

This is the peer reviewed version of the following article:

Heparin-Induced Thrombocytopenia in Cardiac Surgery Patients / Mattioli, Anna Vittoria; Manenti, Antonio; Farinetti, Alberto. - In: SEMINARS IN THROMBOSIS AND HEMOSTASIS. - ISSN 0094-6176. - 44:3(2018), pp. 304-306. [10.1055/s-0038-1637751]

*Terms of use:*

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

08/08/2024 04:12

(Article begins on next page)

## Instructions to Contributors

Dear Contributor:

Enclosed in this document please find the page proofs, copyright transfer agreement (CTA), and offprint order form for your article in *Seminars in Thrombosis and Hemostasis*. Please print this document and complete and return the CTA and offprint order form, along with corrected proofs, within 72 hours.

- 1) Please read proofs carefully for **typographical** and **factual** errors only; mark corrections in the margins of the proofs in blue or black pen, or use **Adobe Acrobat tools** to mark the changes in the PDF file directly. Please be sure to write as clearly as possible so no errors are introduced into your article. **Answer (on the proofs) all author queries marked in the margins of the proofs.** Check references for accuracy. **Please check on the 1st page of your article that your titles and affiliations are correct.** Avoid elective changes, because these are costly and time consuming and will be made at the publisher's discretion.
- 2) Please pay particular attention to the proper placement of figures, tables, and legends. Please provide copies of any formal letters of permission that you have obtained.
- 3) **Please return the corrected proofs, signed copyright transfer agreement, and your offprint order form.**
- 4) As a contributor to this journal you will receive a complimentary PDF file of the article after publication.
  - If you wish to order offprints, **please circle the quantity required** (left column) **and the number of pages in your article.** If you wish to order copies of the journal please enter the number of copies on the indicated line.
  - If you do not want to order offprints or journals simply put a slash through the form, **but please return the form.**

**Please return all materials within 72 hours. E-mail is the easiest way to ensure your corrections are received in a timely manner. Please return the corrected proofs to:**

Ananya Das, Project Manager  
Thieme Medical and Scientific Publishers  
Fax: +91-120-4556649  
Email: [ananya.das@thieme.in](mailto:ananya.das@thieme.in)

Please do not return your materials to the editor or the typesetter.

**Please note:** Due to a tight schedule, if the publisher does not receive the return of your article proofs within 7 days of the date the e-mail was sent to you, the publisher reserves the right to proceed with publication without author changes. Such proofs will be proofread by the editor and the publisher.

Thank you for your contribution to this journal.

# Permission to Publish and Copyright Transfer Agreement

## Manuscript Information:

Journal: \_\_\_\_\_  
\_\_\_\_\_

Manuscript Title: \_\_\_\_\_  
\_\_\_\_\_

Manuscript Number: \_\_\_\_\_

Authors: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Corresponding author's  
contact data: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Corresponding author's  
e-mail address: \_\_\_\_\_

Contact at the publishers: \_\_\_\_\_

E-mail address at  
the publishers: \_\_\_\_\_

*Dear Author,*

*Please*

- read this form carefully,*
- check all Manuscript Information,*
- sign this form with your digital signature and*
- return to us.*

*Thank you very much in advance.*

## Assignment of Rights

We – the Thieme Publishing Group – do not accept any manuscript for publication in a journal that has previously been published elsewhere.

Your consent to the following assignments of rights, also on behalf of the other authors (if several authors contribute to the manuscript), and the signing of this Copyright Transfer Agreement is a necessary requirement for the publication of your manuscript.

