# A COMPARISON OF RECOMBINANT HIRUDIN WITH HEPARIN FOR THE TREATMENT OF ACUTE CORONARY SYNDROMES

THE GLOBAL USE OF STRATEGIES TO OPEN OCCLUDED CORONARY ARTERIES (GUSTO) IIb INVESTIGATORS*

## ABSTRACT

***Background*** Thrombin has a pivotal role in the pathogenesis of acute coronary thrombosis. We compared the clinical efficacy of a potent, direct thrombin inhibitor, recombinant hirudin, with that of heparin (an indirect antithrombin agent) in patients with unstable angina or acute myocardial infarction.

***Methods*** At 373 hospitals in 13 countries, 12,142 patients with acute coronary syndromes were randomly assigned to 72 hours of therapy with either intravenous heparin or hirudin. Patients were stratified according to the presence of ST-segment elevation on the base-line electrocardiogram (4131 patients) or its absence (8011 patients), with the latter characteristic considered to indicate unstable angina or non–Q-wave myocardial infarction.

***Results*** At 24 hours, the risk of death or myocardial infarction was significantly lower in the group assigned to hirudin therapy than in the group assigned to heparin (1.3 percent vs. 2.1 percent, $P=0.001$). The primary end point of death or nonfatal myocardial infarction or reinfarction at 30 days was reached in 9.8 percent of the heparin group as compared with 8.9 percent of the hirudin group (odds ratio for the risk of the end point in the hirudin group, 0.89; 95 percent confidence interval, 0.79 to 1.00; $P=0.06$). The predominant effect of hirudin was on myocardial infarction or reinfarction and was not influenced by ST-segment status. There were no significant differences in the incidence of serious or life-threatening bleeding complications, but hirudin therapy was associated with a higher incidence of moderate bleeding (8.8 percent vs. 7.7 percent, $P=0.03$).

***Conclusions*** For acute coronary syndromes, recombinant hirudin provided a small advantage, as compared with heparin, principally related to a reduction in the risk of nonfatal myocardial infarction. The relative therapeutic effect was more pronounced early (at 24 hours) but dissipated over time. The small benefit was consistent across the spectrum of acute coronary syndromes and was not associated with a greater risk of major bleeding complications. (N Engl J Med 1996;335:775-82.)



IN recent years, the common underlying pathophysiology of acute coronary syndromes involving the fissure or rupture of atherosclerotic plaques with mural or occlusive thrombus has been increasingly recognized.[1-4] Therapy for the various acute coronary syndromes (including unstable angina and nontransmural and transmural myocardial infarction) is remarkably similar, consisting of intravenous heparin, aspirin, and anti-ischemic medications; the only important difference involves the use of thrombolytic therapy, which is restricted to patients with ST-segment elevation.[5-8] Thrombin is a key component of the pathophysiology of acute coronary syndromes. Thrombin plays a pivotal part in coronary-artery thrombosis by promoting platelet aggregation, engendering its own formation by means of an autocatalytic feedback loop, and catalyzing the cross-linkage of the fibrin clot. Although heparin is the mainstay of antithrombin therapy, it works indirectly, requires antithrombin III as a cofactor, and is not effective against thrombin that is already bound to the fibrin clot. Furthermore, heparin can be readily inactivated by platelet factor 4 or plasma proteins, its effects vary considerably within and between patients, and it leads to thrombocytopenia in 5 to 15 percent of patients.[9-13] The prototypical direct inhibitor of thrombin is hirudin, a peptide of 65 amino acids that is derived from the saliva of the medicinal leech (*Hirudo medicinalis*). In pilot trials of patients with unstable angina and acute myocardial infarction, hirudin has shown promise.[7-9] We designed the current study after a trial of 2565 patients showed that high doses of heparin and hirudin were associated with an unacceptable rate of bleeding complications.[14] We compared the clinical effectiveness of hirudin with that of heparin in patients with all types of acute coronary syndromes.

