

# Treatment of Reinfarction After Thrombolytic Therapy for Acute Myocardial Infarction

## An Analysis of Outcome and Treatment Choices in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO I) and Assessment of the Safety of a New Thrombolytic (ASSENT 2) Studies

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**Background**—Early reinfarction after thrombolytic therapy is associated with adverse outcomes and increased mortality. Among patients with reinfarction in the 1992 Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO I) and the 1998 Assessment of the Safety of a New Thrombolytic (ASSENT 2) trials, we investigated temporal and regional differences in the use of repeat thrombolysis, revascularization (angioplasty and/or bypass surgery), or conservative measures and the outcomes of each management strategy.

**Methods and Results**—Data from the 4% of patients (n=2301) who experienced reinfarction after thrombolytic therapy were studied. Baseline characteristics, 30-day mortality, and incidence of total and hemorrhagic strokes were compared among the 3 treatment groups. The 30-day mortality did not differ between the repeat thrombolysis and revascularization groups ( $P=0.72$ ), and it was significantly lower among patients treated by these 2 strategies than in those treated conservatively (11% and 11% versus 28%, respectively;  $P<0.001$ ). Stroke rates did not differ significantly between the 3 treatment strategies ( $P=0.49$ ). From 1992 to 1998, the percentage of reinfarction patients treated with repeat thrombolysis decreased from 29.3% to 18.5% in US centers and from 51.4% to 41.9% in all other centers ( $P<0.001$ ). In contrast, use of revascularization procedures increased from 33.5% to 47.9% in US centers and from 8.1% to 23.0% in all other centers ( $P<0.001$ ).

**Conclusions**—Repeat thrombolysis and revascularization are associated with significantly lower mortality among reinfarction patients. Randomized trials are necessary to assess the exact risks and benefits of rethrombolysis versus interventional revascularization in this subset of high-risk patients presenting with reinfarction after thrombolytic therapy. (*Circulation*. 2001;103:954-960.)

**Key Words:** myocardial infarction ■ trials ■ thrombolysis ■ revascularization ■ reinfarction

Reocclusion of the infarct artery after successful thrombolytic therapy in patients with acute myocardial infarction is associated with adverse outcomes.<sup>1-4</sup> Reocclusion has been demonstrated in 5% to 30% of patients after successful thrombolysis,<sup>5-11</sup> but clinical reinfarction is documented in only 4% of patients<sup>12,13</sup> and most reocclusions (78%) are not associated with clinically overt symptoms or apparent reinfarction.<sup>14</sup>

Reinfarction may be treated in 1 of the following 3 ways: (1) conservatively with antithrombotic and vasodilating medications, (2) repeat administration of thrombolytic therapy,<sup>12,15,16</sup> or (3) with urgent interventional revascularization by coronary angioplasty<sup>3</sup> or bypass operation.<sup>2</sup>

Although many studies have reported on treatment strategies to prevent reinfarction, few studies<sup>2,4</sup> have addressed the use and effectiveness of the different treatment strategies for

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**TABLE 1. Baseline Characteristics of Patients With and Without Reinfarction in the GUSTO-I and ASSENT 2 Studies**

