The redefinition of acute myocardial infarction

Giuseppe Di Pasquale, Alessandro Lombardi*, Gianni Casella

*Division of Cardiology, Maggiore Hospital, Bologna, *Division of Cardiology, Bentivoglio Hospital, Bentivoglio (BO), Azienda USL of Bologna, Bologna, Italy*

Key words:
Diagnosis; Health care policy; Myocardial infarction; Troponin.

In the year 2000 a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee proposed new diagnostic criteria for acute myocardial infarction (MI), emphasizing the role of more sensitive and specific serologic biomarkers of myocardial necrosis. Although several criticisms soon followed this redefinition of acute MI, it was expected that these new criteria would substantially impact the clinical management and prognosis of patients with coronary artery disease. Important consequences on the health care system and government policies were supposed as well. However, 4 years later a substantial proportion of patients with acute MI are still diagnosed according to the old World Health Organization criteria, irrespective of the results of biomarker assays. This finding indicates that the redefinition of acute MI is far from being universally adopted. Thus, the reasons that hampered a widespread diffusion of such criteria, mainly a mixture of technical, logistic and cultural points, and the main, still controversial issues are discussed and commented on.

(Ital Heart J 2004; 5 (Suppl 6): 9S-18S)

Address:
Dr. Giuseppe Di Pasquale
U.O. di Cardiologia
Ospedale Maggiore
Largo Nigrisoli, 2
40133 Bologna
E-mail: g.dipa@libero.it

Introduction

In September 2000, the Joint European Society of Cardiology (ESC) and the American College of Cardiology (ACC) Committee for the redefinition of myocardial infarction (MI) published a consensus statement on a new definition of MI[1]. This new definition immediately raised great interest, but also significant concern and criticism[2-4]. Four years later, the recommendations for the redefinition of MI have not been implemented worldwide in a coordinated fashion[5].

Traditionally, the World Health Organization (WHO) defined MI by the combination of two out of three characteristics: typical symptoms of infarction (i.e., chest pain or discomfort), a rise in plasma or serum cardiac enzymes, and a typical ECG pattern involving the development of Q waves[6]. However, there were at least two reasons for revising these old WHO criteria. First, the advent of sensitive and specific biochemical markers of myocardial necrosis such as troponins. Second, the evidence that also very modest amounts of myocardial damage, as detected by cardiac troponins, carry a worse prognosis.

Therefore, the Joint ESC/ACC Committee for MI redefinition stated that, to satisfy the new diagnostic criteria for acute, evolving or recent MI (Table I), a typical rise and gradual fall (troponin) or a more rapid rise and fall (creatine kinase [CK]-MB) of biochemical markers of myocardial necrosis should be accompanied by at least one of the following: a) ischemic symptoms; b) development of pathologic Q waves on the ECG; c) ECG changes indicating ischemia (ST-segment elevation or depression); d) or coronary artery intervention (e.g. coronary angioplasty).

Thus, according to this new MI definition, such a diagnosis primarily relies on the typical rise and fall of biochemical markers of myocardial necrosis in a clinical setting consistent with myocardial ischemia or coronary interventions.

The advantages of myocardial infarction redefinition

The new definition of MI focuses on the clinical and prognostic significance of any amount of myocardial damage and aims to simplify treatment decisions and uniform the process of classification of outcomes[1].

Rigorous definitions of acute, non-fatal MI were already developed for the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project. These definitions were based on the Minnesota criteria. Since these criteria are difficult to assess and time-consuming, the WHO definition has been usually preferred. However, such simplified definition

Table I. Criteria for the new definition of acute, evolving or recent myocardial infarction as recommended by the Joint European Society of Cardiology/American College of Cardiology Committee.

1. Typical rise and gradual fall of cardiac troponin, or more rapid fall of creatine kinase-MB mass, with at least one of the following features:
a) ischemic symptoms
b) development of pathologic Q wave on the ECG
c) ECG changes indicative of ischemia (ST-segment elevation or depression)
d) coronary artery intervention
2. Pathological findings of an acute myocardial infarction

may miss some small MI that could otherwise carry a worse prognosis. On the other hand, the WHO criteria allow to diagnose as *possible MI*, cases with no clear evidence of myocardial damage. Therefore, the adoption of very sensitive markers of myocardial damage, such as troponin and CK-MB mass, satisfies the clinical needs of an early and careful diagnosis for suspected acute coronary syndromes (ACS) and may allow a correct selection of the therapeutic strategies. This is particularly important when patients with atypical symptoms or equivocal ECG, such as conduction or rhythm abnormalities, are assessed.

Elevated levels of serum troponin are tightly related to outcomes across the broad spectrum of ACS, independently of their ECG presentation (ST-elevation MI [STEMI], non-ST-elevation MI [NSTEMI] or equivocal ECG changes)[7-9]. These important findings have been clearly summarized in a large meta-analysis by Ottani et al.[9] that observed a 3.44 (95% confidence interval 2.94-4.03) higher risk of death or MI at 30 days for patients with positive troponin. This short-term higher risk for patients with elevated troponin was observed either in STEMI (odds ratio 2.86, 95% confidence interval 2.35-3.47) or NSTEMI subgroups (odds ratio 4.93, 95% confidence interval 3.77-6.45). In addition, a clear relationship between the amount of troponin elevation and patient's prognosis has been observed[10]. However, to take full advantage from this MI redefinition, it has to be stressed that the typical rise and fall of cardiac biomarkers should be associated with suggestive symptoms or a clinical setting of myocardial ischemia[1]. Whenever this could not happen, such as when we observe an isolated elevation of troponin or a plateau curve, it is mandatory to complete the diagnosis with other imaging tests, like echocardiography, myocardial scintigraphy, or coronary angiography[1]. When these further tests do not confirm the diagnosis of MI, physicians should search for other causes of myocardial damage (Table II) or false positive results. To reduce the number of false positive results, it should be wise to limit the measurement of biomarkers to patients with a pre-test medium-to-high likelihood of ACS, according to their clinical presentation[5]. In fact,

Table II. Main causes of troponin elevation in the absence of ischemic heart disease.

