Heparin-Induced Thrombocytopenia

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There are two types of heparin-induced thrombocytopenia. Type I is more common, has an early onset, and is mild, transient, and benign. Type I is due to direct heparin-induced platelet aggregation and is rarely associated with thromboembolic sequela. Type II is infrequent, has a late onset, and is more severe. Type II is due to an immune-mediated platelet aggregation caused by IgG and IgM that becomes bound to platelets. In Type II, the antibody titers decline over several months; however, early reexposure can result in a catastrophic secondary immune response. Frequently, Type II is associated with life- or limb-threatening thromboembolic complications (white clots), including stroke. (Stroke 1989;20:1449-1459)

Heparin is commonly used in the treatment of thromboembolic disorders; however, its side effects, other than hemorrhage, are not widely appreciated. Heparin-induced thrombocytopenia (HITP) with thromboembolism (TE) is one such side effect that is of particular importance to neurologists in the treatment of cerebrovascular disease. HITP has been the subject of many reviews1-8 and editorials9-10 but has received very little attention in the neurological literature.

History

After its discovery in 1916,11 heparin was used in the treatment of peripheral venous thrombosis in 193712 and stroke13 the following year. As early as the 1940s, experiments showed that heparin unexpectedly decreased platelet counts in animals,14-17 but its effects in humans were uncertain.16-19 In 1958, Weismann and Tobin20 described arterial TE during heparin therapy, and other reports soon followed.21-24 Roberts et al21 speculated that such TE during heparin therapy might be caused by platelet agglutinates and might be immunologically mediated. In 1973, Rhodes et al25 confirmed the relation between heparin-induced TE and HITP and discovered that a heparin-dependent antiplatelet antibody was responsible for both. Subsequently, the clinical features of HITP and TE have been defined more clearly, and pathophysiologic mechanisms have been investigated.

Clinical Features

In nearly 600 reported cases of HITP, >50% have had thromboembolic events, including venous and arterial emboli that often resulted in stroke, amputation, or death. However, HITP with TE is much more likely to be reported than HITP alone. Prospective studies have revealed that approximately 10% (range 0–30%) of patients on heparin will develop HITP, and nearly 10% of these individuals will have TE.6,26-46 Thus, the incidence of HITP with TE is approximately 1–2%. In a few studies, major hemorrhagic complications have occurred in up to 9% of patients with HITP.33>40 However, in the majority of reports of HITP, TE due to HITP occurs more frequently than hemorrhage. The incidence of HITP may vary depending on its definition, the source and purity of the heparin, the duration of treatment, a history of heparin exposure, and other factors.

Two varieties of HITP may be distinguished by clinical characteristics and, perhaps, by pathophysiologic mechanisms.2,6,7,31,35,42,47,48 A mild degree of thrombocytopenia may occur in nearly everyone exposed to heparin.7,48,49 However, in Type I HITP, platelet counts fall significantly, although they usually remain >50,000/mm³.28-30,31,42 Type I HITP appears 1–5 days after the onset of therapy, and platelet counts often return to normal values in spite of continued heparin therapy.28-30,35,37,38,41,42,44 Type I HITP, by far the more common form, is rarely associated with thromboembolic events7,49 and is probably due to direct heparin-induced platelet aggregation (see below). Type I HITP may result, in part, from the failure of electronic platelet counters to distinguish between single platelets and small heparin-induced platelet aggregates.6
Type II HITP is more severe, has a later onset (usually during the second week of treatment), and is more commonly associated with thromboembolic complications. In case reports, >90% of cases of severe HITP (<50,000/mm³) and 95% of cases of HITP with TE occurred after the fifth day of heparin therapy. Many cases that occurred in <5 days were in patients with a history of heparin exposure.50 Type II HITP is characterized by a severe decrease in the number of platelets, often to <10,000/mm³. In general, the lower the platelet count, the higher the risk of TE.51 Kapsch and Silver52 reported that thrombocytopenic patients without TE had average platelet counts of 68,000/mm³, whereas those with TE had platelet counts of 31,000/mm³. However, other investigators have not confirmed this correlation.53,54 Heparin-induced thrombocytopenia occasionally occurs with normal absolute platelet counts.55-58 A relative thrombocytopenia, with a decrease in platelet count of >40% from baseline (but still >100,000/mm³) has been associated with cerebral ischemic events or death.43,59 Within 5-6 days, the discontinuation of heparin in Type II HITP usually results in a return of the platelet count to normal (with resolution of associated thromboembolic phenomena). Type II HITP is probably an immune-mediated phenomenon, as will be discussed.

