Nonheparin Anticoagulants for Heparin-Induced Thrombocytopenia

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This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors’ clinical recommendations.

A 57-year-old man remains in the hospital after experiencing complications from knee-replacement surgery 7 days ago. Low-molecular-weight heparin prophylaxis is initiated on the first postoperative day. Compression ultrasonography performed for left leg swelling noted on day 7 shows a proximal deep-vein thrombosis. A complete blood count reveals that his platelet count has decreased from $300 \times 10^9$ per liter to $125 \times 10^9$ per liter, and an enzyme immunoassay for heparin-induced thrombocytopenia shows a high titer of antibodies against platelet factor 4 (PF4)–heparin complexes. The patient has normal renal function. The physician in the intensive care unit wonders about the best treatment.

THE CLINICAL PROBLEM

Heparin-induced thrombocytopenia is a prothrombotic disorder mediated by IgG antibodies that bind to conformational epitopes on PF4 when it is complexed with heparin. Typically, the platelet counts are only moderately reduced.1-7 Occasionally, patients do not have thrombocytopenia, but their platelet counts decrease by 50% from pretreatment levels.8

The risk of heparin-induced thrombocytopenia is related to characteristics of the patient, the type of heparin used, and the clinical setting.1,2,9 Older patients and women are at increased risk. Surgical patients have a higher risk than medical patients, possibly because of the release of cytokines during tissue injury, and orthopedic surgery may pose a particularly high risk.1,2,9-11 However, the recent observation that anti-PF4–heparin antibodies can develop in healthy persons after exposure to heparin suggests that some people may be predisposed to antibody formation, which is necessary but not sufficient to cause the clinical syndrome.12

The risk of heparin-induced thrombocytopenia is also related to the duration of heparin exposure and characteristics of the heparin molecule.1,2,4,9,13 When administered to patients after surgery, unfractionated heparin (3000 to 30,000 daltons) carries a higher risk (1.0 to 5.0%) than low-molecular-weight heparin (2000 to 9000 daltons), which is associated with a risk of 0.1 to 1.0%. Fondaparinux (1728 daltons), a synthetic analogue of the antithrombin-binding pentasaccharide within heparin, is associated with a negligible risk of heparin-induced thrombocytopenia.1,2,9-11

Thrombocytopenia usually occurs 5 to 10 days after the initiation of heparin.1,3,5,10,11 Exceptions are rapid-onset heparin-induced thrombocytopenia, which is characterized by an abrupt decrease in the platelet count within hours after heparin exposure in patients with previous heparin exposure who also have anti-PF4–heparin antibodies,14 and delayed-onset heparin-induced thrombocytopenia.
which is characterized by thrombocytopenia and thrombosis occurring several weeks after heparin exposure.\textsuperscript{15} Thrombosis, which occurs in about half of untreated patients, can occur simultaneously with the decrease in the platelet count or can follow within days.\textsuperscript{1,2,4,6,9}

The thromboembolic complications associated with heparin-induced thrombocytopenia can be devastating and include deep-vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and peripheral arterial thrombosis that can progress to limb necrosis necessitating amputation. Less common manifestations include acute systemic reactions and necrotizing lesions at the heparin-injection sites.\textsuperscript{10,11} Venous thrombotic events predominate over arterial events in a ratio of 4:1.\textsuperscript{6} The mortality associated with heparin-induced thrombocytopenia is approximately 5 to 10%, usually secondary to thrombotic complications.\textsuperscript{1,2,9}

Although heparin-induced thrombocytopenia is not rare, it is both simultaneously underrecognized and overdiagnosed.\textsuperscript{3,16} This dichotomy occurs because the syndrome often manifests in patients with other causes of thrombocytopenia and because the tests commonly used to diagnose heparin-induced thrombocytopenia are sensitive but not specific.

