Treatment of Heparin-Induced Thrombocytopenia
A Critical Review

Jack Hirsh, MD, FRCPC, FRACP, FRSC, DSc; Nancy Heddle, MSc; John G. Kelton, MD

Heparin-induced thrombocytopenia (HIT) is a serious complication of heparin therapy that has a high rate of morbidity (thrombosis and amputation) and mortality. In the past, a number of different anticoagulants have been used to treat HIT in an attempt to prevent these complications. More recently, direct thrombin inhibitors have become popular. This systematic review summarizes the risk for thrombosis in HIT patients when heparin therapy is stopped; evidence of the efficacy of thrombin inhibitors in patients with HIT with and without thrombosis; evidence supporting the use of thrombin inhibitors in patients with a history of HIT who require a coronary intervention procedure; and the risk for bleeding when antithrombotic agents are used.

Heparin-induced thrombocytopenia (HIT) is a serious complication of heparin therapy. During the past decade, considerable progress has been made in diagnosing HIT and understanding its pathophysiology; more recently, a number of alternative strategies for treating HIT have been evaluated. In this article, we will review studies that have evaluated new anticoagulants as replacements for heparin in patients with HIT.

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The rationale for using novel anticoagulants in patients with HIT is based on the observation that HIT is caused by heparin-dependent IgG antibodies (HIT-IgG) that bind to a confirmationally modified epitope on platelet factor 4. The binding of heparin and other glycosaminoglycans to platelet factor 4 alters its shape, rendering it immunogenic. The IgG/platelet factor 4/heparin immune complexes bind to platelets through the platelet Fc receptors. The occupancy of these platelet Fc receptors activates intracellular protein kinases, thereby initiating platelet activation, platelet aggregation, and the generation of platelet-derived microparticles. These microparticles are procoagulant, and it is likely that they trigger the thrombotic complications of HIT.

Studies have shown that the morbidity and mortality of HIT are consequences of the venous and arterial thrombi that characterize the disorder. These thrombi, in turn, result from intense thrombin activity in patients with HIT, an observation that provides the rationale for using thrombin inhibitors in these patients.

When HIT is suspected clinically in a patient who has had an acute thrombotic event (HIT and thrombotic syndrome [HITTS]), it is standard practice to stop heparin therapy and replace it with an anticoagulant therapy that does not cross-react with the HIT-IgG.

Recently, an alternative anticoagulant to heparin has been suggested for use in those HIT patients who have thrombocytopenia with no clinically overt evidence of thrombosis. This suggestion is based on evidence that if left untreated, these patients are at high risk for development of a thrombotic event in the ensuing days.

A number of anticoagulants have been used in patients with HIT, including warfarin sodium, dextran, ancrod, low-
molecular-weight heparin, and heparin-like agents such as danaparoid sodium. It is now known that warfarin can be dangerous if substituted for heparin in patients with acute HIT, because it can lead to venous gangrene. Dextran is a weak antithrombotic agent in the setting of acute venous or arterial thrombosis. Anecdot is no longer used in HIT patients, because it does not have thrombin-inactivating activity. Low-molecular-weight heparin should not be used because of cross-reactivity with HIT-IgG. Danaparoid has been used in the treatment of HIT patients, although it exhibits cross-reactivity (in vitro) in 10% to 20% of patients with HIT. Danaparoid is no longer available in the United States for treatment of HIT, but is still available in other countries. In recent years, treatment options for HIT have increased because of the approval in the United States of 2 direct thrombin inhibitors, hirudin (lepirudin) and argatroban.

In this review, we will address the following questions: (1) What is the risk for thrombosis in a patient who has isolated HIT when heparin therapy is discontinued? (2) What is the evidence of the efficacy of thrombin inhibitors in patients with HIT and HITTS? (3) What is the evidence supporting the use of thrombin inhibitors in patients with a history of HIT who require a coronary intervention procedure? and (4) What is the risk for bleeding complications with each antithrombotic agent?

### METHODS

The search for relevant articles was performed in Gateway and EMBASE. The Gateway search engine included MEDLINE/PubMed, OLDMEDLINE, LOCATORplus, MEDLINEplus, DLRLINE, AIDS Meetings, Health Services Research Meetings, Space Life Sciences Meetings, and HSRProj. The search terms used in each database included heparin-induced thrombocytopenia combined with diagnosis, treatment, or natural history in the title or as a text word. The search was restricted to English-language publications and human and clinical studies. All citations from each search strategy were downloaded into a Reference Manager database (Thomson ISI ResearchSoft, Carlsbad, Calif), and the individual databases were combined to remove duplicate citations. The titles and abstracts of the citations in the final database were reviewed independently by 2 individuals (N.H. and a research assistant), and each abstract was coded as relevant or irrelevant, with the relevant articles further coded according to diagnosis, treatment, natural history, and laboratory testing or review article. All relevant articles within each of these 5 categories were retrieved in full. The reference citations in the review articles published back to the year 2000 were also reviewed to identify any additional articles about treatment that may not have been identified by the search strategy described.

### RESULTS

A total of 999 potentially relevant citations were identified in the database of publications. Through the title and abstract review process, 86 articles were identified that dealt with treatment options in HIT. After review of these articles, 9 were identified as meeting the predefined criteria for inclusion in this review. The eligible articles included 1 study that provided information about the prothrombotic nature of HIT; 3 studies that provided information about the risk for thrombosis in HIT patients who are left untreated (Table 1); 3 studies that evaluated the efficacy of lepirudin (Table 2); and 1 study that evaluated the efficacy of argatroban (Table 3).

