Redefinition of Myocardial Infarction
Prospective Evaluation in the Community

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Background—The 2000 European Society of Cardiology/American College of Cardiology definition for myocardial infarction (MI) combines ischemic symptoms, electrocardiographic changes, and troponin rather than creatine kinase levels. The use of troponins will increase the detection of MI by a magnitude to be quantified, and the clinical acceptance of the new definition is unknown.

Method and Results—Subjects presenting to an Olmsted County facility with a troponin T value ≥0.03 ng/mL between November 2002 and March 2005 were prospectively classified through the use of standardized MI criteria, relying on cardiac pain, Minnesota coding of the ECG, and troponin, creatine kinase, and its MB fraction measured simultaneously. Through the use of dynamic changes in troponin, 538 MIs were identified versus 327 with creatine kinase and 427 with only the MB fraction of creatine kinase. This represents a 74% (95% confidence interval [CI], 69% to 79%) increase above the number of MIs identified with creatine kinase and a 41% (95% CI, 37% to 46%) increase above the number identified with criteria including only its MB fraction. When relying on single values of troponin, increases in the number of MIs were always large but varied widely according to the threshold used for troponin. Cases meeting only troponin-based criteria were less likely to have electrocardiographic ST-segment elevation and had better survival than those identified with previous criteria. Clinician diagnoses mentioned MI in 42% (95% CI, 34% to 49%) of cases meeting only troponin-based criteria versus 74% (95% CI, 69% to 78%) for MIs meeting the previous criteria (P<0.001).

Conclusions—The prospective application of the new criteria in the community results in a large increase in the number of MIs and a change in case mix. The clinical acceptance of the new criteria is incomplete, and studies that rely exclusively on dismissal diagnoses to assess MI rates may underestimate the burden of disease as presently defined. (Circulation. 2006;114:790-797.)

Key Words: myocardial infarction criteria biomarkers diagnosis

In 2000, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) recommended a new definition for myocardial infarction (MI)1 that combines ischemic symptoms with changes in the ECG and in biochemical markers of myocardial necrosis and emphasizes the use of troponins. This change acknowledges the widespread use of these markers, partly because of their prognostic value.2,3 Troponins are more specific than other biomarkers in detecting myocardial injury with associated skeletal muscle injury and have a higher sensitivity, allowing detection of small amounts of myocardial necrosis that would have gone undetected by creatine kinase and its MB fraction. Thus, this biomarker change can be expected to have 2 critical consequences: increasing the number of MIs by identifying cases meeting criteria solely through troponin and shifting the clinical spectrum of the disease. Despite the clinical and public health implications of these changes and the controversy4–9 that surrounded the publication of the new criteria, these changes have not been evaluated prospectively. Indeed, current knowledge is based on convenience samples and case series that use different assays and criteria that are incompletely standardized. It is not surprising, therefore, that the reported percent increase in the number of MIs related to the introduction of troponin ranges from 23%10,11 to 195%12 and that data on the resulting change in case mix and outcome are scarce and discrepant.13 Indeed, some reports suggest an
increase in case fatality among cases meeting solely troponin-based criteria, whereas others report the opposite. Recognizing the clinical and public health necessity to rigorously measure the changes resulting from the new criteria, the ESC and ACC recommended that the established definition of MI “be retained” by sentinel centers. The goal of the present study was to prospectively implement this recommendation in the community and apply simultaneously the creatine kinase and troponin-based criteria in all patients with acute coronary syndromes. In doing so, we sought to document the impact of the new criteria on the number of MIs and their case mix. Furthermore, to assess the clinical acceptance of the new criteria, we examined the relation between clinical diagnoses and dismissal codes for all MIs prospectively ascertained.

Methods

The study was conducted in Olmsted County, Minnesota. The Mayo Clinic and Olmsted Medical Center, which provide care for this population, use a unified system that has accumulated comprehensive clinical records in which information is collected by physicians and is retrievable because the Mayo Clinic maintains extensive indices, which, through the Rochester Epidemiology Project, are extended to the records of other care providers to county residents, resulting in the linkage of all medical records from all sources of care through a centralized system.

