Myocardial Infarction Redefined—A Consensus Document of The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction

The Joint European Society of Cardiology/
American College of Cardiology Committee**

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PREAMBLE

This document was developed by a consensus conference initiated by Kristian Thygesen, MD, and Joseph S. Alpert, MD, after formal approval by Lars Rydén, MD, President of the European Society of Cardiology (ESC), and Arthur Garson, MD, President of the American College of Cardiology (ACC). All of the participants were selected for their expertise in the field they represented, with approximately one-half of the participants selected from each organization. Participants were instructed to review the scientific evidence in their area of expertise and to attend the consensus conference with prepared remarks. The first draft of the document was prepared during the consensus conference itself. Sources of funding appear in Appendix A. The recommendations made in this document represent the attitudes and opinions of the participants at the time of the conference, and these recommendations were revised subsequently. The conclusions reached will undoubtedly need to be revised as new scientific evidence becomes available. This document has been reviewed by members of the ESC Committee for Scientific and Clinical Initiatives and by members of the Board of the ESC who approved the document on April 15, 2000.*

I. INTRODUCTION: CONCEPT AND DEFINITION OF MYOCARDIAL INFARCTION

Myocardial infarction (MI) can be defined from a number of different perspectives related to clinical, electrocardiographic (ECG), biochemical and pathologic characteristics. The term MI also has social and psychological implications, both as an indicator of a major health problem and as a measure of disease prevalence in population statistics and outcomes of clinical trials (Fig. 1).

In the distant past, a general consensus existed for the clinical entity designated as MI. In studies of disease prevalence by the World Health Organization (WHO), MI was defined by a combination of two of three characteristics: typical symptoms (i.e., chest discomfort), enzyme rise and a typical ECG pattern involving the development of Q waves. However, current clinical practice, health care delivery systems, as well as epidemiologic studies and clinical trials, all require a more precise definition of MI. Furthermore, the advent of sensitive and specific serologic biomarkers and

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precise imaging techniques necessitate reevaluation of established definitions of MI. The latter technologic advances have high sensitivity to detect very small infarcts that would not have been considered an MI in an earlier era. Current technology can identify patients with small areas of myocardial necrosis weighing <1.0 g. Thus, if we accept the concept that any amount of myocardial necrosis caused by ischemia should be labeled as an infarct (as proposed by this consensus conference), then an individual who was formerly diagnosed as having severe, stable or unstable angina pectoris might be diagnosed today as having had a small MI. The resulting increase in the sensitivity of the defining criteria for MI would mean more cases identified; in contrast, an increase in specificity would lessen the number of false positive MIs. Such changes in definition might have a profound effect on the traditional monitoring of disease rates and outcomes.

In response to the issues posed by an alteration in our ability to identify MI, the ESC and the ACC convened a consensus conference during July 1999 to reexamine jointly the definition of MI. The scientific and societal implications of a new definition for MI were examined from seven points of view: pathology, biochemistry, electrocardiography, imaging, clinical trials, epidemiology and public policy. It became apparent from the deliberations of the consensus committee that the term MI should not be used without further qualifications, whether in clinical practice, in the description of patient cohorts or in population studies. Such qualifications should refer to the amount of myocardial cell loss (infarct size), to the circumstances leading to the infarct (spontaneous or in the setting of a coronary artery diagnostic or therapeutic procedure) and to the timing of the myocardial necrosis relative to the time of the observation (evolving, healing or healed MI).

II. CLINICAL PRESENTATION

It is accepted that the term MI reflects a loss of cardiac myocytes (necrosis) caused by prolonged ischemia. Ischemia is the result of a perfusion-dependent imbalance between supply and demand. Ischemia in a clinical setting can be identified from the patient's history and from the ECG. Possible ischemic symptoms include chest, epigastric, arm, wrist or jaw discomfort with exertion or at rest. The discomfort associated with acute MI usually lasts at least 20 min, but may be shorter in duration. The discomfort may develop in the central or left chest and then radiate to the arm, jaw, back or shoulder. The discomfort is usually not sharp or highly localized and may be associated with dyspnea, diaphoresis, nausea, vomiting or light-headedness. The discomfort can develop in the epigastrium (often confused with indigestion), arm, shoulder, wrist, jaw or back, without occurring in the chest, but such a pattern is atypical. The discomfort is not affected by moving the muscles of the region where the discomfort is localized, nor is it worsened by deep inspiration. The discomfort is not

Table 1. Aspects of MI by Different Techniques

Pathology	Myocardial cell death
Biochemistry	Markers of myocardial cell death recovered from blood samples
Electrocardiography	Evidence of myocardial ischemia (ST-T segment changes)
	Evidence of loss of electrically functioning cardiac tissue (Q waves)
Imaging	Reduction or loss of tissue perfusion
	Cardiac wall motion abnormalities

positional in nature. Symptoms can also include unexplained nausea and vomiting, persistent shortness of breath secondary to left ventricular failure and unexplained weakness, dizziness, lightheadedness or syncope, or a combination of these. These symptoms may be noted in association with chest discomfort or they may occur in the absence of chest symptoms.

