Lepirudin for prophylaxis of thrombosis in patients with acute isolated heparin-induced thrombocytopenia: an analysis of 3 prospective studies

Norbert Lubenow, Petra Eichler, Theresia Lietz, Beate Farner, and Andreas Greinacher

This analysis of 3 prospective multicenter trials in patients with laboratory-confirmed acute heparin-induced thrombocytopenia (HIT) without clinically evident thromboembolic complications (TECs), isolated HIT, assessed the combined individual end points of death, new TECs, and limb amputation. Patients with the same inclusion criteria who did not receive lepirudin or danaparoid served as a contemporaneous control group. Ninety-one patients were treated with lepirudin (intravenous infusion 0.10 mg/kg/h, no bolus, activated partial thromboplastin time [aPTT]–adjusted to 1.5-2.5 times baseline) for a median of 11.0 days (range, 1-68 days). During the observation period (median 24 days), 13 (14.3%) deaths, 4 (4.4%) new TECs, 3 (3.3%) limb amputations (combined 18 [19.8%]), and 13 (14.3%) major bleeding events occurred. In comparison to the control group (N = 47), the combined end point ($P = .0281$) and new TECs ($P = .02$) were reduced, and major bleeding was not significantly different between groups ($P = .5419$). In renal impairment, lepirudin did not reach its steady state within 4 hours, and additional monitoring every 4 hours after start of lepirudin until steady state is reached is recommended. Lepirudin seems to be effective in patients with isolated HIT. Dose reductions in renal impairment are important. Keeping the aPTT in the range corresponding to 600 to 700 μg/L lepirudin during treatment may minimize bleeding complications. (Blood. 2004;104:3072-3077)

Introduction

Heparin-induced thrombocytopenia (HIT) occurs in up to 3% of patients treated with unfractionated heparin[1] and typically manifests 5 to 14 days after the start of heparin therapy.[2] The mechanism appears to involve the development of antibodies of the immunoglobulin G (IgG) class, which bind to platelet factor 4 (PF4)–heparin complexes.[3,4] The interaction of these antigen-antibody complexes with platelets[5] and endothelial cells[6] can contribute to the development of new thromboses.

Thrombin plays a central role in HIT-related thrombosis. In HIT, thrombin generation is enhanced by concomitant activation of platelets,[5] generation of platelet microparticles,[7] and alteration of endothelial cells.[6] Immediate cessation of heparin is necessary when HIT develops. However, since the risk for new thromboses is enhanced in these patients even after cessation of heparin, further parenteral anticoagulation is required.[8,9]

Patients with acute HIT but lacking clinically evident thrombosis (isolated HIT) also require further anticoagulation.[10] As many as 52.8% of these patients have been reported to develop a new thrombosis during the following weeks if they do not receive active treatment.[10] We recently provided evidence that prophylactic-dose anticoagulation is not sufficient to prevent new thromboses in these patients,[11] but that patients with isolated HIT benefit from anticoagulation in therapeutic doses.

Lepirudin (trade name Refludan; Berlex Laboratories, Wayne, NJ; Pharmion, Cambridge, United Kingdom), a recombinant hirudin, acts by direct thrombin inhibition. It is suitable for continuation of the anticoagulation of patients with isolated HIT and is approved for patients with HIT and concomitant thrombosis. We assessed the efficacy of lepirudin in patients with HIT in 3 prospective trials (N = 399).[12-14] In these studies, a proportion of patients suffered from isolated HIT and were treated prospectively with lepirudin. The dosing regimen differed from that used in patients with thrombosis: the bolus was omitted and the initial intravenous dose was reduced by one third but was still adjusted for activated partial thromboplastin time (aPTT).

The present analysis is the largest analysis of the outcomes of lepirudin treatment in patients with acute isolated HIT.

Patients and methods

Patients

Patients were enrolled in 3 consecutive prospective studies of heparin-associated thrombocytopenia (HAT-1, HAT-2, and HAT-3) between March 1994 and May 1997.[12-14] Approval for these studies was obtained from the Greitswald University institutional review board. Informed consent was provided according to the Declaration of Helsinki. They qualified for the present analysis if they had acute HIT defined by decrease in platelet count of at least 30% or to below 100×10^9/L. Additionally, patients were required to have a positive heparin-induced platelet activation (HIPA) test[15]

From the Dept of Immunology and Transfusion Medicine, Ernst-Moritz-Arndt University Greifswald, Greifswald, Germany.

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N.L. and A.G. are consultants for Berlex (Wayne, NJ) and Pharmion (Cambridge, United Kingdom).

Reprints: Andreas Greinacher, Ernst-Moritz-Arndt Universität, Institut für Immunologie und Transfusionsmedizin, Klinikum/Sauerbruchstrasse, 17489 Greifswald, Germany; e-mail: greinach@uni-greifswald.de.

