

Supplementary Appendix

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

Supplement to: Bønaa KH, Njølstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006;354:1578-88.

Electronic Supplementary Appendix

End point classifications, end point definitions, and diagnostic criteria in the *NORVIT* trial

Participants are followed for the occurrence of each type of event listed in the following classification scheme, occurring between the date of inclusion and end of follow-up for the participant in question.

End point classification

Primary end point

is a composite of the following codes:

1.1.1 - 1.1.5, 2.1.1 - 2.1.2, 2.2.0, 1.3.2 - 1.3.4, 2.5.2 - 2.5.4

A participant may experience several events of the composite end point during follow-up. In the Cox regression and Kaplan-Meier analyses, time to the first event of all primary end point codes is calculated for each participant.

Secondary end points

1. Death from all causes: 1.1.1 – 1.9.0
2. Coronary events
 - Fatal myocardial infarction: 1.1.1 – 1.1.5
 - Non-fatal myocardial infarction: 2.1.1 – 2.1.2, 2.2.0
 - Hospitalized unstable angina pectoris: 2.3.1
 - Coronary artery bypass surgery: 2.4.1
 - Percutaneous coronary intervention: 2.4.2
3. Fatal and non-fatal stroke
 - 1.3.2 – 1.3.4 and 2.5.2 – 2.5.4

End point definitions and diagnostic criteria

1. Fatal events

Deaths are classified by the End point committee in the following subgroups:

1.1 Coronary deaths

- 1.1.1 Death within 28 days from the onset of symptoms of a definite myocardial infarction (MI); the event verified as definite MI according to NORVIT criteria (Appendix 1), or autopsy confirming either a recent MI or a recent occluding coronary thrombus.
- 1.1.2 Death within 28 days from the onset of symptoms of a probable myocardial infarction; with the event classified as a probable MI according to NORVIT criteria (Appendix 1), or autopsy confirming probable MI.

- 1.1.3 Death after the onset of chest pain, syncope, acute pulmonary edema, or cardiogenic shock without confirmed MI (death occurring during hospital stay for the index event: see code 1.1.5)
- 1.1.4 Sudden, unexpected death, witnessed or unwitnessed, when there is no reason to presume another cause of death (excluded are patients with sign or symptoms of other fatal disease when the subject was last observed alive); deaths without any information of symptoms; or instantaneous death.
- 1.1.5 Death from ventricular arrhythmia, pulmonary edema, or sudden, unexpected death, occurring during the hospital stay for the index MI, when there is no confirmative evidence for a new MI.
- 1.1.6 Death from MI related to a coronary invasive procedure or surgery.
- 1.2.0 Other cardiac disease, i.e. death from non-coronary heart disease.(examples: myocarditis, primary arrhythmia, valvular disease)
- 1.3 Cerebrovascular deaths

Death within 28 days after the onset of symptoms of stroke. Stroke is classified in the following subgroups according to the NORVIT criteria (Appendix 2).

 - 1.3.1 Subarachnoidal hemorrhage
 - 1.3.2 Cerebral infarction
 - 1.3.3 Intracerebral hemorrhage
 - 1.3.4 Unspecified stroke
 - 1.3.5. Death from stroke related to a surgical or invasive procedure

For subgroups 1.3.2 - 1.3.4, symptoms (neurological deficits) must have been present for 24 hours or until death occurred.
If information on symptoms and clinical findings is missing, the diagnosis should be based on autopsy results.
- 1.4.0 Death from aortic aneurysm.
Dissecting/ruptured aneurysm
- 1.5 Death from pulmonary embolism.
 - 1.5.1 Pulmonary embolism confirmed by scintigraphy, CT, angiography, or autopsy results, regardless whether the diagnosis had been clinically detected or not.
 - 1.5.2 Pulmonary embolism clinically diagnosed, without test results to confirm the diagnosis.
- 1.6.0 Death from other cardiovascular disease
- 1.7.0 Death from malignant disease
- 1.8.0 Violent death: suicide, murder, accident
- 1.9.0 Death from other causes

2. Non-fatal events

2.1 Myocardial infarction

2.1.1 Definite MI

- a) Typical, atypical or inadequately described symptoms (category 1, 2 or 5) + ECG in category 2
or:
- b) Typical symptoms (category 1) + MI biomarker in category 1 or 7, regardless of ECG
or:
- c) Atypical or inadequately described symptoms (category 2 or 5) + MI biomarker in category 1
or 7 + ECG in category 3

2.1.2 Probable MI

- a) Typical symptoms (category 1) + MI biomarker in category 2 + ECG in category 3
or:
- b) Typical symptoms (category 1) + MI biomarker in category 2 + ECG in category 4 or 9
or:
- c) Atypical or inadequately described symptoms (category 2 or 5) + MI biomarker in category 2 +
ECG in category 3
- d) Atypical or inadequately described symptoms (category 2 or 5) + MI biomarker in category 1
or 7 + ECG in category 4 or 9

2.1.3 Silent MI

This code is used only for new silent Q-infarctions diagnosed from routine ECG during follow-up and at the latest by the end of follow-up, as compared with an ECG recorded earlier during follow-up, but after the inclusion in the trial. Clinicians at local hospitals will make the diagnosis.

