A new definition for myocardial infarction: what difference does it make?

Veikko Salomaa1*, Heli Koukkunen2, Matti Ketonen3, Pirjo Immonen-Räihä4, Päivi Kärjä-Koskenkari5, Juha Mustonen3, Seppo Lehto2, Jorma Torppa1, Aapo Lehtonen6, Jaakko Tuomilehto1, Y. Antero Kesäniemi7, and Kalevi Pyörälä2 for the FINAMI Study Group

1Department of Epidemiology, KTL-National Public Health Institute, Mannerheimintie 166, FI-00300 Helsinki, Finland; 2Kuopio University Hospital, Kuopio, Finland; 3Central Hospital of North Karelia, Joensuu, Finland; 4Turku University Hospital, Turku, Finland; 5Oulu City Hospital, Oulu, Finland; 6Turku City Hospital, Turku, Finland; and 7Oulu University Hospital and Biocenter Oulu, Oulu, Finland

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Introduction

For the comparability of different clinical trials and community surveillance projects, it is important that the definition for myocardial infarction (MI) events is as similar and as widely applicable as possible. Besides scientific research, the diagnosis of MI has obvious clinical, social, and legal implications. Therefore, it is essential that this diagnosis is used in a consistent manner because it has important implications in terms of prognosis, need of treatment, and secondary prevention.

The diagnosis of MI events is usually based on symptoms, electrocardiogram (ECG) changes, elevation of biomarkers, and, in fatal cases, autopsy findings. Since the early 1980s, the WHO MONICA definition1,2 or other definitions close to it3 have been widely used for standardized diagnostic classification of suspected cases of MI or coronary heart disease (CHD) death. The situation changed, however, with the widespread adoption of new, more sensitive, and specific biomarkers of myocardial injury, first creatine kinase MB mass (CK-MBm) and then even more with the introduction of cardiac troponins (troponin T and troponin I). There is evidence that the attack rate estimates of MI increase with troponins and the case fatality estimates also change.4–6 As a response to the changed situation, the Joint European Society of Cardiology/American College of Cardiology Committee (ESC/ACC) created a new consensus document redefining MI in year 2000.7

The ESC/ACC redefinition was criticized, however, for excessive reliance on troponins, insufficient attention to the ECG changes, and the lack of coverage of sudden, out-of-hospital CHD deaths.8,9 A new expert team was assembled to fix these problems and the new case definitions were published as an AHA Scientific Statement in 2003.10 At the moment, the 2003 definition has not been applied in any study or validated in a population-based setting. Furthermore, it is not known how the widespread adoption of troponins affects the trend estimates of MI events when used together with the 2003 definition. We have analysed these questions for hospitalized events in a large population-based MI register study. More specifically, the purpose of the present study was to compare the numbers of MI events obtained using troponins and the

*Corresponding author. Tel: +358 9 4744 8620; fax: +358 9 4744 8338. E-mail address: veikko.salomaa@ktl.fi

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2003 definition with the numbers obtained using the earlier definitions (WHO MONICA definition and ESC/ACC definition) or routine clinical diagnosis. A further aim was to compare the clinical characteristics and prognosis of the ‘additional’ MI patients identified by the new definition and troponins with those identified by both the WHO MONICA definition and the new definition.

Methods

Data originate from the FINAMI Study, which is a population-based MI register operating in four geographical areas of Finland. Investigators and institutes participating in the FINAMI Study are listed in the appendix. The combined population aged ≥25 of the FINAMI areas is ≈313,000. The study aimed to record every clinically symptomatic MI and CHD death occurring in this population during the 10-year period 1993–2002. The main sources of information were hospital admission lists, other hospital documents, death certificates, autopsy documents, and medicolegal documents. Trained nurses, supervised by register physicians, collected data on symptoms, biomarkers, and ECG findings on patients suspected of having MI using standardized data collection forms and laptop computers.