	No Reinfarction	Reinfarction	<i>P</i>
Total No. of patients enrolled	55 572 (96.0)	2301 (4.0)	
Days from hospitalization to reinfarction		3 (2–6)	
Male sex	42 057/55 562 (75.7)	1588/2301 (69.0)	<0.001
Age, y	60.8±12.0 61.3 (52.0–70.0)	64.2±11.4 65.3 (56.4–72.7)	<0.001
Previous MI	8867/55 453 (16.0)	527/2300 (22.9)	<0.001
Hypertension	20 974/55 430 (37.8)	1006/2294 (43.9)	<0.001
Diabetes mellitus	8335/55 475 (15.0)	382/2298 (16.6)	0.037
Smoking			<0.001
Current	24 217/54 940 (44.1)	730/2267 (32.2)	
Ex	14 642/54 940 (26.7)	742/2267 (32.7)	
Killip class >1 at admission	7646/55 365 (13.8)	345/2296 (15.0)	0.102
MI site			0.005
Anterior	21 817/55 371 (39.4)	863/2299 (37.5)	
Inferior	31 447/55 371 (56.8)	1374/2299 (59.8)	
Lateral	1564/55 371 (2.8)	42/2299 (1.8)	
Posterior	246/55 371 (0.4)	7/2299 (0.3)	
Other	297/55 371 (0.5)	13/2299 (0.5)	
Weight, kg	79.4±15.6 78 (70–88)	77.8±15.5 76 (68–86)	<0.001
Height, cm	171.0±9.3 172 (165–178)	169.9±9.5 170 (163–177)	<0.001
Systolic BP, mm Hg	130.3±23.2 130 (114–146)	130.6±23.4 130 (114–147)	0.494
Diastolic BP, mm Hg	78.3±14.9 80 (70–90)	78.3±14.5 80 (70–90)	0.982
Heart rate, bpm	75.3±17.6 73 (62–85)	73.3±16.9 71 (60–82)	<0.001
Previous PTCA	2428/55 453 (4.0)	117/2299 (5.1)	0.108
Previous CABG	2293/55 502 (4.1)	137/2300 (6.0)	<0.001

Values are n (%), mean±SD, or median (25th–75th percentile). MI indicates myocardial infarction; BP, blood pressure.

early reinfarction after thrombolysis. We do not know whether intravenous thrombolytic therapy is as effective for reinfarction as for index infarction. Moreover, it is unclear whether the readministration of thrombolytic therapy is associated with the same or a greater risk of bleeding as it is with the first administration. This retrospective comparative analysis used the databases of 2 large-scale, multicenter trials of thrombolytic therapy in acute myocardial infarction and documented the change in the treatment of reinfarction from 1992 to 1998 in the US and non-US centers.

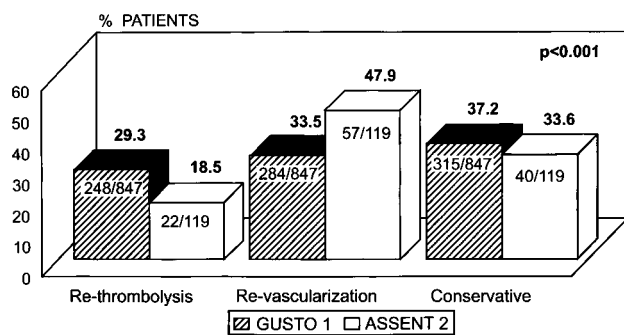
### Methods

The Global Utilization of Streptokinase and Tissue Plasminogen Activator (GUSTO I) and Assessment of Safety and Efficacy of a New Thrombolytic (ASSENT 2) trials are multicenter studies of thrombolytic therapy in acute myocardial infarction that took place between 1991 to 1993 and 1997 to 1998, respectively.<sup>12,13</sup> Population definitions, inclusion and exclusion criteria, and treatment protocols are detailed in the original publications of these studies.<sup>12,13</sup>

### Definitions

Reinfarction was defined in the GUSTO I trial by at least 2 of the following 4 criteria: (1) recurrent ischemic symptoms lasting >15 minutes after resolution of symptoms of the index myocardial infarction, (2) occurrence of new ST-T wave changes or new Q waves, (3) a second elevation in cardiac enzymes to over the normal upper limit (or by a further 20% if already over the normal upper limit), and (4) angiographic reocclusion of a documented previously patent infarct-related artery.