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but no clinically evident thrombosis and were treated with lepirudin according to protocol. Patients with isolated HIT but a recent venous or arterial thrombosis (< 20 days) were analyzed separately to avoid a bias on treatment efficacy caused by the recent thromboembolic event.

Treatment regimen

Lepirudin was given as an intravenous infusion of 0.10 mg/kg/h with no bolus. Infusion rates were adjusted to reach 1.5- to 2.5-fold prolongation of the patient's baseline aPTT value or the mean of the laboratory normal range if the baseline value was not available (1.5- to 3.0-fold prolongation with Actin FS reagent; Dade Behring, Marburg, Germany). If aPTT ratios were less than 1.5 during treatment, the dose was increased by 20%; if aPTT ratios were greater than 3.0, the infusion was stopped for 2 hours and then restarted at a 20% reduced dose. An aPTT check was required 4 to 6 hours after every dose adjustment.

Laboratory methods

HIT antibodies were determined by the HIPA test.[15] Enzyme-linked immunosorbent assay (ELISA) technology was used to measure lepirudin plasma levels and antilepirudin antibodies on day 1 and at least 5 days after start of lepirudin treatment, as described previously.[16] In a subset of patients, thrombin-antithrombin (TAT) levels were measured by ELISA at baseline and at 4 hours after initiation of lepirudin.

Outcome measures

Primary objectives were single and combined end points of new thromboembolic complications (TECs), limb amputations, and death. Secondary objectives included the incidence of major bleeding events (defined as transfusion of ≥ 2 units of red blood cells or intracerebral bleeds), incidence of antilepirudin antibodies, TAT-complex profile, and identification of risk factors for bleeding by comparing the incidences of the combined end point and of major bleeding complications in relation to the aPTT (or lepirudin plasma levels). The observation period was from start of lepirudin treatment until 2 weeks after cessation of lepirudin.

To address the impact of renal function on the pharmacokinetics of lepirudin, we analyzed the time course of lepirudin plasma levels from initiation of therapy until 72 hours in patients with (serum creatinine levels ≥ 88.4 μmol/L [10 mg/L]) or without renal impairment.

Control group

For ethical reasons, a placebo control was not considered feasible in the prospective studies as they also included patients with acute thrombosis. As no active, approved comparator was available during the study period, a randomized trial was not possible. We therefore identified all patients with HIT who fulfilled the same inclusion criteria but were not enrolled in the prospective studies. In these patients, HIT antibodies were confirmed in the same 2 laboratories and during the same time period as the patients enrolled in the prospective trials, namely University of Greifswald and Department of Clinical Immunology and Transfusion Medicine of the University of Giessen. Concordance of results between the 2 laboratories had been secured.[15] Patients were treated at the discretion of the treating physicians but they did not receive parenteral anticoagulation after the diagnosis of HIT had been made. Patients with a recent venous or arterial thrombosis (within 20 days prior to start of treatment) were excluded from this analysis. The time period for comparison was defined for the control group as start of treatment until hospital discharge.

Statistical methods

The incidences of clinical outcomes were described by Kaplan-Meier survival curves, and comparison with the control group was performed by Kaplan-Meier time-to-event analysis with log-rank test. Patient characteristics (age, sex, field of underlying disease) were compared by chi-square test. Comparison of the duration of treatment was performed by the Wilcoxon test.

In patients with major bleeding, all aPTT values up to the event were compared with the aPTT values of patients without a major bleed by using a 2-sample *t* test. Lepirudin infusion rates, lepirudin plasma levels, and serum creatinine levels, as an indicator for renal function, were compared between patients with and without a major bleed using a 2-sample *t* test. Incidences of end points in patients with more than 50% of aPTT values lower than 1.5 times the baseline value and the incidences in the other patients were compared by the Fisher exact test.

All tests were 2-sided and considered to be statistically significant below .05. Data were evaluated using the statistical analyzing system (SAS; version 8.0; SAS, Cary, NC).

Results

Patients

Overall, 399 patients were treated with lepirudin in the HAT-1, -2, and -3 studies (n = 82, 112, and 205, respectively). Patients receiving the "therapeutic dose" for HIT with thrombosis with/without thrombolysis (n = 235), lepirudin during cardiopulmonary bypass (n = 18), or lepirudin subcutaneously (n = 1) were excluded.

