Simple Risk Stratification at Admission to Identify Patients With Reduced Mortality From Primary Angioplasty

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Background—Randomized trials comparing fibrinolysis with primary angioplasty for acute ST-elevation myocardial infarction have demonstrated a beneficial effect of primary angioplasty on the combined end point of death, reinfarction, and disabling stroke but not on all-cause death. Identifying a patient group with reduced mortality from an invasive strategy would be important for early triage. The Thrombolysis in Myocardial Infarction (TIMI) risk score is a simple validated integer score that makes it possible to identify high-risk patients on admission to hospital. We hypothesized that a high-risk group might have a reduced mortality with an invasive strategy.

Methods and Results—We classified 1527 patients from the Danish Multicenter Randomized Study on Fibrinolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2) trial with information for all variables necessary for calculating the TIMI risk score as low risk (TIMI risk score, 0 to 4) or high risk (TIMI risk score ≥5) and investigated the effect of primary angioplasty versus fibrinolysis on mortality and morbidity in the 2 groups. Follow-up was 3 years. We classified 1134 patients as low risk and 393 as high risk. There was a significant interaction between risk status and effect of primary angioplasty (P=0.008). In the low-risk group, there was no difference in mortality (primary angioplasty, 8.0%; fibrinolysis, 5.6%; P=0.11); in the high-risk group, there was a significant reduction in mortality with primary angioplasty (25.3% versus 36.2%; P=0.02).

Conclusions—Risk stratification at admission based on the TIMI risk score identifies a group of high-risk patients who have a significantly reduced mortality with an invasive strategy of primary angioplasty. (Circulation. 2005;112:2017-2021.)

Key Words: angioplasty ■ fibrinolysis ■ mortality ■ myocardial infarction

The initial treatment of patients with acute ST-segment elevation myocardial infarction is either fibrinolysis or primary angioplasty. Several trials have demonstrated a superior effect of primary angioplasty over fibrinolysis, and this observation has been substantiated in meta-analyses. Consequently, current guidelines recommend primary angioplasty as the treatment of choice whenever feasible. There is still no consensus, however, as to whether all patients benefit from an invasive strategy when applied to a community setting, including hospitals without invasive treatment facilities. Reduced mortality has been demonstrated with urgent angioplasty for patients with cardiogenic shock complicating acute myocardial infarction, but no trial that included noninvasive treatment hospitals has succeeded in documenting an effect on mortality for a substantial proportion of patients with acute ST-segment elevation myocardial infarction. The most recent report on the use of primary angioplasty from the Global Registry of Acute Coronary Events (GRACE) showed that 26.7% of patients with acute ST-segment elevation myocardial infarction were treated with primary angioplasty and 47% received fibrinolysis.

It has been shown in a community-based patient sample that the added benefit of primary angioplasty increases with higher overall risk. Consequently, in high-risk patients, primary angioplasty might reduce mortality compared with fibrinolysis. Thus, identifying such high-risk patients would be desirable. If a full community-wide strategy of invasive treatment for all patients with ST-elevation myocardial infarction is not feasible, identifying patients most likely to benefit from the invasive strategy on admission is very important.

The Thrombolysis in Myocardial Infarction (TIMI) risk score for ST-segment elevation myocardial infarction is a

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simple arithmetic score based on data easily obtained at admission. When the TIMI risk score is used at admission, patients can easily be classified as low or high risk without any delay in treatment. Analyses of multiple clinical trials of fibrinolysis and a community-based population that included patients treated with primary angioplasty have validated that a higher TIMI risk score is associated with a greater risk of death from all causes.\(^9,10\)

Thus, for the present study, we applied the TIMI risk score to classify patients as low or high risk in the Danish Multicenter Randomized Study on Fibrinolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2) and hypothesized that high-risk patients would have a greater benefit from primary angioplasty than low-risk patients.

**Methods**

The design and rationale of the DANAMI-2 trial have been published previously.\(^1\) In brief, 1572 patients with acute ST-segment elevation myocardial infarction were randomized to fibrinolysis with intravenous alteplase or primary angioplasty. We recruited 1129 patients from 24 referral hospitals without invasive treatment facilities and 443 patients from 5 invasive treatment centers.

