Background—In 2000, the definition of myocardial infarction (MI) changed to rely on troponin rather than creatine kinase (CK) and its MB fraction (CK-MB). The implications of this change on trends in MI incidence and outcome are not defined.

Methods and Results—This was a community study of 2816 patients hospitalized with incident MI from 1987 to 2006 in Olmsted County, Minnesota, with prospective measurements of troponin and CK-MB from August 2000 forward. Outcomes were MI incidence, severity, and survival. After troponin was introduced, 278 (25%) of 1127 incident MIs met only troponin-based criteria. When cases meeting only troponin criteria were included, incidence did not change between 1987 and 2006. When restricted to cases defined by CK/CK-MB, the incidence of MI declined by 20%. The incidence of non–ST-segment elevation MI increased markedly by relying on troponin, whereas that of ST-segment elevation MI declined regardless of troponin. The age- and sex-adjusted hazard ratio of death within 30 days for an infarction occurring in 2006 (compared with 1987) was 0.44 (95% confidence interval, 0.30 to 0.64). Among 30-day survivors, survival did not improve, but causes of death shifted from cardiovascular to noncardiovascular (P=0.001). Trends in long-term survival among 30-day survivors were similar regardless of troponin.

Conclusions—Over the last 2 decades, a substantial change in the epidemiology of MI occurred that was only partially mediated by the introduction of troponin. Non–ST-segment elevation MIs now constitute the majority of MIs. Although the 30-day case fatality improved markedly, long-term survival did not change, and the cause of death shifted from cardiovascular to noncardiovascular.  

Key Words: biomarkers ■ incidence ■ mortality ■ myocardial infarction

Evaluating temporal trends in the incidence and outcome of myocardial infarction (MI) is essential to monitor the burden of cardiovascular disease, the most common cause of death.1 However, the characterization of MI trends is challenging because the diagnosis of MI is evolving. In 2000, the European Society of Cardiology and the American College of Cardiology recommended a new definition2 that combines ischemic symptoms, ECG changes, and elevation of biochemical markers of myocardial necrosis, preferably troponins in part because of their prognostic value.3,4 This change, which has become operational as the universal definition,5 is expected to be evident in several ways. Compared with creatine kinase (CK) and its MB fraction (CK-MB), markers previously used to detect myocardial injury, troponins are more sensitive, enabling the detection of smaller amounts of necrosis. Thus, troponins were expected to increase the incidence of infarctions and to shift the clinical spectrum of the disease toward less severe forms. Because of the far-reaching clinical and public health implications of these changes and the necessity to rigorously document their impact, the European Society of Cardiology and the American College of Cardiology recommended that the previous definition “be retained” by sentinel centers.6 The importance of this recommendation was further supported by the considerable controversy7 that the new criteria generated. We responded to this stated need in our ongoing coronary disease community surveillance study in Olmsted County, Minnesota, by prospectively applying the CK-MB– and troponin-based criteria simultaneously to all patients with acute coronary syndrome since 2000. Shortly after the implementation of the new criteria, we detected a large increase in the number of infarctions related to the identification of cases by troponin-based criteria. The impact, however, on incidence trends remained to be defined.8 Hence, we sought to docu-
tion the impact of the new criteria on the incidence and outcome of MI and to test the following hypotheses: (1) There has been no overall decline in the incidence of MI over time, but the trends differed according to whether or not cases meeting only troponin-based criteria were considered; and (2) survival after incident MI improved over time, but the improvement differed according to whether or not cases meeting only troponin-based criteria were included.

Editorial see p 666
Clinical Perspective on p 869

Methods

Study Setting
In Olmsted County, a few providers (chiefly Mayo Clinic and Olmsted Medical Center) deliver nearly all medical care to county residents. With the exception of a higher proportion employed in healthcare, the characteristics of this population are similar to those of US whites. Each provider uses a medical record that captures information for all encounters and can be retrieved because the Mayo Clinic might invalidate biomarker values were recorded. For CK and CK-MB, these included skeletal muscle injury, trauma, or surgery; for troponin, these included cardiac trauma (contusion, ablation, pacing, defibrillator firings, cardioversion, endomyocardial biopsy, cardiac surgery), heart failure, renal failure, hypertension, hypotension, critical illness, drug toxicity, hypothyroidism, inflammatory or infiltrative diseases, pulmonary embolism, sepsis, extensive burns, acute neurological disease, and rhabdomyolysis. Troponin T, CK, and CK-MB were measured with a sandwich electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics Corp, Indianapolis, Ind) 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 robust quality control in place. Three ECGs per episode were coded with the use of the Minnesota Code Modular ECG Analysis System.

