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Venous thrombosis following lower-leg cast immobilization and knee arthroscopy: From a population-based approach to individualized therapy

Németh, B.

Citation
Németh, B. (2020, September 2). *Venous thrombosis following lower-leg cast immobilization and knee arthroscopy: From a population-based approach to individualized therapy*. Retrieved from https://hdl.handle.net/1887/136090

Version:	Publisher's Version
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Note: To cite this publication please use the final published version (if applicable).

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Issue date: 2020-09-02

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General introduction and outline of this thesis

GENERAL INTRODUCTION

Venous Thrombosis

Hemostasis is a physiological process that prevents bleeding once vessel damage occurs. By the formation of a blood clot, a regulatory blood flow in the circulatory system is maintained. Blood clot formation (thrombolysis) and clot break down (fibrinolysis) act synergistically and are mechanically closely intertwined. Once this balance gets disturbed, either Venous Thrombosis (VT) or bleeding occurs. VT is a clotting disease which mainly affects the deep veins in the leg, known as Deep Vein Thrombosis (DVT) or the pulmonary arteries, known as Pulmonary Embolism (PE). In the general population, annually, 1.5 per 1000 persons develop VT and the incidence steeply increases with age.[1] Many risk factors for VT have been identified of which orthopaedic surgery is recognized to be a major cause. This can partially be explained by the extensive iatrogenic tissue damage and immobilization due to surgery. Therefore, to prevent post-operative VT, thromboprophylaxis is indicated in the vast majority of patients who undergo orthopaedic surgery.[2] Whereas the effectiveness of thromboprophylaxis has been established in many trials following major orthopaedic surgery (e.g. total hip or knee replacement), it is unclear whether patients treated with lower-leg cast immobilization or those who undergo arthroscopic knee surgery also benefit from this strategy.

Effectiveness of thromboprophylaxis using a population-based approach

Patients treated with lower-leg cast immobilization have an increased risk for the development of VT which was already noted in 1944.[3] Since then, many observational studies have shown an increased VT risk following lower-leg cast immobilization and it has been shown that lower-leg cast is associated with a 56-fold increased risk for VT within 3-months of its application (corresponding to an incidence within 3-months of approximately 2.0%).[4-7] To evaluate prevention of VT following cast application, prior to this thesis, 6 randomized trials have been performed to study whether thromboprophylaxis (during cast immobilization) is an effective treatment.[8-13] The results across these trials did not uniformly suggest effectiveness of thromboprophylaxis. Moreover, as many trials had methodological shortcomings (i.e. underpowered to establish efficacy on prevention of symptomatic VTE, high rates of loss to follow-up, limited validity due to strict selection of high-risk patients and many post-randomisation exclusions) most guidelines are reluctant to state effectiveness of thromboprophylaxis following lower-leg cast immobilization. Therefore, a new large randomized controlled trial to investigate the effectiveness of thromboprophylaxis was highly needed.

In knee arthroscopy patients, a similar pattern and body of evidence exists. The risk for VT is estimated to be 18-fold increased within 3-months following arthroscopy (corresponding to an absolute risk of approximately 1.0% within 3-months).[14-17]. Five randomized trials have been performed, all studying the effectiveness of Low-Molecular-Weight-Heparin (LMWH) versus no treatment for VT prevention.[18-22] A Cochrane review in 2008 concluded that thromboprophylaxis in knee arthroscopy was effective for the prevention of asymptomatic VTE with a relative risk of 0.16 (95%CI 0.05 – 0.52).[23] However, when the authors only included *symptomatic* events, the meta-analysis failed to show a protective effect for anticoagulant therapy (RR 0.42, 95%CI 0.06 – 3.14). In light of this evidence, as in patients treated with lower-leg cast immobilization, the need for a large randomized controlled trial to investigate the effectiveness of thromboprophylaxis was evident. [2] Therefore, we designed and conducted two parallel, pragmatic, multicentre, randomized, controlled, open-label trials (the POT-CAST trial for Prevention Of Thrombosis following lower-leg CAST immobilization and POT-KAST trial, following Knee arthroscopy) in which patients treated with lower-leg cast or those undergoing knee arthroscopy were randomized to receive LMWH versus no treatment to study the effectiveness of thromboprophylaxis. The primary outcome was the occurrence of *symptomatic* VT within 3-months after inclusion. The primary safety outcome was the development of major bleeding within the same time frame. The results of these trials are described in **Chapter 2**. In **Chapter 3** we discuss why thromboprophylaxis is not indicated, this in response to two other randomized trials which showed effectiveness of thromboprophylaxis on asymptomatic VT. In this Chapter we focus on the methodological shortcomings of these trials (asymptomatic outcome, limited sample-size, many patients who were lost to follow-up).

From a population-based approach to individualized therapy

Several studies explored whether a population-based approach (i.e., uniform treatment of an entire population) is an effective way to prevent VT. However, as the majority of patients will not develop VT, many will be unnecessarily exposed to the risks (minor and major bleeding), costs and burden (daily injections when using LWMH) of anticoagulant therapy. In this thesis, we question the validity of this approach for patients with lower-leg cast and for those undergoing knee arthroscopy. Ideally, only high-risk patients need preventive treatment while in those with a low-risk, thromboprophylaxis can be withheld. To achieve such a clinical policy, low- and high-risk patients need to be identified as such. To explore the feasibility of this strategy, we first explore whether high-risk groups can be identified. In **Chapter 4** we investigate the magnitude of the VT risk in patients with a history of VT who are subsequently treated with lower-leg cast immobilization and in **Chapter 5** a similar analysis is performed for patients with a history of VT undergoing different types of surgery (including knee arthroscopy). In addition, in the first part of **Chapter 8**, the risk for VT is calculated for several subgroups in the POT-CAST trial (lower-leg cast population).

Following identification of high-risk groups based on single risk factors, we focus on risk prediction. **Chapter 6** encompasses the development of a prediction model for VT following lower-limb cast immobilization using data from a large population-based case-control study, the MEGA (Multiple Environmental and Genetic Assessment) study, which aimed to identify risk factors for a first VT. In addition, the added value of biomarker assessment for risk prediction is examined. In **Chapter 7**, an analogous model is developed as part of an international collaboration using the Delphi method. For patients undergoing knee arthroscopy, a different prediction model for VT is developed of which results are shown in **Chapter 9**. **Chapter 10** is the result of a fruitful collaboration with a French research group in which we merge the scores of **Chapter 6 & 7** in one final risk prediction score for VT following lower-limb cast immobilization. This prediction model is validated in the POT-CAST trial and developed into a mobile phone application to enhance usability in clinical practice. Finally, in **Chapter 11**, we summarize the transition from a population-based-approach to individualized therapy for the prevention of VT following lower-leg cast immobilization and knee arthroscopy. In addition, potential pathways to be explored for future research are discussed.

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