Symptoms were coded as ‘typical’, ‘atypical’, ‘other’, ‘no symptoms’, ‘insufficient description’, ‘non-cardiac or cardiac non-atherosclerotic’, or ‘no information’ using principles originating from the WHO MONICA Project. Of the biomarkers, the highest value of either troponin T or troponin I was recorded and classified as diagnostic or normal, on the basis of the limit given by the laboratory in question. If the troponin value was considered non-relevant, e.g. because of the timing of the sampling or because of renal insufficiency, it was taken as missing. Of the enzymatic markers of myocardial injury, including CK-MBm, the highest values were also recorded and coded according to the principles of the WHO MONICA Project. Thus, the value was considered ‘definite’ if it exceeded at least twice the upper reference limit of the laboratory. If the value exceeded the upper reference limit, but less than twice, it was considered equivocal. The other alternatives were ‘normal’, ‘unspecific’, or ‘missing’. The biomarkers used in each case were determined according to the usual practices of the hospital in question. The ECGs were Minnesota coded and classified according to the principles of the WHO MONICA Project as ‘definite’, ‘probable’, ‘ischaemic non-evolving’, ‘other’, ‘uncodable’, or ‘ECG absent’.

The local registration centres periodically sent their data to the coordinating centre at the National Public Health Institute, where a series of logical checks were run. Annually, the data were cross-checked for completeness with the National Hospital Discharge Register and the National Causes-of-Death Register. These countrywide registers cover every hospitalization in Finland and all deaths of permanent residents of Finland. Cases identified through cross-checking were sent back to the local registration teams, which evaluated them according to the study protocol for possible inclusion in the register. The National Causes of Death Register was also used to assess the survival status of the patients 1 year after the event.

For these analyses, we considered all suspected MI events during 1997–2002, where the patient was hospitalized alive and stayed alive at least for 1 day. This restriction was applied to make sure that data on biomarkers and ECGs were available. We further required that either troponin T or troponin I and at least one of the enzymatic markers of myocardial injury must be available. Altogether, 6104 CHD events fulfilled these criteria. The flow-chart in Figure 1 describes the excluded and included events. A description of the characteristics of the included events is given in Supplementary material (see Supplementary material online, Table S1).

Diagnostic classification according to the ESC/ACC definition and according to the 2003 definition was mainly carried out using troponins as the biomarker of myocardial injury. The WHO MONICA classification was carried out using enzymatic biomarkers (including CK-MBm). Hospital discharge diagnoses were taken as the routine clinical diagnosis. These were classified to four categories: ICD-10 diagnoses I21–I22 as ‘MI’, I20.0 as ‘unstable angina’, any other I20 as ‘angina pectoris’, and any other diagnosis as ‘other’. The validity of CHD diagnoses in the Finnish Hospital Discharge Register, as well as in the Causes of Death Register, has been shown in several studies.

Statistical methods

The 2003 definition of MI was cross-tabulated with each of the other definitions and the agreement was evaluated using kappa coefficients. Dichotomized data, definite MI vs. all other categories combined, were used for the calculation of kappa coefficients. To simplify the presentation, data on men and women and all age groups were pooled in most tables. Data on men and women or different age groups are shown separately only where substantial differences existed. Differences in clinical characteristics and treatments between patients classified as definite MI according to both the WHO MONICA definition and the 2003 definition only, were examined for first ever MIs with age-standardized proportions and 95% confidence intervals (CI). The age-standardization was carried out using the age distribution of MI patients in the WHO MONICA Project as the standard, and the 95% CIs were calculated on the basis of binomial distribution. The 1 year survival and 1 year event-free survival were analysed primarily using cardiovascular deaths and cardiovascular deaths or non-fatal MIs as endpoints, but the survival analyses were repeated also using all-cause mortality as the endpoint. The follow-up was, in practice, 100%. These analyses were carried out for first MIs using Kaplan–Meier curves and Cox proportional hazards regression. The validity of the proportional hazards assumption was examined graphically. The first models included age, sex, study area, and study year. At the second stage smoking, diabetes, revascularizations, and thrombolysis were also included in the model. All
Results

Altogether, 3064 events fulfilled the criteria of definite MI according to the 2003 definition, whereas 1710 events were definite MIs according to the WHO MONICA definition (Table 1). Of the definite MIs according to the 2003 definition, 1644 (54%) were definite MIs also according to the MONICA definition, 506 (17%) were possible MIs, and 914 (30%) were no MIs. The kappa coefficient for the agreement on definite MI was 0.51.

