

Heparin-Induced Thrombocytopenia in Cardiac Surgery Patients

Anna Vittoria Mattioli, MD, PhD¹ Antonio Manenti, MD¹ Alberto Farinetti, MD¹

¹Department of Surgical, Medical and Dental Department of Morphological Sciences related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy

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Address for correspondence Anna Vittoria Mattioli, MD, PhD, Department of Surgical, Medical and Dental Department of Morphological Sciences related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Via del pozzo, 71 41100 Modena, Italy (e-mail: annavittoria.mattioli@unimore.it).

We read with great interest the paper “Heparin-Induced Thrombocytopenia in Cardiac Surgery Patients” by Pishko and Cuker¹ and we found it very important with a view to clinical prevention. The authors reviewed the epidemiology, clinical diagnosis, and laboratory diagnosis of heparin-induced thrombocytopenia (HIT) in cardiac surgery patients and present a conceptual framework for selecting intraoperative anticoagulation in patients with a history of HIT.

With reference to the findings reported in the paper, we would like to make the following contribution to the discussion. We retrospectively analyzed data from 600 postcardiac surgery patients to evaluate the incremental value of performing 4Ts test and EuroSCORE (European System for Cardiac Operative Risk Evaluation) test in identifying patients at a high risk of developing anti-PF4/heparin antibodies and thrombotic complications. A secondary end point was thrombotic events during the 30-day follow-up.

Anti-PF4/heparin antibodies were tested in all patients using a commercial immunoassay (Asserachrom Human PF4 ELISA [enzyme-linked immunosorbent assay] kits).^{2–4} No functional HIT assay was performed. Preoperative ELISA HIT testing was not performed. Of the 600 patients investigated, 131 (21.8%) were found to have anti-PF4/heparin antibodies in the postoperative period (5–7 days from surgery). This group included both patients who were seropositive prior to surgery and those who seroconverted after surgery. This is a limitation of the study. A previous systematic review found that preoperative antibodies were present in 5 to 22% of cardiac surgery patients.⁵ We calculated the 4Ts score and the EuroSCORE for our patient cohort⁶ using scoring as previously reported.^{7,8} A high-probability 4Ts score was predictive of anti-PF4/heparin antibody formation and thrombotic events (►Table 1⁶). The EuroSCORE did not add any more information in our cohort of patients (►Table 1). The only parameter of the EuroSCORE that added information for stratification was the left ventricular ejection fraction (►Table 2). Reduced ejection fraction is a marker of

severity of cardiac disease and is associated with an increased risk of thrombosis.⁹ Patients with reduced ejection fraction may be more likely to have been treated with heparin, which might favor the development of anti PF4/heparin antibodies in cardiac surgery patients preoperatively leading to possible “early onset” HIT.¹⁰ This is a rare form of HIT characterized by early onset of thrombocytopenia, a confounding factor in patients undergoing cardiac surgery.¹⁰ In fact, in cardiac surgery patients, early onset and persisting thrombocytopenia can be explained by several non-HIT factors (e.g., postoperative multiorgan system failure).¹⁰ Patients with a high probability 4Ts test and a reduced ejection fraction therefore need a more careful evaluation. In these patients, a test for anti-PF4/heparin antibodies would be useful to enable early diagnosis of HIT and, consequently, enable better management of anticoagulant therapy in patients found to have pathological HIT. Patients with HIT are at a high risk of thrombosis, and when pathological HIT is strongly suspected or confirmed, heparin should be stopped according to the American College of Chest Physicians guidelines.⁹ Furthermore, appropriate alternative anticoagulant therapy should be promptly initiated at therapeutic doses until the platelet count has recovered.

