Clinical Investigation and Reports

Lepirudin (Recombinant Hirudin) for Parenteral Anticoagulation in Patients With Heparin-Induced Thrombocytopenia

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Background—We prospectively investigated lepirudin for further parenteral anticoagulation in patients with heparin-induced thrombocytopenia (HIT).

Methods and Results—Patients with confirmed HIT (n=112) received lepirudin according to need for 2 to 10 days (longer if necessary): A1, treatment: 0.4 mg/kg IV bolus, followed by 0.15 mg·kg⁻¹·h⁻¹ intravenous infusion, n=65; A2, treatment in conjunction with thrombolysis: 0.2 mg/kg, followed by 0.10 mg·kg⁻¹·h⁻¹, n=4; and B, prophylaxis: 0.10 mg·kg⁻¹·h⁻¹, n=43. Outcomes from 95 eligible lepirudin-treated patients were compared with those of historical control patients (n=120). Complete laboratory response (activated partial thromboplastin time ratio >1.5 with ±2 dose increases and platelet count normalization by day 10) was achieved in 65 lepirudin-treated patients (69.1%; 95% CI, 59.3% to 78.3%). At 2 weeks after cessation of lepirudin, 11 patients died (9.8%), 10 underwent limb amputation (8.9%), and 20 suffered a new thromboembolic complication (17.9%). The average combined event rate per patient-day decreased from 5.1% in the pretreatment period to 1.5% in the treatment period. Thirty-five days after HIT confirmation, fewer lepirudin-treated patients than historical control patients had experienced ≥1 outcome (cumulative incidence 30.9% versus 52.1%; relative risk [RR] 0.71; P=0.12, log-rank test). Bleeding events were more frequent in the lepirudin group than the historical control group (cumulative incidence at 35 days, 44.6% versus 27.2%; RR 2.57; P=0.0001, log-rank test). No difference was observed in bleeding events requiring transfusion (cumulative incidence at 35 days, 12.9% versus 9.1%; RR 1.66; P=0.23, log-rank test); no intracranial bleeding was observed in the lepirudin group.

Conclusions—Lepirudin effectively prevents death, limb amputations, and new thromboembolic complications and has an acceptable safety profile in HIT patients. Treatment should be initiated as soon as possible if HIT is suspected.

Key Words: heparin • thrombocytopenia • lepirudin • platelets • hirudin

Heparin-induced thrombocytopenia (HIT) typically occurs after 5 to 10 days of heparin therapy, with platelet counts often dropping to ≤50,000 platelets/L.1 Platelet counts normalize only after discontinuation of heparin, usually within 7 to 10 days.2 HIT-associated thromboembolic complications (TECs) can result in significant morbidity, including myocardial infarction, cerebrovascular accident, limb amputation, or even death.3-5 Therefore, immediate cessation of heparin is mandatory when HIT becomes clinically manifest.1 However, many patients require further parenteral anticoagulation because of underlying disease or HIT-associated vessel occlusions.

Lepirudin, a desulfated recombinant hirudin, is a direct thrombin inhibitor. Lepirudin is not inactivated by platelet factor 4 and may be more effective in the presence of platelet-rich thrombi.6,7 It can inhibit clot-bound thrombin8 and does not cross-react with HIT antibodies. Therefore, lepirudin may be particularly useful in the treatment of HIT, in which increased in vivo platelet activation results in the

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release of large amounts of platelet factor 4 and excessive thrombin formation.\textsuperscript{1,9,10}

The primary objective of this study was to confirm the previously reported\textsuperscript{11} clinical efficacy and safety of lepirudin in HIT patients. This study also served to expand experience with administration of lepirudin in HIT patients. Entry criteria for the 2 studies were identical except that patients with renal dysfunction were enrolled in this trial but were excluded from participation in the previous study.

