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Recombinant Hirudin (Lepirudin) for the Improvement of Thrombolysis With Streptokinase in Patients With Acute Myocardial Infarction

Results of the HIT-4 Trial

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OBJECTIVES The purpose of this study was to compare recombinant hirudin and heparin as adjuncts to streptokinase thrombolysis in patients with acute myocardial infarction (AMI).

BACKGROUND Experimental studies and previous small clinical trials suggest that specific thrombin inhibition improves early patency rates and clinical outcome in patients treated with streptokinase.

METHODS In a randomized double-blind, multicenter trial, 1,208 patients with AMI ≤6 h were treated with aspirin and streptokinase and randomized to receive recombinant hirudin (lepirudin, IV bolus of 0.2 mg/kg, followed by subcutaneous (SC) injections of 0.5 mg/kg b.i.d. for 5 to 7 days) or heparin (IV placebo bolus, followed by SC injections of 12,500 IU b.i.d. for 5 to 7 days). A total of 447 patients were included in the angiographic substudy in which the primary end point, 90-min Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 of the infarct-related artery, was evaluated, while the other two-thirds served as "safety group" in which only clinical end points were evaluated. As an additional efficacy parameter the ST-segment resolution at 90 and 180 min was measured in all patients.

RESULTS TIMI flow grade 3 was observed in 40.7% in the lepirudin and in 33.5% in the heparin group ($p = 0.16$), respectively. In the entire study population the proportion of patients with complete ST resolution at 90 min (28% vs. 22%, $p = 0.05$) and at 180 min (52% vs. 48%, $p = 0.18$) after start of therapy tended to be higher in the lepirudin group. There was no significant difference in the incidence of hemorrhagic stroke (0.2% vs. 0.3%) or total stroke (1.2% vs. 1.5%), reinfarction rate (4.6% vs. 5.1%) and total mortality rate (6.8% vs. 6.4%) at 30 days, as well as the combined end point of death, nonfatal stroke, nonfatal reinfarction, rescue-percutaneous transluminal coronary angioplasty and refractory angina (22.7 vs. 24.3%) were not statistically different between the two groups.

CONCLUSIONS Lepirudin as adjunct to thrombolysis with streptokinase did not significantly improve restoration of blood flow in the infarct vessel as assessed by angiography, but was associated with an accelerated ST resolution. There was no increase in the risk of major bleedings with lepirudin compared to heparin. (J Am Coll Cardiol 1999;34:966–73) © 1999 by the American College of Cardiology

Thrombolytic therapy has been shown to preserve ventricular function and improve survival in patients with acute myocardial infarction (AMI) (1,2). Several angiographic studies have demonstrated that an unimpaired flow (Thrombolysis in Myocardial Infarction [TIMI] grade 3) in the infarct vessel at 90 min after initiation of thrombolysis is

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Abbreviations and Acronyms

AMI	=	acute myocardial infarction
aPTT	=	activated partial thromboplastin time
CI	=	confidence interval
ECG	=	electrocardiogram
GUSTO	=	Global Use of Strategies to Open Occluded coronary arteries in acute coronary syndromes
HERO	=	Hirulog Early Reperfusion/Occlusion Study
HIT	=	Hirudin for the Improvement of Thrombolysis
PTCA	=	percutaneous transluminal coronary angioplasty
SC	=	subcutaneous
TIMI	=	Thrombolysis in Myocardial Infarction

associated with a lower mortality than an occluded infarct vessel or TIMI grade 2 flow (3–5). However, current thrombolytic regimens are limited by the fact that only 35% to 60% of patients experience optimal early reperfusion, and about 10% of reperfused vessels reocclude during hospital stay, which is associated with increased morbitidy and mortality (6,7).

Streptokinase is still the most often used thrombolytic agent worldwide. With streptokinase early reperfusion will occur in less than 40% of cases, leaving more room for improvement by better adjunctive therapy than with recombinant tissue-type plasminogen activator. Improvements in adjunctive therapy have been attempted by better platelet inhibition and more specific thrombin inhibitors. More specific thrombin inhibition may be most relevant because of ongoing thrombin formation and activation during thrombolysis, which is not completely suppressed by IV heparin (8). Unlike heparin, the specific thrombin inhibitor hirudin acts independently of antithrombin III, is not inactivated by platelet factor IV and, most importantly, inhibits both free and clot-bound thrombin (9).