Although many patients have symptoms such as those just described, these complaints may go unrecognized or may be erroneously labeled as another disease entity, such as indigestion or a viral syndrome. Myocardial necrosis may also occur without symptoms; it may be detected only by the ECG, cardiac imaging or other studies.

III. DETECTION OF NECROSIS OF MYOCARDIAL CELLS

The presence or absence and the amount of myocardial damage resulting from prolonged ischemia can be assessed by a number of different means, including pathologic examination, measurement of myocardial proteins in the blood, ECG recordings (ST-T segment wave changes, Q waves), imaging modalities such as myocardial perfusion imaging, echocardiography and contrast ventriculography. For each of these techniques, a gradient can be distinguished from minimal to small to large amounts of myocardial necrosis. Some clinicians classify myocardial necrosis as microscopic, small, moderate and large on the basis of the peak level of a particular biomarker. The sensitivity and specificity of each of these techniques used to detect myocardial cell loss, quantitate this loss and recognize the sequence of events over time, differ markedly (Table 1).

1. Pathology. *Myocardial infarction* is defined as myocardial cell death due to prolonged ischemia. Cell death is categorized pathologically as either coagulation or contraction band necrosis, or both, which usually evolves through oncosis, but can result to a lesser degree from apoptosis. Careful analysis of histologic sections by an experienced observer is essential to distinguish these entities.

After the onset of myocardial ischemia, cell death is not immediate but takes a finite period to develop (as little as 15 min in some animal models, but even this may be an overestimate). It takes 6 h before myocardial necrosis can be identified by standard macroscopic or microscopic postmortem examination. Complete necrosis of all myocardial cells at risk requires at least 4 h to 6 h or longer, depending on the presence of collateral blood flow into the ischemic zone,

Table 2. Biochemical Markers for Detecting Myocardial Necrosis

The following are biochemical indicators for detecting myocardial necrosis: 1) Maximal concentration of troponin T or I exceeding the decision limit (99th percentile of the values for a reference control group) on at least one occasion during the first 24 h after the index clinical event, 2) Maximal value of CK-MB (preferably CK-MB mass) exceeding the 99th percentile of the values for a reference control group on two successive samples, or maximal value exceeding twice the upper limit of normal for the specific institution on one occasion during the first hours after the index clinical event. Values for CK-MB should rise and fall; values that remain elevated without change are almost never due to MI. In the absence of availability of a troponin or CK-MB assay, total CK (greater than two times the upper reference limit) or the B fraction of CK may be employed, but these last two biomarkers are considerably less satisfactory than CK-MB.

persistent or intermittent coronary artery occlusion and the sensitivity of the myocytes.

Infarcts are usually classified by size—microscopic (focal necrosis), small (<10% of the left ventricle), medium (10% to 30% of the left ventricle) or large (>30% of the left ventricle)—as well as by location (anterior, lateral, inferior, posterior or septal or a combination of locations). The pathologic identification of myocardial necrosis is made without reference to morphologic changes in the epicardial coronary artery tree or to the clinical history.

The term MI in a pathologic context should be preceded by the words "acute, healing or healed." An acute or evolving infarction is characterized by the presence of polymorphonuclear leukocytes. If the interval between the onset of infarction and death is brief (e.g., 6 h), minimal or no polymorphonuclear leukocytes may be seen. The presence of mononuclear cells and fibroblasts and the absence of polymorphonuclear leukocytes characterize a healing infarction. A healed infarction is manifested as scar tissue without cellular infiltration. The entire process leading to a healed infarction usually requires five to six weeks or more. Furthermore, reperfusion alters the gross and microscopic appearance of the necrotic zone by producing myocytes with contraction bands and large quantities of extravasated erythrocytes.

Infarcts are classified temporally according to the pathologic appearance as follows: acute (6 h to 7 days); healing (7 to 28 days), healed (29 days or more). It should be emphasized that the clinical and ECG timing of an acute ischemic event may not be the same as the pathologic timing of an acute infarction. For example, the ECG may still demonstrate evolving ST-T segment changes, and cardiac troponin may still be elevated (implying a recent infarct) at a time when, pathologically, the infarct is in the healing phase.

2. Biochemical markers of myocardial necrosis. Myocardial necrosis results in and can be recognized by the appearance in the blood of different proteins released into the circulation due to the damaged myocytes: myoglobin, cardiac troponins T and I, creatine kinase, lactate dehydrogenase, as well as many others (Fig. 2). Myocardial infarction is diagnosed when blood levels of sensitive and specific biomarkers, such as cardiac troponin and the MB fraction of creatine kinase (CK-MB), are increased in the clinical setting of acute ischemia. These biomarkers reflect myocardial damage but do not indicate its mechanism. Thus, an elevated value in the absence of clinical evidence of ischemia

should prompt a search for other causes of cardiac damage, such as myocarditis.

