Prognostic Assessment of Patients With Acute Myocardial Infarction Treated With Primary Angioplasty
Implications for Early Discharge

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Background—The aim of this study was to create a practical score for risk stratification in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary angioplasty and to assess the feasibility of early discharge in low-risk patients.

Methods and Results—A prognostic score was built according to 30-day mortality rates in 1791 patients undergoing primary angioplasty for STEMI. For the identified low-risk patients without any contraindication to early discharge, we estimated and compared the costs of conventional care (prolonged 24-hour hospitalization) with the costs of shifting the care from inpatient to outpatient setting (early discharge) between 48 and 72 hours. Independent predictors of 30-day mortality included in the score were age, anterior infarction, Killip class, ischemic time, postprocedural Thrombolysis In Myocardial Infarction (TIMI) flow, and multivessel disease. This score was able to identify a large cohort (73.4%) of low-risk (score ≤3) patients, with a good discriminatory capacity (c statistic=0.907). The mortality rate was 0.1% at 2 days and 0.2% between 2 and 10 days in patients with a score ≤3. The incremental cost-effectiveness ratio for late discharge in low-risk patients was estimated at €1949.33. Therefore, this policy would save 1 life per 1097 low-risk patients, at additional costs of €194 933.33, in comparison with an early discharge policy.

Conclusions—This score is a practical and useful index for risk stratification after primary angioplasty for STEMI, with a significant impact on clinical decision-making and the related costs. It reliably identifies a large group of patients at very low risk, who may safely be discharged early after primary angioplasty. (Circulation. 2004;109:2737-2743.)

Key Words: angioplasty ■ myocardial infarction ■ prognosis ■ cost-benefit analysis

Despite the excellent results of reperfusion therapies for ST-segment elevation myocardial infarction (STEMI), the mortality rate across different patient categories and the safety issue of early discharge remain controversial.1–2 Increasing economic pressures have intensified the need for risk scores to tailor in-hospital treatment of patients with STEMI according to their risk of future events.3 Identification of a low-risk subset of patients seems to be an attractive way to reduce hospitalization and costs.

Although several scores have been introduced as useful tools for bedside risk stratification of patients with STEMI,4–9 they cannot be fully applied to patients treated with primary angioplasty. Currently available risk scores have been developed in patients treated with medical therapy, with or without thrombolysis, without taking into account the procedural variables that significantly affect the outcome of these patients.10–12 Therefore, the present study was conducted to create, by identifying predictors of 30-day mortality, an easy and practical score for early risk stratification in patients with STEMI treated with primary angioplasty.

Methods

Our population comprised a total of 1791 patients with STEMI treated by primary angioplasty between August 1994 and October 2001. Informed consent was obtained from each patient before the angiogram. Our study was approved by the institutional review board. All patients presenting within 6 hours from symptom onset, or between 6 and 24 hours if they had persistent or recurrent chest pain and/or ST-segment elevation, were included.11 All patients received aspirin (500 mg) and heparin (10 000 IU) intravenously before the procedure. All patients were taking aspirin after the procedure. In case of stenting, additional 3-month warfarin therapy (before 1996) or additional 1-month antiplatelet therapy with ticlopidine or clopidogrel (after 1996) was given.

Angiograms were analyzed by an independent core laboratory (Diagram, Zwolle, The Netherlands), blinded to all data apart from the coronary angiogram. Residual stenosis was visually assessed. Procedural success was defined as postprocedural Thrombolysis In Myocardial Infarction (TIMI) 3 flow and residual stenosis <50%.13 Enzymatic infarct size and predischarge ejection fraction were measured as previously described.14

Clinical Outcome

Records of patients who visited the outpatient clinic were reviewed. For all other patients, information was obtained from their physician...
or by telephone interview with the patient. For patients who died during follow-up, hospital records and necropsy data were reviewed. No patient was lost to follow-up.

