

The version of the article by Drs Warkentin and Greinacher, originally published in the August 2003 issue of *The Annals of Thoracic Surgery* (76:638–48) was inadvertently printed without the corrections the authors made in proof. The correct article appears here. *The Annals* regrets the error that occurred.

Heparin-Induced Thrombocytopenia and Cardiac Surgery

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Unfractionated heparin given during cardiopulmonary bypass is remarkably immunogenic, as 25% to 50% of postcardiac surgery patients develop heparin-dependent antibodies during the next 5 to 10 days. Sometimes, these antibodies strongly activate platelets and coagulation, thereby causing the prothrombotic disorder, heparin-induced thrombocytopenia. The risk of heparin-induced thrombocytopenia is 1% to 3% if unfractionated heparin is continued beyond the first postoperative week. When cardiac surgery is urgently needed for a patient with

acute or subacute heparin-induced thrombocytopenia, options include an alternative anticoagulant (bivalirudin, lepirudin, or danaparoid) or combining unfractionated heparin with a platelet antagonist (epoprostenol or tirofiban). As heparin-induced thrombocytopenia antibodies are transient, unfractionated heparin alone is appropriate in a patient with previous heparin-induced thrombocytopenia whose antibodies have disappeared.

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Physicians caring for cardiac surgery patients require an understanding of heparin-induced thrombocytopenia (HIT), as this patient population is at relatively high risk for this antibody-mediated, prothrombotic adverse effect of heparin. Indeed, monitoring of the platelet count for HIT is a standard feature of postcardiac surgical care [1]. Nevertheless, only a small minority of thrombocytopenic postcardiac surgery patients actually have HIT, illustrating the need to view HIT as a clinicopathologic syndrome, ie, the diagnosis should be based on both clinical and serologic grounds [1]. The occasional need to perform urgent cardiac surgery in a patient with acute HIT presents the challenge of choosing an appropriate anticoagulant approach among several available options [2]. Our aim is to review HIT in the context of the cardiac surgical patient, and to combine our North American and European perspectives in providing treatment recommendations.

Currently, three anticoagulants are approved for treatment of HIT (United States: lepirudin [3] and argatroban [4]; European Union: danaparoid [5] and lepirudin; Canada: all three agents). However, neither these nor other available nonheparin anticoagulants (bivalirudin [6]) are approved for use during cardiopulmonary bypass (CPB), necessitating off-label use under exceptional circumstances. The appendix summarizes our review.

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Pathogenesis

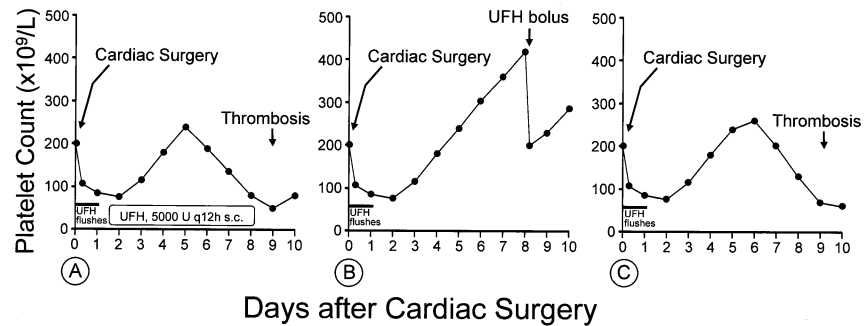
Heparin-induced thrombocytopenia is an immune-mediated disorder resulting when immunoglobulin G antibodies are produced that recognize a self protein, platelet factor 4, when platelet factor 4 has formed complexes with heparin [7, 8]. Multimolecular complexes of heparin, platelet factor 4, and immunoglobulin G form on platelet surfaces, and occupancy of the platelet Fc receptors by HIT-immunoglobulin G produces platelet activation. Heparin chains bind in relation to their chain length to platelet factor 4, perhaps explaining why unfractionated heparin (UFH) is more likely to cause HIT than low-molecular-weight heparin (LMWH) [9–12]. Platelet activation in HIT leads also to activation of coagulation. Once these procoagulant events are triggered, the prothrombotic risk remains for days to weeks, even after heparin has been stopped [13].

Clinical Picture

Timing of Thrombocytopenia

Most often, HIT presents as an unexpected platelet count fall beginning 5 to 10 days after heart surgery (Fig 1A) [14, 15]. Sometimes, HIT presents as an abrupt fall in the platelet count when heparin is administered (Fig 1B). Invariably, such patients have received heparin within the past 100 days (usually within the past 3 weeks). The reason for this temporal association is that the heparin antibodies triggered by the recent heparin exposure are remarkably transient [14]. Rarely, HIT presents several

Fig 1. Temporal profiles of onset of heparin-induced thrombocytopenia after cardiac surgery. (A) Typical-onset heparin-induced thrombocytopenia. (B) Rapid-onset heparin-induced thrombocytopenia. (C) Delayed-onset heparin-induced thrombocytopenia. (UFH = unfractionated heparin.)



days or even a few weeks after discharge from the hospital (delayed-onset HIT; Fig 1C) [16, 17]. This syndrome is associated with high-titer HIT antibodies that activate platelets even in the absence of pharmacologic heparin.

Severity of Thrombocytopenia

Thrombocytopenia in HIT is usually of moderate severity: 80% of patients have platelet count nadirs between 20 and 150 × 10⁹/L (median, 60 × 10⁹/L) [8]. Only 10% have platelet counts below 20 × 10⁹/L, but even these patients do not have signs of thrombocytopenic bleeding (petechiae). The remaining 10% of patients whose platelet count never falls below 150 × 10⁹/L are recognized either because of substantial platelet count falls (>50%) [18] or because of clinical events (thrombosis or skin lesions) suggesting HIT [17]. Using a proportional fall in platelet count such as more than 50% is appropriate because HIT usually occurs in the background of a rising postoperative platelet count (Fig 1) [11, 18, 19].