The most recently described and preferred biomarker for myocardial damage is cardiac troponin (I or T), which has nearly absolute myocardial tissue specificity, as well as high sensitivity, thereby reflecting even microscopic zones of myocardial necrosis. An increased value for cardiac troponin should be defined as a measurement exceeding the 99th percentile of a reference control group. Reference values must be determined in each laboratory by studies using specific assays with appropriate quality control, as reported in peer-reviewed journals. Acceptable imprecision (coefficient of variation) at the 99th percentile for each assay should be defined as ≤10%. Each individual laboratory should confirm the range of reference values in their specific setting. In addition, meticulous laboratory practice must be maintained. Because cardiac troponin values may remain elevated for 7 to 10 days or longer after myocardial necrosis, care should be exercised in attribution of elevated cardiac troponin levels to very recent clinical events (Table 2).

If cardiac troponin assays are not available, the best alternative is CK-MB (measured by mass assay). This is less tissue-specific than cardiac troponin, but the data documenting its clinical specificity for irreversible injury are more robust. As with cardiac troponin, an increased CK-MB value (i.e., above the decision limit for MI) is defined as one that exceeds the 99th percentile of CK-MB values in a reference control group. In most situations, elevated values for biomarkers should be recorded from two successive blood samples to diagnose MI.

Measurement of total CK is not recommended for the routine diagnosis of acute MI, because of the wide tissue distribution of this enzyme. Nevertheless, total CK has a long history, and some physicians may opt to continue to employ it for epidemiologic or scientific purposes. In such a setting, total CK should be combined with a more sensitive biomarker, such as cardiac troponin or CK-MB, for more accurate clinical diagnosis of acute MI. The cut-off limits for total CK should be relatively higher than those for cardiac troponin or CK-MB (at least twice the upper reference limit for CK). Glutamic-oxaloacetic transaminase (ASAT [aspartate amino transferase]), lactate dehydrogenase and lactate dehydrogenase isoenzymes should not be used to diagnose cardiac damage. Along with other clinical factors (e.g., residual left ventricular function), the degree of biomarker elevation is related to clinical risk. A classification for the extent of myocardial damage (microscopic, small,
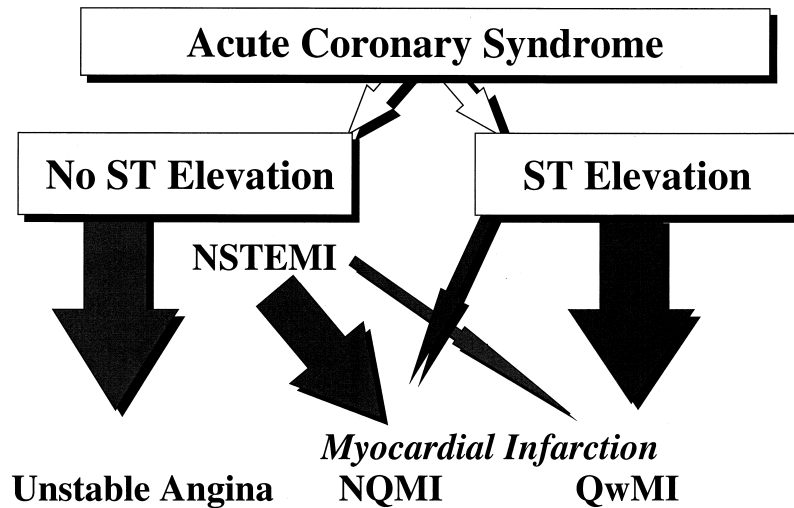
Acute Coronary Syndrome

No ST Elevation **ST Elevation**

NSTEMI

Myocardial Infarction
Unstable Angina **NQMI** **QwMI**

Figure 1. Clinical classification of acute coronary syndromes.
NQMI = non-Q-wave myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; Q-wave MI = Q-wave myocardial infarction; ST = ST segment of ECG tracing.

medium or large) should be employed, although no generally accepted grading system of infarct size exists.

For most patients, blood should be obtained for testing on hospital admission, at 6 to 9 h and again at 12 to 24 h if the earlier samples are negative and the clinical index of suspicion is high. For patients in need of an early diagnosis, a rapidly appearing biomarker (such as CK-MB isoforms or myoglobin), plus a biomarker that rises later (e.g., cardiac troponin), is recommended for confirmation of the diagnosis (Fig. 1).