## METHODS

### Patient Population

Patient enrollment began May 19, 1994, and was completed October 17, 1995. The entry criteria consisted of chest discomfort within the previous 12 hours associated either with transient or persistent ST-segment elevation or depression of more than 0.5 mm or with persistent, definite T-wave inversion of more than 1 mm. Patients were excluded if they were taking warfarin at the time of enrollment or if they had active bleeding, a history of stroke, a contraindication to heparin therapy or renal insufficiency (serum creatinine, >2.0 mg per deciliter [177 $\mu$mol per liter], a relative contraindication to hirudin therapy), a systolic blood

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*The investigators and sites participating in the GUSTO IIb trial are listed in the Appendix.

pressure of more than 200 mm Hg, or a diastolic blood pressure of more than 110 mm Hg. Women of childbearing potential were excluded. If a patient was enrolled and was subsequently found to have a serum creatinine concentration of more than 2.0 mg per deciliter at base line, the study-drug infusion was discontinued. The objective was to enroll a representative cross-section of patients with acute coronary syndromes, with a target of 4000 patients with ST-segment elevation and 8000 patients with no ST-segment elevation. In patients with ST-segment elevation, the decision to use thrombolytic therapy was made by the attending physician. Thrombolytic therapy consisted of either streptokinase or a regimen of accelerated tissue plasminogen activator (t-PA) in which t-PA is infused rapidly over a period of 1½ hours so that two thirds of the dose is given in the first 30 minutes.[15]

The protocol called for the infusion of the study medication for a minimum of three and a maximum of five days, at the discretion of the attending physician. Each patient received either heparin and hirudin placebo or hirudin and heparin placebo on a double-blind basis. Hirudin was initially given in a bolus dose of 0.1 mg per kilogram of body weight intravenously, followed by a continuous infusion of 0.1 mg per kilogram per hour. The desulfated form of recombinant hirudin (desirudin, Ciba–Geigy, Summit, N.J.) was used. Heparin was initially given in a bolus dose of 5000 U intravenously, followed by a continuous infusion of 1000 U per hour.

The activated partial-thromboplastin time was determined before the study drug was infused, at 6 hours, 12 hours, and 24 hours, and then a minimum of once a day during its administration. The activated partial-thromboplastin time was adjusted with the use of a standard nomogram to maintain the value between 60 and 85 seconds.[16] In patients undergoing coronary intervention during the administration of the study drug, specific guidelines allowed the use of a bolus infusion of heparin or placebo and hirudin or placebo to achieve an activated clotting time of at least 300 to 350 seconds and preserve the double-blind nature of the study.

### End Points

The primary composite end point was death or nonfatal myocardial infarction (or reinfarction) in the first 30 days of follow-up. Myocardial infarction and reinfarction have been defined previously[14] and were classified by members of the clinical-events committee, who were unaware of the patients' treatment assignments.

Bleeding complications were categorized according to previous definitions.[14,15] Severe or life-threatening bleeding was defined as intracranial hemorrhage or bleeding that caused hemodynamic compromise requiring intervention. Moderate bleeding was defined as bleeding that required transfusion but was not associated with any hemodynamic compromise.

### Invasive Cardiologic Procedures

Coronary angiography, percutaneous coronary revascularization, and coronary-artery bypass surgery were discouraged for the duration of the study-drug infusion unless there was evidence of recurrent ischemia. For patients who were undergoing elective coronary-artery bypass surgery, it was recommended that the study drug be stopped six to eight hours before surgery, with heparin therapy initiated if indicated on an open basis. In cases of emergency bypass surgery, unblinding of study drug was permitted to avoid inappropriate use of protamine and facilitate the control of hemostasis.

