What is the real hospital mortality from acute myocardial infarction?

Epidemiological vs clinical view

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Aims To examine the general influence of the definition of fatal and non-fatal acute myocardial infarction and coronary deaths on the estimation of in-hospital case-fatality, and to show how the definition of acute myocardial infarction influences time-trends of hospital mortality over 11 years.

Methods and Results As part of the World Health Organization’s MONICA (multinational Monitoring of Trends and Determinants in Cardiovascular Disease) Project in Augsburg all patients aged 25–74 years with a suspected diagnosis of acute myocardial infarction who were hospitalized in the study region’s major clinic were registered prospectively between 1985 to 1995 (n=4889). Patient information, including short-term survival status, was obtained from medical records, by interview of surviving patients, and municipal death certificate files which were validated by an extended identification and validation process. In-hospital case fatality was estimated according to different definitions which closely followed the international MONICA criteria. Epidemiological definitions comprised definite and possible acute myocardial infarction, and events with unclassifiable deaths, while the clinical definition was restricted to definite infarction. Overall, case fatality by the epidemiological definitions was 28 to 29·8% (23·5% of those treated in a coronary care unit) compared to 13·5% using the clinical definition. While over the 11 years, the reduction in case fatality according to the epidemiological definitions was modest, highly significant decreases were observed by applying the clinical definition (from 15·8% in 1985–1988 to 10·8% in 1993–1995, P<0·001 adjusted for age and sex). The discrepancy in case fatality between the definitions is explained by the high proportion of patients who die very early (about 70% of all fatal events during the first 24 h) with the consequence of missing data which may preclude a definite diagnosis of acute myocardial infarction.

Conclusions Applying a broader definition of acute myocardial infarction reveals that in-hospital mortality is higher than believed until now, and it implies that our efforts must be intensified to reduce overall in-hospital coronary heart disease mortality.

Introduction

Mortality from coronary heart disease has declined during the past 10 years[1,2]. Data from the WHO MONICA (multinational monitoring trends and determinants in cardiovascular diseases) project show that about 25% of the decline in mortality rate from coronary heart disease could explained by primary prevention, 29% was explained by secondary prevention due to the reduction of risk factors, and 43% by other therapeutic improvements[3,4]. The decrease in in-hospital case fatality may be linked to the increasing use of established treatment strategies like thrombolysis, aspirin and beta-blockers[5]. Accordingly, clinical trials using the modern therapeutic strategies reported in-hospital case fatality rates as low as 2–6%[6]. On the other hand, hospital- and population-based registries, which did not select out the
more complex patients as is often the case in clinical trials, reported higher case-fatality rates. In-hospital mortality according to clinical registries, however, showed a decrease during the last decade, e.g. from 17-8% in 1975–1978 to 11-7% in 1993–1995[7].

The definition of acute myocardial infarction (AMI) in hospital-based registries, as well as in clinical studies, is usually based on the presence of at least two of three ‘classical’ criteria: typical symptoms, typical ECG abnormalities, and a certain increase in enzymes indicating myocardial injury. This procedure, however, may lead to missing data from very early deaths. Such deaths may result in the supply of insufficient data.

As part of the international WHO MONICA Project we were able to use the more restrictive ‘clinical’ criteria for the definition of fatal and non-fatal AMI, as opposed to the more widely defined epidemiological definition of AMI, especially for fatal cases. We also used an extended identification and validation process, with regional death certificates for case finding to classify very early deaths. The aim of the present study was to investigate the general influence of the definition of AMI on the estimation of in-hospital case fatality, and to show how the definition of AMI influences time-trends of hospital mortality over the time period of 11 years from 1985 to 1995.

Methods

The WHO MONICA Project is a 10-year study monitoring fatal and non-fatal AMI (ICD-9: 410 and 411) and coronary death (ICD-9 412-414), acute coronary care and cardiovascular risk factors in men and women from regionally defined populations and aged 35 to 64 years (extending from 25 to 74 years in some populations)[8]. As part of the international MONICA Project a population-based AMI registry in the study region of Augsburg (Augsburg city and the two adjacent rural districts Augsburg and Aichach Friedberg), Germany, was established in 1984. In the Augsburg area (study population 1985: 156 000 men, and 171 000 women; 1995 200 000 men and 200 000 women; aged 25 to 74 years) all cases of non-fatal and fatal AMI and coronary death were registered according to the WHO MONICA protocol[9]. The methods of case finding and data quality control are described in detail elsewhere[10].