<table>
<thead>
<tr>
<th>Table 1. Summary of 3 Studies That Provide Information About the Risk for a Subsequent Thrombotic Event in Patients With HIT Who Present Initially With Only Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Criteria</strong></td>
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<td><strong>Purpose</strong></td>
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<td><strong>Design</strong></td>
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<td><strong>Patients</strong></td>
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<td><strong>Treatment</strong></td>
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<td><strong>Outcome, No. (%)</strong></td>
</tr>
<tr>
<td>New thrombosis</td>
</tr>
<tr>
<td>Overall risk for thrombosis</td>
</tr>
</tbody>
</table>

Abbreviations: HIT, heparin-induced thrombocytopenia; HITTS, HIT and thrombotic syndrome.

<sup>a</sup>Includes thrombolytics (n = 4), plasmapheresis (n = 3), dextran (n = 17), gamma globulin (n = 1), low-molecular-weight heparin (n = 1), danaparoid sodium (n = 1), hirudin (n = 1), and bivalirudin (Hirulog; n = 1).
Table 2. Summary of Studies of Patients With HIT and HITTS Who Were Prospectively Treated With Lepirudin

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>Assessment of clinical outcomes in HIT and HITTS patients compared with historical controls</td>
<td>Assessment of clinical outcomes in HIT and HITTS patients compared with historical controls</td>
<td>Combined analysis of data from the 2 previous studies to assess clinical outcomes in patients with HITTS</td>
</tr>
<tr>
<td>Design</td>
<td>Multicenter prospective cohort with historical controls</td>
<td>Multicenter prospective cohort with historical controls</td>
<td>Same data as in the 2 previous studies, with analysis restricted to patients with HITTS</td>
</tr>
<tr>
<td>Patient population*</td>
<td>HITTS (n = 56), HIT no thrombosis (n = 18), CPBS (n = 8), total n = 82; 71 included in comparison</td>
<td>HITTS (n = 69), HIT no thrombosis (n = 43), total n = 112; 95 included in comparison</td>
<td>HITTS patients from control group in the 2 previous studies (n = 75)</td>
</tr>
<tr>
<td>Hirudin group</td>
<td>Confirmed HIT (with or without thrombosis), treated 1989-1993 (n = 120)</td>
<td>Confirmed HIT, taken from central registry (1989-1995) (n = 120)</td>
<td>Confirmed HITTS patients from control group in the 2 previous studies (n = 75)</td>
</tr>
<tr>
<td>Historical controls</td>
<td>Day of laboratory confirmation until end of observation period, and during the time of first selected active treatment</td>
<td>Information not provided</td>
<td>Information not provided</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2 wk After stopping lepirudin</td>
<td>2 wk After stopping lepirudin</td>
<td>2 wk After stopping lepirudin</td>
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<tr>
<td>Lepirudin group</td>
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<tr>
<td>Historical controls</td>
<td>2 wk After stopping lepirudin</td>
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<tr>
<td>Outcome measures</td>
<td>Frequency of composite outcome† and frequencies of the individual components</td>
<td>Frequency of composite outcome† and frequencies of the individual components</td>
<td>Frequency of composite outcome† and frequencies of the individual components</td>
</tr>
</tbody>
</table>

Abbreviations: CPBS, cardiopulmonary bypass surgery; HIT, heparin-induced thrombocytopenia; HITTS, heparin-induced thrombocytopenia and thrombotic syndrome.

*Inclusion criteria consisted of a clinical diagnosis of HIT and detectable heparin-dependent IgG antibodies.
†Includes death, amputation, and new thromboembolic events.

RISK FOR THROMBOSIS IN PATIENTS WITH HIT WHEN HEPARIN THERAPY IS DISCONTINUED

Theoretically, patients with HIT and no evidence of thrombosis at presentation remain at risk for thrombosis until the prothrombotic risk is dissipated. Information about the prothrombotic nature of HIT is provided by 1 prospective and 3 retrospective studies (Table 1).12-14 In the prospective study by Warkentin et al,11 665 patients undergoing hip surgery were treated with unfractionated heparin or low-molecular-weight heparin, and venograms were performed 7 to 10 days after surgery. The performance of daily platelet counts identified 9 patients who developed HIT, and 8 (89%) of the 9 had venographic evidence of thrombosis. All HIT patients with thrombosis were within the unfractionated heparin arm of the study. In contrast, among the 656 patients without HIT, only 117 (18%) developed thrombosis (odds ratio, 37; 95% confidence interval [CI], 4.8-1638.0; P<.001). This study emphasizes the prothrombotic nature of HIT, but the reported risk and odds ratio are not generalizable to all patients with isolated HIT, because the baseline risk for thrombosis is high in patients undergoing hip surgery, despite prophylaxis with low doses of heparin.

Estimates of the risk for clinically overt thrombosis when heparin therapy is discontinued in patients with isolated HIT (without thrombosis) is provided from 3 reports.12-14 The data summarized in Table 1 indicate that the risk for thrombosis in patients with HIT in whom heparin therapy is discontinued ranges from 19% to 52%.

