



ASCOT ENDPOINT MANUAL

Version 3

16 August 2002

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Preface to the Endpoint Manual Version 2 (October 2000)

The Endpoint Manual dated 2-April-1998 (version 1) has been successfully used from the start of the ASCOT trial. A revised version of the manual was required for two major reasons:

- (i) To specify the definition of silent myocardial infarction, in light of the decision to include silent myocardial infarction as part of the primary endpoint.
- (ii) To update and clarify the definition of diabetes mellitus in line with WHO 1999 recommendations.

In addition the opportunity has been taken to refine and clarify other definitions.

Version 2 of the Endpoint Manual has been used by the Endpoint Committee for the classification of all Endpoints at and since the fifth Endpoint Committee Meeting on 17 / 18 October 2000.

The main revisions, in the order in which they appear in the Endpoint Manual, are:

1.1 Fatal CHD:

The degree to which a death is sudden may be coded for definite, probable and possible CHD deaths and for deaths in which the cause is unknown.

The mode of CHD death is coded only for definite or probable CHD deaths.

1.2 Symptomatic non-fatal myocardial infarction

The term cardiac enzymes has now been replaced by “biochemical markers of myocardial necrosis” and the values used in the European Society of Cardiology / American College of Cardiology consensus redefinition of MI are given.

1.3 Development of silent MI

Details are now given.

Secondary endpoint: Total cardiovascular events and procedures = cardiovascular mortality + non-fatal MI (symptomatic + silent) + unstable angina + chronic stable angina + life threatening arrhythmias + non-fatal heart failure + non-fatal stroke + transient ischaemic attack + reversible ischaemic neurological deficit + retinal artery thrombosis + retinal vein thrombosis + peripheral arterial disease + revascularisation procedures

2.5 Revascularisation procedures

Coronary revascularisation procedures are separately indicated from other revascularisation procedures.

Revascularisation during an acute myocardial infarction is considered as two separate events.

3.3 Peripheral arterial disease

The definition of peripheral arterial disease has been clarified.

3.4 Life threatening arrhythmia

Now includes the development of complete heart block.

3.5 Development of diabetes

Details are now given for the WHO 1999 definition.

3.6 Development of renal impairment

The development of proteinuria has been clarified to denote the development of ++ proteinuria, present on at least 2 occasions, in a participant with neither proteinuria nor microalbuminuria at baseline.

The Manual now clarifies inclusion and exclusion criteria in relation to each endpoint.

Comments on the Endpoint Manual Version 2 (October 2000)

Members of the Working Group and Endpoint Committee were circulated with the manual in October 2000. In the light of their comments the following clarifications were made by February 12 2001.

1. The definition of diabetes at baseline.
2. The diagnosis of silent MI requiring changes in two contiguous ECG leads.
3. The definition of proteinuria at baseline includes microalbuminuria.

Endpoint Committee: Membership and Method of working

The members are

Ulf Dahlstrom, Linkoping, Sweden

Frej Fyhrquist, Helsinki, Finland

Kjell Midtbo, Oslo, Norway

Harry Hemingway (Chair), London, England

All cases suspected of fulfilling criteria for the fatal and non-fatal events are classified by the Endpoint Committee (see Protocol: Section VB and Appendix 3). This includes endpoints notified by investigators and potential silent myocardial infarctions identified by the core ECG laboratory. All the documentation for each potential endpoint is reviewed independently by two of the Endpoint Committee members. In the event of disagreement, a third member the Endpoint Committee will adjudicate. Final classification requires agreement between two members of the Endpoint Committee. The Endpoint Committee meets to resolve such disagreements and “grey cases.”

Information available to panel members:

All available relevant documents will be provided by investigators for review by the Endpoint Committee. The EPC needs to see the evidence on which diagnoses are based, rather than the opinion of the physician responsible for the patient. Thus the EPC requires photocopies of ECGs or exercise ECGs (rather than their reports), actual values of biochemical markers of myocardial necrosis, and so on. The documentation will include:

- medical records detailing specific symptoms and signs
- hospital discharge summaries
- procedure reports
- operation reports
- copies of resting electrocardiograms (must have the date recorded)
- copies of exercise electrocardiograms
- laboratory test results
- autopsy reports
- death certificates

More information can be requested by Endpoint Committee members

The Monitor has an important function to ensure the quality and completeness of the information provided to the EPC: for example in including local laboratory normal ranges for biochemical markers of myocardial necrosis.

Each endpoint is defined as primary, secondary or tertiary and must occur before a predetermined date of closure of the trial. Primary, secondary and tertiary endpoints are related to primary, secondary and tertiary objectives.