Cost-Effectiveness Analysis
For the identified low-risk patients without any contraindication to early discharge, we estimated and compared the costs of conventional care (prolonged 24 hours of hospitalization, estimated at €256) with those of early discharge (outpatient care from 48 to 72 hours estimated at €78, including outpatient visit, ECG, and cardiac enzyme measurement). The costs for repeat angioplasty and hospitalization in the coronary care unit were estimated at €5400 and €762/d, respectively. Out-of-hospital resuscitation was estimated at €700 and a visit to the emergency unit at €89. Unit charges were calculated on the basis of hospital records of 2001. The balance between costs and effects was assessed by calculation of the incremental cost-effectiveness ratio (average costs per patient for late discharge minus those for early discharge policy divided by the percentage difference in 30-day survival) and the average cost-effectiveness ratio for both groups (the average costs per patient divided by the percentage of survivors at 30 days). A multiple logistic regression analysis was performed to identify independent variables associated with 30-day mortality. The stepwise selection of the variable and estimation of significant probabilities were computed by means of maximal likelihood ratio test. The additional value of each category of variables added sequentially was evaluated on the basis of the increases in the overall likelihood statistic ratio. The final score was built according to the global $\chi^2$ value of the multivariate statistical

| TABLE 1. Demographic, Clinical, and Angiographic Characteristics of Patient Population ($n=1791$) and Validation Set ($n=747$) |
|-----------------|-----------------|-----------------|-----------------|
| Variables       | Population      | Validation Set  | $P$             |
| Age, y          | 60±11           | 61±11           | NS              |
| Male            | 1420 (79.3)     | 583 (78)        | NS              |
| Hypertension    | 399 (22.3)      | 180 (24.1)      | NS              |
| Diabetes        | 157 (8.8)       | 76 (10.1)       | NS              |
| Hypercholesterolemia | 327 (18.3)  | 169 (21.2)      | NS              |
| Smoking         | 842 (47)        | 378 (50.6)      | NS              |
| Previous infarction | 204 (11.4) | 77 (10.3)       | NS              |
| Previous revascularization | 150 (8.4) | 41 (5.5)       | NS              |
| Transferred     | 692 (38.6)      | 299 (40)        | NS              |
| Ischemic time, h | 3.5±1.3        | 3.7±1.4         | NS              |
| Anterior infarction or LBBB | 920 (51.4) | 379 (50.7)      | NS              |
| Killip class >1 | 212 (11.8)      | 72 (9.6)        | NS              |
| Multivessel disease | 963 (53.8) | 373 (49.9)      | NS              |
| Left anterior descending artery | 886 (49.5) | 366 (49)       | NS          |
| Preprocedural TIMI 0–1 | 1321 (73.8) | 528 (70.7)      | NS              |
| Postprocedural TIMI 3 | 1620 (90.5) | 686 (91.8)      | NS              |
| Procedural success | 1599 (89.3) | 676 (90.5)      | NS              |
| Stent, %        | 892 (49.8)      | 433 (58)        | <0.001          |
| PredischARGE EF,* % | 44±11         | 43±11           | NS              |
| LDH48,† U/L     | 1815±1557†      | 1710±1535       | NS              |
| 30-Day death    | 65 (3.6)        | 27 (3.6)        | NS              |

Values are n (%) or mean±SD. LBBB indicates left bundle branch block; EF, ejection fraction; and LDH48, cumulative lactate dehydrogenase enzyme release up to 48 hours.
*Available in 1143 and 597 patients in the study population and validation set, respectively.
†Available in 1069 and 497 patients in the study population and validation set, respectively.

Statistical Analysis
Statistical analysis was performed with the SPSS 10.0 statistical package. Continuous data were expressed as mean±SD and categorical data as percentage. ANOVA was used for continuous variables, and the $\chi^2$ test or Fisher’s exact test was used for categorical variables as appropriate. Univariate relations between variables and 30-day mortality rates were assessed by logistic regression analysis. A probability value <0.05 was considered statistically significant.

- Four categories were identified according to 3 thresholds (55, 65, and 75 years).
- Four categories were identified according to 3 thresholds (2, 4, and 6 hours).

| TABLE 2. Predictors of 30-Day Mortality: Univariate Analysis |
|-----------------|-----------------|-----------------|
| Univariate Analysis | $\chi^2$ | $P$             |
| Killip class     | 304.97          | <0.0001         |
| Postprocedural TIMI flow | 107.32      | <0.0001         |
| No. of diseased vessels | 34.92        | <0.0001         |
| Age*            | 30.29           | <0.0001         |
| Ischemia time†   | 16.08           | 0.001           |
| Anterior infarction | 15.53         | 0.001           |
| Preprocedural TIMI flow | 8.34        | 0.004           |
| Smoking         | 7.14            | 0.008           |
| Female gender   | 4.15            | 0.042           |