**Methods**

**Study Organization and Patient Selection**

This prospective, multicenter, historically controlled trial assessed the clinical efficacy and safety of lepirudin in HIT patients. The study was conducted in accordance with the Good Clinical Practice guidelines of the European Union and the Declaration of Helsinki. A randomized, active-control design was not feasible because no other anticoagulant therapy was approved for the treatment of HIT at the time of the study. As in the previous study, clinical outcomes of lepirudin-treated patients were compared with those of a historical control group. Because of the high risk of serious TECs among patients with HIT, a placebo control was considered unethical.

Patients in the study were centrally selected at the principal investigator’s (A.G.) institution from a group of patients whose serum had been received for HIT testing. All patients with a positive heparin-induced platelet activation test\textsuperscript{12,13} were screened for eligibility with the transferring hospital but remained in their hospital for treatment. Patients were eligible if they had a diagnostic decrease in platelet count by $\geq 50\%$ or to values $< 100$ g/L and/or new TECs during prestudy heparin administration. Exclusion criteria included overt signs of bleeding, pregnancy, alcohol or drug abuse, and anticipated poor compliance.

Historical control patients were taken from a central registry of 182 patients (entered between 1989 and 1995).\textsuperscript{11} These patients had been treated for HIT according to the practice of the individual hospitals before lepirudin or any other recombinant hirudin was available. Like lepirudin-treated patients, historical control patients had been diagnosed with HIT on the basis of a positive heparin-induced platelet activation test. Further medical information (eg, copies of medical charts or hospital discharge summaries) was obtained from the transferring hospitals.

Both lepirudin-treated and historical control patients qualified for a direct comparison of clinical outcomes if none of the exclusion criteria were met (age $< 18$ years, missing date of laboratory confirmation of HIT, time between onset of clinical symptoms and laboratory confirmation $> 21$ days, time between laboratory confirmation and initiation of therapy $> 60$ days, or cardiopulmonary bypass after laboratory confirmation).

**Treatment Regimens**

Patients received 1 of the following lepirudin (Refludan; Hoechst Marion Roussel) dose regimens, according to need, for 2 to 10 days, or longer periods if clinically indicated: A1: for treatment of patients with known TEC, $0.4$ mg/kg IV bolus, followed by $0.15$ mg · kg$^{-1} · h^{-1}$ infusion; A2: for treatment in conjunction with thrombolysis of patients with known TEC, $0.2$ mg/kg IV bolus followed by $0.10$ mg · kg$^{-1} · h^{-1}$ infusion; and B: for prophylaxis of patients with no known TEC, $0.10$ mg · kg$^{-1} · h^{-1}$ infusion.

A maximum of 110 kg body weight was used for dosage calculation. Because lepirudin is renally excreted, the bolus was reduced to $0.2$ mg/kg for patients with serum creatinine values $> 1.5$ mg/dL. Infusion rates were reduced by $50\%$ for serum creatinine values of 1.6 to $2.0$ mg/dL, by $75\%$ for values of 2.1 to $2.5$ mg/dL, and by $90\%$ for values of 2.6 to 6.0 mg/dL. Patients with serum creatinine values $> 6.0$ mg/dL received no infusion and a bolus of $0.1$ mg/kg only on alternate days, and only if the activated partial thromboplastin time (aPTT) ratio was $< 1.5$.

Infusion rates were not adjusted if the aPTT ratio was between 1.5 and 3.0 (unless deemed appropriate for safety reasons, eg, increased risk of bleeding). This range was based on the use of Actin FS or Neothromtin reagents; with other reagents, aPTT target range is usually 1.5- to 2.5-fold prolongation. If normal, the patient’s own baseline value before anticoagulation was used as the aPTT reference value; otherwise, the median of the hospital’s normal range was used. For confirmed on-treatment aPTT ratios $< 1.5$, the infusion rate was increased by $20\%$. For confirmed on-treatment aPTT ratios $> 3.0$, the infusion was discontinued for 2 hours, then restarted at a $20\%$ lower rate. Repeat aPTT determinations were required 4 to 6 hours after any dose adjustment.