For the present study, we used patient data and vital signs obtained at randomization in the DANAMI-2 trial. For each patient, the TIMI risk score was calculated as the arithmetic sum of the following variables obtained at admission: age \(\geq 75\) years = 3 points; age 65 to 74 years = 2 points; systolic blood pressure < 100 mm Hg = 3 points; heart rate > 100 bpm = 2 points; Killip class 2 to 4 = 2 points; weight < 67 kg = 1 point; anterior ST-segment elevation = 1 point; time from symptom onset to treatment > 4 hours = 1 point; and a history of angina, diabetes, or hypertension = 1 point, for a possible score of 0 to 14.\(^*\) Time to treatment was defined as time to onset of fibrinolysis or the time to first injection of contrast in the coronary artery.

Patients were classified as low risk if their TIMI score was 0 to 4 and as high risk if their TIMI score was \(\geq 5\). Survival analyses were carried out using Kaplan-Meier curves with log-rank tests for homogeneity. Hazard ratios were analyzed with Cox regression analysis. Analyses of possible interaction between attributed risk and treatment strategy were performed by entering an interaction term into the regression model. For all analyses, a value of \(P < 0.05\) was considered statistically significant. Analyses were performed with SAS version 9.1 (SAS Institute Inc.).

The primary end point was time to death from all causes. Our secondary end point was the composite end point of death, recurrent myocardial infarction, and disabling stroke. Patients follow-up was 3 years; patients suffering a nonfatal event continued follow-up for the mortality end point. The present study was not prespecified in the original DANAMI-2 protocol.

The DANAMI-2 protocol was approved by the local ethics committee for all participating hospitals. All patients gave written informed consent.

**Results**

The results from the DANAMI-2 trial have been published previously.\(^12\) In summary, there was a relative risk reduction with primary angioplasty for the combined end point of death, reinfarction, and disabling stroke at 30 days of 42% \((P < 0.001)\) but no difference in all-cause mortality \((P = 0.35)\). The present study population consisted of 1527 patients for whom all TIMI risk score variables were available. The information missing was weight for 19 patients; previous angina, diabetes, or hypertension for 9 patients; systolic blood pressure for 4 patients, Killip class for 4 patients; heart rate for 2 patients; and time to treatment for 22 patients. Results were unchanged whether the patients with missing data were included with their highest or lowest possible score. On average, the 45 patients not included in the analysis were insignificantly older (mean difference, 4.3 years; \(P = 0.06\)) and more often female (40% versus 26%; \(P = 0.04\)).

Baseline demographics are shown in the Table. All variables included in the TIMI risk score were more prevalent in the high-risk group than in the low-risk group. Smoking was more prevalent in the low-risk group.

The TIMI risk score was distributed as follows: 0 points, 139 patients; 1 point, 265 patients; 2 points, 259 patients; 3 points, 243 patients; 4 points, 228 patients; 5 points, 147 patients; 6 points, 106 patients; 7 points, 82 patients, and \(\geq 8\) points, 58 patients. No patients had a TIMI risk score \(> 11\) points. The TIMI risk score was a significant predictor of all-cause death \((P < 0.001)\), with a hazard ratio for each additional point in the TIMI score of 1.57 \((95\% \text{ CI}, 1.48\) to 1.68\)).

Figure 1 displays the Kaplan-Meier curves associated with the 2 treatment strategies stratified by risk status according to TIMI risk score. There was a significant interaction between attributed risk and treatment strategy \((P = 0.008)\). For patients classified as low risk, there was no significant difference in 3-year mortality between the 2 treatment arms (primary angioplasty, 8.0%; fibrinolysis, 5.6%; hazard ratio, 1.44; 95% CI, 0.91 to 2.27; \(P = 0.11\)), whereas patients classified as high risk had a significantly lower 3-year mortality rate with the invasive strategy compared with fibrinolysis \((25.3\% \text{ versus } 36.2\%); \text{ number needed to treat, 9}; \text{ hazard ratio, 0.66}; \text{ 95\% CI, 0.45 to 0.94}; \text{ } P = 0.02\). For patients randomized at a referral hospital, there was a significant reduction in mortality with primary angioplasty over fibrinolysis for high-risk patients \((24.6\% \text{ versus } 36.8\%); \text{ number needed to treat, 8}; \text{ } P = 0.02\) but not for low-risk patients \((7.5\% \text{ versus } 6.6\%); \text{ } P = 0.62\). Because of the low difference in mortality for the low-risk patients, this interaction was not statistically significant \((P = 0.07)\). Results for invasive centers were also similar to the overall results but did not show significance because of low patient numbers and number of events.

