CARDIOVASCULAR DISEASE

World Health Organization definition of myocardial infarction: 2008–09 revision

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- **Background** WHO has played a leading role in the formulation and promulgation of standard criteria for the diagnosis of coronary heart disease and myocardial infarction since early 1970s.
- **Methods** The revised definition takes into consideration the following: well-resourced settings can use the ESC/ACC/AHA/WHF definition, which has new biomarkers as a compulsory feature; in resource-constrained settings, a typical biomarker pattern cannot be made a compulsory feature as the necessary assays may not be available; the definition must also have provision for diagnosing non-fatal events with incomplete information on cardiac biomarkers and the ECG; to facilitate epidemiologic monitoring definition must recognize fatal events with incomplete or no information on cardiac biomarkers and/or ECG and/or autopsy and/or coronary angiography.

Results Category A definition is the same as ESC/ACC/AHA/WHF definition of MI, and can be applied to settings with no resource constraints. Category B definition of MI is to be applied whenever there is incomplete information on cardiac bio-markers together with symptoms of ischaemia and the development of unequivocal pathological Q waves. Category C definition (probable MI) is to be applied when individuals with MI may not satisfy Category A or B definitions because of delayed access to medical services and/or unavailability of electrocardiography and/or laboratory assay of cardiac biomarkers. In these situations, the term *probable MI* should be used when there is either ECG changes suggestive of MI or incomplete information on cardiac biomarkers in a person with symptoms of ischaemia with no evidence of a non-coronary reason.

- **Conclusions** This article presents the 2008–09 revision of the World Health Organization (WHO) definition of myocardial infarction (MI) developed at a WHO expert consultation.
- **Keywords** Myocardial infarction, epidemiology, clinical diagnosis, ischeamic heart disease, atherosclerosis

Introduction

Cardiovascular disease is a global public health problem contributing to 30% of global mortality and 10% of the global disease burden.^{1,2} In 2005, from a total of 58 million deaths worldwide, 17 million were due to cardiovascular disease and, among them, 7.6 million were due to coronary heart disease.^{3,4} Myocardial infarction (MI) is one of the five main manifestations of coronary heart disease, namely stable angina pectoris, unstable angina pectoris, MI, heart failure and sudden death. The phrase 'acute coronary syndromes' includes unstable angina, non-ST-elevation MI, ST-elevation MI and sudden cardiac death. In epidemiological studies, the incidence of MI in a population can be used as a proxy for estimating the coronary heart disease burden.

The burden of cardiovascular disease is rising both in high-income countries and low- and middleincome countries (LMICs) because of ageing populations, but the burden is greater in LMICs because of much larger population sizes and widespread exposure to increasing levels of risk factors such as unhealthy diet, physical inactivity, obesity, tobacco use, diabetes, raised blood pressure and abnormal blood lipids. Often in LMICs there is a lack of information on the role of risk factors. It has been shown that risk factors for cardiovascular disease are largely similar in high-income countries as in LMICs.⁵ The consequences of globalization and urbanization are also contributory factors.³ In order to track the trends of this global epidemic, the incidence, prevalence and mortality of coronary heart disease need to be monitored. Case definitions for different presentations of coronary heart disease are required. They need to be scientifically valid, consistent when applied across countries, generally applicable and robust.

The new definition of MI by the World Health Organization (WHO) should facilitate epidemiological monitoring, coding of the clinical diagnosis, validity of death certificates and disease classification. Such a standardized case definition of MI is of special importance since it is a means to obtain reliable and comparable data for evaluation of the effectiveness of prevention and curative strategies in countries with widely varying health systems. The definition has implications for epidemiology, disease monitoring, content of registries, clinical research studies, clinical trials, quality assurance, economic analysis, medicolegal disputes and estimation of health-care costs. At the individual level, the diagnosis of MI has a major impact on physical and psychological health and often on family, legal and insurance matters.