In patients who were switched to oral anticoagulation treatment, the lepirudin dose was reduced to reach an aPTT ratio of 1.5 before the oral anticoagulant was initiated; lepirudin was discontinued when an international normalized ratio $> 2.0$ was reached.

**Efficacy Outcomes**

The proportion of laboratory responders was the primary efficacy criterion for lepirudin-treated patients. Laboratory response was defined as follows: (1) for aPTT, maintenance of an on-treatment aPTT ratio of $> 1.5$ in $\geq 80\%$ of measurements with $< 2$ dose increases, and (2) for platelets, an increase in count by $\geq 30\%$ of the lowest value and to a value $> 100$ g/L by day 10 of lepirudin treatment in thrombocytopenic patients, or maintenance of a normal baseline platelet count on both days 3 and 10. Prespecified clinical outcomes included death, limb amputation, and new TECs. Patients were monitored daily for clinical outcomes for 14 days after cessation of treatment. Cumulative incidences of the combined and individual outcomes were estimated for the entire study period: the pretreatment period (between laboratory confirmation of HIT and start of lepirudin treatment), the treatment period, and the posttreatment period. In addition, average combined outcome rates per patient-day were estimated for each period.

**Safety Outcomes**

Safety outcomes included bleeding, especially major bleeding (fetal or life-threatening, intracranial, permanently or significantly disabling, requiring surgical intervention, and overt bleeding requiring transfusion of $\geq 2$ units of red blood cells), allergic reactions, and other adverse events.

**Comparison With Historical Control**

The primary end point of the comparison with the historical control was the combined cumulative outcome incidence (death, limb amputation, and new TEC). In addition, the cumulative incidences of the individual outcomes, of documented bleeding, and of documented bleeding requiring transfusion were compared.

**Statistical Methods**

Laboratory response was determined for patients who had received lepirudin for at least 48 hours and who were followed up for $\geq 7$ days. Incidences of clinical outcomes were evaluated for all patients on the basis of investigator-reported events; there was no central adjudication of clinical events.

The cumulative incidences of clinical outcomes were estimated by use of Kaplan-Meier survival curves and were not subjected to statistical inference. Average combined outcome rates per patient-day in the pretreatment period were descriptively compared with those in the treatment and posttreatment periods.

Comparisons with the historical control group were conducted by use of a Kaplan-Meier time-to-event analysis with log-rank test.\textsuperscript{14} The protocol-specified main analysis compared cumulative incidences between laboratory confirmation of HIT and the end of the observation period. In the lepirudin group, events that occurred on the day of laboratory confirmation of HIT were included in the analysis if the onset was after the test. In the historical control group, events that occurred on the day of HIT confirmation were excluded from analysis, because it could not be determined whether the onset was before or after the test. An additional “first-selected treatment”
Patients, Compliance, and Treatment

At 46 German hospitals, 112 patients were enrolled. Sixty-five patients were assigned to dose regimen A1, treatment; 4 patients to dose regimen A2, treatment in conjunction with thrombolysis; and 43 patients to dose regimen B, prophylaxis. Baseline characteristics are shown in Table 1. All patients had laboratory-confirmed HIT.

Ninety-three patients (83.0%) completed the study according to protocol. In 19 patients, treatment was discontinued prematurely because of death (n=7), nonfatal adverse event (n=9), withdrawn consent (n=1), or other reasons (n=2). The median duration of treatment was 11 days (range, 0 to 104 days; A1, 13 [0 to 104]; A2, 10 [1 to 58]; and B, 8 [1 to 67]). Treatment was continued for >10 days in 67 patients (59.8%) (A1, 44 [67.7%]; A2, 3 [75.0%]; and B, 20 [46.5%]). The median infusion rates were 0.13 mg·kg\(^{-1}\)·h\(^{-1}\) in regimen A1, 0.07 mg·kg\(^{-1}\)·h\(^{-1}\) in regimen A2, and 0.08 mg·kg\(^{-1}\)·h\(^{-1}\) in regimen B. Dose adjustments for high and low aPTT ratios were made at least once in 30 patients (26.8%) and 31 patients (27.8%), respectively, with no differences in frequency between the dose regimens.

