Guidelines

The new definition of myocardial infarction: analysis of the ESC/ACC Consensus Document and reflections on its applicability to the Italian Health System

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The recent document of the ESC/ACC Committee for the redefinition of myocardial infarction (MI) has introduced the measurement of cardiac troponin as the biochemical standard for the diagnosis of MI. This change has been mainly driven by the demonstration that any amount of myocardial damage, as detected by cardiac troponins, implies a worse long-term outcome of the patient. The results of several studies consistently show that there is a continuous relationship between the degree of troponin elevation and the patient's prognosis. The new definition has important consequences on the diagnostic and therapeutic approaches to patients with acute coronary syndromes; in fact, patients with increased troponins, i.e. patients with MI, necessitate more aggressive treatment than those without troponin elevations, i.e. patients with unstable angina. The application of the new definition is expected to increase the number of cases of MI by about 30% and to decrease mortality.

We believe that several aspects of the new definition need to be discussed before the new criteria for MI are used in clinical practice in Italy. The most relevant issues are the following: 1) the definition of troponin elevation should meet the analytical performance of the available assays, the diagnostic cutoff of which is frequently too imprecise. We propose that troponin elevations be defined as values exceeding the concentration corresponding to a total analytical imprecision of 10%. We disclose such a concentration for the currently available assays and suggest its use in clinical practice to mitigate the possibility of false-positive values; 2) the number of samples required for the diagnosis should be sufficient for the assessment of the changes in concentration over time. When only one sample is available, or when the temporal pattern of the changes in marker concentration is not consistent with the time elapsed from the onset of symptoms, we suggest that objective evidence that myocardial ischemia is the likely cause of myocardial damage should be obtained; 3) the diagnosis of MI after a percutaneous coronary intervention represents a unique situation. In contrast with myocardial damage occurring during spontaneous ischemia, available data do not support the concept that any troponin elevation is associated with an adverse prognosis. In the absence of conclusive studies, we suggest that the diagnosis of MI after a percutaneous coronary intervention be based on conventional criteria.

Finally, we propose this summary with the aim of overcoming some of the more controversial aspects of the ESC/ACC redefinition 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) elevation* of biochemical markers of myocardial necrosis (preferably troponin) 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); d) coronary artery intervention (e.g., coronary angioplasty). *Marker elevations should be accompanied by objective evidence that myocardial ischemia is the likely cause of myocardial damage when: a) only one blood sample is available; b) marker changes over time are not consistent with the onset of symptoms;***

2) pathologic findings of an acute MI.

• *Criteria for established MI.* Anyone 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.

*** if troponin is used, the marker concentration should be higher than the value associated with a 10% coefficient of variation, possibly detected in ≥ 1 of at least two occasions. Changes in concentrations should be consistent with the time elapsed from the onset of symptoms; ** since there is no definite evidence that the degree of troponin elevation is correlated with long-term mortality in this setting of "iatrogenic" myocardial damage, we suggest that the physician continues to rely on conventional criteria.**

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Preamble

The document by the Joint Committee of the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) regarding the redefinition of myocardial infarction (MI) has been drawn up following a Consensus Conference held in July 1999. All of the participants were selected for their expertise in the field they represented. Participants were instructed to review the scientific evidence in their area of expertise with the aim of elaborating a final document. The first draft of the document was prepared during the consensus conference itself and was later revised. The full text of the document was published simultaneously in the *European Heart Journal* and in the *Journal of the American College of Cardiology* in September 2000[1,2]. An identical version was published in *Clinical Chemistry* in March 2001[3].

The publication of this document has given rise to a heated discussion in the international cardiology community. In fact, various cardiologists have voiced their doubts regarding:

• the difficulties one may encounter in daily clinical practice when using the new biochemical definition based above all on the use of troponin. In fact, at the cut-off levels suggested by the document, the analytical imprecision (99th percentile of the distribution of values in the reference population) is too high for most of the laboratory methods presently available;

• the consequences deriving from the identification of a larger number of MI as a result of the use of more sensitive diagnostic criteria.

In Italy, these doubts are to be viewed in the perspective of a practice of medicine in which the measurement of troponin has been added to, but has not replaced, the traditional enzyme markers, thus rendering the diagnostic criteria for MI more heterogeneous.

In view of the above, the Laboratory (SIBioC and SIMeL) and Cardiac (FIC) Scientific Societies have decided to elaborate a common document with the aim of focusing on the more controversial aspects of the problem and to propose some hints which should allow for a more realistic application of the new definition bearing in mind the health and even cultural contexts of our society. For this purpose the Intersociety Study Group "Markers of Myocardial Damage" (GDS-MMD) and a group of experts directly nominated by the same societies have drawn up this document which, after having been preliminarily sent to all Italian cardiologists and laboratorians, has been presented and discussed at a meeting held on October 10, 2001 in Florence (Italy). The method used in preparing this document was that of identifying the more controversial issues contained in the original document of the ESC/ACC and to elaborate them further with the aim of providing suggestions which could be useful in daily clinical practice. The more significant points of the ESC/ACC document are highlighted in italics. Among them, those which seemed worthy of further analysis are followed by a comment in which the suggestions are highlighted in bold. The passages of the original document which were held to be irrelevant for the present discussion have been replaced by square brackets.