Among the same 3064 events, the agreement between the 2003 definition and the ESC/ACC 2000 definition was good (kappa coefficient = 0.98). There were, however, 72 additional events (2%) identified as definite MIs by the 2003 definition, which were no MIs according to the ESC/ACC definition. These were classified partly on the basis of definite ECG and partly on the basis of elevated troponins without ischaemic symptoms, ECG changes, or angioplasty, which are required by the ESC/ACC definition.

Of those 3064 patients with definite MI according to the 2003 definition, 2595 (85%) had received a clinical diagnosis without ischaemic symptoms, ECG changes, or angioplasty, according to both definitions but using conventional enzymes. This definition, when applied using troponins, identified 83% of these additional events (2%) identified as definite MIs by the 2003 definition only than for events classified as definite on the basis of both definitions. This finding was also clear in the Kaplan-Meier survival curves (P < 0.0001, Figure 2A) and remained similar when event-free survival for the combined end-point of cardiovascular death or non-fatal MI was examined (P < 0.0001, Figure 2B). In the group which was classified as no MI according to both definitions, there were only 35 (4.4%) fatal CVD events during the 1 year follow-up in the age range 25–74. The number of fatal and non-fatal CVD events combined was 41 (5.2%).

In Cox proportional hazards models, adjusted for age, sex, study area, and study year, the hazard ratio (HR) of cardiovascular death within 1 year of the first MI event classified as definite according to the 2003 definition only compared with those classified as definite according to both definitions was 1.6 (95% CI 1.1–2.2) among persons aged 25–74 years. For all-cause mortality, the HR was 1.8 (1.3–2.5). For the combined endpoint cardiovascular death or non-fatal MI, the HR was 1.4 (1.0–1.8). After further adjustment for smoking, diabetes, revascularizations, and thrombolysis, the HRs were attenuated and became mostly non-significant: 1.2 (0.8–1.8) for cardiovascular death, 1.4 (1.0–1.9) for all-cause mortality, and 1.1 (0.8–1.5) for cardiovascular death or non-fatal MI. Revascularization was strongly protective and diabetes increased the risk in these patients [HRs for CVD death 0.26 (0.14–0.46) and 1.89 (1.33–2.70), respectively]. Together they contributed most to the attenuation of the HRs. For persons aged ≥75, no differences in prognosis were observed between patients classified as definite MI according to both definitions and those classified as definite according to the 2003 definition only.

Discussion

This is the first evaluation of the new 2003 definition of MI. This definition, when applied using troponins, identified 83% more definite MIs than the WHO MONICA definition using enzymatic markers of myocardial injury. About one-third of these additional events were possible MIs according to the WHO MONICA definition, whereas almost two-thirds were classified as no MI. This means that the 2003 definition not only divides the MONICA possible MI category to definite MIs but also divides the MONICA possible MI category to definite MIs according to the 2003 definition only. Patients fulfilling the 2003 definition but not the WHO MONICA definition were older, had more often diabetes, and received less often thrombolysis and revascularization. The age-standardized 1 year case fatality was higher for events classified as definite on the basis of the 2003 definition only than for events classified as definite on the basis of both definitions. This finding was also clear in the Kaplan-Meier survival curves (P < 0.0001, Figure 2A) and remained similar when event-free survival for the combined end-point of cardiovascular death or non-fatal MI was examined (P < 0.0001, Figure 2B). In the group which was classified as no MI according to both definitions, there were only 35 (4.4%) fatal CVD events during the 1 year follow-up in the age range 25–74. The number of fatal and non-fatal CVD events combined was 41 (5.2%).

