ASCOT MANUAL OF CRITERIA

FOR FATAL AND NON-FATAL ENDPOINTS

Method of working of EPC Members

All cases suspected of fulfilling criteria for the fatal and non-fatal events will be classified by the Endpoint Committee (see Protocol: Section VB and Appendix 3). This therefore includes endpoints in which the classification of an endpoint will already have been proposed for example in the case of silent MI. All events will be reviewed by two of the three Endpoint Committee members. The committee members will review the documentation for each potential endpoint independently of each other. 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 Co-Ordinating Centres will feedback results of agreements / disagreements individually to Committee Members at timely intervals (say quarterly) and the Endpoint Committee will have an early meeting after say the first 100 endpoints in order to ensure consistency and decide the frequency of subsequent meetings. The first 100 endpoints will be reviewed by all three Committee members, in order to establish consistency. The Chair of the Endpoints Committee, HH, will review all endpoints.

Information available to panel members:
All available relevant documents will be provided for review by the committee. These will include:

- hospital discharge summaries
- other medical records
- procedure reports
- operation reports
- dated ECG's
- laboratory test results
- autopsy reports
- death certificates
- more information can be requested by Endpoint Committe 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 cardiac enzymes.

Each endpoint is defined as either primary, secondary or tertiary and must occur before a predetermined date of closure of the trial. The relationship between primary, secondary and tertiary endpoints and primary, secondary and tertiary objectives requires re-examination.

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 + peripheral arterial disease + revascularisation procedures

Tertiary endpoints

(i) Unstable angina

(ii) Chronic stable angina

(iii) Peripheral arterial disease

(iv) Life threatening arrhythmias (VF or sustained VT)]

(v) Development of diabetes mellitus

(vi) Development of renal impairment

1. PRIMARY ENDPOINT

The primary endpoint is Non-fatal MI 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 underlying primary 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 CHD, stroke, other heart + other vascular, cancer, respiratory or other and unknown.

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

- Cause (due to CHD or not) and, for CHD deaths the:
- Certainty (definite or possible)
- Timing: sudden (definite, probable, possible)
- Mechanism: ischaemic, arrhythmic or pump failure

1.1.1. Certainty of CHD cause

1.1.1.1.Definite CHD death

is one in which there is post-mortem evidence of coronary artery disease, and / or new or old myocardial infarction and the absence of another cause of death.

Coding of autopsy

1 = Definite myocardial infarction (marcroscopically visible infarction or recent occlusion of coronary artery)
2 = Possible (chronic occlusion of coronary artery(ies) or stenosis more than
50 % or old myocardial infarction without signs of non-cardiac or non-atherosclerotic cause of death)
3 = Other diagnosis
4 = Death without autopsy
5 = Autopsy report not available

1.1.1.2.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.

1.1.1.3.Possible CHD death

The underlying cause of death on the death certificate is the only evidence.

1.1.2. Timing of CHD death

For CHD deaths coded as definite or probable, the timing of the death will be coded. By definition for possible CHD deaths there will be no additional information on which to code timing. Timing of deaths will be defined as

1.1.2.1.Definite sudden cardiac death

(i) Witnessed, unexpected death and
(ii) Death occurring within 1 hour of the onset of chest pain typical of an MI, acute pulmonary oedema, or cardiogenic shock [these require definition] and
(iii) No known acute or chronic process or event other than CHD that could have been lethal (eg cerebral hemorrhage, ruptured aortic aneurysm, drug overdose)
(iv) Person not confined to home or hospital or other institution because of illness with the 24hours 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.

1.1.2.2.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 with the 24hours preceding death.

1.1.2.3.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 the life should be considered. It may be that a person who lived beyond the first hour merely because of the availability of cardiopulmonary resuscitation shoudl be a definite sudden death.

1.1.2.4.Non-sudden cardiac death

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

For deaths which occur over 28 days after the onset of a major event (eg myocardial infarction) this would not routinely be considered an acute fatal MI.

1.1.3. Mode of CHD death

1.1.3.1.Ischaemic CHD death

Ischaemic CHD death is a CHD death in the presence of acute myocardial infarction or acute ischaemia in the preceding 28 days. It is defined as a definite or probable CHD death in which there is

(i) A definite acute myocardial infarction within the 28 days preceding death or
(ii) Possible acute myocardial infarction preceding the loss of consciousness
(iii) New or increased (unstable) angina before collapse
(iv) New coronary lesion of acute MI at autopsy

Caution should be exerted when interpreting cardiac enzyme and ECG changes occurring after collapse.

