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

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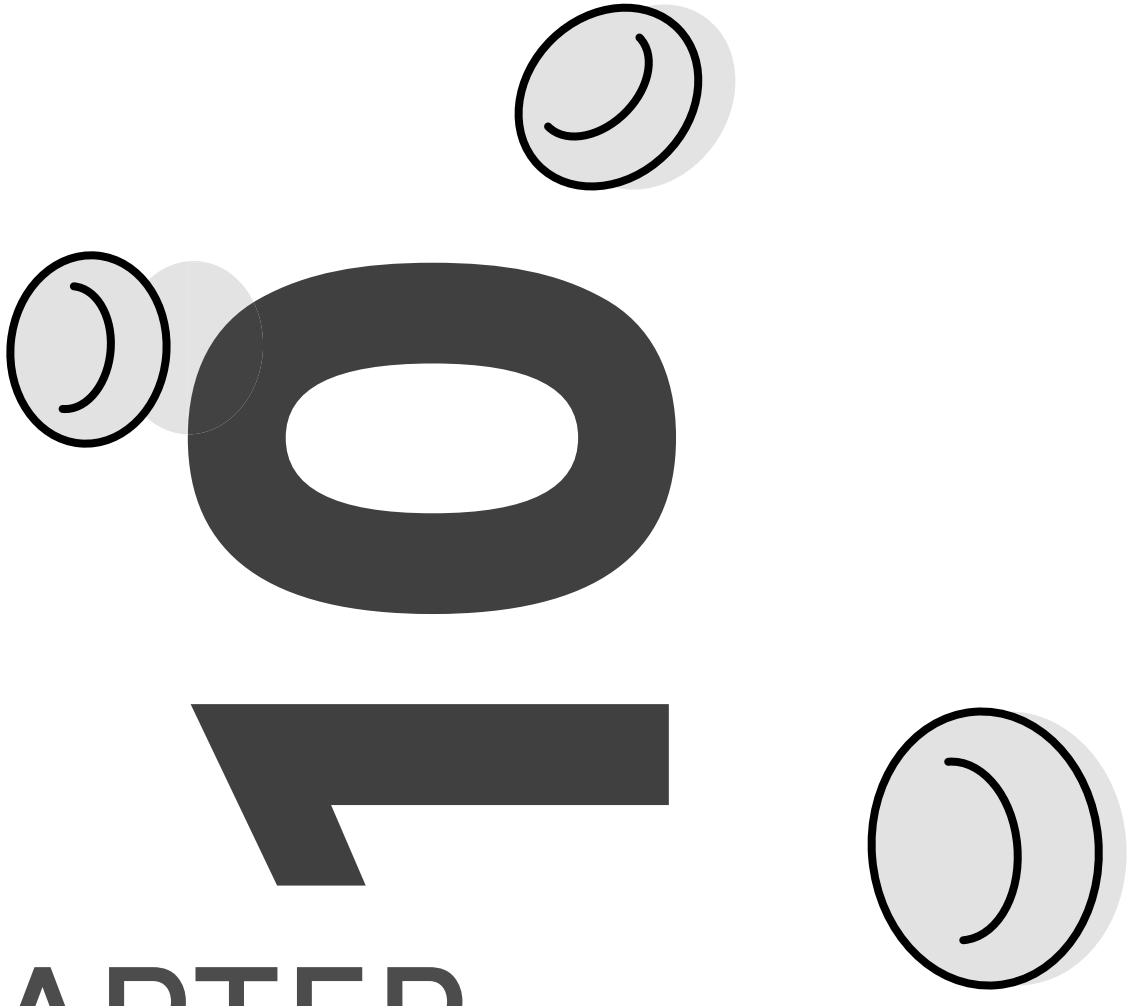
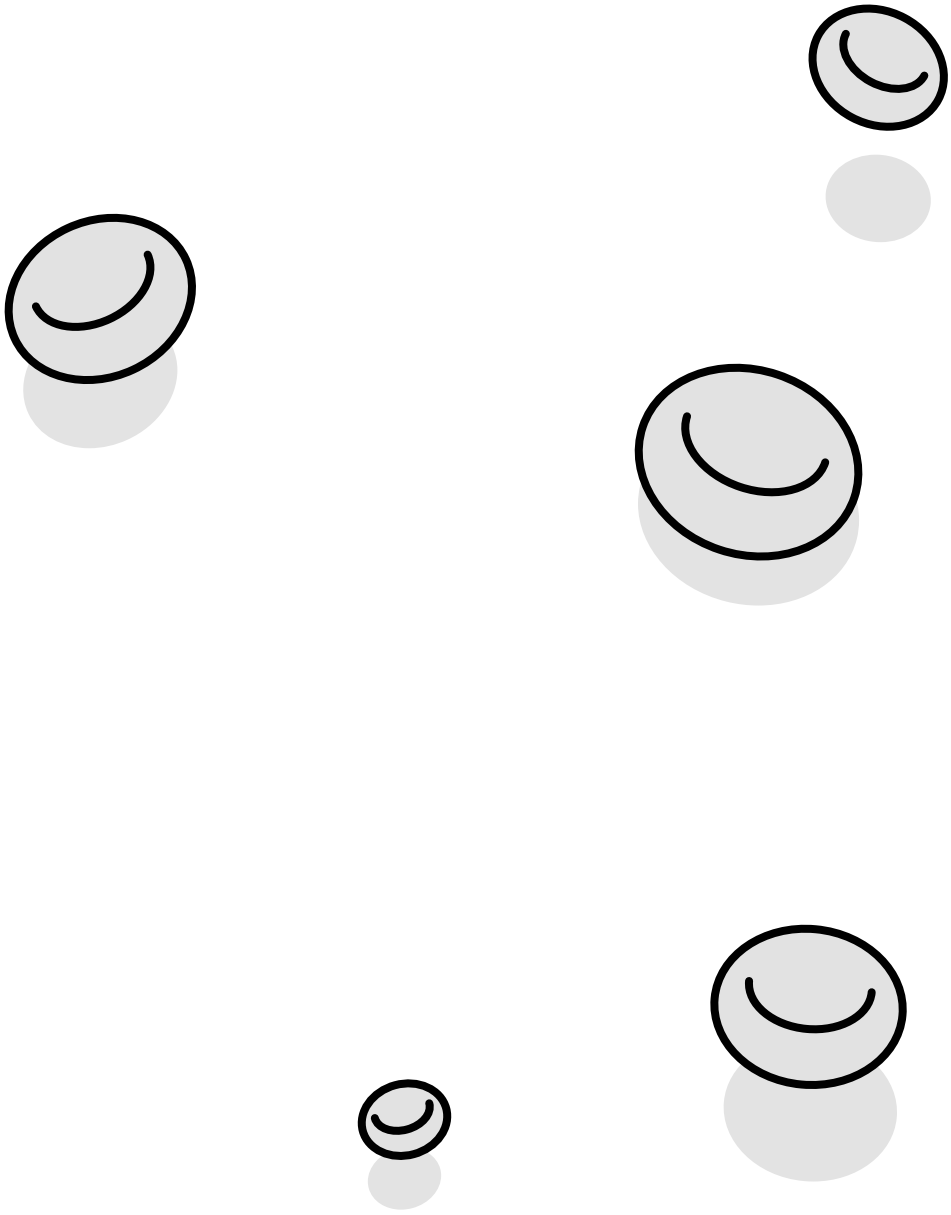