Definition of myocardial infarction

[...] 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 epidemiological studies and clinical trials, all require a more precise definition of MI. Furthermore, the advent of sensitive and specific serologic biomarkers and 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. [...]

Since their introduction, the performance of cardiac troponins in leading the physician to a diagnosis of MI based on the WHO criteria has proved to be similar to that of creatine kinase (CK)-MB[4]. However, as often occurs when a diagnostic method is more sensitive than the corresponding gold standard, it has also been shown that titration of cardiac troponins often led to "false positive" results; in other words, too many patients in whom, according to the traditional WHO criteria an MI would have been excluded, presented with elevated troponin levels. According to the literature, such false positives accounted for 30-40% of all patients who presented with acute ischemia and in whom the traditional criteria would have permitted one to exclude MI[5,6]. However, as clearly shown later, the prognosis of such patients is similar to that of those in whom an MI was diagnosed according to the traditional criteria. This concept derives from a retrospective analysis of three of the main published articles regard-

ing this issue: the FRISC, TRIM and TIMI IIIB studies. These studies included patients who presented with an acute coronary syndrome without persistent ST-segment elevation, i.e. patients with MI and unstable angina[7-9]. As may be deduced from figure 1, the distinction of patients on the basis of the final diagnosis (made according to the conventional WHO criteria) confers a significantly different prognosis to patients with MI compared to those with unstable angina; however, when the latter are reclassified on the basis of an increase in troponin levels, their short-term prognosis (35-40 days) is similar to that of patients in whom an MI was diagnosed. This fact holds true both when only death is considered as an endpoint (TIMI IIIB) as well as when the endpoints include death and non-fatal MI (FRISC and TRIM).

Furthermore, as shown in the TIMI IIIB and FRISC studies[7,9], in patients presenting with an acute coronary syndrome without persistent ST-segment elevation, there is a direct correlation between the serum concentration of cardiac troponins and the short- and long-term risks of death. This correlation may be explained by the fact that increasing troponin levels are probably indicative of more extensive myocardial damage and consequently of a progressively deteriorating ventricular function which, as shown by some preliminary studies[10-12], may even bear an influence on the patient's prognosis.

Clearly, as may be deduced both from the document as well as from the available data, the new definition of MI is strictly oriented to the physician's aims and derives from the concept that the patient's prognosis in case of a diagnosis of MI is definitely worse compared to that of patients in whom MI is excluded.

The scientific and societal implications of a new definition for MI were examined from seven points of view: pathology, biochemistry, ECG, 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).

It is accepted that the term MI reflects a loss of cardiac myocytes (necrosis) caused by prolonged ischemia. 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.

