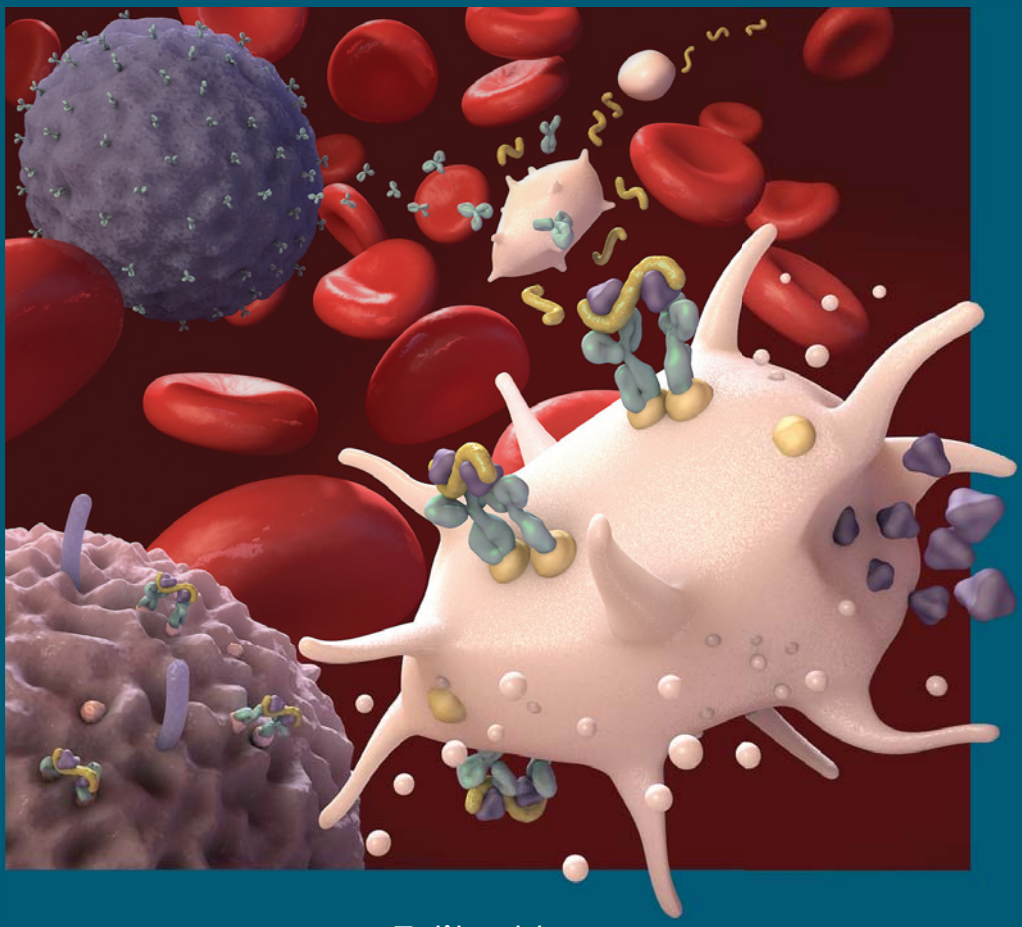
FUNDAMENTAL AND CLINICAL CARDIOLOGY SERIES

HEPARIN-INDUCED THROMBOCYTOPENIA

Fifth Edition



Edited by
Theodore E. Warkentin
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To the late Professor Michael F. X. Glynn, for initiating my hemostasis interests; to Dr. John G. Kelton, for amplifying these through boundless opportunities; and to Erica, Andrew, Erin, and Nathan, for downregulating my passion, as a caring family must.

—T.E.W.

To my co-workers and students for their contributions and efforts; to Sabine, Sebastian, Anja, and Jan.

—A.G.

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Preface

The first edition of *Heparin-Induced Thrombocytopenia* appeared 13 years ago. Even then we were asked: *Why write a book about HIT?* After all, heparin use will progressively diminish, and so correspondingly will incidents of HIT. Yet, both of us continue to see patients with HIT regularly in our own practices, and every week our reference laboratories confirm the presence of platelet-activating anti-platelet factor 4 (PF4)/heparin antibodies in several new patients referred from other hospitals.

We continue to learn new aspects of HIT treatment. For example, "PTT confounding" describes the situation where systematic interruption and underdosing of partial thromboplastin time (PTT)-adjusted direct thrombin inhibitor (DTI) therapy occurs in a patient with HIT who has concomitant coagulopathy, potentially resulting in treatment failure; avoiding this problem with (non-PTT-adjusted) danaparoid (and possibly also fondaparinux) therapy illustrates one of the new treatment concepts that first appears in this fifth edition.

Patients with ventricular assist devices—including "bridge to transplant" candidates—are at highest risk for HIT. If this reaction occurs, the concept of using heparin for subsequent cardiac transplantation—as long as the functional assay is negative, and even if the antigen assay is still positive—is another important result of recent HIT research.

New ideas regarding pathogenesis have emerged: HIT plausibly represents a misdirected antimicrobial immune response, as the key immunogen (PF4) binds not only to heparin but also to bacteria, thereby triggering a "presensitizing" anti-PF4/heparin immune response. Indeed, the rare occurrences of HIT in unusual clinical settings—such as post-infection or after orthopedic surgery performed without heparin use (so-called "spontaneous" HIT)—or perhaps even as a consequence of heparin adulterated with oversulfated chondroitin sulfate—illustrate new aspects of HIT immunopathogenesis.

The growing recognition of heparin-*in*dependent platelet-activating properties of some HIT antibodies—and their transience—helps explain certain unusual presentations such as "delayed-onset" HIT. This phenomenon also accounts for misattribution of heparin-bonded vascular grafts as a cause of HIT post-vascular surgery; in this situation, the more likely explanation is the unusual "autoimmune-like" nature of the HIT antibodies themselves.

Newer, rapid immunoassays to detect HIT antibodies are being developed, but to avoid HIT "overdiagnosis", the importance of quantitative interpretation of immunoassays and of testing for platelet-activating antibodies remains central for correct diagnosis.

Since the fourth edition, fondaparinux has emerged as a rational—and simple—therapy for HIT that might presage future success with the *new* oral anticoagulants (e.g., rivaroxaban, apixaban, dabigatran). This is in marked contrast to the *old* oral anticoagulants—warfarin and other vitamin K antagonists—which are

contraindicated for managing acute HIT because of their propensity to precipitate microthrombosis and limb gangrene. Partially desulfated heparin, which binds to PF4 despite having minimal anticoagulant activity, has the potential to reduce risk of HIT when given together with heparin.

These and numerous other paradoxes and myths concerning HIT are of importance to clinicians who encounter thrombocytopenic patients in diverse clinical settings.

SPECIAL THANKS

A multi-author book depends on many contributors. For us, as editors, it was a delight to produce this fifth edition with many of our colleagues throughout the world. We want to acknowledge the publishing team (Manoj Arun, Oscar Heini, and Claire Bonnett), and also Erin Warkentin for the cover art. In Hamilton, we would like to thank Maria Adamek, Jo-Ann Sheppard, James Smith, Jane Moore, Carol Smith, Diana Moffatt, Aurelio Santos, Rumi Clare, Ishac Nazi, Donnie Arnold, Menaka Pai, Peter Horsewood, and John Kelton; in Greifswald, gratitude is owed to Uta Alpen, Sixten and Kathleen Selleng, Tamam Bakchoul, Thomas Thiele, Gregor Hron, Ariane Sümnig, Birgitt Fürll, Ulrike Strobel, Ricarda Raschke, and Carmen Blumentritt, for their invaluable technical and administrative support, for ideas and discussions, and especially for being part of the team dedicated to research in HIT.

