Ten year mortality in relation to original size of myocardial infarct: results from the Gothenburg metoprolol study

J Herlitz, B W Karlson, Å Hjalmarson

Abstract

Objective—To describe the relation between the extent of a myocardial infarct, measured according to maximum serum enzyme activity of lactate dehydrogenase, and mortality at 10 years.

Patients—In 759 patients with acute myocardial infarction in whom serum activity of heat stable lactate dehydrogenase had been determined every 12 hours for 108 hours after randomisation in an early intervention trial with metoprolol.

Main outcome measure—Mortality at 10 years in relation to quartile of maximum serum lactate dehydrogenase activity and history of cardiovascular disease.

Results—Among all patients mortality at 10 years was 39% in the lowest quartile, 51% in the second quartile, 50% in the third, and 59% in the fourth (p < 0.001 for relation between infarct size and 10 year mortality). Among patients without a history of myocardial infarction, angina pectoris, diabetes mellitus, or hypertension the mortality in each quartile was 29%, 32%, 41%, and 56%, respectively (p < 0.001 for relation between infarct size and 10 year mortality). Among patients with any of these risk indicators the association between the estimated infarct size and mortality at 10 years was weak (p < 0.05).

Conclusion—Estimated size of a myocardial infarct and mortality over 10 years seem to be related but mainly in patients without a history of cardiovascular disease.

(Br Heart J 1994;71:238–241)

Patients and methods

All patients were admitted to the coronary care unit of Sahlgren's Hospital or Östra Hospital in Gothenburg or to the Community Hospital of Skövde between 1976 and 1981. The inclusion criteria for participation in the trial were chest pain lasting at least 30 minutes or electrocardiographic changes indicating acute myocardial infarction with onset of symptoms within the previous 48 hours, or both, and age from 40 to 74 years. The cardiovascular exclusion criteria were a heart rate less than 45 beats/minute; systolic blood pressure less than 100 mm Hg; a PR interval greater than 0.24; and severe congestive heart failure defined as basal pulmonary rales greater than 10 cm. Further exclusion criteria have been presented elsewhere. Patients were given 15 mg metoprolol or placebo intravenously soon after admission to hospital and then 200 mg orally everyday for three months in a double blind fashion. Thereafter most patients with suspected ischaemic heart disease were given β blockade regardless of their original treatment group.

Protocol

The criteria for definite infarction were fulfilment of at least two of the three following conditions: (a) chest pain lasting at least 15 minutes; (b) at least two blood samples with raised serum activity of aspartate aminotransferase (> 0.7 μkat/l) and decreased or normal activity of alanine aminotransferase; and (c) development of Q waves and appearance or disappearance of ST segment elevation followed by T wave inversion in at least two of the 12 leads in a standard electrocardiogram. An electrocardiogram was recorded once daily during the first three days in hospital. Blood samples for analyses of aspartate aminotransferase and alanine aminotransferase activities were collected once daily during the first three days in hospital; samples for measuring heat stable lactate dehydrogenase activity were taken every 12 hours for 48 to 108 hours after arrival. Serum activities of aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase were determined according to the methods of the Scandinavian Committee on Enzymes. The heat labile fraction of lactate dehydrogenase was inactivated according to the method of Brydon and Smith. Infarct size was calculated by measuring the maximum enzyme activity. The mortality over 10 years was...
Table 1 Baseline characteristics of 759 patients in trial. Values are numbers (percentages) of patients unless stated otherwise.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr):</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>62</td>
</tr>
<tr>
<td>Range</td>
<td>40-74</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>592 (78)</td>
</tr>
<tr>
<td>Women</td>
<td>167 (22)</td>
</tr>
<tr>
<td>History of:</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>152 (20)</td>
</tr>
<tr>
<td>Angina pectoris*</td>
<td>265 (35)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>235 (31)</td>
</tr>
<tr>
<td>Diabetes mellitus (21)*</td>
<td>73 (10)</td>
</tr>
<tr>
<td>Smoking (35)*</td>
<td>379 (56)</td>
</tr>
</tbody>
</table>

*Number of patients with missing information.

Figures

assessed from data of the Swedish national death registry.