Thrombosis and Other Sequelae of Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia is strongly associated with thrombosis (odds ratio, 17 to 37) [9, 18, 20]. Approximately 40% to 75% of patients develop thrombosis, with predominance of venous over arterial thrombosis (ratio, 2:1 to 4:1) [13, 17]. Although postcardiac surgery patients with HIT develop similar rates of thrombosis (38% to 81%), arterial thrombi predominate [21–24], likely reflecting additional risk factors (arteriosclerosis, intravascular catheter use) in this patient population. Heparin-induced thrombocytopenia-associated mortality was 28% in the largest study of cardiac surgery patients [21].

Arterial thrombosis most often affects large lower-limb arteries, with thrombotic strokes and myocardial infarction less often seen (ie, the converse of usual localization of atherothrombosis) [17]. Rarely, arterial thrombi affect mesenteric, brachial, renal, or spinal arteries. HIT after coronary bypass grafting is associated with saphenous vein graft occlusion(s) [25]. Venous thromboembolism (deep-vein thrombosis [DVT], pulmonary embolism) is also common. Upper-limb DVT in HIT is strongly associated with use of a central venous catheter [20]. Sometimes, intraatrial or intraventricular thrombosis occurs. Rarely, thrombosis of adrenal veins leads to bilateral adrenal hemorrhagic necrosis and acute adrenal insufficiency.

About 10% to 20% of patients who develop HIT during

subcutaneous heparin therapy develop skin lesions at the injection sites ranging from painful erythematous plaques to skin necrosis [17]. Some patients who develop rapid-onset HIT after intravenous bolus heparin evince an acute systemic reaction that can be inflammatory (fever or chills, flushing), cardiorespiratory (dyspnea, hypertension, cardiorespiratory arrest), gastrointestinal (vomiting, diarrhea), or neurologic (transient global amnesia) [17].

Although increased thrombin generation is universal in HIT, overt (decompensated) disseminated intravascular coagulation leading to hypofibrinogenemia or increased prothrombin time is seen in only 5% to 10% of patients with HIT [7].

Differential Diagnosis

Thrombocytopenia secondary to hemodilution and platelet consumption occurs during cardiac surgery, with the lowest platelet counts (40% to 60% decline) usually seen on postoperative days 2 to 3, followed by thrombocytosis (peaking at two to three times baseline at about day 14), with subsequent return to preoperative baseline by 1 month after surgery. Thrombocytopenia during the first four postoperative days is only rarely attributable to HIT [26]. This is because heparin administered during CPB does not lead to clinically significant levels of HIT antibodies until postoperative day 5 or later, and because clinically significant levels of HIT antibodies are not commonly produced by preoperative heparin given during heart catheterization or for treating acute coronary syndromes.

However, a platelet count fall that begins 5 to 10 days after cardiac surgery (Fig 1A, 1C) or that occurs abruptly after starting heparin in a patient previously exposed to heparin within the past 100 days (Fig 1B), is very suggestive of HIT. However, other complications can produce thrombocytopenia during this time period, both common (septicemia, multiorgan system failure) and rare (post-transfusion purpura [27]).

Laboratory Testing for Heparin-Induced Thrombocytopenia Antibodies

Two commercial enzyme immunoassays (EIAs) are available that are very sensitive for detecting platelet factor 4-reactive HIT antibodies. Platelet activation assays that use washed platelets (eg, platelet serotonin release assay,

heparin-induced platelet activation assay) have similar sensitivity as the EIAs for detecting clinically significant HIT antibodies, but with greater diagnostic specificity [28]. As reference laboratories usually perform these assays, delays in obtaining test results are common. Conventional platelet aggregation assays have limited sensitivity and specificity for detecting HIT antibodies [1, 7].

The high sensitivity of EIAs and washed platelet activation assays means that a negative result usually rules out HIT (high negative predictive value) [29]. However, the high frequency of subclinical HIT antibody seroconversion after cardiac surgery (discussed subsequently) means that a positive assay result does not necessarily prove HIT to be the diagnosis (moderate positive predictive value), particularly if the pretest probability for HIT is low, or the test result is only weakly positive [29].

Frequency of Heparin-Induced Thrombocytopenia After Cardiac Surgery

Several prospective studies have evaluated the frequency of HIT in postoperative cardiac surgical patients who also received postoperative antithrombotic prophylaxis with UFH [11, 28, 30]. Pooling the data, the frequency of HIT was 2.4% (10 of 414 patients). This frequency is consistent with retrospective studies [21-24] that observed an overall frequency of about 2%.

Prospective studies [11, 28, 30-33] have found that 27% to 50% of postcardiac surgical patients form HIT antibodies detectable by EIA; however, only 7% to 40% [11, 28, 31] of these seroconversion events include high-titer immunoglobulin G antibodies that activate platelets in vitro. The observed frequency of HIT after cardiac surgery (1% to 3%) despite much higher seroconversion rates (27% to 50%) indicate that only a small minority (<10%) of antibody-positive patients actually develop thrombocytopenia even when heparin is continued through the postoperative period. In general, patients with the strongest antibody test results are most likely to develop HIT (eg, >90% serotonin release corresponds to a likelihood ratio for HIT of 20) [29].

Francis and colleagues [33] found a higher frequency of HIT antibody formation when UFH of beef lung origin was used for cardiac surgery, rather than UFH derived from porcine gut (49.5% versus 35.2%; $p = 0.037$). This study is consistent with previous comparisons of these two UFH preparations for treatment of DVT, in which beef lung heparin was more likely to cause HIT [12, 34].