The present report focuses on all patients with a suspected diagnosis of AMI who were hospitalized in the study region’s major clinic (Zentralklinikum Augsburg) in which approximately 75% of all AMI cases are treated. Using a list of specific admission diagnosis, the admission book of the clinic is regularly screened for suspect AMI or ischaemic events on a daily basis. Subsequently, ward physicians are questioned by phone to determine whether there is clinical evidence of AMI in patients meeting the screening diagnosis. The final criterion for inclusion in the register is a discharge diagnosis of AMI (ICD-9 410) or of myocardial ischaemia (ICD-9 411). For events meeting these criteria, treatment data are gathered in a concluding chart review. Data of fatal in-hospital events occurring within 24 h after symptom onset were gathered as was the data acquisition for out-of-hospital deaths[10]. Briefly, the death certificates of all who had died within the study region were screened for the following AMI diagnosis: diabetes (ICD-9 250), hyperlipidaemia (272), obesity (278), hypertensive heart disease (401–405), ischaemic heart disease (410–414), other heart disease (420–429), stroke (430–439), and diseases of arteries etc. (440–447).

For all patients with a ‘suspect’ diagnosis on a standardized death certificate, the three regional health departments send questionnaires 2 to 4 weeks after the date of death to the last attending physician and/or coroner who return the information to the register. The coroner is asked to provide information on the events leading to death. The last treating physician is asked for the cardiovascular history of the deceased, including medication prior to death. Information both in the questionnaire and on the death certificate were used to classify the cases according to the international MONICA classification rules (Diagnostic Categories; DC):

DC 1: Definite acute myocardial infarction. Definite ECG or symptoms typical or atypical or inadequately described, together with probable ECG and abnormal enzymes, or symptoms typical and abnormal enzymes with ischaemic or non-codable ECG or ECG not available, or fatal cases, whether sudden or not, with naked-eye appearance of fresh myocardial infarction and/or recent coronary occlusion found at necropsy.

DC 2: Possible acute myocardial infarction or coronary death. Living patients: with typical symptoms whose ECG and enzyme results do not place them in DC 1 and in whom there is not good evidence for another diagnosis for the attack, or fatal cases whether sudden or not (not in DC 1) where there is no good evidence for another cause of death, clinically or at autopsy with symptoms typical or atypical or inadequately described, or without typical or atypical or inadequately described symptoms but with evidence of chronic coronary occlusion or stenosis or old myocardial scarring at necropsy; or with a good history of chronic ischaemic heart disease such as definite or possible myocardial infarction, or coronary insufficiency or angina pectoris in the absence of significant valvular disease or cardiomyopathy.

DC 3: Ischaemic cardiac arrest with successful resuscitation not fulfilling criteria for definite or possible myocardial infarction. Spontaneous cardiac arrest not provoked by medical intervention, electrocution, drowning or other gross physical insults, from presumed primary ventricular fibrillation secondary to ischaemic heart disease, in the absence of significant valvular disease or cardiomyopathy.

DC 4: No acute myocardial infarction. Non-fatal cases with combinations of symptoms and tests that do not
qualify them for the definite category and who do not have typical symptoms that might place them in the possible category, or where the illness episode was explained by another diagnosis and fatal cases, whether sudden or not, not in DC 1 where another diagnosis has been made (clinically or at autopsy).

DC 9: Fatal cases with insufficient data. Cases with no autopsy, no history of typical or atypical or inadequately described symptoms, no previous history of chronic ischaemic heart disease and no other diagnosis.

