Thrombocytopenia in PCI Patients

Recognizing and managing this important adverse event.

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Outcomes from percutaneous coronary intervention (PCI) have substantially improved due to advances in devices and pharmacotherapy.[1,2] The combination of oral or intravenous antiplatelet therapies and antithrombin agents has led to a decrease in the incidence of postprocedure ischemic complications but places patients at risk for complications related to the drugs themselves (ie, bleeding and thrombocytopenia). Both antiplatelet and certain antithrombin therapies have been associated with a risk of developing thrombocytopenia.[3,4] Low platelet counts, in turn, have been independently associated with a substantially increased risk of mortality and hemorrhage among patients undergoing PCI.[5] Given that the development of thrombocytopenia is often an iatrogenic complication, knowledge of the etiology, diagnosis, prevention, and management of this condition is essential for the practicing interventional cardiologist.

THROMBOCYTOPENIA

Definition, Incidence, and Differential Diagnosis

Thrombocytopenia, defined as a platelet count of <100,000 cells/mm^3, is relatively uncommon in the general population. In contrast, the incidence of thrombocytopenia has been reported to be 3% to 16.5% among patients with ischemic heart disease exposed to antiplatelet and antithrombin therapies.[6-11] The etiology of thrombocytopenia in these patients dictates the management strategy and therefore requires particular attention. The differential diagnosis for a low platelet count in the cardiac patient is listed in Table 1. The most important clinical entities for the patient undergoing PCI are pseudothrombocytopenia, drug-induced thrombotic thrombocytopenic purpura (TTP), heparin-associated thrombocytopenia, and heparin-induced thrombocytopenia (HIT) with or without thrombosis.

Laboratory Error and Pseudothrombocytopenia

Potential benign and spurious etiologies for a low platelet count include laboratory error and pseudothrombocytopenia. Repeat blood draw will confirm laboratory error as the cause. Patients receiving glycoprotein IIb/IIIa inhibitor (GPI) have a reported 1% to 3% incidence of pseudothrombocytopenia.[12] Among patients receiving a GPI who develop low platelet counts, 30% will be found to have pseudothrombocytopenia.[13]

Pseudothrombocytopenia is a benign condition of no clinical significance and is caused by platelet aggregation due to either ethylene diamine tetra-acetic acid in the specimen tube or low temperature of the laboratory specimen.[14-17] The diagnosis is confirmed by seeing platelet clumping on examination of a peripheral blood film or with a normal platelet count when a citrate-containing specimen tube is used. Given the benign clinical course of pseudothrombocytopenia, alterations in management strategies are not recommended. The importance of diagnosing pseudothrombocytopenia in the PCI patient cannot be overemphasized, because the discontinuation of antiplatelet therapies is inappropriate and may increase the risk for an adverse event.

TTP

TTP is a rare disorder with an annual incidence of four to 11 cases per million in the US. Recognition of the classic pentad of fever, microangiopathic hemolytic anemia, thrombocytopenia, and neurological and renal abnormalities is imperative because TTP is associated with a 90% mortality rate when left untreated.[18] Sporadic TTP is rare, and autoantibody-mediated deficiency in the metalloproteinase A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13 (ADAMTS 13), which is responsible for the cleavage of von Willebrand factor, is commonly found in these cases.[19] Although there are multiple systemic conditions associated with the development of TTP, medications are implicated in up to 20% of cases.[20] Of par-

TABLE 1. DIFFERENTIAL DIAGNOSIS OF THROMBOCYTOPENIA IN PATIENTS UNDERGOING PCI

Laboratory Related
1. Laboratory error (common)
2. Thrombin-induced platelet clumping (common)

Pseudothrombocytopenia
1. Platelet coagulation with ethylene diamine tetra-acetic acid
2. Low specimen temperature

Decreased Platelet Production
1. Viral infections
2. Alcohol toxicity
3. Chemotherapy
4. Vitamin B12 and folate deficiency