One hundred forty-five patients received the prophylactic "regimen B" (no bolus, 0.10 mg/kg/h, aPTT adjusted). Of these, 20 had a history of HIT but not acute HIT. Four patients with insufficient information were also excluded. Thirty patients had suffered a recent (< 20 days, mean 6.9 days, SD 5.7 days) thrombosis (arterial [20], venous [8], arterial and venous [2]) and were excluded from this analysis, which aims to report on well-defined isolated HIT (ie, patients without thromboembolic

Table 1. Baseline characteristics of lepirudin-treated study patients and control group

Characteristic	Lepirudin-treated patients	Control group*	*P*
No.	91	47	NA
Median age, y (range)	63 (24-86)	65.5 (24-90)	.798
Male (%)	49 (53.8)	23 (48.9)	.584
Median observation period, d	24.0	15.0	.0123
Field of underlying disease			.983
Internal medicine, no. (%)	40 (44.0)	22 (47.8)	—
Cardiovascular surgery, no. (%)	12 (13.2)	5 (10.9)	—
Orthopedic surgery, no. (%)	10 (11.0)	2 (4.3)	—
Traumatology, no. (%)	3 (3.3)	1 (2.2)	—
Combinations/other, no. (%)	26 (28.6)	16 (34.8)	—
Median platelet count nadir, $\times 10^9$/L	45.5	49.0	.645

NA indicates not applicable; —, not assessed.

*Contemporaneous control group of patients who were not enrolled in the lepirudin studies but who tested positive for HIT antibodies in the same laboratories during the same period of time and fulfilled the same inclusion and exclusion criteria. Data were missing for the age of one control case and for the field of underlying disease of one control case.

complication, whether or not HIT related). A total of 91 evaluable patients (49 male, 42 female), aged between 24 and 86 years (median 63 years), with acute isolated HIT remained (Table 1).

The time elapsed between heparin withdrawal and availability of the HIPA test result was up to 1 day in 70 patients, 2 days in 10 patients, 3 days in 3 patients, and longer than 3 days in 8 patients. Time from availability of the test result to start of lepirudin was up to 1 day in 52 patients, 2 days in 15 patients, 3 days in 4 patients, and longer than 3 days in 20 patients.

The mean laboratory baseline aPTT value of all 76 study centers involved in the HAT-1, -2, and -3 studies was available. In 72 patients (79.1%), the patients' aPTT at baseline (mean 32.1 seconds [SD 6.1]) was used for adjustment. In 7 patients (7.7%) in whom there was a prelepirudin treatment aPTT prolongation and in 12 patients (13.2%) with a missing baseline aPTT, the mean normal laboratory value was used.

Efficacy outcomes

The outcome data are available is Table 2. Within the observation period, 4 lepirudin-treated patients (4.4%) experienced a new thrombosis: a cerebrovascular infarction occurred on day 6 of 18 lepirudin treatment days, 1 vena cava thrombosis (with a vena cava filter in situ) occurred 2 days after a 31-day treatment course of lepirudin, and a septic vena iliaca to vena cava inferior thrombosis occurred 16 days after cessation of a 9-day treatment course of lepirudin. One pulmonary embolism was detected incidentally upon autopsy; the patient died of cardiac failure 7 days after cessation of lepirudin, which she had received for 9 days. Limb amputation occurred in 3 patients (3.3%). Thirteen (14.3%) deaths were recorded during (n = 5; 5.5%) and after (n = 8; 8.8%) treatment with lepirudin. The causes of death were multiorgan failure (5), cardiac failure (3), stroke (1), bleeding (after upper lobe mispuncture of right lung; 1), and unknown (3). The combined end point occurred in 18 (19.8%) of 91 patients. The 30 patients with recent TECs had a poorer outcome with a combined end point of 33.3%. This was caused by a higher limb amputation rate (16.6%) and a higher rate of new thromboses (16.6%) than in the patients with acute isolated HIT.

Safety outcomes

Fourteen major bleeding events occurred in 13 (14.3%) patients, with one intracerebral bleed. Minor bleeding occurred in 12 patients (13.2%). The aPTTs and lepirudin plasma levels, up to the major bleeding event, were compared with all aPTTs of patients without a major bleed (Figure 1A-B). All major bleeds occurred during lepirudin treatment: day 1 (gastrointestinal); day 2 (n = 4; nasopharynx, thoracic drain, gastrointestinal [2]); day 6 (n = 2; unclassified, intracerebral); day 7 (intrathoracic after mispuncture); day 9 (sternotomy site); day 11 (bronchial); day 26 (rectal bleeding); day 27 (operation wound); and day 32 (bleeding from puncture site left pleura).

To assess the impact of the degree of anticoagulation on bleeding risk, we used all aPTTs until bleeding occurred and compared them with all aPTTs of the patients without major bleeding. Patients with major bleeding had higher aPTTs until bleeding as compared with patients without major bleeding (mean 73.7 seconds vs mean 53.0 seconds; $P < .0001$) and higher lepirudin plasma levels (mean 1145.0 μg/L vs mean 555.1 μg/L; $P < .0001$). While infusion rates did not differ between the groups (mean 0.044 mg/h vs mean 0.054 mg/h; $P = .2772$), creatinine levels were higher in patients with major bleeding (mean 125.5 μmol/L [14.2 mg/L] vs mean 77.8 μmol/L [8.8 mg/L]; $P \leq .0001$; Figure 1C).

