Randomized Trial of Direct Coronary Angioplasty Versus Intravenous Streptokinase in Acute Myocardial Infarction

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Objectives. The objective of this study was to obtain preliminary data on the relative clinical utility of direct coronary angioplasty compared with that of intravenous thrombolytic therapy for patients with acute myocardial infarction.

Background. The relative merits of intravenous thrombolytic therapy and direct coronary angioplasty as treatment for acute myocardial infarction are incompletely understood, and randomized trials of these treatments have been extremely limited.

Methods. One hundred patients with ST segment elevation presenting to a single high volume interventional center within 6 h of the onset of chest pain were randomized to receive either streptokinase (1.2 million U intravenously over 1 h) or immediate catheterization and direct coronary angioplasty. Patients were excluded for age ≥75 years, prior bypass surgery, Q wave infarction in the region of ischemia or excessive risk of bleeding. All patients were then treated with aspirin (325 mg orally/day) and heparin (1,000 U intravenously/h) for 48 h until catheterization was performed to determine the primary study end point, namely, infarct-related artery patency at 48 h. Secondary end points were in-hospital death, left ventricular ejection fraction at 48 h and time to treatment.

Results. There was no difference in the baseline characteristics of the two treatment groups. Overall patient age was 56 ± 10 years, 83% of patients were male, 11% had prior infarction, 40% had anterior infarction and 97% were in Killip class I or II. Although time to treatment was delayed in the angioplasty group (238 ± 112 vs. 179 ± 98 min, p = 0.005), there was no difference in 48-h infarct-related artery patency or left ventricular ejection fraction (patency 74% vs. 89%; ejection fraction 59 ± 13% vs. 57 ± 13%; angioplasty vs. streptokinase, p = NS for both). There were no major bleeding events, and the mortality rate with angioplasty (6%) and streptokinase (2%) did not differ (p = NS).

Conclusions. These results suggest that intravenous thrombolytic therapy might be preferred over coronary angioplasty for most patients because of the often shorter time to treatment.

(J Am Coll Cardiol 1993;22:376–80)
Hospital, located in São Paulo, Brazil, is a busy tertiary referral center for patients with acute coronary heart disease. Before the start of this study, investigators at Unicórnio Hospital had performed 1,600 angioplasty procedures and treated 1,100 patients with intravenous thrombolytic therapy in the setting of acute myocardial infarction. Patients were eligible for inclusion for this study if they presented with chest discomfort typical of coronary ischemia of 20 min to 6 h duration and had electrocardiographic ST segment elevation ≥1 mm in two or more contiguous leads. Patients were excluded for any of the following: 1) relief of chest pain by sublingual nitroglycerin, 2) history of stroke within 6 months, 3) history of major surgery or trauma within 6 months, 4) history of abnormal bleeding so as to contraindicate the use of thrombolytic therapy, 5) history of prior coronary artery bypass graft surgery; 6) age ≥75 years, and 7) prior Q wave myocardial infarction in the same infarct distribution as the index infarction. This protocol was approved by the Institutional Review Board at Unicórnio Hospital.

Study protocol (Fig. 1). After patients had given written informed consent, they were randomized to receive either 1.2 million U of intravenous streptokinase over 1 h or immediate cardiac catheterization with direct angioplasty to the infarct-related vessel. Randomization was performed using a closed envelope system without patient stratification. Patients eligible for the study but not randomized were characterized in a registry log. Patients randomized to receive intravenous streptokinase also were treated with aspirin (325 mg orally/day) and intravenous heparin (1,000 U/h) until the time of the 48-h catheterization. Patients randomized to direct angioplasty had that procedure performed and were then treated also with aspirin (325 mg/day) and intravenous heparin (1,000 U/h). At 48 h after hospital admission, all patients were taken to the cardiac catheterization laboratory for catheterization to assess infarct artery patency and left ventricular ejection fraction. Thereafter, all patients were treated with continued aspirin and diltiazem (60 mg orally three times daily).