The development of increasing heparin tolerance may serve as an important warning of impending HITP.25,45,52,60-72 This heparin tolerance might result from the release of platelet factor IV, a heparin neutralizing factor, by activated platelets.52,61-63,65 Skin necrosis may also precede the development of HITP.73-75

**Contributing Factors**

**Route of Administration**

Early reports described the occurrence of heparin-induced TE after subcutaneous or intramuscular heparin injection,20-22,24 which were the most common methods of heparin administration. More recently, many cases of HITP and TE have appeared after intravenous administration of heparin. The route of administration does not appear to be a factor, except that some patients with subcutaneous heparin-induced local skin necrosis developed severe HITP with TE when switched to intravenous treatment.73,75

**Dosage**

Studies of the effect of heparin dose on the incidence or severity of HITP have yielded conflicting results in animals and humans.5 Baird and Convery28 reported a case that demonstrated a clear relation between platelet count and heparin dose over 4 months. In the largest series of HITP cases to date, Laster et al54 reported a higher complication rate in patients with HITP who were on high-dose heparin. However, in the majority of studies, no relation between heparin dose and HITP has been found. Heparin dose may correlate with the development of Type I HITP, thought to be a direct heparin effect, but not with Type II HITP, in which an immune mechanism is postulated. Severe (Type II) HITP has even occurred from the small amount (as little as 240-500 units/day) used in heparin flushes.58,79-81

**Source of Heparin**

Heparin is a mixture of sulfated glycosaminoglycans with molecular weights of 5-40 kD.82,83 Fractionation has shown >120 different “heparins” in commercial heparin.84 and there are great variations in chemical composition, platelet aggregating properties, and anticoagulating activity of heparin from different sources.85-90 Bovine lung heparin has a higher degree of sulfation, a greater negative charge, and contains molecular species with a higher average molecular weight than porcine intestinal mucosal heparin.82,91-93 Higher-molecular-weight fractions have been associated with higher antithrombin III affinity,92,93 greater anticoagulant activity,82,91,93,94 and greater platelet aggregating activity.95,96 Finally, bovine lung heparin contains more impurities than porcine intestinal mucosal heparin. Some of these impurities have antigenic or platelet aggregating activity.33,77,82,97-99

Most early reports of HITP described patients treated with bovine lung heparin, probably because that was the most widely used type of heparin until about 1960.99 Several prospective studies have compared the incidence of HITP in bovine and porcine heparin.5 The majority of studies have shown a higher incidence of HITP with bovine lung heparin, with the risk of HITP increased up to three- or fourfold.93 However, most in vitro studies of platelet aggregation have found no difference between bovine lung and porcine intestinal mucosal heparins.34,49,50,62,100-103 Moreover, in a recent trial, 377 patients treated with bovine lung heparin were compared with 290 patients treated with porcine intestinal mucosal heparin.54,49,50,62,100-103 Although comparisons of different studies are difficult, they suggest that bovine lung heparin may be more likely to cause HITP, TE, or both for reasons that are not yet clear.

**Pathogenesis**

In HITP, platelet production is normal or increased, as shown by bone marrow biopsies.† Therefore, the thrombocytopenia must result from increased loss of platelets. Although previously controversial,14-17,104 it now seems clear that the loss of platelets in HITP is due to platelet aggregation rather than to lysis. For example, after either the discontinuation of heparin15,16 or the addition of the heparin antagonist protamine,18 the recovery of platelet count is extremely rapid—too rapid to be

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*References 14-16, 25, 26, 34, 40, 47, 52, 76, 77.
†References 25, 28, 29, 31, 37, 60-65, 69, 72, 100, 103-111.
due to the replacement of lysed platelets by bone marrow. Furthermore, "white clots" composed of aggregates of platelets and fibrin have been found in the blood vessels of patients and animals with HITP and TE. Finally, Chong et al found no release of lactate dehydrogenase after HITP, suggesting that platelet lysis does not occur. The possible role of the sequestration of platelet aggregates by the reticuloendothelial system is uncertain, but at least one case of HITP has been reported in a splenectomized patient.