In the present study a recombinant hirudin (HBW 023, lepirudin) has been tested as an adjunct to streptokinase thrombolysis for AMI. Previous trials (10–12) had shown a narrow therapeutic range for hirudin, resulting in an unacceptably high rate of bleedings with higher doses. The combined analysis of TIMI-9B and GUSTO-IIB (Global Use of Strategies to Open Occluded coronary arteries in acute coronary syndromes) in patients receiving thrombolytic therapy and reduced hirudin doses showed a significant (14%) reduction in the incidence of reinfarctions within 30 days compared with heparin, but no significant differences in mortality (13,14).

A major problem of most phase II trials is their limited information on safety of a new thrombolytic regimen. Given that the size of invasive studies is limited by the availability of resources, novel approaches are needed to resolve this dilemma. In this trial, coronary patency was determined in one-third of the patients, whereas indirect evidence of successful reperfusion by ST-segment analysis and close monitoring for adverse events was performed in all patients.

PATIENTS AND METHODS

Study population. The study was a prospective, randomized, double-blind, international multicenter trial in male and female patients with AMI aged 18 to 75 years. The study protocol was approved by the Ethics Committee of the University of Göttingen and by the relevant institutional review boards of the participating centers. It was conducted according to good clinical practice guidelines, including source data audit. All patients gave witnessed or written consent.

The time interval between symptom onset and start of therapy was to be less than 6 h. A ST-segment elevation $\geq$0.2 mV in at least two precordial leads or ST-segment elevation $\geq$0.1 mV in at least two limb leads had to be present, and the patient had to give informed consent before inclusion into the study. Exclusion criteria were in addition to the usual contraindications to thrombolysis: streptokinase therapy during the last year, heparin therapy within 2 h before study medications and known renal insufficiency (serum creatinine >2.0 mg/dl or 1.77 mmol/liter). Hyperlipidemia was reported as stated by the investigators in the case record form; no further definition was made.

Treatment protocol. Patients were randomized by telephone in Germany or according to the medication number outside Germany. All patients were to receive a loading dose of 300 mg of aspirin followed by 100 to 200 mg daily. The IV bolus dose of lepirudin (0.2 mg/kg body weight) or matching placebo was given before streptokinase (1.5 million units in 60 min intravenously). Subcutaneous lepirudin 0.5 mg/kg or unfractionated heparin 12,500 IE were given twice daily over five to seven days starting within 30 min after the start of streptokinase. Subcutaneous (SC) injections were given at 12-h intervals according to the activated partial thromboplastin time (aPTT) target value of two times normal. A SC injection had to be left out if the aPTT ratio was greater than 2.5 before the third or greater than 2 before the fourth or the following SC injections. After the SC injection had been left out, the aPTT ratio had to be remeasured 12 h later. If the aPTT ratio was still above 1.5, the study medication had to be terminated. The lepirudin dose of 0.5 mg/kg given subcutaneously twice daily has been shown to produce mean plasma concentrations of 300 to 400 ng/ml and mean aPTT values of 50 to 75 s in healthy volunteers (unpublished data).

Study end points. The primary end point was early and complete patency defined as the proportion of patients with TIMI-3 flow in the infarct-related artery 90 min after start of study medication (15). The angiograms were assessed centrally in a core lab by at least two blinded experienced investigators.