Angiography. Angiography was routinely performed using the brachial approach. For those patients randomized to direct angioplasty, of heparin (10,000 U) was given after accessing the brachial arterial. A single injection of the noninfarct-related artery or arteries was followed by multiple injections to visualize the infarct-related artery in orthogonal views. Infarct artery patency was defined as TIMI grade 2 or 3 flow (12). Infarct arteries were prospectively characterized as being either well suited or not well suited for angioplasty. Arteries were defined as not well suited for direct angioplasty if they met any of the following criteria (7): 1) ≥50% stenosis in the left main coronary artery; 2) ≥75% lesions in both the proximal left circumflex and proximal left anterior descending coronary arteries; 3) severe, diffuse, multilevel or multivessel disease; 4) cardiogenic shock, defined as systolic blood pressure <90 mm Hg with clinical signs of multiorgan hypoperfusion; and 5) an unidentifiable infarct-related artery. However, angioplasty was attempted even on arteries not believed to be well suited for that procedure.

Left ventricular analysis. Global left ventricular ejection fraction was determined from the 48-h ventriculograms using the area-length method (13).

Coronary angioplasty. Coronary angioplasty was routinely performed using the brachial approach. Most commonly, 4.3F shaft polyethylene terephthalate balloons were used, employing two to four inflations to a maximum of 8 to 10 atm for 60- to 90-s intervals. The procedure was considered successful if <50% stenosis and TIMI grade 2 or 3 flow resulted.

Follow-up. Patients were followed up for the occurrence of comorbid complications until the time of hospital discharge. Overall mortality, need for blood product transfusion, major bleeding, recurrent ischemia (defined as at least two of the following: angina, ST segment changes consistent with new ischemia or re-elevation of serum creatine kinase levels with isoenzyme confirmation) and the time and peak creatine kinase-MB levels were noted. The standard approach for the treatment of recurrent ischemia in either randomized group was urgent cardiac catheterization and angioplasty, if necessary. In general, blood product transfusion was considered to be indicated for hematocrit <30% or hemoglobin <10 g/dl.

Statistical analysis. All data are reported as mean value ± SD, unless otherwise noted. Comparison of dichotomous variables between treatment groups was made using chi-square analysis. Comparison of continuous variables between treatment groups was made using Student t test.
analyses. A p value ≤ 0.05 was considered significant. The primary end point of this study was infarct-related artery patency at the 48-h study. Prespecified secondary end points included in-hospital death, left ventricular ejection fraction at 48 h, blood product transfusion and the time to treatment. The prior correlation of delayed infarct vessel patency and early postinfarction left ventricular ejection fraction with long-term survival (14,15) was considered to justify the use of 48-h patency as the primary end point of this study. It was recognized that this was a preliminary study that did not have the statistical power to adequately assess differences in major clinical outcomes. Two post-hoc analyses were performed: 1) comparison of major end points excluding patients "not well suited" for angioplasty to minimize any bias originating from inclusion of these patients (whose characteristics could not be ascertained before randomization) while excluding patients with contraindications to thrombolytic therapy; and 2) comparison of left ventricular ejection fraction only for patients with anterior infarction (because right anterior oblique angiography may incompletely assess this variable in patients with large lateral wall motion abnormalities).

**Results**

**Baseline patient characteristics.** The presenting characteristics of the patients randomized in the two study groups are enumerated in Table 1. The two study groups did not differ with regard to age, history of prior myocardial infarction, Killip class or location of infarction. Patients randomized to intravenous streptokinase, however, were treated earlier (179 ± 98 vs. 238 ± 112 min, p = 0.005). Nine potentially eligible patients were not randomized for the following reasons: 1) ongoing cardiogenic shock or prior cardiac arrest (n = 4), 2) referring physician referral (n = 3), and 3) patient refusal (n = 2).

**Table 1. Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PTCA</th>
<th>p Value</th>
<th>SK</th>
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<tbody>
<tr>
<td>Patients (no.)</td>
<td>50</td>
<td>—</td>
<td>50</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57 ± 10 NS 55 ± 10</td>
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<tr>
<td>Male (%)</td>
<td>82 NS 86</td>
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<tr>
<td>Diabetic (%)</td>
<td>12 NS 10</td>
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<tr>
<td>Previous angina (%)</td>
<td>38 NS 34</td>
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<tr>
<td>Previous MI (%)</td>
<td>6 NS 16</td>
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<tr>
<td>Anterior MI (%)</td>
<td>34 NS 46</td>
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<tr>
<td>Infral MI (%)</td>
<td>66 NS 54</td>
<td></td>
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<tr>
<td>Time to treatment (min)</td>
<td>238 ± 112 0.005</td>
<td>179 ± 98</td>
<td></td>
</tr>
<tr>
<td>Killip class I-II (%)</td>
<td>94 NS 100</td>
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<tr>
<td>Killip class III-IV (%)</td>
<td>6 NS 0</td>
<td></td>
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<tr>
<td>Multivessel CAD (%)</td>
<td>40 N5 32</td>
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Data are expressed as mean value ± SD or percent of patients. CAD = coronary artery disease; Inf = inferior; lat = lateral; MI = myocardial infarction; PTCA = direct coronary angioplasty; SK = intravenous streptokinase.