Warkentin and Kelton13 performed a retrospective medical chart review of 62 patients with isolated HIT at presentation to determine the 30-day frequency of thrombosis when heparin therapy was stopped. Some of the patients were treated with warfarin. The frequency of thrombosis was 51.6% at 30 days and did not appear to be influenced by substituting warfarin for heparin. Lower estimates of the risk for thrombosis after cessation of heparin therapy were ob-
tained from 2 other studies. Wallis et al14 performed a retrospective medi-
cal chart review of 121 consecutive patients with HIT. Eight were ex-
cluded. Of the remaining 113 patients, 59% underwent cardiopulmo-
nary bypass surgery. Clinically apparent thrombosis was con-
firmed during hospital admission by objective methods, at surgery, or post 
mortem in 43 (38.0%) of 113 patients with HIT. In 21 patients 
(18.6%), thrombosis developed more than 24 hours after stopping hepa-
rin therapy (mean time, 4 days). Therefore, a conservative estimate of 
the risk for development of throm-
bosis after stopping heparin therapy would be 18.6%, since it is possible 
that subclinical thrombi were present 
in some patients at the time when heparin therapy was stopped. In their 
evaluation of argatroban therapy in patients with HIT thrombosis, Lewis 
et al15 compared outcome measures with those of a historical control 
group of 139 consecutive HIT pa-
patients. In 32 controls (23.0%), evi-
dence of clinically overt thrombosis developed during a follow-up pe-
period of 37 days.

In summary, the available evi-
dence indicates that the risk for throm-
bosis in the days to weeks after stop-
ning heparin therapy is at least 20% 
and possibly as high as 50% in HIT pa-
patients who present with isolated 
thrombocytopenia. This evidence sup-
ports the view that alternate therapy 
with a rapidly acting anticoagulant 
should be initiated when the heparin 
therapy is discontinued.

EVIDENCE OF THE EF FICACY 
OF THROMBIN INHIBITORS 
FOR HIT AND HITTS

The following 3 antithrombotic 
agents have been evaluated in pa-
ients with HIT and HITTS: argatro-
ban, lepirudin, and danaparoid. As 
indicated previously, the danapa-
roid studies failed to meet the cri-
teria for inclusion in this review. In 
some of the studies assessing the 
thrombin inhibitors, the results 
were analyzed by subgroup (HIT and 
HITTS), thereby allowing the mor-
bidity and mortality to be assessed 
separately for each group. In other 
studies, results were presented only 
as aggregate data.

HITTS Patients

Argatroban. The 2 prospective co-
hort studies by Lewis et al14,15 pro-
vide information about the fre-
morbidit y and mortality in 
HIT patients who are treated with ar-
gatroban. Both multicenter studies in-
cluded a prospective cohort of pa-
tients treated with argatroban and 
compared the results with those of a 
group of historical controls. Pa-
tients were eligible for argatroban 
treatment if they had a clinical diag-
nosis of HIT or were known to have a 
history of HIT. The design features 
and results of these 2 studies are 
summarized in Table 3. In the first 
study, which had 307 patients, 160 
received argatroban, and there were 
471 historical controls. The com-
bined outcomes of death, amputa-
tion, and new thromboembolic 
events (TECs) occurred in 25.6% of 
argatroban-treated patients and 
38.8% of controls (relative risk 
reduction [RRR], 0.34). The individ-
ual outcomes within the compo-
site for the argatroban and control 
groups were death in 16.9% and 
21.8%, respectively (RRR, 0.22); am-
putation in 1.9% and 2.0%, respec-
tively (RRR, 0.08); and new TECs in 
8.1% and 22.4%, respectively (RRR, 
0.64).16 In the second study,17 328 pa-
tients were studied. Of these, 189 
received argatroban, and the out-
comes in these patients were 
compared with those observed in 139 
historical controls. The historical con-
trols were from the same pool of con-
trol patients used in the first study, 
with each participating center enroll-
ment up to 3 controls for each argatro-
ban patient studied. The composite 
outcome occurred in 28.0% of ar-
gatroban-treated patients and 38.9% 
of controls (RRR, 0.28). Individual 
outcomes in the argatroban and con-
trol groups were death in 19.0% and 
20.9%, respectively (RRR, 0.09); am-
putation in 4.2% and 2.9%, respec-
tively (RRR, −0.49), and new TECs in 
5.8% and 23.0%, respectively 
(RRR, 0.75). These results are sum-
marized in Table 4.

Table 3. Summary of the 2 Studies Using Argatroban as a Treatment 
for Patients With HIT and HITTS