Secondary end points were the combined and individual

Table 1. Clinical Characteristics of the Entire Study Population and Patients Enrolled in the Angiographic Part

	Total Study (n = 1208)		Angio Substudy (n = 447)	
	Lepirudin (n = 603)	Heparin (n = 605)	Lepirudin (n = 227)	Heparin (n = 220)
Age (yr)	61.1 ± 11.6	61.3 ± 11.9	60.2 ± 11.6	61.6 ± 10.7
Men (%)	76.0	75.9	79.7	73.6
Medical history				
Hypertension	39.6%*	34.2%*	42.3%**	28.6%**
Diabetes	12.9%	13.4%	11.5%	15.0%
Hyperlipidemia	25.0%	24.5%	22.9%	28.2%
Current smoker	43.3%	45.0%	41.4%	42.7%
Previous MI	12.1%	14.5%	12.8%	11.8%
Previous PTCA or CABG	4.3%	5.6%	5.3%	5.9%
Conditions at randomization				
Heart rate (beats/min)	77.1 ± 17.5	76.8 ± 18.4	76.8 ± 17.6	76.4 ± 18.5
Systolic blood pressure (mm Hg)	138 ± 26	137 ± 24	139 ± 28	138 ± 24
Killip class >1 (%)	12.4	11.4	10.6	15.0
Anterior MI (%)	38.9	41.6	44.1	41.8
Time to treatment (min)	172 ± 77	168 ± 80	178 ± 82	174 ± 79

*p = 0.003; **p = 0.048; all other differences p > 0.1 = NS.
CABG = coronary artery bypass graft; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

incidences of death, nonfatal stroke, nonfatal reinfarction, rescue percutaneous transluminal coronary angioplasty (PTCA) or refractory angina pectoris within 30 days after randomization; the individual incidences of hemorrhagic and nonhemorrhagic strokes; the proportion of patients with complete resolution of ST-segment elevation at 90 (70 to 110) and 180 (120 to 240) min and one-year mortality. Refractory angina was defined as recurrent chest pain of more than 5 min duration with electrocardiogram (ECG) changes occurring in the presence of "optimum" medical treatment and requiring an additional intervention in the view of the responsible physician.

The ST-segment resolution was assessed blindly and centrally (by author R.S.) as previously described (16). Complete ST-segment resolution was defined as ≥70% resolution of ST elevation compared with the sum of ST elevation in the baseline ECG, partial ST resolution as 30% to 70% resolution of ST elevation and no ST resolution as <30% of ST elevation.

Major bleeding was defined as any bleeding that was fatal or life-threatening; intracranial, permanently or significantly disabling; or bleeding necessitating surgical intervention or requiring transfusion of two or more units of packed red cells. All other bleedings were classified as minor.

Statistical analysis. If not specifically mentioned, results are based on an intention-to-treat analysis. The per protocol analysis included only patients who had the required amount of ST elevations in the baseline ECG, who received at least 750,000 units of streptokinase and who were given at least the IV bolus and the first SC injection of the double-blind study medication.

The primary angiographic end point was to be obtained in a subset of 400 patients, based on the assumption of a TIMI-3 rate of 35% in the placebo-heparin group versus 50% in the lepirudin group (two-sided Fisher exact test, significance level 5%, power 84%).

For the combined clinical end point the sample size of 1,200 patients is sufficient to detect an event reduction from 20% in the placebo-heparin group to 15% in the lepirudin group (significance level 5%, power 79%).

For comparison of two dependent/independent samples, either the Wilcoxon signed rank-sum test/Mann-Whitney *U* test or the Fisher exact test was applied. For comparisons of three or more independent samples, we used the Kruskal-Wallis test.

RESULTS

Patients. A total of 1,208 patients were randomized from April 17, 1995 to December 7, 1996, in 64 centers in seven European countries; 447 of these patients were entered into the angiographic part of the trial.

The age at inclusion date ranged from 30 to 92 years, with a mean age of 61 years; 76% of the patients were men. The treatment groups in the angiographic substudy were well matched with regard to their baseline characteristics and did not differ from the total study population (Table 1).