Case Ascertainment

All Olmsted County residents at any Mayo Clinic facility who had a troponin T value ≥0.03 ng/mL (upper limit of normal for the assay defined by using the value at which the coefficient of variation for the assay is <10%14) were prospectively identified within 12 hours of the blood draw through the electronic files of the Department of Laboratory Medicine. Nurse coordinators sought written consent with no exclusion criterion from all patients (or the next of kin if the patient could not grant consent) to measure creatine kinase and its MB fraction in unused serum initially stored for additional clinical need. If not available, an additional sample was drawn, in connection with a clinically indicated draw whenever possible. Subjects underwent serial troponin measurements as part of clinical practice, which did not change during the study period. Troponin was measured at baseline and after symptom onset as recommended.

Biomarker Measurements

Troponin T and the MB fraction of creatine kinase were measured by using a sandwich electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics Corp; Indianapolis, Ind). Total creatine kinase testing was measured by using a coupled enzyme reaction method on the Modular Analytics System (Roche Diagnostics Corp). Biomarkers were measured in the laboratories of the Department of Laboratory Medicine and Pathology, which is certified by the Clinical Laboratory Improvement Act of 1988 and the College of American Pathologists, with all quality control procedures in place.

Attending physicians were not informed of the results of creatine kinase and its MB fraction, which are no longer consistently used in routine practice at the Mayo Clinic. This precluded the influence of these tests performed for research purposes on the care delivered.

Clinical and Electrocardiographic Data

Abstractors recorded information on subjects’ demographics and clinical characteristics, including conditions potentially interfering with biomarker levels. For creatine kinase and its MB fraction, these included skeletal muscle injury, trauma, or surgery, and, for troponin cardiac trauma (contusion, ablation, pacing, defibrillator firings, cardioversion, endomyocardial biopsy, cardiac surgery), heart failure, hypertension, hypotension, critical illness, drug toxicity, hypo-
thyroidism, inflammatory or infiltrative diseases, pulmonary embolism, sepsis, extensive burns, acute neurological disease, rhabdomyolysis, and transplant vasculopathy.17 Creatinine concentrations (in milligrams per deciliter), age, and weight in kilograms were used to calculate the creatinine clearance rate with the equation of Cockcroft and Gault [(140–age) × weight in kilograms]/[72 × serum creatinine concentration in milligrams per deciliter]. Three ECGs per episode (first after arrival, last before discharge, and first one after the third hospital day)19 were automatically coded using the Minnesota Code Modular ECG Analysis System.

Myocardial Infarction Validation Algorithms

The validation algorithm integrates cardiac pain, Minnesota code of the ECGs, and biomarker levels. This is the approach used by the World Health Organization21,22,23 and the Atherosclerosis Risk in Communities study.19 The reliability of these methods is excellent. Each case was classified simultaneously by using creatine kinase and its MB fraction and troponin.

For creatine kinase and its MB fraction, 2 approaches were used: first, relying on a combination of creatine kinase and the MB fraction,20 and second, relying solely on the MB fraction values as done in practice until the introduction of troponin. For troponin, the new guidelines were applied.1,20 Thus, all episodes were classified according to the presence or absence of a change (rise or fall) between any 2 measurements.

As the new definition does not define rise or fall, operational definitions are required for implementation. This requires defining changes that are detectable and thus outside the variability parameters of the assay. The variability of the troponin assays varies according to the concentration and is greater at lower concentrations.25 Thus, we selected the value of at least 0.05 ng/mL to define change, as it is greater than the level of imprecision of the assay at all concentrations.

Changes were classified as positive troponin in the absence of conditions interfering with biomarker values.25 As troponin can remain elevated for 2 weeks after events causing its rise, comorbid conditions were considered if they occurred within 2 weeks before the MI. Date (available in 100% of cases) and time (available in 97% of cases) were recorded for each condition. When present, the biomarker results were downgraded. For renal failure, the analysis based on dynamic changes in the troponin values did not downgrade troponin results.26 In secondary analyses, we examined the results while using single troponin values, which are relied on infrequently. Here, troponin results were downgraded if the renal function was severely reduced (creatinine clearance ≤29 mL/min).27 Biomarker results were integrated with the clinical findings (cardiac pain) and the Minnesota code of the ECG to classify each episode according to a computer algorithm as used in several community studies of MI.

Secondary analyses examined the increase in number of MIs that would be observed if criteria relied on a single troponin value rather than on dynamic changes.16 Herein, the episodes were considered to have positive troponin by using increasing multiples of the upper limit of normal for troponin T.

