Venous and arterial thrombotic complications. Solutions in clinical practice

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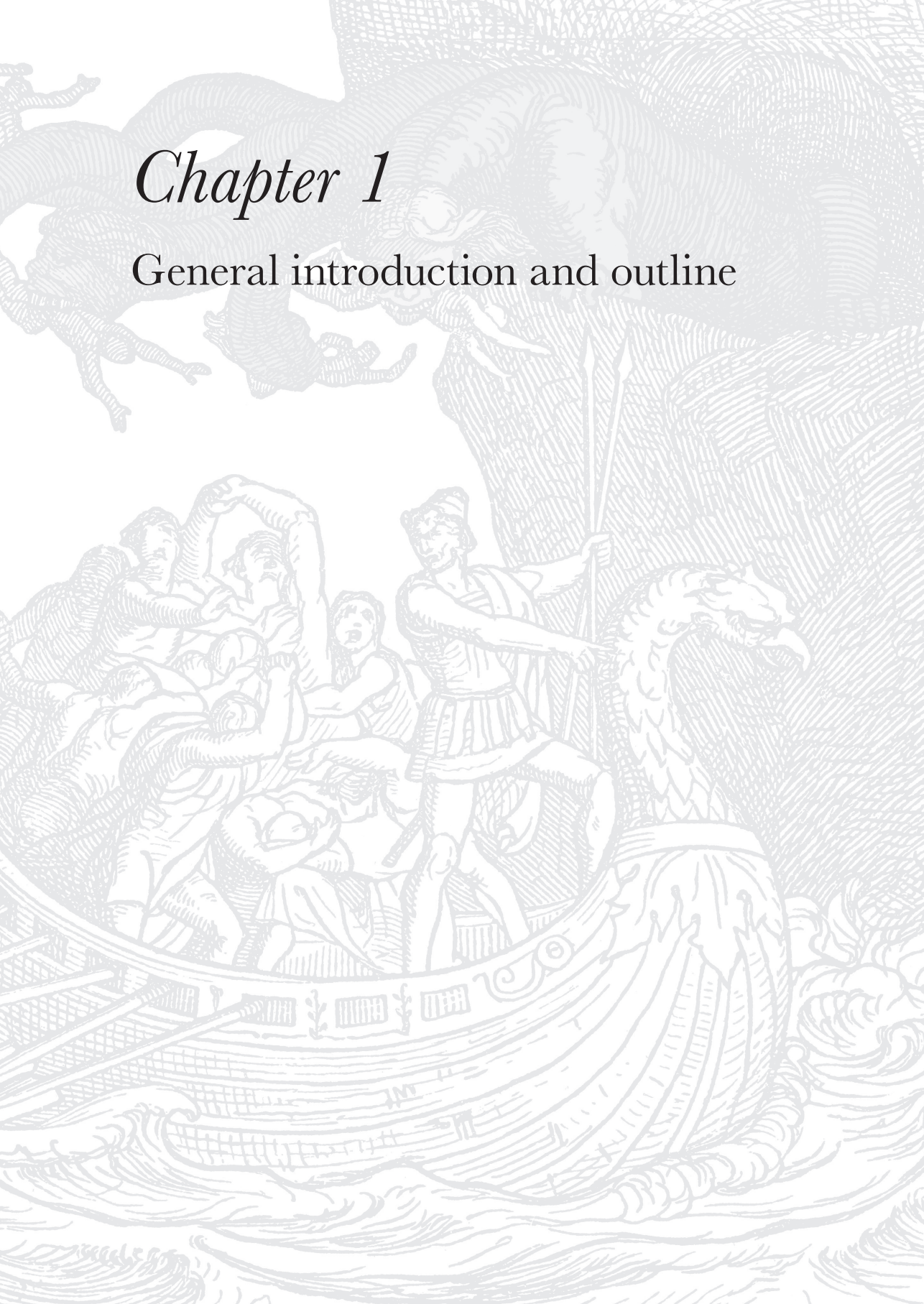