When the composite end point of death, reinfarction, and disabling stroke is used, there is no difference in effect between primary angioplasty and fibrinolysis in the low-risk group \((13.7\% \text{ versus } 15.7\%); \text{ } P = 0.30\), but there is a significant reduction in events with primary angioplasty in the high-risk group \((32.3\% \text{ versus } 45.9\%); \text{ } P = 0.004\). The interaction was not significant \((P = 0.17)\). Event curves are shown in Figure 2.

There was a significant reduction in number of reinfarctions in the low-risk group with primary angioplasty \((6.6\% \text{ versus } 10.4\%); \text{ } P = 0.02\), whereas in the high-risk group, it was not significant because of the lower patient numbers \((10.2\% \text{ versus } 13.5\%); \text{ } P = 0.18\). There was no significant interaction between treatment strategy and risk status \((P = 0.78)\). The number of disabling strokes was low in both the low- and high-risk groups, and there was no significant difference in effect between treatments in either group \((\text{low-risk group, } 1.7\% \text{ versus } 1.6\%, \text{ } P = 0.87; \text{ high-risk group, } 5.3\% \text{ versus } 9.2\%, \text{ } P = 0.11)\).
Our results show that stratifying patients with acute ST-segment elevation myocardial infarction as low or high risk by the use of the TIMI risk score identifies a group of high-risk patients with a lower 3-year mortality rate with primary angioplasty than with fibrinolysis. To the best of our knowledge, this is the first time such a substantial and readily identifiable proportion of patients with acute ST-segment elevation myocardial infarction has been shown to have reduced mortality with primary angioplasty compared with fibrinolysis in a community-setting that included both referral and invasive treatment hospitals.

The statistical interaction between risk status and treatment effect was due in part to an inverse effect in the low-risk group that did not reach statistical significance. This trend strengthens the conclusion that there indeed is an interaction between risk status and the effect of treatment and that the lack of significant effect of primary angioplasty in the low-risk group is not due merely to a low number of events.

Our results are in concordance with the analysis by Kent and coworkers,8 who found that an effect on mortality from primary angioplasty was not likely in patients with an estimated 30-day mortality rate of $\approx 2\%$ or less. The 30-day mortality rate in the low-risk group treated with fibrinolysis in the present study was $2.5\%$, so the low-risk group corresponds well to the group of patients not likely to obtain a reduction in mortality from primary angioplasty according to Kent and coworkers. In contrast to our results, Morrow and coworkers10 found, when validating the TIMI risk score in the National Registry of Myocardial Infarction 3, that there was no difference between the slopes of mortality gradients with increasing risk scores for primary angioplasty and fibrinolysis. This discordance might be due to differences in demographics because the patients in the National Registry of Myocardial Infarction 3 were, of course, not randomized.

Our results are also in concordance with the overall 30-day results from the DANAMI-2 trial. In the present study, there was a larger reduction in the combined end point in the high-risk group than in the low-risk group, but this difference was not significant. Thus, the reduced incidence of the combined end point for patients randomized to primary angioplasty was not exclusive to the high-risk group of patients. The reduced incidence of the combined end point of death, reinfarction, and disabling stroke with primary angioplasty reported previously for the DANAMI-2 trial applies to the entire trial population. This results particularly from the

### Discussion

<table>
<thead>
<tr>
<th>Baseline Demographics</th>
<th>TIMI Score 0–4</th>
<th>TIMI Score $\geq 5$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fx (n=556)</td>
<td>PA (n=578)</td>
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<tr>
<td>Age, y</td>
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<td>59±11</td>
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<tr>
<td>Female gender, %</td>
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<td>22</td>
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<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>History of</td>
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<td>Myocardial infarction*</td>
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<tr>
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<td>17</td>
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<td>Diabetes*</td>
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<tr>
<td>Randomized at invasive center, %</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135±24</td>
<td>138±24</td>
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<tr>
<td>Heart rate, bpm</td>
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<td>73±16</td>
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<td>TIMI risk score components, %</td>
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<tr>
<td>Age $\geq$ 75 y*</td>
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<td>6</td>
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<td>Age 65–74 y*</td>
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<td>Heart rate $&gt;100$ bpm *</td>
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<td>Weight &lt;67 kg*</td>
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<td>Anterior myocardial infarction*</td>
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<td>&gt;4 h to treatment†</td>
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<td>Glycoprotein IIb/IIIa inhibitor, † %</td>
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<tr>
<td>β-Blocker at discharge, %</td>
<td>87</td>
<td>89</td>
</tr>
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</table>

Fx indicates fibrinolysis; PA, primary angioplasty; and BMI, body mass index.