Cardiac trauma	Contusions, ablation, pacing, automatic internal defibrillator discharge, electrical cardioversion, biopsy, cardiac surgery, postoperative non-cardiac surgery
Other cardiac diseases	Congestive heart failure, hypertension, hypotension, pulmonary embolism, infiltrative disease (e.g. amyloidosis, sclerodermia, etc.), drug toxicity (e.g. chemotherapy)
Systemic diseases	Renal failure, hypothyroidism, critical illness (e.g. decompensated diabetes mellitus), inflammatory diseases (myocarditis, sarcoidosis, etc.), sepsis, burns (especially when > 30% total body surface area is involved)
Other conditions	Acute neurological disease including stroke, rhabdomyolysis with cardiac injury, transplant vasculopathy

indiscriminate troponin measurement in all patients who are evaluated in an emergency setting, regardless of their initial presentation, should be avoided, because it would be affected by a high number of false positive results[1].

Diagnosis of myocardial infarction after myocardial revascularization

The Joint ESC/ACC Committee did not recommend how to define MI in patients undergoing percutaneous coronary interventions (PCI) or bypass surgery, although this population is going to increase in the near future and carry a high risk of myocardial damage as well. In fact, an elevation of cardiac biomarkers occurs in 10-40% of patients (10-25% for CK-MB mass and 20-40% for troponin T or I, respectively) after PCI, even in the absence of clinical events[10,11]. It has been proven that also in these situations any increase of cardiac biomarkers is indicative of cell death and is associated with an adverse outcome[11,12]. If this is not questionable for large infarcts that seldom complicate procedures, it is less obvious for the more frequent small cardiac enzyme elevations, not accompanied by symptoms, that are detected after interventions. Such small infarcts are probably the result of microembolization from the atherosclerotic plaque or from the thrombus at the site of the culprit lesion, that have been disrupted during PCI[11]. This relation between even small increases of serum cardiac markers and adverse prognosis is well documented, but its mechanisms are further to be proven. Besides, it is difficult to explain why small infarcts have such a negative effect on prognosis. We may suspect that small myocardial scars resulting from mi-

croembolization may act as a focus for arrhythmogenesis and sudden death. The impaired prognosis could also be due to an underlying unifying factor, like inflammation. Alternatively, it is possible that troponin elevation is not the cause of a poor prognosis, but rather the consequence of diffuse coronary artery disease with an increased plaque burden[11]. Recently, a pooled analysis of several large ACS trials (EPIC, EPILOG, CAPTURE, IMPACT II and PURSUIT) compared the prognostic values of post-procedural MI with those of spontaneous MI as diagnosed by CK-MB elevation[13]. The study observed a linear relationship between increasing elevations of biomarkers and mortality in both groups (Fig. 1) and supports the hypothesis that the death of any heart cell is a negative event regardless of its etiology.

Therefore, the Joint ESC/ACC Committee recommended that, since these post-PCI biomarker elevations identify a discrete amount of myocardial necrosis, they should be labelled as MI by using the same cut-off values of spontaneous elevations as well. Certainly, it is possible that similar degrees of troponin elevation are associated with similar outcomes irrespective of the etiology of myocardial necrosis. However, another possibility is that these populations will have different prognosis even though they have the same magnitude of troponin elevation[14]. For example, a patient with an occluded side branch after PCI, like a small diagonal or marginal artery, may have an excellent prognosis based on factors other than those associated with such a small infarct, whereas a patient presenting with a NSTEMI with a thrombus-rich, fissured and unstable plaque in the left anterior descending coronary artery is likely to have an unstable clinical course and a poor prognosis even though the rise in troponin levels may not be greater (Fig. 2)[15]. Perhaps, patients with elevated biomarkers after an uncomplicated PCI may require careful follow-up and management. On the other hand, troponin elevations occur more frequently after stenting and are higher than that observed after conventional PCI. However, stenting produces better outcomes than conventional PCI and such a risk gradient between different troponin elevations may not be so pronounced. Therefore, the outcome of patients with post-procedural enzyme increases is almost always improved by the procedure itself[13].

Likewise, the new MI criteria do not address specifically the significance of cardiac enzyme increases after coronary artery bypass graft surgery[1]. Myocardial damage after cardiac surgery can be caused by different mechanisms, including direct trauma, focal damage from surgical manipulation, global ischemia from inadequate perfusion, myocardial protection or coronary artery embolism. A great proportion of this damage may be unavoidable and no biomarker is so powerful to distinguish between cell necrosis caused by a postoperation MI to the expected damage associated with the procedure itself. Nevertheless, the higher the elevation of cardiac markers after surgery, the greater the amount of cell death, irrespective of the mechanism of injury. In the Arterial Revascularization Therapies Study (ARTS)[16], which compared multivessel stenting with coronary artery bypass graft surgery, elevated CK-MB levels were detected in 30.5% of patients treated with PCI and 62% of those treated with coronary artery bypass graft surgery. The 12-month mortality rate in the latter group increased significantly when CK-MB levels rose above 5 times normal (7 vs 0% in the 38% of patients without elevated CK-MB levels), and there was

