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

Short title: Lepirudin in isolated HIT

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Abstract

This analysis of three prospective multicenter trials in patients with laboratory-confirmed acute heparin-induced thrombocytopenia (HIT) without clinically evident thromboembolic complications (TEC) - isolated HIT - assessed the combined individual endpoints of death, new TEC, and limb amputation. Patients with the same inclusion criteria, who did not receive lepirudin or danaparoid served as a contemporaneous control group. 91 patients were treated with lepirudin (IV infusion 0.10 mg/kg/h, no bolus, aPTT-adjusted to 1.5-2.5 times baseline) for a median of 11.0 days (range 1-68). 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 endpoint ($P=0.0281$), and new TECs ($P=0.02$) were reduced, major bleeding was not significantly different between groups ($P=0.5419$). 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 600-700 mg/L lepirudin during treatment may minimize bleeding complications.
Key words

Heparin-induced thrombocytopenia, recombinant hirudin, platelets, thrombosis, lepirudin, heparin
Introduction

Heparin-induced thrombocytopenia (HIT) occurs in up to 3% of patients treated with unfractionated heparin,\textsuperscript{1} and typically manifests 5 to 14 days after the start of heparin therapy.\textsuperscript{2} The mechanism appears to involve the development of antibodies of the IgG class, which bind to platelet factor 4 (PF4)-heparin complexes.\textsuperscript{3,4} The interaction of these antigen-antibody complexes with platelets\textsuperscript{5} and endothelial cells\textsuperscript{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,\textsuperscript{5} generation of platelet microparticles,\textsuperscript{7} and alteration of endothelial cells.\textsuperscript{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.\textsuperscript{8,9}

Patients with acute HIT but lacking clinically evident thrombosis (isolated HIT) also require further anticoagulation.\textsuperscript{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.\textsuperscript{10} We recently provided evidence that prophylactic-dose anticoagulation is not sufficient to prevent new thromboses in these patients,\textsuperscript{11} but that patients with isolated HIT benefit from anticoagulation in therapeutic doses.

Lepirudin (Refludan; Berlex Laboratories, Wayne, NJ: USA and Canada; Pharmion, Cambridge, UK: other countries), 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).\textsuperscript{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 IV 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, HAT-1, HAT-2 and HAT-3 between March 1994 and May 1997. 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 x $10^9$/L. Additionally, patients were required to have a positive heparin-induced platelet activation (HIPA) test 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 IV 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 [Dade Behring; Marburg, Germany] reagent). If aPTT ratios were <1.5 during treatment, the dose was increased by 20%; if aPTT ratios were >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. Enzyme-linked immunosorbent assay (ELISA) technology was used to measure lepirudin plasma levels and antilepirudin antibodies on day 1 and ≥5 days after start of lepirudin treatment, as described previously. 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 endpoints of new 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 endpoint and of major bleeding complications in relation to the aPTT (or lepirudin plasma levels).

The observation period was from start of lepirudin treatment until two 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 ≥ 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 Dept. of Clinical Immunology and Transfusion Medicine of the University of Giessen. Concordance of results between the 2 laboratories had been secured. 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, comparison with the control group was performed by Kaplan-Meier time-to-event analysis with log-rank test. Patient characteristics (age, gender, 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 values, as an indicator for renal function, were compared between patients with and without a major bleed using a 2-sample t-test. Incidences of endpoints in patients with > 50% of aPTTs < 1.5 times the baseline value and the incidences in the other patients were compared by Fisher’s exact test.

All tests were 2-sided and considered to be statistically significant below 0.05.

Data were evaluated using the statistical analyzing system (SAS) (version 8.0, SAS Inc., Cary, NC, USA).
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.

145 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, 4 patients with insufficient information were also excluded. 30 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, i.e. patients without thromboembolic 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 one day in 70 patients, 2 days in 10 patients, 3 days in 3 patients and more than 3 days in 8 patients. Time from availability of the test result to start of lepirudin was up to one day in 52 patients, 2 days in 15 patients, 3 days in 4 patients, and more 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%) of our study 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 pre lepirudin treatment aPTT prolongation and in 12 patients (13.2%) with a missing baseline aPTT the mean normal laboratory value was used.

**Efficacy outcomes (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, one 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: multi-organ failure (5), cardiac failure (3), stroke (1), bleeding (after upper lobe mispuncture of right lung, 1), and unknown (3).

The combined endpoint occurred in 18/91 (19.8%) of patients.

The 30 patients with recent TEC had a poorer outcome with a combined endpoint of 33%. 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 to all aPTTs of patients without a major bleed (Figures 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 to all PTTs 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, \( P < 0.0001 \)) and higher lepirudin plasma levels (mean 1145.0 mg/L vs. mean 555.1 mg/L, \( P < 0.0001 \)). While infusion rates did not differ between the groups (mean 0.044 mg/h vs mean 0.054 mg/h, \( P = 0.2772 \)), creatinine levels were higher in patients with major bleeding (mean 14.2 mg/L vs. mean 8.8 mg/L, \( P < 0.0001 \)) (Figure 1c).