Theodore E. Warkentin
Andreas Greinacher

1 History of heparin-induced thrombocytopenia

Theodore E. Warkentin

THE DISCOVERY OF HEPARIN AND ITS FIRST CLINICAL USE

The following account of the discovery and first clinical development of heparin was recorded by the physiologist Best (1959), a codiscoverer of insulin as well as a pioneer in the studies of heparin. Incidentally, in 1916, while working at Johns Hopkins University to characterize procoagulant substances, McLean (1916) identified a natural anticoagulant substance. Further studies of this material were performed by his supervisor, Dr. Howell, who coined the term, "heparin" to indicate its first extraction from animal hepatic tissues (Gr. ἡπαρ [hepar], liver) (Howell and Holt, 1918). Despite its *in vitro* anticoagulant action, the inability of heparin to prevent platelet-mediated thrombosis (Shionoya, 1927) made it uncertain whether it had antithrombotic potential. However, animal (Mason, 1924) and human studies (Crafoord, 1937) showed that heparin could prevent thrombosis. By the 1950s, heparin was established as an important therapeutic agent in the treatment of venous and arterial thrombosis.

THE PARADOX OF HEPARIN AS A POSSIBLE CAUSE OF THROMBOSIS

Weismann and Tobin

On June 1, 1957, at the Fifth Scientific Meeting of the International Society of Angiology (North American Chapter) in New York, two physicians suggested that heparin might cause arterial embolism in some patients. Rodger E. Weismann, a 43-year-old Assistant Professor of Clinical Surgery at the Dartmouth Medical School (Fig. 1.1), and his Resident in Surgery, Dr. Richard W. Tobin, presented their 3-year experience with 10 patients who developed unexpected peripheral arterial embolism during systemic heparin therapy at the Mary Hitchcock Memorial Hospital, in Hanover, New Hampshire. Their first patient with this complication was reported in detail, and to this day represents a classic description of the syndrome:

> This 62-yr-old white woman was admitted to the Hitchcock Hospital Feb 8, 1955, with left retinal detachment, complicating longstanding myopia ... Left scleral buckling was carried out on Feb 10, and strict bed rest was required during the ensuing 3 wk. On her beginning ambulation, on March 6, signs and symptoms of left iliofemoral thrombophlebitis were noted, for which systemic heparinization was begun (… heparin sodium in divided subcutaneous doses, totaling 150–300 mg per day…). On March 16, after 10 days of anticoagulation therapy, sudden signs of right common femoral arterial occlusion led to the diagnosis of common femoral arterial embolism. Successful femoral embolectomy was carried out. She was kept on adequate heparinization and made a satisfactory initial recovery until March 19, ... when signs of sudden occlusion of the distal aorta appeared.

FIGURE 1.1 Photograph of Dr. Rodger Elmer Weismann, taken *circa* 1958.

> ... [P]rompt transperitoneal distal aortic and bilateral iliac embolectomies were performed. In the ensuing 24 h, because unsatisfactory distal circulation persisted, the patient underwent left femoral exploration, with negative findings, and right popliteal exploration, revealing an embolus. She subsequently pursued a favorable course, ... never showing more serious ischemic changes than a small area of superficial gangrene of the right great toe and several small areas of skin infarction of the right leg (Weismann and Tobin, 1958).

The report included a photograph of the emboli removed from the distal aorta and both iliac arteries, with the authors noting their "unusual length and cylindrical shape, suggesting origin in [the] proximal aorta," as well as a corresponding photomicrograph of the embolus. The thromboemboli were described by the authors as "pale, soft, salmon-colored clots" that "histologically ... were comprised mostly of fibrin, platelets and leukocytes; red cells were rare." This appearance was distinguishable from the typical appearance of thrombi originating in the heart (i.e., mulberry-colored thrombi tending to contain cellular elements of the blood in approximately normal proportions), leading the authors to propose "the source for the emboli ... to be aortic mural platelet-fibrin thrombi."

A summary of the 10 reported patients noted that the onset of arterial embolism began between 7 and 15 days, inclusive, of commencing heparin treatment (mean, day 10). Multiple thromboemboli occurred in nine patients; six of the patients died as a direct result of these complications; two survived with extensive amputations, and two were discharged with their extremities intact. The temporal time frame was consistent with the later realization by others that this syndrome represented an immune-mediated reaction initiated by the heparin.

The authors noted that further embolization stopped when the heparin was discontinued, leading to their recommendation that "heparin should be promptly reduced in dosage, and, if possible, discontinued if the presence of fibrin-platelet thrombi adherent to the intima of the aorta is suspected." Aggressive surgical management of emboli was also recommended, as some limbs were salvageable in this way. The authors summarized well the clinical dilemma: "In each instance there was a feeling of futility in the management of the problem, due to anticipation of further emboli from the same or similar sources. Heparin was badly needed to

retard distal thrombosis; yet the agent was probably seriously altering the integrity and attachment of the thrombotic source" (Weismann and Tobin, 1958).

Roberts and Colleagues

The communication of Weismann and Tobin was met with considerable skepticism. When a show of hands was elicited to indicate those surgeons who had also observed similar events, none was raised (Weismann, personal communication, July 1998). However, a few years later, Roberts and colleagues from the University of Pennsylvania in Philadelphia described a series of patients who were remarkably similar to those reported by Weismann and Tobin (Roberts et al., 1964; Barker et al., 1966; Kaupp and Roberts, 1972). The key features were summarized as follows:

> To witness a series of apparently paradoxical events is disconcerting as well as challenging. When such paradoxes involve totally unexpected results following the use of a major therapeutic agent, it is at first difficult to know whether the relationship is causal or merely coincidental. When, however, the same series of events has been seen repeatedly it is difficult to escape the conclusion that there is some causal relationship, even though the mechanism by which it is accomplished may be unknown ... . During the last 9 yr at the Hospital of the University of Pennsylvania, we have seen a group of 11 patients who suffered unexplained arterial embolization for the first time while being treated with heparin for some condition that could not of itself reasonably be expected to cause arterial emboli ... . All patients had been receiving heparin for 10 days or more when the initial embolus occurred ... . All emboli removed were of a light color, seemingly made up primarily of fibrin and platelets, and microscopically appeared to be relatively free of red cells. All patients in this group had multiple emboli ... . Of the four deaths, three were attributed to cerebral vascular accidents presumably embolic in origin and one was thought to have resulted from a perforation of the small bowel 2 wk after the removal of a mesenteric embolus (Roberts et al., 1964).

Roberts' group also viewed the likely pathogenesis as that of embolization of platelet–fibrin-rich material originating within the aorta, rather than the heart. Furthermore, they believed that the thrombi were initially formed on aortic ulcerations that acted as a nidus for thrombus formation. This pathogenesis was suggested by the observation that such adherent thrombi could be removed from the proximal aorta in a few of the patients (Roberts et al., 1964; Kaupp and Roberts, 1972).

An Immune Basis for Heparin-Induced Thrombosis?

The delay between initiation of heparin therapy and onset of embolization caused Roberts and colleagues (1964) to speculate that the etiology could represent an "antiheparin factor," resulting perhaps from "an antigen–antibody mechanism." Furthermore, the observation that the first 21 patients reported with this syndrome from both Hanover and Philadelphia had received heparin exclusively by subcutaneous or intramuscular, rather than intravenous, injection also was offered by Roberts' group as support for immune sensitization. Apparent heparin-induced thrombosis did not seem rare to these investigators: at least 13 of 110 (12%) patients with peripheral arterial emboli managed by the Philadelphia group over a decade were believed to have been caused by preceding heparin treatment (Barker et al., 1966).