In the ASSENT 2 trial, reinfarction was defined in the first 18 hours after the start of drug administration by recurrent signs and symptoms of ischemia at rest accompanied by new or recurrent ST-segment elevations of 0.1 mV in at least 2 contiguous leads that persisted for at least 30 minutes. After 18 hours, reinfarction was defined by the appearance of new Q waves (by Minnesota Code Criteria) in ≥2 leads, new left bundle branch block, and/or enzyme evidence of reinfarction, which was defined as re-elevation of creatine kinase-MB (CK-MB) to above the upper limit of normal and increased by ≥50% over the previous value. If CK-MB was not available, the total CK was evaluated; this measurement had to be either re-elevated to at least twice the upper limit of normal and increased by at least 25%, or re-elevated to 200 U/mL over the previous value; if it was re-elevated to less than twice the upper limit



**Figure 1.** Management strategies for reinfarction in US centers in GUSTO I and ASSENT 2.

of normal, the total CK had to exceed the upper limit of normal by at least 50% and exceed the previous value by 2-fold or to be re-elevated to  $\geq 200$  U/mL. Reinfarction after percutaneous transluminal coronary angioplasty (PTCA; with or without stenting) was defined as a CK-MB (or CK, if MB was not available) more than twice the upper limit of normal and at least 50% greater than the previous value and/or new Q waves (Minnesota Code) in  $\geq 2$  contiguous leads. Reinfarction after coronary artery bypass grafting (CABG) was defined as a CK-MB (or CK, if MB is not available)  $> 5$  times the upper limit of normal and at least 50% greater than the previous value and/or new Q waves (Minnesota Code) in  $\geq 2$  contiguous leads.

Bleeding complications in the ASSENT 2 study were documented by the investigators in the case record forms and included all bleeding events that occurred after reinfarction.

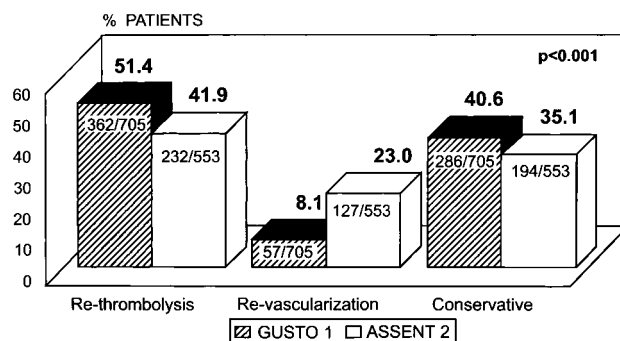
Electrocardiographic characterization of the reinfarction event was made in the GUSTO I study by the investigators, who documented the symptoms and signs on which the recurrent infarction was defined. Among these were ECG changes at the time of reinfarction, including ST-segment elevation  $\geq 1$  mm, ST-segment depression, T-wave changes, and development of a new Q wave.

In the ASSENT 2 study, experienced readers blinded to clinical outcome at the ECG core laboratory analyzed the reinfarction ECGs. ST-segment deviation (of at least 0.1 mV, with at least 0.1 mV depth and 40 ms duration) in at least 2 contiguous leads was recorded based on an analysis of the reinfarction ECGs. Modified Selvester QRS Criteria<sup>17</sup> were used for defining Q-wave (or Q-wave equivalent) infarction, as follows: (1) Q wave of at least 40 ms in leads I, AVL, and V4–V6; (2) Q waves of 20 to 39 ms in leads II, II, and AVF; (3) Q wave of any duration in lead V2; (4) R wave of at least 40 ms in V1 or 50 ms in V2; and (5) R wave  $\leq 0.1$  mV and 10 ms in lead V2.

Treatment of reinfarction was at the discretion of the treating physicians and was not randomized or specified by the protocol of either trial. For this analysis, patients with reinfarction during the index hospitalization were divided into the following 3 groups: those who received repeated thrombolytic therapy (repeat thrombolysis group), those who underwent interventional coronary revascularization (coronary angioplasty and/or coronary bypass surgery) the same or next day after reinfarction and did not receive repeat thrombolytic therapy (revascularization group), and those who did not receive repeated thrombolysis, PTCA, or CABG the same or next day after reinfarction (conservative group). Stroke was defined as a complication of the reinfarction or its treatment only when it occurred after the reinfarction. The outcome of the 3 treatment strategies was evaluated in the separated and combined GUSTO I and ASSENT 2 populations using a multivariate analysis accounting for treatments and all known baseline characteristics, including treatment in US versus Non-US centers.

