Heparin-induced thrombocytopenia and cardiac surgery
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Introduction
Heparin-induced thrombocytopenia (HIT) is an immune-mediated prothrombotic event resulting from platelet activation by an antibody formed during heparin therapy. Clinically, HIT manifests as an unexplained more than 50% decrease in the platelet count, often to less than 100 x 10^9/l that can be associated with thrombosis [1**,2**,3**,4**]. When heparin is administered perioperatively, the incidence of HIT is the highest. When HIT is strongly suspected, heparin should be stopped and suitable treatment should be started immediately, even before laboratory confirmation, especially if a postoperative thrombotic event occurs. This review will discuss the pathophysiology, diagnosis, and treatment of HIT, in addition to alternative anticoagulation strategies.

Pathogenesis/frequency
HIT is mediated by antibodies that develop to a complex of heparin–platelet factor 4 (PF4), a basic protein stored in platelet alpha granules. Heparin–PF4 antibodies are generated when heparin and PF4 bind, creating a conformational change on PF4 that exposes new antigenic binding sites called epitopes [4**]. The antibody producing HIT is an immunoglobulin (IgG) antibody that binds heparin–PF4 complexes on platelet surfaces to form immune complexes. The platelets in turn are activated by the Fc domain of the IgG via FcyIIa receptors. Consequently, platelets release membrane fragments (microparticles) that are prothrombotic and promote thrombin generation/platelet activation. HIT antibodies also activate monocytes, bind to endothelial cells, and further augment the procoagulant state. About 7–50% of heparin-treated patients form heparin–PF4 antibodies; however, HIT occurs in approximately 1–5% of patients receiving unfractionated heparin and less than 1% of patients receiving low-molecular-weight heparin [3**,5]. Cardiac transplant/neurosurgical patients have an increased risk of developing HIT (11 and 15%, respectively) [6,7]. Cardiovascular surgery patients are especially at risk of producing the antibodies

Purpose of review
Heparin-induced thrombocytopenia (HIT) is an important, increasingly recognized antibody-mediated complication of heparin therapy occurring in approximately 0.5–5% of patients receiving heparin for at least 5 days. HIT is a prothrombotic disorder that typically presents with a 50% platelet count drop, thrombotic event manifesting usually 5–14 days after starting heparin, or both. HIT antibodies usually decrease to negative titers/levels within 3 months. When there is clinical suspicion of HIT, heparin should be discontinued and alternative anticoagulation should be considered, as well as laboratory evaluation for HIT.

Recent findings
HIT immunoassay results should be used for clinical decision-making about initial anticoagulation management. Recent data reevaluate the importance of absolute titers of HIT antibodies as a risk factor for clinical occurrence. Although laboratory assays are routinely used, current data suggest that increasing optical densities are more likely associated with a positive ^14C-serotonin release assay and HIT. HIT is also associated with a greater risk for adverse events, so even though alternative anticoagulation is used, clinicians should be aware of this hypercoagulable syndrome.

Summary
For patients with HIT, alternative anticoagulation is available, but for cardiovascular surgery, if the operation cannot be delayed until HIT antibodies have become negative, alternative anticoagulation strategies are recommended, although patients with HIT are at a greater risk for adverse outcomes.

Keywords
anticoagulation, cardiac surgery, heparin-induced thrombocytopenia, hypersensitivity, thrombosis

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HI [8]. HIT antibodies circulate only temporally (half-life <3 months) [9]. The presence and the level of the antibodies, irrespective of thrombocytopenia, are associated with increased adverse events in different groups of patients from acute coronary syndromes to cardiovascular surgery [10,11,12]. HIT increases the risk of thrombosis (odds ratio 37), and the overall thrombotic risk with HIT is 38–76% [13,14]. Thrombosis appears coincident with, or slightly before, the decline in platelet count [13].

**Diagnosis**

HIT should be suspected if the platelet count drops by 50% or new thrombosis occurs 5–14 days after initiating heparin therapy [11,12]. Thrombocytopenia due to other causes, including an intraaortic balloon pump with mechanical destruction, sepsis, or other drug-induced causes of thrombocytopenia, should be excluded [4]. In cardiac patients, Hb/IHa platelet inhibitors are important causes of drug-induced thrombocytopenia [4]. Other confounding issues include cardiopulmonary bypass (CPB) in which a 40–60% decrease in platelet count occurs because of dilution and consumption. HIT after CPB often has a biphasic pattern that decreases after CPB-related thrombocytopenia corrects or a persistently low/decreasing platelet count more than 4 days postoperatively [15,16]. HIT can manifest with a ‘rapid onset’ within minutes to hours of heparin exposure associated with systemic responses caused by preexisting antibodies due to prior exposure [17]. These reactions manifest as hypersensitivity/anaphylaxis and include hypotension, pulmonary hypertension, tachycardia 2–30 min after heparin bolus [4], or all. HIT can also occur days to weeks after exposure (delayed onset HIT) in patients presenting with thrombosis [18].