The diagnostic categories of the international MONICA Project were originally chosen to monitor the whole epidemic of AMI including out-of-hospital deaths with a relatively high proportion classified as DC 9 cases. To deal more specifically with already hospitalized cases which are relatively seldom categorized as DC 3 or 9, and to more closely approximate the clinical diagnosis of AMI, the following definitions for hospitalized cases were used:

**Epidemiological definition I:** DC 1 + DC 2 + DC 3 + DC 9 (fatal as well as non-fatal cases).

**Epidemiological definition II:** DC 1 + DC 2

**Clinical definition:** All cases with DC 1 and/or without obvious ECG abnormalities as described in the MONICA Manual, when a diagnosis of AMI was made by clinicians.

According to the international protocol any event is considered fatal if the patient dies within 28 days from the beginning of symptoms. In the present paper, the 28-day case fatality is considered as in-hospital mortality because the mean hospital stay during the time under study was relatively long in Germany (mean 22.2 days, median 20.0 days), and the occurrence of fatal cases between admission to hospital and day 28 was extremely rare (n=8).

For clarity, because the differences in case fatality-estimations according to the respective AMI definitions did not differ between men and women, we decided not to present the data separately for men and women.

### Statistical analysis

Case fatality rates were computed as (fatal events/fatal+non-fatal events) according to the respective definition used. Groups were compared with Student’s two-tailed unpaired t-test for continuous variables and by chi-square-tests for prevalences. For analysing differences in case fatality according to the investigated time-period, multiple logistic regression analysis was performed simultaneously adjusting for age and sex; P-values <0.05 were considered as statistically significant. All analyses were carried out with the SAS System for Windows Release 6.11.

### Results

#### Epidemiological definition I

Of the 4889 patients hospitalized with an AMI (epidemiological definition I) between 1985 to 1995, 1594 died within 28 days (32.6%). Evaluation of in-hospital death revealed that 42 patients did not in fact die in hospital, and a number of patients died on intensive care wards (mainly after CABG surgery), on other wards with no internal responsibility, or were even already dead on arrival (Table 1). In order to provide comparability with other registries and clinical practice, those cases were excluded from further analysis. The characteristics for the remaining cases are shown in Table 2.

The 28-day case fatality over the whole time period from 1985 to 1995 for all 4576 cases was 29.8% (Table 2). Over time, the 28 day case fatality decreased only slightly, with a borderline significantly lower mortality in the years 1993 to 1995 compared to the time periods before (Table 3).

#### Epidemiological definition II

Excluding all events with an unclassifiable cause of death (DC 9) or DC 3 reduced overall 28-day case fatality of hospitalized AMI patients only slightly to 28.0% (Table 3). If those patients who have been treated during their hospital stay on a coronary care unit are included, the overall 28-day case fatality is reduced to

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**Table 1** Place of in-hospital death (epidemiological definition I; n=1594)

<table>
<thead>
<tr>
<th>Place of death</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal wards not of internal respons</td>
<td>86 (5-4)</td>
</tr>
<tr>
<td>Surgical intensive care units</td>
<td>101 (6-3)</td>
</tr>
<tr>
<td>Dead on arrival</td>
<td>42 (2-6)</td>
</tr>
<tr>
<td>Emergency room</td>
<td>146 (9-1)</td>
</tr>
<tr>
<td>Coronary care unit</td>
<td>799 (50-1)</td>
</tr>
<tr>
<td>General ward</td>
<td>420 (26-3)</td>
</tr>
</tbody>
</table>

**Table 2** Characteristics of all patients hospitalized for AMI (fatal and non-fatal) and treated by internals 1985–1995 (epidemiological definition I)

<table>
<thead>
<tr>
<th>Male sex n (%)</th>
<th>3375 (73-7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (SD)</td>
<td>61.8 (9.15)</td>
</tr>
<tr>
<td>History of previous myocardial infarction, n (%)</td>
<td>1209 (26-4)</td>
</tr>
<tr>
<td>History of previous coronary angiography, n (%)</td>
<td>573 (12-5)</td>
</tr>
<tr>
<td>History of previous CABG, n (%)</td>
<td>203 (4-4)</td>
</tr>
<tr>
<td>History of previous angina, n (%)</td>
<td>1951 (42-6)</td>
</tr>
<tr>
<td>History of diabetes n (%)</td>
<td>1158 (25-3)</td>
</tr>
<tr>
<td>Survived &gt;28 days, n (%)</td>
<td>3211 (70-2)</td>
</tr>
</tbody>
</table>

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23.5%, showing a significant decrease over the three time periods from 25.4% to 20.5% (Table 3).