Increased Platelet Destruction
1. TTP
2. Disseminated intravascular coagulation
3. Cardiopulmonary bypass graft surgery
4. Intra-aortic balloon pump therapy

Dilutional Thrombocytopenia
1. Massive red blood cell transfusion

Drug-Induced Thrombocytopenia (very common)
1. Unfractionated heparin (UFH), low-molecular-weight heparin (includes heparin-associated thrombocytopenia and heparin-induced thrombocytopenia)
2. Glycoprotein IIb/IIIA inhibitors: abciximab, tirofiban, eptifbatide
3. Thienopyridines: clopidogrel and ticlopidine
4. Antibiotics
5. Thiazide diuretics

ticular interest to the interventionist is TTP associated with thienopyridine (clopidogrel and ticlopidine) use. TTP occurs in one per every 5,000 patients exposed to thienopyridines and presents as thrombocytopenia usually within 2 to 4 weeks after exposure.[21,22] Bennett and colleagues described differences between ticlopidine- and clopidogrel-associated TTP using a large database of validated case reports.[23] Patients with ticlopidine-associated TTP more often received >2 weeks of therapy with a thienopyridine before developing TTP and more often presented with severe thrombocytopenia (platelet count <20,000 cells/mm^3). They were less likely to have renal failure. In contrast, patients with clopidogrel-associated TTP had received ≤2 weeks of thienopyridine therapy, had less severe thrombocytopenia, and more often had renal failure. Importantly, patients with ticlopidine-associated TTP were more likely to have ADAMTS 13 deficiency due to autoantibodies, whereas those with TTP due to clopidogrel use did not have low levels of ADAMTS 13. Another case series also found that ticlopidine-associated TTP was associated with the development of antibodies to ADAMTS 13.[24] These data suggest that an autoimmune pathway is responsible for TTP developing >2 weeks after thienopyridine use and a nonimmunologic pathway is responsible for TTP developing within 2 weeks of thienopyridine exposure.

Diagnosis of TTP is confirmed with the presence of >1% fragmented red blood cells (schistocytes) or microangiopathic hemolysis on the peripheral blood smear in the context of other clinical findings of the pentad.[25] Therapy consists of discontinuing of the thienopyridine and plasma exchange. Case series of patients with thienopyridine-associated TTP demonstrate the efficacy of plasma exchange at improving survival.[21,22,26] One study suggested that plasma exchange is especially efficacious in patients with TTP developing <2 weeks after thienopyridine exposure.[23] Plasma exchange should be performed daily until the platelet count is normal, although the optimal duration of therapy is unknown.[18] Another area of uncertainty is whether thienopyridine therapy can be safely reinstituted in patients who have recovered from thienopyridine-associated TTP. An analysis of patients enrolled in the EPISTENT trial who developed ticlopidine-associated TTP showed that 32% had recurrent cardiac symptoms[21] and that cessation of antiplatelet therapy is a major risk factor for the development of stent thrombosis.[27] In addition, TTP has been implicated as a cause of subacute stent thrombosis.[28] Relapses of TTP after reinstitution of thienopyridine therapy have been reported,[22] therefore, the optimal antiplatelet strategy is unclear. A case of successful stenting and treatment with aspirin, ticlopidine, and cilostazol in a patient with a history of clopidogrel-induced TTP has been reported.[29] Given the possibility of two separate pathogenic mechanisms for TTP for ticlopidine and clopidogrel, such a strategy appears reasonable.