A total of 26/66 (39.4%) evaluable patients developed antilepirudin antibodies. Neither the combined endpoint \( (P = 0.7353) \), nor major bleeding events \( (P = 0.1378) \) differed between the antibody-positive and -negative patients.
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 ≥ 10 mg/L, (n=36) and < 10 mg/L (n=55). In these two 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 as compared to 7.82 (SD 21.0) hours in patients without (p=0.0045).

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=0.302). Dose increases (66.2% vs. 70.3%) and decreases (33.8% vs. 29.7%) were equally frequent (p=0.3376).

37 (40.7%) of patients received oral anticoagulants following lepirudin treatment. None of them developed venous limb gangrene.

In 13 of 91 patients (14.3%) more than half of the aPTT-values were below the suggested limit of 1.5 times baseline aPTT. No primary endpoint (i.e. new TEC, 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 of the 13 patients (30.8%) experienced an endpoint (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)) as compared to 8/78 patients (10.3%) with higher aPTTs (p=0.065). Thus a largely subtherapeutic treatment course (<1.5 x 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).

**Comparison with control group**

The control group comprised 47 patients; of these, 11 (23.4%) were treated with phenprocoumon, 5 (10.6%) 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, gender, 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 endpoint was reduced in the lepirudin-treated patients as compared to controls (19.8% vs 29.8%, P = 0.0281) (Figure 4a), primarily because of a reduction in new TECs (4.4% vs 14.9%, P = 0.02). 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 = 0.659 (Fisher’s exact test)). Major bleeding events were numerically more frequent in
the lepirudin treated patients (14.3% vs 8.5%, \( P = 0.5419 \)) (Figure 4b).

**Excluded patients with recent TEC**

The overall outcome of these patients was worse than the outcome of the study group.
Single and combined endpoints (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,\textsuperscript{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 (Fig 3) may explain the high incidence of new thromboses in these patients if heparin is stopped and no alternative anticoagulation is given.\textsuperscript{10} The capability of lepirudin to markedly decrease thrombin generation is demonstrated by the drop in TAT complexes within 4 hours after starting therapy (Fig 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 preexisting 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 historical control was used to judge the efficacy of treatment. This historical 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 two 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 endpoint occurred less often than in the control group \((P = 0.0281)\), mainly because of a reduction in new TECs \((P = 0.02)\). 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 non-randomized control group, i.e. potentially only those patients were not treated with a parenteral anticoagulant in whom the treating physician saw no increased risk for thrombosis. However, as such a bias would be in favor of the control group as it is the case for the shorter observation period of the control group. Both could only lead to an underestimation of the efficacy of lepirudin. However, 11 patients in the control group 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 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 endpoints (death 10.0%, 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 to the control group ($P = 0.5419$), is most likely related to the small number of patients.

The present study provides important information 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, there was a trend to an increased incidence of the combined endpoint 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 ng/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 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 values exceeding 10 mg/L (~ 85 µmol/L). This creatinine level is considerably lower than the recommended level for dose reduction of 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 15 mg/L which is still below the level where dose
adjustments are recommended, whereas it was 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 ($p=0.2772$), although serum creatinine ($p<0.0001$) and lepirudin plasma levels ($p<0.0001$) were significantly higher. This indicates that the creatinine level for dose adjustments of lepirudin should be 10 mg/L rather than 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 h 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 mg/L and by additional monitoring after start of lepirudin every 4 hours until a steady state is reached.
References


Legends to figures

**Figure 1a** aPTT values of patients with a bleeding event vs 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 s) and 75% (79.0 s) quantiles and median (75.0 s), mean (+; 73.7 s) and minimum (50.0 s)/maximum (86.0 s)); the right box-plot summarizes all aPTTs in the patients without a bleed (p<0.0001) (25% (47.0 s) and 75% (60.0 s) quantiles and median (52.9 s), mean (+; 53.0 s) and minimum (42.0 s)/maximum (69.0 s)). The range of the hatched area devides most of the patients in the two groups.

**Figure 1b** Lepirudin plasma levels of patients with bleeding event vs 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) quantiles 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<0.0001) (25% (445.0 µg/L) and 75% (655.0 µg/L) quantiles 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 hatched area devides most of the patients in the two groups.
Figure 1c Serum creatinine values of patients with bleeding event vs patients without. The left box-plot summarizes all values in the patients with a bleed up to the time of bleeding (25% (12.0 mg/L) and 75% (15.0 mg/L) quantiles and median (12.8 mg/L), mean (+; 14.2 mg/L) and minimum (8.0 mg/L)/maximum (34.3 mg/L)); the right box-plot summarizes all creatinine levels in the patients without a bleed (p<0.0001) (25% (7 mg/L) and 75% (9.7 mg/L) quantiles and median (8.0 mg/L), mean (+; 8.8 mg/L) and minimum (6.1 mg/L)/maximum (10.8 mg/L)). The range of the hatched area divides most of the patients in the two groups.

