified as a STEMI the event must meet all of the above criteria for myocardial infarction and one of the four criteria below.
    - New ST segment elevation at the J point in ≥2 contiguous leads, defined as: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads. Subjects must have an interpretable ECG (i.e., without evidence of left ventricular hypertrophy or pre-existing left bundle branch block), *or*
    - New left bundle branch block
- **NSTEMI** – To be classified as a NSTEMI the event must meet all of the above criteria for myocardial infarction and not meet criteria for classification as STEMI. In order to be classified as NSTEMI there must be adequate interpretable ECG documentation associated with the event.

- **Unknown** – Events which meet criteria as specified above for MI but do not meet criteria for STEMI or NSTEMI. All cases where ECG documentation of the acute event is missing, inadequate, or uninterpretable should be classified as Unknown.

  Note: All events adjudicated as MI will be classified as STEMI, NSTEMI, or Unknown; however, it is acknowledged that a significant proportion of peri-procedural (PCI or CABG) events may have missing, inadequate or uninterpretable ECG documentation.

Categorization of MI

Categorization of MI will include measures of MI size and severity including biomarker values, MI type, and post-MI cardiac function.

HOSPITALIZATION FOR UNSTABLE ANGINA

Unstable angina requiring hospitalization is defined as:

1. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥ 10 minutes in duration occurring
   - at rest, or
   - in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity.

AND

2. Prompting an unscheduled hospitalization within 24 hours of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour stay (or a change in calendar date if the hospital admission or discharge times are not available).

AND

3. At least one of the following:

   a. New or worsening ST or T wave changes on resting ECG (in the absence of confounders, such as LBBB or LVH)
      - Transient ST elevation (duration <20 minutes)
        New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply:
        ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or
        ≥ 0.15 mV in women.

- ST depression and T-wave changes
  New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.3 mV in two contiguous leads with prominent R wave or R/S ratio > 1.

b. Definite evidence of inducible myocardial ischemia as demonstrated by:
- an early positive exercise stress test, defined as ST elevation or ≥ 2 mm ST depression prior to 5 mets

OR
- stress echocardiography (reversible wall motion abnormality) OR
- myocardial scintigraphy (reversible perfusion defect), OR
- MRI (myocardial perfusion deficit under pharmacologic stress).

and believed to be responsible for the myocardial ischemic symptoms/signs.

c. Angiographic evidence of new or worse ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.

d. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.

AND

4. Negative cardiac biomarkers and no evidence of acute MI

General Considerations

1. Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive but not diagnostic of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3, would be insufficient to support classification as hospitalization for unstable angina.

2. If subjects are admitted with suspected unstable angina, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not be adjudicated as unstable angina.

3. Planned hospitalization or rehospitalization for performance of an elective revascularization in patients who do not fulfill the criteria for unstable angina should not be considered a hospitalization for unstable angina. For example,
    - Hospitalization of a patient with stable exertional angina for coronary angiography and PCI that is prompted by a positive outpatient stress test should not be considered hospitalization for unstable angina.
    - Rehospitalization of a patient meeting the criteria for unstable angina who was stabilized, discharged, and subsequently readmitted for revascularization, does not constitute a second hospitalization for unstable angina.

4. A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina end point.

CEREBROVASCULAR EVENTS

The distinction between a Transient Ischemic Attack and an Ischemic Stroke is the presence of infarction. Persistence of symptoms is an acceptable indicator of acute infarction.

Transient Ischemic Attack
Transient ischemic attack (TIA) is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, *without* acute infarction.

Stroke
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 hemorrhage or infarction.

- infarction may be documented by brain imaging or,
- persistence of symptoms beyond 24 hours

Classification:

A. Ischemic Stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.

Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

B. Hemorrhagic Stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as A or B.

General Considerations

1. Evidence of vascular central nervous system injury without recognized neurological dysfunction including microhemorrhage, silent infarction, and silent hemorrhage, if appropriate, will not be adjudicated as cerebrovascular events in this trial.

Subdural hematomas are intracranial hemorrhagic events and not strokes.

HEART FAILURE

A **Heart Failure Event** includes hospitalization for heart failure and may include urgent outpatient visits. HF hospitalizations should remain delineated from urgent visits.

A **Heart Failure Hospitalization** is defined as an event that meets ALL of the following criteria:

1. The patient is admitted to the hospital with a primary diagnosis of HF

2. The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)

3. The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following:

a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
b. Decreased exercise tolerance
c. Fatigue
d. Other symptoms of worsened end-organ perfusion or volume overload

4. The patient has objective evidence of new or worsening HF, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including:

a) Physical examination findings considered to be due to heart failure, including new or worsened:
   i. Peripheral edema
   ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)

iii. Pulmonary rales/crackles/crepitations
iv. Increased jugular venous pressure and/or hepatojugular reflux
v. S_3 gallop
vi. Clinically significant or rapid weight gain thought to be related to fluid retention

b) Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
i. 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). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
ii. Radiological evidence of pulmonary congestion
iii. Non-invasive or invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration
OR
iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m^2

5. The patient receives initiation or intensification of treatment specifically for HF, including at least ONE of the following:

a. Augmentation in oral diuretic therapy
b. Intravenous diuretic, inotrope, or vasodilator therapy
c. Mechanical or surgical intervention, including:
i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device)
ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

Using available information, Heart Failure will be categorized based on the following:

1) Left ventricular ejection fraction (LVEF)
2) Type
3) Etiology

An **Urgent Heart Failure Visit** is defined as an event that meets all of the following:

1) The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization.