STATISTICAL METHODS

Fisher’s permutation test was used and a two tailed test was applied. A p value less than 0.05 was regarded as significant. In the multivariate analysis a stepwise logistic procedure was used.

Results

Overall, 1395 patients were included in the trial, of whom 809 (58%) fulfilled the criteria for acute myocardial infarction during their first three days in hospital. Information on serum lactate dehydrogenase activity and mortality over 10 years was available in 759 of these patients (94%).

Table 1 shows the baseline characteristics of these patients. Half were randomly allocated to metoprolol and half to placebo treatment.

MORTALITY IN RELATION TO INFARCT SIZE

Figure 1 shows mortality over 10 years for the four quartiles of lactate dehydrogenase activity when all patients were included in the analyses. Infarct size was significantly related to the overall 10 year mortality, including mortality during the initial stay in hospital, being 39% in the lowest quartile, 51% in the second quartile, 50% in the third, and 59% in the fourth (p < 0.001). When patients who were discharged alive from hospital were analysed separately the relation was weaker (p = 0.048). Mortality over 10 years was similar in those treated with metoprolol and placebo. After the first year the survival curves were parallel.

MORTALITY IN RELATION TO HISTORY OF CARDIOVASCULAR DISEASE, AGE, AND SEX

As shown in table 2 and figures 2 and 3, the estimated infarct size was associated with mortality among patients without a history of

Table 2 Mortality at 10 years in relation to maximum serum heat stable lactate dehydrogenase activity and clinical history

<table>
<thead>
<tr>
<th>Quartile of maximum serum heat stable lactate dehydrogenase activity:</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (%) (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 61</td>
<td>29 (91)</td>
<td>35 (86)</td>
<td>36 (91)</td>
<td>52 (89)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>≥ 61</td>
<td>53 (100)</td>
<td>61 (103)</td>
<td>60 (99)</td>
<td>69 (100)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>42 (148)</td>
<td>52 (149)</td>
<td>47 (148)</td>
<td>60 (149)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Women</td>
<td>32 (41)</td>
<td>46 (41)</td>
<td>54 (41)</td>
<td>62 (42)</td>
<td></td>
</tr>
<tr>
<td>History:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>55 (40)</td>
<td>67 (39)</td>
<td>69 (39)</td>
<td>67 (39)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>35 (150)</td>
<td>44 (151)</td>
<td>45 (150)</td>
<td>60 (151)</td>
<td></td>
</tr>
<tr>
<td>Angina pectoris*:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>49 (65)</td>
<td>59 (66)</td>
<td>62 (66)</td>
<td>55 (65)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>36 (124)</td>
<td>41 (125)</td>
<td>46 (123)</td>
<td>63 (124)</td>
<td></td>
</tr>
<tr>
<td>Hypertension:</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>52 (58)</td>
<td>62 (58)</td>
<td>53 (58)</td>
<td>62 (58)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>36 (132)</td>
<td>45 (132)</td>
<td>48 (130)</td>
<td>57 (133)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus†:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>88 (17)</td>
<td>82 (17)</td>
<td>76 (17)</td>
<td>82 (17)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>33 (168)</td>
<td>46 (168)</td>
<td>49 (164)</td>
<td>56 (170)</td>
<td></td>
</tr>
</tbody>
</table>

*One patient had missing information. †Twenty one patients had missing information.

n = Number of patients evaluated.
myocardial infarction, angina pectoris, diabetes mellitus, or hypertension. Among patients with any of these risk indicators, however, the association between infarct size and prognosis was weak. In addition, the association between infarct size and mortality was stronger in younger than in older patients.

MULTIVARIATE ANALYSIS
In a multivariate analysis considering age, sex, history of cardiovascular diseases, infarct size, and the occurrence of various complications during the stay in hospital the infarct size was not an independent predictor of death during the 10 years of follow-up. Predictors were a history of diabetes mellitus, increasing age, presence of congestive heart failure during the stay in hospital, and a history of myocardial infarction.

Discussion
The main aim in treating patients with acute myocardial infarction is to try to contain the infarct as much as possible. Yet, knowledge about the association between the final extent of the infarct and the very long term prognosis is still insufficient.