The occasional coexistence of HITP and disseminated intravascular coagulation (DIC) has led to the suggestion that HITP is merely a manifestation of DIC caused by heparin or by the condition for which heparin was prescribed. However, in nearly 90% of cases, no other evidence of DIC exists, and in the few cases in which such evidence is present, DIC can usually be attributed to the underlying disease.

Bell et al have suggested that thromboplastin, a heparin contaminant, is involved in the production of concurrent HITP and DIC. Thromboplastin has been shown to induce platelet aggregation and DIC. Bovine lung heparin has a higher concentration of thromboplastin. Although a higher incidence of DIC would be expected in patients treated with bovine lung heparin, concurrent DIC has been reported with approximately equal frequency in patients treated with heparin from both bovine and porcine sources. The possible role of thromboplastin deserves further study.

Adenosine diphosphate (ADP), epinephrine, and collagen cause platelet aggregation (first wave), resulting in the release of ADP from platelets (release reaction), which produces further platelet aggregation (second wave). Heparin has been shown to enhance the first and second waves of aggregation produced by these agents and aspirin has been shown to block the second wave completely. Heparin-induced platelet aggregation is also thought to be mediated by the release reaction because it can be blocked by ethylenediaminetetraacetic acid, apyrase, adenosine, and aspirin. Moreover, Chong and coworkers have shown a reduced concentration of dense body granules in platelets from patients with HITP and suggest that the release reaction results in "exhausted platelets." It would seem that, in both Type I and Type II HITP, at least part of the platelet aggregation is due to the release reaction and second wave of platelet aggregation.

Type I HITP: Direct Effect

A direct platelet aggregating effect of heparin has been demonstrated in animals in vitro and in vivo. Several investigators have demonstrated a direct platelet aggregating effect of heparin in humans in vitro and others have suggested that such a direct effect occurs in humans in vivo as well. This direct effect may explain why some patients with HITP do not have the demonstrable antiplatelet antibodies found in Type II HITP.

The direct platelet aggregating effect of heparin is probably not due to contaminants in heparin preparations. Discrepancies among early animal studies of HITP were often attributed to impurities in different heparin preparations. The frequency of heparin hypersensitivity reactions in humans has declined with better manufacturing processes, presumably because of the removal of active contaminants; however, a decline in the incidence of HITP has not been observed. Moreover, dialyzed heparins, from which low-molecular-weight contaminants have been removed, have shown no loss of platelet aggregating ability. Higher-molecular-weight fractions of heparin have been associated with increased platelet aggregating activity and a high-molecular-weight contaminant (e.g., thromboplastin) could still be responsible for the platelet aggregation. However, Eika found that modification of the heparin molecule itself changed both the anticoagulating and the platelet aggregating properties of heparin. Moreover, concentrations of protamine sulfate sufficient to block the anticoagulant properties of heparin also block its platelet aggregating ability. Finally, in vitro platelet aggregation disappears after digestion of heparin with heparinase. Thus, the evidence suggests that heparin itself, rather than a contaminant, is the cause of direct heparin-induced platelet aggregation.

The frequency, rapid onset, benign nature, reversibility, and lack of demonstrable circulatory antiplatelet antibodies suggest that Type I HITP results from a direct effect of heparin on platelets. Variations in severity, incidence, etc., of Type I HITP may be due to differences in the heparin molecule (e.g., higher-molecular-weight fractions in bovine lung heparin than in porcine intestinal mucosal heparin). However, it is possible that such differences may be compounded by higher concentrations of active contaminants in certain heparin preparations.

Type II HITP: Immune-Mediated

Serum from patients with HITP will often cause the aggregation of normal platelets in the presence of heparin, as shown by optical density measurements using platelet aggregometers, by the measurement of thromboxane B_2 synthesis, serotonin release, complement fixation, and the release of platelet factors IIb and IV. In 1973, Rhodes et al established an immune-mediated mechanism in HITP by demonstrating a heparin-dependent, platelet-aggregating antibody in two patients.
antibody has been found by others* and has been shown to be IgG+ or IgM.