**Laboratory confirmation**

Laboratory testing for HIT includes antigen assays and functional platelet activation assays [19,20,21,22]. Antigen assays such as the ELISA and rapid particle gel immunoassay detect polyclonal antibodies to complexes of PF4 and heparin or complexes of PF4 and other polyanions [19,20,21,22]. The most commonly used commercial ELISAs detect IgG, IgM, and IgA antibodies, and are sensitive for detection of heparin–PF4 antibodies but are not specific for HIT. However, newer commercial assays have been developed that detect IgG antibodies, thus increasing clinical specificity [19,20,21,22]. Although ELISA results can be reported as positive or negative, optical density (OD), antibody titer based on the OD, or all are important for clinical decision-making. The likelihood of a positive 14C-serotonin release assay (SRA) increases proportionally with increased ODs — most cases of HIT were associated with an ELISA OD of more than 1.40 units — weak positive results (0.04–1.00 OD) excluded a diagnosis of HIT in most cases [23]. Further, ‘high-titer negative’ ELISA results may become positive on retesting after several days. Functional tests include the SRA and heparin-induced platelet activation test. These tests detect heparin-dependent, platelet-activating antibodies and are considered the gold standard for the laboratory diagnoses of HIT because of high sensitivity/specificity but require specialized laboratories [19,20,21,22].

**Treatment**

The recommended treatment for patients with strongly suspected or confirmed HIT is discontinuation of heparin and beginning of a nonheparin, alternative anticoagulant such as a direct thrombin inhibitor (e.g. lepirudin, argatroban, and bivalirudin) or danaparoid [11,12]. In addition, documentation of the patient’s HIT status including a sign on the patient’s bed chart stating ‘No heparin: HIT’, or both, may help prevent unintended heparin exposure. Different direct thrombin inhibitors are approved in the United States for use in HIT patients without thrombosis (argatroban), HIT patients with thrombosis (lepirudin and argatroban), and patients with or at risk of HIT undergoing percutaneous coronary intervention (PCI) (argatroban and bivalirudin). Lepirudin and argatroban are also available in some other countries for use in patients with HIT in the noninterventional setting. The direct thrombin inhibitors do not resemble heparin, do not cross-react with heparin–PF4 antibodies, and cannot promote HIT. Danaparoid, a heparinoid with minimal cross-reactivity with heparin–PF4 antibodies, was one of the first agents approved but was widely unavailable. Fondaparinux is a selective factor Xa inhibitor with a low risk for antibody formation; however, fondaparinux has not been prospectively studied in HIT, and data are limited.

Managing HIT should include stopping heparin and continued alternative anticoagulant coverage to prevent thrombotic complications [11,12,23]. However, the risk of excessive bleeding especially recently after cardiac or other surgery should be carefully considered, as bleeding is also associated with adverse outcomes. Low-molecular-weight heparins should be avoided because they cross-react with heparin–PF4 antibodies and worsen HIT [11,12,23]. Heparin should be avoided, at least as long as heparin–PF4 antibody testing is positive [11,12,23]. The British Committee for Standards in Haematology recommends the use of a heparin alternative for most patients needing anticoagulation with previous HIT [24]. Avoiding heparin is feasible in many patients but may be challenging in a few clinical situations, for example cardiovascular surgery (discussed below). For patients with current or previous HIT who need cardiac surgery, the
surgery should be delayed, if possible, until heparin–PF4 antibodies are negative [1∗∗,2]. If heparin use is unavoidable or planned, the heparin exposure should be limited to the surgery itself, with alternative anticoagulation used preoperatively and postoperatively as needed [1∗∗,2,3∗∗,4∗∗].

Preoperative and postoperative alternative anticoagulation therapies: lepirudin
Lepirudin, a recombinant form of hirudin, is the most potent agent with side effects that include an 18% incidence of major bleeding and potential for anaphylactic reactions on reexposure [25–27]. Bleeding risk is related to serum creatinine levels, and dosing adjustments should be made with renal dysfunction [24]. Recommended lepirudin dosing is a 0.4 mg/kg initial bolus, followed by a 0.15 mg/kg/h infusion (reduced in renal injury) adjusted to keep an activated partial thromboplastin time (aPPT) 1.5–2.5 times baseline. A lower first infusion of 0.1 mg/kg/h without a bolus may reduce the bleeding risk.