1.1.3.2.Pump failure

Death due to progressively impaired left ventricular function as manifested by pulmonary congestion or low cardiac output, in the absence of acute ischaemia.

1.1.3.3.Arrhythmic CHD death

CHD death which [must be sudden] in which there is no previous acute MI, or unstable angina and in the absence of progressive heart failure. Arrhythmic CHD death is defined by :
(i) Absence of definite or possible acute MI in last 28 days and
(ii) Absence of new coronary lesion or AMI at autopsy and
(iii) Absence of new or increased angina and
(iv) Absence of symptoms of impaired left ventricular function

Arrhythmic death is thus a classification by default.

1.2. SYMPTOMATIC NON-FATAL MYOCARDIAL INFARCTION

The defintion of non-fatal MI follows that of the MONICA study (Tunstall-Pedoe, Circulation 1994). The definition of myocardial infarction is made on the evidence, in dated records, of enzyme elevations, symptoms and electrocardiographic changes.

1.2.1. Enzymes

Knowledge of local laboratory ranges is essential in interpreting enzyme values.

1 = *abnormal*, one reading at least twice the upper limit of normal when measured within 72 hours or 3 calendar days of onset of symptoms, admission to hospital, or any recurrence of symptoms.
2 = *equivocal*, cardiac enzyme markers are elevated but less than twice the upper limit of normal
3 = *non-specific*, if cardiac 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 periodand 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 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 wittnessed, 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. Acute ECG changes

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 code each ECG.

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 consecuitve 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 hav eto be exactly simultaneous. q

waves will often be present in the same graphs but they are not necessary to the use of this criterion.

1.2.3.2.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 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 idential to those for accompnaying Q waves - the 4 code is more sever. A 4-1 must be present.

1.2.3.3.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	

1.2.3.4.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. ECG's in which suppression codes permit certain Q codes eg diagnostic Q which would allow criteria and to be fulfilled. however all other criteria require supporting evidence from suppressed codes. Therefore unless codes definite or ischaemic are fulfilled then the presence of suppression codes or technically unsatisfactory records should lead to the allocation of classification "uncodable". The implications of this rule are that ventricular conduction abnormalities and arrhythmias occurring in the course of an event are not used as collateral evidence of ischaemia.

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 enzyme abnormalities as follows:

EITHER

Acute ECGs	definite	or
Autopsy	definite	

OR

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

OR

Symptoms	typical	and
ECGs	ischaemic or not available	and
Enzymes	abnormal	

1.2.5. Possible myocardial infarction

Living patients

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

1.3. "SILENT" NON-FATAL MYOCARDIAL INFARCTION

(i) Silent MI is part of the definition of the primary endpoint.

(ii) The definition of major Q / QS changes is changed from all 1-1 and 1-2 codes to all 1-1 codes and all 1-2 codes, except 1-2-6 and 1-2-7.

(iii) Significant serial change criteria are applied according to the Minnesota code manual (Table 15-2; Prineas 1982).

(iv) The investigators are notified of these potential abnormalities, so they can then enquire about the presence or absence of a clinically manifest event. This will avoid misclassifying as "silent" events which are just un-ascertained symptomatic events.

(v) The Endpoint Committee reviews all silent MI's.

(vi) The date of the event of a silent MI should be take as 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.

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

This includes

- CHD (ICD 9 410-414)
- Stroke (ICD 9 430 - 438)
- other heart and vascular disease (390-405, 415-429, 440-459)

2.3. FATAL AND NON-FATAL STROKE

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

1 = Diffuse signs
at least 1 of the following 4 codes:
acute headache nausea, vomiting
loss of consciousness)
meningism

2 = Focal signs
at least 1 of the following 6 codes:
Weakness or loss of strength in arm and/or leg
Sensory loss
Difficulty with speech
Loss of vision
Double vision
Ataxia of limbs or gait

3 = Focal signs plus rheumatic heart disease
0
4 = Other findings (not compatible with 1-3)