HEPARIN-INDUCED THROMBOCYTOPENIA AND PARADOXICAL THROMBOSIS

Heparin-Induced Thrombocytopenia

Routine platelet count measurements were not a feature of hospital laboratory practice until the 1970s, and neither the Hanover nor Philadelphia surgeons reported thrombocytopenia in their patients with heparin-induced arterial thrombosis. Ironically, the first report of severe heparin-induced thrombocytopenia (HIT) involved a patient who did not develop paradoxical thrombosis. Natelson and coworkers (1969) reported on a 78-year-old man with prostate carcinoma and pulmonary embolism (PE), who on day 10 of treatment with therapeutic-dose heparin developed severe thrombocytopenia. Three days after discontinuing the heparin therapy, the patient's fibrinogen level dropped to 1 g/L, attributed to carcinoma-associated disseminated intravascular coagulation (DIC). Heparin treatment was restarted, and although fibrinogen levels normalized, the platelet count reduced to 5×10^9/L, rising to 115×10^9/L six days after stopping heparin administration. Simultaneously, however, the fibrinogen value fell to less than 0.5 g/L. When heparin was given for the third time, the platelet count fell over two days to 10×10^9/L, although the fibrinogen values again normalized. *In vitro* studies showed that heparin added to the patient's citrated platelet-rich plasma produced platelet count reductions. This early report of severe HIT is interesting, as it illustrates the dichotomy of heparin reproducibly producing severe thrombocytopenia while maintaining anticoagulant activity (correction of DIC). However, it remained for later workers to link thrombocytopenia and thrombosis to heparin therapy.

Rhodes, Dixon, and Silver: "HIT with Thrombotic and Hemorrhagic Manifestations"

Laboratory evidence implicating an immune basis for HIT was first provided by studies performed by a vascular surgeon (Donald Silver; Fig. 1.2), together with a hematology resident (R. H. Dixon) and a medical student (Glen R. Rhodes),

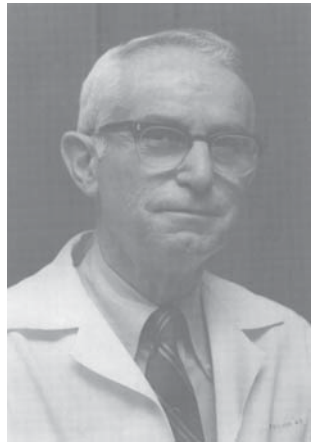

FIGURE 1.2 Photograph of Dr. Donald Silver, taken *circa* 1975.

who subsequently became a vascular surgeon. The first two patients described by Silver's group (Rhodes et al., 1973) developed severe thrombocytopenia (platelet count nadirs, 8 and 10×10^9/L), myocardial infarction, petechiae, and heparin resistance, with complete platelet count recovery on discontinuing heparin treatment.

Both patients developed rapid recurrence of thrombocytopenia when heparin rechallenges were given within 1 week of platelet count recovery.

The immune basis of this syndrome was suggested by several laboratory observations. First, increased platelet consumption was suggested by increased numbers of marrow megakaryocytes, as well as immediate recurrence of thrombocytopenia on reexposure to heparin. Second, a circulating platelet-activating substance was found in both the patients' blood: patient, but not control, serum resulted in aggregation of normal donor platelets in the presence of heparin (Fig. 1.3). Third, the possible identity of the aggregating agent as an immunoglobulin G (IgG) was shown by fractionation of one patient's serum to show the presence of heparin-dependent, complement-fixing activities within the IgG fraction.

A second report from this group (Rhodes et al., 1977) represented the landmark study in establishing HIT as a distinct syndrome. Eight patients were reported with thrombocytopenia that occurred during intravenous therapeutic-dose or subcutaneous prophylactic-dose heparin. The mean platelet count nadir was 25 (range, $5–54 \times 10^9$/L). The predominance of thrombotic, rather than hemorrhagic, complications was demonstrated: seven patients had new or recurrent thromboembolic events, and the remaining patient had a stroke leading to evacuation of a temporal lobe hematoma. Complement-fixing, heparin-dependent antibodies were identified in five of the patients. The authors also cited the previous works by Weismann and Tobin (1958) and Roberts and colleagues (1964) as likely representing the identical syndrome. Thus, for the first time, the concept of an immune-mediated hypercoagulable state, with a predisposition to arterial thromboembolism that occurred in association with thrombocytopenia, was proposed.

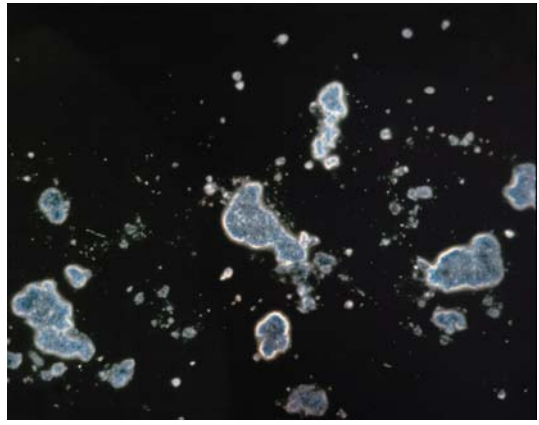

FIGURE 1.3 Heparin-induced thrombocytopenia antibody–induced platelet aggregates from an experiment in the early 1970s. Magnification approximately 250–500×. Photomicrograph provided by Dr. Glen R. Rhodes, Palmyra, VA. *Source*: From Warkentin (2011a).

Platelet-Activating Antibodies in the Pathogenesis of HIT

Although some limited studies of heparin-dependent platelet aggregation by patient serum were performed in the classic paper by Rhodes and colleagues (1973), the next few years saw increasing emphasis on this characteristic feature of HIT antibodies. In 1975, National Institutes of Health investigators Fratantoni et al. described a patient who developed severe thrombocytopenia (4×10^9/L) and PE while receiving therapeutic-dose unfractionated heparin (UFH) to treat deep vein thrombosis (DVT). Recurrent thrombocytopenia resulted following heparin rechallenge. The patient's serum produced both aggregation and serotonin release from normal platelets in the presence of heparin. The platelet-activating factor was presumed, but not proved, to be caused by an antibody.

During the next 5 years, at least eight groups of investigators reported similar patients, confirming the presence of heparin-dependent, platelet-activating antibodies (Babcock et al., 1976; Green et al., 1978; Nelson et al., 1978; Trowbridge et al., 1978; Wahl et al., 1978; Cimo et al., 1979; Hussey et al., 1979; Cines et al., 1980). Babcock and colleagues (1976) described five patients who developed thrombocytopenia (mean platelet count nadir, 28×10^9/L) during heparin treatment; heparin-dependent antibodies were detected that produced platelet factor 3 activity (i.e., patient globulin fractions incubated with heparin, platelet-rich plasma, and celite-activated contact product shortened the clotting time following recalcification). Three patients developed thrombotic complications, and none developed hemorrhage. The five patients were observed within a 6-week time span, leading the authors to suggest that "this syndrome may occur more often than has previously been suspected."

A consistent theme was evident from these various reports. Patients developed arterial or venous thrombotic complications, in association with thrombocytopenia, that generally began after five or more days of heparin treatment. A platelet-activating antibody that aggregated platelets suspended in citrated plasma was usually detected. The platelet count nadirs seen in some of the larger series (e.g., 33 and 48×10^9/L, respectively) observed by Cimo et al. (1979) and Hussey et al. (1979), were higher than in previous reports, indicating that as recognition of the syndrome grew, less severely thrombocytopenic patients were recognized.

The "White Clot Syndrome"

Jonathan Towne, a vascular surgeon in Milwaukee, reported with his colleagues that the pale thrombi characteristic of this syndrome consisted of fibrin–platelet aggregates (electron microscopy). These workers coined the term "white clot syndrome" to describe the characteristic appearance of these arterial thromboemboli (Towne et al., 1979). Ironically, their report was also the first to note the occurrence of phlegmasia cerulea dolens (severe venous limb ischemia) that progressed to venous limb gangrene in two of their patients (i.e., a syndrome of limb loss due to extensive venous thrombosis without arterial white clots). Nonetheless, the designation of white clot syndrome has become virtually synonymous with HIT in both North America and Europe (Benhamou et al., 1985; Stanton et al., 1988), despite the lack of specificity of these thrombi for HIT (see chap. 2).