Detection of *reinfarction* is clinically important because it carries incremental risk for the patient. Reinfarction may present special diagnostic difficulties, because an increase of cardiac troponin can be long-lasting, and when cardiac troponin is persistently high, the timing of the initial myocardial damage is difficult to ascertain. If the first sample on presentation has a high cardiac troponin value, then sequential samples of a biomarker with a shorter time course, such as CK-MB or myoglobin, could be employed to clarify the timing of the infarct.

3. Electrocardiography. The ECG may show signs of myocardial ischemia, specifically ST segment and T wave

Table 3. ECG Changes Indicative of Myocardial Ischemia That May Progress to MI

1. Patients with ST segment elevation:
   New or presumed new ST segment elevation at the J point in two or more contiguous leads with the cut-off points ≥ 0.2 mV in leads V_1, V_2, or V_3 and ≥ 0.1 mV in other leads (contiguity in the frontal plane is defined by the lead sequence aVL, I, inverted aVR, II, aVF, III).
2. Patients without ST segment elevation:
   a. ST segment depression
   b. T wave abnormalities only

New or presumed new ST segment depression or T wave abnormalities, or both, should be observed in two or more contiguous leads. Also, new or presumed new symmetric inversion of T waves ≥ 1 mm should be present in at least two contiguous leads.

changes, as well as signs of myocardial necrosis, specifically changes in the QRS pattern. A working definition for acute or evolving MI in the presence of a clinically appropriate syndrome, as demonstrated by standard 12-lead ECG, has been established by using data from clinical and pathoanatomic correlative studies. The following ECG criteria (in the absence of QRS confounders [i.e., bundle branch block, left ventricular hypertrophy, Wolff-Parkinson-White syndrome]) have emerged as robust determinants for the diagnosis of myocardial ischemia (Table 3). Such ischemic changes may be associated with evolving MI, as discussed subsequently (Fig. 1).

The ECG criteria in Table 3 reflect myocardial ischemia and are not sufficient by themselves to define MI. The final diagnosis of myocardial necrosis depends on the detection of elevated levels of cardiac biomarkers in the blood, as discussed earlier. ST segment elevation in patients with suspected acute MI can resolve rapidly either spontaneously or after therapy. The effect of reperfusion therapy on ST segment changes should be taken into consideration when using the ECG to diagnose MI. Some patients with rapid reversal of ST segment elevation will not develop myocardial necrosis. Moreover, ST segment depression, which is maximal in leads V_1 through V_3, without ST segment elevation in other leads, should be considered as indicative of posterior ischemia or infarction, or both, but imaging studies are usually needed to confirm the presence of ischemia or infarction in an individual patient. In the presence of new or presumed new left bundle branch block, ST segment elevation can accompany the bundle branch block, making it difficult or impossible to recognize an acute

Table 4. Electrocardiographic Changes in Established MI

1. Any Q-wave in leads V_1 through V_3, Q-wave > or = to 30 ms (0.03 s) in leads I, II, aVL, aVF, V_4, V_5, or V_6. (The Q-wave changes must be present in any two contiguous leads, and be > or = to 1 mm in depth.)

infarction, and criteria indicative of acute MI need to be defined by further research. Tall and peaked T waves (hyperacute T waves) have been noted during the very early phases of acute MI.

New or presumed new ST segment depression or T wave abnormalities, or both, should be observed in two or more contiguous leads on two consecutive ECGs at least several hours apart.

Myocardial necrosis or clinically established MI may be defined from standard 12-lead ECG criteria in the absence of QRS confounders (e.g., bundle branch block, left ventricular hypertrophy, Wolff-Parkinson-White syndrome) or immediately after coronary artery bypass graft surgery, utilizing the QRS changes presented in Table 4. A single ECG that meets the Q wave criteria in Table 4 is indicative of a previous MI. Q waves <30 ms in duration associated with ST-T segment depression may represent infarction, but these findings require more research and confirmation. When three or more ECG recordings are obtained, then at least two consecutive ECGs should demonstrate the abnormality in question. Criteria for Q wave depth require more research, as do QRS criteria to establish the diagnosis of posterior MI. Bundle branch block with additional Q waves is included in these descriptions. Right bundle branch block will not interfere with the ability to diagnose Q waves; left bundle branch block usually obscures Q waves; new Q waves in the presence of left bundle branch block should be considered as pathologic.

Not all patients who develop myocardial necrosis exhibit ECG changes. Thus, a normal ECG does not rule out the diagnosis of MI. Since new sensitive biochemical markers enable detection of myocardial necrosis too small to be associated with QRS abnormalities, some patients will have their peak values in the subrange of any QRS changes. Such patients might be considered to have only a microinfarction, but these aspects need further clarification.