Primary endpoints

- (i) Non-fatal MI (symptomatic + silent) + fatal CHD

Secondary endpoints

- (i) All cause mortality
- (ii) Cardiovascular mortality
- (iii) Fatal and non-fatal stroke
- (iv) Fatal and non-fatal heart failure
- (v) Total coronary endpoints = fatal CHD + non-fatal MI (symptomatic and silent) + chronic stable angina + unstable angina + fatal and non-fatal heart failure
- (vi) Total cardiovascular events and procedures = cardiovascular mortality + non-fatal MI (symptomatic + silent) + unstable angina + chronic stable angina + life threatening arrhythmias + non-fatal heart failure + non-fatal stroke + transient ischaemic attack + reversible ischaemic neurological deficit + retinal artery thrombosis + retinal vein thrombosis + peripheral arterial disease + revascularisation procedures

Tertiary endpoints

- (i) Unstable angina
- (ii) Chronic stable angina
- (iii) Peripheral arterial disease
- (iv) Life threatening arrhythmias (ventricular fibrillation, sustained ventricular tachycardia or complete heart block)
- (v) Development of diabetes mellitus
- (vi) Development of renal impairment

1. PRIMARY ENDPOINT

The primary endpoint is non-fatal myocardial infarction (symptomatic + silent) and fatal CHD.

1.1. FATAL CHD

The Endpoint Committee members will review all the documentation provided for all deaths. The final determination of the cause of death will be made by the Endpoint Committee. Thus the Endpoint Committee can over-ride what is written on the death certificate. All causes of death will be based on the underlying cause, the procedures for which are as established and defined by WHO. The underlying causes of death will be classified as coronary heart disease (CHD), stroke, other heart + other vascular, cancer, respiratory or other and unknown.

All deaths with ICD9 410-414 or ICD 10 I20-24 in Part I or Part II of their death certificate will be reviewed and classified by the Endpoint Committee for the:

- Certainty of CHD as the cause (definite, probable or possible)
- Timing: sudden (definite, probable or possible)
- Mechanism: (ischaemic, pump failure or arrhythmic)

For the primary endpoint, fatal CHD is defined as definite + probable + possible CHD death, regardless of timing or mechanism of death.

1.1.1. Certainty of CHD cause of death

Definite CHD death is one in which there is post-mortem evidence of myocardial infarction (macroscopically visible new or old infarction or recent occlusion of coronary artery) or coronary artery disease (chronic occlusion of coronary artery or stenosis more than 50 %) and the absence of another cause of death.

Probable CHD death is one in which there is ante-mortem evidence of definite CHD (i.e. MI, unstable angina or chronic stable angina) and in the absence of another cause of death.

Possible CHD death The underlying cause of death on the death certificate is the only documented clinical evidence of CHD.

1.1.2. Timing of CHD death

For CHD deaths coded as definite, probable or possible, the timing of the death is coded. Timing of death should also be coded when the cause of death is unknown. Timing of deaths is defined as

Definite sudden cardiac death

Witnessed, unexpected death occurring within 1 hour of the onset of chest pain typical of an MI, acute pulmonary oedema, or cardiogenic shock in the absence of any known acute or chronic process or event other than CHD that could have been lethal (eg cerebral hemorrhage, pulmonary embolus, ruptured aortic aneurysm, drug overdose). Person not confined to home or hospital or other institution because of illness within the 24 hours preceding death.

A patient found dead in bed in the morning will be assumed to be sudden only if they were witnessed to be asymptomatic when they went to bed.

Probable sudden cardiac death

- (i) Death between 1 and 24 hours after the onset of symptoms (as above)
- (ii) No known acute or chronic process or event other than CHD that could have been lethal (eg cerebral hemorrhage, ruptured aortic aneurysm, drug overdose)
- (iii) Person not confined to home or hospital or other institution because of illness within the 24 hours preceding death.

Possible sudden cardiac death

Non-witnessed unexpected deaths, exclude all other causes of death (exclude all patients with signs or symptoms of other fatal disease when last observed).

In deciding suddenness of the death, the use of cardiopulmonary resuscitation, defibrillation and mechanical ventilation in prolonging life should be considered. Survival beyond the first hour due to cardiopulmonary resuscitation should be a definite sudden death.

Non-sudden cardiac death

Is defined as a CHD death in which the terminal episode lasts longer than 24 hours.

1.1.3. Mechanism of CHD death

For definite or probable CHD deaths the mechanism or mode of death is coded. For possible CHD deaths, in which the death certificate is the only indication of coronary disease, there is insufficient evidence to code the mode of death.