Heparin Anticoagulation After Cardiac Surgery

Despite the common practice of giving UFH for antithrombotic prophylaxis after cardiac surgery, we are unaware of studies establishing its efficacy in this situation, particularly vis-a-vis its potential to cause HIT-associated thrombosis. A nonrandomized comparison of LMWH and UFH administered after cardiac surgery found a lower risk of HIT with LMWH: 1 of 370 patients (0.3%) versus 9 of 263 patients (3.4%) [11], consistent with studies in postorthopedic surgery patients [9, 12]. How-

ever, LMWH has not been well studied in cardiac surgical patients, and lacks regulatory approval for this indication. We recommend that if UFH or LMWH is given after cardiac surgery (either in therapeutic, prophylactic, or flush doses), appropriate platelet count monitoring for HIT be performed [1].

Management of Heparin-Induced Thrombocytopenia After Cardiac Surgery

The probability of HIT is high if a more than 50% fall in the platelet count begins between postoperative days 5 and 10 and occurs in the absence of alternative explanations, eg, infection. In such patients with high clinical suspicion for HIT, there is emerging consensus that heparin should be stopped, and an alternative, nonheparin anticoagulant substituted. This recommendation is based on the unfavorable natural history of HIT managed by heparin cessation alone (with or without warfarin): 25% to 50% thrombosis at 30- to 37-day follow-up (5% fatal thrombosis) [8, 13]. Further, lower limbs should be routinely screened for venous thrombosis, as clinically silent DVT is common in HIT patients [8]. Heparin-induced thrombocytopenia should also be suspected whenever a patient develops thrombosis while receiving heparin, or if the patient returns to the hospital with thrombocytopenia and thrombosis within the first 2 weeks after cardiac surgery (delayed-onset HIT). The next section summarizes briefly the treatment of HIT, which is discussed in detail elsewhere [7, 8, 35].

Treatment of Thrombosis Complicating Heparin-Induced Thrombocytopenia

The principles of treating thrombosis complicating HIT are (1) stop all heparin, including small doses of UFH used to flush invasive catheters, as well as LMWH; (2) give a rapidly acting, nonheparin anticoagulant, eg, a direct thrombin inhibitor such as argatroban, lepirudin, or bivalirudin, or danaparoid (factor Xa-inhibiting heparinoid); (3) avoid prophylactic platelet transfusions; (4) avoid warfarin until substantial resolution of thrombocytopenia has occurred; and (5) consider adjunctive therapies in specific situations, eg, surgical thromboembolotomy for limb-threatening arterial thrombosis.

The choice of alternative anticoagulant (Table 1) depends on patient-specific factors. Argatroban and lepirudin are excreted through hepatobiliary and renal routes, respectively; thus, argatroban is more suited for patients with renal insufficiency, whereas lepirudin is preferred if the patient has hepatic dysfunction. Bivalirudin predominantly undergoes enzymic degradation in the plasma (80%), with minor renal excretion (20%). Lepirudin is immunogenic, and during repeat courses a bolus should be avoided, as the risk of anaphylaxis is estimated at 0.16% [36]. The direct thrombin inhibitors have short half-lives (lepirudin, 80 minutes; argatroban, 40 to 50 minutes; bivalirudin, 25 minutes), which is useful when dose interruptions are anticipated, eg, for an impending invasive procedure.

Warfarin and other oral anticoagulants should be avoided during acute HIT because they can lead to limb

Table 1. Three Direct Thrombin Inhibitors for Treatment of Heparin-Induced Thrombocytopenia

Anticoagulant	Dosing Protocol for HIT-Associated Thrombosis ^a	Anticoagulant Monitoring ^b	Metabolism	Half-life	Comment
Lepirudin	(± Bolus, 0.4 mg/kg); initial infusion rate, 0.15 mg · kg ⁻¹ · h ⁻¹ ^a	1.5–2.5 × baseline aPTT	Renal	80 min	Relatively contraindicated in renal failure; ^c risk of anaphylaxis, especially on reexposure; minor prolongation of INR
Bivalirudin	No bolus; initial infusion rate, 0.15–0.20 mg · kg ⁻¹ · h ⁻¹	1.5–2.5 × baseline aPTT	Enzymic (80%); Renal (20%)	25 min	Small experience in treating HIT; minor prolongation of INR
Argatroban	No bolus; initial infusion rate, 2 μg · kg ⁻¹ · min ⁻¹	1.5–3.0 × baseline aPTT	Hepatobiliary	40–50 min	Initial dose 0.5 μg · kg ⁻¹ · min ⁻¹ in hepatic insufficiency; moderate to marked prolongation of INR (complicates warfarin overlap)

^a Identical protocols are generally used for isolated HIT, except for lepirudin (no initial bolus; initial infusion rate, 0.10 mg · kg⁻¹ · h⁻¹ adjusted to aPTT 1.5–2.5 × baseline aPTT). However, in contrast to the package insert, and in order to avoid overdosing (especially in elderly patients with unrecognized renal dysfunction), we recommend omitting the lepirudin bolus unless there is life threatening thrombosis. ^b Generally, the patient's baseline aPTT should be used (when applicable) for calculating target range, when appropriate; otherwise, the mean of the laboratory normal range can be used. ^c Substantial dose-reduction in renal insufficiency is required.

aPTT = activated partial thromboplastin time; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio.

necrosis resulting from microvascular thrombosis caused by depletion of the vitamin K-dependent natural anticoagulant, protein C [37, 38]. This complication, which may occur in 5% to 10% of patients with HIT-associated DVT receiving oral anticoagulants, is usually seen when the international normalized ratio rises above 3.5, as this represents a surrogate marker for protein C depletion. After platelet count recovery, if longer-term anticoagulation is needed, then warfarin anticoagulation is commenced that should overlap at least 5 days with the heparin alternative being used. For unknown reasons, argatroban prolongs the international normalized ratio much more than does lepirudin or bivalirudin, complicating monitoring of warfarin during overlapping anticoagulation. In contrast, the long half-life of danaparoid (25 hours) and lack of interference with the international normalized ratio makes it well-suited for treating venous thromboembolism when subsequent overlap with oral anticoagulants is required.