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>Evaluate the efficacy and safety of argatroban in patients with HIT and HITTS</td>
<td>Evaluate the efficacy and safety of argatroban in patients with HIT and HITTS</td>
</tr>
<tr>
<td>Design</td>
<td>Multicenter prospective observational study, comparison with historical controls</td>
<td>Multicenter prospective observational study, comparison with historical controls</td>
</tr>
<tr>
<td>Patient population*</td>
<td>HITTS (n = 144), HIT no thrombosis (n = 160), total, n = 304</td>
<td>HITTS (n = 46), HIT no thrombosis (n = 189), total, n = 418</td>
</tr>
<tr>
<td>Control group</td>
<td>HITTS (n = 46), HIT no thrombosis (n = 147), total, n = 193</td>
<td>HITTS (n = 229), HIT no thrombosis (n = 139), total, n = 368</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Start of treatment and 30 d after treatment</td>
<td>Start of treatment and 30 d after treatment</td>
</tr>
<tr>
<td>Argatroban group Control group</td>
<td>Start of treatment and 30 d after treatment</td>
<td>37 d from baseline (date heparin was stopped after platelet count met inclusion criteria or that platelet count met inclusion criteria after heparin initiation)</td>
</tr>
<tr>
<td>Outcome measures Frequency of composite outcome and the individual components calculated separately for HIT and HITTS</td>
<td>Frequency of composite outcome and the individual components calculated separately for HIT and HITTS</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HIT, heparin-induced thrombocytopenia; HITTS, heparin-induced thrombocytopenia and thrombotic syndrome. 
*Inclusion criteria consisted of a clinical diagnosis of HIT. 
†Includes death, amputation, and new thromboembolic events.
HITTS. The comparisons in each study were made with a historical control group of consecutive patients with HITTS assembled within 4 years of the first trial. The controls for both studies were the same group of 46 matched historical controls. The first study enrolled 190 patients, including 144 argatroban-treated patients and 46 controls. The composite outcome occurred in 43.8% of the argatroban-treated patients and 56.5% of the control patients (RRR, 0.23). Frequencies of the individual outcomes in the argatroban and control groups were death in 18.1% and 28.3%, respectively (RRR, 0.36); amputation in 11.1% and 8.7%, respectively (RRR, −0.28); and new TECs in 19.4% and 34.8%, respectively (RRR, 0.44).18 (Table 5). The second study by Lewis et al14 had a larger cohort of argatroban-treated patients (total enrollment of 275 patients, including 229 argatroban-treated patients and 46 historical controls). The composite outcome occurred in 41.5% of argatroban-treated patients and 56.5% of controls (RRR, 0.27). Frequencies of the individual outcome components in the argatroban and control groups were death in 23.1% and 28.3%, respectively (RRR, 0.18); amputation in 14.8% and 10.9%, respectively (RRR, −0.37); and new TECs in 13.1% and 34.8%, respectively (RRR, 0.62) (Table 5).

**Lepirudin.** Two prospective observational studies described the effect of lepirudin treatment in patients with HIT and HITTS.15,16 Patients were eligible for the prospective studies if they had a clinical diagnosis of HIT or HITTS and HIT IgG detected in their plasma. The outcomes documented in these 2 prospective studies included death, amputation, and new TECs. The frequencies of outcomes observed in a subgroup of the lepirudin-treated patients followed in the prospective study, and were then compared with those of a group of historical controls. The controls were treated with the best available care in a 4-year period before lepirudin was used (1989–1993). For the comparison with historical controls, specific entry criteria were applied to the lepirudin-treated patients and controls in an attempt to ensure similar prognostic and baseline characteristics between the 2 groups. In a subsequent publication, a summary of outcomes in the patients with a diagnosis of HITTS was presented by combining the patients with HITTS from the 2 previous studies.17 The results of this subanalysis were compared with those of the historical controls with a diagnosis of HITTS. One hundred eighty-eight patients were included in this subgroup analysis, including 113 patients receiving lepirudin and 75 historical controls. The combined outcomes (death, amputation, and new TECs) occurred in 22.1% of lepirudin-treated patients and 47.8% of controls (RRR, 0.53). The individual outcomes within the composite for the lepirudin-treated patients and controls were death in 9.7% and 17.6%, respectively (RRR, 0.44); amputation in 6.2% and 10.4%, respectively (RRR, 0.42); and new TECs in 9.7% and 27.2%, respectively (RRR, 0.60). These results are summarized in Table 5.

**Patients With HIT and/or HITTS**

Some of the publications describing the use of thrombin inhibitors in patients with HIT and HITTS presented the findings for the combined group of HIT and HITTS patients, but did not provide a separate analysis for the 2 subgroups.

**Argatroban.** The 2 prospective studies by Lewis et al14,18 using argatroban in patients with HIT and HITTS presented the data by subgroup. However, the completeness of the data presented made it possible to combine data from both groups to present an analysis of the outcomes observed for a cohort of HIT and HITTS patients (Table 6).

In the first study, the 497 patients included 304 treated with argatroban and 193 controls. The argatroban-treated group consisted of 53% patients with HIT and 47% with HITTS. The historical controls consisted of 76% HIT patients and 24% HITTS patients. When patients from the first study with HIT and HITTS were combined, the composite outcome occurred in 34.2% of argatroban-treated patients and 43.0% of the controls (RRR, 0.20). The frequencies of the individual components of the composite outcome were death in 17.4% and 23.3%, respectively (RRR, 0.25); amputation in 6.2% and 3.6%, respectively (RRR, −0.72); and new TECs in 13.5% and 25.4%, respectively (RRR, 0.47).18 In the second study, a total of 418 HIT and HITTS patients were treated with argatroban, with 185 controls.14 In the argatroban group, 45.2% of the patients had HIT and 54.8% had HITTS. In the historical controls, 75.1% of the patients had HIT and 24.9% had HITTS. When the 2 groups were analyzed together, the combined outcome occurred in 35.4% of argatroban-treated patients and 43.2% in the controls (RRR, 0.18). The frequencies of the individual components of the composite outcome for the argatroban-

### Table 4. Summary of the Frequencies of the Composite and Individual Outcome Measures in Patients With HIT Treated With Argatroban

