Supplementary Online Content

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

eAppendix 1. AleCardio Investigators

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eAppendix 2: Eligibility Criteria

Inclusion Criteria

- Age > 18 years
- Established or newly-diagnosed T2DM
- Ability to give informed consent
- Hospitalization for an ACS event within the prior 8 weeks

ACS Criteria

Myocardial Infarction	OR	**Biomarker-Negative ACS (Unstable Angina)**
• Cardiac biomarkers (troponin I or T, CK-MB mass, or CK-MB activity) with at least one determination > 99th percentile or above the local laboratory upper reference limit.		• No elevation of cardiac biomarkers • Chest pain or ischemic symptoms at rest >10 minutes • Prompting Hospitalization or chest pain observation unit within 24 hours of symptoms
AND one of the following:		AND one of the following:
• Chest pain or ischemic symptoms at rest >10 minutes within prior 24 hours • New ECG changes of acute ischemia (LBBB, ST elevations, or ST depressions) • New pathologic Q-waves or R/S >1 in V1-V2 • Regional myocardial scar or ischemia by nuclear, magnetic resonance, echocardiographic, or angiographic imaging.		• New or worsening ECG changes (transient ST elevation, ST depression, or T inversion) • Definite myocardial ischemia on nuclear or echocardiographic imaging • Angiographic stenosis >70% or thrombus in epicardial coronary artery or bypass graft • Need for coronary revascularization

ACS – acute coronary syndrome; CK-MB – creatinine kinase – MB fraction; T2DM – type 2 diabetes mellitus

Exclusion Criteria

Drug-related	• Concomitant treatment with TZD or fibrate • Prior intolerance to TZD or fibrate • Triglycerides (fasting) > 400 mg/dL • Systemic corticosteroid therapy for > 2 weeks within 3 months before screening
Medical	• Clinically apparent liver disease (jaundice, active hepatitis, ALT > 3 x ULN) • Anemia (hemoglobin < 10 mg/dL or hematocrit <30%) • $eGFR_{MDRD}$< 45 ml/min/1.73m^2 • Symptomatic congestive heart failure classified as NYHA class II-IV • Hospitalization with primary diagnosis of heart failure in the 12 months prior to randomization • Peripheral edema felt to be severe in the judgment of the enrolling investigator • Serious comorbid condition in which life expectancy is shorter than the duration of the study
General	• Serious medical condition which could interfere with the conduct of the study • Unwillingness or inability to comply with study procedures (including drug or alcohol abuse) • Positive pregnancy test, breast-feeding women, or women of childbearing potential not using highly effective methods of contraception • Participation in a clinical trial with an investigative device or drug within one month prior to screening.

ALT – alanine transaminase; $eGFR_{MDRD}$ – estimated glomerular filtration rate by Modification of Diet in Renal Disease formula; NYHA – New York Heart Association; TZD – thiazolindinedione; ULN – upper limit of normal.

Endpoint Definitions

The primary efficacy endpoint is the time to first occurrence of any component of the composite of cardiovascular death, non-fatal MI, or non-fatal stroke.

DEATH

Cardiovascular Death

Cardiovascular death includes sudden death, death due to acute myocardial infarction, death due to heart failure, death due to cerebrovascular accident (stroke) and death due to other cardiovascular causes, as follows:

1. **Sudden Cardiac Death**: refers to death that occurs unexpectedly in previously stable patient and should include the following deaths:
   - Witnessed and instantaneous without new or worsening symptoms and also in absence of progressive, prolonged (≥60 minutes) circulatory failure
   - Witnessed within 60 minutes of the onset of new or worsening symptoms unless a cause other than cardiac is obvious
   - Witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording or witnessed on a monitor by either a medic or paramedic)
   - Patient resuscitated from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death, including myocardial infarction, and who died within 24 hours or without gaining consciousness; similar patients who died during an attempted resuscitation
   - Unwitnessed death in the absence of pre-existing progressive circulatory failure or other causes of death (information regarding the patent's clinical status within the week preceding death should be provided).