Drug-Induced Thrombocytopenia

Antiplatelet and antithrombotic therapies have been strongly associated with drug-induced thrombocytopenia, and therefore, the risk of developing drug-induced thrombocytopenia may be higher in patients undergoing PCI who are exposed to these agents.[30] For example, thienopyridine-induced thrombocytopenia without TTP has also been demonstrated.[31] Recent data suggest that clopidogrel cross-

reacts with the platelet GP IIb/IIIa receptor, inducing a conformational change recognized by an antibody.[32] This thienopyridine-antibody-receptor reaction can lead to autoimmune platelet destruction and subsequent thrombocytopenia. Diagnosis is demonstrated with platelet normalization upon discontinuation of thienpyridine therapy and the absence of the classic findings of TTP (such as schistocytes, fever, etc.). However, as stated previously, patients with stents will be at risk for stent thrombosis in the absence of thienopyridine therapy. Although there are no data on the ideal management of autoimmune thrombocytopenia in the setting of thienopyridine therapy, there are case reports of resolution with methylprednisolone and platelet transfusions.[33]

In addition to thienopyridines, other causes of drug-induced thrombocytopenia to consider include GPI and unfractionated or low-molecular-weight heparins. Thrombocytopenia has been reported with all three of the commercially available GPIs (abciximab, eptifibatide, and tirofiban). The reported incidence of thrombocytopenia with abciximab is 2.4% to 9.2%, and the incidence of profound thrombocytopenia (defined as a platelet count <20,000 cells/mm^3) has been reported to be 0.3%.[6] The risk with the small-molecule inhibitors tirofiban and eptifibatide appears to be lower than with abciximab (reported rates are 0.5% to 3.2%).[34,35] In most cases, the platelet count begins to decrease within hours of initiating therapy; however, it is important to note two other syndromes associated with abcixmab: thrombocytopenia in the setting of abciximab readministration and delayed thrombocytopenia. Data from the ReoPro Readministration Registry show that the incidence of thrombocytopenia after re-exposure to the drug is no higher than with the first exposure; however, the incidence of profound thrombocytopenia is much higher (approximately 2.4%).[36] In addition, patients who develop profound thrombocytopenia with the re-exposure are much more likely to require multiple platelet transfusions to normalize the platelet count, whereas profound thrombocytopenia after first exposure often responds to one transfusion. A delayed thrombocytopenia developing 2 to 8 days after abciximab exposure has been reported, but is rare.[37]

Development of GPI-induced thrombocytopenia is analogous to the autoantibody-mediated pathogenesis previously described with thienopyridine-induced thrombocytopenia. However, the autoantibodies to GPI are typically preformed and account for the acute presentation of thrombocytopenia. Once laboratory error and pseudothrombocytopenia have been ruled out, GPI should be discontinued to reduce the risk for profound thrombocytopenia.[38] Platelet counts can be expected to return to normal 7 to 10 days after stopping GPI therapy. Platelet transfusion has been used in patients with profound GPI-associated thrombocytopenia and appears to normalize the platelet count.[38] In general, platelet transfusion should be used if significant hemorrhagic complications occur or if the platelet count decreases below 20,000 cells/mm^3. Subsequent administration of GPI in a patient who has previously developed GPI-associated thrombocytopenia may be reasonable provided that another agent is used.[39]

Heparin-Associated and Heparin-Induced Thrombocytopenia

UFH is the most commonly used antithrombin agent for PCI. Thrombocytopenia that occurs in the setting of heparin therapy can be either heparin-associated thrombocytopenia or HIT. The former is a benign entity that occurs in approximately 5% of patients within 48 hours to 72 hours of exposure to UFH and results in mild thrombocytopenia that resolves despite continued heparin therapy. No specific treatment is warranted. In contrast, HIT and its related clinical entity HIT with thrombosis syndrome (HITTS), is a potentially disastrous complication of heparin therapy that can result in arterial and venous thrombosis, amputation, and death if not recognized and treated promptly.