NONIMMUNE HEPARIN-ASSOCIATED THROMBOCYTOPENIA

Nonimmune Mechanisms in Heparin-Associated Thrombocytopenia

Klein and Bell (1974) reported on two patients who developed severe thrombocytopenia, thrombotic complications, and DIC, with hypofibrinogenemia and

microangiopathic red cell abnormalities; that is, these patients probably had severe HIT. This experience prompted Bell to perform the first prospective study investigating the frequency of thrombocytopenia complicating therapeutic-dose UFH (Bell et al., 1976). Sixteen of 52 patients (31%) developed a platelet count fall to less than 100×10^9/L, and some of these patients developed hypofibrinogenemia and elevated fibrin(ogen) degradation products. The authors speculated that a "thromboplastic contaminant" extracted along with heparin from beef lung could explain the thrombocytopenia. A subsequent randomized controlled trial by Bell and Royall (1980) found the frequency of thrombocytopenia to be higher in patients who received bovine heparin (26%) compared with heparin of porcine intestinal origin (8%).

These investigators found no platelet-activating antibodies in plasma from the patients who developed thrombocytopenia (Alving et al., 1977), leading Bell (1988) to challenge the view that an immune pathogenesis explained HIT. However, as the Johns Hopkins group did not report thrombotic complications in any of their 37 patients who developed thrombocytopenia in their prospective studies, and given the apparent early onset of thrombocytopenia in many of their patients, it is likely that most of their patients did not have immune-mediated HIT.

Nonimmune (Type I) *vs* Immune (Type II) HIT

A confusing situation arose. The terms "heparin-induced thrombocytopenia" or "heparin-associated thrombocytopenia" were often applied to any patient who developed thrombocytopenia during heparin therapy, whether presumed or proved to be caused by heparin-dependent antibodies or otherwise. Investigators in Australia, led by Chong (1981), also observed patients with thrombocytopenia in whom heparin-dependent, platelet-activating IgG antibodies could be identified. In a subsequent report that appeared in the *Lancet*, two distinct syndromes of "HIT" were described by Chong and colleagues (1982). The first, called "group 1," developed severe, delayed-onset thrombocytopenia with thrombotic complications in association with IgG antibodies that caused platelet activation. In contrast, "group 2" patients had mild asymptomatic thrombocytopenia of early onset.

In 1989, at a Platelet Immunobiology Workshop in Milwaukee, it was suggested to Chong that terminology describing these two types of HIT be formalized. Accordingly, Chong recommended the terms in a review article that appeared in Blut (Chong and Berndt, 1989), although (in reverse of the *Lancet* article nomenclature) the early, nonimmune disorder was named "HIT type I" and the later-onset, immune disorder was referred to as "HIT type II." These terms subsequently became popular.

LABORATORY TESTING TO CHARACTERIZE THE HIT SYNDROME

A Sensitive and Specific Platelet Activation Assay for HIT

The development and application of sensitive and specific laboratory tests for detecting HIT antibodies resulted in a new era in HIT research. Historical accounts of these developments can be found elsewhere (Kelton and Warkentin, 2008; Warkentin, 2012).

Many clinical laboratories began to use platelet aggregation assays (Fratantoni et al., 1975; Babcock et al., 1976) to diagnose HIT. Problems with this type of assay, however, included low sensitivity (Kelton et al., 1984) as well as technical limitations in simultaneous evaluation of multiple patient and control samples. In 1983–1984, while working as a research fellow in the McMaster University laboratory of John Kelton, Dave Sheridan overcame problems of low test sensitivity by showing that

washed platelets, resuspended in a buffer containing physiologic concentrations of divalent cations, were very sensitive to platelet activation by HIT sera (Sheridan et al., 1986). The assay, known as the "platelet serotonin release assay (SRA)," was adapted from a method of platelet washing developed at McMaster University by the laboratory of Dr. Fraser Mustard. In particular, the emphasis on using physiologic calcium concentrations was based on observations that "artifacts" of agonist-induced platelet activation were caused by the use of citrate anticoagulation resulting in low plasma calcium concentrations. One example of an artifact induced by citrate is that of two-phase aggregation triggered by adenosine diphosphate (ADP). At physiologic calcium concentrations, only weak single-phase aggregation without thromboxane generation is triggered by ADP (Kinlough-Rathbone et al., 1983). Fortuitously, the washed platelet technique previously developed at McMaster University by Mustard and colleagues that Sheridan evaluated for its HIT serum-sparing properties rendered platelets far more sensitive to the platelet-activating properties of HIT antibodies than assays based on citrated platelet-rich plasma. Modified washed platelet assays have subsequently been developed by other investigators (see chap. 11).

Sheridan and colleagues also made the observation that heparin concentrations strongly influenced platelet activation by HIT sera: therapeutic (0.05–1 U/mL), but not high (10–100 U/mL), heparin concentrations resulted in platelet activation, that is, the characteristic "two-point" serotonin release activation profile of HIT. Later, Greinacher and colleagues (1994) showed that high heparin concentrations in solution release platelet factor 4 (PF4) from PF4/heparin (PF4/H) complexes bound covalently to a solid phase, with a corresponding decrease in binding of HIT antibodies to the surface. Thus, the inhibition of platelet activation by high heparin concentrations probably results from a similar disruption of the multimolecular antigen complex on the platelet surface.

The high sensitivity of washed platelets to activation by HIT antibodies led to new insights into the pathogenesis of platelet activation. For example, 2 years after describing their washed platelet assay for HIT, Kelton and coworkers (1988) reported that the platelet activation process was critically dependent on the platelet Fc receptor. This represented a fundamental new pathobiologic mechanism in a drug-induced thrombocytopenic disorder.

Prospective Studies of Serologically Defined HIT

Although several prospective studies of the frequency of HIT were performed (see chap. 4), until the 1990s, none had systematically evaluated serum or plasma from study participants for HIT antibodies. Often the distinction between "early" and "late" thrombocytopenia was blurred. Thus, the relative frequency and clinical importance of immune versus nonimmune HIT were unclear. This is illustrated by a prospective study reported by Powers and colleagues (1979) that found HIT to be "uncommon" during treatment with porcine mucosal heparin, as "only" four of 120 (3%) patients developed thrombocytopenia, in contrast to the 26–31% frequency of thrombocytopenia reported for bovine lung heparin. However, two of these 120 patients probably died as a result of HIT-associated thrombosis (Warkentin and Kelton, 1990), underscoring the need for a specific laboratory marker for this immune-mediated syndrome.

In a prospective study of HIT that performed systematic testing for HIT antibodies (Warkentin et al., 1995), the authors showed the dramatic clinical effects of

HIT. Of 665 patients participating in a clinical trial of UFH versus low molecular weight heparin (LMWH) after orthopedic surgery, nine patients developed "late" thrombocytopenia serologically confirmed to represent HIT. These patients had a thrombotic event rate far greater than controls. Moreover, the spectrum of thrombosis in HIT patients included venous thromboembolism, rather than only the classic problem of arterial thrombosis. This study also showed that early postoperative thrombocytopenia occurred frequently, but was not explained by HIT antibodies (see chap. 3).

However, even this study did not initially capture the complete clinical profile of HIT. This is because it defined the platelet count fall indicating possible HIT using the "standard" definition of thrombocytopenia, that is, a platelet count fall to less than 150×10^9/L (Warkentin et al., 1995). Subsequent review of the database, together with correlative analysis of the results of systematic serologic testing for HIT antibodies (performed in most study subjects), showed that this standard definition underestimated the number of patients who had HIT (Warkentin et al., 2003). Rather, a proportional fall in platelet count (50% or greater)—in relation to the postoperative peak platelet count—provided a more accurate definition of thrombocytopenia (applicable at least to this postoperative patient population). This improved definition identified twice as many patients as having had HIT in this clinical trial, without compromising diagnostic specificity. Indeed, the study suggested that the risk of immune HIT is about 5% (16/332 = 4.8%) in postoperative orthopedic surgery patients receiving UFH for a week or more (see chap. 4).