### Statistical Analysis

Interim analyses were planned for the primary end point after each increment of 25 percent of the planned number of patients had been enrolled; they were actually performed after data on the primary end point were available for 2731, 5946, and 9627 patients. To monitor the statistical significance of interim differences between treatments, the method of DeMets and Ware was used.[17]

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE PATIENTS WITH ACUTE CORONARY SYNDROMES, ACCORDING TO TREATMENT ASSIGNMENT AND ST-SEGMENT STATUS.*

| CHARACTERISTIC | TREATMENT ASSIGNMENT | | ST-SEGMENT STATUS | |
|---|---|---|---|---|
| | HIRUDIN (N=6069) | HEPARIN (N=6073) | ELEVATED (N=4131) | NOT ELEVATED (N=8011) |
| Age (yr) | 65 (55, 73) | 65 (56, 73) | 63 (53, 71) | 66 (57, 73) |
| Female sex (%) | 30 | 30 | 24 | 33 |
| Systolic blood pressure (mm Hg) | 135 (120, 150) | 135 (120, 150) | 130 (115, 148) | 139 (120, 151) |
| Diastolic blood pressure (mm Hg) | 80 (70, 90) | 80 (70, 90) | 80 (70, 90) | 80 (70, 90) |
| Heart rate (beats/min) | 74 (64, 86) | 74 (64, 85) | 74 (64, 86) | 74 (64, 85) |
| Killip class (%) | | | | |
| I | 88 | 87 | 88 | 88 |
| II | 10 | 12 | 11 | 11 |
| III or IV | 2 | 1 | 1 | 1 |
| Prior myocardial infarction (%) | 27 | 27 | 17 | 32 |
| Prior CABG (%) | 9 | 10 | 5 | 12 |
| Prior PTCA (%) | 9 | 8 | 6 | 11 |
| Hypertension (%) | 44 | 47 | 40 | 48 |
| Diabetes (%) | 17 | 19 | 16 | 19 |
| Hypercholesterolemia (%) | 39 | 39 | 36 | 41 |
| Current smoker (%) | 32 | 31 | 41 | 27 |
| Weight (kg) | 76 (68, 86) | 76 (68, 86) | 77 (68, 86) | 76 (67, 86) |

*For continuous variables, the median values are provided, with the 25th and 75th percentiles given in parentheses. CABG denotes coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

The case report was fully documented for 10 percent of patients, and the documentation process included at least one visit by a monitor to the study sites. In addition, all in-hospital deaths, myocardial infarctions and reinfarctions, strokes, life-threatening bleeding complications, and unanticipated, serious life-threatening adverse events were reviewed. Thus, the medical records of 20 percent of the patients were reviewed.

Statistical analyses included all randomized patients according to the intention-to-treat principle. For the full cohort of patients, the Cochran–Mantel–Haenszel test was used to assess differences in the treatment groups with respect to the primary end point,[18] with stratification according to whether the patients presented with or without ST-segment elevation. This test was also used to analyze discrete secondary end points. In the group without ST-segment elevation, the conventional chi-square test was used to compare treatment-related differences in the primary end point and discrete secondary end points. For secondary end points involving continuous variables, treatments were compared with use of the nonparametric Wilcoxon rank-sum test. All P values are two-sided.

## RESULTS

A total of 12,142 patients were enrolled in 373 hospitals in 13 countries (see the Appendix): 4131 had ST-segment elevation, and 8011 did not. The base-line characteristics of the entire cohort according to treatment assignment and ST-segment status are given in Table 1. As compared with patients with ST-segment elevation, patients without ST-segment elevation were more likely to be older, to be female, to have had prior cardiac disease, and to have an increased prevalence of risk factors for cardiac disease.