A total of 26 (39.4%) of 66 evaluable patients developed antilepirudin antibodies. Neither the combined end point ($P = .7353$) nor major bleeding events ($P = .1378$) differed between the antibody-positive and -negative patients.

Dosing

The mean steady-state dose, defined as the dose of patients who did not have any dose adjustments within the last 24 hours, was 0.062 mg/kg/h (SD 0.037; n = 71). The mean dose at the end of treatment was 0.06 mg/kg/h (SD 0.037; n = 91).

The lepirudin plasma levels in the first 72 hours following treatment initiation are depicted in Figure 2, divided into patients with serum creatinine levels of at least 88.4 μmol/L [10 mg/L] (n = 36) and less than 88.4 μmol/L [10 mg/L] (n = 55). In these 2 patient groups, the time to obtain steady-state levels, defined as time point where dosing remained unchanged after the following aPTT determination, differed: it took a mean of 44.2 (SD 98.3) hours in patients with renal impairment compared with 7.82 (SD 21.0) hours in patients without ($P = .0045$).

Patients without renal impairment had a mean of 3.57 dose adjustments (SD 3.86), whereas renally impaired patients had 9.35 (mean; SD 15.57) dose adjustments. Treatment duration of both groups was only numerically different (mean 12.5 vs 17.5 days; $P = .302$). Dose increases (66.2% vs 70.3%) and decreases (33.8% vs 29.7%) were equally frequent ($P = .3376$).

Thirty-seven (40.7%) patients received oral anticoagulants following lepirudin treatment. None of them developed venous limb gangrene.

Table 2. Death, limb amputations, and new TECs in patients with acute HIT and isolated thrombocytopenia treated with lepirudin and in the control group

	Lepirudin group with isolated thrombocytopenia, n = 91					Lepirudin group with recent TECs, n = 30†		
	Events during treatment	Events following treatment	All patients with events	Control group, n = 47*	*P.* log-rank test	Events during treatment	Events following treatment	All patients with events
Median observation period, d (range)	11.0 (1-68)	9.0 (0-32)	24.0 (3-73)	15.0 (1-141)	NA	9.5 (1-24)	13.7 (1-36)	26.2 (9-48)
New thrombosis, no. (%)	1 (1.1)	3 (3.3)	4 (4.4)	7 (14.9)	.02	4 (13.3)	1 (3.3)	5 (16.6)
Limb amputation, no. (%)	2 (2.2)	1 (1.1)	3 (3.3)‡	0 (0.0)	.2424	4 (13.3)	1 (3.3)	5 (16.6)
Death, no. (%)	5 (5.5)	8 (8.8)	13 (14.3)	10 (21.3)	.0937	0 (0.0)	3 (10.0)	3 (10.0)
Combined end point, no. (%)	8 (8.8)	10 (11.0)	18 (19.8)	14 (29.8)	.0281	5 (16.6)	5 (16.6)	10 (33.3)

NA indicates not applicable.

*Contemporaneous control patients were treated with phenprocoumon, 11 (23.4%), acetylsalicylic acid, 5 (10.6%), and no treatment, 31 (66.0%). Patients may have suffered more than one event.

†Patients with acute isolated HIT but recent non-HIT-related TECs. These patients were excluded from the present study.

‡One limb amputation occurred prior to the start of lepirudin treatment. This event was not included in this table or in the comparison with the control group.