<table>
<thead>
<tr>
<th>Outcome Measure, Treatment Group, No. (%)</th>
<th>Active Treatment</th>
<th>Historical Controls</th>
<th>Relative Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite end point</td>
<td>Argatroban (Lewis et al15) 41/160 (25.6)</td>
<td>57/147 (38.8)</td>
<td>0.34 (0.06 to 0.54)</td>
</tr>
<tr>
<td></td>
<td>Argatroban (Lewis et al15) 53/189 (28.0)</td>
<td>54/139 (38.9)</td>
<td>0.28 (−0.003 to 0.48)</td>
</tr>
<tr>
<td>Death</td>
<td>Argatroban (Lewis et al15) 27/160 (16.9)</td>
<td>32/147 (21.8)</td>
<td>0.22 (−0.27 to 0.53)</td>
</tr>
<tr>
<td></td>
<td>Argatroban (Lewis et al15) 36/189 (19.0)</td>
<td>29/139 (20.9)</td>
<td>0.09 (−0.57 to 0.46)</td>
</tr>
<tr>
<td>Amputation</td>
<td>Argatroban (Lewis et al15) 4/160 (2.5)</td>
<td>4/147 (2.7)</td>
<td>0.62 (−0.047 to 0.59)</td>
</tr>
<tr>
<td>TEC</td>
<td>Argatroban (Lewis et al15) 33/160 (20.6)</td>
<td>32/147 (21.8)</td>
<td>0.38 (−0.027 to 0.59)</td>
</tr>
<tr>
<td></td>
<td>Argatroban (Lewis et al15) 35/189 (18.5)</td>
<td>31/139 (22.6)</td>
<td>0.40 (0.027 to 0.81)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HIT, heparin-induced thrombocytopenia; TEC, new thromboembolic event.
Table 5. Summary of the Frequencies of the Composite and Individual Outcome Measures in Patients With HITTS Treated With Argatroban and Lepirudin

<table>
<thead>
<tr>
<th>Outcome Measure, Treatment (Reference)</th>
<th>Treatment Group, No. (%)</th>
<th>Relative Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite end point</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>63/144 (43.8)</td>
<td>0.23 (−0.12 to 0.43)</td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>95/229 (41.5)</td>
<td>0.27 (−0.05 to 0.44)</td>
</tr>
<tr>
<td>Lepirudin (Greinacher et al15)</td>
<td>25/113 (22.1)</td>
<td>0.53 (0.28 to 0.70)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>26/144 (18.1)</td>
<td>0.36 (−0.23 to 0.65)</td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>53/229 (23.1)</td>
<td>0.18 (−0.49 to 0.51)</td>
</tr>
<tr>
<td>Lepirudin (Greinacher et al15)</td>
<td>11/113 (9.7)</td>
<td>0.44 (−0.27 to 0.75)</td>
</tr>
<tr>
<td>Amputation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>16/144 (11.1)</td>
<td>0.28 (−3.43 to 0.57)</td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>34/229 (14.8)</td>
<td>0.37 (−2.88 to 0.44)</td>
</tr>
<tr>
<td>Lepirudin (Greinacher et al15)</td>
<td>7/113 (6.2)</td>
<td>0.42 (−0.70 to 0.80)</td>
</tr>
<tr>
<td>TEC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>28/144 (19.4)</td>
<td>0.44 (−0.004 to 0.67)</td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>30/229 (13.1)</td>
<td>0.62 (0.32 to 0.78)</td>
</tr>
<tr>
<td>Lepirudin (Greinacher et al15)</td>
<td>11/113 (9.7)</td>
<td>0.60 (0.20 to 0.81)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HITTS, heparin-induced thrombocytopenia and thrombotic syndrome; TEC, new thromboembolic event.

The frequencies of these events were reported in the study, and the actual number of patients with each event was calculated using the n = 75.

Table 6. Summary of the Frequencies of the Composite and Individual Outcome Measures in Patients With HIT and HITTS Treated With Argatroban and Lepirudin

<table>
<thead>
<tr>
<th>Outcome Measure, Treatment (Reference)</th>
<th>Treatment Group, No. (%)</th>
<th>Relative Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite end point</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>104/304 (34.2)</td>
<td>0.20 (−0.01 to 0.37)</td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>148/418 (35.4)</td>
<td>0.18 (−0.03 to 0.34)</td>
</tr>
<tr>
<td>Lepirudin (Greinacher et al15)</td>
<td>18/71 (25.4)</td>
<td>0.52 (0.25 to 0.70)</td>
</tr>
<tr>
<td>Lepirudin (Greinacher et al15)</td>
<td>29/95 (30.5)</td>
<td>0.42 (0.17 to 0.60)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>53/304 (17.4)</td>
<td>0.25 (−0.09 to 0.48)</td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>89/418 (21.3)</td>
<td>0.06 (−0.33 to 0.33)</td>
</tr>
<tr>
<td>Lepirudin (Greinacher et al15)</td>
<td>6/71 (8.5)</td>
<td>0.65 (0.18 to 0.87)</td>
</tr>
<tr>
<td>Lepirudin (Greinacher et al15)</td>
<td>10/95 (10.5)</td>
<td>0.56 (0.13 to 0.79)</td>
</tr>
<tr>
<td>Amputation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>19/304 (6.2)</td>
<td>−0.72 (−3.46 to 0.30)</td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>42/418 (10.0)</td>
<td>−1.07 (−3.50 to 0.004)</td>
</tr>
<tr>
<td>Lepirudin (Greinacher et al15)</td>
<td>4/71 (5.6)</td>
<td>0.32 (−1.24 to 0.82)</td>
</tr>
<tr>
<td>Lepirudin (Greinacher et al15)</td>
<td>9/95 (9.5)</td>
<td>−0.14 (−1.92 to 0.56)</td>
</tr>
<tr>
<td>TEC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban (Greinacher et al15)</td>
<td>41/304 (13.5)</td>
<td>0.47 (0.21 to 0.64)</td>
</tr>
<tr>
<td>Argatroban (Lewis et al14)</td>
<td>41/418 (9.8)</td>
<td>0.62 (−0.44 to 0.75)</td>
</tr>
<tr>
<td>Lepirudin (Greinacher et al15)</td>
<td>13/71 (18.3)</td>
<td>0.42 (−0.03 to 0.69)</td>
</tr>
<tr>
<td>Lepirudin (Greinacher et al15)</td>
<td>17/95 (17.9)</td>
<td>0.43 (0.04 to 0.68)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HIT, heparin-induced thrombocytopenia; HITTS, heparin-induced thrombocytopenia and thrombotic syndrome; TEC, new thromboembolic event.

