Long-Term Outcome After Primary Angioplasty: Report From the Primary Angioplasty in Myocardial Infarction (PAMI-I) Trial

Christopher M. Nunn, MBCHB, FRACP,* William W. O’Neill, MD, FACC,† Donald Rothbaum, MD, FACC,‡ Gregg W. Stone, MD, FACC,§ James O’Keefe, MD, FACC,¶ Paul Overlie, MD, FACC,‖ Bryan Donohue, MD, FACC,¶ Lorelei Grines, PhD,† Kevin F. Browne, MD, FACC,** Ronald E. Vlietstra, MD, FACC,** Tom Catlin,† Cindy L. Grines, MD, FACC,† For The Primary Angioplasty in Myocardial Infarction I Study Group

Hamilton, New Zealand; Royal Oak, Michigan; Indianapolis, Indiana; Mountain View, California; Kansas City, Missouri; Lubbock, Texas; Pittsburgh, Pennsylvania, and Lakeland, Florida

OBJECTIVES This study sought to compare the two-year outcome after primary percutaneous coronary angioplasty or thrombolytic therapy for acute myocardial infarction.

BACKGROUND Primary angioplasty, that is, angioplasty without antecedent thrombolytic therapy, has been shown to be an effective reperfusion modality for patients suffering an acute myocardial infarction. This report reviews the two-year clinical outcome of patients randomized in the Primary Angioplasty in Myocardial Infarction trial.

METHODS At 12 clinical centers, 395 patients who presented within 12 h of the onset of myocardial infarction were randomized to undergo primary angioplasty (195 patients) or to receive tissue-type plasminogen activator (t-PA) (200 patients) followed by conservative care. Patients were followed by physician visits, phone call, letter and review of hospital records for any hospital admission at one month, six months, one year and two years.

RESULTS At two years, patients undergoing primary angioplasty had less recurrent ischemia (36.4% vs. 48% for t-PA, p = 0.026), lower reintervention rates (27.2% vs. 46.5% for t-PA, p < 0.0001) and reduced hospital readmission rates (58.5% vs. 69.0% for t-PA, p = 0.035). The combined end point of death or reinfarction was 14.9% for angioplasty versus 23% for t-PA, p = 0.034. Multivariate analysis found angioplasty to be independently predictive of a reduction in death, reinfarction or target vessel revascularization (p = 0.0001).

CONCLUSIONS The initial benefit of primary angioplasty performed by experienced operators is maintained over a two-year follow-up period with improved infarct-free survival and reduced rate of reintervention. (J Am Coll Cardiol 1999;33:640–6) © 1999 by the American College of Cardiology

Primary angioplasty without antecedent thrombolytic therapy is an effective means of achieving coronary reperfusion in patients presenting with an acute myocardial infarction (AMI) (1–4). Several uncontrolled studies have demonstrated a high rate of coronary reperfusion and beneficial effect on left ventricular function (5–8). Prospective randomized studies comparing thrombolysis with primary angioplasty have demonstrated improved infarct artery patency, reduced recurrent ischemia and improved infarct-free survival during short-term follow-up in the angioplasty-treated patients (9–11). Primary angioplasty has also been shown to reduce the incidence of stroke (12). Long-term outcomes, however, are less well documented with conflicting data suggesting either attenuation or enhancement of short-term results (13,14).

The Primary Angioplasty in Myocardial Infarction (PAMI) trial was a randomized multicenter clinical trial designed to compare primary angioplasty with tissue-type plasminogen...
Activator (t-PA) for acute myocardial infarction. This report presents the clinical outcome after two years follow-up.

METHODS

A description of the trial has been published previously (10). Patients of any age who presented within 12 h of the onset of ischemic chest pain were considered for enrollment if ST segment elevation of at least 1 mm was present in two or more contiguous electrocardiographic leads. Exclusion criteria included an inability to provide informed consent, dementia, complete left bundle branch block, cardiogenic shock and a higher than normal risk of bleeding. The protocol was approved by the investigational review board at each clinical site, and written informed consent was obtained from all patients before enrollment.

