Thrombosis prophylaxis after knee arthroscopy or during lower leg cast immobilization : determining the balance between benefits and risks

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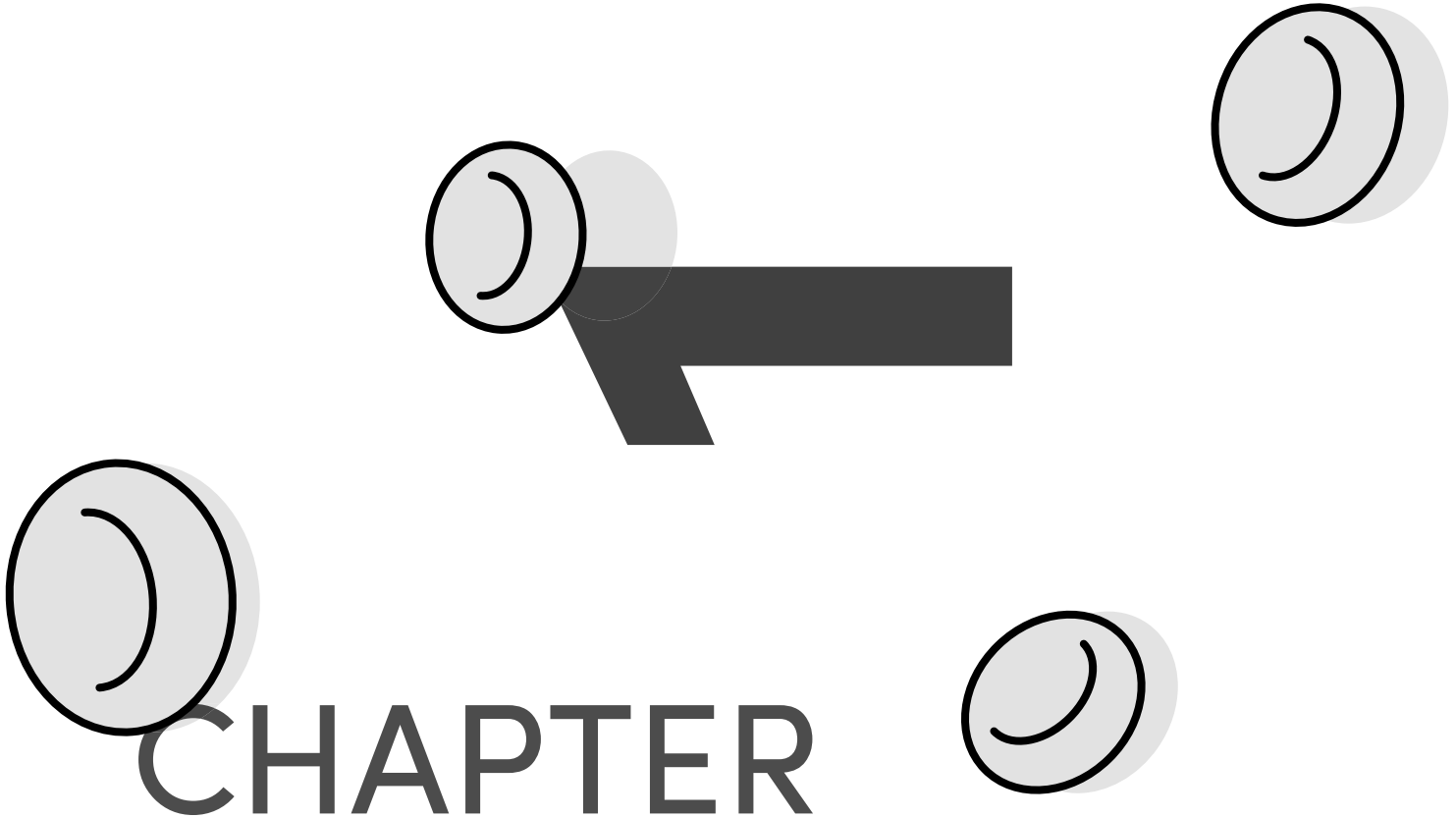
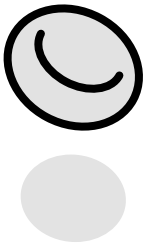
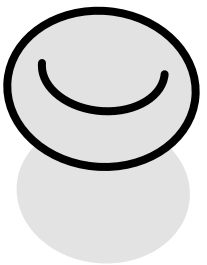
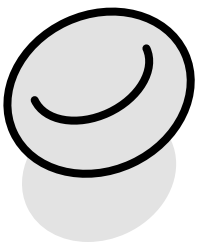


CHAPTER

General introduction and outline of this thesis







Venous thromboembolism (VTE), i.e. deep vein thrombosis (DVT) or pulmonary embolism (PE), is the third most common cardiovascular disease and occurs in 1-2 per 1000 person years in the general population.[1-5] Of all patients with VTE, around two thirds are diagnosed with DVT and one third with PE.[1] The mortality rate of VTE is high, being about 12% in non-cancer patients in one year.[1] Furthermore it leads to chronic morbidity. For example, within two years, up to 50% of patients with DVT develop post-thrombotic syndrome and 4% of patients with a PE suffer from pulmonary hypertension.[6,7]