Follow-Up

Clinical and Hospital Dismissal Diagnoses

We used 2 approaches. First, we used physician-assigned diagnoses of MI as mentioned in the medical record to examine whether physicians would identify as MI cases that met the new definition prospectively applied.

Second, we examined the standardized dismissal diagnosis codes using standardized codes from the Ninth Revision of the International Classification of Diseases; we included the coronary disease codes (410: acute MI, 411: other acute and subacute forms of ischemic heart disease, 412: old MI, 413: angina pectoris, 414: other forms of ischemic heart disease) and the codes corresponding to all other diseases of the heart. These codes are assigned by trained coders using rules from the International Classification of Diseases.
Death
Follow-up was obtained by surveillance of medical records. The ascertainment of death incorporated death certificates filed in Olmsted County, autopsy reports, obituary notices, and electronic files of death certificates obtained from the State of Minnesota Department of Vital and Health Statistics.14

Statistical Analyses
Differences between cases according to the 3 sets of criteria (creatine kinase and its MB fraction, MB fraction of creatine kinase, and troponin) were tested with \( \chi^2 \) tests for categorical variables, \( t \) tests for continuous variables, and rank-sum tests for skewed continuous variables. Pairwise comparisons across the 3 groups were conducted with the Bonferroni correction. Logistic regression was used to examine the association between death within 30 days and a diagnosis of MI by each criteria used.

The institutional review board approved the study. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results
Between November 2002 and March 2005, 2305 consecutive episodes of care were identified in Olmsted County that met criteria for enrollment based on elevated troponin values. Among these, 1851 (80%; 95% confidence interval [CI], 79% to 82%) provided consent and had electrocardiographic and biomarker data obtained for analyses. Seventy-eight percent (95% CI, 76% to 80%) of subjects had 3 or more draws and 18% (95% CI, 17% to 20%) had 2 draws. Date and time were available on 100% of troponin draws, and the median (25th, 75th percentiles) time from the onset of symptoms or first ECG to the first, second, and third draw was 1.1 (0.4 to 4.5), 9.3 (7.9 to 13.5), and 20.8 (15.3 to 45.3) hours, respectively.

Classification According to the Primary Case Definition Relying on Dynamic Changes in the Value of Troponin
The patterns of dynamic troponin changes were as follows: 312 (17%; 95% CI, 15% to 19%) demonstrated a rise only, 226 (12%; 95% CI, 11% to 14%) fall only, 479 (26%; 95% CI, 24% to 28%) a rise and fall pattern, 766 (41%; 95% CI, 39% to 44%) exhibited no change, and 68 (4%; 95% CI, 3% to 5%) had only one single value measured. During the analysis of each biomarker response pattern, in 514 (28%; 95% CI, 26% to 30%) episodes the biomarker results were downgraded as the result of confounders interfering with troponin draws. In such episodes with 2 or more draws, the biomarker results were downgraded from abnormal to equivocal; in such episodes with 1 draw, the results were downgraded from equivocal to normal. The comorbid conditions among subjects in whom the biomarker results were downgraded are listed in Table 1. Renal failure was present in 31% (95% CI, 28% to 35%) of the cases in which no dynamic changes of troponin were observed. To classify each episode, the measurements of biomarkers were integrated with the clinical and electrocardiographic findings through the use of a computer algorithm. There were 606 episodes classified as MI by criteria based on creatine kinase and its MB fraction, the MB fraction alone, or troponin. Among these 606 episodes, 71% (95% CI, 67% to 75%) presented ischemic symptoms in addition to elevated biomarkers, whereas the remainder met the new definition of MI based on the association of elevated biomarkers, Q waves, ischemic electrocardiographic changes, or a coronary intervention.

Table 2 presents the classification according to biomarker used in the definitions. Through the use of the troponin-based criteria, 538 MIs were identified versus 327 MIs with the criteria based on creatine kinase and its MB fraction, representing a 74% (95% CI, 69% to 79%) increase in the number of MIs. As shown, 242 episodes were classified as MI using the troponin-based criteria that were not classified as such by the creatine kinase-based criteria. Of note, 31 episodes were classified as MI, using creatine kinase and its MB fraction, but did not meet the troponin-based criteria because the magnitude of the change failed to reach the predefined threshold of 0.05 in 13 episodes or because of the presence of confounders (heart failure in 10 episodes, other critical illnesses in 8).

