Relationship Between Delay in Performing Direct Coronary Angioplasty and Early Clinical Outcome in Patients With Acute Myocardial Infarction

Results From the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) Trial

Peter B. Berger, MD; Stephen G. Ellis, MD; David R. Holmes, Jr, MD; Christopher B. Granger, MD; Douglas A. Criger, MPH; Amadeo Betriu, MD; Eric J. Topol, MD; Robert M. Califf, MD; for the GUSTO-II Investigators

Background—Time to treatment with thrombolytic therapy is a critical determinant of mortality in acute myocardial infarction. Little is known about the relationship between the time to treatment with direct coronary angioplasty and clinical outcome. The objectives of this study were to determine both the time required to perform direct coronary angioplasty in the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) trial and its relationship to clinical outcome.

Methods and Results—Patients randomized to direct coronary angioplasty (n=565) were divided into groups based on the time between study enrollment and first balloon inflation. Patients randomized to angioplasty who did not undergo the procedure were also analyzed. The median time from study enrollment to first balloon inflation was 76 minutes; 19% of patients assigned to angioplasty did not undergo an angioplasty procedure. The 30-day mortality rate of patients who underwent balloon inflation ≤60 minutes after study enrollment was 1.0%; 61 to 75 minutes after enrollment, 3.7%; 76 to 90 minutes after enrollment, 4.0%; and ≥91 minutes after enrollment, 6.4%. The mortality rate of patients assigned to angioplasty who never underwent the procedure was 14.1% (P=0.001). Logistic regression analysis revealed that the time from enrollment to first balloon inflation was a significant predictor of mortality within 30 days; after adjustment for differences in baseline characteristics, the odds of death increased 1.6 times (P=0.008) for a movement from each time interval to the next.

Conclusions—The time to treatment with direct PTCA, as with thrombolytic therapy, is a critical determinant of mortality.

(Circulation. 1999;100:14-20.)

Key Words: reperfusion ■ myocardial infarction ■ angioplasty ■ mortality ■ survival

Thrombolytic therapy has been proven to reduce the mortality of acute myocardial infarction in prospective, randomized, controlled trials involving >60 000 patients.1 The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial and its angiographic substudy support the hypothesis that the rapid and complete restoration of blood flow is the mechanism by which thrombolytic therapy reduces early mortality in acute myocardial infarction.2–5

Some argue that direct coronary angioplasty should be the treatment of choice for acute myocardial infarction because it is believed to achieve reperfusion more rapidly and completely and in more patients than thrombolytic therapy.6 However, the relationship between mortality and the speed with which reperfusion is achieved has not been established with direct angioplasty as it has been with thrombolytic therapy. In addition, many proponents of thrombolytic therapy argue that the rapidity with which reperfusion was achieved and the high reperfusion rates with direct angioplasty in the randomized trials that compared direct angioplasty and thrombolytic therapy primarily at large tertiary-care medical centers may not be representative of the results that can be achieved in community hospitals.7–10 Indeed, in the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) trial (the largest international randomized trial to date, comparing...
thrombolytic therapy with direct coronary angioplasty in 57 hospitals in 9 countries to more accurately reflect the performance of direct coronary angioplasty), direct coronary angioplasty had less of an advantage over thrombolytic therapy than was present in the other randomized trials.11

Little information has been reported from the GUSTO-IIb trial about the relationship between the time required to perform angioplasty and about hospital delay in performing angioplasty was associated with an increased mortality that could have accounted for the lesser benefit associated with angioplasty in GUSTO-IIb.

Therefore, we analyzed data from the GUSTO-IIb trial to determine the time required to perform angioplasty and the relationship between the hospital delay in performing angioplasty and early clinical outcome.