All patients were initially treated with oxygen, intravenous nitroglycerin, aspirin and intravenous heparin (given as a 10,000-U bolus). Patients were randomized to receive either t-PA (Activase) at a dose of 100 mg (or 1.25 mg/kg for patients weighing less than 65 kg) over 3 h, or undergo immediate angioplasty. Angiographic criteria for exclusion from angioplasty included unprotected left main coronary artery stenosis of more than 70% and, if the infarct artery was patent, critical proximal three-vessel disease or morphologic features of the lesion known to be of high risk for angioplasty, in which case bypass surgery was recommended. Patients did not undergo angioplasty if they appeared unlikely to benefit from angioplasty; if the infarct-related vessel was small, contained a stenosis of less than 70% or could not be identified.

In both treatment groups, intravenous heparin was administered for 3 to 5 days. Patients were routinely treated with intravenous nitroglycerin for at least 24 h, followed by topical or oral nitrates, aspirin (325 mg orally daily) and diltiazem (30 to 60 mg orally four times a day). Unscheduled catheterization and mechanical revascularization was allowed in cases of failure of thrombolysis, recurrence of unstable ischemia or abnormal results on a predischarge exercise test. Failure of thrombolysis was defined as continued chest pain with ST segment elevation more than 120 min after the initiation of thrombolytic therapy. Rescue angioplasty (angioplasty performed after the failure of thrombolysis) was recommended if the vessel had Thrombolysis in Myocardial Infarction (TIMI) grade 0–1 flow.

Data collection and assessment. Data were collected prospectively by research nurses at each of the 12 clinical centers (see Appendix). An independent nurse monitor traveled to each site to review all medical charts from the index hospitalization, with close attention to ischemic end points. Patients were followed by physician visit, phone call, letter and review of hospital records for any hospital admission at one month, six months, one year and two years.

The primary end point was in-hospital death, recurrent myocardial infarction, or recurrent ischemia requiring angioplasty or coronary artery bypass surgery (CABG). The case report form was designed to prospectively collect this information at all follow-up visits.

The diagnosis of myocardial infarction was adjudicated by a committee that was blinded to the treatment received. All electrocardiograms were independently reviewed by a physician to ensure that patients met the criteria for an ischemic end point. Cineangiograms were reviewed at an independent core laboratory to assess the coronary anatomy, visually estimate TIMI flow grades (15) and determine the degree of stenosis by means of a computerized edge-detection algorithm (16). Successful angioplasty was defined as resulting in residual stenosis of less than 50% with TIMI grade 2 or 3 flow. Recurrent ischemia was prospectively defined as reinfarction or rest angina with ST segment or T wave changes. Reinfarction was defined as recurrent chest pain lasting more than 30 min with ST segment elevation and either emergency angiographic confirmation of an occluded vessel or recurrent elevation of cardiac enzymes. Target vessel revascularization (TVR) was defined as subsequent angioplasty of the infarct vessel or CABG.

Statistical analysis. Categorical variables were compared by chi-square analysis and continuous variables by Student t test (17). All p values are two tailed. Survivor functions were estimated using the Kaplan–Meier life table method; Mantel–Cox nonparametric linear log-rank tests were employed for making group comparisons (18). Multivariate analysis using stepwise multiple logistic regression was undertaken for the end point of death, reinfarction or target vessel revascularization at two years.

RESULTS

Between June 1990 and April 1992, 395 patients were enrolled at 12 clinical centers; 195 were randomly assigned to undergo immediate angioplasty without thrombolytic therapy, and 200 to receive intravenous t-PA. At two years, follow-up was achieved in 85.6% of patients. Most of the patients lost were from the single European center, which had a follow-up rate of only 27% compared to 92.5% for the remaining American centers. However, excluding this center from further analysis did not influence the outcome with
regard to the primary end points, and therefore all patients initially enrolled in the study and followed to two years are included in this report.

As previously reported, there were no differences in baseline features between the patients randomized to primary angioplasty versus t-PA (10). In view of the potential bias created by the 14% of patients lost to follow-up, baseline features along with in-hospital events were compared between those followed and those lost to follow-up at two years. The only significant difference was the slightly younger age of the angioplasty patients lost to follow-up (Table 1).

**Clinical events.** As previously reported (10), patients assigned to angioplasty had improved early event-free survival. At 2 years, reinfarction and mortality as individual events both tended to favor primary angioplasty over t-PA (10.8% vs. 16.0%, $p = 0.10$, and 6.2% vs. 9.5%, $p = 0.21$, respectively). The combination of both of these events was significantly reduced by primary angioplasty over tPA (14.9% vs. 23%, $p = 0.034$) (Fig. 1). The incidence of recurrent ischemia was high overall, but was reduced in those patients initially randomized to angioplasty (36.4% vs. 48% for t-PA, $p = 0.026$) (Fig. 2) (Table 2).

