RESEARCH LETTER

blood advances

TO THE EDITOR:

Doppler ultrasound screening in patients with newly diagnosed heparin-induced thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) is a disease that presents with concurrent thrombocytopenia and thrombophilia in the setting of heparin product usage. It is caused by heparin-induced antiplatelet factor 4 (PF4) antibodies that bind PF4 (classically in the presence of heparin), forming large PF4-antibody complexes. Platelet and monocyte Fc receptors bind to the antibody Fc domains in these complexes, leading to platelet activation with release of procoagulant microparticles and expression of tissue factor by activated monocytes. The result is a consumptive coagulopathy with both thrombocytopenia and thrombophilia.[1]

Acute HIT is associated with a high rate of arterial and venous thromboembolism in the first month after diagnosis.[2-4] Heparin discontinuation alone is insufficient to abrogate clotting risk,[5] and so the American Society of Hematology (ASH) 2018 guidelines recommend "discontinuation of heparin and initiation of non-heparin anticoagulant"[6] (p3375) for patients with newly diagnosed HIT. For patients without thrombosis at the time of diagnosis (isolated HIT), the ASH guidelines recommend continuation of nonheparin anticoagulation at therapeutic intensity, at least until platelet recovery, but for no longer than 3 months. In addition, the guidelines suggest "bilateral lower-extremity compression ultrasound to screen for asymptomatic proximal deep vein thrombosis (DVT)"[6](p3364) in patients with acute isolated HIT (ie, no known thrombosis), as this may change the duration of anticoagulation.

However, whereas the recommendation to stop heparin and start an alternative anticoagulant is a strong recommendation based on moderate evidence, the recommendations regarding type of anticoagulation, duration of anticoagulation, and screening ultrasound are all suggestions based on evidence of very low certainty, as reflected in the ASH conditional recommendation that "in patients with acute isolated HIT and an upper extremity CVC [central venous catheter], the guidelines suggest upper extremity ultrasonography in the limb with a catheter to screen for asymptomatic DVT. The ASH guideline panel *suggests* against upper extremity ultrasonography in limbs without CVCs to screen for asymptomatic DVT."[6](p336[4]) This suggestion stems from the fact that there are few published data on the incidence of upper extremity DVT at the time of diagnosis.[7,8] Hong et al found that, among patients with HIT and a CVC, 9.7% (14 of 145) developed upper extremity DVT, and no patients developed upper extremity DVT in HIT without a CVC (0 of 115).[8] This study provided the basis for the current ASH guidelines.

Compared with lower extremity DVT, the risk of pulmonary embolism (PE) with upper extremity DVT is lower but not insignificant. In patients without HIT, symptomatic PE with upper extremity DVT has been recorded between 5.6% and 9% with an estimated 0.7% mortality rate.[9,10] The rate of asymptomatic PE in patients with upper extremity thrombus may be as much as 4 times higher.[11] Given the known prothrombotic state of HIT and the potential morbidity associated with upper extremity thrombus, more information is needed on the risk of upper extremity thrombus in HIT.

At our institution, the hematologist's recommendation to perform routine screening ultrasonography of all 4 extremities vs lower extremity only in patients with HIT varies from provider to provider. To better understand the additive value of including upper extremity ultrasonography, we performed a retrospective analysis of all patients diagnosed with HIT over the past 5 years. Our objective was to determine the rates of

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The original data are available by e-mail request to Eliot C. Williams (williams@medicine.wisc.edu).

Table 1. Data on 17 patients with lower extremity thrombi

Patient ID	Lower extremity vessels with thrombi	Lines/devices	Symptoms
3	Right femoral and popliteal	No	Yes
6	Left CFV and popliteal	No	Yes
7	Right CFV, GSV, femoral, popliteal, posterior tibial and peroneal; left CFV	No	Yes
8	IVC, bilateral iliac, CFV, and DFV; left femoral, popliteal and peroneal; right GSV	No	No
9	IVC; bilateral iliac, CFV, femoral, popliteal, peroneal, and posterior tibial	IVC filter	Yes
11	Bilateral popliteal	No	Yes
12	Right femoral, popliteal, and peroneal	No	No
17	Right femoral, popliteal, posterior tibial, and peroneal; left popliteal	No	No
28	Right CFV and DFV	No	No
29	Right popliteal and GSV	No	Yes
30	Right CFV; bilateral femoral, popliteal, peroneal, and posterior tibial	No	No
31	Bilateral peroneal and posterior tibial	No	No
32	Right CFV, femoral, popliteal, peroneal, and posterior tibial; left GSV	No	Yes
33	Right CFV and GSV	No	No
38	Right CFV	No	Yes
40	Hepatic IVC to left iliac	CoolGard LLE	Yes
41	Left CFV, DFV, and femoral	No	Yes

CFV, common femoral vein; DFV, deep femoral vein; GSV, greater saphenous vein; IVC, inferior vena cava; LLE, left lower extremity.

asymptomatic upper extremity DVT among patients with acute HIT, to quantify the value of screening for this condition.