Preoperative and postoperative alternative anticoagulation therapies: desirudin
Desirudin, another recombinant hirudin, has been extensively studied in orthopedic and cardiac settings [28]. As a prophylaxis in patients undergoing hip replacement surgery, desirudin was significantly more effective in reducing the incidence of deep vein thrombosis than either unfractionated or low-molecular-weight heparin. The two recombinant hirudins for clinical use include desirudin and lepirudin. Desirudin is approved for thrombosis prophylaxis following orthopedic hip replacement surgery and lepirudin for anticoagulation in patients with HIT and thromboembolic complications [29]. Both compounds differ from each other in their N-termini; desirudin possesses a valine–valine and lepirudin possesses a leucine–threonine structure. Otherwise, the desirudin and lepirudin are similar, with molecular weights of 6.96 and 6.98 kDa, respectively [29].

Preoperative and postoperative alternative anticoagulation therapies: argatroban
Argatroban is a heptatically metabolized, small molecule (molecular weight 526 Da) developed from L-arginine. The small size minimizes the risk for antibody formation. The recommended initial dose is an infusion of 2 µg/kg/min (0.5 µg/kg/min if hepatic impairment), adjusted to achieve an aPPT 1.5–3 times baseline. However, a lower dose (0.5 µg/kg/min) should be considered in patients with heart failure, multiple organ system failure, or fluid overload, but dose adjustment for renal failure is not required [30,31]. Although argatroban is also approved for use in patients with or at risk of HIT undergoing PCI, most clinicians now use bivalirudin (see below). Direct thrombin inhibitors, particularly argatroban, prolong the international normalized ratio (INR), and methods for monitoring the argatroban-to-coumarin transition using the INR or chromogenic factor Xa assay should be followed [32].

Preoperative and postoperative alternative anticoagulation therapies: bivalirudin
Bivalirudin is a low-molecular-weight protein developed by adapting hirudin that is cleared by renal elimination and by circulating proteases. Bivalirudin is used extensively in the cardiac catheterization setting and in patients with or at risk of HIT during PCI. Bivalirudin was evaluated in an open-label, prospective study of 52 patients with or at risk of HIT [33]. The primary endpoint of major bleeding occurred in one (2%) patient. Clinical success, defined as a lack of death, emergency bypass surgery, or Q-wave infarction, occurred in 48 (96%) of 50 evaluable patients. The recommended dose is a 0.75 mg/kg initial bolus followed by an infusion of 1.75 mg/kg/h (reduced in renal impairment). Notable added experience exists with this drug in non-HIT patients, and it is the agent most extensively studied and used in cardiac surgery (see below).

Preoperative and postoperative alternative anticoagulation therapies: danaparoid
Danaparoid is a glycosaminoglycan used since 1982 for patients with HIT and is the only alternative anticoagulant evaluated in a randomized controlled trial in HIT that included dextran 70 as the comparator, which is now considered inappropriate therapy [34]. In 1478 clinical experiences with danaparoid in HIT, event rates were 16.2% for mortality, 9.7% for thrombosis, and 8.1% for major bleeding [35]. Other studies report its use, but it is currently unavailable for clinical use.

Preoperative and postoperative alternative anticoagulation therapies: fondaparinux
Fondaparinux is a synthetic pentasaccharide with minimal in-vitro cross-reactivity with HIT sera [36]. It is approved in the United States and elsewhere for prophylaxis and treatment of venous thromboembolism. Prospective, controlled studies in HIT with small numbers have been reported [37]. In addition, there are a few reports of HIT associated with fondaparinux and minimal approaches to reverse its bleeding effects.

Managing heparin-induced thrombocytopenia patients for cardiovascular surgery
If patients are HIT positive based on current criteria, and based on recent understanding about antibody titers, and
cardiac surgery cannot be delayed, nonheparin anticoagu-
lution during the surgery is recommended [1**,2,
3**,4**]. A previous clinical report [4**] included a review
danaparoid or heparin with the short-acting platelet
inhibitors epoprostenol, iloprost, or tirofiban as alter-
ate agents. A retrospective analysis [38] of 57 patients
with HIT for cardiovascular surgery with CPB was
reported using lepirudin anticoagulation. Lepirudin
0.20 mg/kg was added to the priming solution. A
0.25 mg/kg intravenous bolus followed by continuous
infusion of 0.5 mg/min was started before cannulation.
During CPB, lepirudin was monitored using the ecarin
clotting time. Target values were 350–400 s. Fifty-four
(95%) patients fully recovered without evidence of
thromboembolism. Four (7%) patients, each with renal
impairment, had excessive bleeding associated with pro-
longed lepirudin elimination. Argatroban has been
reported during cardiac surgery, on the basis of a ret-
rospective analysis of 21 published adult cases with a
history of HIT, heparin allergy, or antithrombin
deficiency [39]. Other studies have reported its use for
cardiovascular surgery, but bivalirudin has been more
extensively studied for this application as noted below.