In the last decades, many risk factors for VTE have been identified, both genetic and environmental.[8-10] An important risk factor is orthopaedic surgery with an estimated risk of 4% in the 35 days after major orthopedic surgery. Therefore, thrombosis prophylaxis is recommended for most orthopedic procedures.[11,12]

The magnitude of the VTE risk is however not well established for all orthopedic surgery patients. In patients with lower leg cast immobilization the risk of asymptomatic VTE varies from 4-40% during the immobilization period.[13-18] However, the relevance of asymptomatic VTE is unclear since these VTEs usually disappear without symptoms.[19] In contrast to this, the cumulative incidence of symptomatic VTE is far less, varying between 0-5.5%. Furthermore, this risk is inflated by the inclusion of patients with complete leg cast immobilization, without further stratification within these studies.[13-18]

The same methodological problem arises when evaluating the VTE risk in patients after arthroscopy of the knee, which is one the most common orthopedic procedures world-wide, being performed over 4 million times each year.[20] Also in these patients the extend of the risk of VTE is not known. Rates of asymptomatic thrombosis in the control groups of six randomized trials that assessed thrombosis prophylaxis to placebo in patients who had an arthroscopy of the knee varied between 0 and 16%.[21-26] This wide variation in incidence can be explained by differences in follow-up time, varying from one week to 3 months. In addition, patients with more extensive procedures, such as anterior cruciate ligament reconstructions, were also included in four out of six trials, further inflating the risk. Rates of symptomatic thrombotic events, however, were once again much lower and varied between 0 and 5.3%.[21-26] The risk of symptomatic VTE after arthroscopic ACL reconstruction is estimated to be higher (4% in 8 weeks compared to regular knee arthroscopy)[27] because of its more invasive nature (e.g. harvesting autologous

tendon graft, tibial and femoral drilling). Once again, no further distinction between types of arthroscopic procedures was made in the afore mentioned trials. Only one trial exclusively focused on the effect of thromboprophylaxis after ACL reconstruction but included only 36 patients.[28] This trial is therefore largely underpowered and no conclusions can be drawn from this study.

Because of the use of asymptomatic VTE as the primary outcome in trials addressing thromboprophylaxis in patients with lower leg cast immobilization and arthroscopic knee surgery, while presence of symptomatic VTE is of more clinical significance, and as a consequence the limited number of included patients in these trials, an overall risk-benefit balance on thromboprophylaxis cannot be established. Therefore, national and international guidelines are unable to give clear recommendations regarding prophylactic treatment in these patients.[11,12,29] For that matter, large pragmatic clinical trials using symptomatic VTE as primary endpoint are needed to address this problem in these highly frequent interventions (i.e. lower leg casting and arthroscopy).[11]

Aim of this thesis

Since the magnitude of the risk of VTE during cast immobilization of the lower extremity and after arthroscopic knee surgery is unknown, this risk will be studied using a large population-based case-control study, the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA study[30]). In addition, the combined effect on VTE risk of these treatments with well-known genetic and acquired risk factors for VTE will be established (chapter 2 and 3).

Since guidelines cannot give clear recommendations based on current evidence, the clinical practice regarding VTE prophylaxis in these patients in the Netherlands will be studied with a survey study among trauma and orthopedic surgeons. In addition, the rationale for providing prophylactic treatment to these patients is studied (chapter 4).

To provide evidence for the effect of pharmacological VTE prophylaxis in patients during lower leg cast immobilization and after knee arthroscopy, two large pragmatic randomized clinical trials are performed using symptomatic VTE as the primary outcome. In chapter 5 the effect of low-molecular weight heparin on the prevention of symptomatic VTE during cast immobilization of the lower leg will be described (POT-

CAST trial). In chapter 6 the results of low-molecular weight heparin on the prevention of symptomatic VTE after knee arthroscopy will be given (POT-KAST trial).

Because the VTE risk is estimated to be higher after ACL reconstruction, modes of VTE prevention in these patients will be studied separately. In chapter 7 the effect of pharmacological prophylaxis compared to compression stockings after arthroscopically assisted ACL reconstruction will be given.

Lastly, to be able to study individualized VTE prophylaxis treatment strategies, prediction models using the predictive value of genetic, environmental, coagulation factors and other biomarkers for the development of VTE during cast immobilization of the lower extremity and after knee arthroscopy will be developed and validated. The results of these prediction models will be given in chapter 8 and 9.