Table 1. Characteristics of MIs

<table>
<thead>
<tr>
<th>Age, mean±SD, y</th>
<th>MI by Troponin T Only</th>
<th>MI by CK-MB</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=2816)</td>
<td>(n=278*)</td>
<td>(n=849*)</td>
</tr>
<tr>
<td>Overall</td>
<td>68.3±14.9</td>
<td>67.9±15.1</td>
</tr>
<tr>
<td>Women, %</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td>Presence of cardiac pain, %</td>
<td>88</td>
<td>74</td>
</tr>
<tr>
<td>Comorbidity score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 points, %</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>1–2 points, %</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>≥3 points, %</td>
<td>27</td>
<td>39</td>
</tr>
<tr>
<td>MI severity indicators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Killip class 2, 3, or 4, %</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>NSTE MI, %</td>
<td>69</td>
<td>93</td>
</tr>
<tr>
<td>Presence of Q waves, %</td>
<td>54</td>
<td>36</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin at dismissal, %</td>
<td>83</td>
<td>82</td>
</tr>
<tr>
<td>β-blocker at dismissal, %</td>
<td>72</td>
<td>85</td>
</tr>
<tr>
<td>Statins at dismissal, %</td>
<td>41</td>
<td>64</td>
</tr>
</tbody>
</table>

†From weighted logistic regression comparing MIs identified by troponin-based criteria only vs CK-MB–based criteria.

Follow-Up
Follow-up for death relied on 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. Causes of death were classified as cardiovascular, cancer, or other on the basis of codes from the International Classification of Disease, Ninth Revision,17 and the American Heart Association categories were used for cardiovascular deaths.1

Statistical Analysis
Baseline characteristics are presented as frequencies for categorical variables and mean (SD) for continuous variables. Baseline characteristics between groups were compared by logistic regression. Differences in infarction severity across time were tested by logistic regression for binary severity indicators and linear regression for the natural log of peak CK-MB ratio, defined as the ratio of the measured value divided by the upper limit of normal, and age. Age-, sex-, and year-specific incidence rates were calculated. The counts of all definite and probable incident infarctions were used as the numerators, and the denominators were the Olmsted County population as determined by census data for the years 1980, 1990, and 2000 with linear interpolation for the intercensus years and extrapolation after 2000. The rates were directly standardized to the age distribution of the 2000 US population. Standard errors and 95% confidence intervals (CIs) were calculated on the basis of the Poisson error distribution. Temporal trends in incidence were assessed with Poisson regression. Specific counts for each calendar year, age, and sex were used as the unit of observation. A linear and a quadratic component were tested for year and age. All 2-way interactions were tested. The results of the final model, assuming a linear change over time, were summarized by presenting the relative risk of incident infarction within 30 days and death among 30-day survivors for different biomarkers and years. The analyses were performed with the use of SAS version 8.2 (SAS Institute Inc, Cary, NC) and Splus version 8 (TIBCO Software Inc, Palo Alto, Calif). All aspects of the study were approved by the appropriate institutional review boards.

| Table 2. Trends in Characteristics of MI From 1987 to 2006 in Olmsted County, Minnesota |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Age, mean (SD), y                             | 68 (15)                                      | 68 (14)                                      | 69 (16)                                      | 68 (15)                                      | 0.405                                        |
| Women, %                                      | 46                                           | 44                                           | 44                                           | 41                                           | 0.032                                        |
| MI severity indicators                        |                                              |                                              |                                              |                                              |                                              |
| Killip class 2, 3, or 4, %                    | 35                                           | 33                                           | 29                                           | 28                                           | 0.002                                        |
| ST-segment elevation, %                       | 38                                           | 38                                           | 30                                           | 22                                           | <0.001                                       |
| Q waves, %                                    | 45                                           | 62                                           | 61                                           | 55                                           | <0.001†                                       |
| Peak CK-MB ratio, median (25th–75th percentile) | 6.8 (2.6–14.4)                                | 10.2 (3.5–22.6)                              | 6.8 (2.6–22.7)                               | 3.2 (1.3–10.8)                               | <0.001†                                       |
| Treatment                                     |                                              |                                              |                                              |                                              |                                              |
| Reperfusion/revascularization during hospitalization, % | 55                                           | 60                                           | 61                                           | 60                                           | 0.059                                        |
| Aspirin at dismissal, %                       | 71                                           | 82                                           | 87                                           | 89                                           | <0.001                                       |
| β-blockers at dismissal, %                    | 47                                           | 65                                           | 79                                           | 87                                           | <0.001                                       |
| Statins at dismissal, %                       | 1                                            | 10                                           | 52                                           | 78                                           | <0.001                                       |