Treatment of Isolated Heparin-Induced Thrombocytopenia

Isolated HIT indicates when HIT is suspected because of a fall in platelet count alone without a HIT-associated thrombosis having occurred (yet) [12]. Previously, it was assumed that stopping heparin avoided subsequent thrombosis in isolated HIT. However, studies indicate that 25% to 50% of patients managed with heparin cessation develop thrombosis [8, 13]. Thus, in most situations, patients strongly suspected as having isolated HIT should receive a rapidly acting, nonheparin anticoagulant [35].

Anticoagulation During Cardiac Surgery in Patients With Previous or (Sub)Acute Heparin-Induced Thrombocytopenia

Activation of coagulation by contact of blood with the artificial surfaces of the CPB apparatus, as well as the reinfusion of tissue factor-enriched blood from the operative field, mandates high-dose anticoagulation. Well-

known advantages of UFH during CPB include (1) its high efficacy for preventing thrombosis of the CPB circuit; (2) rapid and simple intraoperative monitoring by activated clotting time; and (3) neutralization of heparin by protamine sulfate. No other agent meets these requirements; further, minimal experience with nonheparin anticoagulation during CPB exists. Thus, situations in which UFH is truly contraindicated must be well defined, so as to avoid potentially greater risks of nonheparin

Table 2. Options for Anticoagulation During Cardiac Surgery

A. Acute HIT
1. Postpone cardiac surgery for several weeks (then go to C)
2. Bivalirudin (preferably, if ecarin clotting time monitoring available)
3. Lepirudin (if ecarin clotting time monitoring available and normal renal function)
4. Epoprostenol plus heparin
5. Tirofiban plus heparin
6. Danaparoid (if drug and anti-factor Xa monitoring available)
B. Subacute HIT ^a
1. Postpone cardiac surgery for several weeks (then go to C)
2. Off-pump technique ^b using bivalirudin, lepirudin, or danaparoid
3. Heparin (if washed platelet activation assay for HIT antibodies is negative or enzyme immunoassay negative or weakly positive)
4. See options listed under A
C. Previous HIT ^c
1. Heparin

Each of the numbered items above indicates a separate option for consideration, with options we favor listed first.

^a Subacute heparin-induced thrombocytopenia (HIT) indicates a patient with recent HIT who has detectable HIT antibodies despite resolution of thrombocytopenia. ^b Off-pump surgery requires only about one half to one third the level of anticoagulation compared with cardiopulmonary bypass. ^c Previous HIT indicates that HIT antibodies no longer are detectable.

agents in this setting. Table 2 summarizes various approaches for managing CPB in patients with previous or (sub)acute HIT.

Cardiac Surgery in Patients With Previous Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia antibodies are transient and usually decline to nondetectable levels by 100 days (median, 50 days) using washed platelet activation assays; by EIA, the time to antibody disappearance is somewhat longer (median, 80 days) [14]. If heparin is administered to a patient with previous HIT whose antibodies are no longer detectable, several days are required for B lymphocytes to regenerate antibodies, if they are made at all. Indeed, recent studies [14, 15, 39] indicate that HIT antibody formation does *not* recur more quickly or more often in a patient with previous HIT who is reexposed to heparin, ie, there is no anamnestic (immune memory) response against HIT antigens.

Therefore, UFH is the drug of choice for anticoagulation during CPB in patients with a history of HIT who no longer have circulating HIT antibodies using one or more sensitive assays. We [14, 40] and others [39, 41, 42] have performed this strategy without producing HIT-related complications. When planning a reexposure, it is prudent to avoid preoperative heparin completely, so as to avoid restimulating antibodies, eg, by performing heart catheterization using either argatroban [43], bivalirudin [44], lepirudin [3], or danaparoid [45]. After surgery, nonheparin anticoagulants should be given if antithrombotic prophylaxis is needed, eg, warfarin, danaparoid 750 U twice or thrice daily subcutaneously, or hirudin 15 mg subcutaneously twice daily (see Table 1 if therapeutic-dose anticoagulation is required).

In our opinion, it is also reasonable to use UFH for CPB in a patient with recent HIT who tests weakly positive by EIA if a sensitive washed platelet activation assay is negative. This is because HIT antibodies detectable by activation assays correlate more closely with clinical HIT [28]. One of us (A.G.) has used UFH for CPB in this situation in 2 patients, with no adverse HIT-associated events.

For patients with previous HIT who require urgent heart surgery, there may be no opportunity to perform repeat testing for HIT antibodies. In this situation, we recommend using UFH if HIT occurred more than 100 days earlier. Both of us have used this approach with success when faced with this situation [40]. For patients whose episode of HIT occurred more recently, the decision to use standard UFH depends on the likelihood that significant antibody levels persist and the center's capacity to organize quickly an alternative anticoagulant approach.

Cardiac Surgery in Patients With Acute or Subacute Heparin-Induced Thrombocytopenia

Subacute (or latent) HIT refers to a patient with a recent episode of HIT who continues to have detectable HIT antibodies [8]. Such a patient can develop rapid-onset

HIT if heparin is administered again [14, 15]. The precise risk of giving high-dose UFH for CPB in this situation is not well defined, and anecdotal success using UFH has been reported [46]. Sometimes, cardiac surgery can be avoided, eg, low-dose thrombolysis (tissue-type plasminogen activator, 2 mg/h) plus lepirudin to treat HIT-associated intracardiac thrombosis [47].