Table 1 Cross-tabulation of hospitalized suspected MI eventsa according to the WHO MONICA definition using enzymatic markersb of myocardial injury and the 2003 definition using troponins

<table>
<thead>
<tr>
<th>2003 definitionc</th>
<th>WHO MONICA definition</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Definite</td>
<td>Possible</td>
</tr>
<tr>
<td>2003 definition</td>
<td>1644 (54)</td>
<td>506 (16)</td>
</tr>
<tr>
<td>WHO MONICA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No, n (%)</td>
<td>66 (2)</td>
<td>1097 (36)</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>1710 (28)</td>
<td>1603 (26)</td>
</tr>
</tbody>
</table>

Kappa coefficient = 0.51 for the agreement on definite MI between the two definitions (dichotomized data: definite vs. no definite MI).

aIncludes events where the patient has been hospitalized alive and survived at least 1 day.

bIncludes CK-MBm.

cLuepker et al.10
and no MIs, but also detects a substantial number of definite MIs, which MONICA classified as no MIs. It should be noted that we included in the enzymatic markers CK-MBm, which is also more sensitive and specific than the CK-MB activity, and older enzymatic markers of myocardial injury.15

Survival analyses demonstrated that the prognosis of the additional MIs identified by the 2003 definition was, among patients aged <75 years, worse than the prognosis of patients with definite MI according to the WHO MONICA definition. This finding is consistent with earlier studies suggesting that the detection of troponins in the circulation is a useful prognostic indicator.16,17 Two recent studies from the UK have compared the troponin T-based ESC/ACC definition with the older definitions.

Table 2  Cross-tabulation of hospitalized suspected MI events according to routine clinical diagnosis and the 2003 definition of MI

<table>
<thead>
<tr>
<th>2003 definition</th>
<th>Clinical diagnosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MI</td>
<td>Unstable angina</td>
</tr>
<tr>
<td>Definite, n (%)</td>
<td>2034 (46)</td>
<td>657 (11)</td>
</tr>
<tr>
<td>No, n (%)</td>
<td>239 (8)</td>
<td>531 (17)</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>2595 (54)</td>
<td>126 (4)</td>
</tr>
</tbody>
</table>

Kappa coefficient = 0.77 for the agreement between the clinical diagnosis of MI and the definite MI according to the 2003 definition vs. other categories (dichotomized data).

Table 3  Cross-tabulation of hospitalized suspected MI events according to the 2003 definition using troponins and according to the same definition but using conventional enzymatic markers of myocardial injury

<table>
<thead>
<tr>
<th>Troponins</th>
<th>Conventional enzymesc</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite, n (%)</td>
<td>654 (54)</td>
<td>114 (12)</td>
</tr>
<tr>
<td>No, n (%)</td>
<td>35 (4)</td>
<td>27 (3)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite, n (%)</td>
<td>436 (40)</td>
<td>128 (12)</td>
</tr>
<tr>
<td>No, n (%)</td>
<td>30 (3)</td>
<td>15 (1)</td>
</tr>
</tbody>
</table>

Kappa coefficient for the agreement on definite MI is 0.48 for men and 0.38 for women.

Table 4  Clinical characteristics and treatments (% or mean and 95% CI) of patients aged 25–74 years with first definite MI according to both the WHO MONICA definition and the 2003 definition, and in patients with first definite MI according to the 2003 definition only