of the studies compared outcomes in a subgroup of the lepirudin-treated patients with those documented in a group of historical controls. The proportions of the patients with HIT and HITTS in the 2 studies were not provided. The same controls were used for both studies. In the first prospective study, the composite outcome (death, amputation, and new TECs) occurred in 18.3% of lepirudin-treated patients, including death in 7.3%, amputation in 3.7%, and new TECs in 9.8%. In the second prospective study, 29.5% of lepirudin-treated patients had the combined outcomes of death in 9.8%, amputation in 8.9%, and new TECs in 17.9%. In the second analysis, when a subgroup of the lepirudin-treated patients was compared with a historical control group, the combined outcome was present in 25.4% of the lepirudin-treated patients in the first study and 30.5% of lepirudin-treated patients in the second study. The combined outcome was present in 52.5% of controls, giving an RRR of 0.52 for the first study and 0.42 for the second study. Death occurred in 8.5% of lepirudin-treated patients in the first study, 10.5% of lepirudin-treated patients in the second study, and 24.2% of controls (RRRs, 0.65 and 0.56, respectively). In the first study, 5.6% patients treated with lepirudin ultimately underwent a limb amputation, compared with 8.3% of the controls (RRR, 0.32). For the second study, the percentages with amputation were 9.5% (lepirudin-treated patients) and 8.3% (controls), for an RRR of −0.14. New TECs occurred in 18.3% and 17.9% of lepirudin-treated patients (first and second studies, respectively) and in 31.7% of controls (RRRs, 0.42 and 0.43 respectively).

USE OF THROMBIN INHIBITORS IN PATIENTS WITH A HISTORY OF HIT WHO REQUIRE ANTICOAGULATION FOR CORONARY REVASCULARIZATION

Lewis and associates reported the results of a pooled analysis of 3 prospective studies totaling 91 patients with a history of HIT who un-
derwent 112 elective, urgent, or emergency percutaneous coronary revascularization procedures. The outcome measures were death, myocardial infarction, or revascularization at 24 hours or at hospital discharge. The use of glycoprotein Iib/IIia antagonists was disallowed. The overall event rate was 7.7%, consisting of no deaths, 4 cases of myocardial infarction, and 4 cases of revascularization. The rate of major bleeding was 1.1%. These event rates are consistent with those observed in patients undergoing coronary angioplasty without a history of HIT who are treated with conventional antithrombotic therapy.22

SAFETY OF ANTITHROMBOTIC AGENTS: RISK FOR BLEEDING

The adverse effects associated with argatroban and lepirudin treatment in patients with HIT and HITTS were also assessed.

In the studies by Lewis et al,14,18 major bleeding was defined as being overt and associated with a hemoglobin level decrease of at least 0.2 g/dL that led to a transfusion of at least 2 U of blood, or bleeding that was intracranial, retroperitoneal, or into a prosthetic joint. In the first study, major bleeding occurred in 6.9% of argatroban-treated patients and 6.7% of controls (RRR, -2.56).18 In the second study, the frequencies were 5.7% (argatroban group) and 7.0% (control group), for an RRR of 18.2.14 The frequency of bleeding by the HIT and HITTS subgroups is summarized in the Figure. In the studies using lepirudin, a similar definition of major bleeding was used. In the first lepirudin observational study,13,16 the authors reported that 13.4% of patients receiving lepirudin had major bleeding. In the second observational study, 17.0% of patients treated with lepirudin had major bleeding.16 Neither study reported bleeding outcomes separately for the HIT and HITTS subgroups, and the incidence of major bleeding in the control group was not stated. In the third report by Greinacher et al,17 in which data from HITTS patients in the 2 previous studies were combined, the cumulative incidence of bleeding that required transfusion was higher in the lepirudin-treated group compared with the historical controls (18.8% and 7.1%, respectively) (Figure).

COMMENT

Heparin-induced thrombocytopenia is an important complication of heparin therapy. Studies performed in the past decade have enhanced our knowledge and understanding of the presentation and pathophysiology of HIT and the causes of morbidity and mortality in HIT patients. In typical cases, HIT presents 1 week after the start of heparin therapy and can present as thrombocytopenia (HIT) or thrombocytopenia plus thrombotic complications (HITTS). These thrombi are major causes of morbidity and mortality in HIT, which can include myocardial infarction, stroke, arterial and venous thrombosis, and pulmonary embolism. The clinical observations in HIT have been paralleled by laboratory studies, which have shown that HIT is an intensely thrombotic disorder with evidence of uncontrolled thrombin generation.2 For these reasons, a number of new antithrombotic agents have been evaluated in patients with HIT. The purpose of this report was to provide a critical review of these clinical studies.