For patients with acute or subacute HIT in whom heart surgery cannot be postponed, and for whom standard UFH anticoagulation is considered contraindicated, several off-label approaches exist (Table 2). No single method is appropriate in all circumstances, given patient-dependent factors (eg, renal failure), differences in jurisdictional availability of the nonheparin anticoagulants, accessibility and turnaround time of specialized laboratory monitoring, and prior physician experiences and preferences. Moreover, a team approach involving cooperation among surgeon, cardiologist, cardiac anesthesiologist, critical care physician, hematologist, and laboratory personnel is necessary. When a heparin-free approach is chosen, it is important not to administer heparin accidentally, eg, by heparin-coated intrapulmonary catheters, heparin-coated arterial filters or tubing within the CPB apparatus, or intravascular heparin flushes.

Particularly for patients with subacute HIT, use of an off-pump technique should be considered, as only one third to one half of the usual dose of danaparoid or lepirudin, respectively, than required for CPB is needed, potentially reducing bleeding [48, 49]. Bivalirudin has also been used successfully for off-pump cardiac surgery in HIT patients [50], with similar dosing as that under investigation for non-HIT patients undergoing off-pump surgery (bolus, 0.75 mg/kg, then 1.75 mg · kg⁻¹ · h⁻¹ infusion to maintain activated clotting time > 300 seconds) [51]. (This is the same bivalirudin dosing used in percutaneous coronary interventions [52].)

Recombinant Hirudin

Hirudin is an anticoagulant naturally produced by the salivary gland of the medicinal leech [3]. Two preparations are available by recombinant technology: lepirudin (Refludan, Berlex Laboratories, Montville, NJ) has been studied more extensively for HIT than desirudin (Revasc) [3, 38]. Hirudin is a single-chain 65-amino acid polypeptide (7,000 Da) that forms an irreversible 1:1 complex with thrombin. Hirudin interacts with both the fibrinogen-binding and catalytic sites of thrombin, completely inhibiting all procoagulant actions of thrombin. Unlike heparin, hirudin also inhibits clot-bound thrombin, including thrombin on fibrin lining the CPB circuit. The half-life of hirudin greatly depends on renal function, ranging from 80 minutes (normal kidneys) to more than 200 hours (anephric patient). No antidote exists.

In animal studies, hirudin in fixed doses provided effective CPB anticoagulation. However, in humans undergoing CPB, individualized dosing adjusted by intraoperative laboratory monitoring is required (Table 3). Unfortunately, although the activated partial thromboplastin time is adequate to monitor hirudin when treating thrombosis, the activated partial thromboplastin time-

Table 3. Treatment Protocol for Hirudin (Lepirudin) Anticoagulation During Cardiopulmonary Bypass (modified from [42])

Initial lepirudin dosing (pre-CPB)	
Initial intravenous (iv) lepirudin bolus: and initiate continuous iv infusion: ^a	0.25 mg/kg body weight 30 mL/h (0.5 mg/min)
Lepirudin added to pump circuit volume:	0.2 mg/kg body weight
Target lepirudin plasma level: ^b	>2.5 μ g/mL before start of CPB If <2.5 μ g/mL, give additional bolus (10 mg)
Lepirudin dosing and monitoring while on CPB	
Continue iv infusion (adjusted as below):	30 mL/h (0.5 mg/min)
Frequency of lepirudin level monitoring:	Every 15 min using ecarin clotting time
Intraoperative dose adjustments, based on ecarin clotting time	
Lepirudin plasma level ^b	Dosing modification
>4.5 μ g/mL	Reduce infusion rate by 10 mL/h
3.5–4.5 μ g/mL	No change in infusion rate
<3.5 μ g/mL	Increase infusion rate by 10 mL/h
Special steps toward end of CPB	
Stop lepirudin infusion 15 min before anticipated end of CPB	
After separation from CPB, administer 5 mg lepirudin to the pump circuit to prevent clot formation	

^a 50 mg of lepirudin is dissolved in 50 mL of 0.9% sodium chloride. ^b The target lepirudin level pre-CPB (>2.5 μ g/mL) is lower than the level sought during CPB (3.5–4.5 μ g/mL) because of the addition of lepirudin to the pump circuit volume (0.2 mg/kg body weight).

CPB = cardiopulmonary bypass.

hirudin relation flattens at the high concentrations needed during CPB. Further, the activated clotting time does not correlate well with hirudin levels, although it has been used for this purpose [53]. Reliable ($r^2 > 0.90$) results at this time are only obtained using the ecarin clotting time, which can be measured rapidly using whole blood [54]. However, as accuracy of the ecarin clotting time requires normal (at least 70%) prothrombin levels [55], and because hemodilution during CPB can cause hypoprothrombinemia, supplementation of normal human plasma (1 part normal plasma to 1 part patient whole blood) is recommended for a reliable test [53, 56].

In the United States and Canada, there is the additional option to use a commercial ecarin clotting time method available from PharmaNetics (Morrisville, NC) by way of a humanitarian device exemption (H990012) for the specific situation of CPB when heparin is contraindicated because of HIT [57]. The assay is performed using a point-of-care methodology (Thrombolytic Assessment System; manufactured by PharmaNetics; and marketed as Rapidpoint Coag by Bayer Diagnostics, Toronto, Ontario, and Tarrytown, NY). Practical issues include the time required for obtaining the indemnification agreement and institutional review board approval (United States) or patient-specific regulatory approval (Canada).