2.1.4 MI related to a procedure

Includes cases of MI biomarkers in category 1, 2 or 7 appearing not later than the day after an invasive procedure, regardless of cECG and symptom classifications.

2.2.0 Cardiac arrest with successful resuscitation

Includes cases where a definite or probable MI could not be confirmed (for example because cardioversion was performed)

2.3 Acute coronary events that do not satisfy criteria in category 2.1.1 - 2.2.0:

2.3.1 Hospitalized acute episode of angina pectoris

Includes:

a) Prolonged chest pain

Duration 20 minutes or more, without dynamic ECG-changes or biomarker changes as in definite or probable MI (for example unstable angina)

b) Ischemic episode

Chest pain (one or more episodes, each one < 20 minutes), with either equivocal ECG-changes or non-specifically increased biomarkers, that together do not satisfy the criteria of definite or probable MI.

2.3.2 Acute left ventricular failure, triggered by an ischemic episode

2.3.3 Acute left ventricular failure, not triggered by an ischemic episode

2.4 Revascularizations

will be coded as secondary end points regardless of whether or not they occur in conjunction with another event. Deaths, acute MIs, and strokes that occur within 28 days after CABG/PTCA/carotid surgery will be classified as end points in the respective subgroups.

2.4.1 CABG

2.4.2 PTCA and coronary endarterectomy.

First PTCA after the index MI, including unsuccessful attempts of PTCA

2.4.3 Recurrent PTCA, including unsuccessful attempts of PTCA

2.4.4 Carotid endarterectomy

2.4.5 TPA of other arteries

2.5. Non-fatal stroke

Rapid development of clinical signs of focal or global* disturbance of cerebral function lasting more than 24 hours, and without evidence of a non-vascular cause.

If symptoms last < 24 hours, the diagnosis will be TIA.

* global refers to subarachnoidal hemorrhage and to comatous patients

2.5.1 Subarachnoidal hemorrhage

2.5.2 Cerebral infarction

2.5.3 Intracerebral hemorrhage

2.5.4 Unspecified stroke

2.5.5 TIA

2.5.6 Stroke related to a surgical or invasive procedure

See Appendix for subgroup diagnostic criteria

2.6.0 Aortic aneurysm, which must be:

a) symptomatic

b) operated upon, or

c) surgery is indicated (i.e. cases in which there are contraindications against surgery)

A broadened aortic artery accidentally detected at ultrasound, X-ray or during surgery for another condition, does not satisfy the criteria.

2.7.0 Pulmonary edema

Must have been detected by scintigraphy, angiography, CT or MRI.

2.8.0 Deep vein thrombosis

Must have been detected by ultrasound or venography. A swollen leg or arm is not sufficient to make this diagnosis

2.9.0 Cancer

NORVIT will apply for a linkage to the Cancer Registry to detect incident cases of cancer

2.9.1 Ventricular arrhythmia (not in conjunction with an acute MI)

2.9.2 Atrial fibrillation /flutter (not in conjunction with an acute MI)

2.9.3 Hospitalizations for chest pain and similar symptoms that cannot be classified in code 2.3.1

2.9.4 Hospitalization for cardiovascular investigations, transferral from another hospital in connection with a cardiovascular event, and similar hospitalizations.

APPENDIX 1

Diagnostic criteria; CORONARY EVENTS

1. Symptoms

Codes:

- | | |
|---|--------------------------|
| 1 | Typical |
| 2 | Atypical |
| 3 | Other |
| 4 | None |
| 5 | Inadequately described |
| 9 | Insufficient information |

Code 1: Typical symptoms are

central (retrosternal) chest pain lasting 20 minutes or until pain relief is given, and which is not definitely due to non-cardiological causes. The pain may radiate to jaw, arms, abdomen, back, shoulder. "Ache", "discomfort", "pressure" are synonyms for pain.