**PATHOPHYSIOLOGY AND EFFECT OF THERAPY**

Heparin-induced thrombocytopenia is caused by IgG antibodies that bind to conformationally exposed sites on PF4, a heparin-binding chemokine released by platelet activation.\textsuperscript{4,17} These immune complexes, which assemble on the surface of cells, including platelets, monocytes, and possibly endothelial cells, as well as in the plasma, bind to Fcγ receptor IIa (FcγRIIa) (Fig. 1).\textsuperscript{18,19} Binding to and aggregation of platelet FcγRIIa receptors results in intense platelet activation and the release of procoagulant-rich microparticles.\textsuperscript{18,20} Platelet and monocyte microparticles activate the coagulation cascade by releasing tissue factor, which binds to factor VIIa, leading to the activation of factors IX and X. The microparticles also facilitate coagulation by providing an anionic phospholipid membrane surface. This surface enhances the assembly of clotting cascade complexes, including the initiation complex (tissue factor, factor VIIa, and factor X), the intrinsic tenase complex (factors VIIIa, IXa, and X), and the prothrombinase complex (factor Va, factor Xa, and thrombin) (Fig. 2).\textsuperscript{21,22}

There is dissociation between the development of anti-PF4–heparin antibodies and the risk of the development of heparin-induced thrombocytopenia. Although almost all patients with heparin-induced thrombocytopenia have anti-PF4–heparin antibodies, most patients with anti-PF4–heparin antibodies do not have heparin-induced thrombocytopenia.\textsuperscript{1,10,11,16,23,24} What makes some antibodies pathogenic and not others is not known but may relate to the titer of the antibody or the size of the PF4–heparin complexes. Furthermore, some patients are more prone to the development of pathogenic anti-PF4–heparin antibodies than others. This finding is perhaps best illustrated in patients who undergo coronary-artery bypass surgery; anti-PF4–heparin antibodies develop in 20 to 50% of patients after surgery, with an overall risk of heparin-induced thrombocytopenia of about 1%. In contrast, anti-PF4–heparin antibodies form in only about 10% of patients who undergo orthopedic surgery, but heparin-induced thrombocytopenia develops in half those patients.\textsuperscript{24}

Treatment for heparin-induced thrombocytopenia requires both the immediate discontinuation of all heparins and the administration of a non–cross-reactive anticoagulant that is capable of interrupting the activated coagulation cascade at the level of thrombin or factor X (Fig. 2). Several different agents have been used for this purpose, including the parenteral direct thrombin inhibitor, argatroban; the recombinant hirudins, lepirudin and desirudin; bivalirudin, a synthetic bivalent hirudin analogue; and the parenteral factor Xa inhibitors, danaparoid and fondaparinux. The oral direct thrombin inhibitor dabigatran has not been studied for this purpose.

**CLINICAL USE AND CLINICAL EVIDENCE**

Heparin-induced thrombocytopenia should be suspected in any patient who is receiving or who has recently received heparin or low-molecular-weight heparin and in whom thrombocytopenia (defined as a decrease in platelet count of ≥50%), thrombosis, or skin necrosis at the heparin-injection sites develops. The relative rarity of heparin-induced thrombocytopenia among all patients with thrombocytopenia contributes to overdiagnosis of the disorder.\textsuperscript{25} Overdiagnosis may be re-
duced if testing is restricted to populations with a higher prevalence of disease. To that end, clinical scoring systems have been developed to assess the likelihood of heparin-induced thrombocytopenia, including the 4T score (see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org)\textsuperscript{26} and the HIT Expert Probability (HEP) score\textsuperscript{27} (Table 2 in the Supplementary Appendix). These scoring systems have high negative predictive value but low positive predictive value. Both scores have limitations. The 4T score has modest interobserver agreement,\textsuperscript{28} whereas the HEP score is complex and has not been prospectively validated.\textsuperscript{27} A scoring system has been developed for use in patients who have undergone cardiopulmonary bypass surgery, but it too requires validation.\textsuperscript{29}