HIT should be suspected in a patient who is, or has been, treated with a heparin agent (either UFH or low-molecular-weight heparin) and develops a 50% or greater decrease in platelet count or frank thrombocytopenia (<100,000 cells/mm^3). As summarized previously, other causes for the decreased platelet count should be investigated, but there should be a low index of suspicion for HIT in the appropriate clinical setting. Registry and clinical trial data suggest that the incidence of HIT in the PCI population is approximately 1% to 5%,[40] although this is likely underestimation of the true incidence. The pathophysiology of HIT involves heparin binding to the platelet factor 4 receptor (PF-4), which generates an IgG autoantibody. Activated heparin-PF-4 complex autoantibodies then initiate platelet consumption, resulting in a 5% to 7% bleeding rate among HIT patients.[41,42] The major problem in HIT, however, is a paradoxical thrombotic diathesis caused by platelet activation that is mediated by the interaction between heparin-PF-4 complex and the autoantibody. Activated platelets secrete procoagulative cofactors initiating the coagulation cascade. Thrombotic complications are therefore common and occur in 20% to 50% of HIT patients, with venous events being more common than arterial events.[43] HIT is further described in three subtypes based on the time of onset.[44-46] Typical-onset HIT occurs in 65% of reported cases and, in the heparin-naïve patient, develops 5 to 10 days after heparin exposure. In patients with previous exposure to heparin (<100 days), rapid-onset HIT occurs 10 to 24 hours after heparin exposure and accounts for 30% of HIT cases. Delayed-onset HIT occurs in 2% of HIT patients 10 to 40