4. Imaging. Imaging techniques have been used to assist in 1) ruling out or confirming the presence of acute infarction or ischemia in the Emergency Department; 2) identifying nonischemic conditions causing chest pain; 3) defining short- and long-term prognoses; and 4) identifying mechanical complications of acute infarction. The rationale of acute imaging using echocardiographic or nuclear techniques in patients suspected of having acute ischemia is that ischemia results in regional myocardial hypoperfusion, leading to a cascade of events that can include myocardial dysfunction and ultimately cell death. Only conventional methods such as cross-sectional echocardiography, radionuclide angiography and myocardial single-photon emission computed tomographic (SPECT) perfusion imaging are discussed in this document, and not those that are presently being tested in clinical research studies.

One of the major advantages of echocardiography is that it allows assessment of most nonischemic causes of acute chest pain, such as perimyocarditis, valvular heart disease (aortic stenosis), pulmonary embolism and aortopathies (aortic dissection).

Radionuclide techniques enable the physician to assess perfusion at the time of patient presentation; this can be performed with immediate tracer injection, because image acquisition can be delayed for 60 to 90 min. Quantitative analysis is an advantage of this technique. The accuracy of the studies is high when interpreted by skilled observers. These studies also provide simultaneous information on myocardial perfusion and function.

Biomarkers are more sensitive, more specific and less costly than imaging techniques for the diagnosis of myocardial necrosis. Injury involving >20% of myocardial wall thickness is required before a segmental wall motion abnormality can be detected by echocardiography. In general, >10 g of myocardial tissue must be injured before a radionuclide perfusion defect can be resolved. Neither technique can distinguish ischemia from infarction.

a) Acute ischemia and acute or evolving MI. By its ability to detect regional wall motion abnormalities within minutes of an ischemic injury, two-dimensional echocardiography may be useful in the diagnosis of acute MI. Both the localization and extent of infarction can be determined. An echocardiographic or radionuclide image early after the onset of symptoms is of great help in the assessment of patients with suspected acute MI and a nondiagnostic or noninterpretable ECG. With acute imaging in such patients, a normal echocardiogram or a normal rest gated technetium-99m SPECT study is useful for excluding acute infarction, because of a 95% to 98% negative predictive value when CK-MB is used as the gold standard. However, it is unknown whether these techniques have the same negative predictive value in patients with elevated troponin and a normal CK-MB value.

A wall motion abnormality on echocardiographic or radionuclide imaging may be caused by acute MI or one of a number of several myocardial ischemic conditions, including an old MI, acute ischemia, stunning or hibernation, or a combination. The positive predictive value of echocardiography is ~50% for the diagnosis of acute MI, because of the aforementioned conditions and other non–infarct-related etiologies of wall motion abnormalities (e.g., dilated cardiomyopathy). The positive predictive value for gated SPECT is also limited, because abnormal regional perfusion and/or an old MI, acute ischemia, stunning and/or hibernation may cause regional dysfunction. Attenuation artifacts and inexperienced interpreters may also lead to false positive scan interpretation.

b) Established MI. Echocardiography is useful after a sudden event for analysis of residual left ventricular function. Determination of left ventricular function has prognostic value. Left ventricular function can be evaluated during exercise or dobutamine stress; the results of such testing conveys information on myocardial viability. The number of segments involved allows one to calculate a wall motion score as a measure of residual left ventricular

function, which has early and late prognostic value in predicting complications and survival. Coexisting mitral valve dysfunction, infarct expansion, mural thrombus and mechanical complications of infarction are easily identified. Echocardiography is the diagnostic procedure of choice for identification of mechanical complications of MI.

Radionuclide techniques can also be used in the healing or healed phases of infarction for prognostication. In conjunction with exercise or vasodilator stress, measuring the extent of defect reversibility can identify the extent of ischemia. Detecting defects in more than one coronary artery zone can identify multivessel disease. A variety of prognostic findings can be identified (e.g., lung uptake of the tracer thallium-201, ischemic left ventricular cavity dilation, defect size that corresponds to infarct size). Finally, the extent of myocardial viability can be estimated by quantitative perfusion imaging with either thallium-201 or technetium-99m perfusion tracers.

IV. MI IN SPECIFIC CLINICAL SETTINGS

1. Percutaneous coronary artery intervention. An increase of cardiac biomarkers after coronary angioplasty or implantation of coronary artery stents, or both, is indicative of cell death. Because this necrosis occurs as a result of myocardial ischemia, it should be labeled as an MI according to the new criteria. Large infarcts in this setting may be caused by a complicated procedure and can usually be recognized clinically. In contrast, small or tiny infarcts are more frequent and are probably the result of microemboli from the atherosclerotic lesion that has been disrupted during angioplasty or from the particulate thrombus at the site of the culprit lesion.