When the MB fraction of creatine kinase was used alone without creatine kinase, 427 MIs were identified, resulting in a 41% (95% CI, 37% to 46%) increase in the number of MIs classified with the troponin-based criteria over those identified by the MB fraction of creatine kinase. When the analysis was restricted to the 614 patients presenting with cardiac pain, the number of MIs classified with troponin increased by 65% (95% CI, 59% to 71%) over the number classified using creatine kinase and its MB fraction and by 35% (95% CI, 30% to 41%) over the number classified using the MB fraction of creatine kinase.

**TABLE 1. Distribution of Coexisting Conditions That Led to Downgrading of Biomarker Measurements**

<table>
<thead>
<tr>
<th>Condition</th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>215 (42)</td>
<td>38–46</td>
</tr>
<tr>
<td>Hypotension</td>
<td>216 (42)</td>
<td>38–46</td>
</tr>
<tr>
<td>Critical illness (including sepsis)</td>
<td>136 (26)</td>
<td>23–31</td>
</tr>
<tr>
<td>Rhabdomyolysis, crush/contusion/bruising,</td>
<td>107 (21)</td>
<td>17–25</td>
</tr>
<tr>
<td>cardiopulmonary resuscitation/defibrillation,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cardiac surgery/ablation, endomyocardial biopsy,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>internal defibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td>60 (12)</td>
<td>9–15</td>
</tr>
<tr>
<td>Acute neurological disease</td>
<td>39 (8)</td>
<td>5–10</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>23 (4)</td>
<td>3–7</td>
</tr>
<tr>
<td>Hypothyroidism, drug toxicity, inflammatory or</td>
<td>12 (2)</td>
<td>1–4</td>
</tr>
<tr>
<td>infiltrative disease, transplant vasculopathy,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pericarditis</td>
<td></td>
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</tr>
</tbody>
</table>

Each episode could have more than one coexisting condition. These frequencies apply to 514 episodes in which biomarker values were downgraded.

**TABLE 2. Classification of Cases as Myocardial Infarctions by the Biomarker Used in the Algorithm Relying on Dynamic Changes in Troponin**

<table>
<thead>
<tr>
<th>Troponin T</th>
<th>MI</th>
<th>No MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine kinase and its MB fraction</td>
<td>296</td>
<td>31</td>
</tr>
<tr>
<td>No MI</td>
<td>242</td>
<td>1282</td>
</tr>
<tr>
<td></td>
<td>538</td>
<td>1313</td>
</tr>
</tbody>
</table>
Classification According to Definition Relying on Single Values of Troponin

In cases where only a single value of troponin was available, increasing multiples of the normal value of troponin were used as thresholds. The percent increase in the number of MIs at each threshold compared with the fixed number of MIs from the 2 sets of reference criteria (creatine kinase and the MB fraction combined and the MB fraction alone) was calculated. Compared with the criteria based on creatine kinase and the MB fraction, the percent increase in number of MIs meeting troponin-based criteria decreased with increasing troponin threshold. The percent increase ranged from 112% (95% CI, 109% to 116%) for troponin values exceeding the upper limit of normal of 0.03 ng/mL to 50% (95% CI, 45% to 56%) for 4 times the upper limit of normal (Figure 1).

When the threshold of twice the upper limit of normal was used for troponin, analogous to the threshold used for creatine kinase in the conventional criteria, the percent increase in the number of MIs was 79% (95% CI, 74% to 83%) when compared with reference criteria incorporating creatine kinase and the MB fraction and 45% (95% CI, 40% to 50%) when only the MB fraction was considered.

Changes in Case Mix

Compared with cases identified with the criteria based on creatine kinase and its MB fraction, those meeting only troponin-based criteria were older, more likely to be women, and in a lower Killip class (Table 3). They were also less likely to have cardiac pain.