THE TARGET ANTIGEN OF HIT: PF4/HEPARIN

In 1992, Jean Amiral, working in the laboratory of Dominique Meyer, reported that the antigen recognized by HIT antibodies was a complex between heparin and PF4, an endogenous platelet α-granule protein (Amiral et al., 1992). This important discovery created an explosion of basic studies in numerous laboratories that led to further characterization of the basic pathogenesis of HIT (see chaps. 5–10). Amiral's discovery also fostered the development of new assays for HIT antibodies based on enzyme immunoassay techniques (see chap. 11).

The antigen site(s) recognized by HIT antibodies were identified as being on PF4, rather than on heparin itself or a compound antigen (Li et al., 2002) (see chaps. 6 and 7). This observation highlights intriguing parallels between HIT and the antiphospholipid syndrome. This latter disorder is also characterized by pathogenic antibodies directed against one or more proteins that express neoepitopes when bound to certain negatively charged phospholipid surfaces (see chap. 3). The presence of neoepitopes on the "self" protein, PF4, suggests that HIT can be conceptualized as a transient, drug-induced, platelet- and coagulation-activating autoimmune disorder. Indeed, high-titer HIT antibodies that are able to activate platelets *in vitro* even in the absence of pharmacologic heparin have been associated with the onset of thrombocytopenia and thrombosis beginning several days after heparin has been discontinued, so-called delayed-onset HIT (Warkentin and Kelton, 2001) (see chap. 2).

CENTRAL PARADIGM OF HIT

The "central paradigm" of HIT is that of a clinicopathologic syndrome in which laboratory detectability of heparin-dependent IgG antibodies is central (Warkentin et al., 1998, 2011b; Warkentin, 2011a,b), as the pathologic antibodies activate platelets

via their FcγIIa receptors (i.e., the platelet IgG receptors). This concept of HIT was also supported by a murine double transgenic model expressing both human PF4 and FcγIIa receptors (Reilly et al., 2001) (see chap. 10).

HIT as a Clinicopathologic Syndrome

The term "clinicopathologic" (or "clinical-pathological") syndrome, as applied to HIT, indicates that a patient must have one or more clinically evident events—almost always prominent thrombocytopenia and oftentimes associated new or progressive thrombotic events—as well as detectability of heparin-dependent platelet-activating antibodies. (The term "detectability" is used to indicate that antibodies are expected to be present if the appropriate assay is performed using a blood sample obtained during—or soon after—the period of thrombocytopenia. However, in practice, the presence of such antibodies is often inferred when high levels of anti-PF4/H antibodies are detected by a PF4-dependent immunoassay.) Thus, a patient without discernable clinical events does not have HIT, and a patient in whom these antibodies cannot be detected—no matter how persuasive the clinical picture—also does not have HIT (see chaps. 3 and 11).

Iceberg Model of HIT

Serosurveillance studies of heparin-treated patients led to the recognition that platelet-activating HIT antibodies comprise a subset of patients with anti-PF4/H antibodies of IgG class, and that patients with IgG class antibodies represent a subset of those who form antibodies of any of the three major immunoglobulin classes, IgG, IgA, and IgM. Crucially, clinical HIT is found only within the patients who form platelet-activating antibodies. Figure 1.4 depicts these interrelationships as an "iceberg model," in which clinically evident HIT is represented by the portion of the iceberg that protrudes above the waterline (Warkentin, 2011b). Just as only 10% of an iceberg juts out of the water, similarly only approximately 10% of immunoassay-positive patients in one clinical trial developed HIT (Warkentin et al., 2005b) (however, in certain other patient populations, such as postcardiac surgery patients, less than 2% of immunoassay-positive patients evince HIT) (Warkentin et al., 2000). More recently, the striking relationship between strength of immunoassay test result [expressed in optical density (OD) values], and the probability of platelet-activating antibodies being detected, has been recognized (Fig. 1.4).

Overdiagnosis of HIT

Because thrombocytopenia occurs very often for non-HIT reasons among heparin-treated patients, and because many immunoassay-positive patients do not have HIT, a growing problem has been the "overdiagnosis" of HIT. Overall, approximately 50% of immunoassay-positive patients recognized through clinically driven test requests will not have HIT (Greinacher et al., 2007; Lo et al., 2007; Warkentin et al., 2008b), and this proportion increases to 80–85% when critically ill patients are considered (Levine et al., 2010).

TREATMENT OF THROMBOSIS COMPLICATING HIT

Thrombosis is a remarkably common complication of HIT. The greatly increased relative risk for thrombosis in HIT (~10 to 15) exceeds that of virtually all other prothrombotic risk factors (see chap. 2). And, unlike most other risk factors, HIT

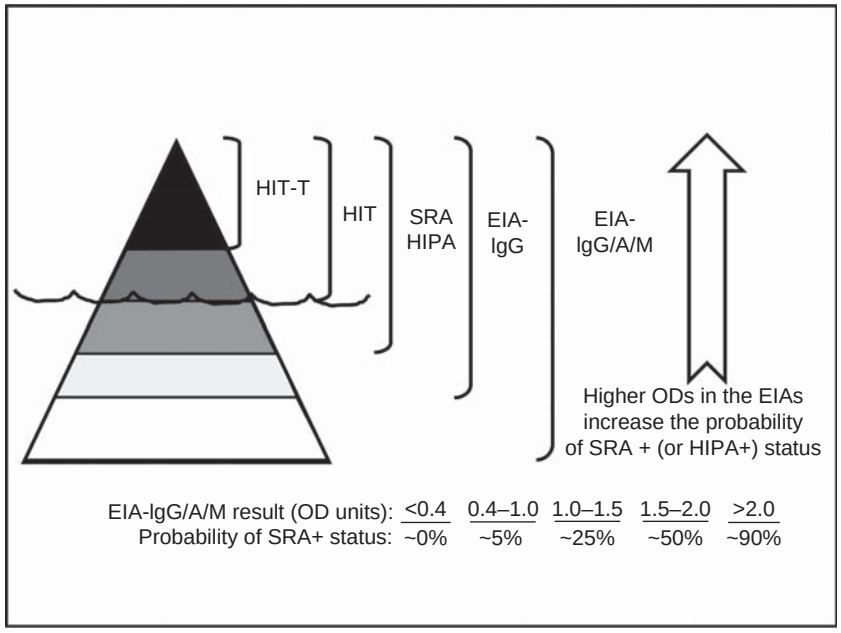

FIGURE 1.4 "Iceberg model" of HIT. Clinical HIT, comprising HIT with (HIT-T) or without thrombosis, is represented by the portion of the iceberg above the waterline; the portion below the waterline represents subclinical anti-PF4/H seroconversion. Three types of assays are highly sensitive for the diagnosis of HIT: the washed platelet activation assays, SRA, and HIPA test, the IgG-specific PF4-dependent EIAs (EIA-IgG), and the polyspecific EIAs that detect anti-PF4/H antibodies of the three major immunoglobulin classes (EIA-IgG/A/M). In contrast, diagnostic specificity varies greatly among these assays, being the highest for the platelet activation assays (SRA and HIPA) and lowest for the EIA-IgG/A/M. This is because the EIA-IgG/A/M is most likely to detect clinically irrelevant, non–platelet-activating anti-PF4/H antibodies. The approximate probability of SRA+ status in relation to a given EIA result, expressed in OD units, was obtained from the literature (Warkentin et al., 2008b). *Abbreviations*: EIA, enzyme immunoassay; HIPA, heparin-induced platelet activation (test); HIT, heparin-induced thrombocytopenia; OD, optical density; PF4/H, PF4/heparin; SRA, serotonin release assay. *Source*: From Warkentin (2011b).

exerts its prothrombotic effects only over a few weeks. The treatment of HIT is discussed in chapters 12–17. Here, we discuss only a few vignettes relating to the initial use of selected treatments for HIT.