In the setting of percutaneous coronary artery interventions, small infarcts may, and should, be detected by serial blood sampling and analysis before and after the procedure (6 to 8 h and 24 h, respectively). The peak level of the myocardial biomarkers may be pronounced and of relatively greater magnitude because of the reperfusion associated with the procedure. Myocardial cell injury occurring after angioplasty may be a one-time event, as compared with the often repetitive nature of spontaneously occurring episodes of myocardial ischemia and necrosis. However, it is likely that patients who develop a coronary embolism and small infarcts have atherosclerotic lesions that are apparently unstable, and hence represent a subgroup at risk for future events. Indeed, it has been convincingly demonstrated that the risk of subsequent ischemic heart disease events (death or MI) is related to the extent of cardiac troponin or CK-MB increase, and the prognosis for these individuals is usually worse than that for patients who do not develop these small increases in biomarkers after interventional procedures. Accordingly, patients with elevated biomarkers after an otherwise uncomplicated procedure may require particularly careful instructions to respond appropriately to recurrent symptoms.

2. Cardiac surgery. Myocardial damage in association with cardiac surgery can be caused by different mechanisms, including direct trauma by sewing needles; focal trauma from surgical manipulation of the heart; global ischemia from inadequate perfusion, myocardial cell protection or anoxia; coronary artery or venous graft embolism; and other complications of the procedure. A portion of this damage may be unavoidable. Moreover, no biomarker is capable of distinguishing damage due to an acute infarction from the usually small quantity of myocardial cell damage associated with the procedure itself. Nevertheless, the higher the value for the cardiac biomarker after the procedure, the greater the amount of damage to the myocardium, irrespective of the mechanism of injury.

V. IMPLICATIONS OF DIFFERENT DEFINITIONS OF MI

The recent introduction of cardiac troponins T and I into routine daily clinical practice allows for highly accurate, sensitive and specific determination of myocardial injury. In the setting of myocardial ischemia, it is now possible to define infarcts of minimal size as well as larger infarcts. It is now clear that any amount of myocardial damage, as detected by cardiac troponins, implies an impaired clinical outcome for the patient. This is apparently true for individuals with spontaneous events, as well as for patients who undergo coronary artery interventions. A review of currently available data demonstrates no discernible threshold below which an elevated value for cardiac troponin would be deemed harmless. All elevated values are associated with a worsened prognosis. It should be emphasized that there is a continuous relation between minimal myocardial damage, characterized by elevation of cardiac troponin without elevation of other cardiac biomarkers (e.g., CK-MB) and large infarcts, characterized by complications such as heart failure or shock. Thus, any amount of myocardial necrosis caused by ischemia should be labeled as MI. Additional descriptors are needed to describe the state of residual left ventricular function, the extent and severity of coronary artery disease and the stability or instability of the patient's clinical course.

1. Epidemiology. Monitoring of cardiovascular disease in a population is of utmost importance, because it enables the investigator to analyze possible causal factors and to assess the effect of various preventive measures, such as changes in diet or life-style, as well as the effect of medications. The incidence of a new MI and the prevalence of established infarcts represent important epidemiologic variables. The application of the new, more sensitive diagnostic criteria for MI will cause the recorded incidence of MI to rise and the case fatality rate to fall. Thus, a new definition of MI will confuse efforts to follow trends in disease rates and outcomes that are now being used to monitor the impact of public health measures and treatments. However, this would not be a valid reason to hold onto old definitions of MI which no longer reflect current scientific thinking. In

fact, changes in definitions have already occurred, albeit unnoticed—for example, through substitution of newer biomarkers (CK-MB, troponin) for older ones (ASAT, CK). Continued tracking of these trends will require methods for adjusting the new criteria to the old; for example, specific surveillance centers will be needed to measure total CK and CK-MB, together with the newer biomarkers.

Established definitions of MI (e.g., Minnesota code, WHO MONICA) should be retained by specific epidemiologic centers for comparison with previously collected data. At the same time, these centers should use the current biomarker-based definition of acute MI to compare earlier data with subsequent data collected at research centers employing more recent standards for defining acute MI.

2. Clinical trials. Myocardial infarction can be used either as an entry criterion or as an end point in a clinical trial. Entry criteria in clinical investigations dealing with suspected acute or evolving MI or unstable angina reflect the initial working diagnosis at the time the patient is enrolled in the trial. This will not necessarily correspond to the final diagnosis of MI, because spontaneous or therapeutically induced changes may alter the likelihood of developing myocardial necrosis. Usually, a combination of chest discomfort of a determined length of time and ECG abnormalities (ST segment elevation or a new bundle branch block) is required for the initial working diagnosis of MI. Trials of long-term management may require a definite or hospital discharge diagnosis of MI, usually on the basis of ECG Q waves and biochemical markers. Independent of the precise entry criteria chosen, the randomization process will ensure balanced groups of patients for comparison of different treatment modalities. Modification of the definition of MI may impact patient selection or the generalizability of the trial outcome, or both.