The study drug was actually administered to 98.4 percent of patients, with no difference between treatment groups in the percentage who actually received treatment; in both groups treatment was initiated a median of 0.5 hour (25th and 75th percentiles, 0.3 and 0.8) after randomization. The mean (±SD) duration of therapy was 75±29 hours in the hirudin group and 75±29 hours in the heparin group. Treatment was continued for at least 72 hours in 70.2 percent of the patients in the hirudin group and 70.6 percent of the patients in the heparin group. For the patients in whom treatment was stopped early (before 72 hours), the reasons were as follows: the need for procedures in 26 percent of patients, physician preference in 25 percent, bleeding in 12 percent, transfer to another hospital in 7 percent, death in 6 percent, misdiagnosis in 6 percent, an adverse event in 3 percent, and miscellaneous or unknown reasons in the remaining 15 percent. Among the patients with ST-segment elevation, 74 percent received thrombolytic therapy, consisting of t-PA in 70 percent of patients and streptokinase in 30 percent. The median length of time from the onset of thrombolytic therapy to the initiation of treatment with the study drug was 35 minutes in the hirudin group (25th and 75th percentiles, 15 and 68, respectively) and 35 minutes in the heparin group (25th and 75th percentiles, 15 and 71). The relevant adjunctive medications given and procedures performed in the trial are summarized in Table 2. Figure 1 shows the effects of hirudin and heparin on the activated partial-thromboplastin time. During the infusion, 94.6 percent of the patients assigned to heparin required an adjustment in the dosage, as compared with 71.5 percent of those assigned to hirudin ($P<0.001$).

The incidence of death or myocardial infarction at 30 days — the primary composite end point — is given in Table 3. After 24 hours of therapy, the risk of death or myocardial infarction was significantly lower in the group assigned to hirudin (1.3 percent, vs. 2.1 percent for heparin; odds ratio, 0.61; 95 percent confidence interval, 0.46 to 0.81; $P=0.001$). The difference in this risk between groups was also significant 48 hours after the initiation of therapy (2.3 percent and 3.1 percent, respectively; odds ratio, 0.73; 95 percent confidence interval, 0.59 to 0.91; $P=0.001$). Figure 2 shows the Kaplan–Meier estimates of the risk of death or myocardial infarction in the first 72 hours after randomization.

The 30-day event rates for the primary end points of death or nonfatal myocardial infarction for all patients, patients with ST-segment elevation, and patients without ST-segment elevation are presented in Figure 3. At 30 days 9.8 percent of the heparin group had reached the primary end point, as compared with 8.9 percent of the hirudin group (odds ratio, 0.89; 95 percent confidence interval, 0.79 to 1.00; $P=0.06$). This effect of hirudin was not influenced by ST-segment status (Table 3). However,

**TABLE 2.** ADJUNCTIVE MEDICATIONS GIVEN AND PROCEDURES PERFORMED DURING HOSPITALIZATION IN PATIENTS WITH ACUTE CORONARY SYNDROMES, ACCORDING TO TREATMENT ASSIGNMENT AND ST-SEGMENT STATUS.

| MEDICATION OR PROCEDURE* | TREATMENT ASSIGNMENT | | ST-SEGMENT STATUS | |
|---|---|---|---|---|
| | HIRUDIN | HEPARIN | ELEVATED | NOT ELEVATED |
| | percent | | | |
| Aspirin | 97 | 98 | 98 | 97 |
| Nitrates | | | | |
| Oral or topical | 84 | 84 | 78 | 88 |
| Intravenous | 77 | 79 | 82 | 76 |
| Calcium-channel blockers | 52 | 51 | 37 | 59 |
| Beta blockers | | | | |
| Intravenous | 17 | 17 | 25 | 13 |
| Oral | 73 | 72 | 73 | 72 |
| ACE inhibitor | 33 | 34 | 39 | 32 |
| Coronary arteriography | 58 | 57 | 59 | 57 |
| PTCA | 22 | 23 | 31 | 19 |
| CABG | 12 | 11 | 8 | 14 |

*ACE denotes angiotensin-converting enzyme, CABG coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