Symptoms registered for a coronary event apply to a period of 28 days following the onset. If more than one episode occurs during this interval, the lowest symptom category will be coded. Example: Code= 1 if typical pain occurred on day 5, while atypical symptoms occurred on day 1. The date of event is nevertheless day 1, when the symptoms caused a medical consultation.

If symptoms are typical, but duration is not stated, category 5 should be used. If words like "prolonged", "longlasting" are used, or if it is evident from the context that pain must have lasted for more than 20 minutes, category 1 should be used.

Typical chest pain leading to syncope, shock or pulmonary edema, is coded as category 1 even if unconsciousness/death occurs within 20 minutes.

Code 2: Atypical symptoms are

- atypical pain
- acute left ventricular failure, in the absence of typical symptoms
- cardiogenic shock, in the absence of typical symptoms
- syncope, in the absence of typical symptoms

AND absence of other heart disease AND no evident non-cardiac cause

Atypical pain may be pain attacks of short duration, or pain in arms, jaw, or abdomen, without concurrent chest pain.

Code 3: To be used in cases of adequate description of symptoms that do not satisfy code 1 or 2, and for symptoms due to a defined non-cardiac cause or non-atherosclerotic heart disease (pericarditis)

Code 4: To be used in cases of non-fatal events where the patient did not report any symptoms, or in fatal cases where eye witnesses did not sense that the patient had any symptoms before death occurred (instantaneous death)

Code 5: To be used in cases of typical pain of non-defined duration, precluding the use of code 1

Code 9: To be used if information is inadequate for any other code

2. MI biomarkers in serum

Codes:

- 1 Very much elevated MI biomarkers
- 2 Moderately elevated MI biomarkers
- 3 Non-specifically elevated MI biomarkers
- 4 Normal MI biomarkers
- 5 Inadequate serum sampling
- 6 Troponin I or CK-MB slightly elevated ("gray zone")
- 7 Troponin I between diagnostic cut-off value and 2 x diagnostic cut-off value
- 9 Insufficient data for other codes

Code 1: Serial change of enzymes, at least one reading ≥ 2 x upper reference limit when measured within 72 hours after the onset of symptoms, hospitalization, or after a new episode during the 28-days interval from the original date of onset.

Code 2: Serial change of enzymes, but all readings < 2 x upper reference limit, measured within 72 hours after the onset of symptoms.

Code 3: Very much elevated ($\geq 2x$) serum-enzymes, but no normalizing, or the elevation may be due to another disease, defibrillation, or surgery, or less than 3 weeks since index MI ; however, if suspected recurrent MI: new, acute elevation of troponin of at least 50% in the post MI recovery-phase is coded in category 1 or 2, dependent on the magnitude of elevation.

Code 4: To be used when enzyme test was taken during relevant time interval, was adequately reported, and was within the reference range.

Code 5: To be used when enzyme test has been taken, but not within the 72 hours interval after the onset of symptoms.

Code 6: Troponin I between upper reference value and diagnostic cut-off value.

(when only troponin has been analysed, or if all other biomarkers were within reference range)

Code 7: Troponin I between diagnostic cut-off value and 2 x diagnostic cut-off value.

Code 9: To be used when enzyme test has not been done, and when analysis results are unavailable.

Troponin I is classified as:

Code 1: Elevated: ≥ 2 x diagnostic cut-off value

Code 4: Normal: 0.0 – upper reference value

Code 6: "Gray zone" : Upper reference value – diagnostic cut off for Troponin I (and CK-MB when the laboratory uses such a classification)

Code 7: Slightly elevated: between diagnostic cut off value and 2 x diagnostic cut off value

In those cases when the laboratory in charge did not set a diagnostic cut off value for Troponin I, the value 2.0 is to be used.

No laboratory has stated a diagnostic cut-off value for Troponin T, and therefore Troponin T follows regular classification scheme for enzymes.

Hierarchy between troponin and other MI biomarkers:

1. If troponin is the only MI biomarker used: highest reading to be coded.

2. If troponin and other markers are analysed. Troponin and CK-MB are equal, highest maximum reading of the two is coded even if the other biomarker is within reference range.
3. Highest reading of Troponin or CK-MB to be coded regardless of whether CK is elevated or is within reference range.
4. Maximum CK reading to be coded if neither CK-MB nor Troponin has been analysed.
5. ASAT (SGOT) value to be coded only if no other, and more relevant biomarker has been analysed.

3. ECG criteria

Codes:

- | | |
|---|---|
| 1 | Silent MI as defined by ECG |
| 2 | Definite new MI as defined by ECG |
| 3 | Possible new MI as defined by ECG |
| 4 | Other ECG findings, inclusive of normal ECG |
| 5 | Uncodable ECG |
| 7 | Atrial fibrillation |
| 9 | ECG not available |

Code 1: Silent MI

Routine ECG shows a pathological Q-wave, width ≥ 0.04 sec and amplitude $\geq 25\%$ of the following R-wave amplitude, appearing after a EKG recorded earlier during follow-up, and after the inclusion in the trial.