Two general types of serologic assays are used to diagnose heparin-induced thrombocytopenia: quantitative direct-binding assays that detect antibodies and functional assays that detect platelet activation induced by these antibodies. The direct-binding assays (or enzyme immunoassays) are readily available and measure antibodies binding to PF4–heparin complexes or similar molecules. These tests have a high sensitivity (approaching 100\%) but a low specificity.\textsuperscript{24,30,31} Thus, a negative test essentially rules out the diagnosis, and heparin-based anticoagulants can be used while alternative causes for the thrombocytopenia are sought.\textsuperscript{9-11} However, false positive results are common, which leads to a potential for overdiagnosis, even with modifications such as grading the relative amount of antibody (by measuring the optical density) and restricting antibody detection to the IgG subclass.\textsuperscript{30,31} In contrast, functional assays, such as the serotonin-release assay or the heparin-induced platelet-
Figure 2. The Coagulation Cascade.

The IgG–PF4–heparin immune complexes that characterize heparin-induced thrombocytopenia bind to the FcγRIIa on platelets, Fcγ receptor I (FcγRI) on monocytes, and potentially other cell surfaces. Tissue factor is expressed on the surface of the cell and on the released microparticles. This enhances the activation of factor VIIa, which in turn activates factor Xa and ultimately generates thrombin. The tissue factor–factor VIIa complex also activates factor IX, a component of the intrinsic pathway of coagulation. The hypercoagulable state caused by heparin-induced thrombocytopenia can result in venous or arterial thrombosis, particularly at sites of vascular damage. The agents used in treating heparin-induced thrombocytopenia inhibit clotting downstream of these sites of activation. Danaparoid and fondaparinux inhibit factor Xa, whereas argatroban and the hirudin-related agents inhibit thrombin.\textsuperscript{21,22}

aggregation test, have both a high sensitivity and a high specificity. The use of these tests is limited in clinical practice because of the lack of standardization, limited availability, and long turnaround times.\textsuperscript{1,2,9,23,32}

We think that patients with a high pretest probability (based on clinical experience or the application of a clinical scoring system) and a strongly positive IgG anti-PF4–heparin enzyme immunoassay do not need a functional test to confirm the diagnosis, although this strategy has not been validated in prospective studies. However, in patients who do not have a high clinical probability of heparin-induced thrombocytopenia, the enzyme immunoassay may be misleading and should not be used as the sole diagnostic test.

The most appropriate anticoagulant for use in patients with heparin-induced thrombocytopenia remains uncertain, but on the basis of the biology of the disorder, several attributes can be identified. It must be immediate-acting and capable of interrupting the activated coagulation cascade at the level of thrombin or factor Xa (Fig. 2); it should be associated with a low bleeding risk; it should not require monitoring or should be easily monitored; and perhaps most important, the physician should be familiar with its use. These attributes are important because, since it is often overdiagnosed, currently many patients receive treatment for heparin-induced thrombocytopenia even though they do not have this condition. Studies evaluating the anticoagulants used for heparin-induced thrombocytopenia have important methodologic limitations, including the use of historical controls, small sample sizes, and inconsistencies in the diagnosis of the disorder.\textsuperscript{10,11}

The characteristics of the anticoagulants used for the management of heparin-induced thrombocytopenia are listed in Table 1. Table 3 in the Supplementary Appendix describes the risks of bleeding and new thrombosis associated with these medications.