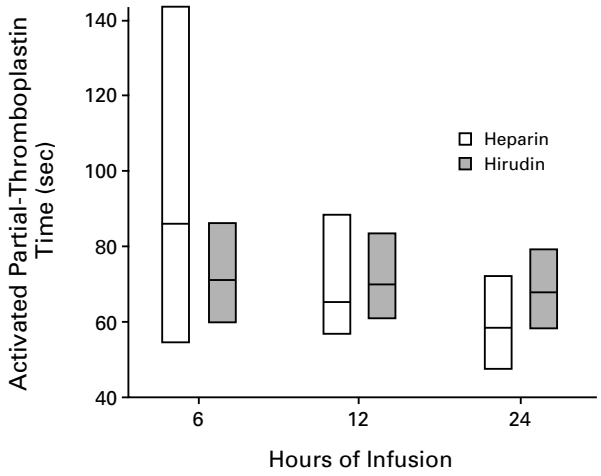


**Figure 1.** Activated Partial-Thromboplastin Times after 6, 12, and 24 Hours of Treatment with Intravenous Hirudin or Heparin. In each box plot the lower and upper ends represent the 25th and 75th percentiles, respectively, and the horizontal line represents the median.

there were no significant differences between hirudin and heparin in the incidence of other clinical events, such as recurrent ischemia, heart failure, arrhythmias, or cardiogenic shock. The secondary composite end point of death, myocardial infarction, or disability from stroke was reached in 9.2 percent of the hirudin group and 10.2 percent of the heparin group ($P = 0.07$).

The bleeding complications and incidence of stroke in the treatment groups are shown in Table 4. Although it was not a statistically significant difference, there was a higher incidence of intracranial hemorrhage among patients without ST-segment elevation who were treated with hirudin, as compared with those treated with heparin (0.2 percent [6 events] vs. 0.02 percent [1 event]), and a higher overall rate of moderate bleeding in the group treated with hirudin (8.8 percent vs. 7.7 percent, $P = 0.03$).

## DISCUSSION

In this trial of acute coronary syndromes, we observed a high (9.4 percent) event rate for the composite end point of death or myocardial infarction at 30 days despite a therapeutic approach that included the use of aspirin, heparin, beta-blockers, nitrates, and calcium-channel blockers. Although patients with ST-segment elevation were younger, were more likely to be male, and had fewer cardiac risk factors and a lower incidence of prior ischemic heart disease than patients without ST-segment elevation, they had a higher risk of death at 30 days (6.1 percent vs. 3.8 percent) and a similar rate of myocardial infarction (5.5 percent vs. 6.0 percent), most cases of which were actually reinfarctions. Although many of the demographic factors were suspected to differ between patients with ST-segment elevation and patients without ST-segment elevation after myocardial infarction or acute ischemia, our results establish that the latter group has a greater number of characteristics that are associated with more advanced coronary artery disease.

We compared the effect of heparin with that of a direct thrombin inhibitor, recombinant hirudin, which is a more potent anticoagulant.[7-10] Mechanistically, hirudin has the advantage of affecting clot-bound thrombin, not requiring any cofactors, and not being inactivated by plasma proteins or platelet factor 4. Although the hypothesis that potent, direct inhibition of thrombin would improve clinical outcomes appears valid on the basis of our observations