*From weighted logistic regression for dichotomous variables and weighted linear regression for continuous variables using continuous year.
†P value for year.

Results
The MI Incidence Cohort
From 1987 to 2006, an estimated total of 2816 incident infarctions occurred in Olmsted County. Medical history available before the event covered a mean (SD) time of 39 (20) years. The mean (SD) age at index was 68 (15) years. Of the 2816 incident events, 1222 (43%) occurred among women (Table 1) and 1107 (39%) among persons aged ≥75 years. The distribution of age at index did not change over time, whereas the percentage of MIs experienced by women decreased over time (Table 2).

Of all incident events, 1689 occurred before the introduction of troponin in August 2000 and 1127 thereafter. Among these, 278 (25%) did not meet infarction criteria as defined by CK-MB and met only troponin-based criteria. Compared with cases identified by CK-MB–based criteria, those meeting only troponin-based criteria were older, were more likely to be women, and had more comorbidities (Table 1). They were less likely to experience pain and to present with Q waves and were in a lower Killip class. Most infarctions meeting only troponin-based criteria were non–ST-segment elevation MIs (NSTEMIs). These differences were independent of age and sex. With regard to treatment, MIs meeting only troponin-based criteria were less likely to receive evidence-based therapies. Among all MIs, the use of reperfusion/revascularization during hospitalization increased over time, without reaching statistical significance. The use of aspirin, β-blockers, and statins at dismissal increased over time (Table 2).

Incidence of Hospitalized MI
Temporal trends differed according to the type of biomarker used for diagnosis (Figure 1). When all infarctions were included irrespective of the biomarker used for diagnosis, the incidence rates did not change between 1987 and 2006. The overall age- and sex-adjusted incidence rate of hospitalized infarctions was 186 per 100 000 (95% CI, 150 to 221) in 1987 and 180 per 100 000 (95% CI, 151 to 209) in 2006 (P=0.171
for the year effect). When only cases meeting CK/CK-MB criteria were considered, a significant temporal decline in the incidence of MI was detected ($P=0.020$) as the age- and sex-adjusted incidence rate of hospitalized infarctions declined to 141 per 100,000 (95% CI, 115 to 167) in 2006. This represents a 1.1% per year decline in the incidence of infarctions meeting CK/CK-MB criteria. Thus, if a linear decline from 1987 to 2006 is assumed, the age- and sex-adjusted relative risk of experiencing an MI as defined by CK/CK-MB in 2006 compared with 1987 was 0.80 (95% CI, 0.67 to 0.98), indicating a 20% decline in incidence rates over the last 2 decades.

Although the incidence of MI was higher in men (Figure 1) and in older persons (data not shown), none of the aforementioned trends differed by age or sex. The incidence trends diverged markedly according to the presence or absence of ST elevation (Figure 2). The incidence rates of ST-segment elevation MI (STEMI) declined by 41% over the time period irrespective of troponin (relative risk, 0.59; 95% CI, 0.47 to 0.76) for STEMI including troponin-only cases versus relative risk, 0.56; 95% CI, 0.44 to 0.71 for STEMI excluding troponin-only cases). The incidence rates of NSTEMI increased by 49% over time when troponin-only cases were included (relative risk, 1.49; 95% CI, 1.23 to 1.81). Temporal trends in NSTEMI did not change when troponin-only cases were excluded.

The incidence rate analyses were repeated with the use of a minimum difference of 0.03 ng/mL between any 2 troponin measurements to define a change in values. Doing so increased the estimated number of incident infarctions by 1.2% without affecting temporal trends, which attests to their robustness.

