Characterization and clinical course of patients not receiving aspirin for acute myocardial infarction: Results from the MITRA and MIR studies

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Background Clinical trials have shown the efficacy of aspirin for acute myocardial infarction (AMI). However, not all patients receive aspirin for AMI. The aim of this study was to provide information on characteristics and clinical course of patients not treated with aspirin for AMI.

Methods We analyzed the data of the Myocardial Infarction Registry (MIR) and the Maximal Individual Therapy of Acute Myocardial Infarction (MITRA) registry. MITRA and MIR were prospective multicenter registries of patients with ST segment elevation myocardial infarction in Germany.

Results Of 22,572 patients registered from 1994 to 1998, 1767 (7.8%) did not receive aspirin within the first 48 hours after admission. Multivariate analysis revealed two main factors associated with withholding aspirin for AMI: relative contraindications to aspirin (gastric ulcer [odds ratio (OR) 4.9, 95% confidence interval (CI) 3.7-5.7], renal insufficiency [OR 1.4, 95% CI 1.1-1.8]), and critical clinical state at admission (cardiogenic shock [OR 1.5, 95% CI 1.2-2.1] and prehospital resuscitation [OR 1.8, 95% CI 1.4-2.2]). In addition, these patients were significantly less likely to receive reperfusion therapy and adjunctive medical therapy such as β-blockers and angiotensin-converting enzyme inhibitors. In-hospital mortality after adjustment for baseline characteristics was 27.2% in patients without aspirin compared with 11.1% in patients treated with aspirin.

Conclusions Only a minority of AMI patients (7.8%) did not receive aspirin. Relative contraindications to aspirin and a critical clinical state at admission were the main factors associated with withholding aspirin for AMI. Even after adjustment for patient characteristics, the mortality of patients without aspirin was almost three times higher. (Am Heart J 2001;141: 200-5.)
The aim of this study was to characterize this special patient subset and to analyze their clinical course.

Methods

The Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) study and the Myocardial Infarction Registry (MIR) were prospective multicenter registries of the current treatment of ST elevation myocardial infarction in Germany. In MITRA, 8194 patients were recruited from 1994 to 1998 in 54 hospitals ranging from universities to small community hospitals in the southwest of Germany. MIR was a nationwide registry that included 14,378 patients in 217 mainly community hospitals from 1996 to 1998.

In both registries, all patients with ST segment elevation myocardial infarction or left bundle branch block (LBBB) who were seen in the hospital up to 96 hours after the onset of pain were registered consecutively.

Definitions

ST segment elevation myocardial infarction (AMI) was diagnosed in the presence of the following two criteria: (1) persistent angina pectoris for ≥20 minutes and (2) ST segment elevation of ≥1 mm in at least two contiguous peripheral leads or ≥2 mm in at least two contiguous precordial leads or LBBB.

Diagnosis of AMI was confirmed by elevation of cardiac enzymes of more than twice the upper normal range.

Acute therapy

In case of thrombolysis, front-loaded recombinant tissue plasminogen activator (rtPA) or streptokinase were administered. Primary angioplasty was performed in institutions with facilities for acute intervention. Adjunctive medication was recommended as established in randomized clinical trials of AMI: aspirin, β-blockers, and angiotensin-converting enzyme (ACE) inhibitors were recommended if no contraindications were present. The recommended dose of aspirin was 500 mg orally or intravenously at admission followed by a daily dose of 100 mg orally. Any aspirin therapy was documented during the early in-hospital period (48 hours after admission) and at discharge. Data on the dose or route of application of aspirin were not collected.

Active bleeding at admission was the only absolute contraindication to aspirin. Contraindications to fibrinolysis included stroke within the last 3 months, surgery or trauma within the last 14 days, gastric or duodenal ulcers, or active bleeding. In the case of β-blockers, overt heart failure, bradycardia ≤50 beats/min, atrioventricular (AV) block II or III, or severe chronic obstructive pulmonary disease were regarded as contraindications. ACE inhibitors were considered contraindicated in the case of cardiogenic shock or systolic blood pressure ≤100 mm Hg.