**TABLE 3.** THE INCIDENCE OF THE PRIMARY CLINICAL END POINTS AT 30 DAYS IN PATIENTS WITH ACUTE CORONARY SYNDROMES.

| GROUP | HIRUDIN | | HEPARIN | | ODDS RATIO (95% CI)* | P VALUE |
|---|---|---|---|---|---|---|
| | NO. OF PATIENTS | % | NO. OF PATIENTS | % | | |
| All patients | 6069 | | 6073 | | | |
| Death | | 4.5 | | 4.7 | 0.95 (0.80–1.13) | 0.58 |
| Myocardial infarction | | 5.4 | | 6.3 | 0.86 (0.74–1.00) | 0.04 |
| Death or myocardial infarction | | 8.9 | | 9.8 | 0.89 (0.79–1.00) | 0.058 |
| Patients with ST-segment elevation | 2075 | | 2056 | | | |
| Death | | 5.9 | | 6.2 | 0.94 (0.73–1.2) | 0.64 |
| Myocardial infarction | | 5.0 | | 6.0 | 0.82 (0.63–1.07) | 0.15 |
| Death or myocardial infarction | | 9.9 | | 11.3 | 0.86 (0.70–1.05) | 0.13 |
| Patients without ST-segment elevation | 3994 | | 4017 | | | |
| Death | | 3.7 | | 3.9 | 0.96 (0.76–1.21) | 0.72 |
| Myocardial infarction | | 5.6 | | 6.4 | 0.87 (0.73–1.05) | 0.152 |
| Death or myocardial infarction | | 8.3 | | 9.1 | 0.90 (0.78–1.06) | 0.22 |

*CI denotes confidence interval.

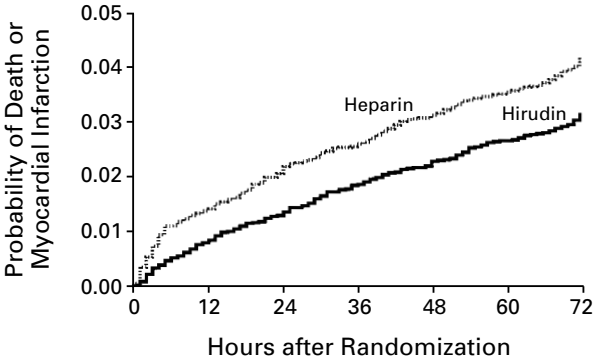


**Figure 2.** Kaplan–Meier Estimate of the Probability of Death or Myocardial Infarction or Reinfarction during the First 72 Hours after Randomization, According to Treatment Assignment.

at 30 days, the extent of the benefit was small (11 percent reduction in risk) and of marginal statistical significance. However, hirudin was associated with a significant and substantial reduction in the risk of death or myocardial infarction at 24 and 48 hours. The small benefit at 30 days was similar in patients with ST-segment elevation and in those without ST-segment elevation.

Our results are discrepant with those of the recent Thrombolysis in Myocardial Infarction (TIMI) 9 trial, which indicated no advantage of hirudin over heparin for patients treated with thrombolytic therapy.[19] There was a similar proportionate reduction (14 percent) in reinfarction with hirudin in that trial, but the mortality rate with hirudin therapy was slightly higher than that with heparin therapy (6.1 percent vs. 5.1 percent; odds ratio, 1.21; 95 percent confidence interval, 0.88 to 1.65). The only conspicuous differences between the TIMI 9 trial and our study were a longer interval from randomization to the initiation of the study drug (median, 44 vs. 35 minutes), a longer duration of treatment (96 vs. 75 hours), and fewer patients over 75 years of age (11 percent vs. 18 percent). Accordingly, the reason for the lack of concordance between the two trials remains unclear.

The reasons for the borderline evidence of the incremental efficacy of hirudin over heparin in the current trial are also uncertain. Among the possibilities are an inadequate dose of hirudin, an insufficient duration of treatment, or the lack of durability of the effects of hirudin. In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa trial, a much higher dose of recombinant hirudin was used (a bolus dose of 0.6 mg per kilogram followed by an infusion of 0.2 mg per kilogram per hour), but the bleeding-related side effects could not be tolerated and the incidence of intracerebral hemorrhage among patients receiving thrombolytic therapy was