*P<0.05 for comparison between the 2 TIMI score groups.
†P<0.05 for comparison between the fibrinolysis and primary angioplasty groups within the same TIMI score group.
markedly reduced rate of reinfarction in the primary angioplasty group and the fact that the effect of treatment does not interact with risk groups. TIMI risk score was developed to predict mortality and thus includes parameters not as strongly related to the risk of reinfarction.

Our finding that primary angioplasty reduces mortality for high-risk patients admitted to referral hospitals without facilities for primary angioplasty was the hypothesis of the randomized AIR-PAMI study, which was terminated early as a result of low inclusion rates. The data from AIR-PAMI showed a nonsignificant trend toward reduced 30-day mortality with primary angioplasty, and we substantiate this finding because our data demonstrate that high-risk patients admitted to a referral hospital in the DANAMI-2 trial indeed did have reduced mortality at 3 years. The definition of high-risk patients in AIR-PAMI was based on the same variables as contained in the TIMI risk score, but classification of high risk required only the presence of 1 high-risk criterion, whereas our definition of high risk requires a minimum of 2 high-risk criteria present to obtain a TIMI score of at least 5.

Recently, a paper from the GRACE investigators reported that there was no benefit in outcomes for patients admitted to a hospital with invasive facilities compared with patients admitted to a hospital without invasive facilities. This analysis was based on all patients with acute coronary syndrome, including patients with unstable angina and non–ST-segment elevation myocardial infarction, which constitutes a patient group with a much lower overall risk than our high-risk group. Furthermore, analyses were performed according to whether the hospital had invasive facilities, and not whether patients were actually treated invasively. Thus, the analysis of the GRACE registry with its different focus is not comparable to ours.

The present results could have important implications for clinical practice. Because previous analyses showed an increased benefit of primary angioplasty in patients at greater risk, the next step has been to identify such a group of high-risk patients. Our analysis suggests that the TIMI risk score might serve as an impetus to perform urgent angioplasty by making it possible to rapidly identify on admission those patients whose mortality risk would most likely be reduced by an invasive approach. This will be of particular importance in communities with limited resources for primary angioplasty where not all patients can be offered this treatment strategy and where risk stratification would make it possible to prioritize high-risk patients with particular benefit of an invasive strategy. It is possible that the added costs of implementing a community-wide program is due more to the setup of the infrastructure rather than the individual transfers, so it might be just as costly to implement a system to transport only high-risk patients as to transport all patients with ST-elevation myocardial infarction. However, the TIMI risk score would still be beneficial in deciding who should be transported for primary angioplasty in communities with low capacity.

Because the TIMI risk score for risk stratification of patients was not published before DANAMI-2 was conducted, the present study constitutes a post hoc analysis not specified in the original protocol. However, the idea to investigate using the TIMI risk score to identify high-risk patients who would possibly benefit more from primary angioplasty was conceived before any analyses were made. Our decision to use a TIMI score ≥5 to define the high-risk group is identical to the definition used by the TIMI Study Group. The TIMI Study Group further divided the groups with TIMI risk scores <5 into a low-risk group and an intermediate group, but we chose to collapse these 2 groups into 1 because we considered a high-risk versus low-risk variable to be more operational and because the 2 groups showed similar results in our analyses (data not shown).

Although the TIMI risk score assigns 1 point for anterior myocardial infarction or new left bundle-branch block, patients with left bundle-branch block were excluded from the
DANAMI-2 trial to avoid diagnostic uncertainty, so this variable is different from that of the original TIMI risk score. Because there were no patients with left bundle-branch block in the 2 treatment groups, this should not cause any discrepancy between groups and thus should not affect the analysis.

In summary, although individual trials and a meta-analysis show a clear benefit of primary angioplasty compared with fibrinolysis on the combined end point of all-cause death, reinfarction, and disabling stroke, no benefit on mortality of a community-wide invasive strategy including invasive and referral hospitals has been demonstrated. The reason could be that patients at low risk of death do not obtain a significant reduction of mortality and that this dilutes the benefit obtained by high-risk patients. Thus, by identifying a group of easily recognizable high-risk patients, we have shown that these patients do indeed have a significantly reduced mortality with an invasive strategy. This signifies that not only patients in cardiogenic shock but also a substantially larger proportion of patients with acute ST-segment elevation myocardial infarction (26% of the DANAMI-2 population) would experience a lower mortality with a community-wide implementation of an invasive strategy of primary coronary angioplasty.

References


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