Preprocedural TIMI Flow and Mortality in Patients With Acute Myocardial Infarction Treated by Primary Angioplasty

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OBJECTIVES The aim of the study was to evaluate the impact of preprocedural Thrombolysis In Myocardial Infarction (TIMI) flow on one-year mortality in patients with ST-segment elevation myocardial infarction (STEMI) treated by primary angioplasty.

BACKGROUND Although there is an excellent outcome conferred by primary angioplasty in patients with STEMI, the prognostic role of early recanalization in these patients has yet to be investigated.

METHODS Our population is composed of 1,791 patients with acute myocardial infarction treated by primary angioplasty at our institution from 1994 to 2001. All angiographic, clinical, and follow-up data were prospectively collected. According to the TIMI risk score, patients were stratified in low- and high-risk groups.

RESULTS Preprocedural TIMI flow was related to postprocedural TIMI flow grade 3 (p = 0.002), myocardial blush grade 2 to 3 (p < 0.001), enzymatic infarct size (p < 0.001), predischARGE ejection fraction (p < 0.001), and one-year mortality (p < 0.05). Multivariate analysis showed that preprocedural TIMI flow grade 3 was an independent predictor of one-year survival in high-risk patients (p < 0.05).

CONCLUSIONS This study shows that preprocedural TIMI flow grade 3 is an independent predictor of one-year survival in high-risk patients with acute myocardial infarction treated by primary angioplasty. These data suggest that all efforts should be made to obtain early and optimal restoration of antegrade flow, particularly in high-risk patients and when transportation to tertiary centers, with a conceivable further time delay, is required. (J Am Coll Cardiol 2004; 43:1363–7) © 2004 by the American College of Cardiology Foundation

Primary angioplasty has been shown to improve the outcome of patients with ST-segment elevation myocardial infarction (STEMI), in comparison with thrombolysis (1–6). Nevertheless, the time delay required for transportation to a center with angioplasty facilities represents a major drawback of primary angioplasty and may potentially result in a worse outcome, particularly in high-risk patients (7).

The aim of this study was to investigate the prognostic role of preprocedural Thrombolysis In Myocardial Infarction (TIMI) flow in patients with STEMI undergoing primary angioplasty.

METHODS Our population consisted of 1,791 patients with STEMI treated by primary angioplasty at our institution from 1994 to 2001, for whom complete one-year follow-up data were available. Informed consent was obtained from each patient before angiography. All patients presenting within 6 h from symptom onset, or between 6 and 24 h if they had continuous symptoms and signs of ischemia, were included (8). All patients received aspirin (500 mg) and heparin (10,000 IU) intravenously before the procedure. After the procedure, all patients received aspirin and additional warfarin for three months (before 1996) or ticlopidine (1996 to 1999) or clopidogrel for one month (1999 to 2001), in case of stent implantation. Because the benefit of glycoprotein IIb/IIIa inhibitors has only been shown recently (9), only 5% of our patients received this drug.

Patients were classified according to preprocedural TIMI flow (TIMI flow grade 0 to 1, 2, or 3). According to the TIMI risk score (10), patients were stratified into low- and high-risk groups. Variables included in this score were age, Killip class >1, anterior infarction, time to treatment, history of hypertension and/or diabetes and/or preinfarction angina, systolic blood pressure, weight, and heart rate. A risk score ≥4 was used to identify the high-risk population (10).

Angiographic data analysis. All angiograms were reviewed by an independent core laboratory (Diagram, Zwolle, the Netherlands), which was blinded to all data apart from the coronary angiograms. Myocardial blush grade (MBG), TIMI flow, and procedural success were assessed as previously described (11). Residual stenosis was visually assessed. Procedural success was defined as postprocedural TIMI flow grade 3 and residual stenosis <50%.

Enzymatic infarct size. Enzymatic infarct size was calculated, as previously described, by cumulative enzyme release (LDH) from serial measurements up to 48 h after symptom onset (12).
Left ventricular function. Before hospital discharge, left ventricular ejection fraction (EF) was measured by radionuclide ventriculography. The multiple-gated equilibrium method was used after in vivo labeling of patients’ red blood cells with technetium-99m pertechnetate.

Follow-up. Records of patients who visited our outpatient clinic were reviewed. For all other patients, information was obtained from the patient’s general physician or by a direct telephone interview with the patient. No patient was lost to follow-up.

Statistical analysis. Statistical analysis was performed with the SPSS version 10.0 statistical package. Analysis of variance and the chi-square test were used for continuous and categorical variables, respectively. Bonferroni’s correction was applied in case of multiple comparisons. The following p values were adjusted by Bonferroni’s correction for multiple (n = 3) comparisons: §p < 0.05 vs. TIMI flow grade 0–1; ¶p < 0.005 vs. TIMI flow grade 0–1, †p < 0.05 vs. TIMI flow grade 2.