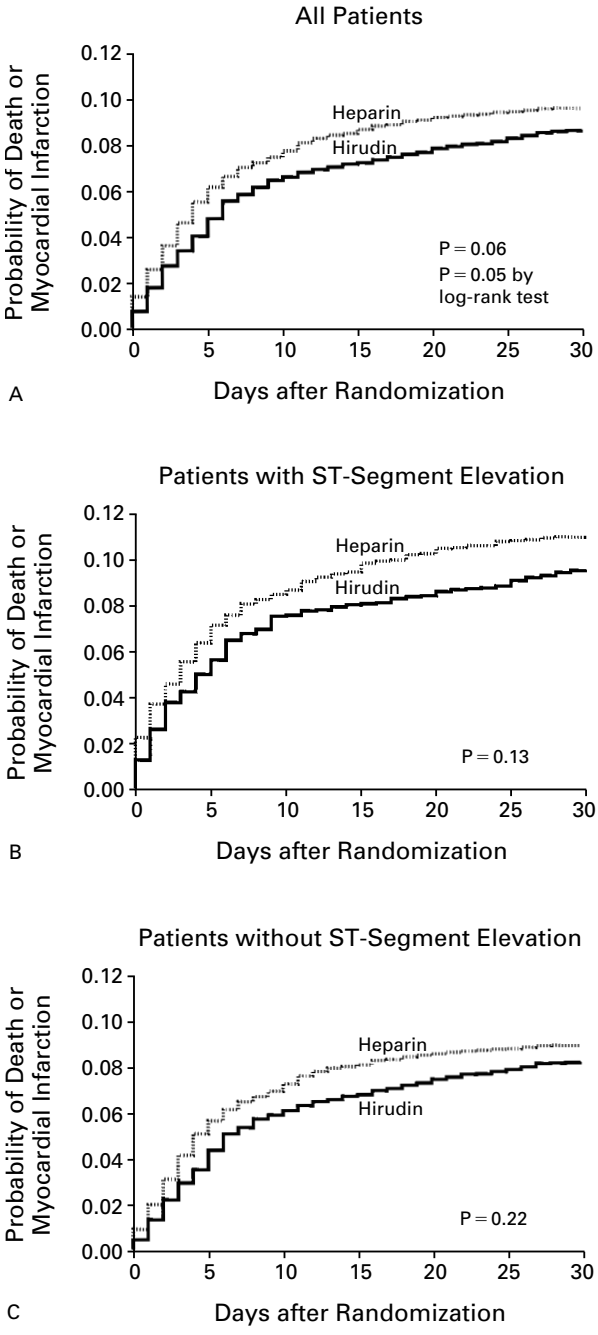


**Figure 3.** Kaplan–Meier Estimate of the Probability of Death or Myocardial Infarction or Reinfarction in All Patients (Panel A), Those with ST-Segment Elevation (Panel B), and Those without ST-Segment Elevation (Panel C).

Unless otherwise indicated, the P value was determined by the Cochran–Mantel–Haenszel test.

excessive (1.6 percent).[14] Even among patients who did not receive thrombolytic therapy, there was a 0.5 percent incidence of hemorrhagic stroke in the group given hirudin as compared with an incidence of 0 percent in the group given heparin. There was no

**TABLE 4.** THE INCIDENCE OF BLEEDING COMPLICATIONS AND STROKE IN PATIENTS WITH ACUTE CORONARY SYNDROMES.

| GROUP | HIRUDIN | | HEPARIN | | P VALUE |
|---|---|---|---|---|---|
| | NO. OF PATIENTS | % | NO. OF PATIENTS | % | |
| All patients | 6069 | | 6073 | | |
| Severe bleeding | | 1.2 | | 1.1 | 0.49 |
| Moderate bleeding | | 8.8 | | 7.7 | 0.03 |
| Transfusion | | 9.7 | | 8.6 | 0.04 |
| Intracranial hemorrhage | | 0.3 | | 0.2 | 0.24 |
| Stroke* | | 0.9 | | 0.8 | 0.43 |
| Patients with ST-segment elevation | 2075 | | 2056 | | |
| Severe bleeding | | 1.1 | | 1.5 | 0.20 |
| Moderate bleeding | | 8.6 | | 7.8 | 0.32 |
| Transfusion | | 9.0 | | 8.9 | 0.93 |
| Intracranial hemorrhage | | 0.5 | | 0.4 | 0.84 |
| Stroke* | | 1.3 | | 0.8 | 0.14 |
| Patients without ST-segment elevation | 3994 | | 4017 | | |
| Severe bleeding | | 1.3 | | 0.9 | 0.06 |
| Moderate bleeding | | 8.9 | | 7.7 | 0.06 |
| Transfusion | | 10.2 | | 8.4 | 0.01 |
| Intracranial hemorrhage | | 0.2 | | 0.02 | 0.06 |
| Stroke* | | 0.8 | | 0.7 | 0.72 |