Methods

Study Organization

The GUSTO-IIb Direct PTCA substudy was a prospective substudy of the GUSTO-IIb trial.11,12 Fifty-seven hospitals in 9 countries participated in the substudy comparing direct coronary angioplasty with thrombolytic therapy. To participate, each site was required to perform ≥200 angioplasty procedures a year and to have ≥1 interventionist who performed ≥50 angioplasties yearly. Eight-five percent of participating sites and operators performed >400 and 75 angioplasties yearly, respectively. A 24-hour on-call team was mandated, but there was no requirement about the speed with which angioplasty had to be performed for participation in the trial. Sites were required to be able to provide operating room backup if emergency bypass surgery was necessary.

Patient Population

Patients presenting to a participating hospital within 12 hours after symptom onset (chest pain lasting ≥20 minutes accompanied by ECG signs of ≥0.2-mV ST-segment elevation in ≥2 contiguous leads or left bundle-branch block) were eligible for enrollment. Exclusion criteria were identical to those in the main GUSTO-IIb trial. Patients gave informed consent before study enrollment. The protocol was approved by the Institutional Review Board at each hospital.

Randomization and Treatment Strategies

Eligible patients (n=1138) were randomized to either primary PTCA (n=565) or accelerated tissue plasminogen activator (t-PA; 15-mg intravenous bolus followed by an infusion of 0.75 mg/kg over 30 minutes, not to exceed 50 mg, and then 0.50 mg/kg over the next 60 minutes, not to exceed 35 mg, for a total maximum of 100 mg). Patients receiving t-PA (n=573) were not included in any of the analyses in the present study.

Primary Angioplasty

Angioplasty was performed with the intent of restoring normal antegrade blood flow in the infarct artery as soon as possible. The infarct artery was the only target, except in patients with hemodynamic deterioration despite restoration of its patency. For patients with coronary anatomy unfavorable for angioplasty, including those with left main stenoses or critical 3-vessel disease, the protocol recommended that bypass surgery be strongly considered instead of angioplasty. In patients whose infarct arteries showed Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow before the angioplasty procedure, the decision of whether to perform angioplasty was left to the judgment of the operator.13

Concomitant Therapy

All patients received standard medical care, including chewable aspirin at the time of enrollment. In the GUSTO-IIb substudy, patients were assigned in a 2 × 2 factorial design to either heparin or hirudin as in the main GUSTO-IIb trial. After coronary angiography was completed, if it was determined that angioplasty was indicated, the study thrombin inhibitor was titrated in a double-blind fashion by 3000-U heparin or 30-mg hirudin increments to achieve an activated clotting time of ≥350 seconds. After the angioplasty procedure, the study drug was temporarily stopped to allow for early sheath removal. Patients then received a 3- to 5-day infusion of either heparin or hirudin with adjustment to maintain the activated partial thromboplastin time in the 60- to 85-second range. Because there was no difference in the clinical outcome of angioplasty patients treated with hirudin versus heparin, all angioplasty patients were analyzed together regardless of which thrombin inhibitor they received.11,12 Other cardiac medications were administered at the discretion of the physician. Similarly, the use of intra-aortic balloon counterpulsation, functional (stress) testing, delayed angiography, angioplasty, and bypass surgery was left to the investigator.

Time to Angioplasty

 Patients randomized to angioplasty (n=565) were divided into groups based on the time between their enrollment in the study and the first angioplasty balloon inflation. These groups included patients in whom this time interval was ≤60 minutes (n=104), 61 to 75 minutes (n=109), 76 to 90 minutes (n=76), and >90 minutes (n=140). A fifth group of patients randomized to balloon angioplasty who never underwent the procedure was also analyzed (n=93). These time intervals were chosen because they permit comparison with patency rates after thrombolytic therapy, which are usually analyzed at 60 and 90 minutes.

Of the 93 patients in whom angioplasty was not performed, 5 died within 2 hours, before angioplasty could be performed. Six had left main disease >50% and were referred for bypass surgery. Ten others had severe multivessel disease and were also referred for bypass surgery. Three patients underwent immediate bypass surgery for anatomic reasons related to the infarct artery. One patient had severe mitral regurgitation requiring surgery. In 36 patients, the infarct artery was <70% stenotic, there was TIMI 3 flow, or both. In the remaining 32 patients, the exact reasons that PTCA was not performed remain unknown.