Table 1. Demographic, Clinical, and Angiographic Characteristics According to Preprocedural TIMI Flow

<table>
<thead>
<tr>
<th>TIMI Flow Grade</th>
<th>0–1 (n = 1,321)</th>
<th>2 (n = 217)</th>
<th>3 (n = 253)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>60 ± 11</td>
<td>60 ± 11</td>
<td>60 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>80.1</td>
<td>77</td>
<td>77.1</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>8.1</td>
<td>7.4</td>
<td>12.3</td>
<td>NS</td>
</tr>
<tr>
<td>Previous infarction (%)</td>
<td>11.5</td>
<td>11.5</td>
<td>10.7</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior infarction or LBBB (%)</td>
<td>49.3</td>
<td>56.7</td>
<td>57.7</td>
<td>0.012</td>
</tr>
<tr>
<td>Killip class I (%)</td>
<td>87.2</td>
<td>89.9</td>
<td>91.7</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic time (min)</td>
<td>214 ± 128</td>
<td>216 ± 118</td>
<td>215 ± 210</td>
<td>NS</td>
</tr>
<tr>
<td>Multivessel disease (%)</td>
<td>55.7</td>
<td>50.7</td>
<td>46.2</td>
<td>0.014</td>
</tr>
<tr>
<td>Post-TIMI flow grade 3 (%)</td>
<td>89</td>
<td>95.4</td>
<td>93.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Procedural success (%)</td>
<td>87.9</td>
<td>94.1</td>
<td>92.9</td>
<td>0.005</td>
</tr>
<tr>
<td>MBG 2–3† (%)</td>
<td>71.5</td>
<td>86†</td>
<td>84†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stent (%)</td>
<td>48.9</td>
<td>52.1</td>
<td>52.6</td>
<td>NS</td>
</tr>
<tr>
<td>PredischARGE ejection fraction† (%)</td>
<td>43 ± 11</td>
<td>44 ± 11</td>
<td>47 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDH 42h ‡ (U/L)</td>
<td>2,045 ± 1,629</td>
<td>1,350 ± 1,152‡</td>
<td>951 ± 971¶</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Data available in 1,771 patients, †1,143 patients, and 81,069 patients. Data are presented as the mean value ± SD or percentage of patients. The following p values were adjusted by Bonferroni’s correction for multiple (n = 3) comparisons: §p < 0.05 vs. TIMI flow grade 0–1; ¶p < 0.005 vs. TIMI flow grade 0–1, †p < 0.05 vs. TIMI flow grade 2.

†LBBB = left bundle branch block; TIMI = Thrombolysis In Myocardial Infarction; MBG = myocardial blush grade; LDH42h = enzymatic infarct size from serial measurements of lactate dehydrogenase.
reported in Table 2, preprocedural TIMI flow was not an independent predictor of one-year mortality.

Preprocedural TIMI flow and mortality in low- and high-risk patients. The relationship between preprocedural flow and mortality was also investigated in high- and low-risk patients, according to the TIMI risk score. A high-risk population of 560 patients (31.3%) and a low-risk population of 1,231 patients (68.7%) were identified, with one-year mortality rates of 14.5% and 1.8%, respectively (OR 7.43, 95% CI 4.59 to 12.01; p < 0.0001).

Preprocedural TIMI flow was significantly related to one-year mortality only in high-risk patients (OR 1.86, 95% CI 1.15 to 2.99; p < 0.01) (Fig. 1). In these patients, the difference in outcome was evident at 30 days and persisted until one-year follow-up, with the best outcome observed in patients with preprocedural TIMI flow grade 3 (OR 0.26, 95% CI 0.08 to 0.83; p < 0.01 vs. TIMI flow grade 0 to 2) (Fig. 2). As depicted in Figure 3, preprocedural TIMI flow grade 3 in high-risk patients was associated with a better outcome in both patients who presented early (<4 h) and in those who presented late (>4 h), as compared with preprocedural TIMI flow grade ≤2. The mortality rate remained stable across the study period and was comparable between patients treated with a stent or balloon (Fig. 3). On multivariate analysis performed in high-risk patients (Table 3), preprocedural TIMI flow grade 0 to 2 was an independent predictor of one-year mortality (OR 3.19, 95% CI 1.01 to 10.17; p < 0.05).

DISCUSSION

The main finding of the present study is that preprocedural TIMI flow grade 3 is an independent predictor of one-year survival in high-risk patients with STEMI undergoing mechanical reperfusion.

Preprocedural TIMI flow and mortality in STEMI patients. Several explanations may account for the potential impact of preprocedural TIMI flow on outcome in patients with STEMI treated by primary angioplasty. As demonstrated in animal models (13), the duration of coronary occlusion is a main determinant of myocardial infarct size. Thus, late reperfusion is expected to result in less myocardial salvage and, conceivably, higher mortality, as compared with early reperfusion, even when optimal mechanical reperfusion is applied. Furthermore, a delay in reperfusion may be associated with an older, organized intracoronary thrombus, in comparison with early reperfusion. This may result in a higher incidence of distal embolization with less postprocedural TIMI flow grade 3 and poor myocardial perfusion—all major predictors of mortality in STEMI (11,14). In our study, patients with better preprocedural flow showed a higher rate of postprocedural TIMI flow grade 3 and MBG 2 to 3.