The vast majority (94%; 95% CI, 90% to 97%) of MIs meeting only troponin-based criteria were non–ST-elevation MIs (among these, the frequency of ST depres-

**TABLE 3. Baseline Characteristics of Myocardial Infarctions by the Type of Biomarker Used in the Diagnostic Algorithm Relying on Dynamic Changes in Troponin**

<table>
<thead>
<tr>
<th></th>
<th>Troponin T</th>
<th>MB Fraction of Creatine Kinase</th>
<th>Creatine Kinase and Its MB Fraction</th>
<th>T vs MB</th>
<th>T vs CK/CKMB</th>
<th>MB vs CK/CKMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>72 ± 13</td>
<td>66 ± 16</td>
<td>68 ± 16</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>0.217</td>
</tr>
<tr>
<td>Women, % (95% CI)</td>
<td>52 (44–60)</td>
<td>46 (36–56)</td>
<td>43 (37–48)</td>
<td>0.343</td>
<td>0.042</td>
<td>0.525</td>
</tr>
<tr>
<td>Presence of cardiac pain, % (95% CI)</td>
<td>63 (56–70)</td>
<td>63 (53–72)</td>
<td>78 (73–82)</td>
<td>0.929</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Killip class 2, 3, or 4, % (95% CI)</td>
<td>23 (17–30)</td>
<td>26 (17–37)</td>
<td>36 (30–41)</td>
<td>0.587</td>
<td>0.004</td>
<td>0.092</td>
</tr>
<tr>
<td>Electrocardiographic characteristics</td>
<td></td>
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<tr>
<td>Anterior location of MI, % (95% CI)</td>
<td>36 (29–43)</td>
<td>22 (14–31)</td>
<td>49 (44–55)</td>
<td>0.014</td>
<td>0.003</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non–ST-segment–elevation MI, % (95% CI)</td>
<td>94 (90–97)</td>
<td>89 (82–94)</td>
<td>72 (67–77)</td>
<td>0.117</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of Q waves, % (95% CI)</td>
<td>44 (36–52)</td>
<td>41 (30–52)</td>
<td>69 (64–74)</td>
<td>0.604</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Biomarkers</td>
<td></td>
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<tr>
<td>Peak ratio of creatine kinase</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Tertile 1, % (95% CI)</td>
<td>56 (48–63)</td>
<td>14 (8–22)</td>
<td>21 (17–26)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tertile 2, % (95% CI)</td>
<td>26 (19–33)</td>
<td>62 (52–71)</td>
<td>23 (18–28)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tertile 3, % (95% CI)</td>
<td>3 (1–7)</td>
<td>19 (12–28)</td>
<td>48 (42–53)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.042</td>
</tr>
<tr>
<td>MB fraction of creatine kinase, median (25th–75th percentile)</td>
<td>5.1 (3.6–7.5)</td>
<td>18.5 (14.6–31.9)</td>
<td>33.0 (9.5–121.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.042</td>
</tr>
<tr>
<td>Multivessel disease at angiography, % (95% CI)*</td>
<td>65 (53–75)</td>
<td>55 (42–68)</td>
<td>68 (61–74)</td>
<td>0.234</td>
<td>0.608</td>
<td>0.061</td>
</tr>
</tbody>
</table>

Distributions obtained from 177 MIs meeting only troponin T–based criteria, 102 MIs meeting the criteria for the MB fraction of creatine kinase, and 327 MIs meeting the criteria for creatine kinase and its MB fraction. Peak ratio of creatine kinase is the ratio of the value measured divided by the upper limit of normal (176 U/L for women, 336 U/L for men).

*Proportion of patients who underwent angiography within 30 days was 53% (95% CI, 44–61) among cases meeting only troponin T–based criteria, 67% (95% CI, 57–77) among cases defined by the MB fraction of the creatine kinase and 69% (95% CI, 63–74) among cases defined by creatine kinase.
tion of at least 0.5 mm was similar across the groups). As expected, the peak ratio of creatine kinase and its MB fraction levels was greater among MIs meeting creatine kinase–based criteria than among those meeting only troponin-based criteria.

The chief difference between cases meeting criteria based on the MB fraction of the creatine kinase and those meeting only troponin-based criteria was older age for cases identified with troponin only.

When cases meeting only troponin-based criteria were compared with those meeting the other criteria, the differences in case mix as assessed by cardiac pain, Killip class, and ECG findings were independent of age and sex.