Clinical definition

Applying the clinical definition of AMI reduced the overall 28-day case fatality considerably to 13.5%. The decrease in case fatality over time was highly significant for all investigated time periods (from 15.8% 1985–1988 to 10.8% 1993–1995; Table 3).

Time course of in-hospital death

The figure shows the percentage distribution of hospitalized fatal events by time of death (first 24 h vs days 2 to 28) and AMI definition.

Characteristics of fatal cases (Epidemiological definition I)

Table 4 shows the characteristics of fatal hospitalized cases according to time of death. Those who died during the first 24 h were significantly younger and comprised a significantly higher proportion of men than those who died from days 2 to 28 after onset of symptoms. Except for history of previous angina, which was significantly more often reported in 24 h fatal cases, neither other markers indicating a history of coronary heart disease nor the history of major cardiovascular risk factors were different between the two groups (Table 4).

Table 5 gives the numbers of fatal cases classified by diagnosis on death certificates according to the 9th revision of the ICD. The proportion of patients with an ICD-9 diagnosis of acute myocardial infarction (410) was higher in the group who died from days 2–28 (86.3%) than in those who died during the first 24 h
In the latter, 26·5% were classified as having died of ischaemic heart disease (ICD-9 411–414). The proportion of patients with diagnosis of other heart disease or diseases not related to the cardiovascular system were low in both groups.

The autopsy rates for in-hospital fatal cases were low (11·5% of those who died during the first 24 h, and 8·4% for those who died from days 2 to 28, respectively). An autopsy diagnosis of AMI (ICD-9 410) was made in 77·8% of the former group, and 87·9% in the latter, respectively. Except for three cases, the rest of the necropsy cases had a diagnosis of ischaemic heart disease without morphological signs of an acute occlusion of a coronary artery (410–414; data not shown).

**Discussion**

It has already been shown that the clinical view of case fatality from AMI in those reaching hospital alive is different from the population’s view, which comprises out-of-hospital deaths leading to considerably higher case fatality rates for acute episodes of coronary heart disease. In the present study, we also demonstrated that even in-hospital case fatality rates may differ considerably with respect to the definition of AMI used, and information available on circumstances of death and the patient’s history.

The international MONICA Project attempted to measure the whole epidemic of coronary heart disease incidence and mortality rates from the population point of view and, therefore, implemented specific diagnostic categories for the definition or exclusion of AMI cases. In contrast to the clinical definition of AMI which closely resembled DC 1 of the MONICA diagnostic categories, a broader definition of AMI including DC 2, 3 and 9 are used in order to avoid underestimating AMI morbidity of the population at risk.

Our data show that the proportion of cases with unclassifiable deaths (DC 9) or with DC 3 of in-hospital cases is low as compared to out-of-hospital events. However, even applying the epidemiological definition II (only DC 1 and 2) yielded an overall 28-day case fatality rate of 28·0%, which is substantially higher than proposed by other hospital-based registries. This holds true even when only patients treated on a coronary care unit (ccu) are included, thereby excluding those hospitalized for coronary heart disease or another disease resulting in in-hospital sudden cardiac death without the opportunity of reaching a ccu (28-day case fatality 23·5%). On the other hand, by applying the clinical definition of AMI, the respective case fatality rate is considerably reduced to only 13·5%. This is close to case fatality rates reported by other hospital-based registries.

It already has been shown that the low mortality rates of 2%–7% observed in clinical trials are due to selection processes (bias). Accordingly, the mortality rate in thrombolytic therapy trials for trial-ineligible patients was significantly higher than in the trial-eligible group (19% vs 4%) and even studies of primary angioplasty, which were supposed to include many thrombolytic ineligible patients, showed a fivefold higher mortality in the trial-ineligible group (21% vs 4%). Thus, our data with a case fatality rate of 13·5%...
by the clinical AMI definition seems to give a more realistic picture of in-hospital case fatality in unselected patients with a confirmed diagnosis of AMI.