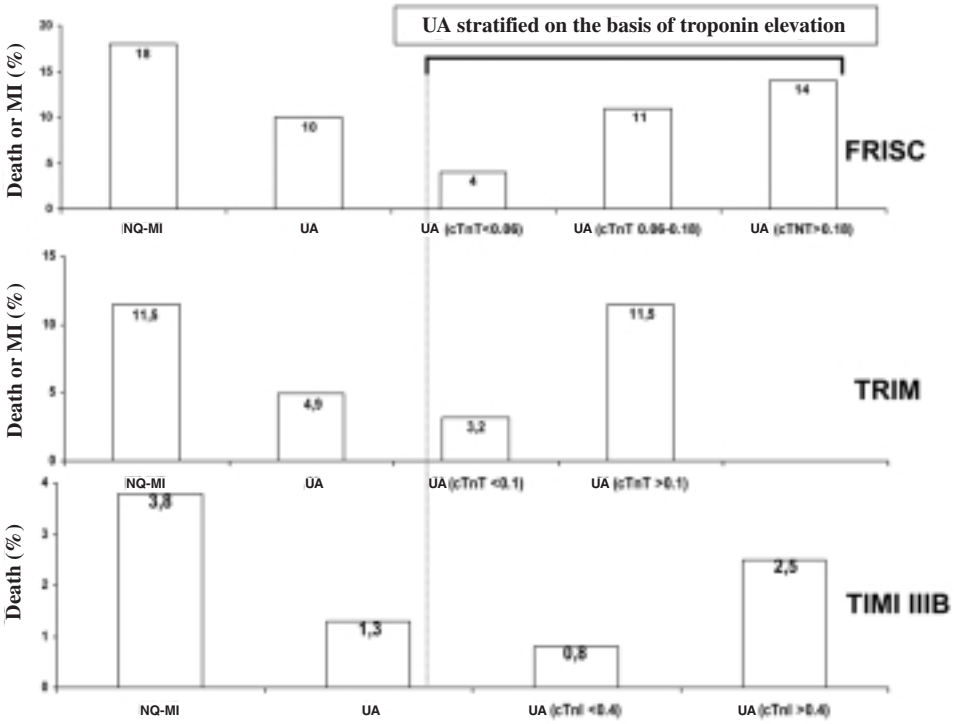

Figure 1. *Short-term incidence of mortality or of mortality and infarction/reinfarction in three clinical studies (FRISC, TRIM, TIMI IIIB) which have shown the prognostic value of troponin increases in patients with acute coronary syndromes. The incidence of events in patients with a non-Q-wave myocardial infarction (NQ-MI) and in those with unstable angina (UA), defined according to the traditional criteria (total creatine kinase or creatine kinase-MB increase) is shown* on the left. *The incidence of events among patients with UA further stratified according to the presence (and the amount) of troponin elevation is shown* on the right. *As may be seen, the incidence of events among patients with increased troponin levels is similar to that observed for patients with a NQ-MI as traditionally defined. cTnI = troponin I; cTnT = troponin T.*

[...] 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.

[...] 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.

[...] Myocardial necrosis may also occur without symptoms; it may be detected only by the ECG, cardiac imaging or other studies.

The increase in the number of MI with atypical symptoms renders the clinical diagnostic criterion less well founded than in the past[13].

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.

[...] 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 I).

Pathology. [...] Cell death is categorized pathologically as either coagulation or contraction band necrosis, or both.

[...] After the onset of myocardial ischemia, cell death is not immediate but takes a finite period to develop.

[...] It takes 6 hours 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 to 6 hours or longer, depending on the presence of collateral blood flow into the ischemic zone, 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).

[...] 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.

[...] 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 5 to 6 weeks or more. [...]

Biochemical markers of myocardial necrosis. [...] MI is diagnosed when blood levels of sensitive and specific biomarkers, such as cardiac troponin and 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 cardiac causes of increased serum troponin levels in the absence of myocardial damage are in fact numerous (Table II). Obviously, the common occurrence of myocardial damage in clinical contexts in which it was not previously diagnosed obliges the physician to determine whether such damage occurs in the clinical setting of acute myocardial ischemia (thus leading to the diagnosis of MI). In many of the situations listed in table II, the finding of myocardial damage is definitely associated with a worse prognosis.

However, with the purpose of limiting the number of cases with a finding of myocardial damage in the absence of an MI, it is advisable that troponin

Table I. *Aspects of myocardial infarction 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*

Table II. Non-ischemic causes of cardiac troponin elevation.

Myocarditis/pericarditis
Heart failure (including acute pulmonary edema)
Hypertension
Low blood pressure (especially if associated with cardiac arrhythmias)
Critically ill patients (in particular diabetics)
Hypothyroidism
Acute cor pulmonale
Cardiac trauma
Chemotherapy-induced myocardial toxicity
Heart transplant rejection
Chronic renal insufficiency
Sepsis

measurement be limited to those patients with a medium to high probability of acute myocardial ischemia. Regardless of the initial diagnostic suspect, indiscriminate troponin measurement in all patients who are evaluated in an emergency or critical clinical setting is to be avoided.

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 (Table III). 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-CV) 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. [...]

One of the main problems encountered when relying on troponin measurement in daily clinical practice, is the diagnostic cut-off level. At present confusion reigns supreme. This, owing to the fact that the adopted reference limits are mainly derived from the package inserts of the commercial kits which still suggest the 97.5th percentile or do not provide adequate information.

On the basis of the definitions given in the ESC/ACC document, the manufacturers of the diagnostic kits are now obliged to provide the troponin concentration corresponding to the 99th percentile of the given analytical system. Furthermore, it is mandatory that for each method the level of analytical imprecision (expressed as the CV) of the concentration corresponding to the reference limit, which according to the document should not exceed 10%, be reported. Unfortunately, most analytical methods presently available do not meet this requirement (CV ≤ 10% at a troponin concentration equal to the 99th percentile)[14]. In fact, it should be borne in mind that not all analytical systems presently used in daily clinical practice are equally accurate and that most commercially available kits cannot yet guarantee such high standards[15].

In practice the analytical platforms used for troponin measurement which presently cannot yield a 10% CV at a concentration equal to the 99th percentile should use, as a cut-off value for the diagnosis of MI, higher concentrations corresponding to the minimum level for which the CV is equal to 10% (Table IV)[1,2,16-24]. Obviously, all this could lead to a global reduction in the clinical sensitivity of the analytical systems used for the diagnosis of MI but should also largely permit the physician to avoid the occasional increase in serum troponin levels in the absence of a clinical picture suggestive of myocardial damage[25,26].

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 cut-off level for MI) is defined as one that exceeds the 99th percentile of CK-MB levels 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 (aspartate amino transferase), lactate dehydrogenase and lactate dehydrogenase isoenzymes should not be used to diagnose cardiac damage.

For the same reason (obsolescence), it is recommended that the measurement of the total CK and of its MB isoenzyme (determined as its catalytic activity) be abandoned[27].