2. **Death due to Myocardial Infarction**: death occurring up to 14 days after a documented MI verified either by diagnostic criteria outlined for MI or by autopsy findings showing recent MI or recent coronary thrombus and where there is no conclusive evidence of another causes 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 myocardial infarction that occurs as direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause.

3. **Death due to Heart Failure**: refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another causes of death and includes 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 but only if this is due entirely to heart failure symptoms
   - Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction or as a consequence of an arrhythmia occurring in the absence of worsening heart failure
   - Cardiogenic shock 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 is defined as systolic blood pressure (SBP) < 90 mm Hg 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 as SBP ≥ 90 mm Hg as a result of positive inotropic or vasopressor agents alone and/or with mechanical support in less than 1 hour.

This category will include sudden death during an admission for worsening heart failure.

4. **Death due to Cerebrovascular Accident** (intracranial hemorrhage or non-hemorrhagic stroke): refers to death occurring up to 30 days after documented stroke (verified by CT/MRI imaging or by autopsy findings showing recent stroke) and where there is no conclusive evidence of another cause of death.

5. **Death due to Other Cardiovascular Causes**: death must be due to fully documented cardiovascular cause not included into above categories (e.g. dysrhythmia, pulmonary embolism or other cardiovascular intervention).

Non-cardiovascular Death

Death occurs and is due primarily to an identifiable non-cardiovascular cause or etiology. Specific diagnoses may include respiratory failure, pneumonia, trauma, suicide, or any other non- cardiovascular defined causes (e.g., liver disease, etc.) not included in the previous categories. Only death due to a documented non-cardiovascular cause will be classified as noncardiovascular.

Presumed Cardiovascular Death

All deaths not attributed to the above categories of cardiovascular death and not attributed to a non-cardiovascular cause, will be presumed cardiovascular deaths and as such be part of the CV mortality endpoint.

MYOCARDIAL INFARCTION

Spontaneous Myocardial Infarction

A diagnosis of a qualifying MI event in a clinical setting consistent with myocardial ischemia will be defined by abnormal levels of cardiac biomarkers (troponin I or T or CK-MB mass) with at least one determination > the 99th percentile or above the upper reference limit as specified by the local laboratory. Preferably the diagnosis should be based on two measurements of troponin I or T showing a rise and/or fall in pattern. And at least one of the following:

- Chest discomfort or symptoms of myocardial ischemia (≥10 minutes) at rest within 24 hours prior to Hospitalization for MI
- ECG changes indicative of acute myocardial ischemia [in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)] as listed below or new left bundle branch block:
- 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
- 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
- Development of pathological Q-waves or R-waves on the ECG as described below:
    - Any Q-wave in leads V2–V3 ≥0.02 s or QS complex in leads V2 and V3 Q-wav ≥0.03 s 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) (The same criteria are used for supplemental leads V7–V9, and for the Cabrera frontal plane lead grouping)
    - R-wave ≥0.04 s in V1–V2 and R/S ≥1 with a concordant positive T-wave in the absence of a conduction defect
    - Regional loss of viable myocardium based on imaging evidence of new or presumed new wall motion or perfusion deficit [e.g. echocardiography, left ventriculography during cardiac catheterization, radionuclide angiography, single-photon emission tomography, magnetic resonance imaging (MRI)].

In patients where recurrent myocardial infarction is suspected from clinical signs or symptoms following the initial infarction, recurrent infarction is diagnosed if there is a ≥20% increase of the value in the second cardiac biomarker sample.

Procedure-Related MI

Percutaneous coronary interventions (PCI): for PCI in patients with normal baseline Troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 × 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized. When Troponin is not available, CK-MB greater than 3x upper limit of normal will be considered the threshold for myocardial infarction.

Coronary artery bypass grafting (CABG): for CABG in patients with normal baseline Troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 × 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction. When Troponin is not available, CK-MB greater than 5x upper limit of normal will be considered the threshold for myocardial infarction.