### Statistical Analysis

Clinical and historical data are presented by numbers and percentages for categorical variables and by mean, standard deviation, and 25th, 50th (median), and 75th percentiles for continuous variables.



**Figure 2.** Management strategies for reinfarction in non-US centers in GUSTO I and ASSENT 2.

Differences between patients with and without reinfarction and between reinfarction treatment groups were evaluated with an exact  $\chi^2$  test, a *t* test, or a Kruskal-Wallis test, whichever was appropriate.

A multiple logistic regression analysis was performed in the subset of patients experiencing reinfarction to check for treatment differences in 30-day mortality and stroke after adjustment for all known baseline characteristics. These baseline characteristics included study, study medication, medical center (US versus non-US), sex, diabetes, hypertension, infarct location, Killip class at entry, previous myocardial infarction (before randomization in the study), current smoker, age, height, weight, systolic and diastolic blood pressures, race, heart rate, previous PTCA, previous CABG, and ST-segment elevation reinfarction.<sup>18</sup>

## Results

### Baseline Characteristics

The incidence of reinfarction in the GUSTO I (1628 patients) and the ASSENT 2 trials (673 patients) was 4% in both studies (Table 1). Baseline characteristics were similar in both studies. Table 1 presents the baseline characteristics for the combined populations of the 2 studies. Advanced age, female sex, nonsmoking and ex-smoking status, previous myocardial infarction, prior hypertension, and previous CABG were significantly associated with reinfarction. Diabetes mellitus (16.7% versus 15.0%) and inferior location of myocardial infarction (59.8% versus 56.8%) were more prevalent among reinfarction patients, as were lower height, weight, and heart rate. In the combined studies, no difference was found in the incidence of Killip classification  $> 1$  on admission among patients with or without reinfarction. Reinfarction occurred an average of 3 days (25 to 75 percentile, 2 to 6 days) after the initiation of thrombolytic therapy in both studies.

### Treatment Strategies

Figures 1 and 2 show the proportional use of the 3 reinfarction treatment strategies in medical centers in the United States and elsewhere. Centers outside the United States used repeated thrombolytic therapy almost twice as often as US centers in both the GUSTO I and ASSENT 2 studies. Non-US centers referred significantly fewer patients to interventional coronary revascularization. The differences in treatment strategies between the 2 geographic areas were highly significant ( $P < 0.001$  for each of the studies).

From 1992 (GUSTO I) to 1998 (ASSENT 2), fewer patients with reinfarction were treated with repeated throm-

