

The New Definition of Myocardial Infarction

Diagnostic and Prognostic Implications in Patients With Acute Coronary Syndromes

Mark A. Meier, MD; Wisam H. Al-Badr, MD; Jeanna V. Cooper, MS; Eva M. Kline-Rogers, MS; Dean E. Smith, PhD; Kim A. Eagle, MD; Rajendra H. Mehta, MD, MS

Background: The clinical implications of the recently revised criteria for diagnosis of acute myocardial infarction (AMI) in patients with suspected acute coronary syndromes are unknown.

Methods: To evaluate the prognostic implications of the new diagnostic criteria for AMI, we studied 493 consecutive patients with suspected acute coronary syndromes admitted to University of Michigan, Ann Arbor, between May 1, 1999, and January 1, 2000. Patients with positive cardiac enzymes and symptoms suggestive of coronary ischemia (n=275) were divided into 2 groups: group A, with elevated peak creatine kinase-MB fraction and/or new electrocardiographic changes suggestive of AMI regardless of troponin status (diagnosed as AMI by old criteria), and group B, with normal peak creatine kinase-MB fraction but elevated troponin I level (additional patients diagnosed as having AMI by new criteria).

Results: As compared with group A (n=224), patients in group B (n=51) were older women, with increased co-

morbidities such as previous stroke or aortic stenosis, and had fewer in-hospital procedures. In-hospital adverse events (reinfarction, heart failure, shock, and mortality) were similar between the groups, whereas 6-month mortality was higher among group B patients (16.3% vs 5.8%; $P=.03$). This difference was not statistically significant after adjustment for differences in baseline characteristics between the groups (odds ratio, 1.6; 95% confidence interval, 0.5-5.9).

Conclusions: The new criteria result in a substantial increase in the diagnosis of AMI. Furthermore, they help to identify patients with acute coronary syndromes who have greater comorbidities and worse 6-month outcomes who are otherwise missed by the old criteria. Additional studies are needed to confirm these preliminary findings and to determine the financial implications of the new criteria.

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ACUTE MYOCARDIAL infarction (AMI) is a clinical and pathological entity that has been independently defined in the past by various organizations by means of a combination of clinical, laboratory, and electrocardiographic (ECG) criteria.¹⁻⁵ Until recently, diagnosis of AMI was based on the revised World Health Organization (WHO) criteria that require 2 of the following 3 conditions for diagnosis: ischemic symptoms, ECG changes consistent with ischemia, and elevated enzyme levels, usually creatine kinase-MB (CK-MB).⁶

Although the use of troponins to diagnose AMI has been previously proposed,⁷⁻¹⁰ in September 2000, a joint committee of the European Society of Cardiology and the American College of Cardiology (ESC/ACC) published a new definition of AMI that for the first time officially included troponins.¹¹ According to these cri-

teria, elevated levels of enzymes (including CK-MB or troponin I or T) with either symptoms or ECG changes suggestive of ischemia constitute an AMI. The inclusion of troponins was based on a large body of evidence showing that an elevated troponin level correlates with pathologically proved myocardial necrosis¹² and carries poor prognosis in patients with suspected acute coronary syndromes.¹³⁻²¹

The clinical implications of applying the new criteria with troponins in terms of their diagnostic and prognostic impact in patients with suspected acute coronary syndromes have not yet been defined. The objectives of this study were to address the following issues: (1) Does the new definition influence the number of patients diagnosed as having AMI in those with suspected acute coronary syndromes? (2) Is there a difference in the in-hospital and 6-month clinical outcomes between patients diagnosed as having AMI

From the Division of Cardiology, Department of Internal Medicine, University of Michigan, Ann Arbor.

PATIENTS AND METHODS

PATIENT POPULATION

For this study, we included all patients admitted to the University of Michigan Medical Center, Ann Arbor, between May 1, 1999, and January 1, 2000, with suspected acute coronary syndromes. To be admitted, these patients were at least at intermediate to high risk for their symptoms to represent a coronary event by the criteria established per the ACC–American Heart Association guidelines.²² The project was approved by the institutional review board at our institution. Four hundred ninety-three consecutive symptomatic patients met the inclusion criteria within the study period, although 1 patient with insufficient laboratory data was excluded from analysis. Twenty-one patients were readmitted within the study period, and only their index admission was included in our analysis. Thus, 471 patients were available for the final data analysis.