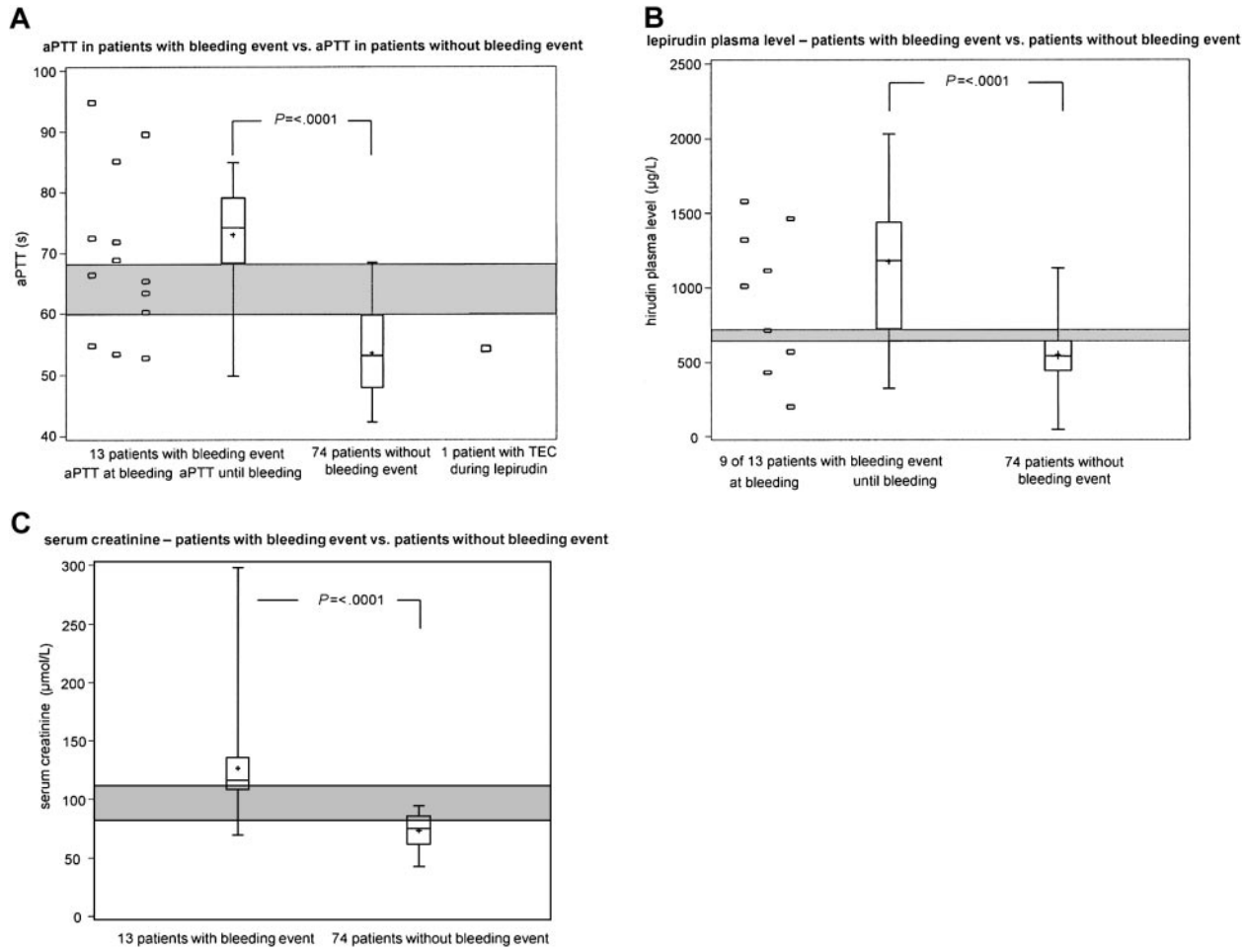

Figure 1. The aPTTs, lepirudin plasma levels, and creatinine levels of patients with and without a major bleed. (A) The aPTT values of patients with a bleeding event versus patients without. On the left, the individual aPTT values at the time of bleeding are given. The left box plot summarizes all aPTTs in the patients who had a major bleeding event up to the time of bleeding: 25% (67.0 seconds) and 75% (79.0 seconds) quartiles and median (75.0 seconds), mean (+; 73.7 seconds), and minimum (50.0 seconds)/maximum (86.0 seconds). The right box plot summarizes all aPTTs in the patients without a bleed ($P < .0001$): 25% (47.0 seconds) and 75% (60.0 seconds) quartiles and median (52.9 seconds), mean (+; 53.0 seconds), and minimum (42.0 seconds)/maximum (69.0 seconds). The range of the gray area divides most of the patients in the 2 groups. (B) Lepirudin plasma levels of patients with bleeding event versus patients without. On the left, the individual values at the time of bleeding are given (n = 9). The left box plot summarizes all values in the patients with a bleed up to the time of bleeding: 25% (670.0 µg/L) and 75% (1422.0 µg/L) quartiles and median (1152.0 µg/L), mean (+; 1145.0 µg/L), and minimum (270.0 µg/L)/maximum (2048.0 µg/L). The right box plot summarizes all plasma levels in patients without a bleed ($P < .0001$): 25% (445.0 µg/L) and 75% (655.0 µg/L) quartiles and median (552.0 µg/L), mean (+; 555.1 µg/L), and minimum (15.6 µg/L)/maximum (1180.0 µg/L). The range of the gray area divides most of the patients in the 2 groups. (C) Serum creatinine levels of patients with bleeding event versus patients without. The left box plot summarizes all values in the patients with a bleed up to the time of bleeding: 25% (106.1 µmol/L [12.0 mg/L]) and 75% (132.6 µmol/L [15.0 mg/L]) quartiles and median (113.2 µmol/L [12.8 mg/L]), mean (+; 125.5 µmol/L [14.2 mg/L]), and minimum (70.7 µmol/L [8.0 mg/L])/maximum (303.2 µmol/L [34.3 mg/L]). The right box plot summarizes all creatinine levels in the patients without a bleed ($P < 0.0001$): 25% (61.9 µmol/L [7 mg/L]) and 75% (85.7 µmol/L [9.7 mg/L]) quartiles and median (70.7 µmol/L [8.0 mg/L]), mean (+; 77.8 µmol/L [8.8 mg/L]), and minimum (53.9 µmol/L [6.1 mg/L])/maximum (95.5 µmol/L [10.8 mg/L]). The range of the gray area divides most of the patients in the 2 groups.