Upon acceptance of your manuscript by us you assign to us (on behalf of all authors), without geographical or language restriction and for the duration of the legal copyright term, the rights to use your article, for all print runs/updates, including the rights to:

- reproduce and distribute copies of the article in printed form (e.g., in a periodical or journal, medical textbook or other target group oriented book, paperback book, special edition for secondary markets or special customers, brochures, advertising supplements, edited volumes, etc.);
- reproduce and distribute the article in electronic media formats (e.g., magnetic tape, CD-Rom, CDI, DVD, electronic paper, hardware RAM, hard-disk, USB memory stick) and make available to the public (e.g., internet, intranet or other wired or wireless data networks), in particular by displaying on stationary or mobile visual display units, monitors, PDA, mobile phones, smart phones or other devices by download (e.g., e-pub, PDF, App) or retrieval in any other form;
- publish ourselves or to authorize the publication of excerpts in other works or articles, in audio-visual accompanying materials or interactive products or services, and including the transfer of rights of use to third parties (e.g., under the terms of licensing agreements);

– translate, transfer and process into other languages or versions (e.g., podcast, audiobook or other image and sound carriers), broadcast by means of television, cable or satellites, radio or other audio-visual media, to rent out and lend, store in an electronic archive and to use in any other type of format that may become known in the future and – where applicable – for all other rights protected by organizations assessing and/or collecting fees for copyright use. Furthermore you assign to us all statutory royalty claims under relevant law insofar we mandate an organization to administer such rights for publishers and authors; we accept the assignments.

Any adaptations, if appropriate for the exercise of the rights of use granted to us, shall be processed by us. Please forward any inquiries that are addressed to you regarding the above-mentioned rights of use for our attention and response.

### Open Access / Repositories

The rights of use are assigned to us exclusively – subject to your rights in accordance with our Open Access Guidelines. Our Open Access Guidelines state that immediately after the publication of the article by us, you and the other authors are entitled to make the published version of the article available to the public on your homepage and on the homepage of your institution for your own scientific and other non-commercial purposes. Twelve months after publication by us, you and the other authors are entitled to make the accepted manuscript version available to the public on other non-commercial websites, provided that you make full reference to the published version (“Green Open Access”). For further details please click the button “Information on Green Open Access.”

For more information on our Open Access Program please visit <http://open.thieme.com>.

### Duties of care

Product liability laws set high standards for your duty of care as the author of a scientific manuscript. This is especially the case when you give therapeutic information and/or specify doses. Therefore please check this information carefully in the typeset page-proofs of your article. Your task will be much easier if you have the information counterchecked – depending on the sensitivity of the information within the article – by specialist colleagues. Only you, as the author, have the specialist knowledge to be able to assess the accuracy of the information. For further information on how to indicate corrections, please click the button “Correction markup symbols”.

### Author’s Declaration

I have taken note of the information on the duties of care under product liability law; I agree to the assignments of rights in accordance with the foregoing sections “Assignment of Rights” and “Open Access / Repositories” also on behalf of the other authors (if several authors have contributed to the article).

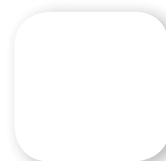
I declare that no third party rights will be infringed through the publication. Any material contained in the manuscript (including illustrations, tables, or other material) from third-party sources will be identified as such through citation, indicating the source. If required, I have obtained the copyright permission from the publishers concerned.

The above-mentioned assignments of rights also relate to the illustrations in your manuscript. We do not accept any illustrations for which it has not been granted all rights of use in accordance with this contract.

Should one of the foregoing regulations be or become invalid in whole or in part this shall not affect the validity of the other provisions. Any invalid provision shall be replaced by a regulation that comes as close as possible to the purpose of the invalid provision in economic terms, insofar as legally permissible.

This article is ready to print after the execution of the corrections indicated by me.