Code 2: Definite new MI

- 2.1 No pathological Q-wave on admission; development of pathological Q-wave, width ≥ 0.04 sec and amplitude $\geq 25\%$ of R-wave amplitude.
- 2.2 Definite pathological Q-wave present on admission + sequential development of ST-T changes and/or sequential development of persisting negative T-wave.

Code 3: Possible new MI

- 3.1 New Q-wave, but Q-width < 0.04 sec and/or Q-amplitude $< 25\%$ of R-wave amplitude.
- 3.2 New or sequential development of ST-T changes in one or more leads:
In anterior leads ≥ 1 mm; in inferior leads ≥ 0.5 mm as compared to the isoelectrical line.
- 3.3 New or sequential development of persisting negative T-wave in one or more lead, regardless of size of deviation from isoelectrical line.

Code 4: Normal ECG:

No or unspecified changes in ECG.

Code 5: ECG cannot be coded for technical reasons or because of suppression codes (bundle branch block)

Code 9: ECG was not recorded or is unavailable.

4. Autopsy results

Code 1: Definite MI

Signs of acute MI and/or fresh occluding thrombus in coronary vessels apparent for the pathologist at the autopsy. Old MI changes may be present.

Code 2: Old MI.

Code 3: New cerebral infarction.

Code 4: New intracerebral hemorrhage.

Code 5: Autopsy not performed.

Code 6. Old cerebral infarction or old intracerebral hemorrhage.

Code 7. No sign of myocardial infarction or cerebral stroke.

Code 9: Information is missing whether or not autopsy was performed, or autopsy results are unavailable

5. Thrombolysis

During a hospital stay because of MI

Code 1. Streptokinase (Streptase) or non-specified thrombolytic drug

Code 2: Alteplase (Actilyse)

Code 3. Reteplase (Rapilysin)

Code 5: No thrombolytic treatment

Code 9: Insufficient information whether thrombolytic treatment was given or not

6. Stress –ECG (A-ECG)

In conjunction with code 2.3.1: A-ECG performed in connection with the relevant event (i.e. during the hospital stay)

Code 1. Negative A-ECG

Code 2: Negative A-ECG, submaximal exertion

Code 3: Inconclusive A-ECG

Code 4: Positive A-ECG (coronary chest pain or ischemic ECG-changes)

Code 5: A-EKG not performed

Code 9: Insufficient information whether A-ECG was performed or not

APPENDIX 2

Diagnostic criteria for STROKE

Rapid development of clinical signs of focal or global* disturbance of cerebral function of more than 24 hours duration, or death occurring before 24 hours, and without any suspicion of a non-vascular cause. If duration of otherwise typical symptoms < 24 hours, the diagnosis will be TIA.

* refers to subarachnoidal hemorrhage and to unconscious patients

Diagnostic criteria for subgroups of stroke:

1.3.1 /2.5.1 Subarachnoidal hemorrhage

Diagnosis based on symptoms, clinical neurological findings and CT, MRI (or cerebral angiography) (4S...." and CT, MR or spinal fluid analysis"), or findings during surgery

1.3.2 / 2.5.2 Cerebral infarction

Diagnosis made in the absence of signs of hemorrhage at CT, MR or in spinal fluid.

No distinction is drawn between non-embolic and embolic cerebral infarction.

1.3.3 / 2.5.3 Intracerebral hemorrhage

Intracerebral hematoma detected by CT or MRI , with or without breakthrough bleeding in ventricles (blood in spinal fluid)

1.3.4 / 2.5.4 Unspecified stroke

Symptoms and neurological signs typical for stroke, but no additional investigations performed (X-ray, CT, MRI, etc)

2.5.5 TIA

TIA must be confirmed by a physician, based on central neurological deficits, hemiparesis, hemi- tempo reduction, aphasia, dysarthria, or sensoric deficit from a suspected cerebrovascular origin. Coordination disturbances and balance problems in relation to vertigo (gyratoric or nautic) will be judged by the End point committee in each individual case, and must be seen in relation with other symptoms and signs indicating a brain stem/cerebellum disorder (diplopia, other sight disturbances etc.).

Uncharacteristic dizziness is not sufficient for this diagnosis.

1.3.5/2.5.6 Stroke related to an invasive procedure

Stroke occurring after an invasive procedure, and not later than the day following the procedure.