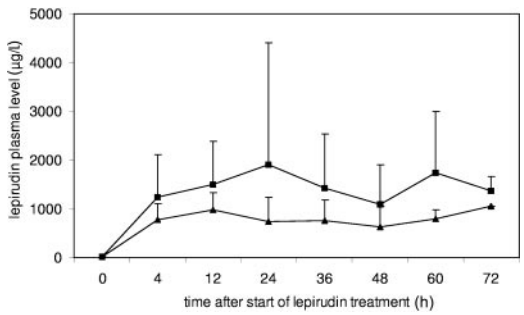

Figure 2. Time course of lepirudin plasma levels. The time course of lepirudin plasma levels from initiation of therapy until 72 hours in patients with serum creatinine levels of at least 88.4 µmol/L (10 mg/L) (■; n = 36) or less than 10 mg/L (▲; n = 55) shows that patients with serum creatinine levels of at least 88.4 µmol/L (10 mg/L) required several days until the steady state at the aimed range was reached. Both groups were in a similar range 4 hours after start of lepirudin treatment. Therefore, aPTT should also be assessed in all patients 8 hours after start of treatment to identify those with drug accumulation.

In 13 (14.3%) of 91 patients, more than half of the aPTT values were below the suggested limit of 1.5 times baseline aPTT. No primary end point (ie, new TECs, limb amputation, or death) occurred *during* treatment in any of these 13 patients. One patient had a major bleed during lepirudin treatment. *After* cessation of lepirudin, 4 (30.8%) of the 13 patients experienced an end point (2 TECs; 2 days following a 31-day treatment course and 16 days after a 9-day treatment course) and 2 patients died (7 days after a 3-day treatment course and 11 days following a 10-day treatment course) compared with 8 (10.3%) of 78 patients with higher aPTTs ($P = .065$). Thus, a largely subtherapeutic treatment course (< 1.5 × aPTT prolongation) may give rise to an increased frequency of complications.

TAT levels

TAT levels, as measured by ELISA, dropped from a median of 18.5 µg/L (range, 2.4-59.3 µg/L) before treatment to a median of 6.79 µg/L (range, 3.2-37.1 µg/L) after initiation of treatment (Figure 3).

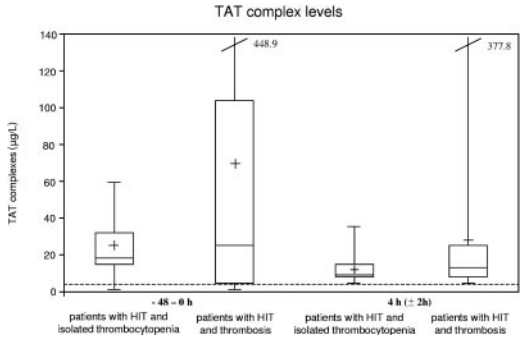

Figure 3. Thrombin-antithrombin (TAT) levels before and after lepirudin treatment in patients with acute isolated HIT (n = 8) and in patients with HIT and thrombosis n = 47[9]. Medians and 25% and 75% quartiles are given. The normal range for TAT levels is 1.0 to 4.1 μg/L (dotted line indicates upper limit). In patients with isolated HIT, TAT levels decreased from a median of 18.5 μg/L (range, 2.4-59.3 μg/L) to a median of 6.79 μg/L (range, 3.2-37.1 μg/L); in the patients with HIT and TECs they decreased from a median of 29.3 μg/L (range, 0.3-448.9 μg/L) to 9.1 μg/L (range, 4.3-377.8 μg/L).[9] A + indicates the mean.

Comparison with control group

The control group comprised 47 patients: 11 (23.4%) were treated with phenprocoumon, 5 (10.6%) were treated with acetylsalicylic acid, and 31 (66.0%) received no treatment for HIT. No parenteral anticoagulant drugs, including low-molecular-weight heparin, danaparoid, or lepirudin, were given to these patients. In both the lepirudin and control group (Table 1), age, sex, and field of underlying disease were comparable. The median observation period was shorter for the control group. However, this potential bias would only be in favor of the control group.