2) All signs and symptoms for HF hospitalization (i.e., 3) symptoms; 4) physical examination findings/laboratory evidence of new or worsening HF, as indicated above) must be met
3) The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

INTERVENTIONAL CARDIOLOGY

1. **Percutaneous Coronary Intervention (PCI) Status:**

   a. Elective: The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of myocardial infarction (MI) or death. For stable in-patients, the procedure is being performed during this hospitalization for convenience and ease of scheduling and **NOT** because the patient's clinical situation demands the procedure prior to discharge.

   b. Urgent: The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns that there is risk of myocardial ischemia, MI, and/or death. Patients who are outpatients or in the emergency department at the time that the cardiac catheterization is requested would warrant hospital admission based on their clinical presentation.

   c. Emergency: The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. "As soon as possible" refers to a patient who is of sufficient acuity that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours.

   d. Salvage: The procedure is a last resort. The patient is in cardiogenic shock when the PCI begins (i.e., the time at which the first guide wire or intracoronary device is introduced into a coronary artery or bypass graft for the purpose of mechanical revascularization) **OR** within the last ten minutes prior to the start of the case or during the diagnostic portion of the case, the patient has also received chest compressions or has been on unanticipated circulatory support (e.g., intra-aortic balloon pump, extracorporeal mechanical oxygenation, or cardiopulmonary support).

2. **Percutaneous Coronary Intervention (PCI):** Placement of an angioplasty guide wire, balloon, or other device (e.g., stent, atherectomy catheter, brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft for the purpose of mechanical coronary revascularization. In the assessment of the severity of coronary lesions with the use of intravascular ultrasound, CFR, or FFR, insertion of a guide wire will **NOT** be considered PCI.

PERIPHERAL (NON-CORONARY) VASCULAR INTERVENTION

1. **Peripheral Vascular Intervention (PVI):** Peripheral vascular intervention is a catheter-based or open surgical procedure designed to improve peripheral arterial or venous blood flow or otherwise modify or revise vascular conduits. Procedures may include, but are not limited to, balloon angioplasty, stent placement, thrombectomy, embolectomy, atherectomy, dissection repair, aneurysm exclusion, treatment of dialysis conduits, placement of various devices, intravascular thrombolysis or other pharmacotherapies, and open surgical bypass or revision.

   In general, the intention to perform *percutaneous* peripheral vascular intervention is denoted by the insertion of a guide wire into a peripheral artery or vein.
   The target vessel(s) and the type of revascularization procedure (e.g., surgical bypass, thrombectomy, endarterectomy, percutaneous angioplasty, stent placement, thromboembolectomy, and thrombolysis) should be specified and recorded. For the sake of simplicity, this definition applies to the extracranial carotid artery and other non-cardiac arteries and veins and excludes the intracranial vessels and lymphatics.

2. **Procedural Status: Non-Elective and Elective:**

   a. **Non-Elective:** Non-elective procedures include emergent and urgent procedures. A non-elective procedure is a procedure that is performed without delay, because there is clinical consensus that the procedure should occur imminently. Non-elective procedures imply a degree of instability of the patient, urgency of the medical condition, or instability of the threatening lesion.

      - **Emergent:** A procedure that is performed immediately because of the acute nature of the medical condition (e.g., acute limb ischemia, acute aortic dissection), and the increased morbidity or mortality associated with a temporal delay in treatment.

      - **Urgent:** An urgent procedure is one that is not emergent but required to be performed on a timely basis (≤ 24 hrs) (e.g., a patient who has been stabilized following initial treatment of acute limb ischemia, and there is clinical consensus that a definitive procedure should occur within the next 24 hours).

   b. **Elective:** An elective procedure is one that is scheduled and is performed on a patient with stable disease, or in whom there is no urgency and/or increased morbidity or mortality associated with a planned procedure.

MALIGNANCIES

All reported neoplasms, with the exception of those confirmed as benign and non-melanoma skin cancers that are diagnosed after randomization or that were present prior to randomization and then worsened or recurred post randomization will be reviewed and classified as follows using pathology data as the primary source of classification.

- Malignant neoplasm - an abnormal mass of tissue that can invade and destroy nearby tissue, and that may spread (metastasize) to other parts of the body.
- Benign neoplasm – an abnormal mass of tissue that cannot invade/destroy nearby tissue or metastasize.
- Not a neoplasm – neither of the above.

In addition, the CEC will determine the following:

1. Timing of malignancy
   - Clinically evident at time of randomization
   - Diagnosed after randomization

2. Site of malignancy
   - Bladder
   - Bowel
   - Brain
   - Breast
   - Esophageal
   - Genital
   - Leukemia
   - Lip, oral, pharynx
   - Liver, gall bladder
   - Lung
   - Lymphoma
   - Pancreatic
   - Prostate
   - Renal
   - Skin
   - Stomach
   - Thyroid
   - Uterine
   - Other

3. Extent of malignancy
   - Solid Neoplasm
      - Local disease only, no spread beyond the primary organ
      - Spread to contiguous organs
      - Metastatic

- Leukemia, lymphoma and other blood malignancy
    - Acute
    - Chronic
    - Unknown

HEPATIC EVENTS

Event triggers can be found in the trial Data Management Plan. Each event will be assessed for causality, severity and patterns of liver injury.

Causality Scale

When completing the adjudication forms, the HAC members will express their opinions regarding the probability of Drug-Induced Liver Injury (DILI) using the five-point likelihood causality scale described by Rockey et al. in the table below. This includes both numerical and descriptive terms to grade cases as definitely, highly likely, probable, possibly, or unlikely related to DILI below.

- Definite: Causality should be considered to be definite if attribution of the study drug to the liver injury is believed to exceed 95% likelihood with an association beyond a reasonable doubt.

- Highly Likely: The designation highly likely should be applied when there is an estimated 75% to 95% likelihood of an association and a clear and convincing evidence for the association.

- Probable: Cases should be considered probable when the likelihood of an association is considered to be between 50% and 75%, with an indication that the association is supported by the predominance of the evidence. Although appearing to show an association, such cases should not be graded higher because of an atypical course, the absence of essential clinical information, or the presence of another possible explanation or diagnosis.

- Possible: Cases should be considered to be possible if they are believed to have a 25% to 50% likelihood of an association because, although it was still possibly related, the involvement by the study drug is equivocal and not supported by the preponderance of the evidence.

- Unlikely: Cases should be ranked as unlikely if they are regarded to have less than a 25% likelihood of resulting from the medication, and another etiology is considered to be responsible.