Ischaemic CHD death is coded in the presence of:

- (i) Definite acute MI within 28 days before death or
- (ii) Possible acute MI preceding the loss of consciousness or
- (iii) Unstable angina before loss of consciousness or
- (iv) New coronary lesion of acute MI at autopsy

Caution is required in interpreting biochemical markers of myocardial necrosis and ECG changes occurring after collapse.

Pump failure CHD death is coded in the presence of progressively impaired left ventricular function as manifested by pulmonary congestion or low cardiac output, in the absence of acute ischaemia.

Arrhythmic CHD death is coded in the

- (i) Presence of a sudden CHD death and
- (ii) Absence of definite or possible acute MI (AMI) in last 28 days and
- (iii) Absence of new coronary lesion or AMI at autopsy and
- (iv) Absence of new or increased angina and
- (v) Absence of symptoms of impaired left ventricular function

Arrhythmic death is thus a classification by default.

1.2. SYMPTOMATIC NON-FATAL MYOCARDIAL INFARCTION

Exclusion criterion at study onset: history of symptomatic MI.

All symptomatic MI occurring in the trial (first and recurrent) are coded using the definition of the MONICA study (Tunstall-Pedoe, Circulation 1994) and in line with European Society of Cardiology and American College of Cardiology 2000 recommendations. The definition of myocardial infarction is made on the evidence, in dated records, of biochemical markers of myocardial necrosis, symptoms and electrocardiographic changes.

1.2.1. Biochemical markers of myocardial necrosis

Knowledge of local laboratory ranges is essential in interpreting these biochemical values.

1 = *abnormal*

The table outlines the MONICA definition (which covers CK, AST, LDH) and the European Society of Cardiology / American College of Cardiology 2000 consensus redefinition of myocardial infarction.

	Decision limit	Timing	Number of occasions	Evidence of rise and fall required?
Creatine kinase (CK) / B fraction of CK / aspartate aminotransferase (AST) / Lactate dehydrogenase (LDH)	at least twice the upper limit of normal for that institution	within 72 hours or 3 calendar days of onset of symptoms, admission to hospital, or any recurrence of symptoms.	1	no
Troponin T or I	>99 th percentile	<24 hours from index clinical event	1	no; but troponins may remain elevated for 7d
CK-MB	>99 th percentile	not stated	2 successive samples	yes
CK-MB	at least twice upper limit of normal for that institution	"first hours"	1	no

2 = *equivocal*, markers are elevated but less than twice the upper limit of normal.

3 = *non-specific*, if markers are elevated, more than twice the upper level, but there are other reasons (surgery, liver disease, defibrillation, infection).

4 = *normal*, when cardiac markers are tested within relevant time period and are within normal levels

5 = insufficient data, when data is not done or not available

1.2.2. Symptoms

1 = *typical*: pain described as an ache, burning, discomfort, squeezing, heaviness or pressure which is situated in the central sternum or precordium lasting at least 20 minutes, with no definite non-cardiac or cardiac non-atherosclerotic cause. There may be several symptomatic periods during the hospital stay. Details of the most severe episode of pain will be recorded for the diagnosis. If the patient has symptoms that are typical, additional symptoms such as shock, syncope and left ventricular failure will not change the symptom classification.

2 = *atypical*: this will be considered as (a) one or more of atypical pain, acute LV failure, shock, syncope and (b) the absence of cardiac disease other than CHD and (c) no definite noncardiac or cardiac nonatherosclerotic cause.

3 = *other symptoms*: symptoms that are well described but do not satisfy the atypical or typical category. Symptoms due to a definite noncardiac cause or to a definite nonatherosclerotic heart disease (eg of pericarditis) should be coded 3.

4 = *no symptoms*: this is applied to non-fatal cases where the patient reported no symptoms, during the attack, as eye witnessed, or when the patient was completely normal and uncomplaining before the moment of death or fatal syncope.

5 = *inadequately described symptoms* for cases otherwise satisfying criteria for typical pain but in which the duration of the pain is not described, so that it is not possible to classify the symptoms as typical

9 = insufficient data or lack of evidence to classify the symptoms.

1.2.3. Development of acute ECG changes

Inclusion criterion: ECG abnormalities (LV strain pattern, abnormal Q waves, LBBB, ST-T changes compatible with IHD) as one of the three qualifying risk factors.

The classification of the acute ECGs will be based on the following Minnesota codes. Members of the EPC will refer to these in reaching their decisions, but need not formally assign a Minnesota code to each acute ECG. Members of the EPC will be provided with ASCOT ECGs taken at randomisation and follow up and changes on acute ECGs not present on earlier study ECGs will be taken into account.