Patients with elevated cardiac enzyme levels (peak values rather than initial values were used) were stratified into 2 groups. Group A consisted of patients who would have been diagnosed as having AMI by the old (WHO) criteria. These patients had an elevated peak CK-MB level and/or new ECG changes or symptoms suggestive of AMI regardless of troponin (I or T) status. Although patients with chest pain and ECG evidence of new ST-segment elevation or left bundle-branch block in the absence of an elevated CK-MB level would additionally have met the requirement for AMI by the WHO criteria, we did not have any patients in this subgroup. Hence, all patients diagnosed as having an AMI by the WHO criteria had an elevation of CK-MB level (regardless of cardiac troponins). Group B contained symptomatic patients with a negative CK-MB finding but an elevated troponin I level, and without ECG evidence of new ST-segment elevation or left bundle-branch block. Thus, group B consisted of patients who would have been diagnosed as having an AMI by the ESC/ACC, but not by WHO criteria. Patients with enzyme elevations noted only after percutaneous coronary intervention (9 patients with elevated CK-MB level and 9 patients with normal CK-MB level but elevated troponin I level) were excluded from further analysis.

DATA COLLECTION

Although patients with acute coronary syndromes were prospectively identified, assistants with no knowledge of

the present study collected data on patient demographics, medical history and comorbid conditions, admission signs and symptoms (including ECG interpretations), in-hospital management and events, and mortality by means of retrospective chart reviews and computerized records. A standard data collection form and standard definitions were used. Similar information collection techniques in addition to telephone calls were used to conduct a 6-month follow-up with respect to death status and further hospitalizations for suspected acute coronary syndromes, heart failure, and arrhythmia. Verbal consent was obtained at each follow-up telephone call. All primary data were entered into a spreadsheet manually by individuals unaware of the study design or preliminary results.

LABORATORY DATA

The CK-MB and troponin I analyses were performed with a microparticle enzyme immunoassay (Abbott AxSym System; Abbott Diagnostics Division, Abbott Park, Ill). As determined by our laboratory, the CK-MB assay was performed for all creatine kinase values greater than 100 IU/L and was considered positive for values greater than 6 IU/L or 2.5% of total creatine kinase. The CK-MB level was assumed to be normal for creatine kinase values less than 100 IU/L. Troponin I level was considered to be elevated and consistent with an AMI at levels greater than 2.0×10^{-6} mg/mL according to the standards set forth by our laboratory.

DATA ANALYSIS

Summary statistics were presented as frequencies and percentages or as mean \pm SD unless stated otherwise. The 2 groups were compared by means of a χ^2 test or Fisher exact test, when appropriate, for categorical variables and a 2-sample 2-tailed *t* test for continuous variables. *P* values less than .05 were considered indicative of a significant difference between the 2 groups. Multivariable logistic regression analysis was performed with variables suggestive of marginal significance on univariate analysis (*P* < .20) to assess independent predictors of in-hospital and 6-month mortality. All statistical analyses were performed with SAS 8.1 for Windows (SAS Institute Inc, Cary, NC).

by the WHO criteria vs those diagnosed only by the new criteria? We hypothesized that more AMI would be detected by means of the new definition and, further, that the prognosis of patients with AMI diagnosed with the 2 criteria may be significantly different.

RESULTS

A total of 224 patients had an elevated CK-MB level with or without troponin elevation (group A), while 51 patients were found to have a negative CK-MB finding but an elevated troponin I level (group B). Patients in group B tended to be older (67.5 vs 63.8 years; *P* = .05) and less often male (**Table 1**). In addition, they were significantly more likely to have a history of stroke or transient ischemic attack (19.6% vs 9.0%; *P* = .03) and aortic

stenosis (7.8% vs 0.9%; *P* = .01). Other comorbidities were not significantly different between the 2 groups.

There was a nonsignificant trend for group B patients to present with atypical symptoms and to have a higher heart rate and blood pressure on admission (**Table 2**). The degree of heart failure was similar among the 2 groups.

Procedures were used less frequently in group B than group A (intra-aortic balloon pump [0.0% vs 10.3%; *P* = .01], pulmonary artery catheter [3.9% vs 17.4%; *P* = .01], and percutaneous coronary interventions [17.7% vs 54.5%, *P* < .001]) (**Table 3**). Patients in group B also had fewer coronary artery bypass operations during their hospital course, although this did not reach statistical significance.