Statistical analysis

Data collection. Each participating center was committed by written consent to include each patient with ST segment elevation myocardial infarction during the study period. The patients provided written informed consent for processing their anonymous data.

Data of the prehospital and early in-hospital period (48 hours) were collected within the first 2 to 3 days in the intensive care unit. Clinical events during the hospital stay were reported on a second form at discharge. All data sheets were sent to the central data processing center (Department of Cardiology, Herzzentrum Ludwigshafen) for monitoring and registration.

Data analysis. Absolute numbers, mean values, and percentages were used to describe the patient population and the odds ratio and 95% confidence intervals were computed. Categorical values were compared by chi-square analysis or Fisher exact test as appropriate. Continuous variables were compared by the 2-tailed Wilcoxon rank sum test. Multivariate logistic regression analysis was used to determine factors influencing aspirin therapy (ie, patient demographics: age, sex, location of infarction, cardiogenic shock, prehospital resuscitation, nondiagnostic first electrocardiogram, unknown prehospital delay, reperfusion therapy; concomitant diseases: history of AMI, stroke, peptic ulcer, renal insufficiency; hospital type: with cardiology department or without). A second model was created without patients who died within the first 48 hours after admission. Multiple logistic regression was also used to analyze the association between aspirin and reperfusion therapy as well as concomitant medication. Adjustments were made for age, sex, location of infarction, prehospital delay, and concomitant diseases.

Mortality rates were adjusted for baseline patient characteristics (age, sex, prehospital resuscitation, cardiogenic shock, and concomitant diseases) in the two patient groups.

All P values are results of 2-tailed tests. A P value of <.05 was considered significant.

All statistical analyses were performed with the SAS statistical package (version 6.12) (SAS Institute, Cary, NC).

Results

Of 22,572 patients included in the MITRA and MIR registries from 1994 to 1998, 1767 (7.8%) did not receive aspirin within the first 48 hours after AMI.

Baseline patient characteristics

Patients without aspirin for AMI were different from those who received aspirin in all categories of baseline characteristics. They were older (mean age 73 years vs 67 years), more often female (43.6% vs 33.9%), had more concomitant diseases, and were much more often in critical condition at admission (cardiogenic shock, prehospital resuscitation) than patients receiving aspirin (Table I).

Active bleeding was found in only 4.9% of all patients without aspirin for AMI and in 0.3% of patients with aspirin. Relative contraindications (history of gastric or duodenal ulcer, renal insufficiency) were also found more often in patients without aspirin (9.6% vs 3.3% and 7.8% vs 3.0%). In addition, contraindications to fibrinolysis (active bleeding, recent stroke, trauma, surgery, or peptic ulcer) were more frequently found in patients without aspirin (17.7% vs 5.7%). Patients who were admitted to a hospital with a separate department
of cardiology showed a nonsignificant tendency toward a higher frequency of aspirin therapy than did patients who were admitted to general hospitals.

Multivariate analysis revealed two main variables associated with withholding aspirin therapy for AMI: relative contraindications to aspirin (gastric ulcer [odds ratio (OR) 4.9, 95% confidence interval (CI) 3.7–5.7] and renal insufficiency [OR 1.4, 95% CI 1.1–1.8]) and critical condition at admission (cardiogenic shock, OR 1.5, 95% CI 1.2–2.1; prehospital resuscitation OR 1.8, 95% CI 1.4–2.2). These numbers did not change significantly after the exclusion of high-risk patients who died in the first 48 hours after admission to the hospital from this analysis (Figure 1). Any of these conditions were present in 77.9% of the patients without and in 51.6% of those with aspirin for AMI, leaving the reasons for withholding aspirin unclear in 22.1% of all cases.