At present, the following 3 drugs are approved in a number of countries for the treatment of HIT: danaparoid, argatroban, and lepirudin. Danaparoid (Organon, Roseland, NJ) is a heparinoid derived from porcine intestinal mucosa, composed of heparin sulfate, with lesser amounts of dermatan sulfate and chondroitin sulfate. It is a heparinoid derived from porcine intestinal mucosa, composed of heparin sulfate, with lesser amounts of dermatan sulfate and chondroitin sulfate. Its mechanism of action is the inhibition of factor Xa, with lesser effects on factor IIa. It exhibits in vitro cross-reactivity with the antibody causing HIT (HIT-IgG) in about 20% of cases. Although in vivo cross-reactivity is uncommon, it can occur.

Argatroban and lepirudin are direct thrombin inhibitors. Both are active against soluble and clot-bound thrombin, with lepirudin having a higher thrombin-binding affinity than argatroban. Argatroban is a small (molecular weight, 526.6 Da) synthetic peptide derived from L-arginine. It has a half-life of about 45 minutes, with clearance primarily through the liver and minimal renal clearance. At a dosage of 2 µg/kg per minute, most patients quickly achieve therapeutic blood levels as measured by 1.5 to 3 times the baseline activated partial thromboplastin time.

Lepirudin is a 65–amino acid peptide with a molecular weight of approximately 7000 Da. Originally extracted from leeches, lepirudin is now produced as a recombinant polypeptide. It is given intravenously as a bolus dose followed by a constant infusion dosage of 0.15 mg/kg per hour adjusted to prolong the activated partial thromboplastin time ratio to 2 to 3.
Lepirudin has a half-life of 60 to 90 minutes, with elimination primarily through the kidneys.

As a first step in our analysis, we used a comprehensive search process. Although a large number of studies were initially identified, only a few met eligibility criteria. Indeed, we were unable to identify any well-designed randomized controlled trials that evaluated different treatments for HIT. The absence of randomized trials in this area probably reflects the recent introduction of these thrombin inhibitors for the management of HIT and ethical concerns of conducting placebo-controlled trials in patients with HITTS. Consequently, all conclusions are limited regarding the value of the direct thrombin inhibitors for the treatment of HIT and HITTS. Specifically, valid comparisons between event rates in the active treatment and historical control groups or between the 2 direct thrombin inhibitors cannot be made.

In this report, we examined the following 4 issues related to the treatment of patients with HIT: the risk for subsequent thrombosis in patients with HIT in whom the heparin therapy is discontinued; the efficacy of thrombin inhibitors in patients with HIT and HITTS; the use of thrombin inhibitors in patients with a history of HIT who require a coronary intervention; and the risk for bleeding associated with these therapies.

Three retrospective studies examined the risk for thrombosis when heparin therapy was discontinued in patients with HIT (Table 1). The results of all 3 studies are consistent and indicate that when patients with HIT have their heparin therapy discontinued and are treated with warfarin or no therapy, 18.6% to 51.6% of them are at risk for a subsequent thrombosis. The highest frequency (51.6%) probably reflects the high baseline risk for thrombosis in this study population of orthopedic patients. The frequencies of thrombosis reported in the other 2 studies were similar and probably give realistic estimates (18.6%–23.0%) for a more general population of HIT patients. These studies indicate that an alternate anticoagulant is needed when heparin therapy is discontinued in a patient with HIT.

Before the availability of thrombin inhibitors, other types of anticoagulants were frequently used in patients with HIT or HITTS when heparin therapy was discontinued. Estimates of morbidity and mortality associated with these anticoagulants can be obtained from the event frequencies reported in the historical controls used in the argatroban and lepirudin studies. Death was reported in approximately 23% of patients, amputation in 4% to 8% of patients, and new TECs in 25% to 32% of patients. The frequency of the composite outcome varied from 43% to 52.5%.

The evidence of the efficacy of thrombin inhibitors in patients with HIT and HITTS is based on 2 prospective studies that evaluated argatroban and 2 that evaluated lepirudin. The 2 studies by Lewis and associates using argatroban were the only prospective studies reporting the efficacy of a thrombin inhibitor in patients with HIT alone. In 349 argatroban-treated patients with HIT, the adverse outcome was high at 25.6%, with death occurring in 16.9% of patients, amputation in 1.9%, and new TECs in 8.1%. Although these event rates were lower than in the historical controls, the lack of a randomly assigned control group makes the validity of any comparison questionable. At present, no data describe the use of lepirudin in patients with HIT.

Three prospective observational studies provide information about the use of a thrombin inhibitor for patients with HITTS. Two of the studies were in patients treated with argatroban, and 1 study described the use of lepirudin in patients with HITTS. Since all 3 studies used historical controls, their main value lies in the descriptive information that they provide of event rates in patients with HITTS who are treated with a direct thrombin inhibitor. In studies using argatroban, the composite outcome of death, amputation, and new TECs occurred in approximately 42.4% of patients. Death was the most frequent of the composite outcomes (18%–23%), whereas the frequencies of new TECs and amputation were similar to those reported in patients with HIT. In the only observational study that evaluated lepirudin in patients with HITTS, the composite outcome occurred in 22.1% of patients (death, 9.7%; amputation, 6.2%; and new TECs, 9.7%). Although these frequencies are lower than those reported by Lewis et al for argatroban in patients with HITTS, it is inappropriate to draw conclusions from these indirect comparisons because baseline factors were likely to be different between the 2 study populations.