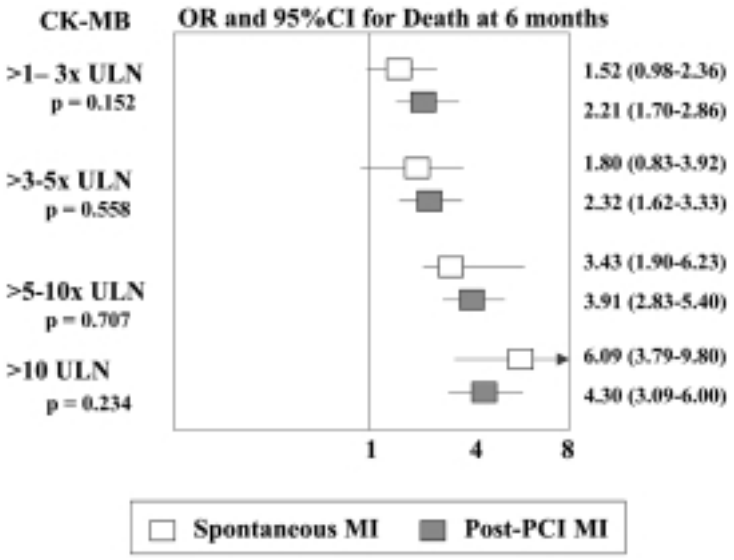

Figure 1. *Odds ratio (OR) for 6-month cumulative death at different ranges of creatine kinase (CK)-MB elevation after spontaneous myocardial infarction (MI) or percutaneous coronary intervention (PCI) based on data from EPIC, EPILOG, CAPTURE, IMPACT II and PURSUIT trials. CI = confidence interval; ULN = upper limit of normal.*

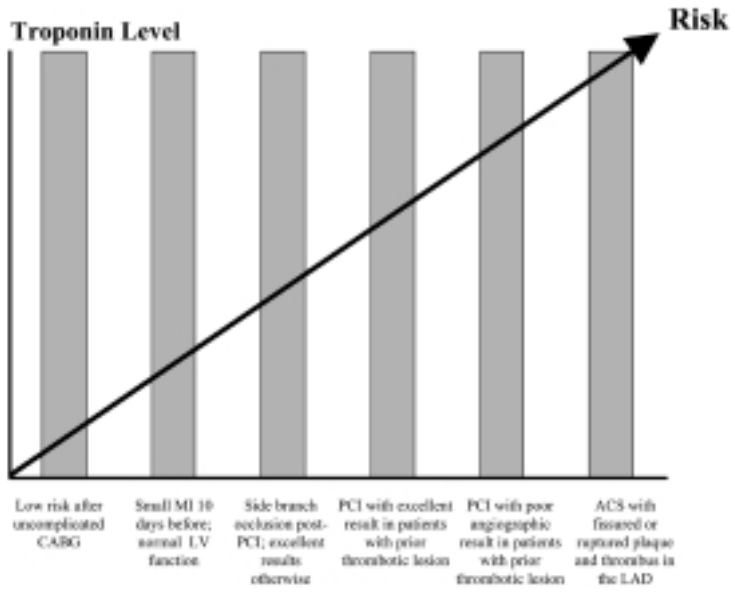

Figure 2. *Comparison of true myocardial infarction diagnosis revealed by conventional World Health Organization criteria, the new European Society of Cardiology/American College of Cardiology redefinition: creatine kinase-MB activities and troponin at different cut-off values (< 10% coefficient of variation, < 10% coefficient of variation at the 99th percentile and < 20% coefficient of variation at the 99th percentile as well). Data derived from 80 consecutive patients with suspected acute ischemic chest pain[15]. ACS = acute coronary syndrome; CABG = coronary artery bypass graft; LAD = left anterior descending coronary artery; LV = left ventricular; PCI = percutaneous coronary intervention.*

a trend toward a higher mortality rate in those with CK-MB levels above 3 times normal (5.4%). Other available data suggest very conservative criteria for a laboratory diagnosis of MI after surgery. In fact, the GUARDIAN study[17] demonstrated that CK-MB elevation becomes relevant when values more than 20 times upper limit of normal are observed. Above this cut-off value the 7-month survival was reduced to 79.8% as compared to 96.6-92.2% of the 5-20 upper limit of normal range.

Unfortunately, scarce data exist on the relationship between troponin elevation after coronary artery bypass graft surgery and clinical outcomes and no relevant threshold value has been established in this setting so far[1,14].

Concerning post-procedural MI diagnosis, a consensus document of the Italian Federation of Cardiology (FIC)[5] recommends that myocardial damage following revascularization procedures should not be labelled as MI and that post-procedural MI diagnosis should still be based on conventional WHO criteria. Since published studies are controversial[11,12,16-19], the FIC advocates for careful follow-up of patients with post-procedural enzyme elevations and stresses the need of careful research studies. In particular, the FIC has promoted a multicenter, prospective registry supported by the Italian Society of Invasive Cardiology (GISE) and the Study Group on Atherosclerosis, Thrombosis and Vascular Biology. This study should test multiple serum markers in more than 4000 unselected patients post-PCI and follow them for 2 years. The results will be available in the near future.