**Hospital readmission and angioplasty rates.** Hospital readmission rates at two years in the angioplasty group were 58.5%, compared to 69.0% in the t-PA patients ($p = 0.035$). Angioplasty in the follow-up period was performed in 27.2% of patients randomized to primary angioplasty versus 46.5% of patients treated with t-PA ($p < 0.0001$). Most of these were confined to the infarct-related artery (18.5% vs. 43% for the angioplasty vs. t-PA groups respectively, $p < 0.0001$) (Table 2).

The requirement for coronary artery bypass surgery in both the angioplasty and t-PA arms was similar (18.5% vs. 16.0%, respectively) (Table 2). Thus repeat angioplasty or CABG of the original infarct-related artery during the 2 years after hospital discharge was required in 33% of angioplasty-treated patients compared with 54% of t-PA-treated patients ($p = 0.001$). As seen in Figure 3, freedom from the combined end point of death, recurrent myocardial infarction, repeat angioplasty or CABG at two years was

**Table 1.** Baseline Features of Patients Lost to Follow-up Compared With Those Followed to Two Years

<table>
<thead>
<tr>
<th></th>
<th>PTCA Lost to Follow-up</th>
<th>PTCA Followed</th>
<th>t-PA Lost to Follow-up</th>
<th>t-PA Followed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>31</td>
<td>164</td>
<td>23</td>
<td>177</td>
</tr>
<tr>
<td>Baseline features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.0 ± 13.9</td>
<td>60.5 ± 10.8†</td>
<td>58.7 ± 10.0</td>
<td>60.3 ± 11.7</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>83.9</td>
<td>72.6</td>
<td>86.6</td>
<td>68.4</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>16.1</td>
<td>15.2</td>
<td>13.0</td>
<td>14.4</td>
</tr>
<tr>
<td>Anterior MI (%)</td>
<td>41.9</td>
<td>35.4</td>
<td>34.8</td>
<td>33.3</td>
</tr>
<tr>
<td>Not low risk (%)</td>
<td>58.1</td>
<td>49.4</td>
<td>47.8</td>
<td>54.8</td>
</tr>
<tr>
<td>In-hospital events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reinfarction (%)</td>
<td>0</td>
<td>3.0</td>
<td>4.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Nonscheduled PTCA/CABG (%)</td>
<td>6.5</td>
<td>10.4</td>
<td>17.4</td>
<td>20.3</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ± SD. †Percutaneous transluminal coronary angioplasty (PTCA) followed vs. PTCA lost to follow-up, $p = 0.05$.

CABG = coronary artery bypass surgery; MI = myocardial infarction; Not low risk = anterior myocardial infarction or age >70 years or pulse greater than 100; t-PA = tissue-type plasminogen activator.

**Figure 1.** Actuarial infarct-free survival curves for acute infarct patients either undergoing primary angioplasty (PTCA) (**solid line/solid squares**) or receiving tissue plasminogen activator (tPA) (**dotted line/empty squares**).

**Figure 2.** Actuarial recurrent ischemia-free survival curves for acute infarct patients either undergoing primary angioplasty (PTCA) (**solid line/solid squares**) or receiving tissue plasminogen activator (tPA) (**dotted line/empty squares**). Recurrent ischemia is defined as reinfarction or rest angina with electrocardiographic changes.
53.3% in the angioplasty arm versus 37.0% in the t-PA group (p < 0.0001).

**Multivariate analysis.** Multivariate logistic regression analysis of 21 variables was performed to determine independent predictors of the combined end point of death, reinfarction or target vessel revascularization at two years. Only randomization to angioplasty was independently associated with a reduced event rate, whereas older patients and those with hypertension were associated with increased events (p = 0.0001) (Table 3). In patients randomized to angioplasty, the predictors of death or reinfarction at two years were hypertension, smoking, reduced time to randomization and restoration of less than TIMI 3 (overall model p < 0.001) (Table 4).