Definition of MI

MI is defined by the demonstration of myocardial cell necrosis due to significant and sustained ischaemia. It is usually, but not always, an acute manifestation of atherosclerosis-related coronary heart disease. MI results from either coronary heart disease, which implies obstruction to blood flow due to plaques in the coronary arteries or, much less frequently, to other obstructing mechanisms (e.g. spasm of plaquefree arteries). Plaques are always a consequence of atherosclerosis. Coronary heart disease may relate to stable or unstable underlying plaques. Unstable plaques are characterized by activated inflammation of the vascular wall at the site of plaques. There may be erosion, fissuring or even rupture of the plaques. Platelets can accumulate at the site of an active plaque, further obstructing blood flow and leading to unstable angina. Rupture of atherosclerotic plaques usually leads to acute coronary syndromes or overt MI. Atherosclerotic plaques may expand slowly but more often enlarge in steps. After platelets accumulate on the surface, the healing process adds a further layer to the plaque, which eventually can become fibrous, lipid laden and calcified.

The clinical presentation of MI varies from a minor coronary event to life-threatening clinical situations or sudden death. Those who survive the initial event are vulnerable to repeat attacks of MI. As alluded to above, information on the distribution of MI in a population, if standardized, provides useful information regarding the burden of coronary artery disease in a population. If standardized data can be collected on sudden coronary death and incident and repeat episodes of MI, then the totality of this burden can be determined.

WHO has played a leading role in the formulation and promulgation of standard criteria for the diagnosis of coronary heart disease and MI.^{6–9} In the 1970s, the case definition of MI used in international collaborative projects was based on the WHO European AMI registry criteria.⁷ This definition was further revised in a joint report with the International Society and Federation of Cardiology in 1979.⁸

The WHO European Myocardial Infarction registry criteria⁷ were based on clinical history, findings on the electrocardiogram (ECG), enzyme measurements in blood and postmortem findings. MI was diagnosed in the presence of one of the following:

(i) ECG showing unequivocal pathological Q waves and/or ST segment elevation or depression in serial recordings;

or

(ii) history of typical or atypical angina pectoris, together with equivocal changes on the ECG and elevated enzymes;

or

(iii) history of typical angina pectoris and elevated enzymes with no changes on the ECG or not available;

or

(iv) fatal cases, whether sudden or not, with nakedeye appearances of fresh MI and/or recent coronary occlusion at necropsy (antemortem thrombus, haemorrhage into an atheromatous plaque or embolism).

In the revised WHO criteria used in the multicentre MONICA project conducted in the 1970–80s, Minnesota coding was used to evaluate the ECG rather than the subjective methods of the above criteria.^{9–11} Explicit coding rules were defined for enzymes and symptoms. Most importantly, all possible situations with incomplete information on the ECG, enzymes or symptoms were covered.

Since then, advances in diagnostic technology, including new biomarkers and imaging methods that are more specific and/or sensitive, have enabled the detection of even minor myocardial cell necrosis. These advances called for a re-evaluation of the case definition of MI. In 2000, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) revised the definition of MI.¹² In 2003, the American Heart Association (AHA) in collaboration with the World Heart Federation (WHF), ESC, Centers for Disease Control and Prevention and the National Heart Lung and Blood Institute issued a scientific statement on the case definitions of acute coronary heart disease in epidemiology and clinical research studies for evaluating trends and event rates on the basis of retrospective surveillance.13 More recently, the ESC, ACC and AHA in collaboration with the WHF published and updated the 2000 ESC/ACC consensus document.¹⁴ This revised definition makes the detection of a rise and/or fall of cardiac biomarkers in the clinical setting of myocardial ischaemia essential for the diagnosis of MI. New cardiac biomarker assays are more costly than older assays and are not accessible to large segments of the population in LMICs where the incidence of coronary heart disease is rising. The new definition cannot easily be used to identify non-fatal events with incomplete information on cardiac biomarkers, or fatal events occurring in or out of hospital with incomplete information on cardiac biomarkers, with or without only one ECG recording and/or availability of autopsy data and/or information from coronary angiography. Furthermore, events in patients reaching hospital, although suspect, may not have complete clinical information, including measurement of the new biomarkers. A major problem with the revised definition¹⁴ is that although it is quite appropriate for high-resource settings, it falls short of the clinical and epidemiologic needs in low-resource settings.