Clot formation can occur at hirudin concentrations less than 2 μ g/mL [58, 59], and the goal is to achieve stable intraoperative hirudin levels at approximately 4 μ g/mL [42, 54]. With normal renal function, hirudin levels decline quickly after stopping the infusion. In renal impairment, drug accumulation can cause severe bleeding [40], and ultrafiltration during (or modified ultrafiltration immediately after) CPB or hemofiltration or hemodialysis after surgery may be required (using filters appropriate for removing lepirudin) [60]. After discontinuation of

CPB, the blood in the reservoir must be anticoagulated with an additional bolus of lepirudin (Table 3); if this blood is to be reinfused, a cell saving device should be used to wash out the drug. In patients who have received hirudin for several days before CPB, hirudin will have saturated the extravascular compartment, thus contributing to greater hirudin levels after CPB as hirudin redistributes back into the intravascular space (80% of lepirudin distributes in the extravascular space). From experience to date, major bleeding is a frequent problem in HIT patients who receive lepirudin for CPB.

Bivalirudin

Bivalirudin (Angiomax, The Medicines Company, Parsippany, NJ) is a 20-amino acid synthetic peptide modeled after hirudin, which consists of two peptide fragments (connected by a tetraglycine spacer) that respectively recognize the fibrinogen binding site (exosite I) and catalytic site of thrombin. Unlike lepirudin, this bivalent interaction with thrombin is reversible once plasma enzymes (including thrombin itself) cleave the arg3–pro4 bond on bivalirudin. Its short half-life (25 minutes) and predominant enzymic elimination are advantageous for use in CPB. As with lepirudin, the ecarin clotting time is recommended for intraoperative monitoring during CPB [61], although anecdotal success (and some failure) using activated clotting time monitoring exists. For off-pump procedures (at lower bivalirudin concentrations) the activated clotting time can be used [51]. Extracorporeal hemoconcentration can remove up to 70% of circulating bivalirudin and can be applied after discontinuation of the infusion either routinely or specifically in the patient with renal dysfunction [62].

Bivalirudin has been used successfully off-label for anticoagulation during both off-pump [50] and on-pump [61, 63, 64] cardiac surgery in patients with acute or

Table 4. Treatment Protocol for Bivalirudin Anticoagulation During Cardiopulmonary Bypass (Under Investigation^a)

Initial bivalirudin dosing (pre-CPB)	
Initial intravenous (iv) bivalirudin bolus: and initiate continuous iv infusion:	1.5 mg/kg body weight 2.5 mg · kg ⁻¹ · h ⁻¹ (42 μg · kg ⁻¹ · min ⁻¹)
Bivalirudin added to pump circuit volume:	50 mg
Target bivalirudin plasma level:	>10 μg/mL before start of CPB If <10 μg/mL, give additional bolus (0.25 mg/kg) and increase infusion rate by 0.25 mg · kg ⁻¹ · h ⁻¹
Bivalirudin dosing and monitoring while on CPB	
Continue iv infusion (adjusted as below):	2.5 mg · kg ⁻¹ · h ⁻¹ or greater (as above)
Frequency of bivalirudin level monitoring:	Every 30 min using ecarin clotting time
Intraoperative dose adjustments, based on ecarin clotting time (ECT)	
<i>Bivalirudin plasma level (ECT)^b</i>	<i>Dosing modification</i>
>15 μg/mL (>500 s)	Reduce infusion rate by 0.25 mg · kg ⁻¹ · h ⁻¹
10–15 μg/mL (400–500 s)	No change in infusion rate
<10 μg/mL (<400 s)	Give additional bolus (0.25 mg/kg) and increase infusion rate by 0.25 mg · kg ⁻¹ · h ⁻¹
Special steps at end of CPB	
Stop bivalirudin infusion at end of CPB, then either:	
(A) Within 10 min of stopping bivalirudin infusion: First, reinfuse appropriate portion of pump volume to patient, and then give 50-mg bivalirudin bolus to the circuit to prevent clotting; start an infusion of 50 mg · h ⁻¹ into the circuit only, and continue to recirculate; any subsequent reinfusion of remaining pump volume to patient should be processed through a cell saving device (which removes >90% of bivalirudin); or	
(B) Promptly empty remaining pump volume into cell saving device (replacing the pump contents with crystalloid), thus avoiding need for postseparation bivalirudin boluses to circuit; process blood for reinfusion with cell saving device to remove bivalirudin	

^a Up-to-date information on protocol amendments are available from the manufacturer of bivalirudin. ^b The target bivalirudin concentration (10–15 μg/mL) corresponds to an ecarin clotting time (ECT) of 400–500 s using the RapidPoint Coag (Bayer); with other ECT methods, the bivalirudin concentration should be determined using a calibration curve.

CPB = cardiopulmonary bypass.

previous HIT. In addition, bivalirudin compared favorably in a randomized trial against heparin in non-HIT patients undergoing off-pump surgery [51]. Bivalirudin was therefore evaluated in a 20-patient pilot study (on-pump, non-HIT), and is currently under investigation in a phase 3 multicenter pivotal trial comparing bivalirudin (Table 4) with UFH for on- and off-pump cardiac surgery in patients with and without HIT.

The enzymic metabolism of bivalirudin presents certain practical issues. Surgical techniques that allow blood to lie stagnant should be avoided, as local bivalirudin levels will decrease owing to its metabolism by proteases (including thrombin) produced in blood exposed to wound or foreign surfaces, leading to local clot formation. As a caveat related to this issue, the presence of visible thrombus in an area of pooled blood, such as in the pericardial cavity, should not be interpreted by the surgeon as indicative of the need for additional anticoagulation, as this may only reflect local bivalirudin metabolism and not correlate with intravascular levels. If blood cardioplegia is used, the blood should be directly sourced from the circuit, and (after mixing with the cardioplegia solution) immediately reinfused into the coronary system. For the same reason, assessment of graft blood flow and testing for leakage should preferably be performed with albumin and saline solutions or, alternatively, using blood taken directly from the patient and used immedi-

ately for this assessment. Because hypothermia somewhat reduces the proteolysis of bivalirudin, the patient's core temperature should be maintained at close to 37°C following coming off CPB or completion of the final anastomoses in off-pump procedures, and care should be taken to maintain body temperature during the early postoperative period by active measures.