**Parenteral Direct Thrombin Inhibitors**

The parenteral direct thrombin inhibitors are widely used for managing heparin-induced thrombocytopenia (Fig. 2). Argatroban is approved by the Food and Drug Administration (FDA) in the United States for the treatment of heparin-induced thrombocytopenia, and bivalirudin is approved in the United States for percutaneous coronary intervention in patients who have or are at risk for heparin-induced thrombocytopenia. Desirudin is not approved for use in heparin-induced thrombocytopenia, but it is approved for prevention of deep-vein thrombosis after hip-fracture surgery. Lepirudin is approved for use in heparin-induced thrombocytopenia, but production was halted for business reasons in Europe in 2011 and in North America in 2012. Direct thrombin inhibitors cause a dose-dependent increase in the activated partial-thromboplastin time, which allows for simple monitoring; however, activated partial-thromboplastin time–based monitoring of these
agents can be confounded by consumptive coagulopathy, warfarin therapy, and liver disease.

Argatroban is a synthetic direct thrombin inhibitor derived from the amino acid L-arginine that reversibly binds to the active site of thrombin, inhibiting its catalytic activity. It has an immediate onset of action, and a steady-state anticoagulant effect is achieved within 1 to 3 hours. The standard regimen is an intravenous infusion of 2 μg per kilogram of body weight per minute. A reduced initial infusion rate is recommended for patients with impaired liver function, critically ill patients, and patients who have undergone cardiac surgery (Table 1). Because of its short half-life, the anticoagulant effect ends soon after the drug is discontinued, and rebound hypercoagulability may occur if the drug is discontinued while a procoagulant state still exists.33

Bivalirudin is a hirudin analogue that binds to both the active and fibrin-binding sites of circulating and clot-bound thrombin. It has a short half-life (approximately 25 minutes) and is cleared both renally and by enzymatic degradation. It is administered intravenously by continuous infusion. Bivalirudin has been used as the anticoagulant during cardiac surgery in patients with active or a recent history of heparin-induced thrombocytopenia.34 The dose for treatment of heparin-induced thrombocytopenia has not been established, although a regimen of 0.15 to 2.0 mg per kilogram per hour, adjusted for the activated partial-thromboplastin time, has been suggested (Table 1).35

Lepirudin and desirudin are recombinant hirudin derivatives that also directly inhibit free and fibrin-bound thrombin. The two recombinant hirudins differ slightly from one another and from the natural agent hirudin in amino acid sequence. Lepirudin has been extensively studied and approved for use in heparin-induced thrombocytopenia but is no longer being manufactured. Data regarding the use of desirudin in heparin-induced thrombocytopenia are limited, but a dose of either 15 or 30 mg subcutaneously every 12 hours has been suggested.

Danaparoid

Danaparoid is a mixture of nonheparin, low-molecular-weight, sulfated glycosaminoglycans including heparan sulfate, dermatan sulfate, and chondroitin sulfate. Danaparoid causes long-acting antithrombin-dependent inhibition of factor Xa.35 It was withdrawn from the U.S. market by the manufacturer in 2002 because of a short supply, but it is available and approved for the management of heparin-induced thrombocytopenia in