[...] For most patients, blood should be obtained for testing on hospital admission, at 6 to 9 hours and again at 12 to 24 hours 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.

Table III. *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 hours 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 (> 2 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.

Table IV. Examples of the possible influence of the analytical inaccuracy of some troponin assays on the diagnosis of myocardial infarction*.

Method	99th percentile§ (μg/l)	Concentration associated with a CV 10%§§ (μg/l)
Abbott AxSYM	0.50	2.90 (5.8 × 99th percentile)[16]
Bayer ACS:180	0.07	0.30 (4.3 × 99th percentile)[17]
Bayer ACS:Centaur	0.15	1.40 (9.3 × 99th percentile)[18]
Beckman Access 2nd generation	0.04	0.06 (1.5 × 99th percentile)[19]
Dade Dimension RxL 2nd generation	0.07	0.15 (2.1 × 99th percentile)[20]
DPC Immulite	0.40	1.20 (3 × 99th percentile)[21]
Ortho Vitros	0.10	0.35 (3.5 × 99th percentile)[22]
Roche Elecsys 3rd generation	0.01	0.03 (3 × 99th percentile)[23]

CV = total coefficient of analytical variation. * = this table will be available on the website of each Scientific Society and kept updated on the basis of the recent literature data; § = cut-off level for the diagnosis of myocardial infarction as suggested by the Joint Committee ESC/ACC[1,2]; §§ = cut-off level for the diagnosis of myocardial infarction as suggested by the Committee for the Standardization of Markers of Myocardial Damage of the International Federation of Clinical Chemistry and Laboratory Medicine[24].

As previously underlined, when dealing with subjects presenting with chest pain, the rapid evaluation protocols should be reserved for those with an at least moderate suspicion of acute myocardial ischemia. This, in order to determine the risk of acute and short-term ischemic events. On the other hand, the indiscriminate measurement of cardiac markers in all patients who present with chest pain may lead to an increase in the number of "false positive" cases.

Two different biochemical strategies may be employed. The first is based on the combined use of two markers – one characterized by a rapid increase in serum levels and the other, such as troponin, by a slower increase but a high specificity for cardiac tissue[28,29]. As recently shown in a systematic review of the literature[30], at present myoglobin is the first marker to rise, and increases in the serum concentration are detectable within 2-3 hours of the onset of symptoms. This marker is potentially useful in case of patients who present to the Emergency Department with chest pain, since, in the initial phases and within 4 hours of hospitalization, its negative predictive value in excluding an MI is practically 100%[31].

The "two marker" strategy is recommended if the clinical picture permits the physician to modify the patient's outcome by discharging him earlier from the Emergency Department or by facilitating the identification of candidates for a more aggressive therapeutic strategy. Apart from blood sampling at the time of admission, samples should be taken 4, 8 and 12 hours following hospitalization[28].

The second strategy, which includes the use of troponin alone, may be employed in those cases in which clinical decision-making is not so urgent or in circumstances in which the prevalence of acute myocardial ischemia is much higher than in the Emergency Department (for example the coronary care unit) and therefore ruling out of MI is less important. In such cases, the use of an early marker such as myoglobin is not strictly necessary and troponin measurement alone at the time of admission and 6 and 12 hours later is sufficient[32].

The 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.

[...] 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.

Apart from the few cases reported by Falahati et al.[33], data regarding the use of troponins for the diagnosis of a reinfarction are scarce. Undoubtedly, persistently elevated troponin levels following an MI may obscure new increases, especially if modest.

For this reason, in case of a clinically suspected reinfarction, a marker with a more rapid release kinetics such as myoglobin or CK-MB may be profitably employed[27].

Once again it must be stressed that if CK-MB is employed, measurement by mass assay is obligatory[34]. In fact, the use of monoclonal antibodies specific for the MB isoenzyme has provided immunochemical methods for the determination of the protein concentration of the enzyme ("CK-MB mass"). These methods, besides being rapid and easy to use even in an emergency setting, are characterized by a practically absolute specificity for CK-MB and by an analytical sensitivity ≤ 1 μg/l and thus allow for the detection of even minimal variations in the serum concentrations of the isoenzyme in case of non-extensive myocardial lesions.

Once it has been decided to replace CK-MB by troponin, it may be useful to use both methods for a period of time. This, in order to compare the results in the light of the patient's clinical picture. So doing, the sen-

sitivity of troponin in revealing myocardial damage, especially when of ischemic origin, is highlighted.

Electrocardiography. [...] 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 V).

[...] The ECG criteria in table V reflect myocardial ischemia and are not sufficient by themselves to define MI.

[...] A single ECG that meets the Q wave criteria in table VI is indicative of a previous MI.

[...] 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.