1.2.3.1. Definite MI on acute ECGs

A. Development in serial records of a q wave

The groups of Minnesota code that are important are :-

No Q = includes 1-2-6

Equivocal Q = 1-2-8 and any 1-3

Diagnostic Q = 1-1-1 through to 1-2-5 and 1-2-7

ST segment depression = 4-1 and 4-2

ST segment elevation = 9-2

Major T wave inversion = 5-1 and 5-2

- | | |
|---|----|
| 1. No Q code to diagnostic Q | OR |
| 2. Equivocal Q to diagnostic Q plus no ST depression to ST depression | OR |
| 3. Equivocal Q to diagnostic Q plus no ST elevation to ST elevation | OR |
| 4. Equivocal Q to diagnostic Q plus no T wave inversion to T wave inversion | OR |
| 5. No Q to equivocal Q plus no ST depression to ST depression | OR |
| 6. No Q to equivocal Q plus no ST elevation to ST elevation | OR |
| 7. No Q to equivocal Q plus no T wave inversion to T wave inversion | OR |

AND/OR

B. Evolution of an injury current which lasts more than one day

ST segment elevation (9-2) lasting more than one day (is present on consecutive records of different dates)

AND

T wave progression on three or more records from 5-0 to 5-2 or from 5-3 to 5-1, with an abnormal code present on consecutive records of different dates.

Note: The ST segment elevation does not have to be present in the same leadgroups as the T progression, nor does it have to be exactly simultaneous. Q waves will often be present in the same electrocardiograms but they are not necessary to the use of this criterion.

Probable MI on acute ECG s

Evolution of repolarisation changes

1. Major ST depression (4-1) present in one ECG and no major ST depression (no 4-1 or 4-2) in another ECG.* OR
2. ST elevation (9-2) present in one ECG and absent (no 9-2) in another ECG.* OR
3. Major T wave inversion (5-1 or 5-2) present in one ECG and absent (no 5-1 or 5-2) in another ECG *

* These changes can go in either direction

NB Note that repolarisation changes are not identical to those for accompanying Q waves - the 4 code is more severe. A 4-1 must be present.

Ischaemic ECG

Minnesota codes	any 1-1-	OR
	any 1-2 (NOT 1-2-6)	OR
	any 1-3	OR
	any 4 code (4-1 to 4-4)	OR
	any 5-1 to 5-3 (NOT 5-4)	OR
	7-1-1 (LBBB)	OR
	9-2	

Other ECG

All other ECG findings including normal ECG, unavailable ECG and uncodable ECG - due to technical reasons or because of the presence of suppression codes. Ventricular conduction abnormalities and arrhythmias occurring in the course of an event are not used as collateral evidence of definite or probable MI.

The following Minnesota codes lead to suppression of all or most of these items, and a set of ECG records in which such findings are present in all records should be considered uncodable (unless codable Q waves are present, for example in an ECG showing a 7-4).

- 6-1 Third degree A-V block suppresses all 1,4,5 and 9-2.
- 6-4-1 Persistent Wolff-Parkinson White Pattern suppresses all other codes.
- 6-8 Artificial pacemaker suppresses all other codes.
- 7-1-1 Complete left bundle branch block suppresses 1-2-3, 1-2-7, 1-2-8, 1-3-2, 1-3-6 and all 4,5 and 9-2 codes but the presence of a codable Q downgrades it to 7-4.
- 7-2-1 Complete right bundle branch block suppresses 1-2-8, and all 4,5 and 9-2 codes.
- 7-4 Intraventricular block suppresses all 4,5 and 9-2 codes.
- 8-2-1 Ventricular fibrillation and asystole suppress all other codes.
- 8-2-2 Idioventricular rhythm suppresses all other codes.
- 8-4-1 Supraventricular tachycardia above 140/minute suppresses all other codes.

1.2.4. Definite myocardial infarction

This diagnosis will be made on the basis of combinations of symptoms, ECG and biochemical abnormalities as follows:

EITHER

Acute ECGs	definite	or
Autopsy	definite	

OR

Symptoms =	typical, atypical or inadequately described	and
ECGs =	probable changes	and
Biochemical =	abnormal	

OR

Symptoms	typical	and
ECGs	ischaemic or not available	and
Biochemical	abnormal	

1.2.5. Possible myocardial infarction

Living patients

Symptoms= typical and
ECG and biochemical marker codings do not allow the diagnosis of definite AMI and no good evidence of other diagnosis

Recurrent MIs are coded. However, within a 28 day period only one non-fatal MI, unstable angina or chronic stable angina can be coded (the most serious or most certain event) to avoid difficulties in distinguishing what is likely to be one symptomatic process.