**TABLE 2. Baseline Characteristics of Patients in the 3 Treatment Groups (GUSTO-I and ASSENT 2 Combined)**

	Rethrombolysis (n=864)	Revascularization (n=525)	Conservative (n=835)	<i>P</i>
Male sex	619/864 (71.6)	368/525 (70.1)	540/835 (64.7)	0.006
Age, y	63.8±10.7	61.6±11.6	66.7±11.4	<0.001
	65.0 (56.1–71.8)	62.0 (52.2–70.2)	68.0 (59.8–75.6)	
Days from hospitalization to reinfarction	3 (1–5)	3 (1–6)	4 (2–7)	<0.001
Previous MI	198/864 (22.9)	97/525 (18.5)	219/834 (26.3)	0.004
Hypertension	357/861 (41.5)	232/524 (44.3)	388/833 (46.6)	0.105
Diabetes mellitus	136/864 (15.7)	79/524 (15.1)	153/833 (18.4)	0.206
Smoking				0.023
Current	271/857 (31.6)	190/516 (36.8)	239/818 (29.2)	
Ex	299/857 (34.9)	160/516 (31.0)	267/818 (32.6)	
Killip class >1 at admission	116/861 (13.5)	57/525 (10.9)	158/833 (19.0)	<0.001
MI Site				0.780
Anterior	325/863 (37.7)	200/524 (38.2)	314/835 (37.6)	
Inferior	513/863 (59.4)	314/524 (59.9)	496/835 (59.4)	
Lateral	18/863 (2.0)	6/524 (1.1)	16/835 (2.1)	
Posterior	4/863 (0.5)	0/524 (0.0)	3/835 (0.4)	
Other	3/863 (0.3)	4/524 (0.8)	3/835 (0.4)	
Previous PTCA	46/864 (5.3)	27/525 (5.1)	39/833 (4.7)	0.825
Previous CABG	50/864 (5.8)	26/525 (5.0)	56/834 (6.7)	0.411
ST-segment elevation re-MI	789/810 (97.4)	401/447 (89.7)	621/725 (85.7)	<0.001
Weight, kg	77.6±15.1	80.0±15.6	76.6±16.0	<0.001
	76 (68–85)	79.5 (70–89)	75 (66.9–85.0)	
Height, cm	170.1±9.3	170.2±10.2	169.4±9.5	0.241
	170 (165–176)	170 (163–177.8)	170 (162.5–176.4)	
Systolic BP, mm Hg	131.8±24.0	129.8±22.5	130.2±23.3	0.202
	130 (115–150)	126 (113–145)	130 (115–145)	
Diastolic BP, mm Hg	78.9±14.6	78.1±14.2	77.8±14.6	0.192
	80 (70–90)	80 (70–89)	80 (70–90)	
Heart rate, bpm	71.2±15.9	73.3±16.3	75.6±18.1	<0.001
	70 (60–80)	72 (61–83)	73.5 (62–84.5)	

Values are n (%), mean±SD, or median (25th–75th percentiles). MI indicates myocardial infarction; BP, blood pressure.

bolytic therapy (from 29.3% to 18.5% in US centers and from 51.4% to 41.9% in all other centers; Figures 1 and 2). This change was balanced by a significant increase in the use of urgent coronary angioplasty or bypass surgery (from 33.5% to 47.9% in US centers and from 8.1% to 23.0% in all other centers). As a result, the proportion of patients treated conservatively decreased by 3.6% in the US centers and by 5.5% in all other centers.

### Baseline Characteristics by Treatment Groups

Table 2 summarizes the baseline characteristics of the patients in the 3 treatment groups in the combined GUSTO I and ASSENT 2 populations. Patients treated conservatively tended to be women, older, and less often current smokers and to have a higher rate of previous myocardial infarction and a higher incidence of Killip classification >1 on admission. Among patients treated conservatively, the timing of

reinfarction was, on average, 1 day later. The proportion of reinfarction patients developing recurrent ST-segment elevation infarction was significantly higher among patients in the rethrombolysis treatment group compared with the revascularization and conservative treatment groups (97.4% versus 89.7% and 85.7%, respectively;  $P<0.001$ ).

### Clinical Outcome by Treatment Groups

Tables 3 and 4 summarize indices of myocardial damage after reinfarction and mortality and safety outcomes of the 3 treatment groups for the GUSTO I and ASSENT 2 populations. In the GUSTO I study, fewer patients in the rethrombolysis group developed a new Q wave after the reinfarction (6.3% compared with 11.7% and 10.1% in the revascularization and conservative groups, respectively;  $P=0.006$ ). Conversely, in the ASSENT 2 study, new Q waves developed in only 15.7% of the patients in the conservative group but in