Patients in whom either the time of enrollment or the time of balloon angioplasty was not available (n=43, 8%) were excluded from this analysis. To determine whether bias was present in the ascertainment of these data, we compared the baseline characteristics and clinical outcome of patients in whom these time data were and were not available. There were no significant differences in any of the baseline characteristics included in Table 1 or in 30-day mortality between patients in whom these time data were and were not available.

Statistical Analyses

Prespecified baseline variables were compared among the analysis subgroups by use of a χ² test for categorical variables and Wilcoxon rank sum test for continuous variables. Logistic regression models were used to assess the relationship between the analysis subgroups and the outcomes of interest while controlling for certain baseline characteristics. Baseline variables used in the analysis were as follows: age, weight, height, race, sex, family history of coronary heart disease, hypertension, diabetes, peripheral vascular disease, hypercholesterolemia, smoking status (current smoker, history of smoking, or nonsmoker), previous angina, previous infarction, previous cerebrovascular disease, prior PTCA, prior CABG, blood pressure, heart rate, baseline Killip class, and minutes from symptom onset to enrollment. Because a
large number of comparisons were performed, a probability value of 0.05 was not considered to represent a significant difference between variables. Only probability values ≤0.005 were considered significant. In the logistic regression model, values of ≤0.05 were considered significant. All analyses were performed with SAS software.14

The primary end point of this study was all-cause mortality within 30 days. To find the best possible predictor of the 30-day death end point, the time from study enrollment to first balloon inflation was modeled as a continuous, categorical, and ordinal variable. The best relationship was achieved when the time from enrollment to first balloon inflation was analyzed in categories (chosen to allow comparison with previously reported patency rates with thrombolytic therapy, as described above) that roughly represented quartiles of the study population based on time to inflation; these categories were assigned values from 1 to 5. The time-to-inflation variable was then