In patients with intermediate-to-high likelihood of complications, as predicted by EuroSCORE, the addition of 4Ts score improved the prediction of events (►Table 1). These patients need a more careful follow-up, and immunological tests for anti-PF4/heparin antibodies, followed by functional HIT confirmation, could help prevent thrombotic complications related to pathological HIT.^{2–5,7–9,11,12} We agree with Pishko and Cuker that it is necessary to distinguish the common platelet count fall associated with CPB and surgery from the much less common platelet count fall associated with HIT. The 4Ts score and the EuroSCORE might help to identify high-risk patients that need close follow-up to avoid thrombotic complications related to HIT.

Table 1 Thrombotic events in patients stratified according 4Ts score and EuroSCORE

	High score, n (%)	Intermediate score, n (%)	Low score, n (%)
4Ts score (n = 131 patients)	57 (43.5%)	36 (27.4%)	9 (6.8%)
EuroSCORE (n = 131 patients)	57 (43.5%)	33 (25.1%)	12 (9.1%)

Abbreviation: EuroSCORE, European System for Cardiac Operative Risk Evaluation.

Table 2 Association of thrombosis with 4Ts score in all patients who yielded intermediate and high 4Ts score, in patients with a high EuroSCORE, and in patients with low ejection fraction

	4Ts score		
	Low (reference)	Intermediate, HR (95% CI)	High, HR (95% CI)
Total population (131 patients)	1	1.05 (0.76–1.01)	1.74 (0.9–2.2) ^a
Patients with a high EuroSCORE value (87 patients)	1	1.12 (0.34–1.15)	1.24 (0.42–1.56)
Patients with low ejection fraction (55 patients)	1	0.98 (0.66–0.98)	2.0 (0.56–2.34) ^a

Abbreviations: CI, confidence interval; EuroSCORE, European System for Cardiac Operative Risk Evaluation; HR, hazard ratio.

^ap < 0.05.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed consent

Informed consent was obtained from all individual participants included in the study.

References

- Pishko AM, Cuker A. Heparin-induced thrombocytopenia in cardiac surgery patients. *Semin Thromb Hemost* 2017;43(07):691–698
- Husseinzadeh HD, Gimotty PA, Pishko AM, Buckley M, Warkentin TE, Cuker A. Diagnostic accuracy of IgG-specific versus polyspecific enzyme-linked immunoassays in heparin-induced thrombocytopenia: a systematic review and meta-analysis. *J Thromb Haemost* 2017;15(06):1203–1212
- Mattioli AV. Prevalence of anti-PF4/heparin antibodies and the HIT syndrome in cardiovascular medicine. *Semin Thromb Hemost* 2004;30(03):291–295
- Mattioli AV, Bonetti L, Carletti U, Ambrosio G, Mattioli G. Thrombotic events in patients with antiplatelet factor 4/heparin antibodies. *Heart* 2009;95(16):1350–1354
- Yusuf AM, Warkentin TE, Arsenaault KA, Whitlock R, Eikelboom JW. Prognostic importance of preoperative anti-PF4/heparin antibodies in patients undergoing cardiac surgery. A systematic review. *Thromb Haemost* 2012;107(01):8–14
- Mattioli AV, Manenti A, Farinetti A. 4Ts score and EuroSCORE in cardiac surgery. *J Thromb Thrombolysis* 2018 Feb;45(02):291–292
- Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(3, Suppl):311S–337S
- Nashef SAM, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;16(01):9–13
- Tang L, Wu YY, Lip GY, Yin P, Hu Y. Heart failure and risk of venous thromboembolism: a systematic review and meta-analysis. *Lancet Haematol* 2016;3(01):e30–e44
- Warkentin TE, Moore JC, Vogel S, Sheppard JA, Warkentin NI, Eikelboom JW. The serological profile of early-onset and persisting post-cardiac surgery thrombocytopenia complicated by “true” heparin-induced thrombocytopenia. *Thromb Haemost* 2012;107(05):998–1000
- Mattioli AV, Bonetti L, Zennaro M, Ambrosio G, Mattioli G. Heparin/PF4 antibodies formation after heparin treatment: temporal aspects and long-term follow-up. *Am Heart J* 2009;157(03):589–595
- Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2, Suppl):e495S–e530S