Patients in group B were less likely to have received unfractionated or low-molecular-weight heparin

Table 1. Patient Demographics, Cardiac Risk Factors, and Comorbid Conditions*

	Group A	Group B	P Value
Demographics			
No. of patients	224	51	
Age, mean ± SD, y	63.8 ± 13.9	67.5 ± 11.8	.05
Sex, No. (%) M	152 (67.9)	29 (56.9)	.14
Cardiac risk factors, No. (%)			
Diabetes	71 (31.7)	17 (33.3)	.82
Hypertension	131 (58.5)	34 (68.0)	.21
High cholesterol level	119 (53.6)	28 (54.9)	.87
Smoker	120 (53.6)	34 (66.7)	.09
Comorbidities, No. (%)			
Previous MI	66 (29.7)	21 (24.1)	.11
CHF	39 (17.4)	15 (29.4)	.05
Stroke/TIA	20 (9.0)	10 (19.6)	.03
PTCA	34 (15.2)	9 (17.7)	.66
CABG	35 (15.6)	9 (17.7)	.72
PVOD	29 (13.0)	9 (17.7)	.39
Angina	120 (53.6)	30 (58.8)	.50
Aortic stenosis	2 (0.9)	4 (7.8)	.01
Renal insufficiency	37 (16.6)	11 (21.6)	.40
Atrial fibrillation	20 (9.0)	6 (12.0)	.51

*MI indicates myocardial infarction; CHF, congestive heart failure; TIA, transient ischemic attack; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; and PVOD, peripheral vascular occlusive disease. Group A had elevated peak creatine kinase-MB fraction; group B had normal peak creatine kinase-MB fraction but elevated troponin I level.

Table 2. Clinical Signs and Symptoms on Admission*

	Group A	Group B	P Value
Chest pain, No. (%)	192 (85.7)	39 (76.5)	.10
Killip class, No. (%)			
I	162 (72.3)	34 (66.7)	.42
II	36 (16.1)	12 (23.5)	.21
III	12 (5.4)	3 (5.9)	>.99
IV	14 (6.3)	2 (3.9)	.41
Heart rate†	84.1 ± 25.0	91.1 ± 20.0	.17
Systolic BP†	138.5 ± 30.0	145.0 ± 34.6	.22
Diastolic BP†	80.3 ± 20.1	82.0 ± 19.9	.59

*BP indicates blood pressure. Group A had elevated peak creatine kinase-MB fraction; group B had normal peak creatine kinase-MB fraction but elevated troponin I level.

†Mean ± SD.

(74.5% vs 88.4%; $P = .001$) and glycoprotein IIb/IIIa receptor antagonists (21.6% vs 43.1%; $P = .005$). The use of aspirin or β -blockers in the early phase (within 24 hours of admission) did not differ between the 2 groups.

At discharge, patients in group B more often received β -blockers, but use of ticlopidine hydrochloride or clopidogrel bisulfate, angiotensin-converting enzyme inhibitors, and aspirin did not differ between the 2 groups.

In-hospital events did not differ significantly between groups A and B (**Table 4**). However, every outcome measured tended to occur less frequently in group B, and the length of stay was shorter for patients in group B (5.3 vs 6.8 days; $P = .04$). No patients were entirely lost to follow-up, although rehospitalization status was un-

Table 3. Management in Hospital and at Discharge*

	Group A	Group B	P Value
In-hospital treatment, No. (%)			
IABP	23 (10.3)	0 (0.0)	.01
PA catheter	39 (17.4)	2 (3.9)	.01
PCI	122 (54.5)	9 (17.7)	<.001
CABG	9 (4.0)	1 (2.0)	.47
Early medical treatment, No. (%)			
β -Blockers	162 (72.3)	43 (84.3)	.08
Aspirin	209 (93.3)	46 (90.2)	.44
UFH/LMWH	198 (88.4)	38 (74.5)	.01
GpIIb-IIIa	116 (43.1)	11 (21.6)	.005
Discharge medical treatment, No. (%)			
Clopidogrel or ticlopidine hydrochloride	96 (42.9)	15 (29.4)	.07
β -Blockers	157 (70.1)	43 (84.3)	.04
Aspirin	181 (80.8)	42 (82.4)	.80
ACEI	114 (50.9)	21 (41.2)	.21