Reference list

1. Naess IA, Christiansen SC, Romunstad P, et al. Incidence and mortality if venous thrombosis: a population-based study. *J Thromb Haemost.* 2007;5(4):692-9
2. Nordstrom M, Lindblad B, Bergqvist D, et al. A prospective study of the incidence of deep vein thrombosis within a defined urban population. *J Intern Med.* 1992; 232(2):155-60
3. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. *Thromb Haemost.* 2000;83(5):657-60.
4. Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med.* 1998;158(6):585-93
5. Spencer FA, Emery C, Joffe SW, et al. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. *J Thromb Thrombolysis.* 2009;28(4):401-9.
6. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. *J Thromb Thrombolysis.* 2009;28(4):465-76.
7. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation.* 2011;123(16):1788-830.
8. Bates SM, Ginsberg JS. Clinical practice. Treatment of deep vein thrombosis. *N Engl Js Med.* 2004;351(3):268-77
9. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet.* 1999;353(9159):1167-73.
10. Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. *Circulation.* 2003;107(23 Suppl 1):I9-16.
11. Falck-Ytter Y, Francis CW, Johanson et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e278S-e325S.
12. NICE guideline. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. Nice.org.uk/guidance/ng89. Published 21 march 2018. Accessed 05 March 2019.
13. Jorgensen PS, Warming T, Hansen K, et al. Low Molecular Weight Heparin (Innohep) as thromboprophylaxis with low-molecular-weight-heparin as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study. *Thromb Res* 2002; 105(6): 477–80.
14. Kock HJ, Schmit-Neuerburg KP, Hanke J,et al. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilization of the leg. Lancet 1995; 346(8973): 459–61.
15. Kujath P, Spannagel U, Habscheid W. Incidence and prophylaxis of deep venous thrombosis in outpatients with injury of the lower limb. Haemostasis 1993; 23(Suppl. 1): 20–6.

16. Lapidus LJ, Ponzer S, Elvin A, et al. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. Acta Orthop 2007; 78(4): 528–35.
17. Lapidus LJ, Rosfors S, Ponzer S, et al. Prolonged thromboprophylaxis with dalteparin after surgical treatment of achilles tendon rupture: a randomized, placebo-controlled study. J Orthop Trauma 2007; 21(1): 52–7.
18. Lassen MR, Borris LC, Nakov RL. Use of the low-molecularweight heparin reviparin to prevent deep vein thrombosis after leg injury requiring immobilization. N Engl J Med 2002; 347(10):726–30.
19. Chan NC, Stehouwer AC, Hirsh J et al. Lack of consistency in the relationship between asymptomatic DVT detected by venography and symptomatic VTE in thromboprophylaxis trials. Thromb Haemost. 2015;114(5):1049-57.
20. van Adrichem RA, Nelissen RG, Schipper IB, et al. Risk of Venous Thrombosis after Arthroscopy of the Knee: results from a large population-based case-control study. J Thromb Haemost. 2015;13(8):1441-8.
21. Camporese G, Bernardi E, Prandoni et al. Low-molecular-weight heparin versus compression stockings for thromboprophylaxis after knee arthroscopy: a randomized trial. *Ann Intern Med*. 2008;149(2):73-82.
22. Marlovits S, Striessnig G, Schuster R, et al. Extended-duration thromboprophylaxis with enoxaparin after arthroscopic surgery of the anterior cruciate ligament: a prospective, randomized, placebo-controlled study. *Arthroscopy*. 2007;23(7):696-702.
23. Michot M, Conen D, Holtz D, et al. Prevention of deep-vein thrombosis in ambulatory arthroscopic knee surgery: A randomized trial of prophylaxis with low--molecular weight heparin. *Arthroscopy*. 2002;18(3):257-63.
24. Roth P. Prophylaxis of deep vein thrombosis in outpatients undergoing arthroscopic meniscus operation [Thromboembolieprophylaxe bei ambulant durchgefürten arthroskopischen Meniskusoperationen]. *Orthopädische Praxis*. 1995;5:345-8.
25. Wirth T, Schneider B, Misselwitz F, et al. Prevention of venous thromboembolism after knee arthroscopy with low-molecular weight heparin (reviparin): Results of a randomized controlled trial. *Arthroscopy*. 2001;17(4):393-9.
26. Camporese G, Bernardi E, Noventa F et al. Efficacy of Rivaroxaban for thromboprophylaxis after knee Arthroscopy (ERIKA). A phase II, multicentre, double-blind, placebo-controlled randomized study. *Thromb Heamost*. 2016;116(2):349-55.
27. Struijk-Mulder MC, Ettema HB, Verheyen CC, Buller HR. Deep vein thrombosis after arthroscopic anterior cruciate ligament reconstruction: a prospective cohort study of 100 patients. *Arthroscopy*. 2013;29(7):1211-6.
28. Canata GL, Chiey A. Prevention of venous thromboembolism after ACL reconstruction: a prospective, randomized study. *ISAKOS (International Society of Arhtroscopy, Knee Surgery and Orthopedic Sports Medicine)*. 2003;Poster 71.

29. Richtlijnen database. Antitrombotisch beleid. https://richtlijnendatabase.nl/richtlijn/antitrombotisch_beleid/antitrombotisch_beleid_-_korte_beschrijving.html#verantwoording. . Published 21 April 2016. Accessed 12 April 2019.
30. Blom JW, Doggen CJ, Osanto S, et al. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005; 293(6): 715–22.