Major problems with the new myocardial infarction definition

The biomarker diagnostic cut-off controversy. The Joint ESC/ACC Committee stated that an elevation of cardiac troponin T or I above the 99th percentile (i.e. > 3 SD) of a reference control group on at least one occasion during the first 24 hours of the index clinical event is the new criterion for diagnosis of MI[1]. Such an elevation has to be determined by a test with < 10% coefficient of variation[1]. In the absence of troponin testing, CK-MB mass elevation above the 99th percentile on two following samples or a value twice this limit is recommended; this marker however identifies only 75% of troponin-positive cases[15,20,21].

This consensus statement was soon subjected to several criticisms because at the time of this redefinition, none of the available troponin assays had been shown to fulfill the Committee's recommendations[2-4]. Furthermore, no indication on what constitutes a reference control group was given. These criticisms were not trivial since tests used for diagnosis and management must be reliable and accurate especially when serious medical illness, like ACS, are addressed.

At that time, only few methods met the ESC/ACC requirements (≤ 10% coefficient of variation at a troponin concentration equal to the 99th percentile) and not all analytical systems available were equally accurate and guarantee high standards[20]. Thus, there remain some concern about the robustness of troponin results, not only between troponin I and troponin T, but also among the different assays for troponin I which use dif-

ferent antibodies. Interestingly, when performances of available troponin tests were compared important differences in normal values appeared[21]. Ferguson et al.[15] prospectively tested the clinical implication of new MI criteria in patients with suspected acute chest pain by means of two different troponin I kits with different sensitivity. They documented a relevant variability in MI diagnosis with the different methods (Fig. 3).

Furthermore, the issue of what constitutes a "reference control group" is not trivial. Consensus exists on considering as a reference control group at a given institution a sample of subjects free from clinically evident cardiovascular diseases and matched for age with a similar population with ACS referred to the same institution[1]. Thus, formal local reference range studies are important to determine whether single laboratories fulfill the recommended criteria for precision at the detection limit[21]. Unfortunately, very few institutions have provided a reference control group so far.

Therefore, several experts suggest to use a cut-off value of ≤ 0% imprecision (which is above the 99th percentile of the reference range for all assays) until assays improve[21]. This would increase the possibility of both false-positive and false-negative results. Recently, the number of troponin assays that fulfill the ESC/ACC recommendations is increasing both for troponin T and troponin I.

Implementation of the new myocardial infarction definition: still a long way to go

Another criticism to the new MI definition has been the knowledge that the Joint ESC/ACC Committee did not give any recommendation for an implementation strategy. Surprisingly, many hospitals worldwide still do not perform troponin testing. Although troponin testing is available in more than 90% of hospitals across the United States[22], very little use of troponin was reported in UK and Belgium (about 50% of centers) with lesser figures in Spain and eastern Europe[23]. Therefore, such heterogeneous introduction of the new definition has already led to paradoxical situations like hospitals in the same community that use different criteria for the diagnosis of MI and obviously patients with the same disease who receive different diagnoses.

A recent picture of the Italian situation comes from the ANMCO/SIBioC/SIMeL study[24] which involved almost all Italian cardiology departments in a survey that documented a wide variation in the application of cardiac biomarker testing across the country. In fact, CK-MB mass was used in 38% of centers whereas percentages for troponin T and I were 14 and 70%, respectively. In most institutions, the new, specific biomarkers were tested along with the older ones and did not substitute the traditional enzyme determination. Moreover, MI diagnosis was established through CK-MB mass or troponin elevation in 14 and 12% of centers, respectively. Interestingly, the Euro Heart Survey of ACS[25] pointed out that CK-MB (either mass or percent activity) is currently used in 93% of centers across Europe and troponin (I or T) in 63.3%. The same survey demonstrated that 23.4% of patients who had a final diagnosis of unstable angina presented with cardiac biomarker elevation, whereas 21.8% of patients classified as non-Q wave MI and 19.7% of Q-wave MI were troponin-negative indeed. These findings clearly document how difficult would be the diffusion of the new definition in current practice.

It is not surprising that physicians used to deal with older, clinical criteria for MI diagnosis find somewhat difficult to give biochemical tests equal or even greater significance. However, the new criteria offer the opportunity to uniform diagnosis and improve patient care.

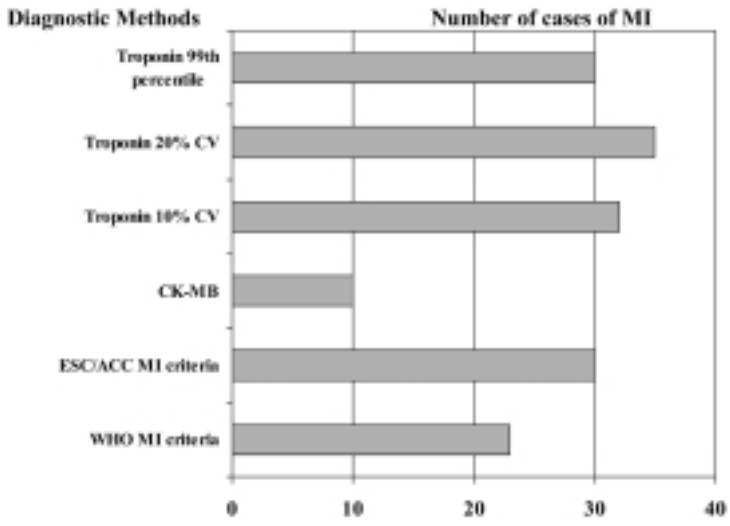

Figure 3. *Increasing risk in different clinical contexts with the same troponin elevations. ACC = American College of Cardiology; CK = creatine kinase; CV = coefficient of variation; ESC = European Society of Cardiology; MI = myocardial infarction; WHO = World Health Organization.*

Perhaps, we would have expected that the Joint ESC/ACC Committee forced a smooth transition between the old and the new definition, driven and coordinated by national cardiac societies as well as the World Heart Federation and the WHO. In fact, major educational efforts are still required to train patients and doctors on the new definition, and national heart foundations should have a leading role in such initiatives. Many patients will now be told that they have had a heart attack which would not have been diagnosed as such before. However, it should be told to most of them that the future after this heart attack would remain excellent.