Study treatment. Ninety-eight percent of all patients received 1.5 million units of streptokinase; only 0.9% did not receive any streptokinase at all. Aspirin was given to 99.5% of the patients. Eight patients in the lepirudin and four in the heparin group did not receive the IV bolus of study treatment. The IV bolus of study medication was given before the streptokinase infusion in 98% of patients. The time between the IV bolus of study medication and start of streptokinase was 2.64 ± 4.47 min in the lepirudin and 2.83 ± 4.00 min in the heparin group. There were no significant differences in the duration of SC injections

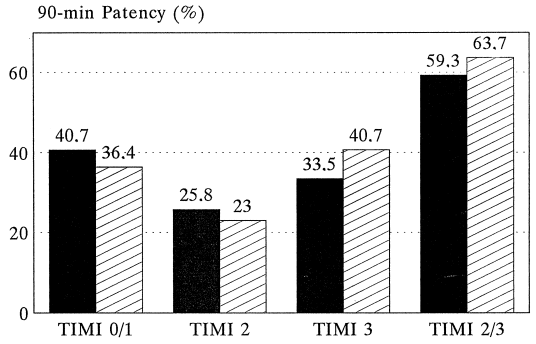

Figure 1. Comparison of the 90-min patency rates of the infarct-related artery in patients treated with streptokinase and lepirudin or heparin. **Solid box**, heparin (n = 209); **striped box**, lepirudin (n = 209).

between the two groups. The SC therapy with lepirudin was interrupted or terminated in 237 patients and that with heparin in 201 patients. The most frequent reason given by the investigators was a high aPTT (42.6% in the lepirudin vs. 33.7% in the heparin group). Termination of study treatment due to prolongation of aPTT beyond the predefined value was observed more often in the lepirudin group (4.4% vs. 0.8%).

Angiographic findings. A total of 447 patients in 25 centers were enrolled in the angiographic substudy. For various reasons 19 (4.2%) patients had no 90-min angiogram. The infarct-related artery could not be identified in 10 patients, leaving 418 (93.5%) patients, 209 in each group, with TIMI flow grading of the infarct-related artery. The mean time between start of streptokinase infusion and angiogram was 90 min (median 90 min, 95% reference interval 70 to 125 min), without any differences between the treatment groups.

The proportions of the infarct-related arteries were evenly distributed between the lepirudin- and heparin-treated patients (left anterior descending coronary artery 38.8% vs. 36%; right coronary artery 39.7% vs. 43%; left circumflex coronary artery 14% vs. 14%; others 7.5% vs. 7%).

Complete patency (TIMI grade 3 flow) of the infarct-related artery was observed in 40.7% (85/209, 95% CI [confidence interval] 33.9% to 47.7%) of the lepirudin-treated patients and 33.5% (70/209, 95% CI 27.1% to 40.3%) of the heparin-treated patients (p = 0.16) (Fig. 1). In patients treated within 180 min after symptom onset both with lepirudin (51/118 = 43.2%) and heparin (49/133 = 36.8%) higher TIMI 3 patency rates were observed than in patients treated after more than 180 min with lepirudin (34/91 = 37.4%) or heparin (21/76 = 27.6%), but these differences were not statistically significant.

Analysis of patients treated per protocol (n = 342) revealed a significant difference in favor of lepirudin versus heparin for TIMI 3 flow at 90 min (76/175 = 43.4%, 95% CI 36 to 51.1%, vs. 54/167 = 32.3%, 95% CI 25.3% to 40.0%, p = 0.045).

ST-segment resolution analysis. All 1,208 patients were considered for this analysis. In 140 patients, the prerandomization ECG was not evaluable for ST-resolution analyses, mainly because the ECGs did not show the required amount of ST-segment elevation. For various reasons, 164 patients had to be excluded from evaluation of the 90-min ECG and 70 patients from evaluation of the 180-min ECG, mostly because of ECGs recorded outside the respective time windows. Thus, 904 and 998 patients form the basis for evaluation at 90 and 180 min, respectively. The ST resolutions at both time points were significantly different in favor of lepirudin (Table 2). More patients had complete and fewer patients had no ST resolution, and the average ST elevation recovery from baseline to 90 as well as to 180 min was significantly greater in the lepirudin group. The differences between lepirudin- and heparin-treated patients for complete ST resolution after 90 min (28% vs. 22%, p = 0.05) and no ST resolution after 180 min (13% vs. 18%, p = 0.035) were statistically significant.