*Four categories were identified according to 3 thresholds (55, 65, and 75 years).
†Four categories were identified according to 3 thresholds (2, 4, and 6 hours).
model and the $\chi^2$ value of each variable. The receiver operating characteristics (ROC) curve was used to identify the best threshold value for both continuous and ordinal variables that were independent predictors of 30-day mortality. The following variables that were available from all patients were entered in the multivariate model when they were significantly related to mortality at univariate analysis: Age, sex, diabetes, hypercholesterolemia, smoking, family history of coronary artery disease, hypertension, previous infarction, revascularization or cerebrovascular accident, quartiles of inclusion period, infarct location, time-to-treatment, door-to-balloon time, Killip class at presentation, preprocedural and postprocedural TIMI flow, angiographic evidence of collaterals, multivessel disease, procedural success, and the use of stent.

Kaplan-Meier curves were used to estimate the event rate and to evaluate the stability of the score over time. The discriminatory capacity of the risk score was assessed by the area under the ROC curve ($c$ statistic) as an index of model performance. 17

**Validation Set**

This score has been validated in another cohort of patients ($n=747$) with STEMI treated by primary angioplasty from October 2001 to February 2003.

**Results**

Patient characteristics in the study population and the validation set are reported in Table 1. The actual hospitalization length was 5.9±6.7 days.

**Predictors of 30-Day Mortality**

The overall rate of 30-day mortality was 3.6%. Predictors of mortality at univariate and multivariate analysis are shown in Table 2 and Table 3, with the respective $\chi^2$ value to show the power of each variable to predict mortality.

**Zwolle Risk Score for STEMI**

Because of the global $\chi^2$ of the statistical model (210), a total of 21 points (10 $\chi^2=1$ point) were assigned to the independent variables according to their $\chi^2$ value in the multivariate model. Subsequently, according to the rate of events, different points were assigned to the values of each variable. By ROC curve, we identified the threshold value with the best discriminatory capacity for age ($\geq 60$ years), ischemic time

### Table 3. Predictors of 30-Day Mortality: Multivariate Analysis

<table>
<thead>
<tr>
<th>Step</th>
<th>$\chi^2$</th>
<th>Model</th>
<th>$-2$ Log Likelihood</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>KILLIP class</td>
<td>142.03</td>
<td>142.03</td>
<td>416.67</td>
</tr>
<tr>
<td>Step 2</td>
<td>TIMI flow post</td>
<td>29.65</td>
<td>171.68</td>
<td>387.02</td>
</tr>
<tr>
<td>Step 3</td>
<td>Age*</td>
<td>16.56</td>
<td>188.25</td>
<td>370.45</td>
</tr>
<tr>
<td>Step 4</td>
<td>Ischemia time†</td>
<td>10.04</td>
<td>198.29</td>
<td>360.41</td>
</tr>
<tr>
<td>Step 5</td>
<td>Anterior MI</td>
<td>6.79</td>
<td>205.08</td>
<td>353.62</td>
</tr>
<tr>
<td>Step 6</td>
<td>No. diseased vessels</td>
<td>5.75</td>
<td>210.83</td>
<td>347.87</td>
</tr>
</tbody>
</table>

*Four categories were identified according to 3 thresholds (55, 65, and 75 years).
†Four categories were identified according to 3 thresholds (2, 4, and 6 hours).

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**Figure 1.** Zwolle risk score for STEMI summarized for printing on a laminated card for clinical use. TIMI flow post indicates postprocedural TIMI flow. RR and 30-D indicate relative risk and 30-day, respectively.
(≥4 hours), and number of diseased vessels (>2). The score is reported in Figure 1. As depicted in Figure 2, this score was able to create a gradient in mortality risk across the population. Our score showed a strong predictive capacity ($c$ statistic = 0.907), even when it was limited to patients at lower risk (score ≤ 3) for 30-day mortality ($c$ statistic = 0.762). The prognostic capacity of the score was stable over multiple time points during 1-year follow-up (Figure 3).

This score was also able to identify a large cohort (n = 1315, 73.4%) of low-risk patients (score ≤ 3) with a very low mortality rate at 2 days (0.1%) and between 3 and 10 days (0.2%) (Figure 4). Medical therapy at discharge is reported in Table 4. The relation with ejection fraction and enzymatic infarct size (Table 4) clarifies the link between this score and mortality.