### TABLE 1. Baseline Characteristics of Patients Randomized to Coronary Angioplasty in GUSTO-IIb

<table>
<thead>
<tr>
<th>Group 1 (≤60 min)</th>
<th>Group 2 (61–75 min)</th>
<th>Group 3 (76–90 min)</th>
<th>Group 4 (≥91 min)</th>
<th>Group 5 (No PTCA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=104)</td>
<td>(n=109)</td>
<td>(n=76)</td>
<td>(n=140)</td>
<td>(n=93)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.3</td>
<td>20.2</td>
<td>27.6</td>
<td>27.1</td>
<td>32.3</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>97.1</td>
<td>97.3</td>
<td>94.7</td>
<td>92.1</td>
</tr>
<tr>
<td>Black</td>
<td>1.0</td>
<td>0.0</td>
<td>2.6</td>
<td>5.7</td>
</tr>
<tr>
<td>Other</td>
<td>1.9</td>
<td>2.7</td>
<td>2.6</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Smoking class</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>41.8</td>
<td>46.8</td>
<td>43.4</td>
<td>43.9</td>
</tr>
<tr>
<td>Former smoker</td>
<td>26.2</td>
<td>20.2</td>
<td>25.0</td>
<td>22.3</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>32.0</td>
<td>33.0</td>
<td>31.6</td>
<td>33.8</td>
</tr>
<tr>
<td><strong>Family history of CHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29.8</td>
<td>26.6</td>
<td>30.3</td>
<td>39.6</td>
<td>26.9</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37.5</td>
<td>33.9</td>
<td>57.9</td>
<td>39.3</td>
<td>32.3</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.2</td>
<td>15.6</td>
<td>15.8</td>
<td>15.7</td>
<td>19.4</td>
</tr>
<tr>
<td><strong>Peripheral vascular disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.9</td>
<td>6.4</td>
<td>5.3</td>
<td>2.9</td>
<td>7.5</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35.6</td>
<td>23.9</td>
<td>38.2</td>
<td>28.6</td>
<td>34.4</td>
</tr>
<tr>
<td><strong>Previous MI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.6</td>
<td>8.3</td>
<td>15.8</td>
<td>15.0</td>
<td>17.2</td>
</tr>
<tr>
<td><strong>Previous angina</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.7</td>
<td>31.2</td>
<td>47.4</td>
<td>42.9</td>
<td>50.5</td>
</tr>
<tr>
<td><strong>Cerebrovascular disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.9</td>
<td>0.0</td>
<td>2.6</td>
<td>1.4</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>Prior PTCA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.9</td>
<td>4.6</td>
<td>7.9</td>
<td>7.1</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>Prior CABG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>0.0</td>
<td>5.3</td>
<td>2.1</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Baseline Killip class</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>96.2</td>
<td>91.7</td>
<td>92.1</td>
<td>87.9</td>
</tr>
<tr>
<td>II</td>
<td>2.9</td>
<td>7.3</td>
<td>6.6</td>
<td>12.1</td>
</tr>
<tr>
<td>III</td>
<td>0.0</td>
<td>0.0</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>IV</td>
<td>1.0</td>
<td>0.9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Minutes from symptom onset to enrollment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>142</td>
<td>149</td>
<td>148</td>
<td>168.5</td>
<td>201</td>
</tr>
<tr>
<td></td>
<td>(94, 184)</td>
<td>(106, 240)</td>
<td>(114, 253)</td>
<td>(110, 274)</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>60.5</td>
<td>62.7</td>
<td>63.6</td>
<td>63.6</td>
</tr>
<tr>
<td></td>
<td>(49, 67)</td>
<td>(52, 71)</td>
<td>(55, 70)</td>
<td>(53, 73)</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>76</td>
<td>75</td>
<td>79.5</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>(70, 85)</td>
<td>(68, 82)</td>
<td>(68, 88)</td>
<td>(66, 90)</td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>170</td>
<td>170</td>
<td>170</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td>(167, 177)</td>
<td>(165, 175)</td>
<td>(163, 178)</td>
<td>(162, 178)</td>
</tr>
<tr>
<td><strong>Systolic BP, mm Hg</strong></td>
<td>130</td>
<td>130</td>
<td>140</td>
<td>133</td>
</tr>
<tr>
<td></td>
<td>(116, 141)</td>
<td>(120, 150)</td>
<td>(127, 150)</td>
<td>(116, 150)</td>
</tr>
<tr>
<td><strong>Diastolic BP, mm Hg</strong></td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>(70, 90)</td>
<td>(70, 90)</td>
<td>(72, 90)</td>
<td>(70, 89)</td>
</tr>
<tr>
<td><strong>Pulse, bpm</strong></td>
<td>69</td>
<td>74</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>(57, 80)</td>
<td>(63, 88)</td>
<td>(66, 87)</td>
<td>(64, 86)</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; MI, myocardial infarction.

Patients are separated into groups based on time from study enrollment to first angioplasty balloon inflation. All numbers are percentages except for the following, which are reported as median (25th, 75th percentiles): age, weight, height, systolic and diastolic blood pressure, and pulse.
treated as a 1-degree-of-freedom linear variable in the analysis. The logistic model assessing the relationship between 30-day death and category of time from study enrollment to first balloon inflation was partially adjusted for the baseline variables of age, systolic blood pressure, baseline Killip class (I to II or III to IV), smoking status (noncurrent smoker versus current smoker), and diagnosis or treatment of cancer in the last 5 years. Owing to the small sample size and low event rate, complete adjustment for other baseline variables was not performed. This model appears adequate, however, because the time effect remained consistent as each new adjusting factor was added to the model.