*This category includes stroke from any cause.

indication of improved efficacy with high doses of both hirudin and heparin: the rate of death or myocardial infarction was 11.7 percent in the hirudin group and 11.0 percent in the heparin group. In a trial involving patients with unstable angina and non–Q-wave myocardial infarction who were given a similar recombinant hirudin at a dose intermediate between that used in GUSTO IIa and the current trial (a bolus dose of 0.4 mg per kilogram followed by an infusion of 0.15 mg per kilogram per hour), the incidence of bleeding complications was twice as high in the hirudin group as in the heparin group.[20] Although with the doses of hirudin used in the current trial (a bolus of 0.1 mg per kilogram and an infusion of 0.1 mg per kilogram per hour) there was no worrisome increase in major bleeding complications, there was an increased incidence of intracerebral hemorrhage (1 per 1000 patients treated) and a higher rate of moderate bleeding. Collectively, these data suggest that there is a narrow therapeutic window for treatment with recombinant hirudin and that the administration of doses higher than those tested in the current trial may increase the risk of bleeding complications without substantially improving efficacy. A longer infusion of hirudin might increase efficacy, but the lack of benefit in the TIMI 9 trial, in which therapy was administered an average of 30 percent longer than in the present study, makes this possibility less likely.

Other factors besides the dose or duration of treatment may explain the borderline results. All the beneficial effects of hirudin were evident within the first 24 hours. Beyond that point, the event-rate curves neither diverged nor converged. This failure to prevent events beyond 24 hours may be attributed either to rebound hypercoagulability after the infusion of thrombin inhibitors was stopped or to a lack of "passivation" of the arterial surface that continued to allow the formation of platelet thrombus.[21-24] A similar lack of durability of the effect of thrombin inhibitors has been noted in three recent trials.[25-27] Serial assays of prothrombin fragment (F 1.2) during hirudin therapy[28-30] have confirmed the inability of hirudin to block the generation of thrombin. The consequent accumulation of thrombin may have detracted from the ability of hirudin to inhibit the activity of thrombin and thus reduce ischemia.

Our data call into question the existence of a pivotal role for thrombin in acute coronary thrombosis. In contrast, recent trials have provided evidence of the high efficacy of blockade of platelet glycoprotein IIb/IIIa in acute coronary syndromes.[21-23] Although thrombin is an important agonist of platelet aggregation, it represents 1 pathway of platelet activation among nearly 100.[24] At appropriate doses, an effective platelet glycoprotein IIb/IIIa inhibitor, which modulates the final common pathway of aggregation, blocks virtually all these agonists. In the future, the combination of direct thrombin inhibition and blockade of platelet glycoprotein IIb/IIIa, which has shown promise in experimental models,[31] may prove to have particular therapeutic value.

Hirudin led to a very consistent anticoagulant effect over time, independently of the use of thrombolytic therapy, a feature that represents a practical advantage. Heparin not infrequently engenders an immune thrombocytopenia, which can result in serious thrombotic complications.[32] However, heparin, which is inexpensive, performed quite well as an antithrombin agent in the current trial and should still be regarded as the standard therapy. Recombinant hirudin resulted in a small but demonstrable and consistent effect, especially on the rate of reinfarction, in the group of patients with acute coronary syndromes as a whole. Whether the practical advantage of hirudin, its small clinical benefit, and its somewhat increased bleeding risk will limit its use to select patients with acute coronary syndromes requires independent cost–benefit analysis.

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## APPENDIX

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