**Table 2. Infarct-Related Artery Patency Results 48 Hours After Angioplasty**

<table>
<thead>
<tr>
<th>Patency (90 min) (%)</th>
<th>PTCA</th>
<th>p Value</th>
<th>SK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patency (48 h) (%)</td>
<td>74 NS 80</td>
<td></td>
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<tr>
<td>LVEF at 48 h (%)</td>
<td>59 ± 13 NS 57 ± 13</td>
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<tr>
<td>Peak CK-MB (U)</td>
<td>83.4 ± 70.1 0.05 56.8 ± 34.3</td>
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<tr>
<td>Time to CK-MB peak (h)</td>
<td>14.4 ± 5.9 NS 15.5 ± 5.5</td>
<td></td>
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<tr>
<td>Major bleeding events (%)</td>
<td>0 NS 0</td>
<td></td>
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</tr>
<tr>
<td>Blood product transfusion (%)</td>
<td>0 NS 0</td>
<td></td>
<td></td>
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<tr>
<td>Mortality (%)</td>
<td>6 NS 2</td>
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</tbody>
</table>

Data are expressed as mean value ± SD or percent of patients. CK-MB = creatine kinase MB isoenzyme; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

Suitability for direct coronary angioplasty. Forty (80%) of the 50 patients randomized to angioplasty were deemed to be well suited for direct angioplasty and 10 patients (20%) were believed to be not well suited for that procedure. The reasons that patients were judged to be not well suited for angioplasty were as follows: 1) ≥75% lesions in both the proximal left anterior descending and left circumflex coronary arteries (n = 11); 2) cardiogenic shock (n = 3); 3) ≥50% stenosis in the left main coronary artery (n = 2); and 4) severe, diffuse, multilevel or multivessel disease (n = 2).

**Immediate results of coronary angioplasty.** Coronary angioplasty was successful in 40 (80%) of 50 patients. Emergency bypass surgery was required in 2 (4%) of 30 patients. Angioplasty was successful in 36 (90%) of 40 patients believed to be well suited and 4 (40%, p < 0.001) of 10 patients believed to be not well suited for the procedure.

**Infarct-related artery patency at 48 h (Table 2).** Forty-eight hour infarct-related artery patency by TIMI grade is shown in Table 2. The overall patency rates (TIMI grade 2 or 3 flow) did not differ. If the patients classified as not well suited for angioplasty were excluded, then patency in the angioplasty group would have been 87.5% (p = NS vs. the streptokinase group).

**Secondary end points.** There were three deaths (6%) in the patients randomized to coronary angioplasty and one death (2%) in the patients randomized to intravenous streptokinase (p = NS). The causes of death in the angioplasty group were 1) cardiogenic shock 7 days after successful left anterior descending coronary artery angioplasty in a patient with prior inferior wall myocardial infarction; 2) cardiogenic shock after unsuccessful ostial left anterior descending coronary artery angioplasty in a patient with prior inferior wall myocardial infarction; and 3) emergency bypass surgery in a patient 2 days after unsuccessful angioplasty of a highly calcified left anterior descending artery stenosis. The single patient in the intravenous streptokinase group who died of heart failure during the hospital stay had successful reperfusion at 48 h, but with a previous large anterior wall myocardial infarction.
Left ventricular ejection fraction. There was no difference in the left ventricular ejection fraction at 48 h between the two groups (angioplasty 59 ± 13%, streptokinase 57 ± 13%, p = NS). For patients with anterior infarction, ejection fraction was 56 ± 18% in the angioplasty group and 54 ± 13% in the streptokinase group (p = NS).

Blood product transfusion. No patients in either group required blood product transfusion.

Time to treatment. As noted, the time to treatment with coronary angioplasty was longer than that with intravenous streptokinase (Table 1).