Results

Baseline Characteristics

The baseline characteristics of patients in GUSTO-IIb randomized to angioplasty are revealed in Table 1. There were few differences between patients in whom the time between enrollment and the first balloon inflation was \( \leq 60 \) minutes, 61 to 75 minutes, 76 to 90 minutes, or \( > 90 \) minutes, and patients randomized to balloon angioplasty who never underwent the procedure. Patients in whom there was greater delay in performing angioplasty had more severe heart failure at the time of enrollment, although few patients in the study (5.1%) had baseline Killip class III or IV heart failure. The median time from study enrollment to reperfusion was 76 minutes (25th and 75th percentiles were 61 and 95 minutes, respectively).

Angiographic Characteristics and Left Ventricular Ejection Fraction

Multivessel disease (defined as a diameter stenosis \( \geq 70\% \) in at least 2 of the 3 major coronary arteries or their major branches, or a left main stenosis \( \geq 50\% \)) was present in 26 patients (25%) treated \( \leq 60 \) minutes after study enrollment, 43 (40%) treated 61 to 75 minutes after enrollment, 23 (31%) treated 76 to 90 minutes after enrollment, and 53 patients (38%) treated \( > 91 \) minutes after study enrollment. Multivessel disease was present in 30 patients (39%) who underwent angiography but did not undergo angioplasty (\( P=0.13 \)).

Ventriculography performed before the angioplasty procedure in 309 patients revealed that the median left ventricular ejection was 60% (with 25th and 75th percentiles of 50% and 67%, respectively) for patients treated within 1 hour of study enrollment, greater than the median ejection fraction of 50% in patients treated 61 to 75 minutes after enrollment (45%, 58%), 51% in patients treated 76 to 90 minutes after enrollment (43%, 60%), and 50% in patients treated \( > 91 \) minutes after study enrollment (40%, 59%). Patients who did not undergo angioplasty had a mean ejection fraction of 50% (40%, 62%) as well.

Correlates of Delay

We examined the baseline clinical characteristics in Table 1, the frequency of multivessel disease, and 3 characteristics on the qualifying ECG (infarction site, total amount of ST-segment elevation, and total amount of ST-segment shift, including both ST-segment elevation and depression) in an attempt to identify clinical and ECG correlates of hospital delay in performing direct coronary angioplasty. None of these characteristics were associated with greater or lesser delay in performing the angioplasty procedure. There was also no apparent relationship between time to treatment and whether heparin or hirudin was used or the annual angioplasty caseload (\( \leq 625 \) cases per year at 30 medical centers versus \( > 625 \) cases per year at 27 medical centers), although these subset analyses were underpowered to detect significant differences.

Clinical Outcome

There were differences in clinical outcome between the different groups of patients (Figure). Mortality within 30 days of enrollment was lowest in patients treated within 60 minutes of enrollment and progressively higher among patients with greater delay between enrollment and first balloon inflation (\( P=0.001 \)). Mortality was highest among patients in whom angioplasty was not performed. A relationship between mortality and time to angioplasty was still evident after patients in whom angioplasty was not performed were excluded (\( P=0.035 \)).

Among the 73% of patients in whom TIMI 3 flow was ultimately achieved, the mortality rate was 1.5%, whereas it was 11.7% in the 27% of patients who achieved TIMI 0, 1, or 2 flow.

The median time to death, with 25th and 75th percentiles in parentheses, was 0 days (0, 0) for patients treated within 60 minutes, 5 days (0.5, 11.5) for patients treated 61 to 75 minutes after enrollment, 7 days (4, 17) for patients treated 76 to 90 minutes after enrollment, 1 day (1, 4) for patients treated \( > 91 \) minutes after enrollment, and 0 days (0, 2) for patients assigned to angioplasty who did not undergo an angioplasty procedure.