Table: Clinical Assessment of Causality Scale:

Causal Relationship	Likelihood	Description
Definite	> 95%	The evidence for the study drug causing the injury is beyond a reasonable doubt
Highly Likely	75 - 95%	The evidence for the study drug causing the injury is clear and convincing but not definite
Probable	50 - 74%	The preponderance of the evidence supports the link between the study drug and the liver injury
Possible	25 - 49%	The evidence for the study drug causing the injury is equivocal but present
Unlikely	< 25%	There is evidence that an etiological factor other than the study drug caused the injury is clear

Rockey D.C., et al. for the US Drug-Induced Liver Injury Network. Causality Assessment in Drug-Induced Liver Injury Using a Structured Expert Opinion Process: Comparison to the Roussel-Uclaf Causality Assessment Method. HEPATOLOGY 2010;51:2117-2126

For cases that do not meet any of the above description, two additional likelihood causality scale terms will be included, as described below:

Excluded: Cases should be ranked as excluded if there is a definite and documented alternative cause for the abnormality.

Not Assessable: Cases should be ranked as not assessable if critical data is missing that interferes with a fair assessment.

Only one option can be selected for each case.

Severity Scale

For each case, the HAC members will also express their opinions regarding the severity using the scoring system described below, which has been used by the Food and Drug Administration in the past, including as part of the dabigatran Advisory Committee.

Table: Severity Scale

Scale	Definition
1	ALT or AST > 3X ULN, usually transient and reversible by adaptation (mild)
2	Also TB > 2X ULN, after or concurrent, indicating early functional loss (Hy's Law Case)
3	Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4	Acute liver failure, with secondary failure of brain or kidney function due to liver injury
5	Fatal, or requiring liver transplantation due to liver failure

In addition to the above scale, the option “not applicable and/or no liver injury” will be available for cases where options 1 to 5 do not apply. Only one option can be selected for each case for options 1 to 5, however, the option “not applicable and/or no liver injury” can be selected in conjunction with one option from 1 to 5.

Patterns of Liver Injury

For each case, the pattern of liver injury will be assessed and reported on the adjudication form in accordance with the below definitions, as described by Farrell G, Schiff’s Diseases of the Liver, 11th edition (in press).

Table: Definition of Patterns of Liver Injury

Hepatocellular	Cholestatic	Mixed
ALT >2-3 XULN and Normal ALP **OR** ALT/ALP ratio ≥ 5[a]	ALT >2 XULN **OR** ALT/AP ratio ≤ 2[a]	ALT >2-3 XULN and ALP >2 XULN **OR** ALT/ALP ratio between 2 and 5[a]

[a] The ALT and SAP values are expressed as multiples of the upper limit of normal

For cases that do not meet any of the above description, 2 additional patterns of liver injury terms will be included:

Other Type: Pattern of liver injury not meeting any of above definitions.

Not Applicable: For cases where there is no liver injury noted.

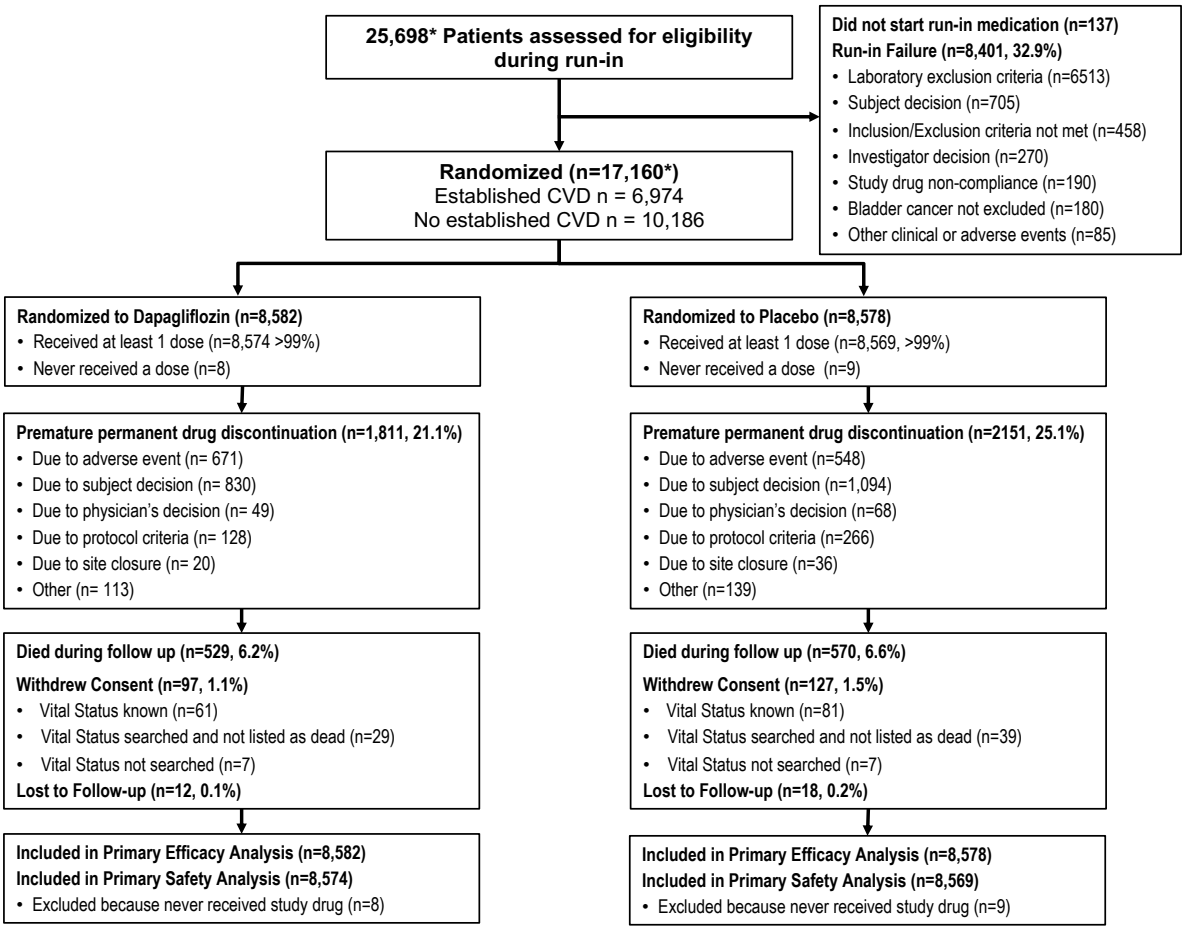
Only one option can be selected for each case.