Recurrent ischemia. Recurrent ischemia occurred in four patients (8%) randomized to direct coronary angioplasty. Two patients (4%) were managed medically, one (2%) underwent repeat angioplasty and one (2%) was referred for bypass surgery. Within the group of patients randomized to streptokinase, recurrent ischemia occurred in five patients (10%) and urgent angioplasty was successfully performed in three (75%) of four patients in whom it was attempted. Delayed coronary angioplasty (performed between 5 and 10 days after presentation) was performed successfully in 19 (95%) of 20 streptokinase-treated patients in whom it was attempted. Elective coronary artery bypass surgery was performed in 6 streptokinase-treated patients (15%) because of three-vessel disease or anatomy unsuitable for coronary angioplasty.

Discussion

For patients equally eligible for intravenous thrombolytic therapy or direct coronary angioplasty or for patients whose heightened risk of hemorrhage excludes them from consideration of intravenous thrombolytic therapy, the role of direct angioplasty remains to be defined. Prior nonrandomized studies (4–6,11) have suggested equal or better coronary artery patency with angioplasty, but the inherent time delay in most clinical settings and heightened cost of keeping many catheterization laboratories available for around the clock treatment of many patients with acute myocardial infarction with angioplasty would seem to favor application of intravenous thrombolytic therapy to all patients who are eligible.

Comparison with previous preliminary studies. Several other small-scale randomized trials comparing direct coronary angioplasty with thrombolytic therapy of patients with acute myocardial infarction were performed in the same general time frame as this study but have not been published in full. Thus, DeWood et al. (16) randomized 54 patients within 6 h of onset of chest pain to either direct coronary angioplasty or intravenous recombinant tissue-type plasminogen activator (rt-PA). Infarct-related artery patency at 90 min was 74% in patients randomized to rt-PA and 67% in patients randomized to angioplasty. However, if one excludes 6 of 27 patients allocated to angioplasty because of anatomy poorly suited for that procedure, the angioplasty success rate in the remaining patients was 86%. There was no difference between the two groups of randomized patients with regard to the other primary end point of rest and exercise ejection fraction measured 2 months after infarction. Analysis in that study (16) was confounded by the large numbers of patients crossing over to angioplasty from the tPA randomized arm. Gibbon et al. (17) randomized 103 patients presenting with ST-segment elevation infarction within 12 h of symptom onset to direct coronary angioplasty or rt-PA given intravenously. There was no difference between groups in the primary study end point of myocardial salvage assessed by acute and late tomographic imaging with technetium-99m-sestamibi. Zijlstra et al. (18) reported results from 56 randomized patients and noted superior infarct-related artery patency and ejection fraction in the angioplasty group, but these results were considered preliminary. The results of the present study support the results of these other small randomized trials, showing in general no major difference in infarct-related artery patency or follow-up left ventricular function, thus considerably strengthening the overall assessment of general equivalence of these two forms of therapy.

Limitations of the present study. The present study has several limitations. 1) Similar to other reported randomized trials addressing this issue, our study is underpowered to detect differences in infarct-related artery patency and, to a greater extent, clinical events. If one were to assume an 80% infarct artery patency rate in patients given intravenous thrombolytic therapy and if one were to assume a 90% patency rate with coronary angioplasty, a study sample of 438 patients would be required to have a power of 0.80 at \( p = 0.05 \). 2) The measurement in this study of left ventricular ejection fraction at 48 h does not allow for full recovery from myocardial “stunning” (15,19). Therefore, the impact of differences of overall or relative vessel patency between these two modes of therapy on left ventricular myocardial recovery may not be completely ascertained. 3) By protocol, our study used “intention to treat” analysis, wherein angioplasty was performed in all patients randomized to this treatment, regardless of coronary anatomy. This is not the way clinical medicine is practiced and alternative forms of revascularization certainly might have been considered in those patients not appearing to be well suited for coronary angioplasty. If one were to eliminate the results from those patients whose anatomy was not judged to be well suited to angioplasty, then angioplasty was successful in 90% of attempts. 4) This study was performed in an era just before the routine surveillance of the adequacy of heparin anticoagulation in the catheterization laboratory by means of measuring activated clotting times, as is now routine. Strict attention to the adequacy of heparin therapy (20) might have improved the results with coronary angioplasty.

Conclusions. These results suggest that intravenous thrombolytic therapy might be preferred over coronary angioplasty for most patients because of the inherent time delay and probable increased expense with angioplasty.
that coronary angioplasty might quite rationally be applied when the risk of bleeding is high and reperfusion therapy is otherwise indicated.

We are grateful for the expert secretarial assistance provided by Patti Durnwald.

References