Multivariate Analysis

Logistic regression analysis was performed to further evaluate the relationship between time to first inflation and 30-day mortality. After adjustment for age, systolic blood pressure, baseline Killip class, smoking status, and diagnosis or treatment of cancer in the last 5 years, the time from enrollment to first balloon inflation was a significant predictor of 30-day death (\( P=0.008 \)). Each time interval was associated with a 1.6 times (95% CI, 1.13 to 2.26; \( P=0.008 \)) greater risk of death than the interval preceding it (eg, \( < 60 \) minutes to 61 to 75 minutes). This increase in...
the odds of death associated with delay was roughly equivalent to a 7-year increment in age (OR, 1.56; 95% CI, 1.16 to 2.11; P = 0.004). Inclusion of initial TIMI flow grade had no detectable impact on the relationship between time to reperfusion and mortality.

**Symptom Onset of Angioplasty**

We also analyzed the time from symptom onset to angioplasty. The data do not demonstrate as strong a relationship between mortality and time from symptom onset to angioplasty as is evident in the relationship between mortality and the time from study enrollment to angioplasty. The mortality of patients with a duration of symptoms <90 minutes until angioplasty was performed was 0% (n = 4); for patients with symptoms for 91 to 120 minutes until angioplasty, 6.7% (n = 14); for those with symptoms for 121 to 180 minutes until angioplasty, 1.1% (n = 87); for patients with symptoms for 181 to 240 minutes, 3.5% (n = 116); for those with symptoms for 241 to 300 minutes, 6.9% (n = 71); and for patients with symptoms for >300 minutes until angioplasty, 4.9% (n = 117). Among patients in whom angioplasty was not performed, the mortality rate was 14.1% (n = 93).

**Discussion**

The most important finding of this study is that in patients with acute myocardial infarction who were randomized to direct coronary angioplasty, hospital delay in performing the angioplasty procedure appeared to be associated with an increase in 30-day mortality. The time to angioplasty in the GUSTO-IIb study was longer than in some of the randomized trials, which may have contributed to the lesser benefit seen with direct angioplasty in this study than in other randomized trials comparing direct coronary angioplasty with thrombolytic therapy.

**GUSTO-IIb**

Several differences between GUSTO-IIb and the other randomized comparisons of direct coronary angioplasty and thrombolytic therapy are worth emphasizing. GUSTO-IIb used accelerated t-PA, the thrombolytic regimen demonstrated to have the lowest mortality in clinical trials. Most of the other randomized studies used thrombolytic regimens that achieve lower 90-minute patency rates; patency rates with thrombolytic therapy have been shown to correlate with early 30-day mortality. In addition, the time from enrollment in the study to the administration of thrombolytic therapy was more rapid in GUSTO-IIb than in most of the randomized trials, which also may have contributed to a lower mortality in the group receiving thrombolytic therapy. Furthermore, the time to angioplasty in several of the randomized trials was more rapid than in GUSTO-IIb (Table 2), although it must be emphasized that GUSTO-IIb deliberately included a wide variety of hospitals to better reflect practice patterns throughout the world. The time required to perform angioplasty in GUSTO-IIb might most appropriately be compared with the time required to perform angioplasty in the more representative second National Registry of Myocardial Infarction.

In this registry of 3648 patients treated with direct coronary angioplasty at 421 hospitals in the United States, the median time from hospital presentation to angioplasty was 2 hours, longer than the median time from enrollment to treatment of 76 minutes in GUSTO-IIb, despite not having to take additional time to obtain informed consent, as required in GUSTO-IIb.

**Duration of Symptoms Before Angioplasty**

Our analysis of the relationship between mortality and the duration of symptoms until angioplasty revealed a weaker association than was seen with the relationship between mortality and time from hospital arrival until angioplasty. The duration of a patient’s symptoms is inherently subjective, and patients may not report their symptom duration accurately. Furthermore, infarct arteries often open and close in the course of an infarction, which might make the relationship between symptom duration and outcome less strong. It also may be that patients who are sicker in some ways come to the hospital more rapidly than less sick patients, which would introduce bias into the analysis. Although we strongly support public health efforts to reduce delay between symptoms of infarction and presentation to the hospital, the component of delay that is directly under physicians’ control is the delay in achieving reperfusion after patients present to the hospital. It is this important component of delay that we primarily addressed in this study.