**Dismissal Diagnoses and Death**

In the medical record, a diagnosis of MI was mentioned in 42% (95% CI, 34% to 49%) of the cases meeting only troponin-based criteria, markedly lower than the 74% (95% CI, 69% to 78%) among cases meeting the creatine kinase–based criteria (P=0.001). The corresponding codes used for the dismissal diagnosis reflect this difference as presented in Figure 2, which presents the distribution of the codes according to the type of biomarker used in the classification algorithm. The coding practices differed according to the type of criteria (P=0.001). This is largely related to the fact that MIs meeting only troponin-based criteria are more likely to be coded as unstable angina (code 411) or other diseases of the heart (chiefly hypertensive heart disease) than those meeting the creatine kinase–based criteria.

Thirty days after presentation, 5% (95% CI, 2% to 9%) of the cases meeting only troponin-based criteria had died, which is less than half the fatality rate of MIs meeting the criteria for creatine kinase and its MB fraction (11%; 95% CI, 8% to 15%). After adjustment for age and sex, MIs meeting only troponin-based criteria had a 65% reduction in the relative odds of death at 30 days compared with cases meeting creatine kinase criteria (odds ratio, 0.35; 95% CI, 0.16 to 0.76). No difference in 30-day case-fatality rate was noted between MIs meeting the criteria for creatine kinase and its MB fraction versus the MB fraction alone.

**Discussion**

This study prospectively evaluated the new definition that relies on troponin to diagnose MI in the community. It has resulted in a large increase in the number of MIs. The magnitude of this increase depends on the approach used to incorporate troponin in the diagnostic algorithms and the reference criteria used. When dynamic changes in troponin values were required, the number of MIs increased by 74% compared with criteria using creatine kinase and the MB fraction and by 41% compared with criteria relying only on the MB fraction. When single values of troponin were used, varying degrees of increase in the number of MIs were observed, ranging from 112% to 24%. The new definition augments the population of MIs with cases that differ from those identified previously, in particular with regard to case fatality. The clinical acceptance of the new definition, however, is incomplete, as less than half of the cases identified with the new criteria are documented as MI in the medical record, and a similar proportion are coded as such on dismissal.

**Increase in the Number of Myocardial Infarctions**

One of the concerns generated by the new definition was that the incidence of MI would increase as a result of the preferential reliance on troponin.5,9,29 Studies that addressed this question used mostly convenience samples from case series and often single values of troponin.6–8,10,13 Although all documented increases in the number of MIs, the estimates of the magnitude of the increase varied from 23%.10,11 to 195%.12 The interpretation of these data is further complicated by the fact that the type of biomarker (troponin T versus I), the assays, and cut-points differed across studies. Moreover, the percent increase in the number of MIs is also dependent on the reference criteria used, which also varied across studies. These important methodological limitations15,30,31 hinder the inference from these data. Finally, all studies used single values of troponin such that the increment in the number of MIs related to rise and fall in troponin values, the recommended approach, remained to be documented.

The present study provides needed prospective information and demonstrates that the prospective and rigorous application of the new criteria relying on dynamic changes...
in troponin values results in a 74% increase in the number of MIs compared with the number of MIs that would have been detected using the widely accepted criteria from the World Health Organization and Atherosclerosis Risk in Communities study. The use of single troponin values provides different results than the criteria relying on rise and fall. The increments in the number of MIs, importantly, are always large, even with very conservative cut-points, and are likely to increase as limits of normal of the troponin assays are lowered.

Changes in Case Mix
Another concern raised by the redefinition was that the characteristics of MIs would change. Prior studies that examined the impact of the new criteria consisted chiefly of smaller case series, retrospective in design, such that the resulting changes in case mix remained incompletely documented. The present study conveys important data in this regard by indicating that the new criteria identify subjects who are older and present infrequently with ST elevation. The prognosis of MIs identified only by troponin-based criteria is not benign, as 5% of the patients meeting only troponin-based criteria died within 1 month of the event, a mortality rate that is higher than previously reported rates of 2% to 3% at 30 days in clinical trials. In the FINAMI study, MIs defined only by troponin-based criteria had worse outcomes than those meeting creatine kinase–based criteria. In our study, however, the short-term mortality of cases identified by troponin alone was markedly lower than that of cases defined by creatine kinase and its MB fraction. These discrepancies probably stem from patient selection factors, as the FINAMI study selected patients in whom physicians ordered both troponin and enzymatic markers, whereas the present study measured enzymatic markers irrespective of physician preference. Altogether, as documented herein, the new definition results in marked changes in the presentation and outcome of a major indicator of the burden of coronary disease. These changes are relevant to clinical care, return to work, rehabilitation, insurability, and health care costs.

