Rationale, design, and baseline characteristics of the SIGNIFY trial: a randomized, double-blind, placebo-controlled trial of ivabradine in patients with stable coronary artery disease without clinical heart failure.
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Supplementary material 1. Definitions of study endpoints (extracted from the Endpoint Validation Committee Charter)

1. FATAL EVENTS

1.1. All-cause mortality

This will consist of all deaths.

1.2. Cardiovascular death

Cardiovascular deaths will include:

- All coronary deaths meeting the definition below (see section 1.2.1),
- Deaths related to cardiovascular procedures other than coronary artery procedures (see section 1.2.2),
- Deaths from stroke (see section 1.2.3),
- Other cardiovascular deaths (see section 1.2.4).

In the case of coronary death, the mode of death (sudden or non-sudden) will be specified.
The following information will be specified for sudden deaths:

- Witnessed instantaneous unexpected death,
- Witnessed within 1 hour after the onset of symptoms,
- Witnessed within 1 to 24 hours after the onset of symptoms,
- Not witnessed unexpected death, including patient found dead.

A witness can be a relative or any person present in the same place, or a person able to report what he/she has viewed or heard from the patient.
In the case a patient collapses, is successfully resuscitated, and then dies without having recovered his/her consciousness, the mode of death will refer to the initial event.
Death during sleep will be considered as “not witnessed unexpected death”.

1.2.1. Coronary death

Coronary deaths will include deaths due to heart failure (HF), deaths due to myocardial infarction (MI), deaths related to coronary artery procedures and presumed arrhythmic deaths.

1.2.1.1. Death from HF

Death occurring when at least one of the components of the HF definition (refer to the description of “new onset or worsening of HF” in section 2.3 below) is present even if the terminal event is an arrhythmia, unless there is an obvious other cause of death.

1.2.1.2. Death from MI

Death occurring up to 28 days after a documented MI (see section 2.1.1) or autopsy findings showing a recent MI or a recent occluding coronary thrombus unless there is an obvious other cause of death.

1.2.1.3. Death related to coronary artery procedure

Death directly related to a coronary artery procedure (investigation/procedure/operation).

1.2.1.4. Presumed arrhythmic death

Death related to a documented fatal arrhythmia, or presumably arrhythmia-related witnessed instantaneous sudden unexpected fatal collapse.

1.2.2. Cardiovascular procedure (other than coronary artery procedure) related death

Death directly related to a cardiovascular investigation/procedure/operation (other than coronary artery procedure).

1.2.3. Death from stroke

Death occurring up to 28 days after a stroke, and that is either due to the stroke (see section 2.2) or caused by a complication of the stroke, unless there is an obvious other cause of death.

1.2.4. Other cardiovascular death

Death must be caused by a fully documented cardiovascular cause (not included above):

- Pulmonary embolism,
- Aortic aneurysm/thrombosis/dissection/rupture,
- Leg ischemic complication/amputation,
- Mesenteric ischemia,
- Other.

1.3. Non-cardiovascular death

Death will be considered non-cardiovascular only if an unequivocal and documented non-cardiovascular cause can be established.

Predefined categories of non-cardiovascular death are:

- Infection,
- Cancer,
- Renal failure,
- Gastrointestinal causes,
- Respiratory failure,
- Trauma/violent death,
- Suicide,
- Non-cardiovascular surgery,
- Other.

1.4. Death of unknown cause

This will correspond to deaths for which it is not possible to specify whether they are cardiovascular or not. In the case of death of unknown cause, the mode of death will be specified as described above for coronary death.

NB: When there are multiple potential causes of death, the adjudicators should make all efforts to define the most probable cause. If the potential causes of death are of equal importance, the death will be adjudicated as death of unknown cause.

1.5. Death of unclassifiable cause

This will correspond to deaths for which no information is available (unclassifiable due to lack of data).

2. NON-FATAL EVENTS

2.1. Myocardial Ischemic Events (MIE)

They will include acute MI and unstable angina.

2.1.1. Acute MI

All confirmed MI will be counted as events, whether they occurred spontaneously or as the direct consequence of an investigational procedure or operation.

MI type 1 or type 2

A diagnosis of acute MI will be made in the case of detection of rise and/or fall of coronary biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia;
- Electrocardiography (ECG) changes indicative of new ischemia [new 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.

MI type 3

Sudden, unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

NB: In this case, the adjudicators have to adjudicate 2 separate events:

- Acute MI/type 3,
- Death due to “acute MI”/mode of death: “sudden”.

MI type 4a

For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis (**MI type 4a**). By convention, increases of biomarkers greater than 3 × 99th percentile URL are designated as defining PCI-related MI.

MI type 4b

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 with at least one value above the 99th percentile URL.

MI type 5

For coronary artery bypass grafting (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 are designated as defining CABG-related MI.

Reinfarction (new acute MI ≤28 days following the initial acute MI)

Recurrent ischemic symptoms with or without ECG changes indicative of new myocardial ischemia within 28 days of the initial infarction, together with an increase ≥20% of the value of cardiac biomarker if the initial biomarker concentration is elevated but stable or decreasing at the time of suspected reinfarction. If the initial biomarker concentration is normal, the criteria for new acute MI apply.