Clinical events. Table 3 shows the incidence of major clinical events during the 30-day study period and the mortality rate at one year. No significant differences existed for the prespecified cardiac end points and all-cause mor-

Table 2. Results of the ECG Substudy: Incidence of Complete, Partial and No ST Resolution at 90 min and 180 min in Patients Allocated to Lepirudin or Heparin Treatment

	ST Resolution			
	At 90 min		At 180 min	
	Lepirudin (n = 445)	Heparin (n = 459)	Lepirudin (n = 500)	Heparin (n = 498)
Complete	123 (28%)	101 (22%)	259 (52%)	237 (48%)
Partial	140 (32%)	143 (31%)	176 (35%)	172 (35%)
Number	182 (41%)	215 (47%)	65 (13%)	89 (18%)
p Value	0.03		0.07	
Σ ST resolution*	41% (9–73)	33% (1–65)	71% (51–92)	69% (41–88)
p Value	0.008		0.03	

*Median values (25th and 75th percentiles).

Table 3. Clinical Events During the 30-Day Study Period and One-Year Mortality

	Lepirudin (n = 603)	Heparin (n = 605)	p Value
Death	41 (6.8%)	39 (6.4%)	NS
Cardiac death	36 (6.0%)	33 (5.5%)	NS
Reinfarction	28 (4.6%)	31 (5.1%)	NS
Cardiogenic shock	17 (2.9%)	18 (3.0%)	NS
Refractory angina	22 (3.6%)	18 (3.0%)	NS
Recurrent angina	63 (10.6%)	54 (9.0%)	NS
Rescue-PTCA	45 (7.5%)	49 (8.1%)	NS
Combined end point*	137 (22.7%)	147 (24.3%)	NS
Death 1 year	59 (9.8%)	54 (8.9%)	NS

*Combined end point: death, nonfatal stroke, nonfatal reinfarction, rescue-PTCA or refractory angina.
Abbreviations as in Table 1.

tality at 30 days and at one year. The risk reduction of the combined end point was 6.6% with lepirudin (22.7% vs. 24.3%).

The reinfarction rate during the five days of study treatment was lower in the lepirudin group (1% vs. 2.5%, p = 0.048) but similar at 30 days (Fig. 2). The combined incidences of death or nonfatal reinfarction at 30 days were 10.4% and 11% in lepirudin- and heparin-treated patients, respectively.

Safety. Seven strokes occurred in the lepirudin group and nine occurred in the heparin group. Only one patient in the lepirudin group and two patients in the heparin group suffered a hemorrhagic stroke; all three patients died. The incidences of major and minor bleedings were similar in both treatment groups (Table 4). Most of the major bleedings were puncture-site related (55% in the lepirudin group and 66% in the heparin group, respectively).

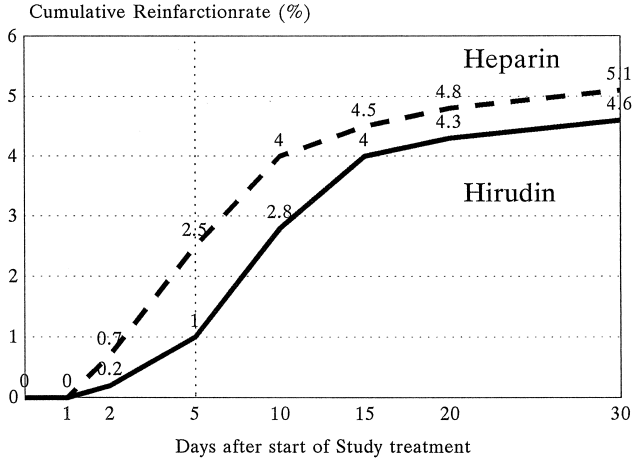

Figure 2. Cumulative rate of reinfarctions during the five days of study treatment and until day 30. After five days the difference between the lepirudin group and heparin group was statistically significant (p = 0.048).