<p>| Table 1. Medications Used for Treatment of Heparin-Induced Thrombocytopenia. |</p>
<table>
<thead>
<tr>
<th>Agent</th>
<th>Clearance</th>
<th>Half-Life</th>
<th>Antidote</th>
<th>Dosing Regimen</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argatroban</td>
<td>Hepatobiliary</td>
<td>40–50 min</td>
<td>No</td>
<td>Intravenous infusion of 2.0 μg per kilogram of body weight per minute (no bolus); decrease initial infusion to 0.5–1.2 μg per kilogram per minute in patients with liver disease or critical illness or after cardiac surgery</td>
<td>Adjust dose to maintain activated partial-thromboplastin time at 1.5–3.0 times baseline value (maximum 10 μg per kilogram per minute)</td>
</tr>
<tr>
<td>Desirudin</td>
<td>Renal</td>
<td>2–3 hr</td>
<td>No</td>
<td>Fixed subcutaneous dose of 15 or 30 mg every 12 hr (most appropriate dose for treatment if heparin-induced thrombocytopenia has not been determined)</td>
<td>None required</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Enzymatic and renal</td>
<td>25 min</td>
<td>No</td>
<td>Dose not established; 0.15–2.0 mg per kilogram per hour (no bolus) has been suggested</td>
<td>Adjust dose to maintain activated partial-thromboplastin time at 1.5–2.5 times baseline value</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>Renal</td>
<td>24 hr</td>
<td>No</td>
<td>Intravenous bolus (1500 U if patient &lt;60 kg; 2250 U if 60 to &lt;75 kg; 3000 U if 75 to 90 kg; 3750 U if &gt;90 kg) followed by intravenous infusion of 400 U per hour for 4 hr, 300 U per hour for 4 hr, then 150–200 U per hour</td>
<td>Adjust to anti-Xa activity of 0.5–0.8 U per milliliter (with use of danaparoid standard curve)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Renal</td>
<td>17–20 hr</td>
<td>No</td>
<td>5.0 mg subcutaneously once daily for patients &lt;50 kg; 7.5 mg for 50–100 kg; 10.0 mg for &gt;100 kg</td>
<td>None required</td>
</tr>
</tbody>
</table>
Canada, Japan, Europe, and Australia. In vitro cross-reactivity of danaparoid with some of the antibodies that cause heparin-induced thrombocytopenia has been reported, but it is usually of only modest clinical significance. Monitoring for anti-Xa activity (calibrated for danaparoid) should be undertaken in patients with weight that is outside the range of 55 to 90 kg and in patients with acute renal failure (Table 1). Danaparoid can be administered subcutaneously or intravenously and does not cross the placenta.10

**Fondaparinux**

Fondaparinux is a synthetic, highly sulfated pentasaccharide that binds antithrombin, causing long-acting inhibition of activated factor X, but not thrombin.36 Fondaparinux is rapidly absorbed (in <30 minutes) after subcutaneous injection, and its half-life permits once-daily dosing (Table 1). Therapeutic doses (5.0 to 10.0 mg subcutaneously) seldom produce a prolongation in the activated partial-thromboplastin time. Although plasma levels can be measured with the use of an anti–factor Xa assay with a fondaparinux standard, routine anti-Xa monitoring is not required.37 The use of fondaparinux for heparin-induced thrombocytopenia in pregnancy has been reported, but experience is limited.10 Fondaparinux can initiate the formation of anti-PF4 antibodies; however, it generally does not support platelet activation by the newly formed immune complexes (Fig. 1).39-40 Fondaparinux-associated heparin-induced thrombocytopenia has been described in a handful of patients.40

**Transition to a Vitamin K Antagonist**

Heparin-induced thrombocytopenia is considered to be a risk factor for subsequent venous thromboembolism. Because this risk is reversible and transient, we suggest that anticoagulation be continued for 4 to 6 weeks in patients with isolated heparin-induced thrombocytopenia40,10,11 and for 3 months in patients with thrombosis. Early introduction of vitamin K antagonists (such as warfarin) should be avoided, since this has the potential to worsen the prothrombotic state through a rapid reduction in protein C, a natural anticoagulant.41 Once the platelet count has returned to a normal level after an acute episode of heparin-induced thrombocytopenia, warfarin should be slowly introduced at a dose of 5 mg or less daily and gradually increased to achieve an international normalized ratio (INR) between 2 and 3. Warfarin should overlap with the chosen parenteral agent for at least 5 days and until the INR is therapeutic.