Myocardial infarction associated with stent thrombosis: the definition criteria for spontaneous MI have to be fulfilled and associated with angiographic confirmation of stent thrombosis as described below based on ARC Definitions of Definite, Probable, and Possible Stent Thrombosis (Cutlip DE, S Windecker, R Mehran, A Boam, DJ

Cohen, G-A van Es, PG Steg, M-A Morel, L Mauri, P Vranckx, E McFadden, A Lansky, M Hamon, MW Krucoff, PW Serruys and on behalf of the Academic Research Consortium, 2007, Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions, Circulation 115:2344-2351).

Definite Stent Thrombosis

- Angiographic confirmation of stent thrombosis (The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis [silent occlusion]). The presence of a thrombus (Intracoronary thrombus) that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:
    1. Acute onset of ischemic symptoms at rest
    2. New ischemic ECG changes that suggest acute ischemia
    3. Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI: Troponin or CK-MB > 99th percentile of URL)
    4. Non occlusive thrombus
       Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) non-calcified 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
    5. 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)

- 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

A probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days
- 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

A possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

BIOMARKER-NEGATIVE ACS (UNSTABLE ANGINA)

A diagnosis of a qualifying a biomarker-negative ACS event (UA) in a clinical setting consistent with myocardial ischemia will be defined by the following:

- No elevation in cardiac biomarkers (cardiac biomarkers are negative for myocardial necrosis)

and

- Chest discomfort or symptoms of myocardial ischemia (≥ 10 minutes) at rest considered to be myocardial ischemia upon final diagnosis

and

- Prompting an unscheduled visit to a healthcare facility and Hospitalization (including chest pain observation units) within 24 hours of the most recent symptoms

And one of the following:

a. New or worsening ST or T wave changes on resting ECG 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.
b. Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect) or stress echocardiography (reversible wall motion abnormality).
c. Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery (native or by-pass graft) that is believed to be responsible for the myocardial ischemic symptoms/signs
d. Need for coronary revascularization procedure (PCI or CABG) during the same hospital stay. This criteria would be fulfilled if the admission for myocardial ischemia lead to transfer to another institution for the revascularization procedure without interceding home discharge.

NON-FATAL STROKE

Stroke is defined as 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 will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown.
For the diagnosis of stroke, the following 4 criteria should be fulfilled:

1. 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)
    - Amaurosis fugax (transient complete/partial loss of vision of one eye)
    - Other new neurological sign(s)/symptom(s) consistent with stroke
    - Other new neurological sign(s)/symptom(s) consistent with stroke

* 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.

2. 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:
    a. Pharmacologic (i.e., thrombolytic drug administration)
    b. Non-pharmacologic [i.e., neurointerventional procedure (e.g. intracranial angioplasty)]

or

    c. Available brain imaging clearly documents a new hemorrhage or infarct

or

    d. The neurological deficit results in death

3. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion)
4. Confirmation of the diagnosis by at least one of the following:
    a. Neurology or neurosurgical specialist
    b. Brain imaging procedure (at least one of the following):
        - CT scan
        - MRI scan
        - Cerebral vessel angiography
    c. 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 forwarded for Phase II Review. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone, but CEC consensus will be 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

<u>Strokes are sub-classified as follows:</u>

1. Ischemic (Non-hemorrhagic): a stroke caused by an arterial obstruction due to either a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology.
2. Hemorrhagic: a stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral hemorrhage (intraparenchymal or

intraventricular), ischemic strokes with hemorrhagic transformation (i.e., no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan), subdural hematoma,* and primary subarachnoid hemorrhage.

*All subdural hematomas that develop during the clinical trial should be recorded and classified as either traumatic versus nontraumatic.

3. Unknown: the stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed.

HOSPITALIZATION FOR HEART FAILURE

Heart failure is defined as the development of signs and symptoms of congestive heart failure (CHF) not present at randomization and not due to other non-cardiac etiologies (e.g., acute renal failure, venous insufficiency, hepatic cirrhosis, pulmonary hypertension, etc.).