When death occurs within 28 days of non-fatal MI, unstable angina or chronic stable angina, both the fatal and non-fatal events will be coded.

1.3. DEVELOPMENT OF SILENT MYOCARDIAL INFARCTION

Inclusion criterion: ECG abnormalities (LV strain pattern, abnormal Q waves, LBBB, ST-T changes compatible with IHD) as one of the three qualifying risk factors.

Silent myocardial infarction is diagnosed when there is appearance of new major Q or QS items without a history of symptomatic myocardial infarction.

A *four step procedure* is followed in order to maximise the diagnostic precision of silent MI. Steps one, two and three are undertaken blind to all clinical details at the ECG Core Centre. Step four is undertaken by the Endpoint Committee with clinical information.

(i) All study ECGs (at randomisation, at 2 year follow up and at study completion) are read and coded blind to all clinical information according to the 'Minnesota code 1982' classification by two trained laboratory technicians (independent of each other) at the Clinical Experimental Research Laboratory, Department of Medicine, Östra University Hospital (ECG Core Centre). Responsible investigator and head of the ECG Core Centre is Associate Professor Sverker Jern MD. According to the specifications of the Minnesota code, a number of pre-evaluation codes are checked for possible suppression of codes 1.1 and 1.2 (see above).

(ii) A comparison is made between ECGs taken at:

2 year follow up vs randomisation

study end vs 2 year follow up

study end vs randomization (in absence of 2 year ECG)

and a list is generated (by computer) of all study participants with a Q or QS code present at one time point but absent on the previous study ECG.

(iii) These ECG pairs in which the later ECG has a new Q or QS code are then visually compared by two independent coders. The purpose of the third step is to exclude obvious errors from further consideration. However, major new Q or QS items occurring in the same set of leads in the immediately preceding ECG, will be included among those ECG pairs for step four.

(iv) Finally, the Endpoint Committee then reviews three sources of information for each case of potential silent MI:

- *all* available ECGs (minimum of 2)
- all the participant's previous endpoints (e.g. details of previous angina, unstable angina)

The Endpoint Committee members will judge the significance of new Q waves on the extent to which:

-there has been significant serial change (Table 15-2; Prineas 1982) (rather than marginal changes that occur within the limits of recording variation)

-changes are found in a new territory and not found in the immediately preceding ECG

- changes are present in at least two contiguous leads

-changes are not confined to Q codes of questionable significance (1-2-6 and 1-2-7)

Silent MI is defined as

Significant serial change in a Q wave

AND

No history of chest pain

In the presence of a history of dated, typical chest pain, the event is coded as a definite symptomatic MI.

In the presence of a history of chest pain with no clear date, then the event is coded as a possible symptomatic MI.

If Investigators identify a silent MI, then paired ECGs should be sent to the Core ECG laboratory for Minnesota coding as outlined above.

The date of the event of a silent MI is the midpoint between the two ECGs between which the significant serial change has occurred.

2. SECONDARY ENDPOINTS

2.1. ALL CAUSE MORTALITY

Death from any cause. All deaths and supporting documentation will be reviewed by the Endpoint Committee. Causes of death, not elsewhere classified are:

Cancer

All cases of death from malignant diseases will be included in this category. ICD 9 140 –239 (ICD 10C00-C97)

Respiratory

ICD 9 460-519 (ICD 10 J00-J99)

Other

Causes of death not listed above will be coded in this category and specified (eg suicide, violent or accidental death).

Unknown

All deaths which cannot be classified as one of the above categories of death will be classified as 'unknown'. In the presence of a death certificate in which the underlying cause of death is given as coronary heart disease or stroke, in the absence of any supporting evidence, the cause of death will be coded as unknown.

2.2. CARDIOVASCULAR DEATHS

Defined as any death in which the underlying cause of death agreed by the Endpoint Committee lies in “Chapter VII Diseases of the Circulatory System, ICD 1975 revision” ICD9 codes 390 – 459 (ICD 10 I00-I99)

This includes

- CHD (ICD 9 410-414) (ICD 10 I20-I25)
- Stroke (ICD 9 430 - 438) (ICD 10 I60-I69)
- other heart and vascular disease (ICD 9 390-405, 415-429, 440-459) (ICD 10 all remaining I codes). This includes any cardiovascular disease death not due to CHD or stroke.

2.3. FATAL AND NON-FATAL STROKE

Inclusion criterion: cerebrovascular events including TIA at least 3 months prior to screening as one of the qualifying three risk factors.

Exclusion criterion: such stroke events less than 3 months prior to screening.