Laboratory Response

Ninety-four patients (83.9%) were evaluable for analysis of laboratory response (including 1 who did not complete the study according to protocol). Eighteen patients could not be evaluated (missing platelet counts on day 3 and/or day 10 [n=15]; lepirudin treatment <48 hours [n=3]). Platelet response was achieved in 87 of 94 patients (92.6%) (A1, 54 of 57; A2, 3 of 3; and B, 30 of 34). Median platelet counts of thrombocytopenic patients increased ~4-fold over the first 10 days (Figure 1A), whereas those of nonthrombocytopenic patients did not change compared with baseline (data not shown). Anticoagulant response was achieved in 68 of 94 patients (72.3%) (A1, 44 of 57; A2, 1 of 3; and B, 23 of 34). Median aPTT ratios reached the target range of 1.5 to 3.0 immediately after initiation of lepirudin and remained there throughout the course of treatment (Figure 1B). Median aPTT ratios in regimens A1 and B did not differ significantly. Complete laboratory response meeting both platelet and anticoagulation criteria was achieved in 65 of 94 patients (69.1%; 95% CI, 59.3% to 78.3%) (A1, 42 of 57; A2, 1 of 3; and B, 22 of 34).

Clinical Efficacy Outcome

From HIT confirmation until 2 weeks after lepirudin cessation, 11 patients (9.8%) died (multiorgan failure [n=3]; sepsis [n=2]; heart failure [n=2]; and pulmonary embolism, ventricular fibrillation, shock, and apnea [n=1 each]) (Table 2). Ten patients (8.9%) underwent limb amputation, and 20 (17.9%) experienced a new TEC. Thirty-three patients (29.5%) had ≥1 of the main outcomes during the study (A1, 33.8%; A2, 50%; and B, 20.9%). Nine patients (8.0%) suffered an event in the 1.9-day pretreatment period, 18 (16.1%) in the 15.2-day treatment period, and 6 (5.4%) in the 13.0-day posttreatment period. Thus, the average combined outcome rate per patient-day showed a marked decrease from 5.1% in the pretreatment period to 1.5% in the treatment and 0.6% in the posttreatment periods, respectively (Figure 2).

Safety Outcome

Adverse events were reported in 73 patients (65.2%) during the study period, with a causal relationship to lepirudin considered possible in 42 (37.5%). Serious adverse events were reported in 43 patients (38.3%), with a causal relationship to lepirudin considered possible in 17 (15.2%). None of the 11 deaths (9.8%) were considered to be causally related to lepirudin. Bleeding was the most common adverse event; 53 patients (47.3%) experienced ≥1 bleeding event during the study. Nineteen patients (17.0%) had major bleeding; 9 (8.0%) at invasive sites, 7 (6.2%) spontaneously, and 3 (2.6%) both at invasive sites and spontaneously. No intracranial or fatal hemorrhage was observed. Six patients (5.4%) experienced topical or generalized skin reactions. Other adverse events included sepsis (4.5%), pneumonia (4.5%), and increased liver enzymes (alanine aminotransferase, 5.4%).

Comparison With Historical Control

Ninety-five of 112 lepirudin-treated patients and 120 of 182 historical control patients qualified for direct comparison of clinical outcomes. Thirty-eight historical control patients were excluded because no or insufficient data beyond laboratory confirmation of HIT were available. In addition, 17 lepirudin-treated patients and another 24 historical control patients were excluded because they met at least 1 of the predefined criteria. None of the 17 excluded lepirudin-treated patients died or experienced a new TEC during the study period, but 1 underwent limb amputation.
Baseline characteristics of lepirudin-treated and historical control patients are summarized in Table 3. Lepirudin-treated patients were slightly younger, more often male, and more often hospitalized for nonsurgical diseases. Although fewer lepirudin-treated patients presented with diagnostic thrombocytopenia, the proportions of patients with TECs at baseline were similar, with a trend toward more proximal venous and arterial TECs in the lepirudin group.