With the direct thrombin inhibitors, dosing of vitamin K antagonists during the overlap period can be challenging since these agents, especially argatroban, cause an increase in the INR. The package insert for argatroban contains information on how to manage the transition to warfarin.42

The most appropriate agent for treating heparin-induced thrombocytopenia has not been established. Very few studies have made direct comparisons between agents, and the quality of evidence supporting the efficacy and safety of the various anticoagulants in these patients is weak.10 Direct thrombin inhibitors and danaparoid are favored treatments in published guidelines because they have been evaluated in large, prospective studies (albeit with methodologic limitations); however, these agents are more difficult to monitor and are rarely used in patients who do not have heparin-induced thrombocytopenia. We think that the use of unfamiliar anticoagulants, which are associated with important bleeding risks, presents one of the biggest challenges to the safe treatment of patients with suspected, presumed, or confirmed heparin-induced thrombocytopenia. This issue is further compounded because heparin-induced thrombocytopenia is often overdiagnosed. On the basis of emerging data showing efficacy and lower bleeding risks, our preference is to use fondaparinux, even though it is not FDA-approved, in patients with normal renal function. We would use argatroban in patients with impaired renal function. Agents with short half-lives, including argatroban, may be preferred in patients who are likely to require invasive procedures.

Routine monitoring of the platelet count in patients receiving heparin-based compounds may permit early diagnosis and treatment of heparin-induced thrombocytopenia. However, such monitoring can also result in unnecessary testing, inappropriate heparin discontinuation and substitution, increased cost, and patient anxiety. No studies have directly addressed this issue and, hence, the need for monitoring is controversial. A decision analysis performed as part of the most recent practice guidelines of the
American College of Chest Physicians (ACCP) on the treatment and prevention of heparin-induced thrombocytopenia suggests that monitoring of the platelet count (every 2 to 3 days from day 4 to day 14 or heparin discontinuation, whichever occurs first) is beneficial only when the risk of heparin-induced thrombocytopenia is greater than 1% (e.g., in postoperative patients receiving prophylactic or therapeutic unfractionated heparin or in patients who have undergone cardiac surgery who are receiving either unfractionated heparin or low-molecular-weight heparin).10

Currently, there is insufficient in vitro or clinical experience to make an evidence-based comment on the use of newer oral thrombin or factor Xa inhibitors for the management of heparin-induced thrombocytopenia. A prospective cohort study evaluating the safety and efficacy of the use of rivaroxaban to manage heparin-induced thrombocytopenia is recruiting patients (ClinicalTrials.gov number, NCT01598168).

Guidelines for the treatment of heparin-induced thrombocytopenia have been published by the ACCP10 and the Hemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology.43 The ACCP makes weak recommendations (grade 2C, or “desirable effects not clearly greater or less great than undesirable effects, low-quality evidence44) for the use of argatroban, lepirudin, or danaparoid over other nonheparin anticoagulants in patients with normal renal function and for argatroban over other nonheparin anticoagulants in patients with impaired renal function. Lepirudin and full-dose danaparoid are favored by the British guidelines; however, argatroban was not available in the United Kingdom when these recommendations were written.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has a high pretest probability of heparin-induced thrombocytopenia. We would perform a platelet-activating assay such as the serotonin-release assay to confirm the diagnosis; however, if such a test were not available, a strongly positive test for IgG anti-PF4–heparin antibodies would be sufficient for the diagnosis in this patient. Heparin should be immediately discontinued, and a nonheparin anticoagulant should be administered in therapeutic doses. Given his normal renal function, we recommend fondaparinux at a dose of 7.5 mg subcutaneously once daily. The platelet count should be followed closely, and a vitamin K antagonist should be started when the platelet count has recovered to at least 150×10^9 per liter. The administration of fondaparinux and the vitamin K antagonist should overlap for at least 5 days or until the INR is within the therapeutic range for 2 consecutive days. Since this patient had thrombosis with heparin-induced thrombocytopenia, we would recommend continuing the vitamin K antagonist for 3 months. The patient should be advised to avoid heparin, especially in the subsequent 3 to 4 months after the diagnosis of heparin-induced thrombocytopenia, and to consult with a specialist if heparin is needed in the future.14

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Ishac Nazi, Jane Moore, and Aurelio Santos for their help in the preparation of an earlier draft of the manuscript and Mark Crowther, Theodore Warkentin, and Peter Horsewood for reviewing an earlier draft of the manuscript.

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