The precise mechanism of the interaction between the antiplatelet antibodies, platelets, and heparin in Type II HITP is unknown. Several mechanisms have been proposed. The antibody could be directed against heparin or a heparin-plasma protein complex and then cross-react with platelets (Figure 1A). Alternatively, the platelet membrane may provide only the physical conditions for the antigen–antibody reaction, and the subsequent complement fixation would destroy platelets as "innocent bystanders" (Figure 1B). This mechanism is unlikely because Chong and coworkers showed that complement fixation did not lead to platelet lysis. Heparin could act as a hapten or an "incomplete antigen" that binds to the platelet membrane. Platelets have been shown to bind [3H]heparin. The resultant new "complete antigen" would then be the heparin molecule plus some nearby platelet membrane component (Figure 1C). Wolf and Wick identified two platelet membrane proteins with heparin affinity that were immunogenic when bound to heparin.

A more widely accepted theory, proposed by Lynch and Howe, is that heparin binds to platelets and, by virtue of its strong negative charge, induces a conformational change in the platelet membrane, thereby exposing an immunogenic substance (Figure 1D). The antigen would be a platelet component normally concealed from immunologic detection. Heparin would be necessary for both initial exposure of the antigen and for recognition of the antigen by any antibodies generated. These investigators suggested that three platelet proteins (i.e., thrombospondin, its digestion product, and glycoprotein V [a substrate for thrombin]) could bind the heparin-dependent antibodies and trigger the activation of platelets. Evidence for a heparin-dependent antibody being directed toward different platelet antigens has been provided by Pfueller and David.

The most commonly used test for Type II HITP has been platelet aggregometry; however, this method has been criticized for its low sensitivity. Moreover, platelet antigens may differ among individuals, and platelet aggregometry may be positive with some normal platelets but not with others. Hence, platelets from more than one normal donor may need to be used in platelet aggregation studies. A more sensitive but nonspecific test is the measurement of platelet-associated IgG. Problems with such tests are beyond the scope of this review but are discussed by others.

The immune-mediated form of HITP is probably a primary immune response because most patients with HITP have no history of heparin exposure.
Any primary immune response requires at least 7-14 days to develop, which is consistent with the time course of Type II HITP. However, humans have endogenous heparin, and certain individuals may already possess the offending antibody. Such susceptible patients might develop HITP via a secondary immune response upon first exposure to heparin therapy.

Some investigators have reported that a history of heparin exposure does not increase the risk of developing HITP significantly, although others have found that a shorter latency of onset is seen in such patients. It is clear that patients with immune-mediated HITP are quite capable of mounting a secondary response if reexposed to heparin early after recovery from HITP—and often with catastrophic results. In other drug-induced thrombocytopenias, reexposure to the offending drug may cause thrombocytopenia within 30 minutes. In three patients, reexposure to heparin shortly after recovery from HITP has resulted in massive pulmonary emboli and death in <30 minutes.

The precise duration of the antibody is unknown, but the risk of recurrence of HITP appears to decline as antibody titers decline. Several studies have shown a decline in antibody titers or platelet aggregation activity over several months.† As the antibody disappears, successively higher doses of heparin or longer periods of observation are required to produce the same amount of platelet aggregation. Several patients did not develop a recurrence of HITP when challenged again 1-4 months later. This disappearance of sensitivity could be related to the natural lifespan of platelets or it could reflect the clearance of IgG over time.

Persistent heparin sensitivity has been reported up to 28 months after recovery from HITP.

Some patients may develop a recurrence of HITP when exposed to heparin from another source, and heparin-dependent antiplatelet antibodies have been found to cross-react with heparin from many sources and lots. However, other patients have a very restricted immune response and will develop a recurrence of HITP only if exposed to the same lot of heparin. The basis for such immunologic variability is not fully understood.

The association with a platelet-aggregating antibody, the delayed time course, severity, shortened latency with prior exposure, and occurrence of secondary immunoresponses all suggest that Type II HITP is immune-mediated. However, clarification of the pathogenesis of Type II HITP will require illumination of the other immune-mediatory effects of heparin.

HITP and TE

The mechanism by which certain patients with HITP develop thromboembolic complications is not known. One factor may be the integrity of the vascular endothelium. Makhoul and coworkers found that 19 of 25 patients with HITP suffered TE in an extremity that had been catheterized; these investigators postulated that endothelial injury predisposed these patients to thromboembolic events. Interestingly, antiplatelet antibodies from some patients with HITP have been found to cross-react with endothelial cells. Further studies are needed to clarify the pathogenesis of TE in HITP.