At all time points after laboratory confirmation of HIT (main analysis), the cumulative combined incidences of death, limb amputation, and new TEC were lower in the lepirudin group than in the historical control group; at 5 weeks, the incidences were 30.9% (95% CI, 21.0% to 40.7%) and 52.1% (95% CI, 40.4% to 63.9%), respectively (Table 4). The differences were not statistically significant in the time-to-event analysis covering the entire study period (P=0.12, log-rank test). Similar results were observed for the individual outcomes of death (10.5% [95% CI, 3.7% to 17.3%] versus 22.3% [95% CI, 12.8% to 31.9%] at 5 weeks; P=0.21) and new TEC (17.4% [95% CI, 9.6% to 25.1%] versus 32.1% [95% CI, 21.1% to 43.1%] at 5 weeks; P=0.26), whereas there was no relevant difference in the incidence of limb amputation (10.0% [95% CI, 3.8% to 16.1%] versus 8.2% [95% CI, 0.8% to 15.5%] at 5 weeks; P=0.43).

None of the potential prognostic factors in the Cox regression model significantly affected the risk of negative outcome. The unadjusted risk ratio for lepirudin patients relative to historical control patients was 0.706 (95% CI, 0.45 to 1.10,}

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**TABLE 2. Crude Incidences of Clinical Efficacy Outcomes in Lepirudin-Treated Patients (n=112)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Before Lepirudin</th>
<th>During Lepirudin</th>
<th>After Lepirudin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>6 (5.4)</td>
<td>5 (4.5)</td>
<td>11 (9.8)</td>
</tr>
<tr>
<td>Limb amputation</td>
<td>1 (0.9)</td>
<td>7 (6.3)</td>
<td>2 (1.8)</td>
<td>10 (8.9)</td>
</tr>
<tr>
<td>New TEC</td>
<td>9 (8.0)</td>
<td>10 (8.9)</td>
<td>1 (0.9)</td>
<td>20 (17.9)</td>
</tr>
<tr>
<td>Combined*</td>
<td>9 (8.0)</td>
<td>18 (16.1)</td>
<td>6 (5.4)</td>
<td>33 (29.5)</td>
</tr>
</tbody>
</table>

*Patients may have had >1 outcome.
and the adjusted risk ratio was 0.709 (95% CI, 0.44 to 1.14, \(P=0.15\)).

For comparison of cumulative incidences during treatment, the first-selected treatment after HIT confirmation was identified for the historical control patients. Complete treatment data could be obtained for 103 patients. Treatments identified included danaparoid sodium (23.0±22.0 days, \(n=32\)), ongoing phenprocoumon (14.3±12.3 days, \(n=22\)), no anticoagulation (10.4±9.7 days, \(n=23\)), and miscellaneous (9.5±8.5 days, \(n=26\): ongoing low-molecular-weight heparin \(n=8\), phenprocoumon \(n=5\), ongoing danaparoid sodium \(n=4\), aspirin \(n=5\), or thrombolytics \(n=4\)).

The mean duration of treatment was similar in the 2 groups (lepirudin, 15.2 days; historical control, 14.9 days). Consistent with the main analysis, the cumulative combined incidences of death, limb amputation, and new TEC were lower in the lepirudin group than in the historical control group at all time points during treatment; at 5 weeks, the incidences were 27.2% (95% CI, 16.0% to 38.4%) and 51.8% (95% CI, 33.6% to 70.0%), respectively (\(P=0.19\), log-rank test). Adjustment for potential prognostic factors in a Cox regression model did not affect the risk ratio (unadjusted, 0.691 [95% CI, 0.393 to 1.213]; adjusted, 0.707 [95% CI, 0.387 to 1.293]).