From 2016 through 2020, 1073 patients at our institution were screened for heparin-PF4 antibodies by immunoassay (Asserachrom HPIA; Diagnostica Stago, Parsippany, NJ). Of those patients, 130 had a positive screening test; 42 of them with a positive enzyme-linked immunosorbent assay (32%) were confirmed to have HIT by either a positive serotonin release assay or a P-selectin expression assay in 33 cases (both at Versiti Diagnostic Laboratories, Milwaukee, WI) or in 9 cases by consultation with a hematologist. Of the 9 cases confirmed by hematology consultation alone, 3 had HIT antibody OD $\geq$2.0, 2 between 1.5 and 1.9, and 4 between 1.19 and 1.45. All 9 cases had a high probability of HIT by 4T score, a consistent clinical picture, and resolution of thrombocytopenia with heparin product cessation. The University of Wisconsin Health Sciences Institutional Review Board approved this study, which was conducted in accordance with the Declaration of Helsinki.

The majority of the patients (86%) with confirmed heparin-induced thrombocytopenia had received only unfractionated heparin before the diagnosis in the form of an IV infusion or subcutaneous injections. Of the remaining patients, 9% had received only low-molecular-weight heparin, and ~5% had been exposed to both low-molecular-weight heparin and unfractionated heparin before diagnosis.

Lower extremity Doppler ultrasonography was performed on 27 of the 42 patients; 17 (63%) of the sonograms showed thrombus in the lower extremities (Table 1) and 41% of them had lower

Table 2. Data on 11 patients with upper extremity thrombi

Patient ID	Upper extremity vessels with thrombi	Lines/devices	Symptoms
4	Right brachial	No	No
5	Left basilic, axillary, and subclavian	Left PICC	Yes
6	Right IJ and innominate	No	Yes
11	Bilateral axillary and proximal cephalic	No	Yes
15	Left IJ, brachial, subclavian, and axillary	No	Yes
17	Left subclavian and basilic; bilateral cephalic	No	No
20	Right IJ and axillary; left basilic	Right PICC	Yes
21	Left IJ	No	No
28	Left subclavian, axillary, and basilic	Left PICC	No
32	Left subclavian, axillary, basilic, cephalic; right basilic and cephalic	No	Yes
42	Right IJ, subclavian, axillary, brachial, basilic, and cephalic	Right PICC	Yes

IJ, internal jugular; PICC, peripherally inserted central catheter.

extremity thrombi with no swelling, pain, erythema, or other symptoms or signs of thrombosis by chart review. All but 1 of the 17 cases (94.1%) had proximal vessel involvement of the lower extremities, as defined by popliteal veins and the more proximal vessels (Table 1). Upper extremity Doppler ultrasonography was performed on only 18 of 42 patients with confirmed HIT. Remarkably, 11 (61%) of the upper extremity Doppler sonograms detected 1 or more thrombi, of which 4 (36%) were asymptomatic. Four of 11 upper extremity clots were considered to be catheter related; 3 of those were symptomatic (Table 2). All but 1 of the 11 cases (90.5%) involved proximal vessels, defined as axillary vessels or more proximal ones (Table 2). HIT cases with upper extremity thrombi were all confirmed by serotonin release assay or P-selectin expression assay serology except 1, which was confirmed by hematology consultation alone (HIT antibody OD 1.63 with high-risk 4T score and consistent clinical picture).

Importantly, the majority (55%) of the patients with upper extremity thrombus did not have a concurrent lower extremity thrombus, which implies that many of the patients would have had an inadequate course of anticoagulation, had the upper extremity Doppler sonograms not been obtained. Two patients did not have concurrent lower extremity clots, symptoms, or upper extremity CVC, and so may not have had adequate anticoagulation if the current ASH imaging guidelines had been followed.

This study has important limitations. It is a relatively small, unblinded, retrospective study, and the decision to perform upper extremity ultrasonography was clinician-dependent and not randomized. However, the study suggests that asymptomatic upper extremity thrombi may be more common than previously thought in HIT, specifically in comparison with the aforementioned results of the study by Hong et al.[8] Considering that HIT is a highly prothrombotic state, the clots in vessels without a CVC would represent an indication for anticoagulant therapy in most instances.

Although further study of this question is clearly needed, we believe that clinicians should consider performing Doppler ultrasonographic examination of all 4 extremities in all patients with HIT, regardless of the presence or absence of symptoms or catheters.

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