For each case, the adjudicators will also indicate whether the pattern of liver injury involves hepatic adaptation by selecting “yes”, “no” or “possible” for hepatic adaptation. Hepatic adaptation has been defined as abnormal liver test results without symptoms or biochemical evidence of significant liver disease.

Section E – SUPPLEMENTAL RESULTS

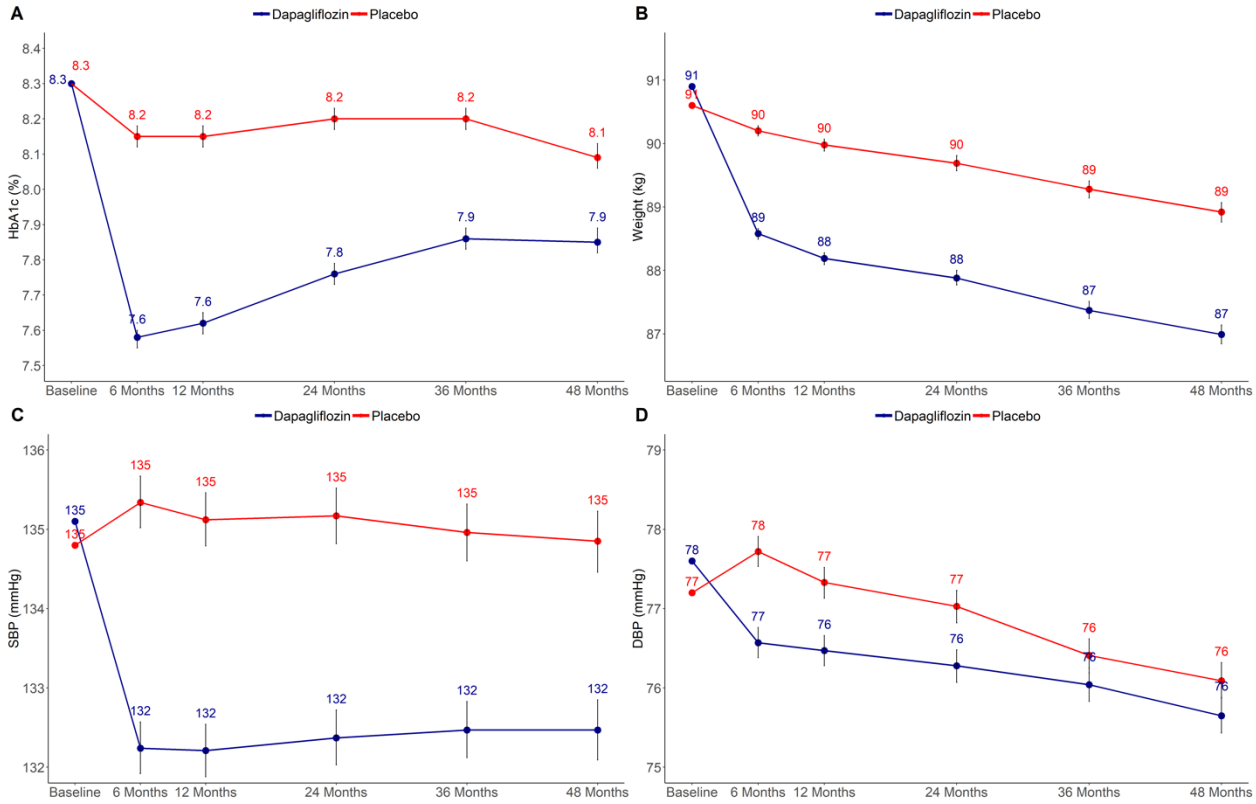
SUPPLEMENTAL FIGURES

Supplemental Figure 1: CONSORT Diagram



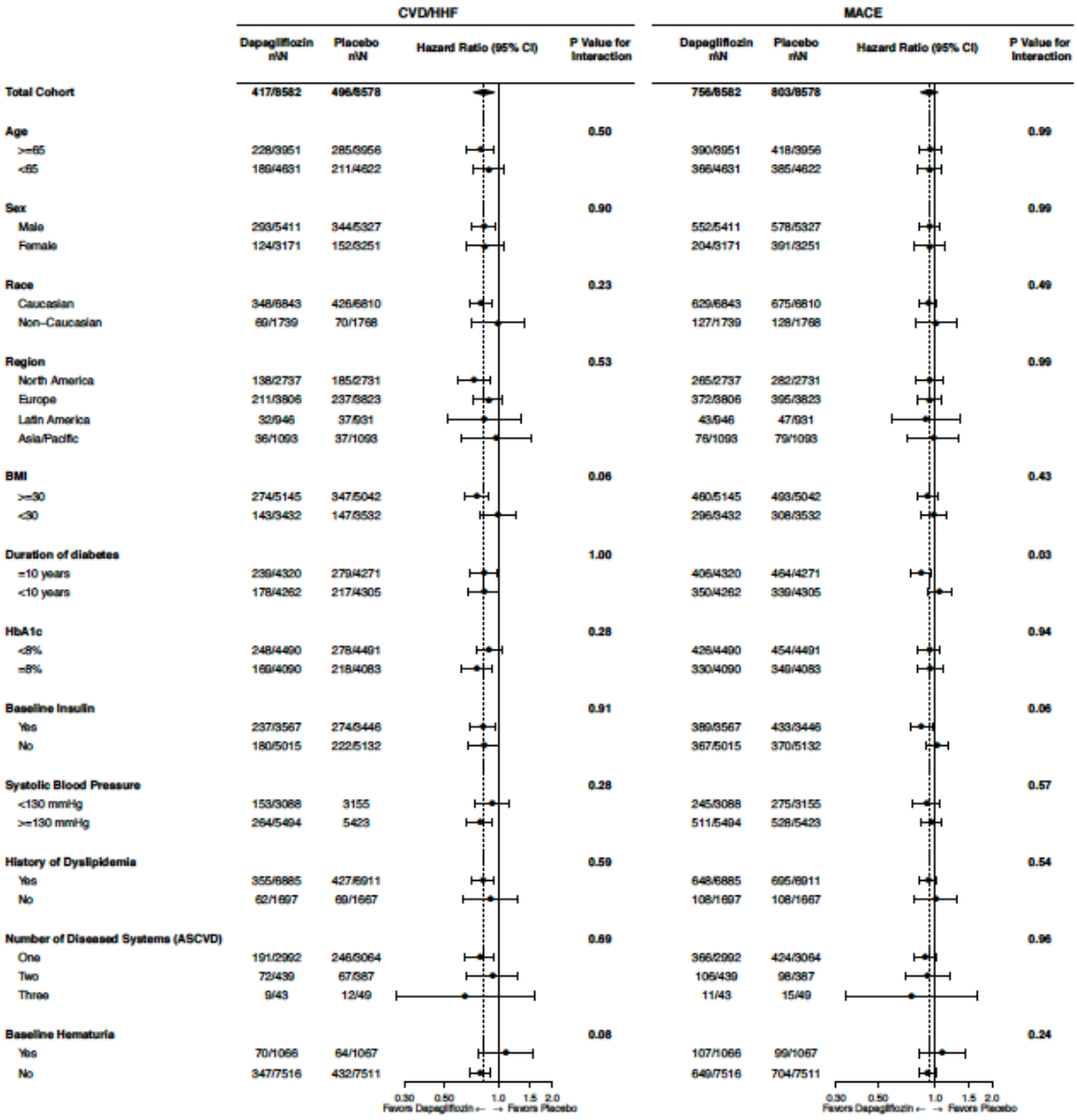
* Does not include 52 subjects excluded from a single site due to GCP violation in another trial (22 patients during run-in and 30 patients after randomization).