**DISCUSSION**

The early results of the PAMI trial demonstrated a significantly reduced incidence of recurrent ischemic events and a trend toward reduced mortality in the angioplasty group at 6 months. These observations have now been extended to 2 years and suggest that the early benefit of primary angioplasty is maintained over this period. Not only were clinical events reduced, but the requirement for rehospitalization and subsequent intervention was substantially less in those patients undergoing angioplasty.

Optimal management of acute myocardial infarction depends upon early and complete restoration of coronary artery patency. Thrombolysis and primary angioplasty are each associated with specific clinical and economic consequences, which must be compared to determine the overall best treatment. The primary end point of this study was the reduced combination of death, reinfarction or recurrent ischemia requiring revascularization. Although subsequent target vessel revascularization is a soft end point, it is important, as it is associated with definite patient morbidity and mortality as well as consumption of health resources. Randomization to angioplasty was the only independent predictor of a reduction in the combined end point of death, reinfarction or target vessel revascularization at two years.

The lower residual stenosis after angioplasty compared to thrombolysis in conjunction with the procoagulant effects of thrombolytics (19) may account for the high incidence of recurrent ischemia and subsequent intervention in patients treated with these agents. Even in those patients with TIMI 3 flow after thrombolysis, the mean residual stenosis approximates 80% compared to 30% to 40% for angioplasty (4,20). The impact of angioplasty in reducing recurrent ischemia and readmissions has also been shown in other prospective trials comparing this treatment with thrombolysis (21,22). The same effect, however, was not apparent in a recent retrospective review (23), which may reflect the inherent referral bias in nonrandomized studies resulting from the influence of physician preference and patient clinical status.

Recent data have revealed that the ultimate goal of reperfusion therapy is not only artery patency but restoration of normal TIMI 3 coronary flow, which has been shown to correlate with reduced regional wall motion abnormalities and improved clinical outcome (24,25). To date, thrombolytic agents have been shown to restore TIMI 3 flow in only just over 50% of cases (24), well below that achieved with primary angioplasty (4,13,20). Multivariate analysis of predictors of 2-year death or reinfarction in this trial highlight the additional importance of restoration of TIMI 3 flow to optimize late outcomes, which for the first time has been shown to be related to late as well as early mortality after primary angioplasty.

**Table 2. Clinical Events at 2 Years**

<table>
<thead>
<tr>
<th>Events</th>
<th>PTCA</th>
<th>t-PA</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital readmission (%)</td>
<td>58.5</td>
<td>69.0</td>
<td>0.035</td>
</tr>
<tr>
<td>Recurrent ischemia* (%)</td>
<td>36.4</td>
<td>48.0</td>
<td>0.026</td>
</tr>
<tr>
<td>Subsequent PTCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target vessel (%)</td>
<td>18.5</td>
<td>43.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nontarget vessel (%)</td>
<td>8.7</td>
<td>3.5</td>
<td>NS</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>18.5</td>
<td>16.0</td>
<td>NS</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>32.8</td>
<td>54.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Reinfarction (%)</td>
<td>10.8</td>
<td>16.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>6.2</td>
<td>9.5</td>
<td>0.21</td>
</tr>
<tr>
<td>Combined reinfarction/mortality</td>
<td>14.9</td>
<td>23.0</td>
<td>0.034</td>
</tr>
</tbody>
</table>

*Reinfarction or rest angina with electrocardiographic changes. Abbreviations as in Table 1.

**Table 3. Predictors of Death, Reinfarction or Target Vessel Revascularization**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient</th>
<th>Odds Ratio</th>
<th>95% Confidence Limits</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioplasty</td>
<td>-0.854</td>
<td>0.426</td>
<td>0.280 to 0.646</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>0.024</td>
<td>1.024</td>
<td>1.006 to 1.043</td>
<td>0.011</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.702</td>
<td>2.019</td>
<td>1.321 to 3.083</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

Figure 3. Actuarial event-free survival curves for acute infarct patients either undergoing primary angioplasty (PTCA) (solid line/solid squares) or receiving tissue plasminogen activator (tPA) (dotted line/empty squares).
It is interesting to note the lack of divergence seen in the 2-year event-free survival curves; however, this has consistently been observed in most other infarct-related studies (26–28). Death and reinfarction occur early after infarction. Moreover, the high early stroke and intervention rates (36% in-hospital angioplasty and 24% in-hospital CABG) seen in patients randomized to t-PA (10) may counterbalance any trend to delayed benefit in the angioplasty patients, possibly reducing any potential for divergence in event-free survival curves. In addition, disease progression will tend to neutralize the treatment effect of any interventional therapy.

