Long-term Mortality after Acute Myocardial Infarction in Relation to Prescribed Dosages of a Beta-Blocker at Hospital Discharge

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Summary. This study was designed to describe the 5-year mortality rate in relation to the dose of metoprolol prescribed at hospital discharge after hospitalisation for acute myocardial infarction (AMI). All patients discharged alive after being hospitalized for AMI at Sahlgrenska Hospital (covering half of the community of Göteborg, with 500,000 inhabitants) during 1986–1987 (period I) and all patients discharged alive after hospitalization for AMI at Sahlgrenska Hospital and Östra Hospital (covering the whole area of the community of Göteborg) in 1990–1991 (period II) were included. Overall mortality was retrospectively evaluated over 5 years of follow-up. In all there were 2161 patients who were discharged after AMI. Seventy-three percent of these patients were prescribed a beta-blocker and 59% were prescribed metoprolol. Of the patients prescribed metoprolol, 34% were on 200 mg, 46% on 100 mg, and 20% on 50 mg or less. Information on 5-year mortality was available for 2142 of the 2161 patients (99.1%). The 5-year mortality was 24% among patients prescribed 200 mg, 33% among patients prescribed 100 mg, and 43% among patients prescribed 50 mg (P < 0.0001). Patients prescribed another beta-blocker had a 5-year mortality of 39%, and patients prescribed no beta-blocker at all had a 5-year mortality of 61%. When correcting for dissimilarities at baseline, patients who were prescribed 100 mg had an adjusted risk ratio for death of 0.79 (95% confidence limit 0.64–0.96; P = 0.021) as compared with patients not prescribed a beta-blocker. The corresponding figure for patients prescribed >100 mg was 0.63 (95% confidence limit 0.48–0.84; P = 0.001). Both patients prescribed high and low doses of metoprolol after AMI appeared to benefit from treatment. There was a trend indicating more benefit when larger doses were prescribed.

Key Words. beta blockers, dosage, prognosis, myocardial infarction

Several large, randomized placebo-controlled trials have shown that long-term beta-blocker therapy after acute myocardial infarction (AMI) improves survival [1–3]. Despite this fact, these drugs are greatly underused by practicing clinicians [4–8]. Moreover, the dosages of beta blockers routinely prescribed seem to be lower than the dosages used in the large randomized controlled trials [4]. The effectiveness of these lower doses in reducing mortality is unknown. It is unlikely that any randomized controlled trial will be designed to examine this question. In one recently published study, it was suggested that lower dosages of beta-blockers were associated with at least as great a reduction in mortality as treatment with higher dosages [9].

The aim of this study was to further evaluate long-term mortality after AMI in relation to the dosages of the beta-blocker metoprolol prescribed. We have previously described the impact of the use of beta-blockers short and long term after the development of AMI in this study population [10–12].

Patients

Period I: Every patient hospitalized via the emergency department at Sahlgrenska University Hospital (one of the two available city hospitals covering the community of Göteborg, with 500,000 inhabitants) fulfilling the criteria for AMI from February 15, 1986 to November 9, 1987 and discharged alive from hospital was included (n = 740; age range 24–101 years).

Period II: Every patient hospitalized because of AMI at both Sahlgrenska University Hospital and at Östra University Hospital (the two city hospitals) between January 1, 1990 and December 31, 1991 and discharged alive was included (n = 1446; age range 31–98 years).

Methods

Diagnosis of AMI


At least two of the following three criteria had to be fulfilled: (1) chest pain with a duration of at least 15 minutes; (2) serum aspartate amino transferase (S-ASAT)

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levels above the normal range in samples from at least two consecutive days, together with elevated serum creatine kinase (CK) levels; (3) the appearance of new pathological Q waves in at least two leads on a 12-lead standard electrocardiogram (ECG).

**Period II (1990–1991).**

Very similar criteria were used as applied during Period I. At least two of the following three criteria had to be fulfilled: (1) chest pain suggestive of AMI, pulmonary oedema, or syncope; (2) elevated serum activity of a heart-specific enzyme above the normal range; (3) development of pathological Q waves in at least two leads on a 12-lead standard ECG.

**Medical history and smoking habits**

For both periods a history of hypertension, diabetes mellitus, congestive heart failure, smoking, etc. was based on information from medical records. During Period I information was also based on patient interviews within a few days after hospital admission. If there were any discrepancies between what the patients reported during the in-person interviews and the information routinely recorded from the medical records, the information from the medical records had priority.

**Complications in hospital**

The occurrence of various complications in hospital was based on information gathered from the medical records. Congestive heart failure was defined according to clinical signs and symptoms, such as auscultatory rales, severe dyspnea, or pulmonary edema described by the attending physician in the records. High-degree AV block was defined as third-degree AV block. Ventricular tachycardia (VT) was defined as VT with a duration of at least 60 seconds and/or VT associated with symptoms necessitating treatment (antiarrhythmics or electrical conversion).

**Methods of ascertainment of study samples**

During Period I all patients with AMI were sampled via a continuous prospective registration of all patients coming to the emergency department with chest pain or other symptoms raising suspicion of AMI. All patients with such symptoms passed through the emergency department during that time period. During Period II all patients with AMI were sampled via a central data registry for all patients being hospitalized in the two city hospitals according to discharge diagnosis. During Period II some patients were hospitalized directly to the coronary care unit (CCU), bypassing the emergency department. Long-term follow-up was assessed via the National Registry of Deaths.

**Medication data**

Information on medication at hospital discharge was gathered from the hospital discharge medical record.

**Statistical methods**

In all correlations Pitman’s nonparametric test was used [13]. In the evaluation of proportions, Fisher’s exact test was used, which is a special form of Pitman’s test [14]. In the multivariate analysis, only those factors listed in Tables 1–3 and being significantly associated with mortality during 5 years were entered into the model. Cox’s proportional hazards model was used. Adjusted $P$ values were calculated simultaneously, considering all factors in Tables 1–3 associated with 5-year mortality at a $P$ value of <0.05. Statistical significance was defined as a $P$ value <0.05 (two sided).

**Results**

In all, there were 2161 patients discharged from the hospital during the two registration periods. Thus,

### Table 1. Age, sex, and previous history in relation to dose of metoprolol

<table>
<thead>
<tr>
<th>Dose of metoprolol (mg)</th>
<th>50 (n = 257)</th>
<th>100 (n = 587)</th>
<th>200 (n = 428)</th>
<th>$P^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (1,1,0)$^b$</td>
<td>76</td>
<td>71</td>
<td>65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>42</td>
<td>31</td>
<td>25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous history (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction (3,1,5)</td>
<td>30</td>
<td>24</td>
<td>22</td>
<td>0.041</td>
</tr>
<tr>
<td>Angina pectoris (4,1,5)</td>
<td>42</td>
<td>40</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure (2,5,0)</td>
<td>14</td>
<td>9</td>
<td>6</td>
<td>0.0014</td>
</tr>
<tr>
<td>Hypertension (1,3,3)</td>
<td>37</td>
<td>33</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (1,2,3)</td>
<td>14</td>
<td>14</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Smoking (42,54,19)</td>
<td>32</td>
<td>36</td>
<td>44</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

$^a$ Association with dose of metoprolol.

$^b$ Number of patients with missing information.