

Diagnostics and mechanisms of hemostasis

Citation for published version (APA):

Heubel-Moenen, F. C. J. I. (2022). *Diagnostics and mechanisms of hemostasis: In patients with mild bleeding disorders and thrombocytopenia*. ProefschriftMaken. <https://doi.org/10.26481/dis.20220131fm>

Document status and date:

Published: 01/01/2022

DOI:

[10.26481/dis.20220131fm](https://doi.org/10.26481/dis.20220131fm)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Impact paragraph

Patients with mild bleeding disorders suffer from disproportionate bleeding after minor injuries, surgery or delivery, leading to use of blood products, re-surgery or prolonged hospitalization^{1,2}. In daily life, bleeding symptoms like epistaxis or heavy menstrual bleeding, can have a great impact on social and school or work-related activities and can lead to lower quality of life³⁻⁶. As pointed out in the preceding chapters, recognition and correct identification of mild bleeding disorders and establishing a personalized treatment plan, are crucial to prevent bleeding and its consequences, with accompanied economic and social benefits. However, in about 50-75% of the patients referred for bleeding evaluation, no reproducible abnormality in hemostatic laboratory tests is found⁷⁻⁹. In patients with bleeding of unknown cause (BUC), providing a personalized treatment plan ensuring save hemostasis for surgery or childbirth, and family counseling is difficult¹⁰.

Patients with a hematologic malignancy often develop low platelet count due to their disease or its treatment. A prophylactic transfusion strategy does not prevent bleeding in all patients on the one hand, and is, on the other hand not always necessary^{11,12}. A personalized transfusion strategy can prevent unwanted complications and can save costs¹³.

The main goal of the studies described in this thesis is to improve diagnostic work-up in patients with a bleeding tendency, to determine the value and place of new diagnostic tests, and to gain more insight in the mechanism of bleeding in different patient populations. The results of this thesis are not only relevant for scientific purposes, but are also of importance in social and economic perspective. The knowledge gained in the preceding chapters of this thesis *(i)* enables critical appraisal and use of established diagnostic tests and diagnostic approaches and, *(ii)* reveals potential pathophysiological mechanisms of bleeding in patients with bleeding of unknown cause (PFA-only) and patients with chemotherapy induced thrombocytopenia (CIT).

Critical appraisal and use of established diagnostic tests and current diagnostic approaches in bleeding evaluation

The studies described in Chapter 2, 3 and 5 investigated widely used and accepted diagnostic tests and approaches in bleeding evaluation.

Chapter 2 revealed that the bleeding assessment tool (BAT) alone is of limited value in the diagnostic work-up of patients referred for bleeding evaluation. A negative BAT was not able to exclude a mild bleeding disorder and a positive BAT increased the likelihood of having a mild bleeding disorder. However, the value of this

increased likelihood in a referred setting is questionable. We believe that the main benefit of the BAT is that it provides a structured and complete interview of the patients' bleeding history. **Chapter 3** showed that both Multiplate and platelet function analyzer (PFA) were not suitable as screening tests for mild platelet function disorders in preoperative patients and patient referred to the hematologist for bleeding evaluation. Although the results of both studies might be regarded as 'negative' findings, and might not lead to significant changes in guidelines, they do have the potential to increase awareness of hematologists and other physicians treating patients with bleeding symptoms, leading to well considered use of the BAT, Multiplate and PFA.

In **Chapter 5** effectiveness, healthcare resource use and costs, and patient burden of two diagnostic approaches for patients referred for bleeding evaluation were compared. The newly proposed all-in-one diagnostic work-up was more effective and reduced patient burden, compared to the conventional stepwise approach, however this was at a higher cost. These findings open the discussion to what a conclusive diagnosis of a mild bleeding disorder and lower patient burden in the diagnostic process is worth. An important benefit of extensive bleeding evaluation, is the reassurance of complete investigation (even if no diagnosis is found) and the ability of putting together all the available pieces of evidence in order to carefully judge on the likelihood of having, or not having, a bleeding disorder.