The occurrence of fatal or non-fatal stroke, its aetiology and sub-types will be defined according to the pattern of clinical symptoms and signs, CT scan, angiography, lumbar puncture, MRI and autopsy.

a) Clinical signs and symptoms

Diffuse signs (at least 1 of the following)

- acute headache,
- nausea, vomiting
- loss of consciousness
- meningism

Focal signs (at least 1 of the following)

- Weakness in arm or leg
- Sensory loss
- Difficulty with speech
- Loss of vision
- Double vision
- Ataxia of limbs

b) CT scan

- 1 = No changes
- 2 = Blood in the subarachnoid space/ventricle
- 3 = Cerebral haemorrhage
- 4 = Infarct
- 5 = Other (eg tumor)
- 6 = Not done
- 7 = Report not available

c) Angiography

- 1 = No changes
- 2 = Cerebral haemorrhage (when contrast medium escape)
- 3 = Infarct (Intracerebral vasography within 3 days)
- 4 = Other (eg tumor)
- 5 = Aneurysm/AVM
- 6 = Investigation not done
- 7 = Report not available
- 8 = Subarachnoid haemorrhage (when contrast medium escape)

d) Lumbar puncture

1 = No bloody liquor (including traumatic tap ie
RBC < 100/cm³, WBC < 10/cm³, protein < 0.6 gm/l
and pressure < 200 mm H₂O)

2 = Bloody liquor (RBC > 2000/m³)

3 = LP not done

4 = Report not available

e) MRI

1 = No changes

2 = Cerebral haemorrhage

3 = Infarct

4 = Other (eg tumor)

5 = Aneurysm /AVM

6 = Investigation not done

7 = Reports not available

8 = Subarachnoid haemorrhage

f) Autopsy

0 = N/A (no death)

1 = Subarchnoid haemorrhage

2 = Cerebral / ventricular haemorrhage

3 = Infarct with cardiac source of embolus

4 = Infarct without embolus

5 = No stroke

6 = Venous thrombosis

7 = Death without autopsy

8 = Autopsy report not available

2.3.1. Ischaemic stroke

A CT or MRI scan or cerebral angiogram carried out within 3 weeks of the clinical event, is so reported, or if the CT scan, MRI scan and angiogram are normal or not carried out, the presentation will have to be compatible with a focal lesion and no excess blood is detected in the CSF.

EITHER

(a) = 2 (clinical symptoms and signs) and

(b) = 4 (CT) or

(c) = 3 (Angiography) or

(e) = 3 (MRI) or

(f) = 4 (autopsy)

OR

(a) = 3 (clinical symptoms and signs) and

(b) = 1 (CT) or

(f) = 4 (autopsy)

OR

(f) = 3 (autopsy)

2.3.2. Haemorrhagic stroke

This includes subarachnoid haemorrhage and intracerebral haemorrhage. This diagnosis will be made if a CT scan or MRI scan demonstrates subarachnoid or intracerebral blood. Alternatively, if CT or MRI scans are not done or reported as normal, haemorrhagic stroke may be coded in the presence of focal or diffuse signs with typical symptoms of meningism, together with either cerebrospinal fluid (CSF) changes of blood staining sufficient to preclude 'traumatic tap' and/or an aneurysm or bleed is identified on cerebral angiography.

EITHER

(a) = 1 (clinical symptoms and signs) and
(d) = 2 (lumbar puncture)

OR

(b) = 2 (CT)

OR

(d) = 2 (lumbar puncture) and
(c) = 5 or 8 (Angiography) or
(e) = 5 or 8 (MRI)

OR

(f) = 1 (autopsy)

Stroke: unknown subtype

This diagnosis will be made for strokes in whom signs, symptoms and investigations are insufficient to allow the classification of ischaemic or haemorrhagic.

(a) = 2 or 5 and
criteria for diagnostic categories 1-4, 6 or 7
not sufficient

2.3.3. Transient ischaemic attack (TIA)

Transient ischaemic attack (TIA) must satisfy all of the following criteria:

- (i) A good clinical history of focal neurological symptoms or signs, which develop within seconds, last at least one minute and resolve completely within 24 hours.
- (ii) Absence of unilateral sensory symptoms, syncope, loss of consciousness, or confusion, convulsions, incontinence of urine or faeces, dizziness, scintillating scotoma or other symptoms associated with migraine.
- (iii) Absence of an alternative cause for the symptoms.
- (iv) In the opinion of the attending physician, TIA is the most likely diagnosis.

A CT or MRI scan may be normal. In the presence of ischaemic changes on CT or MRI, the duration of symptoms determines whether the event is coded as a TIA, RIND or ischaemic stroke.

