



Figure 4. Proportional and absolute effects of canagliflozin compared with placebo on key safety outcome in patients with and without a history of heart failure at baseline.

ARD indicates absolute risk difference over 5 years; CANVAS, Canagliflozin Cardiovascular Assessment Study; ITT, intent-to-treat; CANVAS-R, Canagliflozin Cardiovascular Assessment Study–Renal; CI, confidence interval; HF, heart failure; and HR, hazard ratio. *Based on ITT dataset, whereas all other analyses based on on-treatment dataset. †For these adverse events, the annualized incidence rates are reported based on the CANVAS study alone through January 7, 2014, because, after this time, only serious adverse events or adverse events leading to discontinuation were collected. In the CANVAS-R study, only serious adverse events or adverse events leading to discontinuation were collected for these events.

reported for the EMPA-REG OUTCOME trial. An exception was the observation of a borderline significant greater proportional risk reduction for individuals with a history of heart failure at baseline in the CANVAS Program, which was not matched by a corresponding finding in the analyses of the EMPA-REG OUTCOME trial. This might reflect the different characteristics of the included populations or the slightly different criteria used to define heart failure outcomes between the 2 studies. However, the multiple and post hoc analyses of heart failure done for the CANVAS Program and EMPA-REG OUTCOME had limited statistical power to test for interactions, and the risk of missing real differences or observing spurious chance differences is high.

The CANVAS Program data provide clear evidence of the protective effects of canagliflozin on heart failure and, in conjunction with EMPA-REG OUTCOME, suggest an important role for SGLT2 inhibitors in the prevention of heart failure among patients with type 2 diabetes mellitus. Additional data from ongoing trials in diabetes mellitus will further clarify the impact of SGLT2

inhibitors on this major cause of mortality and morbidity^{25,26} and confirm or refute hypotheses raised by the CANVAS and EMPA-REG OUTCOME trial findings. A series of new trials specifically exploring mechanisms and testing effects on heart failure outcomes among patients without diabetes mellitus^{27–30} will also provide further insight into the mode of action by which benefits are achieved. In conclusion, among patients with type 2 diabetes mellitus and an elevated risk of cardiovascular disease, canagliflozin reduced the risk of cardiovascular death or hospitalized heart failure across a broad range of different patient groups and in addition to concomitant therapies for heart failure. Benefits may be greater in patients with a baseline history of heart failure compared with those without a history of heart failure.

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Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)

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Fracture Adjudication: Bioclinica

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Supplemental Appendix 3. CANVAS Program cardiovascular death and heart failure criteria

Definition of Cardiovascular Death

Cardiovascular death includes death resulting from an acute MI, sudden cardiac death, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

- 1. Death Due to Acute MI** refers to a death by any mechanism (arrhythmia, heart failure [HF], low output) within 30 days after a MI related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a “break” (e.g., a CHF- and arrhythmia-free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute MI). The 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 thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new left bundle branch block (LBBB), or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute MI, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. 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.

Death resulting from a procedure to treat myocardial ischemia (angina) or death due to a MI that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be considered as a death due to other cardiovascular causes.

- 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 instantaneous 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 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 after successful resuscitation from cardiac arrest and without identification of a noncardiac etiology (postcardiac arrest syndrome)
 - f. Unwitnessed death without other cause of death (information regarding the patient’s clinical status preceding death should be provided, if available)

General Considerations

- A subject seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as “sudden cardiac death.” Typical scenarios include:
 - Subject well the previous day but found dead in bed the next day
 - Subject found dead at home on the couch with the television on
- Deaths for which there is no information beyond “Patient found dead at home” may be classified as “death due to other cardiovascular causes” or in some trials, “undetermined cause of death.” Please see *Definition of Undetermined Cause of Death*, for full details.

- 3. Death Due to HF or Cardiogenic Shock** refers to a death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death and not following an acute MI. Note that deaths due to HF can have various etiologies, including one or more acute MIs (late effect), ischemic or nonischemic cardiomyopathy, or valve disease.

Death due to HF or Cardiogenic Shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive HF or cardiogenic shock following implantation of a mechanical-assist device.

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

- a. New or increasing symptoms and/or signs of HF requiring the initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF
- b. HF symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema
- c. Confinement to bed predominantly due to HF symptoms
- d. Pulmonary edema sufficient to cause tachypnea and distress **not** occurring in the context of an acute MI, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
- e. Cardiogenic shock **not** occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening HF

Cardiogenic shock is defined as systolic blood pressure (SBP) <90 mmHg for greater 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 *or*
- Oliguria (urine output <30 ml/hour) *or*
- Altered sensorium *or*
- Cardiac index <2.2 l/min/m²

Cardiogenic shock can also be defined if SBP <90 mmHg and increases to ≥90 mmHg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

General Considerations

HF may have a number of underlying causes, including acute or chronic ischemia, structural heart disease (e.g., hypertrophic cardiomyopathy), and valvular heart disease. Where treatments are likely to have specific effects, and it is likely to be possible to distinguish between the various causes, then it may be reasonable to separate out the relevant treatment effects. For example, obesity drugs such as fenfluramine (pondimin) and dexfenfluramine (redux) were found to be associated with the development of valvular heart disease and pulmonary hypertension. In other cases, the aggregation implied by the definition above may be more appropriate.

4. **Death Due to Stroke** refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.
5. **Death Due to Other Cardiovascular Causes** refers to a cardiovascular death not included in the above categories (e.g., dysrhythmia unrelated to sudden cardiac death, pulmonary embolism, cardiovascular intervention [other than one related to an acute MI], aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or nonsurgical revascularization should be classified as cardiovascular deaths.

Hospitalized Congestive Heart Failure

HF requiring hospitalization is defined as an event that meets the following criteria:

1. Requires hospitalization 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 date change if the time of admission/discharge is not available).

AND

2. Clinical symptoms of HF, including ≥ 1 of the following new or worsening conditions:
 - Dyspnea
 - Orthopnea
 - Paroxysmal nocturnal dyspnea
 - Increasing fatigue/worsening exercise tolerance

AND

3. Physical signs of HF, including ≥ 2 of the following:
 - Edema (greater than 2+ lower extremity)
 - Pulmonary crackles greater than basilar (pulmonary edema must be sufficient to cause tachypnea and distress not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening HF)
 - Jugular venous distension
 - Tachypnea (respiratory rate >20 breaths/minute)
 - Rapid weight gain
 - S3 gallop
 - Increasing abdominal distension or ascites
 - Hepatojugular reflux
 - Radiological evidence of worsening HF
 - A right heart catheterization within 24 hours of admission showing a pulmonary

capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg or a cardiac output < 2.2 l/min/m²

Note: biomarker results (e.g., brain natriuretic peptide [BNP]) consistent with CHF will be supportive of this diagnosis, but the elevation in BNP cannot be due to other conditions such as cor pulmonale, pulmonary embolus, primary pulmonary hypertension, or congenital heart disease. Increasing levels of BNP, although not exceeding the ULN, may also be supportive of the diagnosis of CHF in selected cases (e.g., morbid obesity).

AND

4. Need for additional/increased therapy
 - Initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF and including ≥ 1 of the following:
 - Initiation of or a significant augmentation in oral therapy for the treatment of CHF
 - Initiation of intravenous diuretic, inotrope, or vasodilator therapy
 - Up-titration of 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 HF.

AND

5. No other noncardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms is identified.

Note: it is recognized that some patients may have multiple simultaneous disease processes. Nevertheless, for the endpoint event of HF requiring hospitalization, the diagnosis of CHF would need to be the primary disease process accounting for the above signs and symptoms.