5 = Mixed signs
(a) = 1 + 2 or

(a) = 1 + 3

6 = Signs for rheumatic heart disease
Defect of the mitral valve) or
Rheumatic heart disease) or
Atrial fibrillation) or
Rheumatic heart disease)

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 haemorraghe (when contrast medium excape)

d) Lumbar puncture

1 = No bloody liquor (including traumatic tap ie
RBC < 100/cm^3, WBC < 10/cm^3, protein < 0.6 gm/l
and pressure < 200 mm H_2O)

2 = Bloody liquor (RBC > 2000/m^3)
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. Haemorrhagic stroke

(i) Subarachnoid haemorrhage
This diagnosis will be made if a CT scan or MRI scan demonstrated blood in the subarachnoid space. Alternatively, if CT or MRI scans are not done or reported as normal, this diagnosis will then be made if the clinical presentation is compatible with a diffuse neurological problem with typical symptoms of meningism, together with either cerebrospinal fluid (CSF) changes of blood staining sufficient to preclude 'traumatic tap' and/or an aneurysm 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)

(ii) Intracerebral haemorrhage (including intraventricular, intraparenchymal and intracerebellar haemorrhage)
This diagnosis will be made if a CT scan, MRI scan or cerebral angiogram carried out within 3 weeks of the clinical event is so reported, or in the absence of any such imaging the CSF is reported as blood-stained (with changes sufficient to preclude a `traumatic tap') and the clinical presentation is clearly compatible with an acute focal lesion.

A haemorrhagic stroke can be coded as 1, 2, 6 or 7 (it depends on the clinical signs and symptoms and the findings).

EITHER

(b) = 3 (computetomography) or
(c) = 2 (Angiography) or
(e) = 2 (MRI)
(f) = 2 (autopsy)

OR

(a) = 2 or 5 (clinical symptoms and signs) and
(d) = 2 (lumbar puncture)

(iii) Undifferentiated haemorrhage
This diagnosis will be made in the presence of a clinical presentation including both diffuse and focal neurological signs and when lumbar puncture confirm sufficient blood staining of the CSF to exclude a 'traumatic tap' but no other signs (eg meningism) or investigations (eg CT scan) are available to differentiate between an intracerebral or subarachnoid haemorrhage.

In those cases where both intracerebral and subarachnoid bleeding are apparent on a CT or MRI scan, the stroke will be classified as a subarachnoid haemorrhage if either aneurysms(s) are identified, or the bleeding is clearly predominant in the subarachnoid space. Alternatively, strokes will be classified as intracerebral if either arterio-venous malformations are identified, or the bleeding is predominantly intracerebral.

(a) = 1 or 5 (clinical symptoms and signs) and
(d) = 2 (lumbar puncture)

2.3.2. Ischaemic stroke

(i) Without cardiac source for embolus: This diagnosis will be made if the patient does not have clinical signs of rheumatic heart disease and/or atrial fibrillation and 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.

(ii) With cardiac source for embolus: As above but in the presence of clinical signs of rheumatic heart disease and/or atrial fibrillation.

EITHER

(a) = 3 or 6 (clincial symptoms and signs) and
(b) = 4 (computertomography) or
(c) = 3 (Angiography) or
(e) = 3 (MRI) or
(f) = 4 (autopsy)

OR

(a) = 3 (clinical symptoms and signs) and
(b) = 1 (computertomography) or
(f) = 4 (autopsy)

OR

(f) = 3 (autopsy)

4 = Other Infarct

EITHER

(b) = 4 (Computertomography) or
(c) = 3 (Angiography) or
(e) = 3 (MRI) or
(f) = 4 (autopsy)

OR

(a) = 2 or 5 (clinical symptoms and signs) and
(b) = 1 (computertomography within 2 days)

[carotid artery surgery]

2.3.2.1.Unknown

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

2.3.2.2.Transient ischaemic attack (TIA)

Transient ischaemic attack (TIA) is diagnosed according to time and course of signs and symptoms as well as their severity. The definite diagnosis requires acute remission to health management organization, open center or hospital. TIAs will be diagnosed when symptoms develop within a few seconds, last at least one minute and disappear completely within 24 hours. Localization is marked as in ischaemic events. Signs and symptoms that will not be accepted as TIA attacks will be: unilateral sensory symptoms, syncope, loss of consciousness, or confusion, convulsions, incontinence of urine or faeces, dizziness, focal symptoms associated with migraine or scintillating scotoma.