Supplemental Figure 2: Adjusted Mean HbA1c, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) over time by randomized treatment group. Expressed are values for HbA1c (%), weight in kg, SBP and DBP in mm/Hg.



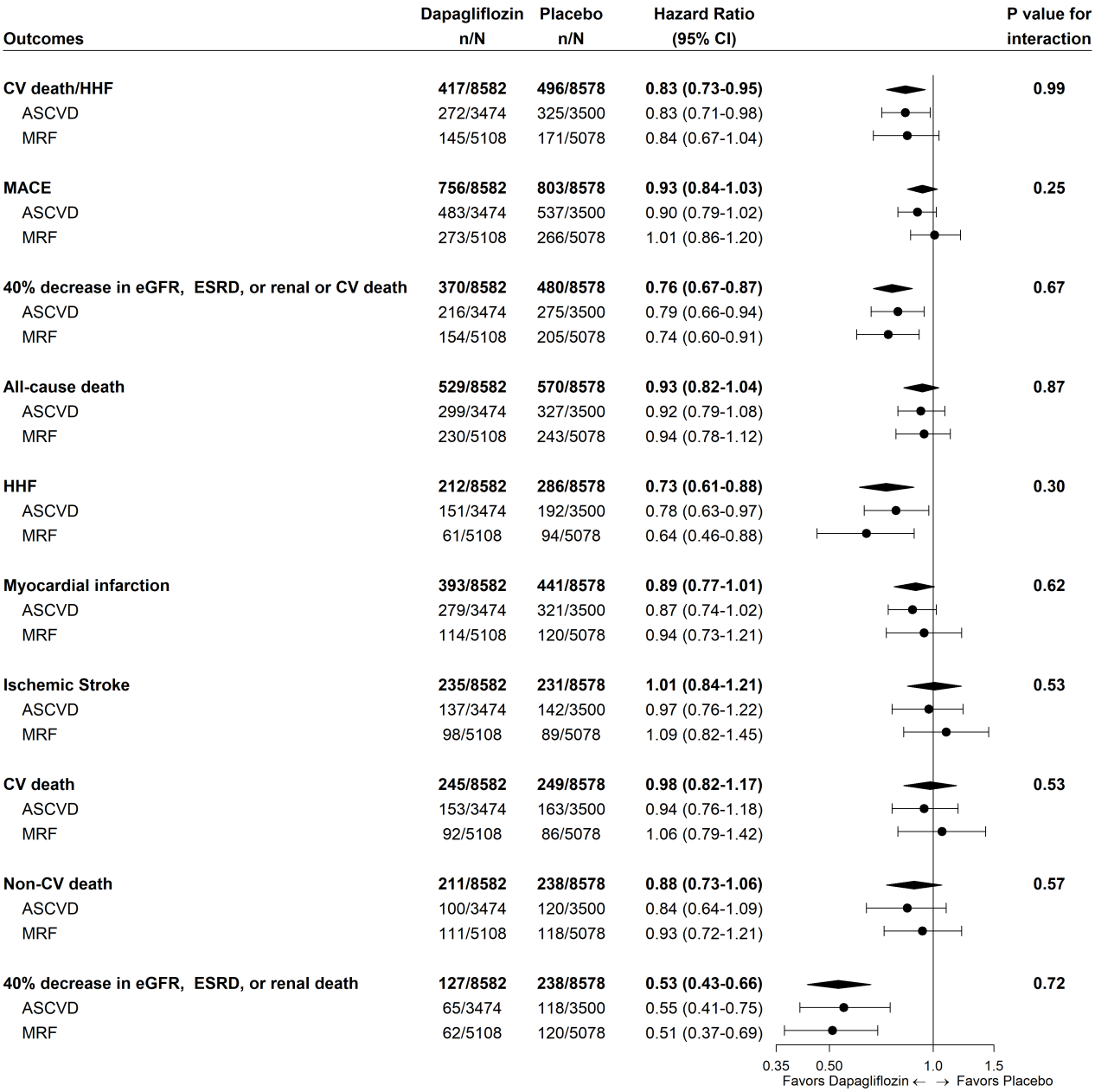
Supplemental Figure 3: Additional Subgroups of the primary efficacy outcomes

N=Number of subjects in treatment group, n=number of subjects with event, CI = confidence interval, CVD = cardiovascular death, HHF = hospitalization for heart failure, MACE = major adverse cardiovascular events, the composite of cv death, myocardial infarction or ischemic stroke, BMI = body mass index, ASCVD = atherosclerotic cardiovascular disease.