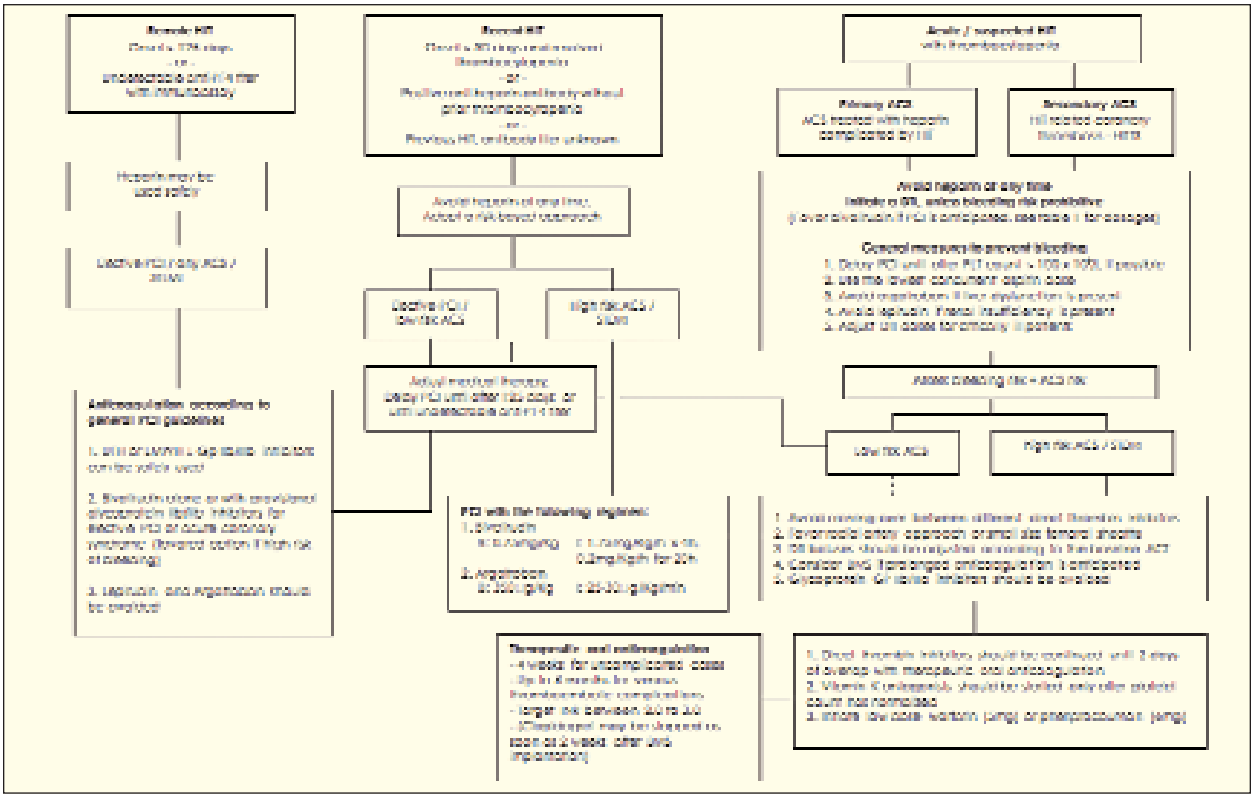

Figure 1. Management algorithm of percutaneous coronary intervention complicated by HIT. (Reprinted with permission from Jolicoeur EM, Wang T, Lopes RD, et al. Percutaneous coronary interventions in patients with heparin-induced thrombocytopenia. Curr Cardiol Rep. 2007;9:396-405.)

days after the cessation of heparin therapy. The 30-day mortality rate among HIT patients is 17% to 30% if no treatment is instituted.[44]

There are several assays available to confirm the diagnosis of HIT (Table 2). The serotonin release assay is based on the principle that antibodies from the blood of HIT patients will bind to and activate platelets from normal donors and lead to the release of serotonin. The heparin-induced platelet aggregation assay uses washed platelets from normal donors and measures platelet aggregation caused by the serum of an HIT patient in the presence of a heparin; this test is one of the most commonly used and is widely available. Other tests include the platelet-rich plasma aggregation test and antibody testing for anti-PF4 antibodies. The former test has reasonable specificity (approximately 80%) but poor sensitivity (30% to 40%).[47] The latter test has a sensitivity of approximately 80% but cannot be used to test for cross-reactivity to other antithrombin agents.[48]

The cornerstone of HIT management is the immediate discontinuation of all heparin-containing treatments, including heparin flushes, as soon as HIT is suspected. A proposed management scheme for HIT in the acute coronary syndrome patient begins with the identification of the HIT subtype (Figure 1). Most thrombotic complications of HIT occur <30 days after the presentation of thrombocytopenia. It is therefore imperative to diagnose the rapid-onset HIT subtype and continue anticoagulative therapy, if indicated. If anticoagulation is required (as in the clinical setting of PCI in a patient with a known history of HIT), one of the three commercially available direct thrombin inhibitors (DTI)—lepirudin, argatroban, and bivalirudin—should be used. Pooled data from studies of DTIs in patients with acute coronary syndromes have shown that the bivalent DTIs (hirudin and bivalirudin) are either noninferior to or perhaps superior to UFH at reducing the risk for death or myocardial infarction (MI); in contrast, the univalent DTIs—danaparoid and argatroban—trended toward worse clinical outcomes.[49-51] In the setting of PCI, the agent with the most evidence is bivalirudin.

Bivalirudin is a bivalent DTI with a half-life of 25 minutes. It produces consistent profound suppression of thrombin and has been studied in the setting of PCI,[52] non-ST-segment elevation acute coronary syndromes,[51] and ST-segment elevation MI.[53] The REPLACE-2 trial of 6,002 patients undergoing elective or urgent PCI demonstrated a significantly lower risk of thrombocytopenia with bivalirudin compared with UFH + GPI (0.7% bivalirudin vs 1.7% UFH +

TABLE 2. LABORATORY TESTS FOR THE DIAGNOSIS OF HEPARIN-INDUCED THROMBOCYTOPENIA

Diagnostic Assay	Sensitivity, %	Specificity,* % Early Platelet Fall	Specificity,* % Late Platelet Fall
Platelet serotonin [^{14}C] release assay	90–98†	>95	80–97‡
Heparin-induced platelet aggregation assay	90–98†	>95‡	80–97‡
Platelet aggregation test using citrated platelet-rich plasma	35–85	90§	82§
Platelet factor 4/heparin enzyme immunoassay	>90	>95	50–93
Combination of sensitive activation and antigen assay	100‖	>95‖	80–97‖