**Score Validation**

There were no major differences between the study population and the validation set, except for the rate of stenting (Table 1). As shown in the validation set (Figure 2), this score was also strongly associated with 30-day mortality ($c$ statistic = 0.902). Confirming the findings in the patient population, the score in the validation set was also able to identify a large subset of low-risk patients (score ≤ 3) with a very low mortality rate at 2 days and between 3 and 10 days (Figure 4).

**Feasibility of Early Discharge**

We found a 9.3% overall incidence of malignant arrhythmia (ventricular tachycardia or fibrillation) requiring electric cardioversion. Most (96%) were observed in the first 48 hours. In fact, among these low-risk patients, only 3 patients (0.2%) had a malignant ventricular arrhythmia after 48 hours, one between 48 and 72 hours and another at 2 weeks after primary angioplasty, and this was related to reinfarction caused by in-stent thrombosis.

Among 1315 low-risk patients identified by our risk score (score ≤ 3), we found a contraindication to early discharge in 218 patients (16.6%) (Table 5). This means that early discharge could have been applied to 1097 low-risk patients (83.4%), or 61.2% of the total population. The actual hospitalization length of these patients was 4.3±4.9 days, compared with 9.2±8.4 days in remaining patients ($P<0.001$). A cardiac arrest was observed in 20 of 665 patients not identified for early discharge, and only 4 of those were fatal.

As the estimated 30-day survival rate in low-risk patients was 99.73% for early discharge and 99.64% for conventional discharge policy, the average cost-effectiveness was €78.90 and €254.70, respectively ($P<0.001$). The incremental cost-effectiveness ratio for late discharge was €1949.33. Thus, the

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**Figure 2.** Bar graphs show risk stratification for 30-day mortality according to the Zwolle risk score in the study population (upper graph) and in the validation set (lower graph).

**Figure 3.** Kaplan-Meier survival curves show the stability of the risk score over time during 30-days’ and 1-year follow-up.
application of a conventional discharge policy (prolonged 24-hour hospitalization) to low-risk patients would save one life per 1097 patients, with additional costs estimated at €194 933.33, in comparison with an early discharge policy.

Discussion

This score is a practical and useful index for risk stratification after primary angioplasty for STEMI, with impact on clinical decision-making and the related costs. It can be calculated at bedside from easily obtainable variables by any care provider with the aid of a simple score card.

Risk Stratification and Early Discharge After Primary Angioplasty

In a trial conducted by Grines et al,, 471 low-risk patients (<50% of screened patients; age <70 years, no persistent arrhythmia, no triple-vessel disease, ejection fraction >45%, and successful reperfusion) were randomly assigned to early discharge or conventional care. Early discharge was applied to 60% of the randomly assigned patients (25% of the total population). The safety of early discharge was demonstrated by the very low 6-month mortality rate (0.8%). Despite this initial report, safety concern of such an approach still remains, as it has only been applied to a minority of patients.

The role of abciximab in reducing hospitalization length has also been addressed in a substudy of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. In contrast to the present study, in which risk stratification was performed according to independent predictors of mortality, this substudy identified high-risk patients according to age (>70 years), ejection fraction (<30%), suboptimal angioplasty result, refractory arrhythmias, and sustained hypotension or pulmonary edema. In up to 40% of patients, early discharge was not applied because of physician preference or patient’s refusal. Therefore, these aspects should also be kept in mind.

**Table 4.** Enzymatic Infarct Size, Ejection Fraction, and Medical Therapy at Discharge According to the Risk Score

<table>
<thead>
<tr>
<th>Score</th>
<th>0–3</th>
<th>4–6</th>
<th>7–9</th>
<th>&gt;10</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH&lt;sub&gt;48&lt;/sub&gt;, U/L</td>
<td>1588±1349</td>
<td>2147±1621</td>
<td>2338±1597</td>
<td>3745±2493</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection fraction,&lt;sup&gt;†&lt;/sup&gt; %</td>
<td>45±10 40±12</td>
<td>39±14 37±11</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers, %</td>
<td>89.4 84.3</td>
<td>67.5 61.1</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin, %</td>
<td>1.3 3.0</td>
<td>7.5 8.3</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone, %</td>
<td>0.5 2.6</td>
<td>2.5 11.1</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors, %</td>
<td>48.1 65.6</td>
<td>50 83.3</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium antagonist, %</td>
<td>2.9 5.9</td>
<td>0 11.1</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins, %</td>
<td>53.6 37.7</td>
<td>20 20</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>†</sup>Cumulative lactate dehydrogenase enzyme release up to 48 hours after symptom onset; available in 1069 patients.