In many trials of MI or unstable angina, as well as of primary and secondary prevention of coronary heart disease events, MI is one of the trial end points, usually in combination with total mortality or cardiovascular mortality. In recent trials, different definitions of MI as an end point have been employed, thereby hampering comparison of trial results and meta-analyses.

Myocardial damage may occur in different clinical settings: spontaneous, during percutaneous intervention, during coronary artery bypass graft surgery or with trauma or myocarditis. It has been uncertain whether a similar amount of damage in different settings has the same prognostic implications. There have been different thresholds for identifying an infarct in trials undertaken up to this time in the U.S.: CK-MB >2 times the upper limit of normal (ULN) for spontaneous MI; CK-MB >3 times the ULN with coronary artery interventions; and CK-MB >5 to 10 times the ULN for bypass surgery. It is important that the background for such choices be subjected to research and verified or rejected from different databases. However, the Joint ESC/ACC Expert Committee reached the consensus opinion that, irrespective of the clinical circumstances (ex-
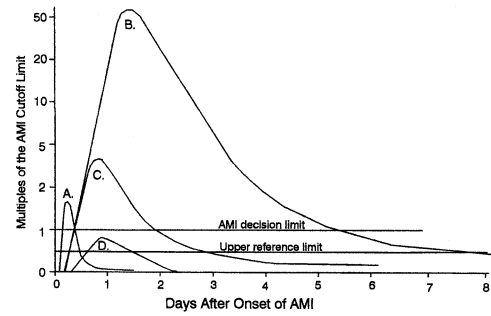

Figure 2. Timing of release of various biomarkers following acute, ischemic myocardial infarction.

Peak A, early release of myoglobin or CK-MB isoforms after AMI; **peak B,** cardiac troponin after AMI; **peak C,** CK-MB after AMI; **peak D,** cardiac troponin after unstable angina. Data are plotted on a relative scale, where 1.0 is set at the AMI cutoff concentration.

AMI = acute myocardial infarction; CAD = coronary artery disease; CK = creatine kinase.

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cept for coronary artery surgery or intended myocardial lesions such as radiofrequency ablation of arrhythmias or septal ablation for hypertrophic cardiomyopathy), the same discriminative value for each biochemical marker should be applied, as they reflect the same amount of myocardial necrosis.

In clinical trials, as in clinical practice, measurement of cardiac troponin T or I is preferred over measurement of CK-MB, as well as total CK and other biomarkers, for the diagnosis of MI. Assessment of the quantity of myocardial damage (infarct size) is also an important trial end point. The use of cardiac troponin will undoubtedly increase the number of events recorded in a particular trial because of its increased sensitivity for detecting MI. Ideally, data should be presented so that trialists can translate the MI end point chosen in one trial into the end point of another trial. Thus, measurements should be presented in a continuous manner (distribution) to allow independent judgment of the clinical end points.

In the design of a trial, investigators should specify the expected effect of the new treatment under investigation. Factors that must be considered include:

1) Reduction in the incidence of spontaneous myocardial damage (events) in treated patients versus control subjects.
2) Reduction in the incidence of angioplasty- or bypass surgery–induced myocardial damage.
3) Reduction in the amount of myocardial damage (infarct size) under any circumstance. Analysis of the actual distribution of infarct sizes observed (area under the curve of a biomarker or peak values) is more appropriate than analysis of the presence or absence of events only.

VI. IMPLICATIONS OF MI IN THE EVOLUTION OF CORONARY DISEASE IN AN INDIVIDUAL PATIENT

Until recently, MI was recognized as a major event, often fatal, and with major implications for survivors. This para-

digm has changed as a result of better management strategies for patients with coronary artery disease, as well as better methods for detecting or excluding myocardial necrosis. The introduction of techniques for measuring cardiac troponin allows for very sensitive and very specific detection of minimal quantities of myocardial necrosis. This new technology serves as the cornerstone of the new definition of MI outlined in this document. It is appreciated that this new definition will attach the label of MI to more patients. Similarly, it will identify more infarcts and more episodes of reinfarction in patients with progressive coronary artery disease. This change in the definition of MI seems reasonable, because it has been definitively shown that any amount of myocardial damage, as detected by cardiac troponins, implies a worsened long-term outcome for the patient. This appears to be true both for spontaneous events and for events associated with coronary procedures. Currently available analyses demonstrate no threshold below which elevations of troponins are harmless and without negative implications for prognosis. Thus, any other definition of MI would involve an arbitrary setting of limits for an abnormal troponin and would be open to criticism and considerable debate. It should be emphasized that there is continuity from "minimal myocardial damage," characterized by elevation of cardiac troponin without apparent elevation of other biomarkers (also termed "infarctlet" or "necrosette"), to the classic "large myocardial infarction," often complicated by heart failure, shock or life-threatening arrhythmia. In applying the proposed new diagnostic criteria to clinical practice, patients should not be labeled primarily as "myocardial infarction" but rather as patients with coronary artery disease with MI. In addition, it is essential that other descriptors of the patient's cardiac status be included, such as current left ventricular function, the extent and severity of coronary artery lesions and an estimate of the evolution of the disease over recent months (i.e., stable or unstable). The crucial elements in this descriptive process can be obtained from invasive diagnostic studies, but may also be reliably estimated from a number of noninvasive studies.