Chapter 1

General introduction and outline

Thrombosis is the formation of a blood clot that obstructs the blood flow through the circulatory system. Thrombosis can occur in veins and arteries. In the 19th century, Rudolf Virchow described the three factors necessary for the formation of thrombosis: blood stasis, changes in the vessel wall and hypercoagulability (1). While Virchow was referring to venous thrombosis, the same processes have been observed in arterial thrombosis. Both diseases have long been considered as separate entities, partly due to differences in mechanistic pathways as well as their distinct clinical presentation. Venous thrombosis occurs under low shear flow conditions due to alteration of blood stasis and composition, and is fibrin-rich due to the large amount of red blood cells (**Figure 1**) (2). Unlike venous thrombosis, arterial thrombosis occurs under high shear flow due to formation of platelet-rich thrombi around ruptured atherosclerotic plaques and damaged vascular endothelium. Venous thrombosis might lead to venous thromboembolism (VTE), while arterial thrombosis causes myocardial infarction and ischemic stroke. Traditional risk factors of venous thrombosis (e.g. surgery, immobilization and cancer) also differ from those that are associated with arterial thrombosis (e.g. smoking, obesity and diabetes). The separate nature of venous and arterial thrombosis has, however, been challenged by numerous reports, suggesting a closer link between both diseases (3-5).

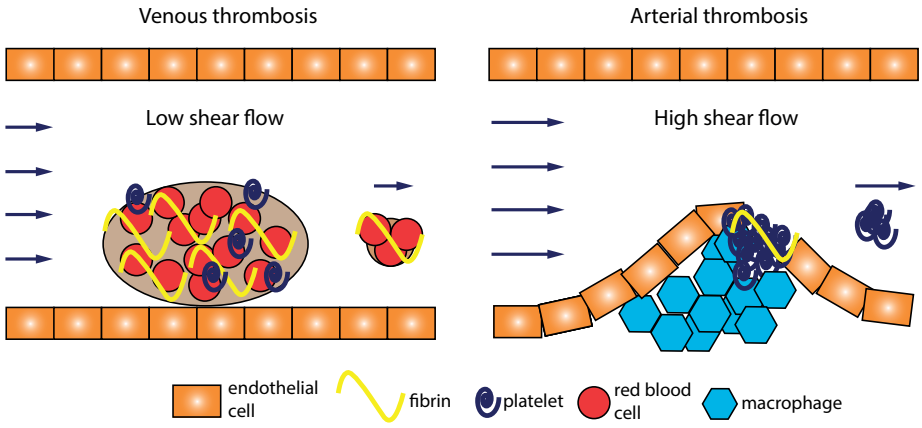

Figure 1. Pathophysiological differences between arterial and venous thrombosis. Figure adapted from Koupenova *et al.* (2017) (2)

The perceived difference between venous and arterial thrombosis is also reflected in the antithrombotic management. Oral anticoagulation is considered first-line treatment in fibrin-rich venous thrombi, whereas antiplatelet therapy is regularly recommended in platelet-rich arterial thrombi. Importantly, the use of antithrombotic drugs is associated with an increased risk of bleeding that potentially results in high risk of morbidity and mortality. Therefore, when deciding on antithrombotic treatment, the risk of thrombosis

should be equally weighed against the risk of bleeding. The appropriate antithrombotic treatment remains challenging and still has many grey areas. Importantly, both diseases are currently the leading causes of death in the Western parts of the world (6).