<sup>†</sup>Available in 1143 patients.
TABLE 5. Low-Risk Patients With Contraindications to Early Discharge (n=218)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia or bleeding complications</td>
<td>47 (21.6)</td>
</tr>
<tr>
<td>Arrhythmia (VT/VF or AV block) at 24 to 48 h</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>9 (4.1)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>14 (6.4)</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>111 (50.8)</td>
</tr>
<tr>
<td>Fever</td>
<td>11 (5.0)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>Reocclusion</td>
<td>16 (7.3)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

Values are n (%). VT indicates ventricular tachycardia; VF, ventricular fibrillation; and AV, atrioventricular.

Although prognostic scores have been introduced in several studies, their complexity has made their application impractical. These scores have been applied to patients treated with medical therapy, with or without thrombolysis, with potential limitations in the application to patients treated by primary angioplasty, in whom survival is mainly affected by procedural outcome. By using postprocedural angiographic outcome, the c statistic for predicting mortality is higher than the risk scores that use only information at the time of presentation.

Consistent with the TIMI risk score, Killip class, anterior infarction, and time-to-treatment were included in our score. These factors have been shown to be main independent predictors of 30-day mortality. The prognostic role of ischemic time in primary angioplasty has been confirmed in a recent study, particularly in high-risk patients. To optimize risk stratification in patients with STEMI undergoing primary angioplasty, additional angiographic parameters were included in our score, as these factors have also been shown to be independent predictors of mortality.

Our score was able to identify a large category of unscored patients at a very low risk (score ≤3) for mortality (0.1% at 2 days and 0.2% between 3 and 10 days), who could potentially be discharged early from the hospital (at 48 hours after the procedure). Because the eligibility for early discharge was identified in 83.4% of these patients (61.2% of the total population), this would have resulted in a significant reduction of in-hospital costs. The incremental cost-effectiveness ratio for late discharge was estimated at €1949.33. This means that a conventional discharge policy (prolonged 24 hours of hospitalization) in low-risk patients would save one life per 1097 patients, with additional costs estimated at €194 933.33 in comparison with an early discharge policy.

Several factors may suggest the safety of an early discharge policy based on our score. The mortality rate between 3 and 10 days observed in this subset of patients was very low, with a very low rate of ventricular arrhythmia between 48 and 72 hours (0.09%). As shown in the Global Utilization of Streptokinase and t-PA for Occluded coronary arteries (GUSTO)-1 trial, the rate of malignant arrhythmia is the highest in the first 48 hours and constant until 1 month after reperfusion. This would be even lower in low-risk patients treated by optimal mechanical reperfusion.

Therefore, the Zwolle risk score may potentially be useful in the design of future clinical trials. The exclusion of very low-risk patients may improve the statistical power of clinical trials, with a smaller sample size, to assess the efficacy of new therapeutic strategies.

Limitations

Because the aim of our model was to identify predictors of 30-day mortality (thus including patients who died before hospital discharge), both medical therapy and ejection fraction at discharge were not included in the multivariate analysis, as these variables were not available in all patients. The outcome of patients at home would probably not be the same as in hospital. However, even if all malignant ventricular arrhythmias (0.09%) resulted in death, as accounted in our analysis, the risk of death would still be very low and early discharge justified.

Although the 30-day mortality rates in patients with a score of 3 were 1.1% and 1.3% in our study population and validation set, respectively, they were included in the low-risk category because the risk of death within 10 days was only 0.4% and 0.7%, respectively. This event would not be prevented by late discharge.

Our cost analysis was based on estimated charges rather than actual charges. However, several aspects, such as the very low-risk and the uncomplicated patient population (which required little additional care) and the short time period analyzed have made our estimation very close to the actual costs of an early discharge policy. This method of analysis has previously been described. However, the cost-analysis was based on the Dutch healthcare system and may therefore not be generally applicable.

Although the use of stents in the validation set was higher than that in our population, additional stenting has not been shown to reduce mortality rates in primary angioplasty for STEMI. Finally, the safety and feasibility of early discharge strategy according to this risk score should be prospectively evaluated.

Conclusions

Our study shows that a policy of early discharge (48 hours after primary angioplasty) could have been applied safely to a large group (>60%) of patients at a very low risk. These patients can easily be identified by the use of our risk score. A more widespread application of early discharge would result in a considerable reduction in costs for the treatment of patients with STEMI.

References

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