Expected changes related to the new myocardial infarction definition

Implementation of the new MI criteria is expected to have a substantial impact on patients with coronary artery disease, their care, physicians, and the use of health care resources. In addition, this MI redefinition would prompt a permanent modification of our common epidemiological knowledge and change the social perception of coronary artery disease for governments, politicians, economists, and health care providers (Table III). Given such tremendous social impact, the Joint ESC/ACC Committee has been strongly criticized for changing the definition of MI since its release. Experts have largely focused their criticisms on the epidemiological and health care impact, on the lack of attention given to the diagnosis of MI in situations where troponin levels cannot be determined, on the difficulties to carry out such redefinition in countries with limited resources and on the lack of recommendations for any implementation strategy.

Epidemiology

Monitoring of cardiovascular disease in the general population is important, because it enables to observe secular trends of the disease, to analyze possible causal factors and to assess the effect of different preventive measures, medications or interventions[21]. The incidence of a new MI and the prevalence of established ones represent important epidemiological variables. Current knowledge is based on classic definition of MI and the substitution of these old ones with the new, more sensitive diagnostic criteria for MI will cause the recorded incidence of MI to rise and the case-fatality rate to fall[21]. In the WHO-MONICA system, patients could be classified as having *definite or possible MI, prolonged angina pectoris or ischemic cardiac arrest*, while the Joint ESC/ACC Committee classifies patients as having *acute, evolving or recent MI*. Therefore, both definitions differ substantially and this would raise difficulties in comparing patient population, longitudinal trends in disease rates and outcomes as well.

Several studies[15,26-28] already reported that according to the new criteria an estimated 30% of patients previously defined as *possible MI* should not receive this diagnosis anymore. On the other hand, 15% of subjects formerly classified as *prolonged angina pectoris* would fulfill the new criteria of MI. Interestingly, the short- and long-term mortality among patients classified as having had MI by troponin or CK-MB elevation is increased, when compared to that of patients classified according to former WHO criteria *definite or possible MI* (Table IV)[21,26]. In the Global Registry of Acute Coronary Events (GRACE) study[29] the use of troponin elevation as MI criterion would lead to 25% more MI cases diagnosed with an expected 1.5 times increase of

Table III. Expected implications of the new acute myocardial infarction (MI) definition.

Epidemiology	Increased incidence and prevalence of MI Substantial reduction of the case fatality rate of MI (e.g. difficulties in comparing patient populations, longitudinal trends in disease rate and outcomes) Impaired diagnostic capabilities in patients who died early (e.g. before troponin levels have time to rise) Official public statistics and life insurance statistics
Health care system and economical issues	Coding of diagnosis-related groups (DRG) Hospital reimbursement (influenced by the local reimbursement method: diagnosis-related grouping, fee-for-service, discounted fee-for-service, managed care) National health care system resource allocation Declaration of disease Employers' sick-leave and disability entitlements
Individual and society perspective	Individual psychological issues Employers' perceptions about employability Driving and flying licences Employers' sick-leave, disability and retirement entitlements Life, health and travel insurances Rehabilitation
Clinical research	Entry criteria Endpoints redefinition in randomized clinical trials Regulatory issues

Table IV. Expected impact of the redefinition of myocardial infarction (MI) on rates and outcomes compared with the earlier WHO-MONICA definition.

	Definite MI	Possible MI	No MI
WHO-MONICA criteria	90	109	47
RR 1-year mortality	1.5	0.7	–
CK-MB criteria	150	–	95
RR 1-year mortality	2.7	–	–
Troponin criteria	189	–	56
RR 1-year mortality	5.7	–	–

Data, derived from a cohort of 245 patients with suspected MI[26], are presented as number of patients and relative risk (RR). CK = creatine kinase.

short-term mortality compared to that of patients classified according to the old definition[30]. Moreover, it can be estimated that 10-38% of patients previously classified as unstable angina would now receive MI diagnosis. Clearly, the new definition of MI is more clinically oriented and follows the concept that when an MI is diagnosed, the patient's prognosis is definitely worse than that of patients in whom MI was excluded. Consequently, classifying all troponin-positive patients as presenting with MI should highlight their high risk and improve their clinical outcome by appropriate application of evidence-based strategies for acute management and secondary prevention[21].

Although this redefinition will constitute a major advance for the clinical management, epidemiologists should continue to audit the prevalence of MI and patient outcome using the older definitions for a transition period in order to obtain comparative data. Afterwards, new epidemiological studies using the new definition of MI are needed to provide comparative data for research in future years.

Another major criticism is the lack of attention to the diagnosis of MI in situations where troponin levels cannot be determined[2-4]. In fact, the new classification, unlike the old one, does not consider the possibility of a diagnostic doubt *(possible MI)*. Unfortunately, the release of troponins and CK-MB in response to prolonged ischemia occurs slowly, at least 3 to 4 hours after the onset of ischemia. Therefore, the new definition of MI cannot take into account patients who present very early, before their troponin levels have time to rise, or who die before signs of myocardial necrosis have developed sufficiently to be detected at autopsy. Thus, there is still a place for definitions of MI not based entirely on troponins.