In the absence of myocardial ischemia-related ECG changes, a diagnosis of MI may be difficult. In such cases the diagnosis is based on the temporal evolution of the serum concentrations of the markers of myocardial damage and troponin measurement is more useful than that of CK-MB. In fact, troponin measurement allows for the identification of a subgroup of patients with severe coronary atherosclerosis associated with unstable coronary plaques. For such patients the long-term prognosis is worse than that of troponin-negative subjects.

Table V. *Electrocardiographic changes indicative of myocardial ischemia that may progress to myocardial infarction.*

1. *Patients with ST-segment elevation:*
- *new or presumed new ST-segment elevation at the J point in 2 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 2 or more contiguous leads. Also, new or presumed new symmetric inversion of T waves ≥ 1 mm should be present in at least 2 contiguous leads.

Table VI. *Electrocardiographic changes in established myocardial infarction.*

Any QR wave in leads V1 through V3 ≥ 30 ms (0.03 s); abnormal Q wave in lead I, II, aVL, aVF or V_4 through V_6 in any 2 contiguous leads and at least 1 mm in depth.

A recent study evaluated 414 patients who were admitted for observation in the Chest Pain Unit and who had presented with chest pain and an ECG which was negative for acute ischemic changes[35]. The patients were followed for 1 year; an increase in troponin (T in this study) levels was observed in 8.9% of cases. Coronary atherosclerosis was present in 90% of patients who had had a troponin elevation but in only 23% of those in whom the troponin titers had not increased[35]. Furthermore, troponin-positive patients more often presented with severe coronary stenosis and with calcified or ulcerated lesions or total occlusions than did troponin-negative subjects. The cumulative frequency of events was significantly higher in troponin-positive patients than in those who were found to be troponin-negative (8 vs 1% for the endpoints death and non-fatal MI)[35]. Having adjusted for the more important basal clinical variables, a troponin elevation was found to be a more robust predictive factor than an increase in CK-MB. When both markers were included in a multivariate statistical model, it was found that CK-MB did not add any useful information to that provided by troponin elevations. These data were confirmed in a similar cohort of patients studied by Newby et al.[36].

Imaging. [...] 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 tomography (SPECT) perfusion imaging are discussed in this document, and not those that are presently being tested in clinical research studies.

[...] Biomarkers are more sensitive, more specific and less costly than imaging techniques for the diagnosis of myocardial necrosis.

[...] Neither technique (echocardiography and scintigraphy), can distinguish ischemia from infarction.

Acute ischemia and acute or evolving myocardial infarction. [...] 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 about 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.

Established myocardial infarction. 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. [...] 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. [...] The extent of myocardial viability can be estimated by quantitative perfusion imaging with either thallium-201 or technetium-99m perfusion tracers.

Myocardial infarction in specific clinical settings

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.

[...] 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.

Peri and postprocedural MI is an unresolved issue and the introduction of troponins has further focalized interest in this controversy. Overall, following percutaneous revascularization procedures CK-MB titers increase in 5-30% of patients whereas an increase in the serum levels of troponin is observed in 30-40% of cases. It is widely agreed that an increase in the serum levels of both markers is indicative of myocardial necrosis. On the other hand, the prognostic significance of such movements is subject of debate[37].

With regard to the prognostic significance of a rise in CK-MB, retrospective studies have suggested a correlation between even small increases (< 3 times the upper reference limit) and the long-term mortality following a percutaneous revascularization procedure[38-41]. It seems that the entity of risk associated with a postprocedural increase in CK-MB titers is similar to that observed in case of such increases following spontaneous ischemia[42]. In a recent prospective study the occurrence of myocardial lesions among 7147 patients submitted to percutaneous revascularization was evaluated by means of blood sampling prior to and 8, 12 and 16-24 hours following the procedure[43]. The frequency of MI, as revealed by biochemical methods, was found to be correlated with the type of procedure (higher in case of atherectomy and stent implantation). However, at ECG the development of new Q waves occurred very rarely with a frequency ranging from 0.4% following stenting to 0.8% following atherectomy. At multivariate analysis, the most important predictors of both the short- and long-term mortality were the presence of new Q waves on the ECG and of CK-MB increases above 8 times the upper reference limit (in the absence of Q waves on the ECG). On the other hand, lesser increases in the CK-MB titers (5-8 times, 3-5 times, < 3 times the upper reference limit) were not found to have predictive significance[43].

Data regarding troponins are still scarce. Bertinchant et al.[44] have shown that troponin I (cTnI) and troponin T (cTnT) increases following a percutaneous revascularization procedure are not associated with a worse long-term prognosis (mean follow-up 19 months). Fuchs et al.[45] reported on a larger series of patients (1129 prospectively enrolled consecutive patients; cTnI levels were determined at 8-hour intervals for the first 24 hours following the procedure). An adverse in-hospital prognosis was observed only for the 175 patients (15.5%) in whom a cTnI peak > 15 times the upper reference limit of the method employed in the study occurred (mortality 1.6 vs 0.6% for patients with a cTnI elevation 5-15 times higher than the reference limit and vs 0.1% for cTnI elevation < 5 times); however, this increased risk was lost at the medium-term follow-up (8 months)[45].