There was an excess of documented bleeding events in the lepirudin group compared with the historical control group (cumulative incidence at 35 days, 44.6% [95% CI, 33.8% to 55.4%] versus 27.2% [95% CI, 16.3% to 38.0%]; RR 2.57; \(P=0.0001\), log-rank test) but no statistically significant difference in bleeding events requiring transfusion (cumulative incidence at 35 days, 12.9% [95% CI, 6.1% to 19.7%] versus

### TABLE 3. Baseline Characteristics: Lepirudin vs Historical Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lepirudin ((n=95))</th>
<th>Historical Control ((n=120))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y</td>
<td>61</td>
<td>67</td>
</tr>
<tr>
<td>Age ≥65 y, %</td>
<td>34.7</td>
<td>59.2</td>
</tr>
<tr>
<td>Female, %</td>
<td>55.8</td>
<td>65.8</td>
</tr>
<tr>
<td>Field of underlying disease, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery/traumatology</td>
<td>44.2</td>
<td>63.3</td>
</tr>
<tr>
<td>Internal medicine/other</td>
<td>55.8</td>
<td>36.7</td>
</tr>
<tr>
<td>Median platelet count at start of prestudy heparin, (g/L)</td>
<td>240</td>
<td>242</td>
</tr>
<tr>
<td>Diagnostic thrombocytopenia during prestudy heparin, %</td>
<td>83.7</td>
<td>96.7</td>
</tr>
<tr>
<td>Median time to detection of thrombocytopenia, (d)</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Median baseline platelet count, (g/L)</td>
<td>81</td>
<td>60</td>
</tr>
<tr>
<td>TEC at baseline, %</td>
<td>66.3</td>
<td>69.2</td>
</tr>
<tr>
<td>Type of TEC (% of total number of patients with TEC)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous-distal</td>
<td>41.3</td>
<td>67.5</td>
</tr>
<tr>
<td>Venous-proximal</td>
<td>39.7</td>
<td>28.9</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>44.4</td>
<td>43.4</td>
</tr>
<tr>
<td>Arterial-peripheral</td>
<td>30.2</td>
<td>20.5</td>
</tr>
<tr>
<td>Arterial-central</td>
<td>31.7</td>
<td>28.9</td>
</tr>
<tr>
<td>Latent HIT§</td>
<td>5.3</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Numbers of evaluable patients differ slightly from total numbers of patients.
†Minimum value on day of HIT confirmation±2 days.
‡Patients may have suffered multiple TECs of different types.
§No clinical signs or symptoms (diagnostic thrombocytopenia and/or TEC) at baseline or during prestudy heparin.
9.1% [95% CI, 3.7% to 14.4%]; RR 1.66; \( P = 0.23 \), log-rank test). Incidences of serious spontaneous bleeding, such as cerebral hemorrhage (lepirudin 0 versus historical control 3 [2.5%]), gastrointestinal hemorrhage (2 [2.1%] versus 6 [5.0%]), or lung hemorrhage (2 [2.1%] versus 2 [1.7%]), were low in both groups.

Discussion

This study was planned to confirm and expand the promising results of our first prospective study of lepirudin in HIT patients.\(^{11}\) Lepirudin led to therapeutic prolongation of the aPTT in 72% of patients. During application of lepirudin, platelet counts normalized rapidly. Because only 2 dose increases were allowed for patients to be considered aPTT responders, the aPTT response rate, which is an indirect measure of the intrapatient stability of anticoagulation, appears to be quite high.