Figure 2 The time course of lepirudin plasma levels from initiation of therapy until 72 hours in patients with serum creatinine ≥ 10 mg/L (■; n=36) or < 10 mg/L (▲; n=55) shows that patients with serum creatinine ≥ 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, in all patients aPTT should be also assessed 8 hours after start of treatment to recognize those with drug accumulation.

Figure 3 Thrombin-anti-thrombin (TAT) levels pre- and post lepirudin treatment in patients with acute isolated HIT (n=8), and in patients with HIT and thrombosis n=47. Medians and 25 and 75% quartiles are given. The normal range for TAT levels is 1.0 – 4.1 µg/L (upper limit: dotted line). 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 TEC 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

**Figure 4a** Cumulative incidences of the combined endpoint for the lepirudin treated patients (dashed line) and the control group (solid line). The endpoint occurred more frequently in the control group (p=0.0281), primarily due to a reduction of new TECs (p = 0.02).

**Figure 4b** Cumulative incidences of major bleeding for the lepirudin treated patients (dashed line) and the control group (solid line). Major bleeding occurred more frequently in the study patients (p=0.5419).
Table 1. Baseline characteristics of lepirudin-treated study patients and control group

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* Contemporaneous control group of patients not enrolled in the lepirudin studies but tested positive for HIT-antibodies in the same laboratories for HIT and fulfilling the same inclusion and exclusion criteria

** One missing age, one missing field of underlying disease.
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 (n=91) with isolated thrombocytopenia | Control group (n=47) || Lepirudin group with recent TECs (n=30)** |
|--------------------------|-----------------------------------------------------|-----------------------|------------------------------------------|
| Median (range) duration  | Events During Treatment: 11.0 (1-68) days          | Events Following Treatment: 9.0 (0-32) days | Events During Treatment: 15.0 (1-141) days | Comparison (log-rank test) | Events Following Treatment: 9.0 (0-32) days |
| New Thrombosis n (%)     | 1 (1.1%)                                            | 3 (3.3%)              | 7 (14.9%)                                | p=0.02                   | 4 (13.3%)                                      |
| Limb Amputation n (%)    | 2 (2.2%)                                            | 1 (1.1%)              | 3 (3.3%)‡                               | p=0.2424                 | 4 (13.3%)                                      |
| Death, n (%)             | 5 (5.5%)                                            | 8 (8.8%)              | 10 (21.3%)                               | p=0.0937                 | 0 (0.0%)                                       |
| Combined Endpoint, n (%) | 8 (8.8%)                                            | 10 (11.0%)            | 18 (19.8%)                               | p=0.0281                 | 5 (16.6%)                                      |

* 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.
‖ Contemporaneous control patients were treated with: phenprocoumon, 11 (23.4%); acetylsalicylic acid, 5 (10.6%), and no treatment, 31 (66.0%).
Figure 1a

APTT in patients with bleeding event vs. APTT in patients without bleeding event

Figure 1b

Lepirudin plasma level – patients with bleeding event vs. patients without bleeding event

Figure 1c

Serum creatinine – patients with bleeding event vs. patients without bleeding event
Figure 2

![Graph showing time after start of lepirudin treatment vs. lepirudin plasma level µg/L.](image-url)
Figure 3

TAT complex levels

- 48 – 0 h
- patients with HIT and isolated thrombocytopenia

48.9

377.8

4 h (+/-2h)
- patients with HIT and thrombosis
- patients with HIT and isolated thrombocytopenia
- patients with HIT and thrombosis

0 20 40 60 80 100 120 140

TAT complexes µg/L
Figure 4a

Cumulative incidences of combined endpoint

<table>
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<tr>
<th>days after start of selected treatment</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
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</thead>
<tbody>
<tr>
<td>patients at risk</td>
<td>91</td>
<td>85</td>
<td>78</td>
<td>70</td>
<td>55</td>
<td>35</td>
<td>19</td>
<td>8</td>
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<tr>
<td>lepirudin</td>
<td>47</td>
<td>38</td>
<td>32</td>
<td>22</td>
<td>16</td>
<td>11</td>
<td>8</td>
<td></td>
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<tr>
<td>control group</td>
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</table>

p=0.0281
Figure 4b

Cumulative incidences of major bleeding

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<th>91</th>
<th>83</th>
<th>76</th>
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<td>32</td>
<td>22</td>
<td>15</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

days after start of selected treatment

p=0.5419

lepirudin
control group
Lepirudin for prophylaxis of thrombosis in patients with acute isolated heparin-induced thrombocytopenia: an analysis of three prospective studies

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

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