This study describes the relation between the estimated extent of a myocardial infarct and the overall mortality during 10 years of follow-up. We have previously described the relation between estimated infarct size and mortality after three months,11 two years,4 and five years8 in the same population of patients.

We found an association between serum lactate dehydrogenase activity and mortality over 10 years in the univariate analysis. Thus 39% of patients with the smallest infarcts were dead after 10 years compared with 50% of patients with the largest infarcts. In the multivariate analysis, however, infarct size did not emerge as an independent predictor of death. Such predictors were instead a history of cardiovascular disease (particularly diabetes mellitus), previous acute myocardial infarction, and age. Therefore the association between infarct size and mortality was stronger when patients without a history of cardiovascular disease were analysed separately.

When the association between infarct size and mortality over five years was analysed the curves diverged during the first year after acute myocardial infarction, but not thereafter.2 In this study the mortality curves in the four quartiles were also parallel between five and 10 years after infarction. Thus the relation between infarct size and mortality over 10 years may reflect the much higher mortality among patients with larger infarcts during the first year after infarction.

The use of enzyme activity to determine infarct size has been criticised for being inaccurate,13,14 although several studies have shown a fairly good correlation between the peak serum enzyme activity and histological infarct size.15-18 Previous studies have also shown a strong correlation between infarct size estimated by enzyme activity and the occurrence of various complications during the early phase17-19 including death.11,20

Criticisms have been raised about the use of serum enzyme activity as an end point in early intervention trials of suspected acute myocardial infarction, because interventions such as β blockers13 and thrombolytic agents16 might influence enzyme kinetics and thereby cause false positive or negative results. Several previous intervention studies, however, have shown a parallel between reduced enzyme activity and other indirect markers of the severity of the infarction.22-25

In this study we found that indices of myocardial function (development of congestive heart failure during admission to hospital) were more strongly related with mortality at 10 years than with estimated infarct size. Previous studies have shown a reasonably good correlation between enzyme release and left ventricular function,26-27 but mainly in patients without previous myocardial infarction,16,28 and estimates of left ventricular function are strongly related to prognosis during the subsequent years.29-32 The very long term prognosis has been suggested to be more closely related to the end systolic volume than to the ejection fraction.33

LIMITATIONS
Because of some contraindications not all sizes of infarct were covered in this study. Patients with pulmonary oedema or hypotension at arrival in hospital were excluded, many of whom had large infarcts. The variability in infarct size, however, ranged from the upper limit of normal values to approximately 18 times normal values, indicating that a broad range of sizes was covered. Furthermore, all ages were not covered as we included only patients up to 75 years of age. Finally, we lack information about the manner of death, and thus only total mortality could be analysed. The somewhat old fashioned criteria for acute myocardial infarction

\[
\text{No cardiovascular history} \quad \begin{array}{c|c|c|c|c}
\text{Cardiovascular history} \\
\hline
\text{Quartile} & \text{First} & \text{Second} & \text{Third} & \text{Fourth} \\
\hline
\text{Mortality at 10 years (100)} & \begin{array}{c}
\text{p<0.001} \\
\text{p<0.05}
\end{array} & \begin{array}{c}
\text{Mortality at 10 years (100)} \\
\text{p<0.001}
\end{array} \\
\hline
\text{Figure 3 Relation between maximum activity of heat stable lactate dehydrogenase and mortality at 10 years in patients with and without history of cardiovascular diseases (myocardial infarction, angina pectoris, hypertension, or diabetes mellitus).}
\]
Ten year mortality in relation to original size of myocardial infarction

should be related to the fact that the patients had an acute myocardial infarction more than 10 years ago.

IMPLICATIONS
Estimated infarct size seems to be associated with mortality over 10 years, mainly in patients without a history of cardiovascular diseases. Thus limitation of infarct size might improve even the very long term prognosis in this patient population. Our results suggest that left ventricular function might be better than infarct size in evaluating early intervention in suspected acute myocardial infarction.

15 Grande P, Fischer Hansen B, Christiansen C, Næsoft J. Acute myocardial infarct size estimated by serum CR-

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