**Comparison of Patency Rates With Direct Coronary Angioplasty and Thrombolytic Therapy**

A single study has compared the time required to achieve reperfusion with coronary angioplasty versus thrombolytic therapy. Such comparisons are fraught with difficulty for many reasons. First, the definition of success differs between the 2 treatments. Successful angioplasty usually requires a residual stenosis of <50%; no such criterion exists for thrombolytic therapy, and in fact, most patients in whom patency is restored with thrombolytic therapy have a residual stenosis >60%. Second, normal antegrade flow (TIMI grade 3 flow) has usually been required for angioplasty to be considered successful, whereas traditionally TIMI grade 2 or

<table>
<thead>
<tr>
<th>Time Interval Reported</th>
<th>Author, Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission to first inflation</td>
<td>de Boer et al, 18 Netherlands trial</td>
</tr>
<tr>
<td>Randomization to first inflation</td>
<td>Berger et al, 20 Mayo Clinic Trial</td>
</tr>
<tr>
<td>Randomization to angiography</td>
<td>Grines et al, 15 PAMI Trial</td>
</tr>
<tr>
<td>Hospital arrival to treatment</td>
<td>Cannon et al, 8 2nd NRMI</td>
</tr>
<tr>
<td>Randomization to first inflation</td>
<td>GUSTO-IIb</td>
</tr>
</tbody>
</table>

PAMI indicates Primary Angioplasty in Myocardial Infarction; NRMI, National Registry of Myocardial Infarction.
3 flow has been required for thrombolysis to be considered a success. Lastly, the time required to transport patients to the catheterization laboratory has been included in analyses of the time required to achieve reperfusion with direct coronary angioplasty, whereas the time required to administer thrombolytic therapy has not been included in the analyses of patency rates with thrombolysis. When one accounts for the time to perform direct coronary angioplasty as well as the time to administer thrombolytic therapy, patency rates are considerably higher with direct coronary angioplasty. In the current study, if one includes the mean of 20 minutes from randomization required to administer t-PA in the thrombolytic arm of GUSTO-IIb and assumes that the 54% patency rate with t-PA in GUSTO-I was achieved in the present study as well, it can be estimated that 54% of patients had normal TIMI 3 flow 110 minutes (20 plus 90 minutes) after study enrollment. In contrast, 72% of the angioplasty patients (373 of 521 patients with available time-to-treatment data) in the GUSTO-IIb substudy received their first balloon inflation within 110 minutes of randomization. The more rapid achievement of patency with direct coronary angioplasty provides the most logical explanation of the improved outcome seen with direct coronary angioplasty in this and other studies.

Limitations
Although GUSTO-IIb is the largest randomized trial to date comparing direct coronary angioplasty and thrombolytic therapy in the treatment of acute myocardial infarction, the study was nonetheless relatively small; there were only 30 deaths within 30 days of enrollment among the 522 angioplasty patients with time-to-treatment data. Therefore, the study was limited in its ability to detect significant correlates of adverse events while controlling for other variables. The improved clinical outcome with more rapid reperfusion is consistent with studies of thousands of patients treated with thrombolytic therapy in which the time to reperfusion has been conclusively shown to be a critical determinant of outcome. There is no reason to believe that timely reperfusion achieved in the catheterization laboratory is any less important than that achieved with thrombolysis. In fact, more timely and complete reperfusion with direct coronary angioplasty is believed to be the basis of the improved outcome with coronary angioplasty compared with thrombolytic therapy. Previous studies have used the time at which the first balloon inflation was performed as a surrogate for the time at which reperfusion was achieved, although admittedly some patients require multiple inflations to achieve reperfusion. In GUSTO-IIb, the time at which normal antegrade flow was established was not recorded. However, it is unlikely that the use of the time to first balloon inflation introduced bias into the study or influenced the results indicating that hospital delay was associated with a higher early mortality.