**"Early" refers to a fall in the platelet count that begins within the first 4 days of starting heparin; "late" refers to a fall that begins on day 5 or later. The data range for the late platelet count fall indicates cardiac patients receiving unfractionated heparin and orthopedic patients receiving low-molecular-weight heparin, respectively.*

†Assumes use of certain quality control maneuvers, including use of weak positive control sera and selected and/or multiple platelet donors. Also, in about 5% of heat-inactivated serum, heparin-independent platelet activation is observed. If a new serum aliquot is heat-inactivated, and the test repeated, an interpretable result is achieved in at least half the cases. However, about 30% to 40% of samples (~2% overall) give a repeated "indeterminate" result and the activation assay is nondiagnositc.

‡Assumes that the heparin-induced platelet aggregation test and serotonin release assay have similar sensitivity and specificity profiles; other platelet activation endpoints that may also give acceptable results using washed platelets include detection of platelet-derived microparticles by flow cytometry.

§Assumes that a 90% specificity in early thrombocytopenia attributable to nonheparin-induced thrombocytopenia (HIT) disorders (eg, nonspecific platelet activation related to acute inflammatory proteins) declines to an 82% specificity in late thrombocytopenia, which may be attributable to subclinical HIT antibody seroconversion.

‖Clinicopathologic definition assumes that at least one sensitive test must be positive for diagnosis of HIT; specificity of the activation assay is indicated.

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GPI; *P*<.001).[52] Similarly, in the ACUITY trial of 13,800 patients with moderate- to high-risk non–ST-segment elevation acute coronary syndromes, the use of bivalrudin alone resulted in a numerically lower (although not statistically lower) incidence of thrombocytopenia compared with either a heparin (either UFH or enoxaparin) plus a GPI or bivalirudin plus a GPI (9.9% bivalirudin alone vs 10.8% bivalirudin + GPI vs 11.1% UFH/enoxaparin + GPI).[51] Data from the HORIZONS ST-segment elevation MI trial have been presented but not yet published.[53]

Bivalirudin has also been studied specifically in the setting of HIT in the ATBAT trial.[54] The ATBAT trial randomized 52 patients with new or previous HIT or HITTS in an open-label fashion to two different doses of bivalirudin. The primary endpoint was a composite of bleeding events, with a secondary endpoint examining clinical outcomes such as PCI success, platelet count, and death or MI. The rate of adverse events was very low in both groups, but importantly, no patient had a decrease in platelet count >50% from baseline, suggesting that bivalirudin is a safe and perhaps preferred antithrombin agent to use for PCI in the patient with HIT or HITTS.

Prevention of Thrombocytopenia

Given the high risk for morbidity and mortality associated with thrombocytopenia and the difficulty in managing these patients, one strategy may be to adopt measures that reduce the risk for developing thrombocytopenia. The options are limited with regard to oral antiplatelet therapy after PCI due to the profound benefit with the combination of aspirin and a thienopyridine.[55] The majority of patients treated with this combination will not experience any decrease in their platelet counts. In contrast, current data suggest that the routine use of GPI during PCI can be avoided with the use of bivalirudin, even in high-risk patients,[51,52] thereby reducing the risk for thrombocytopenia from these agents. In addition to pharmacological strategies, mechanical destruction of platelets can be minimized by prompt removal of intra-aortic balloon pumps.

CONCLUSION

Thrombocytopenia is an important adverse event that the interventionist needs to recognize and know how to manage. Several interventional strategies, both pharmacological and mechanical, can lead to decreased platelet counts in the patient undergoing PCI. Important medication-related causes include thrombotic thrombocytopenic purpura associated with thienopyridines, antibody-related platelet destruction seen with GPI and abciximab readministration, and HIT. If HIT is suspected or proven, DTIs are the

agents of choice, with bivalirudin having the most supportive evidence. Early recognition of thrombocytopenia and rapid assessment of its cause can guide management and improve outcomes among PCI patients with thrombocytopenia. ■

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