Health care system and economical issues

Recent surveys of European and Italian populations have confirmed that NSTEMI is a more frequent diagnosis than STEMI[24,25]. Furthermore, such surveys suggest that up to 20% of patients presenting with NSTEMI might be affected by the redefinition of MI. Such reclassification would clearly determine a higher prevalence of MI that should obviously affect the single national health care systems.

In addition, the new definition of MI would alter significantly the current clinical care of ACS patients. However, since several European countries as well as Italy substantially increased the proportion of ACS patients managed aggressively during the last few years, the MI redefinition should not add tremendous modifications of the current clinical practice in such patients. Perhaps, this redefinition would cause a mild further increase of interventions or antithrombotic treatment in our country.

The effect of MI redefinition on budget allocation depends mainly on how it is managed in different countries[21]. For example, given the complexity of reimbursement methods for medical care in the United States (fee-for-service, discounted fee-for-service, Medicare or other forms of managed care), the magnitude of the economical effects of the redefinition of MI in that country will depend not only on the number of patients shifted from one diagnosis to another, but also on patient and payer mix, and local practice patterns. On the contrary, in those countries, like Italy or France, where budget allocation depends mainly on diagnosis-related groups (DRG), there would be substantial consequences. The increase in the number of diagnosed MI would lead to an increase in the reimbursements for hospitalization, since the fees for the MI DRGs exceed those for unstable angina. According to the new definition, about one third of cases formerly diagnosed as unstable angina would now be classified as MI. This change in diagnosis would produce a 90% increase in budget allocation if the patient is managed medically. However, if the same patient is treated aggressively with coronary angiography and PCI, the overall increase would be only 35% because the budget allocation for these invasive procedures is not affected by a change in diagnosis. Therefore, due to the increasing rate of ACS patients managed aggressively in Italy, this MI redefinition should not have substantial negative economic drawbacks. On the contrary, since reimbursement of the DRG unstable angina is largely inadequate, the MI redefinition would allow to fit the current lag between fees and costs in ACS patient management[5].

The increased number of diagnosed MI will lead to a decreased mortality and to a modified perception of the efficacy of health care interventions. This would affect the health policy since several Italian regulatory agencies use in-hospital mortality as an index of the efficacy of interventions for acute MI. At present, the strong heterogeneity of the diagnostic criteria applied in clinical practice casts doubts on the correct evaluation of interhospital coronary care unit performances. The diffuse application of the new MI definition would

finally allow correct national or interhospital comparison of interventions[24,31].

Individual and community perspective

MI has always been considered by patients and community a severe diagnosis, that strongly affects daily life and long-term expectancy. Therefore, the psychological impact of this diagnosis on individuals and their families should not be underestimated. Of course, telling patients that they have had a heart attack should not be the only information given. Not all MI are the same[14], and the implications for social activities, employment, and patients' prognosis will vary widely according to the extent of myocardial necrosis, the evidence of inducible ischemia, the predisposition to ventricular arrhythmias, the severity of coronary artery disease, whether revascularization has been performed, and the degree of impairment of left ventricular function. This information should be conveyed and discussed with patients and their families.

Therefore, when cardiologists deal with MI patients they must complete this definition:

• by defining its extension and functional impairment, so that family doctors and other caregivers could appreciate the actual risk of the patient, certify or deny his ability at work;

• by properly conveying information to patients and their families about life patterns and prognosis of cases with isolated biomarkers elevation.

With regard to the recognition of social disability and a feared increase of work retirements, in Italy those evaluations are mostly dependent on functional issues (NYHA class, presence or absence of inducible ischemia, complex ventricular arrhythmias, and left ventricular dysfunction) so that no significant effect should be expected.

Clinical research

The precision on how MI is defined is a matter that has major implications for cardiovascular event rates and the design of clinical trials in cardiology. The MI redefinition may affect both the selection of populations entered into studies and the determination of the rate and magnitude of the MI endpoint. However, the new definition of MI should uniform both processes and provide common ground not only for intertrial comparisons, but also for the translation of their results to clinical practice.

The MI definition threshold, as entry criteria or endpoint, has been different across the studies until the last decade when it has been modified by choosing different pathologic thresholds for biomarkers (namely CK-MB). In fact, several relevant studies (GUSTO-IIb, PURSUIT, PARAGON and CURE) that influenced our clinical practice on ACS already included adequate cut-off values of biomarkers (namely a CK-MB threshold value > 2 upper limit of normal for spontaneous MI, > 3 upper limit of normal after coronary angioplasty, and > 5-10 upper limit of normal after cardiac surgery, respectively), although such cut-off were not part of the former MI definition.

The recent implementation (or substitution) of troponins instead of CK-MB should positively affect this policy. In fact, the high sensitivity of troponin would allow the identification of a subgroup of patients with a worse prognosis that is indeed the correct target for interventions and the background evidence of this MI redefinition.

In addition, even in clinical research cardiac enzymes should not be considered as dichotomous tests, but measurements should be presented in continuous manner due to their linear relationship with mortality rates and outcomes[21]. Furthermore, trials must take into account a more comprehensive view of the risk of cardiac patients enrolled. According to the Joint ESC/ACC Committee, it is important to evaluate additional data, particularly clinical presentation and ECG findings, before making decisions about the patient care. Before enrolling patients in clinical trials or deciding how or if to treat them, physicians should consider other key clinical features which indicate an intermediate-to-high likelihood of ACS secondary to coronary artery disease.