Conclusions
Hospital delay in achieving reperfusion with coronary angioplasty in acute myocardial infarction increases mortality, as does delay with thrombolytic therapy. Hospital delay in performing angioplasty should be eliminated, and the time required to perform direct angioplasty should be considered when deciding whether thrombolytic therapy or direct coronary angioplasty should be administered to patients with acute myocardial infarction.

Acknowledgment
The authors gratefully acknowledge Penny Hodgson for her invaluable editorial contributions.

References
1. Fibrinolytic Therapy Trialists’ (FTT) Collaborative Group. Indi-
cations for fibrinolytic therapy in suspected acute myocardial
infarction: collaborative overview of early mortality and major mor-
bidity results from all randomized trials of more than 1000 patients.
2. The GUSTO Investigators. An international randomized trial comparing
four thrombolytic strategies for acute myocardial infarction. N Engl
3. GUSTO Angiographic Investigators. The effects of tissue plasminogen
activator, streptokinase, or both on coronary-artery patency, ven-tricular
function, and survival after acute myocardial infarction. N Engl
Simoons ML, Morris D, Betriu A, Califf RM, Ross AM, for the GUSTO-I
Investigators. Link between the angiographic substudy and mortality
outcomes in a large randomized trial of myocardial reperfusion:
importance of early and complete infarct artery reperfusion.
5. Kleiman NS, White HD, Othman EM, Ross AM, Woodlief LH, Califf
RM, Holmes DR Jr, Bates E, Pistermer M, Vahanian A, Topol EJ, for the
GUSTO Investigators. Mortality within 24 hours of thrombolysis for
myocardial infarction: the importance of early reperfusion. Circulation.
6. Grines CL, BrowneKF, Marco J, Rothbaum D, Stone GW, O’Keefe J,
Overlie P, Bonohue B, Chelliah N, Timmis GC, Vlietstra RE, Szlezelecki
M, Puchrowicz-Ochocki S, O’Neill WW, for the Primary Angioplasty in
Myocardial Infarction Study Group. A comparison of immediate angi-
oplasty with thrombolytic therapy for acute myocardial infarction. N Engl
7. Every NR, Parsons LS, Hlatky M, Martin JS, Weaver WD. A comparison
of thrombolytic therapy with primary coronary angioplasty for acute
8. Cannon CP, Lambrew CT, Tiefenbrunn AJ, French WJ, Gore JM, Weaver
D, Rogers WJ, for the NRMI-2 Investigators. Influence of door-to-
to-balloon time on mortality in primary angioplasty results in 5,648 patients
in the Second National Registry of Myocardial Infarction (NRMI-2).
9. Roger WJ, Dean LS, Moore PB, Wool KJ, Burgard SL, Bradley EL, for the
Alabama Registry of Myocardial Ischemia Investigators. Comparison of
primary angioplasty versus thrombolytic therapy for acute myocardial
VJ, Mahler PR. Comparison of primary angioplasty for myo-
11. The Global Use of Strategies to Open Occluded Coronary Arteries in
Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Inves-
tigators. A clinical trial comparing primary coronary angioplasty with
tissue plasminogen activator for acute myocardial infarction. N Engl
12. The Global Use of Strategies to Open Occluded Coronary (GUSTO IIb)
Investigators. A comparison of recombinant tissue plasminogen activator and intravenous

Downloaded from http://circ.ahajournals.org/ by guest on May 1, 2017


Relationship Between Delay in Performing Direct Coronary Angioplasty and Early Clinical Outcome in Patients With Acute Myocardial Infarction: Results From the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) Trial

Peter B. Berger, Stephen G. Ellis, David R. Holmes, Jr, Christopher B. Granger, Douglas A. Criger, Amadeo Betriu, Eric J. Topol and Robert M. Califf for the GUSTO-II Investigators

Circulation. 1999;100:14-20
doi: 10.1161/01.CIR.100.1.14

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/100/1/14

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/