New or revised definitions need to embrace recent advances in medical science; however, there must be provision in any new definition for persons in LMICs and even resource-constrained settings in developed countries to be able to diagnose MI and monitor rates of MI. Such data are necessary in order to make epidemiological comparisons within and between populations in a standardized manner. Comparisons are important for two reasons. First, the largest increase in the cardiovascular disease burden over the next 10 years will occur in LMICs, where there are resource constraints. Second, there is a social gradient in relation to coronary heart disease in developed countries, with higher prevalence rates and fatality rates in people in lower social classes, who often have suboptimal access to healthcare.^{2,3} Monitoring MI rates in disadvantaged sectors is essential to address such disparities.

New biomarkers (e.g. troponin), although more specific and sensitive, are generally not available as routine biochemical tests in the public health systems of most LMICs. However, assays for the new biomarkers may be available, even in low-income countries, within the private medical sector at a price that is unaffordable for majority of people. As one-third of the world population lives on <2 USD a day and out-of-pocket expenditures for health can be as high as 80% in developing countries, worldwide access to these assays is limited and depends on social determinants.^{3,15,16} Making these assays a compulsory feature of the definition of MI has the potential risk of further widening already existing health inequalities in the cardiovascular domain.¹⁶ Blood samples may not be available if the patient dies outside hospital or soon after arriving at hospital, and laboratory facilities may not be available at all in many settings in LMICs. The new definition accepts one measurement of troponin only if the value exceeds the decision level for MI. If this is not the case, demonstration of a rise and fall of such levels will require at least two measurements, which may be unaffordable to health systems and people in many low-resource settings.

For these reasons, it was felt necessary to allow some flexibility in the definition of MI in order to broaden its applicability to settings with high resources as well as to settings with resource constraints. In 2008, WHO initiated a process to review the WHO definition of MI addressing the above issues. The process consisted in a consultation of experts held at WHO in Geneva, on 16–17 April 2008 followed in 2009 for an extensive peer review. The definition may change again in the future as science advances and blood tests of whatever nature become inexpensive and more widely available in countries with limited resources.

WHO definition and diagnostic criteria of MI Category A definition and diagnostic criteria of MI. ICD-10 code: I 21

The same definition as the ESC/ACC/AHA/WHF definition; for use in settings with no resource constraints.¹⁴

The term MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia (no evidence of a cause other than ischaemia). Any one of the following criteria meets the diagnosis for MI.

- (i) Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischaemia with at least one of the following:
 - (a) symptoms of ischaemia (include various combinations of chest, upper extremity, jaw or epigastric discomfort with exertion or at rest; the discomfort usually lasts $\leq 20 \text{ min}$, often is diffuse, not localized, not positional, not affected by movement of the region and it may be accompanied by dyspnoea, diaphoresis, nausea or syncope);
 - (b) ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)–Minnesota codes: ST-depression 4.1; 4.2; ST-elevation 9.2; LBBB 7.1];
 - (c) development of pathological Q waves in the ECG (Minnesota codes: 1.1.1 through 1.2.5 plus 1.2.7),¹⁷ including:
 - (1) no unequivocal pathological Q waves in the first ECG or in event set of ECG(s) followed by a record with a pathological Q wave or
 - (2) any Q wave in leads V2–V3 ≥ 0.02 s or QS complex in leads V2 and V3 or Q wave ≥ 0.03 s and ≥ 0.01 mV deep or QS complex in leads I, II, aVL, aVF or
 - (3) V4–V6 in any two leads of a contiguous lead grouping (I, aVL, V6:V4–V6: II, III, aVF).
 - (d) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

or

- (ii) Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia (ischaemic symptoms include various combinations of chest, upper extremity, jaw or epigastric discomfort with exertion or at rest; the discomfort usually lasts ≤ 20 min, often is diffuse, not localized, not positional, not affected by movement of the region, and it may be accompanied by dyspnoea, diaphoresis, nausea or syncope.) and accompanied by
 - (a) presumably new ST elevation or new LBBB (Minnesota codes: ST-depression 4.1; 4.2; ST-elevation 9.2; LBBB 7.1) and/or
 - (b) evidence of fresh thrombus by coronary angiography and/or at autopsy,

but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood, and there is no evidence of a non-coronary cause of death.