\_\_\_\_\_  
Date                      Digital Signature



Information on  
Green Open Access



Correction markup  
symbols



Information on the  
digital signature



Order Form for Offprints and additional copies of *Seminars in Thrombosis and Hemostasis*  
(Effective January 2013)

**Please circle the cost of the quantity/page count you require (orders must be in increments of 100)**

Quantity	Pages in Article / Cost				
	1 to 4	5 to 8	9 to 12	13 to 16	17 to 20
<b>100</b>	\$298	\$497	\$746	\$968	\$1,158
<b>200</b>	\$397	\$646	\$970	\$1,258	\$1,495
<b>300</b>	\$496	\$798	\$1,198	\$1,568	\$1,869
<b>400</b>	\$549	\$886	\$1,330	\$1,735	\$2,075
<b>500</b>	\$598	\$966	\$1,450	\$1,886	\$2,262
<b>1000</b>	\$1,076	\$1,739	\$2,610	\$3,385	\$3,995

Volume/Issue #: \_\_\_\_\_ Page Range (of your article): \_\_\_\_\_

Article Title: \_\_\_\_\_

MC/Visa/AmEx No: \_\_\_\_\_ Exp. Date: \_\_\_\_\_

Signature: \_\_\_\_\_

Name: \_\_\_\_\_

Address: \_\_\_\_\_

City/State/Zip/Country: \_\_\_\_\_

Corresponding author will receive a complimentary PDF of the article after publication.

Number of **additional** copies of the journal, at the discounted rate of \$25.00 each: \_\_\_\_\_

**Notes**

1. The above costs are valid only for orders received before publication of the issue. **Reprints ordered after printing will be substantially more expensive.**

2. **A shipping charge will be added to the above costs.**

3. Reprints are printed on the same coated paper as the journal and saddle-stitched.

4. For larger quantities or late orders, please contact reprints department:

Phone: +1(212) 584-4662

Fax: +1(212) 947-1112

E-mail: [reprints@thieme.com](mailto:reprints@thieme.com)

# Heparin-Induced Thrombocytopenia in Cardiac Surgery Patients

**Q1** <sup>Q1</sup> Anna Vittoria Mattioli, MD, PhD<sup>1</sup> Antonio Manenti, MD<sup>1</sup> Alberto Farinetti, MD<sup>1</sup>

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

Semin Thromb Hemost 2018;00:1–2.

**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 Cuker<sup>1</sup> 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.

**Q2** Anti-PF4/heparin antibodies were tested in all patients using a commercial immunoassay (Asserachrom Human PF4 ELISA [enzyme-linked immunosorbent assay] kits<sup>Q2</sup>).<sup>2–4</sup> 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.<sup>5</sup> We calculated the 4Ts score and the EuroSCORE for our patient cohort<sup>6</sup> using scoring as previously reported.<sup>7,8</sup> A high-probability 4Ts score was predictive of anti-PF4/heparin antibody formation and thrombotic events (►Table 1–<sup>6</sup>). 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.<sup>9</sup> 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.<sup>10</sup> This is a rare form of HIT characterized by early onset of thrombocytopenia, a confounding factor in patients undergoing cardiac surgery.<sup>10</sup> 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).<sup>10</sup> 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.<sup>9</sup> 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.<sup>2–5,7–9,11,12</sup> 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.

**Issue Theme** Editorial Compilation V;  
Guest Editors: Emmanuel J. Favaloro,  
PhD, FFSc (RCPA), and Giuseppe  
Lippi, MD.

Copyright © 2018 by Thieme Medical  
Publishers, Inc., 333 Seventh Avenue,  
New York, NY 10001, USA.  
Tel: +1(212) 584-4662.

**DOI** <https://doi.org/10.1055/s-0038-1637751>.  
**ISSN** 0094-6176.

**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) <sup>a</sup>
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) <sup>a</sup>

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

<sup>a</sup>p < 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.

#### Q3

#### References<sup>Q3</sup>

- 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, Arsenault 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* 2017. Doi: 10.1007/s11239-017-1604-z
- 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

# Author Query Form (STH/02548)

**Special Instructions: Author please write responses to queries directly on proofs and then return back.**

Q1: AU: Please confirm that given names (red), middle names (black) and surnames (green) have been identified correctly.

Q2: AU: Please check the change made to the sentence "Anti-PF4/heparin antibodies were tested..." for accuracy.

Q3: AU: Please note that the references have been renumbered because reference 2 was cited out of order.



THIEME