The combined crude incidence of death, limb amputation, and new TEC during the study period (30.4%) is comparable to that observed in the first study (25.4%).\(^{11}\) One of the most important findings of the study was that 45% of the patients with TECs developed this event even before treatment could be started, although the pretreatment period accounted for only 6% of the entire study period. The average combined outcome rate per patient-day decreased sharply from 5.1% in the pretreatment period to 1.5% in the treatment period. Because the vast majority of patients did not receive any heparin in the pretreatment period, our findings strongly support the assumption that heparin cessation alone is not an appropriate therapeutic strategy in HIT.\(^{5}\)

Although the results of our 2 studies were generally consistent, with very similar mortality rates (9.8% versus 8.1%), the individual incidences of limb amputation (8.9% versus 4.1%) and new TEC (17.9% versus 10.8%)\(^{11}\) were higher in the present study. Furthermore, although there was a consistent pattern of lower cumulative combined outcome rates in the lepirudin groups in both studies compared with the historical control group, the differences were statistically significant only in the first study. Apart from chance, a shift in the baseline clinical condition of the patients might account for these gradual differences between the studies. We speculate that patients in the present study presented with a poorer clinical condition at study entry.

The primary adverse effect of lepirudin was bleeding. The majority of bleeding events occurred at invasive sites. Compared with historical controls, there was no difference in serious bleeding events requiring transfusion or serious spontaneous bleeding. In particular, no intracranial or fatal bleeding was observed.

Historically controlled studies have major limitations, in that the selection of the control patients may be a source of bias and the effect of missing data on the study results might be large. However, data available in the literature suggest that no relevant progress has been made in treating HIT patients since the disease was described in a large series of patients in 1984.\(^{3}\) In particular, mortality rates have remained essentially unchanged (≈20% to 30%) over more than a decade,\(^{3,5,17,18}\) 2 to 3 times higher than in our studies. Warkentin and Kelton\(^{5}\) recently reported a 51% TEC rate among HIT patients, which is even lower than the rate we observed in the lepirudin-treated patient group at study entry. However, the outcome of their patients differed substantially from the outcome of the lepirudin-treated patients. Of their patients who received warfarin after HIT was diagnosed, 47% (10 of 21) developed a new TEC. In patients with isolated thrombocytopenia who received no further anticoagulation, 56% (20 of 36) developed a new TEC. The mortality in both of these groups was ≈20%.\(^{5}\)

Only sparse data exist on clinical studies of alternative treatment options. In a large compassionate-use study of danaparoid sodium, ≈17% of the patients died during treatment or within a 6-week follow-up period.\(^{19,20}\) Argatroban, a synthetic thrombin inhibitor, recently was evaluated in a prospective, historically controlled study that was similar in design to our studies. Although the rate of TECs was significantly reduced with argatroban, interpretation was clouded by a significant increase in overall mortality with argatroban (data from an oral presentation at the International Society on Thrombosis and Hemostasis meeting, Florence, Italy, June 12, 1997).

In summary, our study supports earlier findings that lepirudin is an effective treatment option for parenteral anticoagulation of patients with confirmed HIT. The availability of lepirudin now allows effective anticoagulation in HIT patients without delay, which seems to be important in minimizing the risk of further TECs in this serious condition. The optimal treatment strategy for preventing further complications in patients who develop HIT can only be determined in a comparative trial.

**TABLE 4. Cumulative Combined Incidences of Death, New TEC, and Limb Amputation After Laboratory Confirmation of HIT**

<table>
<thead>
<tr>
<th>Days After HIT Confirmation</th>
<th>Lepirudin (n=95)</th>
<th>Historical Control (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients at Risk, n</td>
<td>Cumulative Incidence, %</td>
</tr>
<tr>
<td>7</td>
<td>77</td>
<td>21.1</td>
</tr>
<tr>
<td>14</td>
<td>69</td>
<td>26.4</td>
</tr>
<tr>
<td>21</td>
<td>55</td>
<td>28.7</td>
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<tr>
<td>28</td>
<td>28</td>
<td>30.9</td>
</tr>
<tr>
<td>35</td>
<td>14</td>
<td>30.9</td>
</tr>
</tbody>
</table>

\(^{*}P=0.12\), log-rank test.
Appendix

Principal Investigator: A. Greinacher, Ernst-Moritz-Arndt-Universität Greifswald.


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