The first part of this thesis discusses VTE. For the individual patient, the risk of fatal recurrent VTE versus that of fatal bleeding is of particular relevance when deciding on the duration of therapeutic management. In **chapter 2**, the mortality risk of recurrent VTE is demonstrated after anticoagulation cessation in patients with initially unprovoked VTE. So far, these exact numbers were unknown for patients with unprovoked VTE, even though this knowledge is especially valuable for this specific patient category because of the recommendation for indefinite treatment duration, while patients with provoked VTE are generally treated for a short period of time (7, 8). Furthermore, VTE is frequent complication of cancer and cancer treatment (9). International guidelines currently recommend low-molecular-weight heparin (LMWH) therapy as first-line treatment because of a lower recurrence risk compared to the traditional therapy with vitamin K antagonists (VKA) (10). However, these daily subcutaneous LMWH injections may be burdensome owing to local pain or bruising, allergic reactions, or heparin-induced thrombocytopenia. In **chapter 3**, we prospectively assessed the discontinuation rate of these daily injections. The aim of **chapter 4** was to compare the discontinuation rate between two commonly used LMWH compounds – enoxaparin and nadroparin – in the same patient cohort as chapter 3.

The topic of the second part comprises prevention of arterial thrombosis after heart valve surgery. In patients undergoing bioprosthetic aortic heart valve implantation or mitral valve repair, patients are at risk of thromboembolism (11, 12). The optimal antithrombotic therapy after both procedures is still a matter of controversy. In **chapter 5** and **chapter 6** the rates of thromboembolic and bleeding complications are evaluated of two antithrombotic prevention strategies - VKA and aspirin - after bioprosthetic aortic valve implantation and mitral valve repair respectively.

The last part of the thesis focuses on idarucizumab for urgent dabigatran reversal. Dabigatran is a direct thrombin inhibitor that has a favorable risk-benefit profile compared to VKA for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation and treatment of patients with venous thromboembolism (13, 14). However, the lack of a reversal agent often has been considered as a hurdle for prescribing dabigatran. This has prompted the recent development of specific reversal agent idarucizumab for urgent dabigatran reversal in patients with uncontrolled or life-threatening bleeding or undergoing an emergency procedure (7). Because data on idarucizumab are scarce, **chapter 7** was aimed to determine the appropriateness of its usage as well as the hemostatic effectiveness and clinical outcome in daily practice. In **chapter 8,** dabigatran reversal by idarucizumab is discussed in patients presenting with major gastrointestinal (GI) bleeding, as evaluated in the RE-VERSE AD study (15).

REFERENCES

1. Dalen JE. Pulmonary embolism: What have we learned since Virchow? - Natural history, pathophysiology, and diagnosis. Chest. 2002;122(4):1440-56.
2. Koupenova M, Kehrel BE, Corkrey HA, Freedman JE. Thrombosis and platelets: an update. Eur Heart J. 2017;38(11):785-91.
3. Jerjes-Sanchez C. Venous and arterial thrombosis: a continuous spectrum of the same disease? Eur Heart J. 2005;26(1):3-4.
4. Lowe GDO. Common risk factors for both arterial and venous thrombosis. Brit J Haematol. 2008;140(5):488-95.
5. Prandoni P. Links between arterial and venous disease. J Intern Med. 2007;262(3):341-50.
6. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
7. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 2016;18(11):1609-78.
8. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35(43):3033-69, 69a-69k.
9. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. Journal of Thrombosis and Haemostasis. 2007;5(3):632-4.
10. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):315-52.
11. Heras M, Chesebro JH, Fuster V, Penny WJ, Grill DE, Bailey KR, et al. High-Risk of Thromboemboli Early after Bioprosthetic Cardiac-Valve Replacement. J Am Coll Cardiol. 1995;25(5):1111-9.
12. Russo A, Grigioni F, Avierinos JFO, Freeman WK, Suri R, Michelena H, et al. Thromboembolic complications after surgical correction of mitral regurgitation - Incidence, predictors, and clinical implications. J Am Coll Cardiol. 2008;51(12):1203-11.
13. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-51.
14. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342-52.
15. Pollack CV, Jr., Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017;377(5):431-41.

Part 1

Venous thromboembolism