HITP and Stroke

Stroke, apparently occurring as a result of heparin therapy, has been reported in 29 individuals (Table 1). Only two patients had histories of symptomatic cerebrovascular disease. In most cases, sufficient information was provided to confirm that HITP with TE was the cause of the stroke. Analysis of those cases reveals a mean age of 57.6 (range 21-74) years (seven men, 12 women). The mean latency of onset of HITP was 6.7 (range 0.5-14) days or, excluding those with a history of heparin exposure, 7.5 (range 3-14) days. In one case, the stroke occurred with a normal absolute platelet count. In the other cases, the mean platelet counts were 70,000/mm³ (range 7,000-84,000/mm³). The average recovery time after the cessation of heparin therapy, has been reported in 29 individuals (Table 1). Only two patients had histories of symptomatic cerebrovascular disease. In most cases, sufficient information was provided to confirm that HITP with TE was the cause of the stroke. Analysis of those cases reveals a mean age of 57.6 (range 21-74) years (seven men, 12 women). The mean latency of onset of HITP was 6.7 (range 0.5-14) days or, excluding those with a history of heparin exposure, 7.5 (range 3-14) days. In one case, the stroke occurred with a normal absolute platelet count. In the other cases, the mean platelet counts were 37,100/mm³ (range 7,000-84,000/mm³). The average recovery time after the cessation of heparin therapy.

In patients with symptomatic cerebrovascular disease who are treated with heparin, HITP may be the cause of recurrent stroke. Ramirez-Lassepas et al prospectively followed 137 patients treated with heparin for cerebral infarction (CI) (73 patients), reversible ischemic neurologic deficit (RIND) (22 patients), or transient ischemic attack (TIA) (42 patients). Twenty-one patients (15.3%) had a ≥40% decrease in number of platelets. Of these 21 patients, five suffered extension of their cerebral infarcts, and three of the five died. In the remaining 116 patients, only three new cerebral ischemic events and three deaths were reported. Future investigators studying the efficacy of heparin therapy in stroke should consider HITP to avoid categorizing patients with recurrence or extension of cerebral infarcts as simple failures of anticoagulation.

The type of preexisting symptomatic cerebrovascular disease may influence the risk of stroke in HITP. Recurrent TIAs due to HITP have been reported; however, only one patient with a
history of TIA has been reported to have had a stroke due to HITP. In the study of Ramirez-Lassepas et al, although the incidence of HITP was similar in the three groups, all new cerebral ischemic events occurred in the CI group. Therefore, patients with preexisting stroke may be at greater risk of recurrent stroke due to HITP than patients with TIA or RIND.

In the same study, all patients with cerebral infarcts due to HITP had a drop in platelet count of >100,000/mm³, but only one patient had an absolute platelet count of <100,000/mm³. Of the 29 reported cases of HITP and stroke, the only patient with a history of CI had a stroke due to heparin in the presence of a normal platelet count (Table 1). Therefore, patients with preexisting stroke may have recurrent stroke due to HITP without severe thrombocytopenia.

In stroke due to HITP, atherosclerotic endothelial cell damage may permit the formation of "white clots" in cerebral vessels. However, Type II HITP may produce thrombosis in angiographically normal cerebral vessels. Moreover, the role of cerebral microvascular disease in the production of stroke due to HITP is unknown. It is possible that the pathogenesis of certain strokes differs from that of other forms of arterial TE in Type II HITP.

Treatment

Platelet Counts

The value of routine monitoring of the platelet count has been debated, but most investigators recommend that patients on heparin should have platelet counts performed at the initiation of therapy and periodically thereafter—perhaps daily or every 2–3 days. Others argue that such expensive screening to anticipate the 1–2% of patients with thromboemboli from heparin has not yet been proven to be cost-effective. Some authors suggest that platelet counts need not be checked until after a week of heparin therapy or if symptoms or signs of hemorrhage or thrombosis develop.


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Average 57.6 6.7 37.1† 4.0

F, female; M, male; R, right; L, left; SSS, superior sagittal sinus; MCA, middle cerebral artery territory.