2.1.2 Unstable angina leading to hospitalization or prolongation of hospitalization

Unstable angina is defined as a new onset or worsening of angina pectoris (or equivalent type of ischemic discomfort) sufficient to warrant hospitalization (or prolongation of hospitalization) with any 1 of the 3 following features:

- Angina occurring at rest and prolonged, usually greater than 20 minutes;
- New onset angina of at least Canadian Cardiovascular Society (CCS) classification III severity;
- Recent acceleration of angina reflected by an increase in severity of at least 1 CCS class to at least CCS class III.

In addition, worsening ischemia should be confirmed by one or more of the following:

- Dynamic ECG changes: new or worsening ST or T waves changes on ECG in the absence of left ventricular hypertrophy and permanent LBBB;
- Evidence of ischemia at low threshold on functional testing or new coronary angiographic or computed tomography (CT)-scan changes;
- Coronary revascularization performed as a consequence of ischemic symptoms with resolution of symptoms.

2.2. Stroke

Stroke is defined as an acute disturbance of focal or global neurological function, with symptoms resulting from intracranial vascular disturbance, usually lasting more than 24 hours.

For the purpose of the study, **only symptomatic strokes will be considered for adjudication** (e.g. presence of hemiplegia, focal motor defect, central facial palsy, aphasia, visual field defect, cognitive defect, cerebellous syndrome, coma…).

Strokes will be divided into the following types on the basis of results of neuroimaging techniques (magnetic resonance imaging [MRI], CT-scan):

- **Ischemic stroke**: symptoms lasting more than 24 hours, with no apparent cause other than that of ischemic origin.
  If the duration of the neurological symptoms is less than 24 hours and if there are available results of cerebral MRI or CT-scan with evidence of associated acute cerebral infarction, then the event will be adjudicated as an ischemic stroke.
  An ischemic stroke with hemorrhagic transformation should be adjudicated as "ischemic stroke".
- **Hemorrhagic stroke**: acute episode of focal or global neurological dysfunction caused by intraparenchymal, intraventricular or subarachnoid hemorrhage with no apparent non-cardiovascular cause (e.g. trauma, tumor or infection), evidenced by CT-scan or MRI, regardless the duration of symptoms.
- **Stroke of unknown type**: when the type of stroke cannot be determined with certainty, in particular when the appropriate documentation (neuroimaging; autopsy/ surgery reports) has not been obtained despite all efforts.

2.3. New onset or worsening of HF leading to hospitalization or prolongation of hospitalization

HF is defined by the presence of symptoms such as dyspnea or fatigue either at rest or during exercise, and/or signs of fluid retention (e.g. peripheral edema, pulmonary edema,

raised jugular venous pressure, ascites…), leading to hospitalization (or prolongation of hospitalization).
These symptoms should be associated with:

- The **objective evidence of HF** such as abnormal chest X ray (congestion signs, pleural fluid…), or abnormal echocardiography (dysfunction, pericardial fluid…), or abnormal nuclear investigation, or BNP (brain natriuretic peptide) increase; and
- The **requirement or increase of dedicated treatment for HF** such as intravenous/intramuscular or oral medications for HF (diuretics, vasodilators, positive inotropic agents…).

An event for which the above information is available will be submitted to the adjudicators even if it is not the only event leading to hospitalization or if it occurred during the hospitalization for another event.
Patients with cardiogenic shock will fulfill the definition of HF.

2.4. Coronary revascularization:

- PCI
- CABG

Any documented coronary revascularization (successful or not) will be submitted to adjudicators.
Particular cases:

- In case of 2 or more PCI performed during the same hospitalization to treat the same myocardial ischemic event, only the first one should be adjudicated as an endpoint; the other one(s) will be rejected by the adjudicators, with "prior revascularization during the same admission" as the reason of non-endpoint.
- If several PCI are performed during the same hospitalization to treat different myocardial ischemic events (e.g. a revascularization followed by a post-procedure MI requiring a new revascularization), each revascularization should be adjudicated as an endpoint.
- If a PCI is performed for an acute ischemic event but the revascularization is incomplete and there is a planned readmission for a further revascularization, this should be adjudicated as a deferred urgent revascularization.
- An unsuccessful attempt at coronary revascularization (PCI/CABG) should be adjudicated as an endpoint since there was an indication for coronary revascularization.
- If there is a hybrid case – a PCI and CABG at the same time – these will both be adjudicated separately. The PCI will be confirmed and a new event will be created and adjudicated as CABG (and vice-versa) if the investigator reported only one event.

There are four modalities of coronary revascularization defined as follows:

- **Urgent**, related to acute coronary syndrome (including deferred treatment for this acute event),
- **Non-urgent, driven by symptoms** with or without ischemia,
- **Non-urgent, driven by ischemia** without symptoms,
- **Non-urgent, not related to symptoms and/or ischemia.**

3. HOSPITALIZATION

An admission to hospital is defined as any attendance at hospital requiring completion of the hospital admission procedures and at least an overnight stay or until death of the patient. Accordingly, the date of entry and the date of discharge will be different.
An event leading to the prolongation of an ongoing hospitalization decided for another reason, with or without the transfer of the patient to a specialized hospital department, will be considered as a hospitalization.
Planned (elective) hospitalizations are excluded from this definition.