Table 4. Safety Variables Within 30 Days After Treatment

	Lepirudin (n = 603)	Heparin (n = 605)	p Value
Total stroke	7 (1.2%)	9 (1.5%)	NS
Hemorrhagic stroke	1 (0.2%)	2 (0.3%)	NS
Ischemic stroke	6 (1.0%)	7 (1.1%)	NS
Major bleeding	20 (3.3%)	21 (3.5%)	NS
Minor bleeding	89 (14.8%)	70 (11.6%)	NS

DISCUSSION

The purpose of this study was twofold: to compare lepirudin and heparin as adjuncts to streptokinase thrombolysis, and to evaluate a modified approach for phase II studies for thrombolytic regimens in patients with AMI.

Hirudin has been shown to improve coronary patency with streptokinase in animal models (17). In the TIMI 6 trial, hirudin was as safe as heparin as adjunct to streptokinase, and a trend toward an improved clinical outcome with hirudin was observed (18). Our study was based on the results of the Hirudin for the Improvement of Thrombolysis (HIT-SK [streptokinase]) trial, in which lepirudin compared with heparin improved 90-min patency after streptokinase therapy, but no clear dose relationship was observed (19). Because a hirudin bolus of ≥0.4 mg/kg as adjunct to thrombolysis had been shown to increase the bleeding risk, especially the rate of intracranial bleedings (10–12), and because a reduced bolus dose of 0.1 mg/kg was safe but did not improve clinical outcome in the TIMI 9B study (13), the therapeutic window for hirudin seems rather narrow. Therefore, we chose the bolus dose of 0.2 mg/kg to improve early reperfusion.

In addition, based on pharmacologic studies, SC injections aimed at a prolongation of the aPTT to 1.5 to 2.5 times control were given to diminish the rate of reocclusions and reinfarctions. The TIMI 3 patency at 90 min in the patients treated with heparin was 33%, which is similar to that observed in the GUSTO-I angiographic study after streptokinase and SC heparin (4). With lepirudin there was an improvement of TIMI 3 flow to 41%, which was statistically not significant. However, if only patients treated per protocol (in this analysis patients without the required amount of ST elevations were excluded) were included in the analysis, the advantage of lepirudin (43.4%) versus heparin (32.3%) was statistically significant. This patency rate with lepirudin is somewhat lower than the 47% TIMI 3 patency with streptokinase and another direct thrombin inhibitor, hirulog, in the Hirulog Early Reperfusion/Occlusion (HERO) study (20). However, the angiograms in the HERO trial were obtained somewhat later at 108 ± 24 min compared with 90 ± 18 min in our study, so that ongoing thrombolysis is a likely explanation for the higher patency rate with hirulog.

In addition to the improved TIMI 3 patency with lepirudin, a significantly greater resolution of ST elevation,

an independent marker for myocardial perfusion, was observed both at 90 min and 180 min after start of thrombolysis. Thus, both markers of early reperfusion, patency and ST resolution showed a strong trend toward superiority of lepirudin over heparin for the early restoration of blood flow in the infarct vessel after streptokinase therapy. These results were achieved without any increase in bleeding complications, which had been a major concern after the experience of an increased rate of cerebral hemorrhages with the combination of lepirudin and recombinant tissue-type plasminogen activator in the HIT-3 trial (10).

It also has to be noted that the rate of hemorrhagic strokes was very low, both in the lepirudin (0.2%) group and heparin (0.3%) group, compared with the 0.6% intracranial bleeding rate observed with streptokinase and hirudin in the GUSTO-IIb trial. This might, at least in part, be due to the fact that the patients in our trial were somewhat younger compared with patients who received streptokinase in the GUSTO-IIb trial (mean age 61 years vs. 64 years). Although the sample size of 600 patients does not allow assessment of the true incidence of these rare events, the observed intracranial hemorrhage rate of 0.17% in the lepirudin group excludes a rate of more than 0.93% at the 5% level of significance.

In summary, the reduced lepirudin-bolus dose of 0.2 mg/kg, followed by SC injections with close aPTT monitoring, seems to be as safe as SC heparin, which is current clinical practice in most hospitals after streptokinase thrombolysis.