**Acute management of AMI and in-hospital course**

Univariate analysis showed that patients without aspirin for AMI were less likely to receive reperfusion therapy (fibrinolysis, primary angioplasty, or the combi-
nation of fibrinolysis and angioplasty) than patients with aspirin (22.2% vs 52.4%, \(P < .001\)) (Table II). They were also less likely to receive adjunctive medical therapy. Multivariate analysis showed a significant association of withheld aspirin therapy and less reperfusion therapy and adjunctive medication (reperfusion therapy: OR 0.41, 95% CI 0.35-0.48; \(\beta\)-blocker: OR 0.35, 95% CI 0.31-0.40; ACE inhibitor: OR 0.47, 95% CI 0.41-0.53). In an additional model created without high-risk patients (first electrocardiogram not diagnostic, cardiogenic shock, prehospital resuscitation, death <48 hours after admission, contraindications to fibrinolysis), withholding aspirin therapy was still significantly associated with less reperfusion therapy and less adjunctive medication (reperfusion therapy: OR 0.41, 95% CI 0.34-0.48; \(\beta\)-blocker: OR 0.38, 95% CI 0.33-0.43; ACE inhibitor: OR 0.49, 95% CI 0.43-0.56). However, more than two thirds of the patients (77.5%) who did not receive aspirin initially were treated with aspirin at discharge.

If fibrinolysis was administered in patients without aspirin, complications (stroke, reversible neurologic deficits, gastric bleeding, bleeding requiring transfusion, or allergic reaction to a fibrinolytic substance) were three times more frequent among them (9.9% vs 3.7%, \(P < .001\)).

In-hospital mortality was more than three times higher in patients without aspirin for AMI (38.9% vs 12.9%, \(P < .001\)). After adjustment for baseline characteristics in the two groups (age, sex, resuscitation, cardiogenic shock, concomitant diseases), mortality was 27.2% among the patients without aspirin compared with 11.1% in the patients with aspirin for AMI.

**Table II. Therapy of AMI and clinical course**

<table>
<thead>
<tr>
<th></th>
<th>No aspirin (n = 1767)</th>
<th>Aspirin (n = 20,805)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute management of AMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any reperfusion therapy</td>
<td>22.2 [392/1767]</td>
<td>52.4 [10,898/20,805]</td>
</tr>
<tr>
<td>Fibrinolysis</td>
<td>18.3 [324/1767]</td>
<td>42.4 [8813/20,805]</td>
</tr>
<tr>
<td>Primary angioplasty</td>
<td>2.8 [50/1767]</td>
<td>8.0 [1658/20,805]</td>
</tr>
<tr>
<td>(\beta)-Blocker</td>
<td>21.8 [386/1767]</td>
<td>57.9 [12,037/20,805]</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>29.4 [519/1767]</td>
<td>55.8 [11,601/20,805]</td>
</tr>
<tr>
<td>Contraindications to aspirin*</td>
<td>4.9 [87/1766]</td>
<td>0.3 [69/20,781]</td>
</tr>
<tr>
<td>Contraindications to fibrinolysis†</td>
<td>17.7 [313/1766]</td>
<td>5.7 [1190/20,781]</td>
</tr>
<tr>
<td>Complications after fibrinolysis‡</td>
<td>9.9 [34/342]</td>
<td>3.7 [344/9240]</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>2.8 [49/1767]</td>
<td>1.2 [254/20,805]</td>
</tr>
<tr>
<td>In-hospital course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>38.9 [688/1767]</td>
<td>12.9 [2680/20,805]</td>
</tr>
<tr>
<td>Nonfatal major adverse cardiovascular or cerebral events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reinforcement</td>
<td>2.5 [45/1767]</td>
<td>2.7 [557/20,805]</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.8 [15/1767]</td>
<td>0.5 [105/20,805]</td>
</tr>
</tbody>
</table>

*Active bleeding at admission.
†Active bleeding, stroke within ≤3 months, trauma, or surgery within ≤14 days.
‡Stroke, reversible neurologic deficits, gastric bleeding, bleeding requiring transfusion, allergic reaction to fibrinolytic substance.

**Discussion**

We used data of the MITRA and MIR registries, collected between 1994 and 1998, and analyze patient demographics and clinical courses of patients without aspirin for AMI. These registries provide data on a wide range of patients in routine clinical practice all over Germany. Although randomized clinical trials (RCTs) are the best scientific technique for evaluating the effect of therapies in medicine, they do not provide data on current clinical practice. Patients in RCTs are also usually highly selected, which limits the generalizability of their clinical data.