After separation from CPB, the risk that the circuit may clot rapidly may be even higher than with lepirudin due to bivalirudin's shorter half-life and ongoing metabolism owing to continuing bivalirudin proteolysis. Thus, provision to continue to recirculate pump blood after separation from bypass is made by adding a cross-limb in the bypass circuit at the time of setup, which remains clamped until coming off bypass. After clamping of the venous line, this limb is opened and the contents are recirculated. Within 10 minutes of separation from bypass, should the patient potentially need to return to bypass support, a 50-mg bolus of bivalirudin should be added to the circuit to prevent clotting, and a 50 mg · h⁻¹ infusion into the bypass circuit should also be started and continued until such time as it is clear the patient will not require urgent return to CPB. Once postseparation bivalirudin dosing to the circuit has commenced, any remaining pump volume contents intended for reinfusion to the patient should first be processed using a cell saving device, thus washing away most of the bivalirudin. An-

other approach is simply to drain rapidly the contents of the pump into a cell saving device after separation from bypass (replacing the pump contents with crystalloid) and washing the blood, thus avoiding the possibility of pump clotting without the need to administer additional bivalirudin into the pump.

Danaparoid

Danaparoid sodium (Orgaran; Organon, Oss, the Netherlands) is a mixture of anticoagulant glycosaminoglycans with predominant anti-factor Xa activity and low risk for in vivo cross-reactivity with HIT antibodies [45]. The absence of an acceptable linear correlation between the activated clotting time or activated partial thromboplastin time and the high plasma danaparoid levels required for CPB means that anti-factor Xa levels are required for monitoring [65]. Danaparoid was recently withdrawn from the U.S. market (April 2002), but continues to be available in Canada, continental Europe, Australia, New Zealand, and Japan.

The efficacy of danaparoid for CPB anticoagulation was first shown in dogs before human use for HIT [45, 66]. The largest series [67] describes 53 patients who underwent CPB using a fixed-dose regimen (most without laboratory monitoring). Severe postoperative bleeding (>20 U of blood products required) occurred in 11 (20%) patients; clots in the operative field occurred in 18 (34%) patients. Subsequently, two revised protocols based on patient weight were developed [42, 67], one also recommending intraoperative dose adjustments using a target anti-factor Xa level of 1.5 ± 0.3 U/mL (about twice the usual therapeutic range). However, postoperative bleeding as a result of the long half-life of and lack of antidote for danaparoid remains a problem.

Heparin Plus Antiplatelet Therapy

During the 1980s, CPB in patients with acute or subacute HIT was sometimes accomplished by giving standard-dose UFH once platelet inhibition was achieved using the potent antiplatelet agent, iloprost [68]. An analog of prostacyclin, iloprost inhibits platelet activation by stimulating adenylate cyclase, thus raising platelet adenosine monophosphate levels. Recently, this approach has experienced a revival with epoprostenol sodium (Flolan), a freeze-dried preparation of prostacyclin itself [69, 70]. Epoprostenol is approved for use in patients with primary pulmonary hypertension. Its very short half-life (6 minutes) means that continuous intravenous infusion is necessary.

Complete inhibition of heparin-dependent platelet aggregation by HIT antibodies is generally achieved by doses ranging from 15 to $30 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Thus, one protocol [69] that aims to avoid intraoperative monitoring of platelet aggregation gradually increases epoprostenol infusion (in $5 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ increments made at 5-minute intervals) until the target rate ($30 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) is reached, whereupon standard-dose UFH anticoagulation is given. The infusion is continued until 15 minutes after protamine. The major adverse effect is vasodilation, leading to severe hypotension that requires intraoperative vasopressors.

Conventional antiplatelet agents (aspirin, dipyridamole) do not reliably inhibit HIT antibody-induced platelet aggregation. However, inhibition of the platelet fibrinogen receptor using an anti-glycoprotein IIb/IIIa agent, such as tirofiban (Aggrastat) or abciximab (ReoPro), can block platelet aggregation (though not platelet activation) by HIT antibodies. Using the short-acting agent, tirofiban, Koster and colleagues [71] reported success (44 of 47 patients discharged on schedule from the hospital). Tirofiban is given 10 minutes before standard-dose UFH as a $10\text{-}\mu\text{g}/\text{kg}$ bolus followed by $0.15 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ continuous infusion, before stopping tirofiban 1 hour before the end of surgery. Unfractionated heparin is neutralized with protamine, and postoperative anticoagulation is achieved using lepirudin. However, in patients with severe renal impairment, tirofiban persists in the circulation and can cause major bleeding refractory to platelet transfusions: three such cases led the manufacturer (MSD Sharp & Dohme, Haar, Germany) to discourage use of this off-label protocol (letter to German cardiac surgeons, 2002). In such patients, extracorporeal elimination of tirofiban (eg, ultrafiltration at the end of CPB or modified zero-balanced ultrafiltration after CPB) might be required.

Miscellaneous

Low-molecular-weight heparin has been used for CPB in some patients with HIT. However, as proper dose-finding studies are lacking, only partial neutralization (60%) is achieved using protamine, and as LMWH can precipitate acute HIT in patients with circulating antibodies, we do not recommend LMWH for anticoagulation during CPB.

Although the direct thrombin inhibitor argatroban has been used successfully for CPB anticoagulation in dogs, experience with its use in humans is limited to cardiovascular procedures not requiring CPB [72]. Thus, it cannot be recommended for use in CPB.

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Appendix

Heparin-Induced Thrombocytopenia and the Cardiac Surgeon, Cardiologist, and Cardiac Anesthesiologist: Summary of Key Points

Definition of Immune Heparin-Induced Thrombocytopenia

1. Heparin-induced thrombocytopenia is defined as thrombocytopenia (see number 3) or thrombosis plus one or more positive tests for HIT antibodies (see also number 5).