Finally, clinical trial results should therefore be expressed in a more articulated way (i.e. specifying left ventricular impairment) to improve and facilitate understanding of single patient risk and comparison between different study endpoints by different weighing of small infarcts, larger ones and death. Therefore, applying the same definition of MI to clinical practice and to trials should resolve the difficulties in translating trial results into practice.

Conclusions

In the year 2004, when the resources are available, troponin testing should be considered mandatory for prognostic evaluation of ACS patients, diagnosis of MI, and treatment selection. The use of the new definitions of MI is far from optimum but is going to improve rapidly. Today a heart attack is not the same as before and the new definition will lead to better patient care and outcomes. However, there is much work to be done to ensure that assays are of an appropriate standard and to educate patients, doctors and community to these substantial changes.

Riassunto

Nell'anno 2000 un documento di consenso redatto da un Comitato congiunto della Società Europea di

Cardiologia e dell'American College of Cardiology ha proposto nuovi criteri per la diagnosi di infarto miocardico acuto (IMA). Al centro di questi criteri innovativi risiedeva la forte enfasi attribuita ai nuovi marcatori biochimici di necrosi, più sensibili e specifici dei precedenti, ed un maggior rigore nella definizione di IMA.

Rispetto ai precedenti criteri dell'Organizzazione Mondiale della Sanità (OMS), questa nuova definizione, in gran parte sostenuta dall'avvento delle troponine, aveva la prerogativa di essere strettamente orientata a finalità cliniche e di essere ispirata dal concetto che alla diagnosi di IMA consegue sempre una prognosi peggiore rispetto ai casi nei quali questa diagnosi è esclusa. Tuttavia moltissime critiche sono state immediatamente sollevate; prima di tutto si è obiettato che nel momento in cui questi criteri sono stati proposti gran parte dei metodi diagnostici disponibili per il dosaggio delle troponine non raggiungevano gli standard richiesti dalla nuova definizione stessa; in secondo luogo questi nuovi criteri non affrontavano con chiarezza né il criterio diagnostico né il peso prognostico relativo del danno miocardico dopo rivascolarizzazione. In realtà le critiche non erano strettamente limitate a questi aspetti tecnici, ma erano spinte dal prevedibile impatto epidemiologico, clinico ed organizzativo conseguente a questa ridefinizione dell'IMA. Infatti è evidente che i nuovi criteri dell'IMA determinano un incremento della stessa diagnosi di infarto, della sua prevalenza e, conseguentemente, una riduzione della sua fatalità. Ne consegue la necessità di rivedere completamente le attuali conoscenze epidemiologiche, rendendo difficile il confronto con i trend storici della patologia. Non meno importanti sono le implicazioni socio-economiche destinate ad avere un forte impatto sul sistema e sulle politiche sanitarie. Secondo questi nuovi criteri più del 30% dei pazienti con angina instabile è riclassificato come IMA. Dal momento che un sistema sanitario come quello italiano suddivide la quota di rimborso e finanziamento per gli ospedali in base ai gruppi diagnostici (DRG), l'attribuzione di un DRG più costoso ad un consistente gruppo di pazienti determina un importante incremento del budget per la patologia infartuale. Paradossalmente nella realtà italiana se da una parte questa riclassificazione incrementa i finanziamenti complessivi, dall'altra questa ridistribuzione di risorse può compensare l'attuale sotto-finanziamento del DRG dell'angina instabile. Accanto a queste conseguenze di ordine economico-sanitario la nuova diagnosi di IMA ha un effetto importante anche su altri aspetti sociali "minori", quali la certificazione di malattia, le richieste di invalidità, l'idoneità lavorativa od alla guida e l'aumentato ricorso a programmi riabilitativi, i quali hanno comunque un forte impatto individuale. Ad un maggior numero di pazienti verrà inoltre attribuita una diagnosi di IMA, pur con un significato spesso benigno, che in precedenza non sarebbe mai stata fatta con le ovvie conseguenze psicologiche. Non ultimo la stessa ricerca clinica vede modificati i criteri di selezione, gli obiettivi e la definizione degli eventi degli studi stessi.

In conclusione, 4 anni dopo la proposta di nuovi criteri diagnostici, un numero consistente di pazienti con IMA riceve ancora una diagnosi basata sui vecchi criteri OMS, indipendentemente dal risultato dei marcatori di necrosi. Questo dato evidenzia una limitata applicazione dei nuovi criteri di IMA nella pratica clinica. Le ragioni di questa modesta diffusione sono attribuibili ad un insieme di motivi tecnici, logistici e culturali. Sarà compito delle società scientifiche, nei prossimi anni, superare questi ostacoli per rendere uniforme la classificazione dei pazienti infartuati.