Potential pathophysiological mechanisms of bleeding

In Chapter 4, 6 and 7, new experimental tests were evaluated in patients with bleeding of unknown cause (e.g. PFA-only patients) and patients with chemotherapy induced thrombocytopenia (CIT), in order to explore different mechanisms of bleeding. Our data adds new information to the recognized knowledge gaps of bleeding mechanisms in these patients. This will aid both physicians treating patients with congenital bleeding disorders and physicians treating patients with hematologic malignancies.

Chapter 4 described multiparameter microfluidic platelet function analysis in bleeding patients with a prolonged platelet function analyzer closure time as the only aberrant finding in their diagnostic work-up. Results showed altered microfluidic thrombus formation indicating a shear-dependent platelet function defect not detected by the static conventional hemostatic tests.

Chapter 6 described platelet activation processes and procoagulant activity in CIT patients and showed defective receptor signaling related to impaired mitochondrial function in platelets from these patients. In **Chapter 7** the fibrinolytic potential of whole blood clots of CIT patients was explored with tPA-ROTEM, before and after

platelet transfusion. Results showed that clots of CIT patients were more susceptible to tPA induced lysis compared to healthy individuals. Platelet transfusion resulted in less hyperfibrinolytic profiles, but not in all patients. Besides platelets, other factors are likely to influence clot lysis in CIT patients.

All studies are registered at the Dutch Trial Registry. Results described in this thesis have been, and will be, published in international peer review journals, and presented on (inter)national congresses. In this way, our results are shared with a broad audience of hematologists and other physicians treating bleeding patients and researchers in the field. We hope that in the end, we are able to change the statement 'we might never know why *most* patients bleed', into 'we might never know why *some* patients bleed'.

Reference

1. Orsini S, et al. Bleeding risk of surgery and its prevention in patients with inherited platelet disorders. *Haematologica* 2017;102(7):1192-203.
2. Greaves M, Watson HG. Approach to the diagnosis and management of mild bleeding disorders. *J Thromb Haemost* 2007;5 Suppl 1:167-74.
3. Sanders YV, et al. Von Willebrand disease in the Netherlands: the WiN study. *Ned Tijdschr Geneesk* 2014;158:A6518.
4. de Wee EM, et al. Health-related quality of life among adult patients with moderate and severe von Willebrand disease. *J Thromb Haemost* 2010;8(7):1492-9.
5. Blaauwgeers MW, et al. Congenital platelet disorders and health status-related quality of life. *Res Pract Thromb Haemost* 2020;4(1):100-5.
6. De Wee EM, et al. Impact of von Willebrand disease on health-related quality of life in a pediatric population. *J Thromb Haemost* 2011;9(3):502-9.
7. Quiroga T, et al. High prevalence of bleeders of unknown cause among patients with inherited mucocutaneous bleeding. A prospective study of 280 patients and 299 controls. *Haematologica* 2007; 92(3):357-65.
8. Thomas W, Downes K, Desborough MJR. Bleeding of unknown cause and unclassified bleeding disorders; diagnosis, pathophysiology and management. *Haemophilia*, 2020.
9. Gebhart J, et al. High proportion of patients with bleeding of unknown cause in persons with a mild-to-moderate bleeding tendency: Results from the Vienna Bleeding Biobank (VIBB). *Haemophilia* 2018; 24(3):405-13.
10. Rodeghiero F, et al. Fundamentals for a Systematic Approach to Mild and Moderate Inherited Bleeding Disorders: An EHA Consensus Report. *HemaSphere* 2019;3(5).
11. Wandt H, et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. *Lancet* 2012; 380(9850):1309-16.
12. Stanworth SJ, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *N Engl J Med* 2013;368(19):1771-80.
13. Schiffer CA, et al. Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2018;36(3):283-99.