Danaparoid Sodium

In 1982, a 48-year-old vacationing American developed DVT and PE following a transatlantic flight to Germany. Heparin treatment was complicated by thrombocytopenia and progression of venous thrombosis. Professor Job Harenberg of Heidelberg University, who had performed phase I evaluations of the experimental glycosaminoglycan anticoagulant, danaparoid, requested this agent from the manufacturer (NV Organon, The Netherlands). The platelet count recovered and the venous thrombosis resolved (Harenberg et al., 1983, 1997). Over the next 6 years, this patient developed recurrent thromboembolic events, and was successfully treated each time with danaparoid. This favorable experience led to a

named-patient, compassionate-release program ending in March 1997, during which time, more than 750 patients were treated with this agent. Additionally, Chong and colleagues (2001) performed a randomized, controlled clinical trial evaluating danaparoid for treatment of HIT (see chap. 16)—this remains the only successfully completed randomized trial evaluating a therapy for HIT.

Recombinant Hirudins (Lepirudin, Desirudin)

The medicinal leech, *Hirudo medicinalis*, has been used for medical purposes for many centuries. Given the observation that the medicinal leech can prevent clotting of blood it has ingested, crude preparations derived from this animal were given experimentally at the beginning of the twentieth century. However, because this treatment's daily cost (75 Reichsmark) in 1908 was equivalent to the monthly salary of a factory worker, it was judged to be infeasible. After World War I, Haas, at Justus-Liebig University in Giessen, began his experiments using crude extracts of leech heads for hemodialysis. The major complication in these animal experiments was severe bleeding. The first human hemodialysis patients were treated by him with hirudin during dialysis when a more purified, but still crude protein extract of leech heads became available (Haas, 1925).

In 1956, Dr. F. Markwardt began his work to extract the active component of the leech at the Ernst-Moritz-Arndt University, in Greifswald. Still today, elderly peasants in the small villages around Greifswald tell stories of how they earned their pocket money by collecting leeches for the researchers at the nearby medical school.

The production of large amounts of hirudin by recombinant technology allowed the assessment of this direct thrombin inhibitor in clinical trials. Dr. Andreas Greinacher, at that time working at the Justus-Liebig University in Giessen, first used a recombinant hirudin, or r-hirudin (lepirudin [Refludan]) to anticoagulate a patient who developed acute HIT following heart transplantation. After Greinacher's move to Greifswald, he further assessed the use of r-hirudin in patients with HIT in two clinical studies that led to the first approval of a drug for parenteral anticoagulation of patients with HIT in both the European Union (March 1997) and the United States (March 1998) (Greinacher et al., 1999) (Table 1.1).

Fifteen years after its first approval, the manufacturer (Bayer) announced that they would discontinue marketing lepirudin on a worldwide basis effective March 31, 2012; however, it may continue to be available in some jurisdictions through another manufacturer (Cellgene, U.K.)/distributor (Pharmore, Germany). In addition, another r-hirudin, desirudin (Revasc [E.U.], Iprivask [U.S.A.])—first approved in the E.U. (1997) and subsequently in the United States (2003)—is now available in both Europe and the United States, albeit for an indication other than HIT (Table 1.1). In the Middle East, r-hirudin rb variant (Thrombexx, Rhein-Minapharm, 10th of Ramadan City, Egypt) is another therapeutic option (see chap. 14).

Warfarin-Induced Venous Limb Gangrene

A theme of this book is the central importance of increased thrombin generation in the pathogenesis of thrombosis complicating HIT. The recognition that warfarin therapy can be deleterious in some patients with HIT illustrates the importance of uncontrolled thrombin generation in this disorder.

In December 1992, in Hamilton, Canada, while receiving ancrod and warfarin treatment for DVT complicating HIT, a 35-year-old woman developed progressive venous ischemia, culminating in venous limb gangrene. This occurred despite a

TABLE 1.1 U.S. Approvals for Four Direct Thrombin Inhibitors

	Date of U.S. approval			
Use	**Lepirudin**	**Desirudin**	**Argatroban**	**Bivalirudin**
HIT indications				
For patients with HIT and associated thromboembolic disease to prevent further thromboembolic complications	March 6, 1998			
For prophylaxis or treatment of thrombosis in patients with HIT[a]			June 30, 2000	
Anticoagulation in patients with or at risk for HIT undergoing PCI			April 3, 2002	
For patients with or at risk of HIT/HITTS undergoing PCI				November 30, 2005
Non-HIT indications				
Use as an anticoagulant in patients with unstable angina undergoing PTCA				December 15, 2000
Use (with provisional use of GP IIb/IIIa inhibitor) as an anticoagulant in patients undergoing PCI				June 13, 2005
Prophylaxis of DVT in patients undergoing elective hip replacement surgery[b]		April 4, 2003[c]		

[a]Dosing guidance from U.S. Food and Drug Administration for seriously ill pediatric patients, May 3, 2008.
[b]Approval in EU is for hip and knee replacement surgery.
[c]Approval in the EU received November 11, 1997.
Abbreviations: DVT, deep vein thrombosis; GP, glycoprotein; HIT, heparin-induced thrombocytopenia; HITTS, heparin-induced thrombocytopenia/thrombosis syndrome; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.

supratherapeutic international normalized ratio (INR). The following day, Kelton observed an area of skin necrosis on the abdomen of this patient, suggesting the diagnosis of warfarin-induced skin necrosis. The author questioned whether the warfarin had also contributed to the pathogenesis of the venous limb gangrene. This hypothesis was directly tested just 2 months later when a second young woman developed severe phlegmasia cerulea dolens of an upper limb during treatment of DVT complicating HIT with ancrod and warfarin. Treatment with vitamin K and plasma given by pheresis reversed the phlegmasia. Further laboratory studies supported this hypothesis of a disturbance in procoagulant–anticoagulant balance during treatment of HIT with warfarin (Warkentin et al., 1997) (see chaps. 2, 3, and 12).

Increasingly, HIT became viewed as a syndrome characterized by multiple prothrombotic events, including not only platelet and endothelial cell activation, but also profound activation of coagulation pathways. This conceptual framework provides a rationale for antithrombotic therapy that reduces thrombin generation in patients with HIT (Warkentin et al., 1998).

TREATMENT OF ISOLATED HIT

Isolated HIT refers to HIT diagnosed on the basis of thrombocytopenia alone, rather than because of HIT-associated thrombosis. Often, the initial reason for administering heparin includes routine postoperative prophylaxis or a medical indication, such as acute stroke or myocardial infarction. Until the early 2000s, the standard approach upon suspecting HIT in such patients was discontinuation of heparin, sometimes with substitution of oral anticoagulants.

Natural History of Isolated HIT

During the mid-1990s, new data indicated a high risk for venous thrombosis in postoperative orthopedic patients who developed HIT, particularly for PE (Warkentin et al., 1995) (see chap. 2). Thus, HIT came to be viewed as a dramatic, albeit transient, prothrombotic state, even when the original indication for heparin was routine antithrombotic prophylaxis.

In July 1992, the author became aware of a 68-year-old patient whose platelet count fell from 151 to 51×10^9/L between days 5 and 8 after coronary artery bypass surgery, during routine postoperative heparin antithrombotic prophylaxis. The heparin was stopped, and laboratory testing confirmed HIT. The platelet count recovered, and the patient was discharged to home on postoperative day 12. Three days later, the patient complained of dyspnea, and then died suddenly. Postmortem examination showed massive PE (Warkentin, 2005). This tragic outcome prompted the question: Is mere cessation of heparin sufficient for a patient with isolated HIT?

To address this problem, the author studied the natural history of HIT (Warkentin and Kelton, 1996). From a database of patients with serologically proven HIT, a 62-patient cohort with isolated HIT was identified: the cumulative 30-day thrombotic event rate was 52.8% (see Fig. 4.5 in chap. 4). The rate of thrombosis was similarly high whether heparin was simply stopped or substituted with warfarin.