On the other hand, an increase in troponin titers following a procedure performed in patients with ongoing myocardial damage is clearly associated with a worse prognosis. In a recent study, it was observed that patients who presented with increased preprocedural troponin titers and with a further increase postoperatively (defined as a troponin concentration higher than the preprocedural titer) had a significantly worse in-hospital and 6-month mortality compared to patients in whom such a postprocedural increase did not occur (9.8 vs 0% and 24 vs 3.7% respectively)[46].

In conclusion, prospective studies seem to reveal the existence of a cut-off value (especially for troponin) above which there is a direct correlation between the detection of myocardial damage and the medium- and long-term prognoses. In contrast to acute spontaneous myocardial ischemia, this threshold seems to be many times the upper reference limit for the cardiac marker being analyzed. This might seem paradigmatic, but the paradigm is only apparent. In fact, a diagnosis of MI implies the recognition of myocardial damage related to coronary atherothrombotic disease. However, the severity of the two conditions (spontaneous and iatrogenic) is not directly correlative since it is also influenced by other variables including, above all, the ventricular function[47]. During catheter-mediated revascularization resulting in correction of the atherothrombotic disease, distal microembolization of the plaque may occur or the second order coronary branches be sacrificed. Hence, the only residual prognostic determinant is the ventricular function which may be adversely influenced by the procedure-related iatrogenic damage. Obviously, if the procedure is successful, the degree of iatrogenic necrosis is by definition "small"; likewise, in case of a globally preserved ventricular function, the long-term prognosis should not be significantly affected. On the other hand, in case of preexistent ventricular dysfunction, a new lesion may have a significant impact on the future prognosis. This, even in the light of a possibly incomplete revascularization (not such a rare occurrence following percutaneous procedures). The above lends support to the finding, in all prospective studies, of a threshold lesion above which there is a correlation with the prognosis. This is in contrast with that reported in retrospective studies, consisting of subanalyses of large clinical trials, which seemed to strengthen the hypothesis of the existence of a progressive gradient similar to that observed for acute coronary syndromes.

Whilst awaiting definitive studies on this topic, postrevascularization iatrogenic damage may be considered as a non-MI lesion (even though this might seem a contradiction in terms). In fact, in contrast with spontaneous ischemia, the demonstration of a direct and continuous relationship between the entity of protein marker increase and the prognosis is uncertain. The problem remains mainly for troponins for which definitive data regarding the cut-off levels to be adopted (which depend on the lack of standardization and on the analytical sensitivity of the commercially available assays) are still lacking.

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.

Again, there seems to be a correlation between the extent of myocardial damage as revealed by the increases in the markers of myocardial damage (CK-MB and troponin) and the patient's prognosis, at least in the short term. In the absence of definitive data, it may be held that the entity of the increase in the serum levels of the markers following any cardiac surgery procedure is a quality index of the surgeon's performance.

Implications of different definitions of myocardial infarction

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.

[...] 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.

Epidemiology. [...] 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 (aspartate amino transferase, 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 epi-

demiologic 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. [...]

For epidemiological purposes, the new definition of MI imposes a substantial change in the classification of a suspected acute coronary attack. In spite of the fact that they were initially involved in the elaboration of the ESC/ACC document, epidemiologists have underscored some limitations of the new definition: the biochemical criterion has become an essential parameter for the diagnosis and it is necessary to document a rise followed by a more or less rapid decline in the levels of the chosen marker. This may give rise to problems when classifying those cases in which the patient arrives to the hospital and dies prior to the rise in the serum levels of the biomarker and those in which the patient comes to observation after peak concentrations have been reached. Actually, the document containing the new definition seems quite confusing if not contradictory. In fact, 1) in table III it is stated that "a single measurement above the cut-off level" is sufficient for the diagnosis of necrosis, 2) on page 547 it is recommended that "for a diagnosis of MI, it is necessary that elevated levels of the biochemical markers be found in two consecutive blood samples, whilst 3) the summary of the definition includes a "typical rise and a gradual decrease (troponin) or a more rapid rise and decrease (CK-MB) in the serum levels of the biochemical markers" as a criterion for the definition of acute MI. Clearly, the entire curve of marker release is absolutely redundant for the diagnosis and would even hinder the correct classification of many cases, both early as well as delayed. The response to these criticisms[48] clarifies that it was not the author's intention to request the entire definition of the curve for a diagnosis of MI. However, further clarification of this point remains desirable.

It may be suggested that:
1) in case of a cardio-specific marker (troponin), the finding of a rise above the cut-off level satisfies the biochemical criterion of MI: a) when the temporal variations in the serum levels are consistent with the onset of symptoms (Fig. 2)[29]; b) in all other cases, i.e. when only one measurement is available or when the serum levels remain relatively stable over time, it is necessary to obtain objective evidence that myocardial ischemia is the probable cause of the myocardial lesion. This implies the documentation of specific myocardial necrosis-related findings (see above) at ECG or at imaging techniques or the documentation of coronary disease at stress testing or coronary angiography or, in case of a fatal outcome, of an autopsy confirming the presence of myocardial necrosis;
2) in case one is using CK-MB, the temporal variations in the serum levels of this marker must still be coherent with the onset of symptoms (increasing during the first 24 hours, declining during the following hours, etc.).