2.3.2.3.Reversible ischaemic neurologic deficit (RIND)

Reversible ischemic neurologic deficit (RIND) will be diagnosed according to the same criteria as TIA. Signs and symptoms last at least 24 hours, and disappear almost completely within 6 weeks. No other diagnostic findings to fit hemorrhagic, embolic or atherotrombotic deficits will be found.

2.3.2.4.Other heart and vascular disease death

Any cardiovascular disease death not due to CHD or stroke.

2.3.2.5.Cancer

All cases of death from malignant diseases will be included in this category.
ICD 9 140 -239

2.3.2.6.Respiratory

ICD 9 460-519

2.3.2.7.Other

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

2.3.2.8.Unknown

All deaths which cannot be classified as one of the above categories of death will be classified as 'unknown'.

2.4. FATAL AND NON-FATAL HEART FAILURE

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
- ventricular S 3: (third heart sound)
- bilateral ankle odema
- hepatomegaly
- raised JVP
- 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

b. Impaired left ventricular systolic or diastolic dysfunction

Echocardiography: LV ejection fraction is <= 35% 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. 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. TOTAL CORONARY EVENTS

Total coronary events =

Non-fatal MI (symptomatic + silent) AND
fatal CHD AND
unstable angina AND
chronic stable angina

2.6. TOTAL CARDIOVASCULAR EVENTS AND PROCEDURES

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	+
peripheral arterial disease	+
revascularisation procedures	

Revascularisation procedures are defined as:

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

(ii) Carotid procedures:
- endarterectomy
- bypass

(iii) Femoral-popliteal procedures
- angioplasty
- bypass

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) *not a definite acute MI on this admission*

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

(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

The Braunwald classification is helpful in defininig unstable angina.
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?
Did the patient have any of the following conditions at the time of these anginal episodes? Anaemia, fever, infection, hypotension, uncontrolled hypertension, tachyarrythmia, unusual emotional stress, thyrotoxicosis, hypoxaemia secondary to respiratory failure?

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

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 one or more 70% or greater stenoses in other major artery.

-positive exercise ECG (> 1mm ST depression)

- positive thallium scintigraphy

The EPC considered and reject stipulating separate criteria for women.

3.3. PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease is defined as chronic or acute leg ischaemia or aortic aneurysm

(i) Chronic leg ischaemia / Intermittent claudication

Will be defined using the Edinburgh claudication questionnaire. Without comcomitant signs or test abnormality this is likely to be over sensitive.

(ii) Acute leg ischaemia

Is defined as

(a) Symptoms / signs

- pain
- weakness of distal muscles
- cold extremity
- loss of peripheral pulses

(b) Investigation abnormality

- B-mode ultrasound or arteriography

(c) Revascularisation or reperfusion treatment

(iii) Aortic aneurysm

Thoracic or abdominal aneurysm is defined in presence of

(a) Symptoms / signs

- mass
- leak
- rupture
- dissection

(b) Imaging

- abdominal ultrasound
- transoesophageal echocardiography
- CT scan
- MRI scan

3.4. LIFE THREATENING ARRHYTHMIA

(i) Sustained ventricular tachycardia requiring urgent cardioversion (DC shock) or

(ii) Cardiac arrest (requiring resuscitation)

3.5. DEVELOPMENT OF DIABETES

In order to establish the diagnosis which has developed either before or during the study, it will be necessary to perform glucose evaluations as outlined by WHO criteria (see Protocol, Appendix IC).

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.

In subjects with a fasting venous plasma glucose concentration of <6 mmol/l the diagnosis is excluded and those with a value of ≥7.00 mmol/l shall be diagnosed as diabetic.

For those undergoing a (75gm) glucose tolerance test, a 2 hour value of 11.1 mmol/l is diagnosed as diabetes, in the range 7-11.1 mmol/l is diagnosed as impaired glucose tolerance and <7 mmol/l is non-diabetic.

The above diagnoses are based on current WHO guidelines which are due to be modified imminently, in which case the definitions will be modified accordingly.

3.6. DEVELOPMENT OF RENAL IMPAIRMENT

This will be defined as

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

(ii) the development of persistent dipstix proteinuria (≥ one plus protein)