**TABLE 3. Clinical Outcome of Patients in GUSTO I by the 3 Treatment Groups**

	Rethrombolysis (n=610)	Revascularization (n=341)	Conservative (n=601)	<i>P</i>
PTCA and/or CABG after rethrombolysis	185/610 (30.3)			
Peak CK, IU/L*	330 (143; 980)	963 (326; 1525)	570 (308; 1066)	<0.001
Peak CK-MB, IU/L*	26 (11; 75)	23 (11; 78)	32 (14; 75)	0.060
New Q wave*	37/584 (6.3)	36/307 (11.7)	60/556 (10.1)	0.006
Overall stroke*	16/609 (2.6)	7/339 (2.1)	12/592 (2.0)	0.751
Intracranial hemorrhage*	8/609 (1.3)	0/339 (0.0)	3/592 (0.5)	0.046
Ischemic*	5/609 (0.8)	6/339 (1.8)	7/592 (1.2)	0.418
Unclassified*	3/609 (0.5)	1/339 (0.3)	2/592 (0.3)	0.999
Hospital mortality	71/610 (11.6)	36/341 (10.6)	163/598 (27.3)	0.001
30-Day mortality	70/610 (11.5)	37/340 (10.9)	170/598 (28.4)	0.001

Values are n (%) or median (25th; 75th percentiles).

\*Occurring after reinfarction.

18.1% and 27.5% of those in the rethrombolysis and revascularization groups, respectively ( $P=0.04$ ). The overall stroke rate was not significantly different among the treatment groups in the combined trials. However, the rate of intracranial hemorrhage was significantly different ( $P=0.046$ ) among treatment groups in the GUSTO I study.

Mortality, both in-hospital and 30-day, was significantly higher for the conservative group ( $P<0.0001$ ), even after adjusting for all known baseline characteristics, including an ST or non-ST-segment elevation myocardial infarction (Table 5). The 30-day mortality was significantly higher in the conservative group compared with the rethrombolysis

group (odds ratio, 2.2; 95% confidence interval, 1.5 to 3.1;  $P<0.001$ ) and the revascularization group (odds ratio, 2.2; 95% confidence interval, 1.4 to 3.3;  $P<0.0001$ ), but it did not differ significantly between the revascularization and repeat thrombolysis groups in the combined population of the GUSTO I and ASSENT 2 trials (odds ratio, 1.0; 95% confidence interval, 0.6 to 1.6;  $P=0.99$ ). After adjustment for all other factors, the 30-day mortality rate was not statistically different in US versus non-US centers ( $P=0.53$ ). Results were similar when the analysis was restricted to only the population with ST-elevation myocardial infarction.

**TABLE 4. Clinical Outcome of Patients in the ASSENT 2, by the 3 Treatment Groups**

	Rethrombolysis (n=254), n (%)	Revascularization (n=184), n (%)	Conservative (n=234), n (%)	<i>P</i>
PTCA and/or CABG after rethrombolysis	111/253 (43.8)			
Peak CK, IU/L				0.024
Normal values	43/193 (22.3)	12/127 (9.5)	15/144 (10.4)	
>Normal $\leq$ 2 $\times$ normal	32/193 (16.6)	23/127 (18.1)	29/144 (20.1)	
>2 $\times$ $\leq$ 5 $\times$ Normal	48/193 (25.4)	41/127 (32.3)	48/144 (33.3)	
>5 $\times$ Normal	69/193 (35.8)	51/127 (40.2)	52/144 (36.3)	
Peak CK-MB, IU/L				0.029
Normal values	20/147 (13.6)	16/111 (14.4)	6/130 (4.6)	
>Normal $\leq$ 2 $\times$ normal	29/147 (19.7)	14/111 (12.6)	23/130 (17.7)	
>2 $\times$ $\leq$ 5 $\times$ Normal	27/147 (18.4)	26/111 (23.4)	41/130 (31.5)	
>5 $\times$ Normal	71/147 (48.3)	55/111 (49.5)	60/130 (46.2)	
New Q wave*	37/205 (18.1)	36/120 (27.5)	23/147 (15.7)	0.040
Bleeding*	73/254 (28.7)	57/184 (31.0)	43/234 (18.4)	0.005
Overall stroke*	2/254 (0.8)	3/184 (1.6)	2/234 (0.9)	0.712
Intracranial hemorrhage*	1/254 (0.4)	2/184 (1.0)	0/234 (0.0)	0.281
Ischemic*	0/254 (0.0)	1/184 (0.5)	2/234 (0.8)	0.372
Unclassified*	1/254 (0.4)	0/184 (0.0)	0/234 (0.0)	0.999
Hospital mortality	23/254 (9.1)	19/184 (10.3)	65/233 (27.9)	0.001
30-Day mortality	27/254 (10.6)	19/184 (10.3)	67/234 (28.6)	0.001

\*Occurring after reinfarction.