Monitoring for Heparin-Induced Thrombocytopenia After Heart Surgery

2. Platelet count monitoring for HIT (as part of a complete blood count) is indicated after cardiac surgery as long as the patient is receiving heparin (either in therapeutic, prophylactic, or flush doses), at least every other day until hospital discharge or postoperative day 14 (whichever occurs sooner).

3. A platelet count fall of 50% or greater from baseline or any thrombosis that occurs 5 to 14 days after cardiac surgery is suggestive of HIT, even when heparin is not being given in the postoperative period (delayed-onset HIT). (The appropriate baseline platelet count is *not* the preoperative platelet count, but rather the highest platelet count in the postoperative period.)

Laboratory Testing for Heparin-Induced Thrombocytopenia

4. Commercially available EIAs and washed platelet activation assays (eg, platelet serotonin release assay or the heparin-induced platelet activation test) are very sensitive for detecting HIT antibodies; thus, with rare exception, a negative test with one of these assays rules out HIT (high negative predictive value).

5. Heparin-induced thrombocytopenia antibody seroconversion of no clinical consequence is common after heart surgery (about 25% to 50% by EIA), and thus the presence of HIT antibodies in the absence of an otherwise unexplained platelet count fall or clinical sequelae such as thrombosis does not indicate HIT.

6. Serum or plasma from patients with acute HIT usually has strong positive HIT antibody results (eg, serotonin release > 80%; EIA optical density > 1.0). In general, the greater the magnitude of a positive HIT antibody test result, the greater the likelihood the patient has HIT.

7. Heparin-induced thrombocytopenia antibodies are transient, and so acute serum or plasma should be tested to investigate a putative episode of HIT.

Frequency of Heparin-Induced Thrombocytopenia and Heparin-Induced Thrombocytopenia-Associated Thrombosis After Heart Surgery

8. In patients receiving unfractionated heparin after cardiac surgery, the frequency of HIT is 1% to 3% by postoperative days 7 to 14.

9. At least 50% of patients with HIT develop arterial or venous thrombotic complications, often beginning after heparin has been stopped because of suspicion of HIT.

Management of Heparin-Induced Thrombocytopenia After Cardiac Surgery

10. Discontinue all heparin if there is a high suspicion of HIT, including heparin administered by intravascular catheter flushes, and consider removing heparin-coated devices.

11. In general, HIT-associated thrombosis should be treated with one of the following alternative anticoagulants: lepirudin (United States, Canada, European Union, Australia, New Zealand), argatroban (United States, Canada), danaparoid (Canada, European Union, Australia, New Zealand), or bivalirudin (United States, Canada, New Zealand).

12. Warfarin and other oral anticoagulants are contraindicated during acute HIT, as acute protein C depletion can lead to microvascular thrombosis causing venous limb gangrene. Oral anticoagulants should be delayed pending substantial recovery of the platelet count (to at least $100 \times 10^9/L$), started in low initial doses (maximum, 5 mg) and during concomitant anticoagulation with an agent such as lepirudin, argatroban, or danaparoid. The alternative anticoagulant should be stopped (after a minimum 5-day overlap) only when platelet count recovery is complete and therapeutic oral anticoagulation is achieved.

13. Low-molecular-weight heparin is contraindicated for treatment of HIT.

14. Prophylactic platelet transfusions should be avoided when HIT is strongly suspected, as platelets theoretically may increase thrombotic risk and spontaneous bleeding is uncommon in patients with HIT.

15. For patients strongly suspected of having HIT but without clinical evidence of thrombosis (isolated HIT), an alternative anticoagulant in therapeutic doses is recommended because of the high risk of developing thrombosis. It is also recommended that noninvasive imaging for lower-limb thrombosis be performed because of the high frequency of DVT in patients with HIT.

Cardiac Surgery in a Patient With Previous or Acute Heparin-Induced Thrombocytopenia

16. Standard anticoagulation with UFH is recommended for cardiac surgery in patients with previous HIT in whom HIT antibodies are no longer detectable, or only weakly detectable, by EIA.

Cardiac Surgery in a Patient With Acute or Subacute Heparin-Induced Thrombocytopenia

17. Two general approaches are available for patients in whom standard UFH anticoagulation is contraindicated because of acute or subacute HIT: (1) give an alternative anticoagulant for CPB (eg, bivalirudin, lepirudin, danaparoid), being careful to avoid all intraoperative and postoperative heparin exposure (eg, by means of heparin-bonded arterial filters in the CPB apparatus, heparin-coated pulmonary artery catheters, heparin flushes, and so forth); or (2) give standard heparin anticoagulation together with a platelet antagonist (eg, epoprostenol or tirofiban).

(Subacute HIT indicates that the patient's platelet count has recovered from acute HIT, but HIT antibodies remain detectable, and so there is the potential for rapid-onset HIT if heparin is administered.)

18. No single option listed in number 17 can be generally recommended, given the absence of prospective comparative studies, as well as important differences in jurisdictional approval and availability of the various agents and in appropriate laboratory monitoring and prior physician experience, as well as patient-dependent factors such as renal insufficiency, all of which influence choice of anticoagulant approach.

Reducing Risk of Heparin-Induced Thrombocytopenia After Heart Surgery

19. Unfractionated heparin derived from porcine intestinal mucosa is preferred over heparin obtained from bovine lung, as the risk of HIT antibody formation is less, and porcine heparin has been associated with a lower risk of HIT in other patient populations.

20. There is evidence that LMWH may be less likely than UFH to cause HIT when administered for postoperative antithrombotic prophylaxis. However, LMWH is not well studied in postcardiac surgery patients.