Heart failure (HF) requiring Hospitalization is defined as an event that meets the following criteria:

a. 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

b. Clinical symptoms of heart failure including at least one of the following:
New or worsening
   - dyspnea
   - orthopnea
   - paroxysmal nocturnal dyspnea

And

c. Physical signs of heart failure, including at least one 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 myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure)
   - estimated jugular venous distension > 10 cm
   - tachypnea (respiratory rate > 20 breaths/minute)

And

d. Laboratory Values, including at least one of the following:
   - Chest X-Ray consistent with congestion
   - Left ventricular ejection fraction < 0.4 within 6 months

   NOTE: Biomarker results (e.g., brain natriuretic peptide (BNP)) consistent with congestive heart failure 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.

And

e. Additional/Increased therapy
Initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure and including at least two of the following:
   - Initiation of intravenous diuretic, inotrope, or vasodilator therapy or significant augmentation of therapy
   - Uptitration of intravenous therapy, if already on therapy
   - Continuous oxygen administration or confinement to bed predominantly due to heart failure symptoms (or both)
   - 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.

And

f. No other non-cardiac 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 heart failure requiring hospitalization, the diagnosis of congestive heart failure would need to be the primary disease process accounting for the above signs and symptoms.

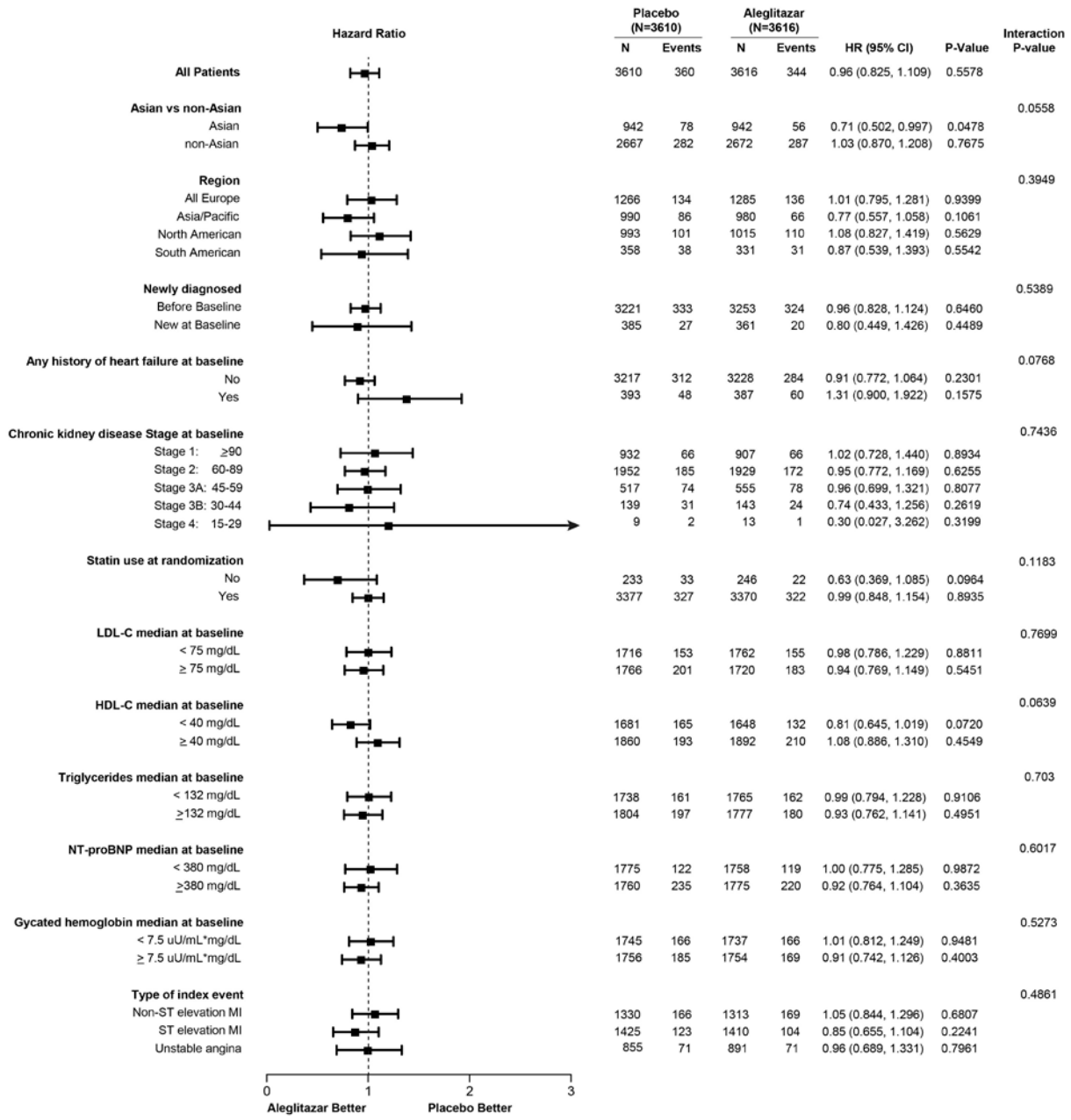
Or

Cardiogenic shock 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 is defined as systolic blood pressure (SBP) < 90 mm Hg 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:

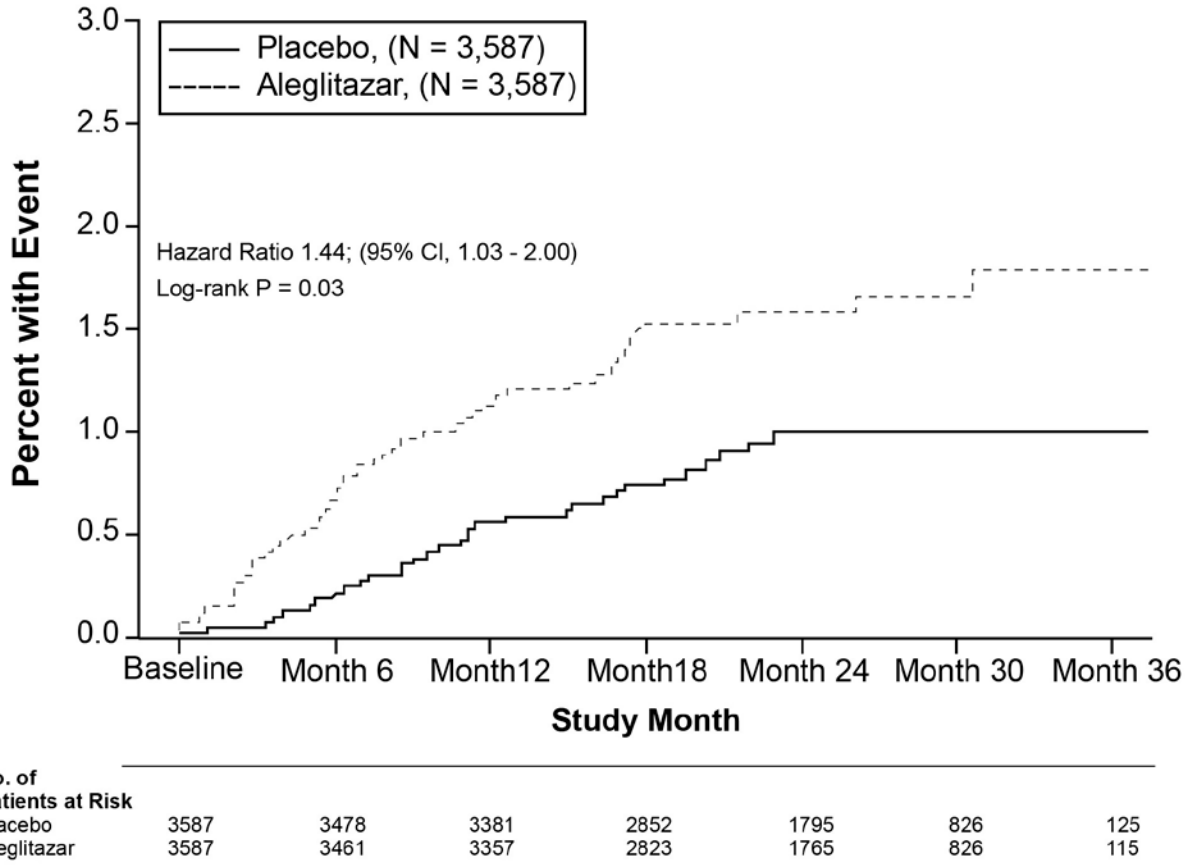
- Cool, clammy skin or
- Oliguria (urine output < 30 mL/hour) or
- Altered sensorium or
- Cardiac index < 2.2 L/min/m2