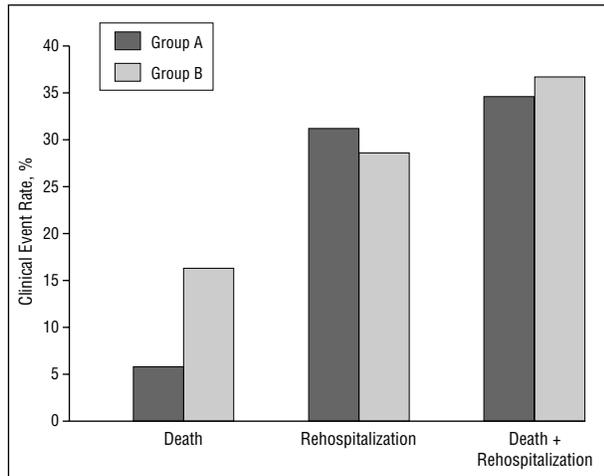
*IABP indicates intra-aortic balloon pump; PA, pulmonary artery; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; UFH/LMWH, unfractionated or low-molecular-weight heparin; GpIIb-IIIa, glycoprotein IIb/IIIa receptor inhibitors; and ACEI, angiotensin-converting enzyme inhibitors. Group A had elevated peak creatine kinase-MB fraction; group B had normal peak creatine kinase-MB fraction but elevated troponin I level.

Table 4. In-Hospital and 6-Month Outcomes

	Group A	Group B	P Value
In hospital, No. (%)			
Reinfarction	6 (2.7)	0 (0.0)	.60
Death	17 (7.6)	2 (3.9)	.54
CHF	25 (11.2)	3 (5.9)	.32
Shock	19 (8.5)	1 (2.0)	.14
AF/flutter	30 (13.4)	3 (5.9)	.16
Sustained VT	13 (5.8)	1 (2.0)	.48
VF	13 (5.8)	0 (0.0)	.14
VT or VF	23 (10.3)	1 (2.0)	.06
LOS, mean ± SD, d	6.8 ± 7.2	5.3 ± 3.8	.04
6-Month follow-up, No. (%)			
Death	12 (5.8)	8 (16.3)	.03
Rehospitalization	64 (31.2)	14 (28.6)	.72
Death + rehospitalization	71 (34.6)	18 (36.7)	.78

*CHF indicates congestive heart failure; shock, cardiogenic shock (Killip class IV); AF/flutter, atrial fibrillation or flutter; VT, ventricular tachycardia; VF, ventricular fibrillation; LOS, length of stay; and death + rehospitalization, death and/or rehospitalization for heart disease. Group A had elevated peak creatine kinase-MB fraction; group B had normal peak creatine kinase-MB fraction but elevated troponin I level.

available for 2 patients in group A. At 6 months after discharge, 12 patients in group A and 8 patients in group B had died (5.8% vs 16.3%; $P = .03$; odds ratio, 3.2; 95% confidence interval, 6-8.3; $P = .02$) (**Figure**). This difference remained significant after adjustment for age and sex (odds ratio, 3.1; 95% confidence interval, 1.7-8.2; $P = .02$). However, after adjustment for age, sex, and baseline differences in patient characteristics, the 6-month mortality was not significantly different between the groups (odds ratio, 1.6; 95% confidence interval, 0.5-5.9; $P = .45$). Similarly, there was no difference in the com-



Clinical events at 6-month follow-up (death, readmission for cardiac reasons, and combined end point of death and readmission).

posite end point of death plus rehospitalization for heart disease at 6-month follow-up.

COMMENT

Our study demonstrates that, when compared with the old definition established by the WHO for AMI diagnosis, the new criteria proposed by the joint committee of the ESC/ACC detects more patients with AMI among those admitted with suspected acute coronary syndromes. In fact, the additional 51 patients detected as having AMI only by the new definition would have been missed by the WHO criteria. Not only did the use of the new definition allow more AMI to be diagnosed, but also it did not miss the diagnosis of AMI in a single patient who was diagnosed as having AMI by the WHO criteria.