- or
- (iii) Autopsy findings of an acute MI.

Category B definition and diagnostic criteria of MI if the requirements for diagnostic tests in Category A (above) have not been met. ICD-10 code: I 21

Whenever there is incomplete information on cardiac biomarkers (preferably troponin) and other diagnostic criteria needed to apply Category A, the term *MI* should be used if:

- (i) Both of the following criteria are present:
 - (a) symptoms of ischaemia (ischaemic symptoms include various combinations of chest, upper extremity, jaw or epigastric discomfort with exertion or at rest; the discomfort usually lasts ≤20 min, often is diffuse, not localized, not positional, not affected by movement of the region, and it may be accompanied by dyspnea, diaphoresis, nausea or syncope) and
 - (b) development of unequivocal pathological Q waves [no pathological Q wave in the first ECG or in the event set of ECG/s followed by a record with a pathological Q wave—any Q wave in leads V2–V3 ≥ 0.02 s (Minnesota code 1.2.1) or QS complex in leads V2 and V3 (Minnesota code 1.2.7). Q-wave ≥ 0.03 s and ≥ 0.1 mV deep (Minnesota codes 1.1.1; 1.2.2) or QS complex in leads I, II, aVL, aVF or V4–V6 in any two leads of a contiguous lead grouping I, aVL, V6: V4–V6: II, III, aVF (Minnesota codes 1.1.7; 1.3.6)].

(ii) Death with a history of coronary heart disease and/or documented cardiac pain within 72 h before death and no evidence of non-coronary cause of death, or autopsy evidence of chronic coronary heart disease, including coronary atherosclerosis and myocardial scarring.

Category C definition and diagnostic criteria of probable MI. ICD-10 code: I 24.9

In resource-constrained settings, individuals with MI may not satisfy criteria of definitions in Category A or B. This may be due to delayed access to medical services and/or unavailability of electrocardiography and/or lack of facilities for laboratory assay of specific cardiac biomarkers.

The term *probable MI* should be used when there is insufficient information to decide whether or not there was an MI based on definitions in Categories A and B above, but

- (i) Either one of the following is present in a person with symptoms of ischaemia (include various combinations of chest, upper extremity, jaw or epigastric discomfort with exertion or at rest; the discomfort usually lasts ≤ 20 min, often is diffuse, not localized, not positional, not affected by movement of the region, and it may be accompanied by dyspnoea, diaphoresis, nausea or syncope), with no evidence of a non-coronary reason:
 - (a) development of unequivocal pathological Q waves (no pathological Q wave in the first ECG or in the event set of ECG/s followed by a record with a pathological Q wave— Minnesota codes 4.1; 4.2; 5.1; 5.2; 9.2—or development of new ischaemia—new ST-T changes and an equivocal change in Q waves—Minnesota code 1.2.8 or any 1.3 code—demonstrated between the ECGs associated with the event or between a previously recorded ECG and the event ECG);
- or
- (b) incomplete information on cardiac biomarkers (preferably troponin) provided that myocardial damage of other reasons (Table 2) and other clinical conditions that can cause a rise in cardiac biomarkers are excluded.

or

(ii) Autopsy findings suggestive of MI but not conclusive.

In all cases (including Categories A, B and C), several biomarker [troponin or creatine kinase (CK)-MB] determinations, which are all normal, exclude the diagnoses of MI or probable MI.