Furthermore, the new definition does not take into account the possibility of a diagnostic doubt and, unlike the WHO and MONICA definitions, does not include "possible" MI. Undoubtedly, the new definition gives more importance to the clinical than to the epidemiological aspects. On the other hand, some data suggest that, in contrast to the MONICA definition of MI, one that is mainly oriented on the biochemical criterion allows for prognostic stratification of the patients and is hence useful, together with the interpretation of the ECG taken at the time of admission, when deciding on the therapeutic strategies to adopt[49].

Implications of myocardial infarction 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.

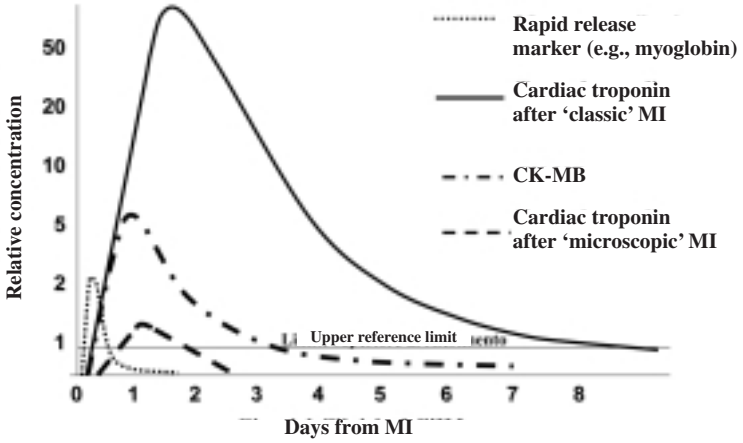

Figure 2. *Kinetics of the release of the main cardiac markers following irreversible myocardial damage during acute myocardial ischemia. CK = creatine kinase; MI = myocardial infarction. From Wu et al.[29], modified.*

This paradigm 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.

[...] 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). [...]

Undoubtedly, a diagnosis of MI should be followed by a quantification of the severity of coronary artery disease, the perception of which varies, for example, according to the type of culture of the society to which the patient belongs or to his level of education. These, and other factors, should be borne in mind when informing the patient and/or his family about the disease. The increased sensitivity of the diagnostic criteria inevitably leads to an increase in the number of false positives but also permits to exclude with more certainty the possibility of events in patients in whom an MI is not diagnosed. One way of describing the type of lesion occurring in troponin-positive patients who do not present with the typical CK-MB rise, i.e. those patients who were previously labeled as having unstable angina, is to tell them that they have had such a small MI that until recently it would have gone undiagnosed. In fact, most of the MI which were traditionally classified as non-Q are not associated with global or regional variations in ventricular function and, as such, are diagnosed only on the basis of the rise in the serum levels of the biochemical markers.

Social and public policy implications of redefining myocardial infarction

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 aggregate of patients with a particular diagnosis is the basis for health care planning and policy and resource allocation.

[...] 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 United States but to stroke in Japan. These arbitrary and cultural criteria need re-examination.

[...] 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: DRG, hospital reimbursement, mortality statistics, sick leave and disability applications and clinical guideline preparation will all be affected. [...]

Undoubtedly, a new definition of MI leads to changes which may even be radical and the consequences of which must be foreseen and evaluated in detail before their use leads to counterproductive long-term effects. With regard to the applicability to the Italian Health reality, three aspects deserve special consideration: 1) the declaration of disability (with all the related implications in terms of disease certification and of pension), 2) the costs related to the reimbursement of the DRG fees, and 3) the definition and prognosis of MI.

With regard to the first aspect, the consequences of the definition of MI seem to be rather limited since the tables presently used (Ministry of Health, 1992) (Table VII) for the declaration of disability and, if pertinent, for pension purposes are based on a functional evaluation of the severity of coronary disease (according to the NYHA functional class and to the presence or absence of inducible ischemia, complex ventricular arrhythmias and left ventricular failure). This type of

Table VII. Ministry of Health: table of invalidity percentages for disabilities and disabling diseases (February 2, 1992, ordinary supplement to the Government Gazette. General series - 47).