**MI Severity**

When all infarctions irrespective of the biomarker used for diagnosis were analyzed, most patients were in Killip class 1, but the proportion of those in Killip class 2, 3, or 4 declined over time, as did the proportion of patients with ST-segment elevation (Table 2). ECG Q waves were observed in 54% of cases, and the frequency increased during the first half of the period, followed by a decrease thereafter. The CK-MB ratio showed a similar pattern.

The trends in hemodynamic presentation, ECG findings, and CK-MB ratio were similar when cases meeting only troponin criteria were excluded. The median time between symptom onset and first ECG (ascertained in 97% of cases) was 1.7 (25th to 75th percentile, 0.8 to 4.4) hours and did not change over time.

**Fatality**

Among all incident infarctions, the 30-day case fatality rate (Figure 3) was higher in women and in older persons and decreased markedly over time. Indeed, after adjustment for age and sex, the overall 30-day case fatality rate declined by 4.3% per year ($P=0.001$). Thus, compared with the reference year of 1987, for an incident infarction occurring in 2006, the age- and sex-adjusted hazard ratio of death within 30 days of the event was 0.44 (95% CI, 0.30 to 0.64; $P<0.001$), indicating a 56% decline in 30-day case fatality rate over the last 2 decades. The temporal trends in 30-day case fatality did not differ by age or sex (year×age interaction, $P=0.630$;
year×sex interaction, $P=0.884$) and were similar when cases meeting only troponin-based criteria were excluded.

Among all incident infarctions, the mean (SD) follow-up was 6.0 (5.3) years. Among persons who survived for 30 days after the incident infarction, survival did not improve further over time. Indeed, compared with 30-day survivors of an infarction occurring in 1987, the age- and sex-adjusted hazard ratio of death among 30-day survivors of an infarction occurring in 2006 was 1.04 (95% CI, 0.81 to 1.35; $P=0.717$). Further adjustment for cardiovascular risk factors, comorbidity, and Killip class yielded similar results. The temporal trends in long-term survival among 30-day survivors did not differ by age or sex (year×age interaction, $P=0.168$; year×sex interaction, $P=0.798$) and were similar when cases meeting only troponin-based criteria were excluded.

The distribution of the causes of death after hospitalized MI changed over time ($P=0.001$). During the first year quartile (1987–1991), 62% of deaths were ascribed to cardiovascular causes compared with 50% during the most recent year quartile (2002–2006).

When cardiovascular death was examined among persons who survived at least 30 days, survival free of cardiovascular death improved over time. Indeed, compared with 30-day survivors of an infarction occurring in 1987, the age- and sex-adjusted hazard ratio of cardiovascular death among 30-day survivors of an infarction occurring in 2006 was 0.54 (95% CI, 0.38 to 0.75; $P=0.001$). These findings were similar when cases meeting only troponin criteria were excluded.

The 5-year Kaplan-Meier survival estimate (95% CI) after incident infarction was 67% (65% to 69%), lower than that expected among the Minnesota population of 79% ($P<0.001$ for comparison between observed and expected survival). When the analysis was stratified by year groups, similar estimates of observed and expected survival were obtained over time.

**Discussion**

These prospective data indicate that the epidemiology of MI changed markedly over the past 2 decades, a change only partly related to the introduction of troponin. Indeed, if troponin had not been adopted as part of the universal definition of MI, a 20% decline in incidence of infarctions (defined by CK/CK-MB) would have been observed over the past 2 decades. Although the substantial increase in NSTEMI is mediated by the preferential reliance on troponin, the present data extend the report of the Framingham Heart Study on an earlier time period (1960–1999) in which the rates of MI declined over time. The marked reduction in the proportion of infarctions in the community that present with ST-segment elevation is particularly noteworthy because it is consistent across studies and sustained over time.25,26 Importantly, the beginning of this trend, the magnitude of which is striking, predates the introduction of troponin. Although explanations can only be speculative, one hypothesis is that the increasing use of medications such as aspirin and β-blockers before admission may reduce the size and severity of infarctions.27 The new criteria identify older subjects who seldom present with ST-segment elevation and now constitute the vast majority of events. This underscores the importance of optimizing the care of NSTEMIs, which are less likely to receive evidence-based care than STEMI.28