Supporting the prognostic role of preprocedural flow in primary angioplasty, Stone et al. (15) found only preprocedural but not postprocedural TIMI flow grade 3 to be an independent predictor of mortality. The prognostic importance of preprocedural reperfusion has also been reported by Brodie et al. (16). In a cohort of 1,490 patients treated by primary angioplasty, they found preprocedural TIMI flow grade 2 to 3 to be associated with the amount of cardiac enzyme release, EF, and mortality on univariate analysis. The relationship between preprocedural flow and outcome was not studied in the multivariate analysis. In fact, the prognostic role of preprocedural flow may be overridden by the high rate of postprocedural TIMI flow grade 3 obtained in patients treated by primary angioplasty, as suggested by the absence of a relationship between time to treatment and mortality found by previous authors (17,18).

Consistent with Brodie et al. (16), we found a significant relationship between preprocedural TIMI flow and enzymatic infarct size and predischarge EF. Despite the same rate of postprocedural TIMI flow grade 3 and MBG 2 to 3, patients with preprocedural TIMI flow grade 3 had a smaller enzymatic infarct size and better predischarge EF, as compared with patients with preprocedural TIMI flow grade 2.

In contrast to previous reports, we investigated the role of preprocedural TIMI flow according to the patient’s risk profile at presentation, because it is conceivable that early recanalization, by increasing myocardial salvage, may particularly affect the outcome of high-risk patients. In fact,
when we analyzed one-year mortality, we found preprocedural TIMI flow grade 3 to be an independent predictor of outcome only in high-risk patients. Preprocedural TIMI flow grade 3 was associated with a better outcome in both patients who presented early (≤4 h) and in those who presented late (>4 h), whereas in patients with preprocedural TIMI flow grade ≤2, a further impairment in outcome was observed in patients who presented late (Fig. 3).

Supporting the role of ischemic time in primary angioplasty, Antoniucci et al. (7) found that total ischemic time was related to mortality only in high-risk patients.

All these data demonstrate that in patients with STEMI undergoing angioplasty, preprocedural TIMI flow is a major independent predictor of mortality in high-risk patients.

**Study limitations.** Although the TIMI risk score was derived from patients treated by thrombolysis, the included variables still represent major independent predictors of outcome in patients treated by primary angioplasty (19,20). In fact, the TIMI risk score was also able to identify a high-risk population in our study.

Some variables in our study, particularly enzymatic infarct size and predischarge EF, were not available from all patients, and therefore could not be included in the multivariate analysis. However, it is clear that the benefits of preprocedural TIMI flow grade 3 on mortality are related to more extensive myocardial salvage, and thus better EF and more limited enzymatic infarct size.

Although potential changes in medical therapy and an

### Table 3. Multivariate Analysis for Predictors of One-Year Mortality in High-Risk Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Killip class &gt;1</td>
<td>4.12 (2.41–7.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Post-TIMI flow grade 0–2</td>
<td>2.85 (1.72–4.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age ≥70 yrs</td>
<td>2.29 (1.38–3.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>2.05 (1.13–3.7)</td>
<td>0.018</td>
</tr>
<tr>
<td>Preprocedural TIMI flow grade 0–2</td>
<td>3.19 (1.01–10.17)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.
Increasing rate of stenting may have occurred across our study time, with an important impact on clinical outcome, the prognostic role of preprocedural TIMI flow grade 3 was stable across the study period (Fig. 3).

**Clinical implications and conclusions.** Although primary angioplasty has been demonstrated to be superior to thrombolytic therapy, several areas for improvement still remain. Transportation to tertiary centers with angioplasty facilities has been shown to be safe and feasible (21). However, the time delay due to transportation remains a major drawback to primary angioplasty, particularly in high-risk patients. The results of our study suggest that all efforts should be made to obtain optimal restoration of antegrade flow as early as possible during transportation. Although the independent predictive value of preprocedural TIMI flow grade 3 in high-risk patients would argue that it is independent of the time delay to treatment, early drug administration has been shown to be associated with higher rates of vessel patency and aborted infarction (22, 23). Therefore, the alliance between early pharmacologic therapies and angioplasty for acute myocardial infarction, the so-called "facilitated angioplasty," may be attractive and is currently an area of great interest (24–26). Further trials are needed to investigate this combined approach, particularly in high-risk patients who will, as demonstrated by our data, benefit most from early and optimal recanalization.

**REFERENCES**


21. Moon JC, Kalra PR, Coats AJ. DANAMI-2: is primary angioplasty superior to thrombolysis in acute MI when the patient has to be transferred to an invasive centre? Int J Cardiol 2002;85:199–201.