Code		Min	Max	Fixed
6445	Mild coronary disease (NYHA class I)	11	20	0
6446	Moderate coronary disease (NYHA class III)	41	50	0
6447	Severe coronary disease (NYHA class III)	71	80	0
6448	Very severe coronary disease (NYHA class IV)	0	0	100

evaluation largely ignores the specific diagnosis (MI, unstable angina, stable angina) since it is aimed at the determination of the long-term consequences of coronary disease in terms of a reduced functional capacity. For example, just as a patient with unstable angina, a subject presenting with an acute coronary syndrome and an isolated rise in the troponin serum titers is assigned to code 6445 (mild coronary artery disease) if the minimal myocardial damage diagnosed is not consequent to severe coronary artery disease or to areas of hibernating myocardium which are so extensive as to significantly decrease the ventricular function at rest. However, since in a forensic context, this type of evaluation is somewhat subjective, it is possible that when determining whether his disease is work-related or otherwise (INAIL), the patient be still assigned a certain degree of disability for the sole reason that he has been diagnosed as having an MI. If, as occurs in the vast majority of cases, the disease is not recognized as being work-related and therefore the patient's disability is evaluated in terms of social insurance (INPS), it should be borne in mind that for this disability to result in an immediate reimbursement, it must exceed 67% – i.e. it should correspond to severe or very severe coronary artery disease. The latter cases are not subject to the consequences deriving from the application of the new definition. Similar considerations hold for sick leave. On the other hand, the consequences deriving from the application of the new definition in case of a private insurance mainly depend on the policy of the individual insurance.

In general, with regard to the recognition of social disability, it does not seem that the application of the new definition of MI to the Italian Health reality necessitates any changes in the evaluation criteria for disability. The consequences in economic terms seem limited.

On the other hand, the implications in terms of the DRG reimbursements seem to be more relevant. Undoubtedly, the increase in the number of diagnosed MI leads to an increase in the reimbursements for hospitalization. In fact, the fees for the MI DRGs exceed those for the unstable angina ones (Table VIII). According to the new definition, one third of cases of unstable angina would be classified as MI. For example, in a county such as Emilia Romagna where 12 000 patients are hospitalized yearly for acute coronary syndromes, the consequences on the economy would be relevant. On the basis of the data published in a recent observational study (AI-CARE 2 study), it is calculated that according to the new definition approximately 1100 patients per year would be labeled as having an MI. This would lead to a mean difference of €1807.60/hospitalization in the DRG fee (in a situation in which during hospitalization approximately 50% of patients with unstable angina are submitted to coronary arteriography and 20% to surgical or percutaneous revascularization). However, it should be borne in mind that at present the reimbursement for the unstable angina DRG is largely unsatisfactory. In fact, the costs of hospitalization approximate €2944 in case of an uncomplicated course and €3925 in case of complications (AI-CARE 2 data) whereas the relative DRG reimbursements are €1653 and €3187 respectively. Hence, it may be concluded that the new definition of MI will probably render the economic handling of cardiac hospitalizations more simple.

The increase in the number of diagnosed MI consequent to the introduction of the new definition criteria will lead to a decreased mortality and consequently to a significantly modified perception of the efficacy of health interventions. This may in turn bear an influence on health policy. In some Italian counties, the Health Agencies use the in-hospital mortality as an index of the efficacy of the health interventions for acute MI. The present heterogeneity of the diagnostic criteria employed in daily clinical practice renders the monitoring of this parameter useless for a correct evaluation of the activity of the coronary care units, however the dissemination of strictly defined diagnostic criteria will make it possible to realistically evaluate the efficacy of the health interventions in case of an acute MI.

Table VIII. Hospital assistance fees for admissions in the case of acute events. 10th ACFA-DRG version. Emilia Romagna Region: year 2000.

DRG	Reimbursement (€)	Weight
140M - Angina pectoris	1654.21	0.6219
124M - Cardiovascular diseases except for MI, including cardiac catheterization and a complicated diagnosis	3186.54	1.2029
125M - Cardiovascular diseases except for MI, including cardiac catheterization but no complicated diagnosis	2017.80	0.7587
121M - Cardiovascular diseases including MI and cardiovascular complications, alive	5176.45	1.6114
122M - Cardiovascular diseases including MI but no cardiovascular complications, alive	4122.88	1.1532
123M - Cardiovascular diseases including MI, dead	4088.27	1.4090

MI = myocardial infarction.

The following is a summary of the definition of MI[1-3], modified according to the positions assumed in the present manuscript.

Definition of myocardial infarction.

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

1) elevation* of the biochemical markers of myocardial necrosis (preferably troponin) with variations in the serum levels which are coherent with the time of onset of symptoms associated with 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); d) coronary artery intervention (e.g., coronary angioplasty)**. *Marker elevations should be accompanied by objective instrumental evidence that myocardial ischemia is the likely cause of myocardial damage when: a) only one blood sample is available; b) marker changes over time are not consistent with the onset of symptoms;*

2) pathologic findings of an acute MI.

• *Criteria for established MI.* Anyone 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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* if troponin is used, the marker concentration should be higher than the value associated with a 10% coefficient of variation, possibly detected in ≥ 1 of at least two occasions. Changes in concentrations should be consistent with the time elapsed from the onset of symptoms; ** since there is no definite evidence that the degree of troponin elevation is correlated with the long-term mortality in this setting of "iatrogenic" myocardial damage, we suggest that the physician continues to rely on conventional criteria.

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