The rate of reinfarctions during the five days of study treatment was significantly diminished with lepirudin, but was similar at the end of the study period at day 30. The reason might be a more potent thrombin inhibition with lepirudin during the treatment phase, and a catch-up effect after cessation of therapy, as has been observed in previous trials with direct thrombin inhibitors (21). In contrast, in a combined analysis of the GUSTO-IIb and the TIMI 9B studies, a moderate but significant 14% reduction of reinfarctions with hirudin was still present at 30 days.

However, the early advantage of lepirudin did not translate into an improvement in clinical outcome at 30 days or at one year. These findings are different from the results of a subgroup analysis of the GUSTO-IIb study, which showed a 28% reduction in death and a 46% reduction in reinfarction in 530 patients treated with streptokinase and hirudin in comparison with 552 patients treated with streptokinase and heparin (22). This strikingly large difference in a post hoc analysis in favor of hirudin may be due to a particularly high event rate of 14.4% (30-day mortality or reinfarction), especially an uncommonly high rate of reinfarctions (8.4%), in the streptokinase/heparin group in GUSTO-IIb.

In our prospective study this combined 30-day mortality and reinfarction rate was 10.4% and 11% in the hirudin and heparin groups, respectively. Because lepirudin was given before thrombolysis in almost all our patients, the timing of administration of hirudin does not explain the difference to the GUSTO-IIb trial, where the study drug was given a mean of 35 min after thrombolysis. Pharmacologic studies with lepirudin did not show any significant differences for mean plasma levels (410 ng/ml vs. 400 ng/ml) and mean aPTT prolongations (aPTT ratio 2 vs. 2.1) between a continuous IV infusion of 0.1 mg/kg/h and SC administration of 0.5 mg/kg twice daily (unpublished data). In our study, higher aPTTs were seen under lepirudin treatment compared to heparin treatment; therefore, inadequate dosing or ineffective anticoagulation by SC administration lepirudin does not seem to be an issue. Hence, the apparent difference between our study and GUSTO-IIb may be due to a chance finding of the retrospective analysis in GUSTO-IIb.

In summary, specific thrombin inhibition with lepirudin tends to accelerate infarct vessel patency induced by streptokinase, without an increase in major bleeding complications. This early benefit was not associated with a significant improvement in clinical outcome at 30 days.

Size and design of phase II trials. The second problem addressed in the HIT-4 trial was the adequate design and sample size of phase II trials. Dose-finding studies for thrombolytic regimens in patients with AMI are primarily designed to identify the most effective dose of a new thrombolytic or adjunctive agent (23). The current gold standard for efficacy is early (60 to 90 min) angiographic infarct vessel patency (24). The size of invasive studies is limited by the availability of resources; thus, novel approaches are needed to resolve this problem (25). In addition to coronary patency, further noninvasive surrogate end points for efficacy are required. Early ST-segment resolution is a highly significant predictor of survival after acute myocardial infarction and can be used to compare thrombolytic regimens (26).

In our study, results of both efficacy parameters were consistent, underscoring the value of ST resolution as a surrogate end point. The safety profile of a new reperfusion regimen can only be assessed by a substantial increase in sample size of phase II trials. In settings where invasive markers of efficacy are used, only limited numbers of patients can be investigated owing to the availability of resources. The inclusion of a larger number of patients not studied invasively (a so-called safety cohort) is an alternative that we used in our study. The sample size of over 600 patients in both treatment groups seems sufficient to get a realistic estimate of the safety of a new regimen compared with a standard therapy, in our case streptokinase with SC heparin. To detect a 20% increase in the rate of intracranial hemorrhages, which was 0.33% in the heparin group, we would need 95,000 patients to achieve a power of 80% with a p level of 0.05. Obviously, this number of patients is unrealistic for clinical trials. Our modified approach, combining invasive and noninvasive efficacy parameters and including a safety cohort, may facilitate the search for

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improved reperfusion treatment strategies in patients with AMI.

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APPENDIX

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