During the observation period, the combined end point was reduced in the lepirudin-treated patients compared with controls (19.8% vs 29.8%; $P = .0281$; Figure 4A) primarily because of a reduction in new TECs (4.4% vs 14.9%; $P = .02$). None of the 11 phenprocoumon-treated patients developed venous limb gangrene. Of the 7 new thromboses occurring in the control group, 2 occurred in the 11 patients receiving phenprocoumon (22.2%) and 5 in the 36 patients not receiving phenprocoumon (16.1%; $P = .659$; Fisher exact test). Major bleeding events were numerically more frequent in the lepirudin-treated patients (14.3% vs 8.5%; $P = .5419$; Figure 4B).

Excluded patients with recent TECs

The overall outcome of these patients was worse than the outcome of the study group. Single and combined end points (Table 2), as well as major bleeding (8/30; 26.6%), were more frequent.

Discussion

This study aims to assess the efficacy and safety of lepirudin treatment in patients with acute isolated HIT. It is the largest study yet of prospectively lepirudin-treated patients with isolated HIT. Only 1 of 91 patients experienced a new thrombosis during active treatment. New thrombosis is the most important outcome indicator of any HIT therapy,[17] and the low incidence of new thromboses in our study strongly suggests that lepirudin is efficacious in isolated HIT.

The high pretreatment TAT levels indicate that activation of the clotting cascade is very strong in patients with isolated HIT. The increased initial TAT levels (Figure 3) may explain the high incidence of new thromboses in these patients if heparin is stopped and no alternative anticoagulation is given.[10] The capability of lepirudin to markedly decrease thrombin generation is demonstrated by the drop in TAT complexes within 4 hours after starting therapy (Figure 3).

Of the 13 deaths, most were related to the underlying disease rather than to HIT (eg, multiorgan failure [5], cardiac failure [3]). Limb amputations after start of lepirudin (n = 3; 3.3%) occurred because of pre-existing antiphospholipid syndrome with microangiopathy and foot necrosis 60 days prior to lepirudin use in 1 patient. Another patient suffered from acute deterioration of peripheral arterial occlusive disease 5 days prior to lepirudin use. No clinical information prior to lepirudin treatment was available for the third patient.

In previous studies of lepirudin in HIT, a historic control was used to judge the efficacy of treatment. This historic patient population dates back to before 1994. At that time, isolated HIT was barely recognized. We, therefore, identified all patients diagnosed as having isolated HIT in the same 2 laboratories and during the same time period as the patients enrolled in the prospective trials but who were not treated with a parenteral anticoagulant. These patients served as a contemporaneous control group. In the lepirudin-treated group, the combined end point occurred less often than in the control group ($P = .0281$), mainly because of a reduction in new TECs ($P = .02$). The incidence of new thrombosis in our control group was 14.9%, which is much lower than what is expected based on published data.[10] This might indicate a potential bias of this nonrandomized control group (ie, potentially only those patients were not treated with a parenteral anticoagulant in whom the treating physician saw no increased risk for thrombosis); however, such a bias would be in favor of the control group, as is the case for the shorter observation period of the control group. Both could only lead to an underestimation of the efficacy of lepirudin. In the control group, 11 patients received oral vitamin K antagonists only. Due to induction of a temporary protein C deficiency, vitamin K antagonists are prothrombotic during the initial treatment period; thus, a bias in favor of lepirudin might have

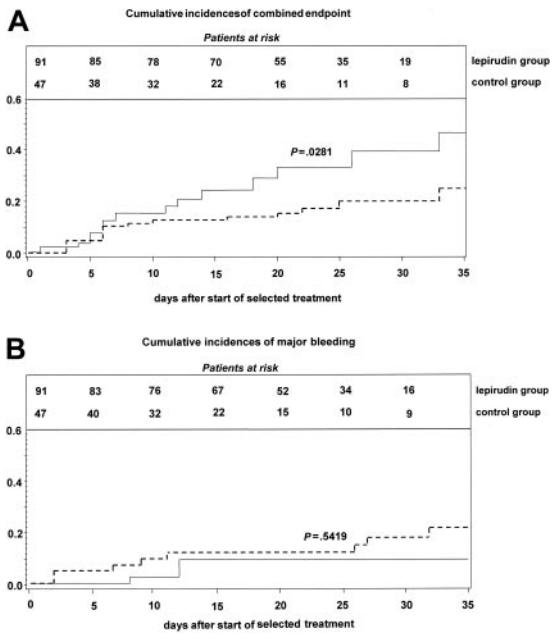

Figure 4. End points in the lepirudin-treated patients compared with controls. (A) Cumulative incidences of the combined end point for the lepirudin-treated patients (dotted line) and the control group (solid line). The end point occurred more frequently in the control group ($P = .0281$), primarily due to a reduction of new TECs ($P = .02$). (B) Cumulative incidences of major bleeding for the lepirudin-treated patients (dotted line) and the control group (solid line). Major bleeding occurred more frequently in the study patients ($P = .5419$).

occurred in these 11 patients. Such a bias is unlikely, however, as neither limb amputations nor new thromboses were more frequent in the control group patients receiving oral anticoagulants.