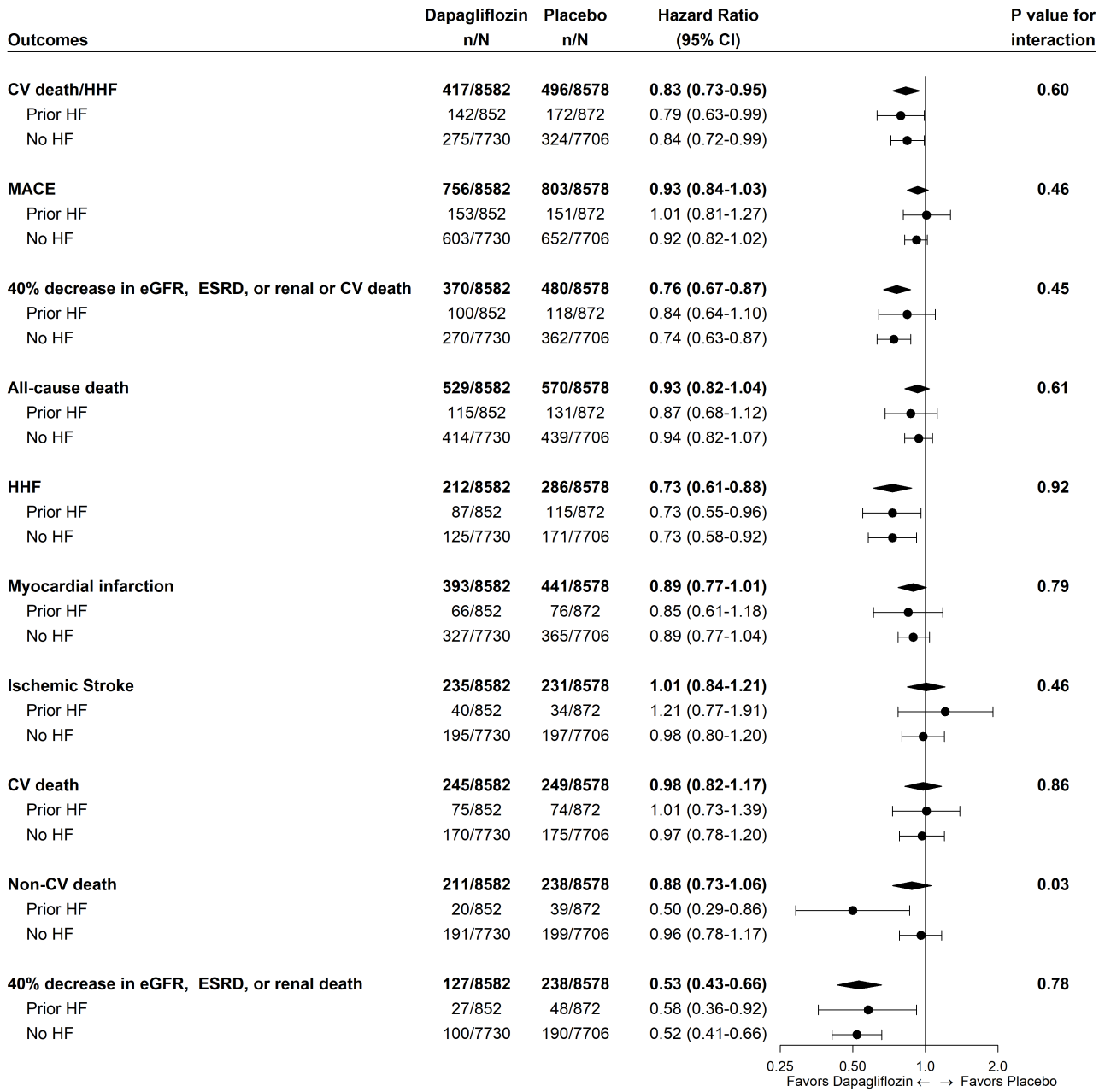
Supplemental Figure 4: Key Outcomes by Enrollment Stratum (Composites and Components)

N=Number of subjects in treatment group, n=number of subjects with event, CI = confidence interval, CV = cardiovascular, HHF = hospitalization for heart failure, ASCVD = atherosclerotic CV disease, MRF = multiple risk factors, eGFR = estimated glomerular filtration rate, ESRD = end stage renal disease.