Definition of a prior MI (same as the ESC/ACC/AHA/ WHF definition),¹⁴ ICD-10 code: I 25.2

The term *prior MI* should be used in the presence of any one of the following:

- (i) pathological Q waves [any Q wave in leads V2–V3 ≥0.02 s—Minnesota code 1.2.1—or QS complex in leads V2 and V3—Minnesota code 1.2.7. Q-wave ≥0.03 s and ≥0.1 mV deep—Minnesota codes 1.1.1; 1.2.2—or QS complex in leads I, II, aVL, aVF or V4–V6 in any two leads of a contiguous lead grouping I, aVL, V6: V4–V6: II, III, aVF (Minnesota codes 1.1.7; 1.3.6)] with or without symptoms;
- (ii) imaging evidence of a region of loss of viable myocardium that is thinned and has a motion abnormality, in the absence of a non-ischaemic cause; and
- (iii) pathological findings at autopsy of a healed or healing MI.

Recurrent MI, ICD-10 code: I 22

Incident MI is defined as the person's first MI ever. When features of MI occur in the first 28 days after an incident event, the event is not counted as a new event for epidemiological purposes. If features of MI occur after 28 days of an incident event, it is considered to be a new infarct (a recurrent event).

Reinfarction, ICD-10 code: I 21

The term *reinfarction* is used for an MI that occurs within 28 days of an incident or a recurrent MI.

Fatal coronary heart disease is death with none of the above and no other cause of death with any one of the following:

- (i) symptoms suggestive of myocardial ischaemia (ischaemic symptoms include various combinations of chest, upper extremity, jaw or epigastric discomfort with exertion or at rest; the discomfort usually lasts ≤20 min, often is diffuse, not localized, not positional, not affected by movement of the region, and it may be accompanied by dyspnoea, diaphoresis, nausea or syncope), including cardiac arrest;
- (ii) documented history (based on clinical records and ECG) of coronary heart disease; and
- (iii) pathological findings of coronary atherosclerosis and myocardial scarring at autopsy.

Peri-procedural MI (same as the ESC/ACC/AHA/WHF definition) (14), ICD-10 code: I 21

For percutaneous coronary interventions or coronary artery bypass grafting in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile of upper reference limit are indicative of peri-procedural myocardial necrosis.

By convention, for percutaneous coronary interventions-related MI, cardiac biomarker values three times greater than the 99th-percentile upper reference limit are considered diagnostic. It is essential that the increases occur from a normal baseline. If values are rising, distinguishing between the rise due to the acute event (whether appreciated or not) or due to the procedure itself is difficult.

By convention, for coronary artery bypass grafting– related MI, cardiac biomarkers values five times greater than the 99th-percentile upper reference limit plus either new pathological Q waves or new LBBB or angiographically documented new graft or native coronary artery occlusion or imaging evidence of new loss of viable myocardium are considered diagnostic.

MI associated with stent thrombosis as documented by angiography or autopsy.

Unstable angina

Unstable angina is diagnosed when there are new or worsening symptoms of ischaemia (or changing symptom pattern) and ischaemic ECG changes (Minnesota codes 4.1; 4.2; 5.1; 5.2; 9.2) with normal biomarkers. The distinction between new angina, worsening angina and unstable angina is notoriously difficult and based on a clinical assessment and a careful and full clinical history.

Implications

So that there is uniformity in the reporting of data, MIs should be reported as outlined above. In that way, the outcomes of clinical trials and the findings in registries across the globe can be applied and compared more appropriately. There are many conditions that confound the ECG diagnosis of MI and the diagnosis of MI using biomarkers (Tables 1 and 2).¹⁴

The Category C definition of probable MI is required mainly because of inequities in access to health services that prevail in low-resource settings. Furthermore, in settings where resources are very constrained, situations may arise where even the tests required for a diagnosis of probable MI are not available and other reasons for the symptoms are not known. In countries where this is likely to happen, the use of code 'unclassifiable MI' should be considered for epidemiological purposes.