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Both definitions</th>
<th>2003 Definition only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>68.5 (65.2–71.8)</td>
<td>67.2 (62.9–71.5)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>61.1 (60.4–61.8)</td>
<td>63.8 (63.0–64.6)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>21.4 (18.4–24.4)</td>
<td>30.1 (25.8–34.4)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>32.6 (29.5–35.6)</td>
<td>31.6 (27.5–35.6)</td>
</tr>
<tr>
<td>Thrombolysis (%)</td>
<td>41.4 (37.8–44.9)</td>
<td>9.9 (7.0–12.9)</td>
</tr>
<tr>
<td>Revascularization (%)</td>
<td>33.3 (29.9–36.8)</td>
<td>25.2 (21.1–29.3)</td>
</tr>
<tr>
<td>28 day CVD case fatality (%)</td>
<td>6.8 (4.9–8.8)</td>
<td>9.5 (6.7–12.3)</td>
</tr>
<tr>
<td>1 year CVD case fatality (%)</td>
<td>10.2 (7.9–12.5)</td>
<td>16.2 (12.9–19.6)</td>
</tr>
<tr>
<td>1 Year total case fatality (%)</td>
<td>11.6 (9.2–14.0)</td>
<td>21.4 (17.7–25.2)</td>
</tr>
<tr>
<td>Hard event during 1 year (%)</td>
<td>16.6 (13.8–19.3)</td>
<td>22.7 (18.7–26.6)</td>
</tr>
</tbody>
</table>

aIncludes first MIs, where the patient has been hospitalized alive and survived at least for 1 day. Proportions are age-standardized. 1 year CVD case fatality uses cardiovascular deaths as the end-points and total case fatality uses all-cause mortality as the endpoint. Hard event means either cardiovascular death or non-fatal MI.

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**Table 4**

**Clinical characteristics and treatments (% or mean and 95% CI) of patients aged 25–74 years with first definite MI according to both the WHO MONICA definition and the 2003 definition, and in patients with first definite MI according to the 2003 definition only.**

- **Men (%):** 68.5 (65.2–71.8) vs. 67.2 (62.9–71.5), p = 0.73
- **Mean age (years):** 61.1 (60.4–61.8) vs. 63.8 (63.0–64.6), p < 0.001
- **Diabetes (%):** 21.4 (18.4–24.4) vs. 30.1 (25.8–34.4), p = 0.004
- **Smokers (%):** 32.6 (29.5–35.6) vs. 31.6 (27.5–35.6), p = 0.72
- **Thrombolysis (%):** 41.4 (37.8–44.9) vs. 9.9 (7.0–12.9), p < 0.001
- **Revascularization (%):** 33.3 (29.9–36.8) vs. 25.2 (21.1–29.3), p = 0.004
- **28 day CVD case fatality (%):** 6.8 (4.9–8.8) vs. 9.5 (6.7–12.3), p = 0.066
- **1 year CVD case fatality (%):** 10.2 (7.9–12.5) vs. 16.2 (12.9–19.6), p = 0.009
- **1 Year total case fatality (%):** 11.6 (9.2–14.0) vs. 21.4 (17.7–25.2), p < 0.001
- **Hard event during 1 year (%):** 16.6 (13.8–19.3) vs. 22.7 (18.7–26.6), p = 0.037

aIncludes first MIs, where the patient has been hospitalized alive and survived at least for 1 day. Proportions are age-standardized. 1 year CVD case fatality uses cardiovascular deaths as the end-points and total case fatality uses all-cause mortality as the endpoint. Hard event means either cardiovascular death or non-fatal MI.

bLuepker et al.10
One of them found, consistent with our study, worse prognosis in the additional patients classified as MIs on the basis of the ESC/ACC definition than in those classified as MIs with the older definitions, whereas the other found no difference in the 6 month prognosis of the two groups. A recent study from Denmark reported a higher mortality in patients with non-ST-elevation MI than in patients with ST-elevation MI, which is in good agreement with our findings.