**TABLE 5. Results of 30-day Mortality by Multiple Regression Analysis on Combined of the GUSTO I and ASSENT 2 Databases**

Variable	OR	95% CI	P
Treatment strategy			<0.001
Conservative vs revascularization	2.155	1.401, 3.314	
Conservative vs rethrombolysis	2.165	1.531, 3.058	
Rethrombolysis vs revascularization	0.996	0.620, 1.598	
Study drug vs ASSENT:TNK			0.494
GUSTO:combo	0.926	0.526, 1.630	
GUSTO:SK+IV heparin	1.167	0.675, 2.017	
GUSTO:SK+SC heparin	1.201	0.687, 2.099	
GUSTO:t-PA	1.058	0.590, 1.899	
ASSENT:t-PA	0.672	0.339, 1.334	
ST-elevation re-MI	0.657	0.416, 1.039	0.078
Sex, male vs female	1.210	0.791, 1.851	0.380
Diabetes mellitus	1.301	0.891, 1.900	0.178
Hypertension	1.238	0.907, 1.688	0.179
Infarct site			0.136
Anterior vs other	1.238	0.491, 3.120	
Inferior vs other	0.905	0.359, 2.284	
Killip class I at admission	0.629	0.436, 0.909	0.015
Previous MI	1.376	0.973, 1.947	0.074
Current smoker vs others	0.685	0.465, 1.009	0.051
Age (y)	1.071	1.052, 1.090	<0.001
Height (cm)	1.030	1.007, 1.054	0.009
Weight (kg)	0.997	0.985, 1.010	0.649
Systolic blood pressure (mm Hg)	0.987	0.977, 0.997	0.007
Diastolic blood pressure (mm Hg)	0.998	0.983, 1.014	0.833
White vs others	0.595	0.331, 1.069	0.092
Heart rate (bpm)	1.022	1.013, 1.031	<0.001
Previous PTCA	0.466	0.191, 1.136	0.072
Previous CABG	1.974	1.128, 3.455	0.020
US vs non-US center	0.898	0.643, 1.253	0.525

TNK indicates tenecteplase; SK, streptokinase; t-PA, tissue plasminogen activator; and MI, myocardial infarction.

In the ASSENT 2 population, detailed bleeding event data were collected. In this study, bleeding complications occurred significantly more often in the patients treated with repeated thrombolytic therapy (29%) and interventional revascularization (31%) than in those treated conservatively (18%;  $P=0.005$ ).

## Discussion

Despite the fact that 4% of patients treated with thrombolysis for acute myocardial infarction experience in-hospital clinical reinfarction with an associated increase in mortality, few reports describe or evaluate the treatment strategies used in this population. The relative advantages and disadvantages of interventional revascularization compared with repeat thrombolysis for reinfarction have not been quantified. Both treatments are available in many hospitals, but coronary intervention procedures are usually associated with at least 1 to 3 hours of logistic delay, especially after working hours. Repeat

thrombolysis has considerable appeal because of its universal and rapid availability after onset of reinfarction. In most clinical settings, readministration of the thrombolytic agent is the only form of treatment available for patients with early reinfarction who are unresponsive to a standard medical regimen.<sup>14</sup> The GUSTO I and ASSENT 2 databases gave us a unique opportunity to review the worldwide change in practice over the last 8 years in the treatment of reinfarction after thrombolytic therapy before hospital discharge.