In MITRA and MIR, only a minority of patients (7.8%) did not receive aspirin for AMI, a smaller number than those reported in earlier studies.\(^8\)\(^-\)\(^12\) This is largely due to the increase of the adoption of effective medications after the publication of randomized trials and guidelines.\(^10\)\(^\)\(^11\) However, it may also be an effect of the participation in these registries and quality control measurements.\(^3\)

Analysis of the data revealed two main factors influencing aspirin therapy in patients with AMI today: clinical state at admission and absolute and relative contraindications to aspirin.

**Clinical state at admission**

Patients in critical condition at admission (cardiogenic shock, prehospital resuscitation) were significantly less likely to receive aspirin for AMI. Acute management of life-threatening hemodynamic instability may be the main focus in the early phase after AMI and some patients may have died before they had the possibility to receive aspirin. However, more than two
thirds of the patients without aspirin during the acute phase of AMI received aspirin at discharge, and logistic regression analysis revealed that patients who recovered from prehospital resuscitation were among the patients most likely to do so (OR 1.9, 95% CI 1.2-3.2).

Absolute and relative contraindications to aspirin

In the current study, absolute contraindications to aspirin (active bleeding at admission) were rare (0.3% of the patients with aspirin and 4.9% of the patients without aspirin) and accounted for only a small number of patients without aspirin for AMI.

Relative contraindications to aspirin are far more common. They include gastric or duodenal ulcers, renal insufficiency, hypersensitivity to aspirin, and concurrent anticoagulant therapy. Data on hypersensitivity to aspirin or anticoagulant therapy were not collected in MITRA and MIR, but multivariate analysis revealed history of peptic ulcer and renal insufficiency as independent determinants of withholding aspirin (Figure 1): 18.1% of the patients with impaired renal function and 19.8% of the patients with a history of peptic ulcers did not receive aspirin for AMI. Given the indisputable benefits of aspirin for AMI, these numbers indicate that in routine clinical practice concerns among physicians about the inherent complications of aspirin therapy still lead them to withhold this highly effective drug from a substantial number of patients without the objective necessity to do so. In addition, withholding aspirin was significantly associated with withholding reperfusion therapy and other medication of proved benefit such as β-blockers and ACE inhibitors even after the exclusion of high-risk patients from multivariate analysis. Although the contraindications to aspirin and fibrinolysis and ACE inhibitors overlap, these findings show that patients without aspirin for AMI represent a subgroup of patients who are treated less aggressively than others.

Univariate analysis showed a trend toward higher rates of aspirin therapy in hospitals with a cardiology department. Although these numbers did not reach statistical significance in the multivariate analysis, they suggest that patients will be more likely to receive aspirin if they are treated by a cardiologist. Recent studies have shown similar findings.9,11,14

Recent studies have also shown the underutilization of therapies of proved benefit and higher mortality rates for AMI in older patients as well as women.15-17 In the current study, univariate analysis suggested underutilization of aspirin among women and elderly patients. These findings were not confirmed by multivariate analysis.

In-hospital course

In-hospital mortality was more than three times higher among patients without aspirin compared with patients with aspirin for AMI.

Registries are not designed to make statements on the causal influence of medical therapy on clinical outcomes. Second, the patients without aspirin were a small and highly selected group. Hence we did not perform a multivariate analysis on the influence of aspirin on in-hospital mortality. After adjustment for baseline patient characteristics, however, the in-hospital mortality rates were still almost three times higher among the patients without aspirin. This difference is greater than in ISIS-2 and cannot completely be attributed to the missing aspirin therapy. It suggests, however, that as a patient characteristic that is associated with a number of adverse conditions, withheld aspirin for AMI indicates a higher risk for in-hospital death.

Conclusions

In current clinical practice in Germany, only a minority of patients (7.8%) do not receive aspirin for AMI. Our study revealed two main factors influencing the application of aspirin:

1. Patients in critical condition at admission. If these patients survived the early phase of AMI, they were most likely to receive aspirin later during their hospital stay.
2. Absolute contraindications account for only a small number of patients without aspirin. Relative contraindications to aspirin such as gastric or duodenal ulcers and renal insufficiency still lead physicians to withhold this highly effective drug from a substantial number of AMI patients.

References

9. Wagner S, Schneider S, Schiele R, et al. Acute myocardial infar-