**Study limitations.** The study is limited by the modest numbers of patients involved and was powered to assess the primary end point of in-hospital death, reinfarction or recurrent ischemia requiring angioplasty or CABG. Although readmission and reintervention rates over long-term follow-up were not prespecified end points, the protocol and case report form were designed to capture this information out to two years follow-up.

A major limitation is the 86.3% follow-up rate, which may have resulted in some adverse events in the follow-up period not being captured. In an attempt to address this issue provisional analysis was undertaken excluding the one center that had only a 27% follow-up rate. Clinical outcomes, however, were unchanged. In addition, the baseline clinical features and in-hospital events of patients lost to follow-up were the same as those of patients followed to two years. The one possible exception was in the angioplasty arm, where patients lost to follow-up were marginally younger, which if anything would bias results in favor of t-PA.

Blinding of patients in this trial was not feasible, and reporting bias may therefore have potentially influenced the results. To reduce reporting bias, electrocardiograms and hospital records were independently reviewed to ensure all ischemic end points met the prespecified criteria and all angiograms were analyzed by the core lab.

The t-PA regimen used preceded the acceptance of front loading, and this may have had an impact on vessel patency and clinical outcome. However, even with front-loaded t-PA the restoration of TIMI III flow is still well below that achieved with primary angioplasty (24) and is thus unlikely to significantly negate the benefit of primary angioplasty shown here. In addition new developments in angioplasty technique and procedure, such as platelet glycoprotein IIb/IIIa receptor inhibitors and stents (29,30), have recently been shown to further improve immediate clinical outcome as well as reduce the requirement for reintervention. Thus although clinical practices tested in this study have continued to evolve, the evidence that a strategy which achieves high coronary artery patency can result in long-term clinical benefit remains highly clinically relevant today.

Finally, these results were achieved in experienced investigational centers and therefore may not be applicable to all institutions. By ensuring efficient triaging and prompt intervention, however, results similar to PAMI I and the Netherlands study (9) can be achieved in smaller, less experienced units, as reflected in a recent New Zealand report (31).

**Conclusions.** This study demonstrates that when primary angioplasty is undertaken with experienced personnel and appropriate facilities, early clinical benefits are maintained over a 2-year follow-up period. Cardiac event rates, however, remain high, and it is hoped that trials currently underway addressing the role of new technologies and adjunctive pharmacotherapy will further improve the acute and long-term outcomes of patients undergoing a primary mechanical reperfusion strategy for AMI.

**APPENDIX**


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**Table 4. Predictors of Death or Reinfarction at 2 Years in Patients Randomized to Angioplasty**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient</th>
<th>Odds Ratio</th>
<th>95% Confidence Limits</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2.1215</td>
<td>8.344</td>
<td>1.720 to 40.485</td>
<td>0.009</td>
</tr>
<tr>
<td>Time to randomization</td>
<td>−0.0167</td>
<td>0.983</td>
<td>0.970 to 0.997</td>
<td>0.016</td>
</tr>
<tr>
<td>Current smokers</td>
<td>2.2722</td>
<td>9.701</td>
<td>1.757 to 53.549</td>
<td>0.009</td>
</tr>
<tr>
<td>TIMI flow postangioplasty</td>
<td>−1.6157</td>
<td>0.199</td>
<td>0.051 to 0.771</td>
<td>0.020</td>
</tr>
</tbody>
</table>

TIMI = Thrombolysis in Myocardial Infarction.
St. Mary of the Plains, Lubbock, Texas—P. Overlie and M. Quijada; Allegheny General Hospital, Pittsburgh, Pennsylvania—B. Donohue, R. Begg and L. Zahren; United Hospital, Grand Forks, North Dakota—N. Chelliah, R. Wolf and N. Endres; Heart Institute of St. Joseph Hospital, Atlanta, Georgia—C. Cates, W. Knopf and J. Sheftel; Florida Hospital South, Orlando, Florida—R. Ivanhoe and C. Simpkiss, and North Central Heart Clinic, Wausau, Wisconsin—J. Freeman.

Reprint requests and correspondence: Dr. C. M. Nunn, Department of Cardiology, Waikato Hospital, Private Bag 3200, Hamilton, New Zealand.

REFERENCES