Similar findings were reported later by Wallis and colleagues (1999) from Loyola University. These investigators also found a high frequency of subsequent thrombosis (43 of 113, or 38%) in patients with isolated HIT managed by discontinuation of heparin. Surprisingly, a trend was observed for the highest risk of thrombosis in those patients in whom heparin was stopped most promptly (see Table 4.7).

Further evidence supporting an unfavorable natural history of untreated HIT was provided by a prospective cohort study (Greinacher et al., 2000). These investigators found that the thrombotic event rate was 6.1% per day during the mean 1.7-day interval between diagnosis of HIT (and cessation of heparin) and initiation of lepirudin therapy. This event rate corresponded closely to the 10% rate of thrombosis observed in the Hamilton study in the first 48 hours after diagnosis of isolated HIT (Warkentin and Kelton, 1996).

Argatroban

A synthetic small-molecule thrombin inhibitor derived from L-arginine, now known as argatroban, was used in Japan during the 1980s as a treatment for chronic arterial occlusion (Tanabe, 1986). During this time, argatroban also underwent investigation as treatment for HIT in Japan, particularly in the setting of hemodialysis (Matsuo et al., 1988). In 1993, exclusive rights to the compound for the United States and Canada were acquired from Mitsubishi-Tokyo Pharmaceuticals, Inc. (now Mitsubishi Tanabe Pharma Corporation) by Texas Biotechnology Corporation (TBC; Houston, Texas, U.S.A.). In 1995, clinical evaluation of this agent for HIT began in the United States, using a prospective, multicenter, open-label design with historical controls, the ARG-911 study (Lewis et al., 2001) (see chap. 13). Two groups of patients were studied: HIT without thrombosis (i.e., isolated HIT) and HIT complicated by thrombosis (HIT/thrombosis syndrome [HITTS]). Eligibility was based on clinical suspicion of HIT, and serologic confirmation of the diagnosis, therefore, was not required. Both patient groups received the identical therapeutic-dose regimen of argatroban (initially, 2 μg/kg/min, then adjusted by activated partial thromboplastin time [aPTT]). The favorable results of the ARG-911 and subsequent studies (ARG-915, ARG-915X) led to the approval of argatroban on June 30, 2000, by the U.S. Food and Drug Administration (FDA) as "anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT" (Table 1.1). Thus, for the first time in the United States, a drug was approved for the novel indication of prevention of thrombosis in isolated HIT. A marketing partnership between TBC (subsequently, Encysive; later acquired by Pfizer) and SmithKline Beecham [now, GlaxoSmithKline (GSK)] commenced in August 1997. Marketing of argatroban began on November 13, 2000. In April 2002, argatroban received approval for anticoagulation in patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

In the United States, marketing exclusivity of GSK for argatroban ended in May 2011. Currently (February 2012), there are ready-to-use "alternative formulations" of this compound available from Sandoz (125 mL vial [1 mg/mL]) and from the Medicines Company (50 mL vial [1 mg/mL]), as well as the GSK product (2.5 mL vial [100 mg/mL], to be reconstituted into 250 mL). GSK continues to hold patent rights covering the formulation of argatroban until June 2014.

In Canada, market authorization for argatroban began on June 4, 2001. Table 1.2 provides information for approval status and date of market authorization for argatroban use in HIT in Asia and Europe.

Therapeutic-Dose Anticoagulation for Isolated HIT

The approval by the FDA of identical therapeutic-dose regimens of argatroban for both prophylaxis and treatment of HIT highlighted the emerging view that HIT is a high-risk prothrombotic state. This contrasted with the earlier concept that HIT was

TABLE 1.2 Availability of Argatroban For Use in HIT Outside of North America

Country	Trade name	Date of market authorization	Use[a]
Japan	Novastan and Slonnon	July 16, 2008 May 20, 2011	HIT Hemodialysis in HIT PCI in HIT
Sweden	Novastan	October 15, 2004	HIT
Netherlands	Arganova	May 25, 2005	HIT
Germany	Argatra	June 1, 2005	HIT
Austria	Argatra	September 22, 2005	HIT
Iceland	Novastan	October 31, 2005	HIT
Denmark	Novastan	January 3, 2006	HIT
Norway	Novastan	January 20, 2006	HIT
Italy	Novastan	March 13, 2008	HIT
Finland	Novastan	April 12, 2011	HIT
France	Arganova	June 21, 2011	HIT
Spain	Pending	November 2011	HIT

[a]Indication wording may vary by country.
Abbreviations: HIT, heparin-induced thrombocytopenia; PCI, percutaneous coronary intervention.

generally benign, provided that thrombocytopenia was promptly recognized and heparin discontinued. Further support for the new view included studies showing HIT to be a profound hypercoagulable state (markedly elevated molecular markers of *in vivo* thrombin generation) (Warkentin et al., 1997; Greinacher et al., 2000) and recognition that many patients already have subclinical DVT at the time that isolated HIT is first recognized (Tardy et al., 1999).

Indeed, therapeutic doses of an alternative anticoagulant might be generally applicable for treatment of most patients with isolated HIT (Farner et al., 2001) (see chaps. 12–17). For example, although the prophylactic-dose regimen of lepirudin for HIT is initially lower than the therapeutic-dose regimen (0.10 mg/kg/hr, rather than 0.15 mg/kg/hr, and without an initial lepirudin bolus), subsequent dose adjustments are made using the aPTT; thus, the eventual infusion rate approaches the one given using the therapeutic regimen. A high success rate (91.4%) was observed using such "prophylactic" doses of lepirudin for isolated HIT (Farner et al., 2001).

In contrast, the prophylactic-dose regimen using danaparoid (750 U bid or tid) may be somewhat less effective than therapeutic-dose danaparoid (usually, 150–200 U/hr after an initial bolus) for preventing new thromboembolic complications in acute HIT: 81.4% versus 91.6% (Farner et al., 2001) (see chap. 16). If this difference is real, it could be explained by greater efficacy of the therapeutic-dose regimen, in which at least twice as much danaparoid is usually given (3600–4800 *vs* 1500–2250 U/24 hr). The implication of Farner's study is that the approved prophylactic-dose regimen of danaparoid may not be optimal, either when used for its approved indication in Europe (i.e., prevention of HIT-associated thrombosis) or for the corresponding "off-label" use for HIT elsewhere (Warkentin, 2001) (see chap. 16).

Bivalirudin

The 20-amino acid hirudin analog, bivalirudin (Angiomax, formerly, Hirulog), was first used over 10 years ago in the United States on a compassionate use basis for the treatment of four patients with HIT (Nand, 1993; Reid and Alving, l994; Chamberlin et al., 1995). Since then, it has undergone limited off-label use for the treatment of HIT (Francis et al., 2003), often in patients with both renal and hepatic compromise (see chap. 15). In contrast to its limited use in managing HIT, bivalirudin is widely used for anticoagulation in the setting of percutaneous transluminal coronary angioplasty as well as other types of PCI (Warkentin et al., 2008a). Indeed, bivalirudin is the only direct thrombin inhibitor that is approved for an indication beyond that involving HIT (Table 1.1). In November 2005, approval was also granted for use of bivalirudin for anticoagulation of patients with (or at risk of) HIT (or HIT-associated thrombosis) undergoing PCI (Table 1.1).

REDUCING THE RISK OF HIT

Low Molecular Weight Heparin

For over 50 years, UFH has been used in numerous clinical situations. However, UFH has several limitations, and efforts to develop potentially superior LMWH preparations began during the 1980s. Advantages of LMWH included better pharmacokinetics (e.g., improved bioavailability, predictable and stable dose response obviating the need for monitoring, lower risk of resistance to anticoagulation, longer plasma half-life) and favorable benefit–risk ratios in experimental animals (Hirsh, 1994; Hirsh et al., 2001). Advantages of UFH include its low cost, widely available laboratory monitoring, and potential for neutralization using protamine. But the question remained: Was the risk of HIT lower with LMWH? This was an important and relevant question, particularly as differences in risk of HIT exist even among UFH preparations derived from different animal sources (see chap. 4). As discussed earlier ("Prospective Studies of Serologically Defined HIT"), there is indeed evidence that LMWH has both a lower risk of HIT antibody formation and (more importantly) a lower risk of HIT and HIT-associated thrombosis. Table 1.3 provides a historical timeline of the introduction of the LMWH enoxaparin in the United States in various clinical situations.