Implications
The introduction of troponin will lead to increases in the incidence of MI as measured by dismissal diagnoses if clinicians readily adopt the new marker for diagnostic purposes and if coding practices follow this pattern. The rapid and widespread adoption of troponin in clinical practice is undeniable. However, data on subsequent clinical diagnosis and coding practices are scarce. In the Atherosclerosis Risk in Communities study, episodes meeting standardized criteria for MI are less likely to be coded as code 410 in more recent years, characterized by increasing use of troponin. This suggests that coding practices did not change in a way commensurate with the increasing use of troponin. The present prospective data add knowledge to these retrospective findings by demonstrating that a dismissal diagnosis of MI is assigned to less than half of the cases identified by troponin. Thus, relying on dismissal codes to characterize the occurrence of MI across time and populations will underestimate the burden of disease as now defined. This is important as surveillance systems rely on dismissal codes. Our results, which could only be obtained via the prospective approach presented herein, thus have relevance to the understanding of the use of national statistics pertaining to MIs.

This calls attention to the fact that in retrospective surveillance studies, broader sets of codes validated on a study-by-study basis may be needed to accurately enumerate MIs. As coding practices will likely evolve over time, it will be crucial to repeat the validation of the codes during these times of changing diagnostic criteria.

Altogether, our study provides important quantitative data in support of the hypothesis that, as a result of the redefinition, “the number of cases of MI will rise but case fatality will fall.” Indeed, one crucial consequence of the biomarker change will be an increase in the prevalence of MI and thus of coronary disease. Furthermore, the present findings underscore that relying on single values of troponin will give different results than the approach that requires dynamic changes in troponin values.

Finally, our results document that the impact of the redefinition of MI on population indicators will be conditional on physician acceptance, currently incomplete and probably evolving.

Strengths and Limitations
The internal validity of the present data is strong, as our ascertainment identified consecutive patients who were then evaluated according to rigorous validation criteria. Moreover, the participation rate was 80%, despite the acuteness of MI. This is similar to the median of participation rates in studies that, like ours, reported participation rates. Participants were younger with less comorbidity than nonparticipants. The sex distribution and clinical and MI characteristics were similar between participants and nonparticipants, as was adjusted survival. Thus, participation does not affect the applicability of our results.

Clinicians checked the creatine kinase and MB fraction, in addition to troponin in 29% of the subjects, and the results describing the clinical acceptance of troponin may not be fully applicable to other settings. However, this did not affect the classification of the cases, because all were classified by using epidemiologic criteria independent of clinical practice. Our case-finding approach identified patients who had at least 1 troponin value $\geq$0.03 ng/mL. To ensure that this did not lead to omitting clinical cases of MI, we retrieved information on subjects who had troponin T measured during the study period and reviewed the records of cases that received a diagnosis code of MI. None met validation criteria. Thus, our approach resulted in the complete ascertainment of all MIs, which documents the generalizability of our results. The definitions used for coexisting conditions that can affect the accuracy of troponin were based on clinical criteria. Although not fully standardized, they are most consistent with clinical approaches to the use of troponin.

Although the absolute values would differ, examining the impact of testing with troponin I would require a
similar approach, and our study outlines the operational framework to do so.

The ability to prospectively examine the impact of the new definition using standardized criteria and consistent assays and to evaluate its clinical acceptance within the same population is a unique strength of the present study. This addresses the stated need for “sentinel centers” deemed necessary to understand the implications of the new definition.1

The clinical impact of the redefinition of MI cannot be assessed without the use of standardized, highly reliable criteria.19 Its public health impact cannot be understood without simultaneously examining, in the same population, the corresponding clinical diagnoses and dismissal coding practices.

Conclusions

The prospective evaluation of the new MI definition in the community indicates that it leads to a large increase in the number of MIs and augments the population of persons with MI with cases defined only by troponin-based criteria, which differ from cases identified with previous criteria. The acceptance of the new criteria is incomplete. Thus, reliance on selected dismissal diagnoses to measure MI rates and outcomes may underestimate the burden of disease as presently defined, underscoring the importance of prospective approaches to accurately estimate this burden and of continued surveillance.

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References


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