The group of 30 patients with acute HIT and recent (< 20 days) but not HIT-related thrombosis had higher rates of combined (33.3%) and single end points (limb amputation [16.6%], new TECs [16.6%]) and a higher bleeding rate (major bleeding [26.6%]) than those with isolated HIT. They may be a more severely affected patient population, similar to those with HIT and thrombosis.[9]

Major bleeding was the most frequent severe side effect of lepirudin treatment. That it was only numerically more frequent compared with the control group ($P = .5419$) is most likely related to the small number of patients.

The present study provides important information on how bleeding risk may be further reduced in lepirudin-treated patients: the 25% to 75% quartiles of aPTT values were 67 to 79 seconds in patients with bleeding but 47 to 60 seconds in patients without (Figure 1A). As we found in patients with HIT and thrombosis in a previous study,[9] there was a trend to an increased incidence of the combined end point in patients with aPTTs in more than 50% of time points below 1.5 times the normal mean laboratory aPTT. In patients with acute isolated HIT we therefore suggest aiming for an aPTT between 1.5 times the mean of the normal laboratory range and approximately 65 seconds (Figure 1A). New thromboses were not more frequent in patients treated within this range when compared with those treated with the higher-range lepirudin dose. This recommendation corresponds to lepirudin plasma levels between 600 and 700 μg/mL (Figure 1B), which are independent of the aPTT reagent reactivity. Because of the differing sensitivities of aPTT reagents to lepirudin, laboratories involved in lepirudin monitoring should generate a dose-response curve with lepirudin-spiked plasma to be certain of the individual aPTT response of their laboratory.

Caution is warranted in patients with renal impairment (Figure 1C), especially with creatinine levels exceeding 88.4 μmol/L [10 mg/L]. This creatinine level is considerably lower than the recommended level for dose reduction of 141.4 μmol/L [16 mg/L] given in the package insert. Indeed, the 75% quartile of the creatinine levels of the patients with bleeding complications in our study was 132.6 μmol/L [15 mg/L], which is still below the level where dose adjustments are recommended, whereas it was 85.7 μmol/L [9.7 mg/L] in those patients without major bleeding (Figure 1C). Lepirudin is almost exclusively eliminated renally, thus, the risk of accumulation increases with decreasing renal function. It is noteworthy that infusion rates until bleeding for lepirudin-treated patients with bleeding events did not significantly differ from infusion rates for patients without bleeding ($P = .2772$), although serum creatinine ($P < .0001$) and lepirudin plasma levels ($P < .0001$) were significantly higher. This indicates that the creatinine level for dose adjustments of lepirudin should be 88.4 μmol/L [10 mg/L] rather than 141.4 μmol/L [16 mg/L].

This study also indicates that the monitoring recommendations for lepirudin should be modified. Patients with renal impairment do not reach a steady state within 4 hours after start of treatment. Even if the 4-hour value was in the therapeutic range, lepirudin may accumulate if the dose is not reduced (Figure 2). Of the 14 major bleedings in this study, 35.7% occurred within the first 2 days after start of lepirudin, indicating the relevance of appropriate dose control at the beginning of treatment. We therefore recommend at least one further control of the aPTT 8 hours after start of lepirudin and then every 4 hours until steady state is reached. This is a reasonable general recommendation, as HIT patients are often elderly patients and mild renal impairment might not be noticed.

To assess a clearly defined patient population, we excluded those patients with acute HIT, but recent, non-HIT–related TECs. As these patients had a higher rate of TECs and a higher rate of major bleedings, it is unclear whether they would benefit from a lower aPTT range as recommended for the patient population assessed in the present study.

We conclude that the study shows favorable safety and efficacy parameters for lepirudin treatment in patients with acute isolated HIT (ie, HIT with thrombocytopenia but without acute thromboembolic complications). The bleeding risk associated with lepirudin treatment in patients with isolated HIT may be reduced by aiming for an aPTT of between 1.5 times the mean of the normal laboratory range and approximately 65 seconds, corresponding to lepirudin plasma levels of 600 to 700 μg/L and by additional monitoring after start of lepirudin every 4 hours until a steady state is reached.

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