The additional patients identified by the 2003 definition differed from those identified by the WHO MONICA definition in important clinical characteristics and treatments. They received less thrombolysis, which is not surprising, because they most likely represent non-ST-elevation MIs, where
thrombolytic treatment is not recommended. However, according to recent results and treatment recommendations, these patients should receive urgent revascularization, which most of them did not receive. The fact that the additional patients were older and had diabetes more often may have made the clinical presentation atypical and contributed to the lower frequency of angioplasties. Cox proportional hazards regression analyses demonstrated that the lower frequency of revascularizations and greater prevalence of diabetes were the main contributors to the worse prognosis of patients identified by the 2003 definition only. We had no information on drug treatments prescribed for secondary prevention purposes and the utilization of rehabilitation services. It is possible that differences in these have also contributed to the worse 1 year prognosis of the additional patients.

There were a small number of events that were definite MIs according to the WHO MONICA definition but not according to the 2003 definition. Most probably these have been false positives, because it is known that cardiac troponins have greater specificity than the older enzymatic markers of myocardial injury. Furthermore, two-thirds of events classified as possible MIs according to the WHO MONICA definition were not MIs when the more specific 2003 definition was applied. This was not a surprise, because the MONICA definition for non-fatal possible MI is based on prolonged chest pain only and may thus include false positives.

The adoption of new, sensitive biomarkers apparently increases the accuracy of the monitoring of MI incidence in the population. At the same time, it poses a considerable challenge for the assessment of long-term trends. Our data suggest that the number of non-fatal MI events increased by ~15% in men and ~38% in women because of the use of troponins. The 28 day case fatality of hospitalized events increased significantly. These estimates can be used for taking into account the effect of troponins when calculating the trends in coronary events. The generalization of these Finnish figures to other populations needs to be done with caution, because there probably are local variations in the ways of diagnosing and treating MI events. In particular, the cut-off limits for biomarkers may not be comparable among different hospitals.

The strengths of the present study include its population-based design and a large amount of coronary events registered in a real life setting according to a standardized protocol. Interestingly, the recent study of Terkelsen et al., carried out in a similar setting in Denmark, but using the ESC/ACC definition instead of the 2003 definition, reported survival findings that are consistent with ours. A limitation is that for the troponin-based 2003 definition, we had no cases of probable or possible MI but used dichotomous data (definite MI/no MI) instead. This was because of the fact that we deliberately excluded all sudden out-of-hospital deaths and required that either troponin I or troponin T and at least one of the cardiac enzymes had to be available. In these conditions when using troponins, the 2003 definition becomes dichotomous and differs only little from the ESC/ACC definition. The fact that all patients in the FINAMI areas did not have both enzymes and troponin measured is not likely to lead to a selection bias, because the choice of a routine set of biomarkers depended mainly on the policy and administrative decisions of each hospital and not on the clinical characteristics of a patient.

Conclusions

In summary, combination of the 2003 definition and the use of troponins identified 83% more definite MIs in hospitalized patients than the WHO MONICA definition. Two thirds of these additional events were not even possible MIs according to the MONICA definition. The prognosis of these additional patients aged <75 was worse than that of patients identified as definite MI by both definitions. This suggests that among persons with suspected acute coronary syndrome, the 2003 definition, when applied with troponins, identified a sizable new group of MI patients at high risk of dying or having a reinfarction.

Supplementary material

Supplementary material is available at European Heart Journal online.

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Appendix: Investigators of the FINAMI register

Central Hospital of North Karelia: Matti Ketonen, Pertti Palomäki, Juha Mustonen
University Hospital of Kuopio: Heli Koukkunen, Seppo Lehto, Heikki Miettinen, Kalevi Pyörälä
Oulu University Hospital and Biocenter Oulu: Tapani Jerkkola, Antero Kesäniemi
Oulu City Hospital: Päivi Kärjä-Koskenkari
University Hospital of Turku: Matti Arstila, Pirjo Immonen-Räihä, Tapio Vuorenmä
Turku City Hospital: Aapo Lehtonen
Finnish Heart Association: Matti Romo
KTL-National Public Health Institute: Anne Juolevi, Kari Kuulasmaa, Matti Niemelä, Markku Mähönen, Veikko Salomaa, Jorma Torppa, Jaakko Tuomilehto

References

New definition for MI

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