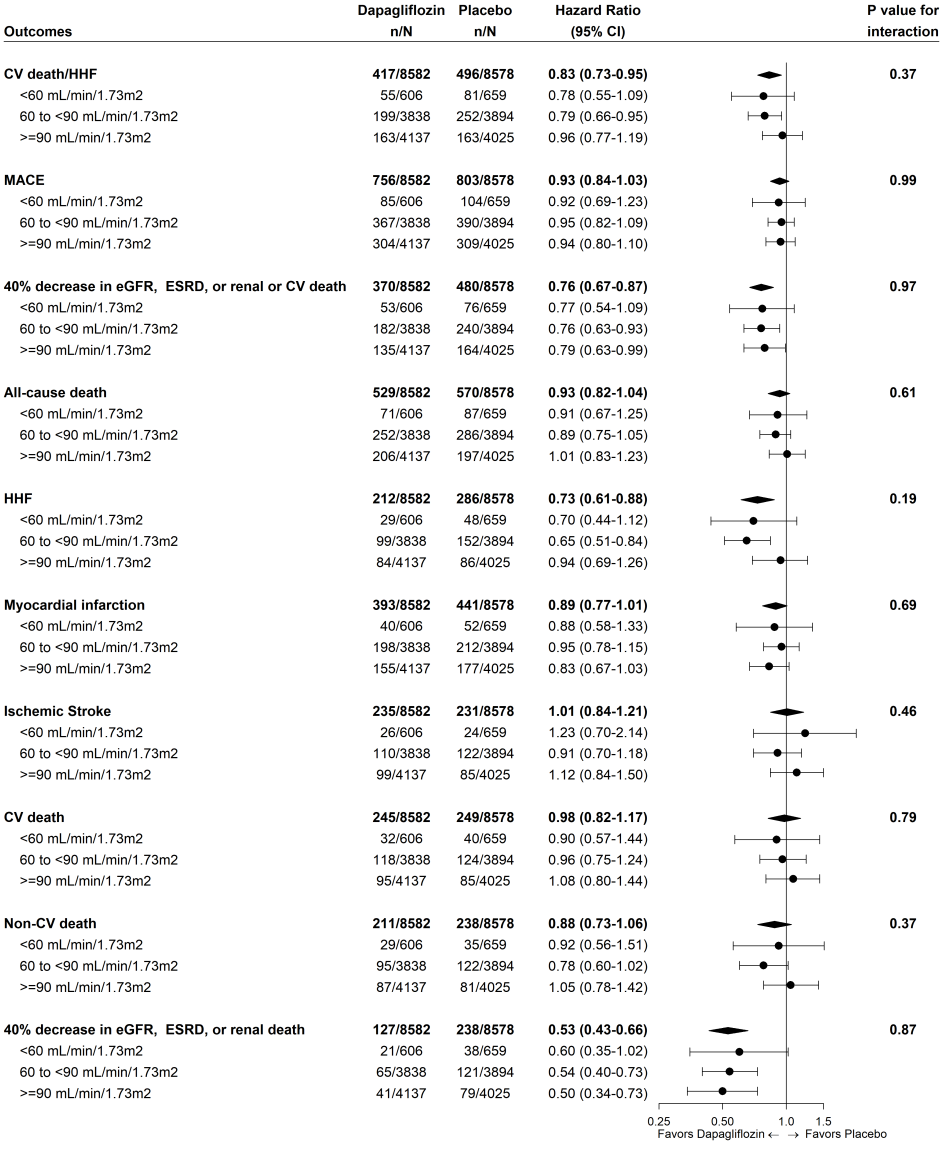
Supplemental Figure 5: Key outcomes by baseline HF status

N=Number of subjects in treatment group, n=number of subjects with event, CI = confidence interval, CV = cardiovascular, HHF = hospitalization for heart failure, HF = heart failure, eGFR = estimated glomerular filtration rate, ESRD = end stage renal disease.



Supplemental Figure 6: Key trial outcomes by baseline renal function (CKD-EPI)

N=Number of subjects in treatment group, n=number of subjects with event, CI = confidence interval, CV = cardiovascular, HHF = hospitalization for heart failure, HF = heart failure, eGFR = estimated glomerular filtration rate, ESRD = end stage renal disease. CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration equation[1].



Supplemental Table 1: Demographic characteristics of patients randomized vs entered into run-in but not randomized.

	Randomized (%)	n	Not Randomized (%)	n
N		17160		8538
Age >= 65 years	46.1	7907	55.9	4770
Age >= 75 years	6.4	1096	14.4	1229
Female	37.4	6422	41.8	3571
Male	62.6	10738	58.2	4967
Race				
White	79.6	13653	74.8	6388
Black or African American	3.5	603	6.9	591
Asian	13.4	2303	14.3	1218
American Indian or Alaska Native	0.6	104	0.6	54
Native Hawaiian/Pacific Islander	0.1	22	0.2	15
Other	2.8	475	3.2	272
Ethnicity Hispanic or Latino	15.0	2568	15.6	1336
Region				
North America	31.9	5468	39.2	3348
Europe	44.5	7629	37.6	3213
Latin America	10.9	1877	10.5	895
Asia Pacific	12.7	2186	12.7	1082
Strata (actual): Established CV Disease	40.6	6974	42.4	3595

Supplemental Table 2: Sensitivity Analyses of the Primary Endpoints

Competing Risk: A pre-specified sensitivity analysis for the co-primary efficacy endpoints was performed to account for the competing risks of non-CV and undetermined death based on Fine and Gray model. Per Protocol: An additional sensitivity analysis was performed excluding subjects with important protocol deviations as described in the statistical analysis plan, section 2.2. MACE = Major adverse cardiovascular events = the composite of cardiovascular death, MI or ischemic stroke. CVD/HHF = cardiovascular death or hospitalization for heart failure, NI = non-inferiority

Endpoint	Primary Pre-specified N=17160	Competing Risk N=17160	Per Protocol N=15083
MACE	0.93 [0.84-1.03] p=0.17 p(NI)<0.001	0.93 [0.85-1.03] p=0.18 p(NI)<0.001	0.94 [0.85-1.05] p=0.29 p(NI)<0.001
CVD/HHF	0.83 [0.73-0.95] p=0.005	0.83 [0.73-0.95] p=0.006	0.83 [0.72-0.95] p=0.008

Supplemental Table 3: Serious Adverse Events (SAE) by preferred term.
Listed are terms with a frequency ≥ 0.2% in either treatment arm.
Patients with events in more than 1 category are counted in each category. Patients with multiple events in the same category are counted only once in that category.
Dataset includes SAEs that occurred after the first dose of study drug to the earlier of 30 days after last dose of study drug or the Closing Visit. SAE coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. This table represents preferred terms reported by investigators, was not used for efficacy assessments and does not correspond directly to safety or efficacy outcomes adjudicated or refuted by the independent clinical events committee.