Population studies all documented a favorable decline in early mortality among younger individuals contrasting with a persistently high fatality rate among the elderly over a period of time ranging from 1975 to 1995.15,23,29,30 Importantly, the
mortality of infarction in the community remained high and was consistently higher than that reported in clinical trials, reflecting their inherent selection processes. Although only clinical trials can test the efficacy of a novel treatment, reports from community surveillance provide important complementary insights into the effectiveness of treatments once implemented. The present study demonstrates that the marked improvement in early fatalities after MI persisted over time and that notable survival gains were realized in women and the elderly, among whom disparities had been detected previously. Conversely, no further improvement in long-term survival was noted concomitantly with a shift in the assignment of death from cardiovascular to noncardiovascular causes.

Strengths, Limitations, and Implications

The prospective examination of the impact of the new definition using standardized criteria and the simultaneous measurement of both sets of biomarkers independent of clinical practice are unique strengths of this study, which responds to the call for “sentinel centers” deemed necessary to understand the implications of the new definition. The internal validity of the present data is robust because our ascertainment identified consecutive cases validated rigorously. Given the racial and ethnic composition of Olmsted County, these data need replication in other populations.

Our goal was to measure trends in hospitalized incident infarctions while focusing on the impact of biomarkers. We did not capture silent infarctions or sudden deaths. Because biomarkers would not have been measured in either entity, this does not affect the validity of our results. We previously reported on temporal trends in sudden death in Olmsted County. These studies indicated that out-of-hospital deaths related to coronary and cardiovascular disease declined by 1.8% per year since 1979. These findings are comparable to the 1.1% per year decline in the incidence of infarctions meeting CK/CK-MB criteria reported herein.

The present study has important implications to understanding trends in MI incidence in the face of changing definitions. We demonstrated a profound change in the epidemiology of MI only partially mediated by the introduction of a new biomarker.

Indeed, although the introduction of troponin masked a decrease in the incidence of MI that would have been observed if biomarkers had not changed, the declining incidence of STEMI is not related to the introduction of troponin. Moreover, the severity of infarctions declined, and the outcomes continued to improve over time, irrespective of the change in biomarkers. Importantly, the improvement in survival was detectable for early case fatality rate and long-term cardiovascular deaths but not for long-term survival among 30-day survivors.

Conclusion

This prospective community study delineates a substantial change in the epidemiology of MI only partially mediated by the introduction of troponin. NSTEMIs now constitute the vast majority of MIs in the community. Although the 30-day case fatality of infarctions improved markedly, long-term survival among 30-day survivors did not improve, and the cause of death shifted from cardiovascular to noncardiovascular. These data underscore the importance of community surveillance to understanding the burden of coronary disease in populations.

Sources of Funding

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Disclosures

Dr. Jaffe consults for the following companies: Beckman, Siemens, Critical Diagnostics, Ortho Clinical Diagnostics, Singula, Nanosphere, Novartis, Inverness Medical, and GSK. The remaining authors report no conflicts.

References


CLINICAL PERSPECTIVE

In 2000, the definition of myocardial infarction (MI) changed to rely on troponin rather than creatine kinase (CK) and its MB fraction (CK-MB). The implications of this change on trends in MI incidence and outcome are not defined. We studied 2816 community patients hospitalized with a first MI from 1987 to 2006 with prospective measurements of troponin and CK-MB from August 2000 forward. Outcomes were MI incidence, severity, and survival. After troponin was introduced, 278 (25%) of 1127 incident MIs met only troponin-based criteria. When cases meeting only troponin criteria were included, incidence did not change between 1987 and 2006. When restricted to cases defined by CK/CK-MB, the incidence of MI declined by 20%. The incidence of non–ST-segment elevation MI increased markedly by relying on troponin, whereas that of ST-segment elevation MI declined regardless of troponin. The age- and sex-adjusted hazard ratio of death within 30 days for an infarction occurring in 2006 (compared with 1987) was 0.44 (95% confidence interval, 0.30 to 0.64). Among 30-day survivors, survival did not improve, but causes of death shifted from cardiovascular to noncardiovascular.

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Trends in Incidence, Severity, and Outcome of Hospitalized Myocardial Infarction
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