2.3.4. Reversible ischaemic neurologic deficit (RIND)

Reversible ischemic neurologic deficit (RIND) must satisfy the same criteria as TIA, except signs and symptoms last at least 24 hours, and resolve completely within 6 weeks.

2.3.5. Retinal artery thrombosis / retinal vein thrombosis

Retinal vascular thromboses are defined as typical symptoms: (unilateral visual loss) and fundoscopic signs. These include: venous dilation with retinal haemorrhages throughout the fundus (retinal vein thrombosis) and cloudy white retinal oedema and cherry red spot at macula (retinal artery thrombosis).

2.4. FATAL AND NON-FATAL HEART FAILURE

Exclusion criterion: heart failure NYHA class II-IV.

Heart failure is defined as:

- (i) ≥ 2 New Symptoms / Signs / Response to treatment AND
- dyspnea at rest or ordinary exertion, night cough, or orthopnoea
 - sinus tachycardia
 - pulmonary rales
 - third heart sound
 - bilateral ankle oedema
 - hepatomegaly
 - raised jugular venous pressure
 - diuresis and relief of symptoms with loop diuretic
- (ii) ≥ 1 Investigation abnormality AND
- a. Chest x-ray findings:
acute pulmonary odema
congestion with interlobar lines (considered due to heart failure)
cardiothoracic ratio >0.5 , or report of enlarged heart
- b. Impaired left ventricular systolic function
Echocardiography: LV ejection fraction is $\leq 40\%$ or there is a statement of mild, moderate or severe LV systolic impairment.
MUGA: Ejection fraction
Angiography: ejection fraction, raised left ventricular end diastolic pressure
- (iii) Statement of a diagnosis of heart failure by the attending physician

NB. There is no requirement that the patient be hospitalised for heart failure. This definition of heart failure includes heart failure due to coronary heart disease (e.g. when there are Q waves on the ECG), chronic rheumatic heart disease and other causes. If the underlying aetiology is a myocardial infarction, then the same patient may contribute both types of event.

2.5. REVASCULARISATION PROCEDURES

Revascularisation procedures are defined as:

- (i) Coronary revascularisation
- coronary angioplasty
 - atherectomy
 - stent implantation
 - coronary artery bypass graft (CABG)

For study participants undergoing primary angioplasty for acute myocardial infarction, both events are coded. It is recognised that the degree of diagnostic certainty of the acute myocardial infarction may be reduced by such intervention.

- (ii) Carotid procedures
 - endarterectomy
 - bypass
- (iii) Femoral-popliteal procedures
 - angioplasty
 - bypass
- (iv) Renal artery procedures
 - angioplasty
 - stenting

3. TERTIARY ENDPOINTS

3.1. UNSTABLE ANGINA

All patients admitted to hospital with chest pain should be evaluated for being a potential case of acute myocardial infarction and, once that is ruled out, unstable angina. It is recognised that the distinction between possible acute MI and definite unstable angina is difficult.

For patients with multiple CHD events occurring during a 28 day period, only one event should be classified and this should be the most serious (MI > unstable angina > chronic stable angina).

A case of definite unstable angina is defined as satisfying each of the following conditions:

(i) *admission to hospital with chest pain, but not an acute MI on this admission*

(ii) *angina symptoms which are new, or severe or increasing*

The Braunwald definitions are used:

New onset = angina starting within the two months prior to admission.

Severe or frequent angina ≥ 3 episodes per day.

Did the patient have chronic stable angina and in the previous 2 months develop *distinctly increased* frequency, severity or duration of episodes / attacks? In the last 2 months, were the angina attacks precipitated by distinctly less exertion than previously? Was there 1 or more episodes of anginal pain at rest in the preceding 2 months? Was there 1 or more episodes of anginal pain at rest in the preceding 48 hours?

(iii) *investigation evidence of ischaemia (transient ST-T wave changes during pain or positive exercise ECG or thallium scan or angiographic evidence of coronary artery disease within 6 months of episode*

At the time of onset of unstable angina what medication was the patient taking? No anti-anginals, drug therapy for chronic stable angina, maximal medical therapy including intravenous nitrates for unstable angina.

3.2. CHRONIC STABLE ANGINA

Exclusion criterion: currently treated angina pectoris.

Chronic stable angina is defined as the combination of typical chest pain and test abnormality. It does not require hospitalisation.

- (i) ≥ 2 Features of typical chest pain: AND
- quality: ache, burning, discomfort, squeezing, heaviness or feeling of pressure
 - duration: several minutes, but less than 20 min
 - location: central sternum, precordium
 - precipitation: exercise or emotional upset
 - relief: by rest or nitroglycerine
 - in the opinion of the attending physician the chest pain / discomfort was due to myocardial ischaemia
- (ii) ≥ 1 Test abnormality:
- coronary angiography showing $>50\%$ stenosis in left main stem or at least one stenosis of at least 70% in another major artery.