Preferred term	Number (%) of patients	
	Dapa 10 mg	Placebo
	(N=8574)	(N=8569)
Patients with at least 1 SAE	2925 (34.1)	3100 (36.2)
Angina unstable	243 (2.8)	238 (2.8)
Acute myocardial infarction	228 (2.7)	195 (2.3)
Pneumonia	163 (1.9)	183 (2.1)
Angina pectoris	138 (1.6)	146 (1.7)
Cardiac failure	120 (1.4)	165 (1.9)
Cardiac failure congestive	89 (1.0)	122 (1.4)
Atrial fibrillation	94 (1.1)	121 (1.4)
Coronary artery disease	94 (1.1)	69 (0.8)
Osteoarthritis	91 (1.1)	76 (0.9)
Cerebrovascular accident	89 (1.0)	71 (0.8)
Ischaemic stroke	85 (1.0)	79 (0.9)
Myocardial infarction	84 (1.0)	96 (1.1)
Acute kidney injury	67 (0.8)	101 (1.2)
Non-cardiac chest pain	82 (1.0)	85 (1.0)
Cellulitis	76 (0.9)	80 (0.9)
Death	40 (0.5)	43 (0.5)
Sepsis	53 (0.6)	49 (0.6)
Hypoglycaemia	61 (0.7)	73 (0.9)
Prostate cancer	62 (0.7)	53 (0.6)
Transient ischaemic attack	63 (0.7)	46 (0.5)

Preferred term	Number (%) of patients	
	Dapa 10 mg	Placebo
	(N=8574)	(N=8569)
Chronic obstructive pulmonary disease	45 (0.5)	48 (0.6)
Urinary tract infection	37 (0.4)	51 (.6)
Myocardial ischaemia	37 (0.4)	51 (0.6)
Peripheral arterial occlusive disease	41 (0.5)	47 (0.5)
Acute respiratory failure	26 (0.3)	34 (0.4)
Diabetic foot	33 (0.4)	27 (0.3)
Hyperglycaemia	27 (0.3)	46 (0.5)
Syncope	28 (0.3)	30 (0.4)
Basal cell carcinoma	29 (0.3)	26 (0.3)
Peripheral vascular disorder	31 (0.4)	16 (0.2)
Cardiac arrest	24 (0.3)	19 (0.2)
Peripheral ischaemia	28 (0.3)	26 (0.3)
Chest pain	27 (0.3)	15 (0.2)
Respiratory failure	25 (0.3)	18 (0.2)
Benign prostatic hyperplasia	26 (0.3)	29 (0.3)
Cataract	26 (0.3)	25 (0.3)
Hypotension	26 (0.3)	11 (0.1)
Carotid artery stenosis	24 (0.3)	20 (0.2)
Diabetic ketoacidosis	22 (0.3)	17 (0.2)
Hypertension	23 (0.3)	25 (0.3)
Cholelithiasis	24 (0.3)	34 (0.4)
Gastroenteritis	23 (0.3)	23 (0.3)
Osteomyelitis	21 (0.2)	30 (0.4)
Pulmonary embolism	23 (0.3)	19 (0.2)
Cholecystitis acute	19 (0.2)	16 (0.2)
Cerebral infarction	21 (0.2)	26 (0.3)
Intervertebral disc protrusion	21 (0.2)	14 (0.2)
Skin ulcer	22 (0.3)	21 (0.2)
Peripheral artery stenosis	21 (0.2)	17 (0.2)
Aortic stenosis	18 (0.2)	16 (0.2)
Cardiac failure acute	16 (0.2)	26 (0.3)
Gangrene	18 (0.2)	24 (0.3)

Preferred term	Number (%) of patients	
	Dapa 10 mg	Placebo
	(N=8574)	(N=8569)
Urosepsis	20 (0.2)	22 (0.3)
Atrial flutter	18 (0.2)	28 (0.3)
Septic shock	16 (0.2)	20 (0.2)
Sudden death	19 (0.2)	17 (0.2)
Adenocarcinoma of colon	17 (0.2)	17 (0.2)
Anaemia	16 (0.2)	21 (0.2)
Dehydration	15 (0.2)	13 (0.2)
Diverticulitis	17 (0.2)	16 (0.2)
Ankle fracture	16 (0.2)	10 (0.1)
Atrioventricular block complete	15 (0.2)	11 (0.1)
Breast cancer female	15 (0.2)	16 (0.2)
Cardiogenic shock	13 (0.2)	13 (0.2)
Ventricular tachycardia	19 (0.2)	11 (0.1)
Cholecystitis	14 (0.2)	19 (0.2)
Pneumonia aspiration	12 (0.1)	5 (<0.1)
Acute coronary syndrome	14 (0.2)	27 (0.3)
Diabetic metabolic decompensation	12 (0.1)	24 (0.3)
Gastrointestinal haemorrhage	16 (0.2)	12 (0.1)
Bradycardia	11 (0.1)	16 (0.2)
Femur fracture	14 (0.2)	18 (0.2)
Bronchitis	13 (0.2)	32 (0.4)
Diabetes mellitus inadequate control	11 (0.1)	24 (0.3)
Fall	11 (0.1)	19 (0.2)
Hypertensive crisis	12 (0.1)	23 (0.3)
Lumbar spinal stenosis	13 (0.2)	16 (0.2)
Nephrolithiasis	12 (0.1)	16 (0.2)
Gastritis	12 (0.1)	17 (0.2)
Bladder cancer	11 (0.1)	23 (0.3)
Cardiac failure chronic	12 (0.1)	19 (0.2)
Coronary artery stenosis	10 (0.1)	18 (0.2)
Iron deficiency anaemia	11 (0.1)	14 (0.2)
Lung neoplasm malignant	10 (0.1)	14 (0.2)

Preferred term	Number (%) of patients	
	Dapa 10 mg	Placebo
	(N=8574)	(N=8569)
Musculoskeletal chest pain	11 (0.1)	17 (0.2)
Humerus fracture	9 (0.1)	15 (0.2)
Ischaemic cardiomyopathy	8 (<0.1)	14 (0.2)
Asthma	5 (<0.1)	16 (0.2)
Dyspnoea	4 (<0.1)	15 (0.2)

REFERENCES

1. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.