References

1. Alpert JS, Thygensen K, Antman E, Bassand JP. Myocardial infarction redefined. A consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000; 36: 959-69.
2. Dargie H. Myocardial infarction: redefined or reinvented? Heart 2002; 88: 1-3.
3. Richards AM, Lainchbury JG, Nicholls MG. Unsatisfactory redefinition of myocardial infarction. Lancet 2001; 357: 1635-6.
4. Tunstall-Pedoe H. Comment on the ESC/ACC redefinition of myocardial infarction by a consensus dissenter. Eur Heart J 2001; 22: 613-5.
5. Galvani M, Panteghini M, Ottani F, et al. The new definition of myocardial infarction: analysis of the ESC/ACC Consensus Document and reflections on its applicability to the Italian Health System. Ital Heart J 2002; 3: 543-57.
6. Report of the Joint International Society and Federation of Cardiology/World Health Organization Task Force on Standardization of Clinical Nomenclature. Nomenclature and criteria for diagnosis of ischemic heart disease. Circulation 1979; 59: 607-9.
7. Bahit MC, Criger DA, Ohman EM, Granger CB, Wagner GS. Thresholds for the electrocardiographic change range of biochemical markers of acute myocardial infarction (GUSTO-IIa data). Am J Cardiol 2002; 90: 233-7.
8. deFilippi CR , Tocchi M, Parmar RJ, et al. Cardiac troponin T in chest pain unit patients without ischemic electrocardiographic changes: angiographic correlates and long-term clinical outcomes. J Am Coll Cardiol 2000; 35: 1827-34.
9. Ottani F, Galvani M, Nicolini FA, et al. Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes. Am Heart J 2000; 140: 917-27.
10. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. N Engl J Med 1996; 335: 1333-41.
11. Califf RM, Abdelmeguid AE, Kuntz RE, et al. Myonecrosis after revascularization procedures. J Am Coll Cardiol 1998; 31: 241-51.
12. Hong MK, Mehran R, Dangas G, et al. Creatine kinase-MB enzyme elevation following successful saphenous vein graft intervention is associated with late mortality. Circulation 1999; 100: 2400-5.
13. Akkerhuis KM, Alexander JH, Tardiff BE, et al. Minor myocardial damage and prognosis: are spontaneous and percutaneous coronary intervention-related events different? Circulation 2002; 105: 554-6.

14. White HD. Things ain't what they used to be: impact of a new definition of myocardial infarction. Am Heart J 2002; 144: 933-7.
15. Ferguson JL, Beckett GJ, Stoddart M, Walker SW, Fox KA. Myocardial infarction redefined: the new ACC/ESC definition, based on cardiac troponin, increases the apparent incidence of infarction. Heart 2002; 88: 343-7.
16. Costa MA, Carere RG, Lichtenstein SV, et al. Incidence, predictors, and significance of abnormal cardiac enzyme rise in patients treated with bypass surgery in the Arterial Revascularization Therapies Study (ARTS). Circulation 2001; 104: 2689-93.
17. Klatte K, Chaitman BR, Theroux P, et al, for the GUARDIAN Investigators (The GUARD during Ischemia Against Necrosis). Increased mortality after coronary artery bypass graft surgery is associated with increased levels of postoperative creatine kinase-myocardial band isoenzyme release: results from the GUARDIAN trial. J Am Coll Cardiol 2001; 38: 1070-7.
18. Iakovou I, Mintz GS, Dangas G, et al. Increased CK-MB release is a "trade-off" for optimal stent implantation: an intravascular ultrasound study. J Am Coll Cardiol 2003; 42: 1900-5.
19. Williams DO. A twist in our understanding of enzyme elevation after coronary intervention. J Am Coll Cardiol 2003; 24: 1906-8.
20. Apple FS, Quist HE, Doyle PJ, Otto AP, Murakami MM. Plasma 99th percentile reference limits for cardiac troponin and creatine kinase MB mass for use with European Society of Cardiology/American College of Cardiology consensus recommendations. Clin Chem 2003; 49: 1331-6.
21. Newby LK, Alpert JS, Ohman EM, Thygensen K, Califf RM. Changing the diagnosis of myocardial infarction: implications for practice and clinical investigations. Am Heart J 2002; 144: 957-80.
22. Apple FS, Murakami MM, Panteghini M, et al. International survey of cardiac troponin users. Clin Chem 2001; 47: 587-9.
23. Bardaji A, Bueno H, Fernandez-Ortiz A, Heras M. Applicability of a new definition of myocardial infarction and the opinion of Spanish cardiologists. Rev Esp Cardiol 2003; 56: 23-8.
24. Ottani F, Galvani M, Dolci A, et al, a nome del Gruppo di Studio Interdisciplinare Intersocietario ANMCO-SIBioC-SIMeL. I marcatori di danno miocardico nella diagnosi di infarto miocardico acuto: la realtà italiana nell'anno 2000. Ital Heart J Suppl 2002; 3: 933-42.
25. Hasdai D, Behar S, Boyko V, Danchin N, Bassand JP, Battler A. Cardiac biomarkers and acute coronary syndromes - the Euro Heart Survey of Acute Coronary Syndromes experience. Eur Heart J 2003; 24: 1189-94.
26. Porela P, Helenius H, Pulkki K, et al. Epidemiological classification of acute myocardial infarction: time for a change? Eur Heart J 1999; 20: 1459-64.
27. Hamm CW, Goldman BU, Heeschen C, et al. Emergency room triage of patients with acute chest pain by means of rapid testing of cardiac troponin T or troponin I. N Engl J Med 1997; 337: 1648-53.
28. Newby LK, Kaplan AL, Granger BB, et al. Comparison of cardiac troponin T versus creatine kinase-MB for risk stratification in a chest pain evaluation unit. Am J Cardiol 2000; 85: 801-5.
29. The GRACE Investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) project: a multinational registry of patients hospitalized with acute coronary syndromes. Am Heart J 2001; 141: 190-9.
30. Goodman S, Johnson J, Sullivan C, et al. What is an MI? Prospective analysis of the diagnostic and prognostic impact of adding troponins to the definition of myocardial infarction. (abstr) J Am Coll Cardiol 2001; 37: 358A.
31. Packham C, Gray D, Weston C, Large A, Silcocks P, Hampton J. Changing the diagnostic criteria in patients with a suspected heart attack affects the measurement of 30-day mortality but not long term survival. Heart 2002; 88: 337-42.