It is interesting that the in-hospital events and mortality of patients in group B were similar to those in group A. However, the mortality at 6 months was higher for group B. This was due to the dissimilarities in baseline characteristics of the patients, since the adjusted odds ratio of death in the 2 groups was not significant when adjusted for the differences in these baseline characteristics. In other words, our data suggest that the new criteria identify patients with AMI who are likely to be missed by the previous diagnostic criteria or, at best, labeled as having unstable angina, and who have more comorbid conditions leading to a higher 6-month mortality as a result of their greater comorbidities. Our findings are consistent with those from the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa trial, which demonstrated higher 30-day all-cause mortality for patients with a normal CK-MB level and elevated troponin T level than for patients with an elevated CK-MB level.¹⁶

Our study has important clinical implications in patients with symptoms suggestive of acute coronary syndromes. First, a substantial proportion of patients with suspected acute coronary syndrome (10.8%) in our study were classified as having AMI, and not classified as having unstable angina or being missed completely, as a result of the new criteria. Furthermore, these additional pa-

tients diagnosed as having AMI by the new definition had more comorbid conditions and as a result were at greater risk of adverse events. Missed diagnosis of such a high-risk cohort has been shown to be associated with worse outcomes.^{23,24} Second, the new criteria, by facilitating the identification of patients who are at increased risk of adverse outcomes, will allow physicians to tailor specific treatment strategies that may help decrease mortality in this high-risk subset. This may include the use of glycoprotein IIb/IIIa receptor antagonists, low-molecular-weight heparin, clopidogrel, and/or an invasive strategy. Many studies have confirmed the benefits of glycoprotein IIb/IIIa receptor antagonists²⁵⁻²⁷ and low-molecular-weight heparin^{28,29} in improving outcomes in patients with acute coronary syndromes who have elevated troponin levels. Similarly, an aggressive early invasive strategy has been shown to be particularly useful, especially in combination with the above agents, for improving outcomes in the subset of patients with acute coronary syndromes who have evidence of myocardial necrosis.^{25,30,31} In our study, patients in group B received fewer invasive procedures (including revascularization) and were treated less frequently with heparin and glycoprotein IIb/IIIa antagonists. This may be because physicians considered group B patients to have unstable angina rather than AMI without ST-segment elevation (hence “less sick”), or this may have occurred as a result of increased comorbidities in these patients. On the basis of current evidence, it is likely that the use of a more aggressive approach in our patients in combination with newer antiplatelet agents or low-molecular-weight heparin would have resulted in better outcomes.

Finally, because the new criteria would lead to an increase in the number of patients diagnosed as having AMI in those presenting with symptoms suggestive of acute coronary syndromes, this would have significant financial implications from the provider perspective. In the era of diagnosis-related group-based payment, hospitals are reimbursed more for an AMI than for a diagnosis of unstable angina. As the patients diagnosed as having AMI by the new criteria would have been labeled as having unstable angina in the past by the WHO criteria, the same patient would generate more revenue (appropriately) for health care institutions now than before the new criteria were published. This, however, needs to be confirmed in future studies.

One limitation of our study is that we included patients who were admitted to the hospital for acute coronary syndromes. Therefore, these patients had at least an intermediate, but more likely a high, probability of their symptoms being related to a coronary event. As such, our study findings may not be extrapolated to all patients presenting with suspected acute coronary syndromes, particularly those with a low probability of coronary events. Furthermore, our study enrolled a relatively small number of patients. Thus, our study findings need to be confirmed in future large investigations in different risk groups. Finally, elevated cardiac markers of necrosis are only one of the many components in the risk stratification of acute coronary syndromes. The most optimal risk stratification strategy involves the collective use of patients’ clinical presentation, physical examination, labo-

ratory and ECG data, and noninvasive and/or invasive tests findings. Our study did not evaluate this strategy.

We conclude that, unlike the WHO definition, the use of the new ESC/ACC criteria enhances identification of a high-risk subset of patients with AMI. Identification of high-risk patients with AMI allows physicians to target more aggressive treatments in this cohort that have the potential of improving their outcomes. Further studies are needed to confirm our findings, to understand the mechanisms of the difference in patient risk between the 2 groups, and to evaluate the health care cost implications of the new criteria for AMI.

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Corresponding author and reprints: Rajendra H. Mehta, MD, MS, Department of Internal Medicine, University of Michigan, 2215 Fuller Rd, 7E, 111A, Ann Arbor, MI 48105 (e-mail: rmehta@umich.edu).

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