 - positive exercise ECG ($\geq 1\text{mm}$ ST depression). In all cases the ECG tracings will be reviewed by EPC members.

 - positive thallium scintigraphy.

 - abnormal resting ECG showing ischaemic Q, ST or T changes.

The EPC considered and rejected stipulating separate criteria for women. Breathlessness on exertion is not considered a sufficient symptom for angina.

3.3. DEVELOPMENT OF PERIPHERAL ARTERIAL DISEASE

Inclusion criterion: peripheral arterial disease according to questionnaire or a recent history of surgical intervention for peripheral arterial disease as one of the qualifying three risk factors.

Peripheral arterial disease is defined as symptomatic chronic or acute leg ischaemia or aortic aneurysm. Asymptomatic peripheral arterial disease is not included.

Chronic or acute lower limb ischaemia

Is defined as

- (i) Typical symptoms and signs AND
- calf, thigh or buttock pain which is precipitated by exercise and relieved by rest
 - rest pain
 - weakness of distal muscles
 - cold extremities
 - loss of lower limb pulses
- (ii) ≥ 1 test abnormality AND
- Ankle – brachial blood pressure index < 0.9 in either leg.

3.4. LIFE THREATENING ARRHYTHMIA

Exclusion criterion: second or third degree A-V block, uncontrolled arrhythmias.

Ventricular fibrillation or sustained ventricular tachycardia requiring urgent cardioversion (DC shock) or complete (third degree) heart block. ECG tracings will be reviewed in all cases by EPC members.

3.5. DEVELOPMENT OF DIABETES

Inclusion criterion: NIDDM as one of the qualifying three risk factors.

Diabetes mellitus is defined by the World Health Organisation 1999 criteria in one of three ways:

- (i) Fasting plasma glucose ≥ 7.0 mmol/l on two occasions.
- (ii) 2 hour post 75g glucose load plasma glucose ≥ 11.1 mmol/l.
- (iii) "Unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms" (WHO 1999).
This is operationalised as a random plasma glucose ≥ 11.1 mmol/l on two occasions +
symptoms consistent with diabetes (e.g. thirst, polyuria, polydipsia, excessive weight loss)

If a patient has a fasting venous plasma glucose value of 6-6.9 mmol/l during the study, the patient should return for a glucose tolerance test.

Definition of diabetes at baseline "Development of diabetes" will not be accepted in ASCOT participants in the presence of the following abnormalities at screening or randomisation:

- (i) a glucose value ≥ 7.0 mmol/l (fasting) or ≥ 11.1 mmol/l (random)
- (ii) a history of "diabetes mellitus" or a history of "non-insulin dependent diabetes mellitus" (NB these are two separate data items).
- (iii) impaired fasting glucose AND glycosuria.

In such patients diabetes is likely to have been present at baseline, and therefore can not be a new development. Note that glycosuria or impaired fasting glucose in the absence of any other abnormality will not be included as indicating the presence of diabetes at baseline.

3.6. DEVELOPMENT OF RENAL IMPAIRMENT

Inclusion criterion: microalbuminuria / proteinuria as one of the qualifying three risk factors.

Exclusion criterion: serum creatinine >200micromol/l

Development of renal impairment is defined as

(i) Follow up serum creatinine measurement $\geq 50\%$ greater than the baseline assessment made at screening. OR

(ii) The development of + proteinuria, present on at least two occasions, in a participant with no proteinuria or microalbuminuria at baseline. In the CRF, dipstix proteinuria is recorded as positive or negative. However the investigators have recorded the degree of positivity, and therefore will need to provide in all cases details of the *extent* of proteinuria.

History:

- 1997 August Outline manual sent to Endpoint Committee (EPC) (Drs Harry Hemingway, Frej Fyhrquist, Kjell Midtbo)
- 1998 January First draft (substantial revisions) prepared by HH
- 1998 February 15 HH and FF met, discussed and agreed amendments. HH prepared second draft circulated to EPC.
- 1998 March 12 Discussed at Steering Group
- 1999 August 4 First EPC meeting, Goteborg
- 1999 October 25 Second EPC meeting, Goteborg
- 2000 February 14 Third EPC meeting
- 2000 September 11 Fourth EPC meeting
- 2000 October 17/18 Fifth EPC meeting: version 2 of Endpoint Manual
- 2001 February 12 Incorporation of comments from Working Group and others (see Preface) and Version 2 circulated to investigators and sites.