Patients who undergo coronary artery revascularization (coronary angioplasty or bypass surgery) are at risk for myocardial damage, or rather MI according to the new definition. These risks have always been present in the setting of coronary artery interventions, but they have been highlighted by the new, more sensitive biomarkers. Detection of a very small myocardial infarct in this setting augurs a worse prognosis for the patient, rather than if biomarkers had been normal. However, it should be appreciated that long-term patient outcome and prognosis may be improved significantly by the revascularization procedure. For example, a patient with unstable angina and severe left anterior descending coronary artery stenosis will benefit from coronary artery stenting, despite a small elevation in blood troponin levels. The benefit far outweighs the negative impact of the small, procedure-related infarct. It goes without saying that every measure should be taken to prevent even such small infarcts in the setting of coronary artery interventional procedures.

VII. SOCIAL AND PUBLIC POLICY IMPLICATIONS OF REDEFINING MI

Modification of the definition of a specific diagnosis such as MI has a number of implications for individual citizens as well as for society. The process of assigning a specific diagnosis to a patient should be associated with a specific value to the patient. The resources spent on recording and tracking a particular diagnosis must also have a specific value to society to justify the effort. A tentative or final diagnosis is the basis for advice about further diagnostic testing, treatment, life-style changes and prognosis for the patient. The aggregate of patients with a particular diagnosis is the basis for health care planning and policy and resource allocation.

One of the goals of good clinical practice is to reach a definitive and specific diagnosis that is supported by current scientific knowledge. The approach to the definition of MI outlined in this document meets this goal. In general, the conceptual meaning of the term "acute MI" has not changed, although new sensitive diagnostic methods have been developed to diagnose this entity. Thus, the current diagnosis of acute MI is a clinical diagnosis based on patient symptoms, ECG changes and highly sensitive biochemical markers, as well as information gleaned from various imaging techniques. However, it is important to characterize the extent of the patient's myocardial injury and residual left ventricular function, as well as the severity of coronary artery disease, rather than merely making a diagnosis of MI.

Many patients with coronary artery thrombosis leading to MI die suddenly. Difficulties in the definitions of sudden and out-of-hospital death make attribution of the cause of death variable among physicians, regions and countries. For example, out-of-hospital death is generally ascribed to ischemic heart disease in the U.S. but to stroke in Japan. These arbitrary and cultural criteria need reexamination.

It is important that any revised criteria for the definition of MI involve comparability of this definition over time so that adequate trend data can be obtained. Furthermore, it is essential to ensure widespread availability and standard application of measures generating these criteria to ensure comparability of data from various geographic regions. Shifts in criteria resulting in substantial increases or decreases in case identification will have significant health resource and cost implications. Moreover, an increase in sensitivity of the criteria for acute MI might entail negative consequences for some patients who are not currently labeled as having had an MI. In contrast, increasing diagnostic sensitivity for MI can have a positive impact on society:

- Increasing the sensitivity of diagnostic criteria for MI will result in more cases identified, thereby allowing appro-

priate secondary prevention and hopefully reduced health care costs in the future,

- Increasing the specificity of diagnostic criteria for MI will result in elimination of noncases, thereby leading to reduced costs for hospital stays and secondary prevention.

Finally, it should be appreciated that the proposed modification of the definition of MI may be associated with consequences for the patient with respect to psychological status, life insurance, professional career, as well as driving and pilot licenses. The diagnosis is associated with societal implications as well: diagnosis-related grouping (DRG), hospital reimbursement, mortality statistics, sick leave and disability applications and clinical guideline preparation will all be affected.

To meet this challenge, physicians must be adequately informed of the changing diagnostic criteria. Educational materials will need to be created, and treatment guidelines must be appropriately adapted. Professional societies, particularly the ACC, the American Heart Association and the ESC, should take steps to facilitate the rapid dissemination of the revised definition to physicians, other health care professionals, administrators and the general public.

SUMMARY

Definition of MI. *Criteria for acute, evolving or recent MI.* Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
   a) ischemic symptoms;
   b) development of pathologic Q waves on the ECG;
   c) ECG changes indicative of ischemia (ST segment elevation or depression); or
   d) coronary artery intervention (e.g., coronary angioplasty).
2) Pathologic findings of an acute MI.

Criteria for established MI.

Any one of the following criteria satisfies the diagnosis for established MI:

1) Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
2) Pathologic findings of a healed or healing MI.

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APPENDIX A

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APPENDIX B

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APPENDIX C

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