It is interesting to note that although not commonly advocated and despite concerns about bleeding complications, a significant proportion of patients with reinfarction were treated with a repeat dose of thrombolytic agent: 30% to 20% in US centers and almost half of the patients in all other centers. Over time, the increase in interventional revascularization procedures was associated with a decrease in the use of repeat thrombolytic therapy, but it only minimally affected the proportion of patients who were treated conservatively. This retrospective analysis has 3 major conclusions. First, patients with reinfarction are at a high risk for increased in-hospital and 30-day mortality. Second, as previously demonstrated,<sup>4</sup> patients with reinfarction who are treated with either pharmacological or interventional reperfusion therapies have significantly lower mortality. It should be noted, however, that although known baseline variables were accounted for, other unaccounted baseline characteristics might have biased the group of patients treated conservatively.

A third and debatable conclusion is that repeat administration of thrombolytic therapy and urgent revascularization strategies for reinfarction are generally safe and have comparable and acceptable bleeding risks. Although the ASSENT 2 results demonstrate significantly higher rates of bleeding events, the incidence of intracranial hemorrhage or life-threatening bleeding after re-exposure to thrombolytic agent or revascularization procedures was not significantly affected.

Our results are not conclusive, and they certainly do not negate all safety concerns. Thrombolytic therapy is usually not readministered to patients who have a bleeding complication after the first thrombolytic dose; hence, selection bias may cause less bleeding in the patients treated with repeat thrombolytic therapy. It is interesting to note that reinfarction occurred 1 day later in the patients treated conservatively. Earlier treatment of reinfarction with repeat thrombolysis or coronary intervention may involve a higher risk for a bleeding complication. In addition, patients in the GUSTO I study who were treated with repeat thrombolytic therapy suffered a higher rate of intracranial hemorrhage than the patients treated in the interventional and conservative groups (1.3% compared with 0.0% and 0.5%, respectively;  $P=0.046$ ). In the ASSENT 2 study, there was no difference in the rate of intracranial hemorrhage among the 3 treatment groups (0.4%, 1.0%, and 0.0% in the rethrombolysis, revascularization, and conservative groups, respectively;  $P=0.28$ ). However, in this study, only a few patients (3 of 672) suffered an intracranial hemorrhage; thus, no comfort can be gleaned from these data.

Despite a large overall sample size and excellent data recording, our analysis has a number of important limitations. Neither GUSTO I nor ASSENT 2 were specifically designed

to assess treatment strategies for early reinfarction. Criteria for diagnosing reinfarction likely failed to identify some episodes of myocardial necrosis, because study protocols did not mandate standardized ECG monitoring or cardiac enzyme collection after recurrent ischemic symptoms and revascularization procedures. Also, treatment assignment after reinfarction to the conservative, readministration of thrombolytic agent, or early revascularization groups was not randomly assigned. Selection bias of younger, healthier, more hemodynamically stable patients in the more aggressive treatment strategies might therefore greatly affect mortality and bleeding outcomes. Finally, low event rates, particularly for overall stroke and intracranial hemorrhage, leave our analysis underpowered to make strong comparative conclusions between treatment strategies for these important safety outcomes.

Despite these limitations, a more aggressive approach toward patients presenting with reinfarction after thrombolytic therapy is associated with improved prognosis. Repeat thrombolytic therapy should be considered, especially where and when timely cardiac catheterization and interventional capabilities are not readily available.<sup>4</sup> However, the risk of repeat thrombolysis is to be weighed carefully with the improved mortality gained at likely risk of increased bleeding, as shown in ASSENT 2.

Finally, it is important to note that although the percentage of patients in whom no attempt was made to reopen the occluded coronary artery slightly decreased from 1992 to 1998, these patients still amounted to more than a third of the reinfarction patients in the ASSENT 2 trial. The results of this analysis clearly decree that more aggressive therapy might benefit these high-risk patients. A randomized trial comparing coronary intervention versus repeat thrombolytics is necessary to evaluate the exact risks and benefits of the two reperfusion strategies.

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Assessment of the Safety of a New Thrombolytic (ASSENT 2) Studies**

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