**Bivalirudin**

Bivalirudin has become the agent most used to replace
heparin in patients with HIT requiring cardiac surgery. An
early case series [40] reported four patients with suspected
HIT who underwent coronary artery bypass grafting using
CPB and bivalirudin anticoagulation. Patients received a
1.5 mg/kg loading dose before cannulation and continuous
2.5 mg/kg/h infusion during CPB. Anticoagulation was
monitored using activated clotting times with a target of
500 s. Anticoagulation during CPB was effective, and total
operating times were acceptable. One patient experienced
excessive postoperative bleeding.

Larger, prospective studies compared bivalirudin with heparin in non-HIT patients undergoing cardiac surgery
using CPB [41*] or undergoing coronary artery bypass
grafting without CPB [42*]. Bivalirudin was administered
to 206 patients, providing anticoagulation with a safety
profile similar to that of heparin. Bivalirudin dosing in
surgery without CPB is similar to that used in PCI.
Cautions when using this agent include intraoperative
techniques to prevent blood from being stagnant when
using bivalirudin, which is metabolized by enzymes
present in blood exposed to wound or foreign surfaces.
Therefore, direct retransfusion of shed pericardial/medi-
sternal blood into the cardiotomy container should be
avoided with the use of bivalirudin to avoid systemic
activation and circulation of thromboemboli. Alterna-
atively, shed pericardial blood can be processed via cell
salvage systems when using bivalirudin.

**Antibody negative**

If heparin–PF4 antibodies are negative after a HIT
episode, guidelines recommend heparin over non-
heparin anticoagulants during cardiac surgery [1**,4**].
The risk of complications, including bleeding associated
with nonheparin anticoagulants, during cardiac surgery
may exceed the risk of recurrence of HIT with brief
heparin reexposure [1**,2,3**,4**]. Added concerns with
alternative anticoagulants for cardiac surgery include
limited experience and the lack of a reversal agent
[1**]. Heparin use should be confined to the intra-
operative period, with alternative anticoagulation used
preoperatively and postoperatively as needed [1**]. As
previously discussed, heparin–PF4 antibodies are tran-
sient. In one study [9] of 144 patients with HIT, the
median time to a negative antibody result after an initial
positive result was 50 days by activation assay and 85 days
by antigenic assay.

**Conclusion**

HIT is an antibody-mediated prothrombotic disorder
that should be considered if a patient experiences a

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**Table 1 Direct thrombin inhibitors for clinical use**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Availability</th>
<th>Indications</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivalirudin</td>
<td>0.75 mg/kg bolus followed by 1.75 mg/kg/h infusion for the duration of PCI, with 0.3 mg/kg based on ACT; cardiothoracic surgery dosing depends on vs. off pump [40,41*,42*]</td>
<td>Available in the United States, Europe, and Canada</td>
<td>PCI or in patients with HIT</td>
<td>ACT</td>
</tr>
<tr>
<td>Argatroban</td>
<td>2 µg/kg/min initial infusion adjusted to &lt;10 µg/kg/min when aPTT is 1.5–3× baseline (HIT); 25 µg/kg/min infusion and 350 µg/kg bolus until ACT &gt;300 s</td>
<td>Available in the United States</td>
<td>Prophylaxis and treatment of thrombosis in HIT and PCI in patients with HIT</td>
<td>aPTT and ACT (PCI)</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>0.4 mg/kg bolus dose and 0.15 mg/kg infusion to target aPTT of 1.5–2.5 times</td>
<td>Available in the United States and Europe</td>
<td>HIT and prevention of further VTE</td>
<td>aPTT</td>
</tr>
<tr>
<td>Desirudin</td>
<td>15 mg subcutaneously q12h (orthopedic)</td>
<td>Approved in the United States and Europe for hip arthroplasty</td>
<td>Total hip arthroplasty (HIT)</td>
<td>None</td>
</tr>
</tbody>
</table>

ACT, activated clotting time; aPTT, activated partial thromboplastin time; HIT, heparin-induced thrombocytopenia; PCI, percutaneous coronary intervention; VTE, venous thromboembolism.

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platelet count drop of 50% thrombosis occurring 5–14 days after the start of heparin, with other diagnoses excluded. Heparin should be discontinued if HIT is suspected, confirmatory laboratory testing performed, and parenteral alternative anticoagulation should be considered if there is a thrombotic risk. HIT antibodies are transient, and heparin should be avoided as long as the antibody test is positive. In patients with HIT who need cardiac surgery, the surgery should be delayed, if possible, until HIT testing is negative. Alternative anticoagulation should be used perioperatively as needed. HIT is a prothrombotic disease that even with alternative anticoagulation is associated with a significant risk of life-threatening morbidity and death. Table 1 summarizes the direct thrombin inhibitors used in HIT.

Acknowledgements
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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- - of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 118–119).


A study reporting use of bivalirudin in cardiac surgery.


A study reporting use of bivalirudin in cardiac surgery.