Cardiogenic shock can also be defined as SBP ≥ 90 mm Hg as a result of positive inotropic or vasopressor agents alone and/or with mechanical support in less than 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 endpoint.

eFigure 1. Hazard Ratios for Primary Endpoint in Subgroups

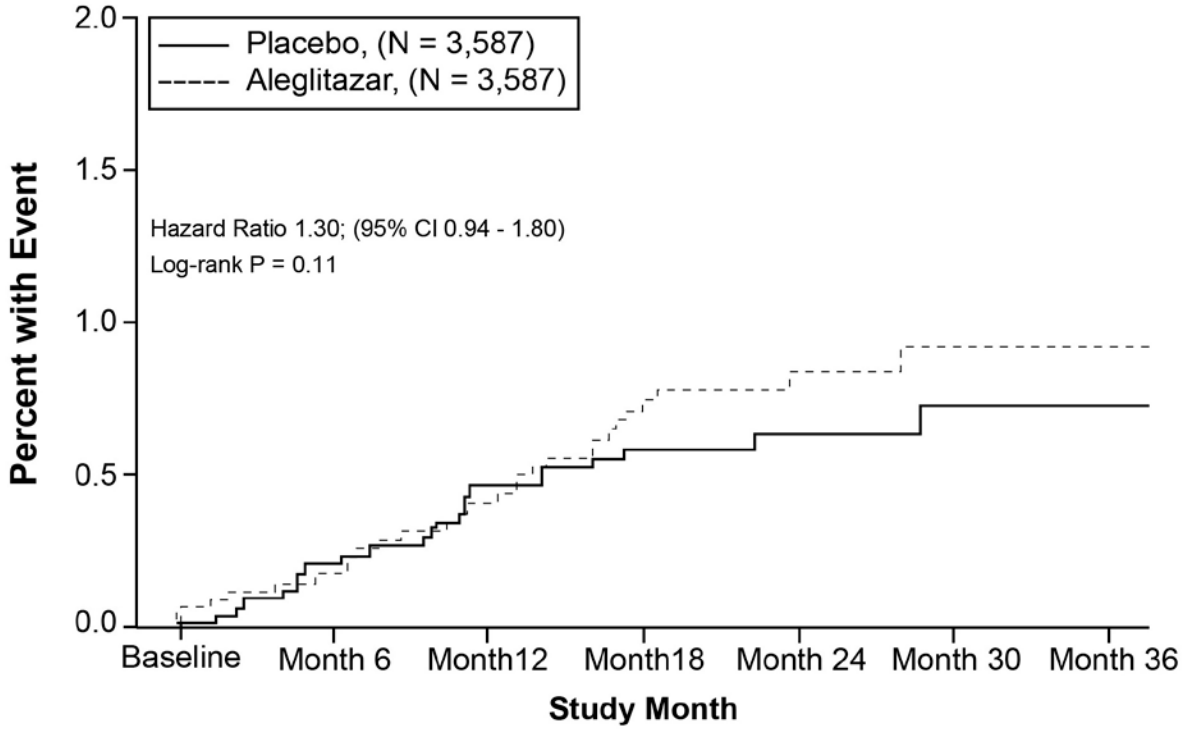


eFigure 2. Gastrointestinal Hemorrhages



Cumulative Kaplan-Meier Estimates of Time to First Occurrence of Gastrointestinal Hemorrhage
Includes only patients who received at least one dose of study drug and according to drug actually received.

eFigure 3. Bone Fractures



No. of Patients at Risk							
Placebo	3587	3477	3383	2859	1799	820	124
Aleglitazar	3587	3478	3381	2842	1769	819	113

Cumulative Kaplan-Meier Estimates of Time to First Occurrence of Bone Fracture
Includes only patients who received at least one dose of study drug and according to drug actually received.