Furthermore, applying the broader definition, especially of fatal AMI (epidemiological definition I or II), and analysing the time course of in-hospital death, revealed that 68% to 71% of all 28-day fatal cases occurred within 24 h of symptom onset, in contrast to only 19% with the clinical AMI definition, the latter closely resembling the relationships observed in clinical studies[18]. This discrepancy may be due to the fact that not only out-of-hospital, but even early in-hospital deaths often have missing data which preclude a definite diagnosis of AMI. This then leads to the exclusion of early deaths from conventional registries or clinical trials[19,20]. The prospective nature of the present study, which identified and followed-up suspect cases during hospitalization (sometimes called ‘hot pursuit’), and the subsequent validation process, especially of patients who died early, on the basis of all regional death certificates, allowed us to identify a considerable number of in-hospital deaths which are — in all probability — due to acute manifestation of coronary heart disease. Those cases are usually missed in conventional registers which are often based on retrospective case finding[7,13] or self-reporting by local study co-ordinators[21,22].

Characterization of early occurring deaths, e.g. during the first 24 h after symptom onset, revealed that they did not significantly differ from later deaths in terms of markers indicating a history of coronary heart disease or major cardiovascular risk factors. However, those who died early were significantly younger and more often of male sex than those who died later, an observation for which we do not have an adequate explanation, especially because the very early out-of-hospital fatal cases are usually of older age[23,24]. Of interest, a previous history of angina pectoris was more common in earlier deceased subjects, presumably indicating a more unstable or more severe form of underlying coronary heart disease.

The proportion of subjects with a diagnosis of coronary heart disease (e.g. ICD-9 410 or 411) on the death certificate was high in both groups, but significantly higher in the group who died after the first 24 h (86.3% vs 96.7%, P<0.001). This may be a consequence of the presence of more diagnostic tools for 24 h survivors to justify a diagnosis of AMI or coronary heart disease for the clinician. A similar picture was obtained from the few cases where necropsy was done. We cannot exclude some misclassification of early deaths (for example, pulmonary embolism or malignant non-ischaemic arrhythmia recorded as coronary heart disease events). However, even if there was some misclassification it must be assumed that hospital mortality from AMI is considerably higher than believed till now.

There are only a few studies that used a similar approach to our study. A previous analysis of 29 MONICA centres revealed that the median 28-day case fatality for hospitalized events in the age range 35 to 64 years was 22% for men and 27% for women[12]. One MONICA centre in Canada using comparable epidemiological definitions of AMI reported about similar 28-day case fatality, of 26% (1984) to 18% (1993) in the age-group 25 to 74 years[25]. By contrast, the ARIC study — using similar broad definitions of AMI (definite and possible) as in our study, and investigating a similar time-period — reported on hospital case fatality-rates between 9.0% (women) and 10.6% (men, 35 to 74 years, respectively)[26]. On the other hand, the only MONICA centre in the U.S.A., Stanford, did not differ in terms of hospital case fatality from the average of all of the above mentioned MONICA centres, indicating that other reasons, like their retrospective approach, may account for the relatively low case fatality reported in the ARIC hospitals.

Although we observed a significant decrease in 28-day case fatality over the three time-periods irrespective of AMI definition, the decrease was modest with epidemiological definition I and strongest with the clinical definition of AMI. Accordingly, only the patient group surviving long enough to fulfill the clinical criteria for AMI seems to profit from the increasing use of evidence-based therapies like aspirin, beta-blockers and thrombolysis[7,23]. This suggests that even in-hospital we are only treating the tip of the iceberg of AMI events really successfully, and it remains to be shown that the increasing and early use of newer therapeutics (e.g. G IIb/IIIa-Inhibitors) and the incremental use of very early invasive strategies[27,28] are able to reduce the very early in-hospital deaths.

In conclusion, our data indicate that a high proportion of early occurring in-hospital deaths which — with conventional clinical definitions — are usually not considered as AMI cases, are in fact due to an acute manifestation of coronary heart disease, presumably AMI, and that our efforts must be intensified to reduce early in-hospital coronary heart disease mortality.

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