When feasible, the diagnosis of acute MI should be based on raised troponin levels because of the sensitivity and specificity of these markers. Troponin elevations are usually an indication of damaged myocardial cells and cell death. Raised troponin levels are associated with increased risks of death and recurrent MI. Enzymes such as glutamine oxaloacetic transaminase (aspartate aminotransferase) and lactate dehydrogenase are still being used for diagnosis of MI in some laboratories. CK has a wide tissue distribution. If total CK is used for clinical diagnosis of MI, the cut-off limits should be at least twice the upper reference limit for CK; different cut-off limits should be available for men and women and other causes of an elevation of CK such as exercise should be absent.¹⁸ CK-MB (measured by mass assay) is less tissue specific than cardiac troponin. Assay of non-specific cardiac biomarkers should be phased out and replaced with CK-MB fraction or, preferably, with troponin. However, given the critical financing issues related to health care and other competing health priorities in LMICs, it may take many years to bring about such changes.

ECG may be normal QS complex in lead V1 Q wave <0.03 s and <1/4 of the R wave amplitude in LIII is normal if the frontal axis is 30 and 0° Q wave may be normal in aVL if the frontal QRS axis is between 60 and 90° Septal Q waves <0.03 s and <1/4 of the R wave amplitude in leads I, aVL, aVF, V4 and V6 Q/QS complexes in Pre-excitation, obstructive or dialated cardiomyopathy, LBBB, left anterior hemiblock, left and right ventricular hypertrophy and acute cor pulmonale the absence of MI False positives Benign early repolarization Brugada syndrome Peri-/myocarditis Pulmonary embolism Subarachnoid haemorrhage Metabolic disturbances such as hyperkalaemia Failure to recognize normal limits for J-point Lead transposition or displacement Cholecystitis Prior myocardial infarction with Q-waves and/or persistent ST elevation False negatives Paced rhythm LBBB

 Table 1 Conditions that confound or simulate the ECG diagnosis of MI

Source: Modified from ref. 14.

Cardiac causes	Cardiac contusion due to trauma or cardiac surgery, Ablation, pacing, implantable cardioverter-defibrillator firings Cardioversion Endomyocardial biopsy Acute and chronic congestive heart failure Aortic dissection Aortic valve disease Hypertrophic cardiomyopathy Tachyarrhythmia, bradyarrhythmia, heart block Apical ballooning syndrome Post-percutaneous coronary intervention patients who seem to have no complications Rhabdomyolysis with myocyte necrosis Myocarditis or myocardial extension or endo-/pericarditis
Non-cardiac causes	Pulmonary embolism, severe pulmonary hypertension Renal failure Stroke, subarachnoid haemorrhage Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, scleroderma Drug toxicity Critically ill patients, especially with respiratory failure or sepsis Burns, especially if affecting >30% of body surface area Extreme exertion

Table 2 Elevation of troponin in the absence of MI

Source: Modified from refs 14, 18 and 19.

There will be some advantages and disadvantages with these revised definitions. For the individual patient, the new definition may cause changes in the eligibility to continue in certain occupations and the ability of persons to obtain insurance. Many patients who in the past would have been diagnosed as having unstable angina will now be diagnosed as having had an MI.

The application of the more sensitive new diagnostic criteria for MI will cause the recorded incidence of MI to rise and the case fatality to fall with a reduction in false-positive and false-negative cases. This may confuse efforts to follow trends in disease rates and outcomes that are used to evaluate the impact of public health measures and treatment.^{19–21} There will be significant health resource and cost implications but expenditures will be better directed as a consequence of more accurate diagnosis, improved patient outcomes and decreased mortality rates.

Comparison with previous epidemiological studies using the old definition will be problematic. When interpreting trends and comparing data collected in different settings, there is a need to take note of the different definitions that may have been used in collecting the data. For accurate tracking of MI rates, methods for adjusting the new criteria to the old may be required. For example, specific surveillance centres in LMICs may be needed to measure total CK and CK-MB together with new biomarkers for a transition period, or to apply both new and old diagnostic criteria for a given period of time to assess the difference in terms of incidence, prevalence and mortality rates.

A specific problem for the assessment of event rates and their trends in the population is death when there is insufficient evidence to classify the event as a coronary death, and there is no other known cause. The number of such deaths may be substantial.¹⁰ It is important for the epidemiological reporting that such deaths are also monitored.

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