Fondaparinux

Fondaparinux (Arixtra) is a synthetic pentasaccharide anticoagulant modeled after the antithrombin-binding site of heparin. It selectively binds to antithrombin, causing rapid and specific inhibition of factor Xa. In contrast to LMWH, HIT antibodies usually fail to recognize PF4 mixed with fondaparinux, both in platelet activation and PF4-dependent antigen assays (Warkentin et al., 2005a).

Interestingly, evidence suggests that although HIT antibody formation occasionally occurs in association with fondaparinux use, such antibodies fail to react in HIT assays in which fondaparinux replaces UFH or LMWH *in vitro* (Pouplard et al., 2005; Warkentin et al., 2005a). These *in vitro* observations underwent direct *in vivo* confirmation when a serologic substudy of the "Matisse trials" of venous thromboembolism therapy proved that fondaparinux was substantially less likely than heparin (unfractionated or LMWH) to precipitate rapid-onset HIT among patients who had unrecognized heparin-dependent platelet-activating antibodies [0/10 (0%) *vs* 4/4 (100%); $P < 0.001$] (Warkentin et al., 2011a). Although HIT has rarely been observed in association with fondaparinux thromboprophylaxis

TABLE 1.3 U.S. Approvals for Enoxaparin and Fondaparinux

	Date of U.S. approval (if applicable)	
Use[a]	**Enoxaparin**[b]	**Fondaparinux**
Prophylaxis after hip replacement surgery	March 29, 1993	December 7, 2001
Prophylaxis after knee replacement surgery	March 9, 1995	December 7, 2001
Prophylaxis after hip fracture surgery		December 7, 2001
Extended prophylaxis after hip replacement surgery	January 30, 1998	
Extended prophylaxis after hip fracture surgery		June 17, 2003
Prophylaxis after general (abdominal) surgery	May 6, 1997	May 26, 2005
Prophylaxis for unstable angina and non-Q wave myocardial infarction (given together with aspirin)[c]	March 27, 1998	
Acute DVT, with or without PE, together with warfarin[d,e]	December 31, 1998	May 28, 2004
Prophylaxis in medical patients at risk for DVT or PE	November 17, 2000	

[a]Use described may not necessarily conform precisely to the wording of the approved indications.
[b]Other LMWH preparations (dalteparin, tinzaparin) have been approved (at later times) for various indications (not shown).
[c]Fondaparinux has been studied for treatment of patients with acute coronary syndrome, and is approved in Canada (although not in the United States) for this indication.
[d]Wording of approved indication for enoxaparin includes "inpatient" treatment of acute DVT with or without PE and "outpatient" treatment of acute DVT without PE.
[e]Wording of approved indication for fondaparinux: "for the treatment of acute DVT when administered in conjunction with warfarin sodium; and the treatment of acute PE when administered in conjunction with warfarin sodium when initial therapy is administered in the hospital."
Abbreviations: DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism.

following orthopedic surgery (Warkentin et al., 2007; Salem et al., 2010; Burch and Cooper, 2012), the frequency appears to be less than that of LMWH; further, for theoretical reasons, even this putative association between fondaparinux and HIT does not mean that fondaparinux might not itself be a highly effective therapy for HIT (discussed subsequently; see also chaps. 12 and 17).

Fondaparinux is approved in the United States, Canada, and the European Union for antithrombotic prophylaxis in orthopedic surgery as well as other clinical situations (Table 1.3). Data exclusivity for fondaparinux in the United States expired in 2008, and in July 2011, a generic formulation of fondaparinux entered the U.S. marketplace (produced by Dr. Reddy's Laboratories); in September 2011, an "authorized generic" supplied by GSK and marketed by Apotex became available. Data exclusivity for fondaparinux expired in the EU in spring 2012.

RECENT DEVELOPMENTS

HIT as a Misdirected Ancient Immune Response

Recently, Greinacher and coworkers provided evidence that bacterial infection can be associated with anti-PF4/H antibody formation in mice (Krauel et al., 2011). The pathophysiologic basis was the observation that bacterial surfaces bind PF4, thereby creating the HIT antigens. A human correlate was identified by this same group

(Greinacher et al., 2011), when it was reported that periodontitis—a common bacterial infection that is increasingly prevalent in the older population—is associated with natural levels of anti-PF4/H antibodies. The concept has emerged that HIT could represent a misdirected ancient immune response, as PF4-dependent antibodies triggered by bacterial infection would automatically be able to recognize numerous different bacterial species (as many species bind PF4), but that would have the adverse effect of predisposing to HIT if the powerful polyanion, heparin, is administered. Indeed, there is evidence that antiphospholipid antibodies might also have connections with antibacterial effects—in this case, β_2-glycoprotein I (which is highly conserved in the animal kingdom) plays a role in scavenging of lipopolysaccharide (Agar et al., 2011a,b). Thus, PF4 and β_2-glycoprotein I could play key roles in innate immunity, and both HIT and antiphospholipid syndrome could be examples of a misdirected host defense.

HIT Treatment: From Niche to Mainstream?

To date, treatment of HIT has focused on "niche" agents—danaparoid, argatroban, r-hirudin—that have few or no indications beyond that of HIT and associated thrombosis. However, in recent years, several new oral anticoagulants (e.g., dabigatran, rivaroxaban, apixaban, edoxaban; see chap. 17) have entered the marketplace in one or more jurisdictions. It seems likely that as these nonheparin agents become increasingly used for treating patients of diverse clinical scenarios, that some of these will include HIT and HIT-associated thrombosis. Just as fondaparinux has numerous (non-HIT) indications, and has gradually gained traction as a reasonable option for management of suspected HIT (see chaps. 12 and 17), perhaps too these newer agents will undergo a similar evolution to plausible HIT treatment options (Krauel et al., 2012). If this proves to be the case, management of HIT could eventually become as simple as taking a pill once or twice a day!

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TABLE 2.7 American College of Chest Physicians Recommendations for Platelet Count

Monitoring for HIT

Year Risk of HIT and platelet count monitoring (Day 4 to 14, while on heparin a) High risk (>1%) b Intermediate risk (0.1–1.0%) c Low risk (<0.1%) d

2004 At least EOD Every 2–3 days (when practical e) Not recommended

2008 At least EOD Every 2–3 days (when practical e) Not recommended

2012 Every 2–3 days Not recommended Not recommended

a The crucial time period for monitoring “typical onset” HIT is between days 4 to 14 (fi rst day of heparin = day 0),

where the highest platelet count from day 4 (inclusive) onward represents the “baseline.” Platelet count monitoring

can cease before day 14 when heparin is stopped.

b High risk: patients receiving prophylactic- or therapeutic-dose UFH after major surgery.

c Intermediate risk: medical/obstetrical patients receiving prophylactic- or therapeutic-dose UFH, or receiving

LMWH after fi rst receiving UFH; postsurgery patients receiving prophylactic-dose LMWH or UFH “fl ushes.”

d Low risk: medical/obstetric patients receiving LMWH, or only UFH “fl ushes”; any patient receiving UFH or LMWH

≤4 days; any patient receiving prophylactic- or therapeutic-dose fondaparinux.

e Platelet count monitoring may not be practical when UFH or LMWH is given to outpatients.

Abbreviations: EOD, every other day; HIT, heparin-induced thrombocytopenia; LMWH, low molecular weight

heparin; UFH, unfractionated heparin.

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5 Chapter 5: Nonimmune heparin-platelet interactions: Implications for the pathogenesis of heparin-induced thrombocytopenia

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