*History of exposure to heparin.
†In one patient; other two not reported in detail.
‡Excluding case reported by Atkinson et al.
It would seem prudent to check baseline platelet counts before administering heparin to patients and to repeat the platelet count at 5 days. Beyond 5 days of heparin therapy, platelets may be checked every 1 or 2 days. Earlier platelet counts would be appropriate in patients with histories of heparin exposure or previous episodes of HITP. Patients with previous episodes of HITP might benefit from in vitro platelet aggregation tests to detect persistent sensitivity before being reexposed to heparin, although such tests are not widely available. Finally, platelet counts should be checked any time that thromboembolic or hemorrhagic events occur during the course of heparin therapy. This approach decreases costs by avoiding platelet counts in patients unlikely to develop serious complications while closely monitoring patients in high-risk groups.

Discontinuation of Heparin

Nearly all investigators agree that, if a patient develops HITP with thrombosis, heparin must be discontinued immediately,* and in vitro studies of platelet aggregation should be performed if available.9,50,52,121 Van Der Weyden et al recommend heparin reversal with protamine sulfate, but in the vast majority of patients discontinuing heparin has been sufficient to produce rapid recovery. If continued anticoagulation is desired, substitution with warfarin has been recommended.† Finally, beginning warfarin and heparin together and then discontinuing heparin after 2–3 days would theoretically, eliminate most cases of delayed severe Type II HITP with TE and obviate the need for monitoring platelet counts.

Low-Molecular-Weight Heparin

Platelet interactions are reduced with heparin molecules of <5–8 kD.96,141 In several cases, improvement of thrombocytopenia and TE followed the administration of synthetic low-molecular-weight heparin.53,130,139 Animal studies have been promising, and extensive clinical trials with these compounds are in progress.83 However, low-molecular-weight heparin has produced in vitro aggregation of platelets from several patients with HITP and a recurrence of HITP in one patient.131 The new heparinoid Org 10172 has shown no activity with heparin-dependent anti-platelet antibodies50,136 and has been used to treat HITP successfully in one patient.136 Experience with these compounds is limited, and more information on their potential benefits and risks must be obtained before their general use can be recommended.

Platelet Transfusion

Some patients have received platelet transfusions for severe HITP, but most investigators have failed to demonstrate a substantial rise in platelet counts.* Some patients have suffered severe thromboembolic events that appeared to be temporally related to platelet transfusions.62,103 Mandt et al159 have recommended platelet transfusions for bleeding or for a platelet count of <20,000/mm³, and Stevenson106 considered transfusions "indicated for profound HITP even when thrombosis exists." However, Babcock et al128 suggested that "although platelet transfusion might be appropriate for the patients with HITP with hemorrhagic manifestations, on the basis of the failure to achieve a sustained rise in the platelet count and the temporal association with further thrombosis in one patient, we do not recommend administration of platelet concentrates. . . ."

Antiplatelet Agents

Aspirin and/or other antiplatelet agents, such as dextran or dipyridamole, can block the second wave of platelet aggregation and have been recommended in the treatment of HITP.† Although experience is limited, some investigators have reported more rapid recovery in patients treated with aspirin or dextran.6,67,121,140,155 Aspirin has also been used as prophylaxis against the recurrence of HITP and thrombosis.50,54,71,125,143 However, concurrent use of aspirin and heparin is associated with a considerable risk of hemorrhagic complications. Short-acting nonsteroidal anti-inflammatory agents (e.g., ibuprofen) may be safer to use in combination with heparin. Concern over the irreversibility and prolonged duration of the antiplatelet effect of aspirin was expressed by Ellison et al,160 who reported that three patients with HITP were treated successfully with a new prostacyclin analogue, iloprost (ZK), which has a half-life of 15–30 minutes. Iloprost is more effective than aspirin at blocking in vitro heparin-induced platelet aggregation58 and has been successful in preventing recurrence of HITP in patients who required reexposure to heparin.142,143

Other Therapy

Thrombolytic therapy (i.e., streptokinase or urokinase) has also been used in HITP with TE.53,57,129,161 One case of Type II HITP treated successfully with plasmapheresis has been reported.140

Conclusion

HITP is a common side effect of heparin therapy. Approximately 1–2% of patients treated with heparin will develop severe HITP with thromboembolic complications, including stroke. Patients with pre-existing stroke may be at greater risk of recurrent stroke due to HITP, even without significant thrombocytopenia, than patients with TIA or RIND. Neurologists should become familiar with the features of HITP and TE to avoid categorizing recur-

†References 5, 10, 47, 51, 54, 63, 65, 67, 73, 120, 121.

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