Evidence supporting the use of thrombin inhibitors in patients with a history of HIT who require anticoagulation because of a coronary intervention procedure was also assessed. Because these patients no longer have active HIT, complications associated with their treatment would reflect the efficacy of the thrombin inhibitor. Consistent with this hypothesis are the results of Lewis et al, who pooled data from 3 prospective studies of 91 patients with a history of HIT who were treated with argatroban during 112 urgent or emergency coronary revascularization procedures. The outcomes in this patient population were consistent with those of the patients without a history of HIT who were treated with conventional antithrombotic therapy during coronary angioplasty.

Bleeding event rates with direct thrombin inhibitors can be estimated from the argatroban and lepirudin studies. The criteria for major and minor bleeding episodes were similar between the 4 prospective studies. In general, the bleeding rates were high (6%–18%) in patients with HIT and HITTS treated with thrombin inhibitors, a finding that would be expected with anticoagulant therapy in the population under study. In contrast, the risk for bleeding in patients with a history of HIT who are treated with argatroban during coronary interventions is lower (1.1%).

Together, these prospective studies further emphasize that HIT/HITTS is a serious condition that is associated with a high frequency of morbidity and mortality. Even
when HIT/HITTS is treated with direct thrombin inhibitors, 9% to 22% of the patients will die, and an additional 6% to 18% will require amputation or experience development of a new thromboembolic event.

Properly designed randomized trials are needed to determine the relative efficacy and safety of thrombin inhibitors in patients with HIT and HITTS. However, on the basis of observational studies in patients with untreated HIT and of experience with the use of thrombin inhibitors in patients with and without HIT, the following recommendations are suggested. When a diagnosis of HIT or HITTS is suspected, heparin therapy should be stopped and replaced with an effective anticoagulant that does not cross-react with HIT-IgG. Lepirudin and argatroban are effective anticoagulants. Lepirudin is cleared in the urine and accumulates in patients with renal insufficiency. In contrast, argatroban is eliminated by means of hepatic metabolism and excreted in the bile. Therefore, in patients with suspected HIT or a history of HIT who require anticoagulant therapy, argatroban should be used if the patients have renal impairment, and lepirudin should be used in those patients with hepatic dysfunction. The decision to use one or the other in patients with normal renal or hepatic function is one of personal preference.

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Corresponding author: Jack Hirsh, MD, FRCP, FRACP, FRSC, DSc, Henderson Research Centre, 60 Wing, Second Floor, Henderson Hos-

pital, 711 Concession St, Hamilton, Ontario, Canada L8V 1C3 (e-mail: jhirsh@thrombosis.hhsc.org).

REFERENCES

1. Amiril J, Bridye F, Dreyfus M, et al. Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocyto-


2. Kelton JG, Smith JW, Warkentin TE, Hayward CP, Denomme GA, Horsewood P. Immunoglobulin G from patients with heparin-induced thrombocyto-


4. Warkentin TE, Hayward CP, Boshkov LK, et al. Sera from patients with heparin-induced thrombocyto-

topia generate platelet-derived microparticles with procoagulant activity: an explanation for the thrombotic complications of heparin-induced thrombocyto-


5. Boshkov LK, Warkentin TE, Hayward CP, Andrew M, Kelton JG. Heparin-induced thrombocyto-


6. King DJ, Kelton JG. Heparin-associated thrombocyto-


8. Warkentin TE, Elavathil LJ, Hayward CP, John-

ston MA, Russell J, Kelton JG. The pathogen-

esis of venous limb gangrene associated with hepa-


10. Magnani HN. Heparin-induced thrombocyto-


12. Weiss DL, Workman DL, Lewis BE, Steen L, Pi-

farre R, Moran JF. Failure of early heparin cessa-

tion as treatment for heparin-induced thrombo-


13. Warkentin TE, Kelton JG. A 14-year study of hepa-


vestigators. Lepirudin (recombinant hirudin) for parenteral anticoagulation in patients with heparin-


binant hirudin (lepirudin) provides safe and ef-

fective anticoagulation in patients with heparin-


17. Greinacher A, Eichler P, Lubenov N, Kwasny H, Luz M. Heparin-induced thrombocytopoenia with thromboembolic complications: meta-analysis of 2 prospective trials to assess the value of paren-

18. Lewis BE, Walls DE, Berkowitz SD, et al. Argatro-

ban anticoagulant therapy in patients with heparin-


20. Chong BH, Gallus AS, Cade JF, et al. Prospective randomised open-label comparison of danapa-

roid with dextran 70 in the treatment of heparin-


21. Farmer B, Eichler P, Kroll H, Greinacher A. A com-

parison of danaparoid and lepirudin in heparin-

induced thrombocytopoenia. Thromb Haemost.

2001;85:950-957.

22. Pogma JJ, Ohman EM, Weitz J, Lincoff AM, Harr-

ington RA, Berger P. Antithrombotic therapy in patients undergoing percutaneous coronary in-


23. Wilde MI, Markham A. Danaparoid: a review of its pharmacology and clinical use in the manage-


24. Chong BH, Ismail F, Cade J, Gallus AS, Gordon S, Chesterman CN. Heparin-induced thrombocyto-

penia: studies with a new low molecular weight hepa-


25. Keng TB, Chong BH. Heparin-induced thrombo-

cytopoenia and thrombosis syndrome: in vivo cross-reaction with danaparoid and successful treat-


tan (brand of argatroban): a small-molecule, di-


28. Schiele F, Vuilenenot A, Kramarz P, et al. Use of recombinant hirudin as antithrombotic treat-

ment in patients with heparin-induced thrombo-


29. Parent F, Bridye F, Dreyfus M, et al. Treatment of severe venous thrombo-embolism with intrave-