CHAPTER

Summary and general discussion



Orthopedic surgery is well recognized as a risk factor for venous thromboembolism (VTE) and the use of thrombosis prophylaxis is recommended for most orthopedic procedures.[1,2] However, for knee arthroscopy and lower leg cast immobilization, the magnitude of this risk has previously not been studied thoroughly, limiting clear recommendations for thrombosis prophylaxis.[1-3]

In this thesis the magnitude of the risk of symptomatic VTE, the combined effects of genetic and acquired risk factors, the current prophylactic strategies in the Netherlands, the effect of thrombosis prophylaxis on risk reduction of symptomatic VTE (in contrast to asymptomatic VTE), the predictive value of environmental, genetic risk factors and biomarkers for the development of VTE and the prediction of events in patients with lower leg cast immobilization and after knee arthroscopy have been studied.

Overview of main findings

Thrombosis risk in lower leg cast immobilization

The risk of VTE associated with cast immobilization of the lower leg is described in chapter 2. A 56-fold increased VTE risk compared to the general population was found in the first 3 months of lower leg cast immobilization. In these first 3 months 90% of the cases occurred. This corresponds to an estimated absolute risk of VTE of 1% in 3 months (based on an incidence of 0.75 per 1000 person-years in the general population).[4] In addition, a higher risk of VTE was found in patients treated with cast immobilization for a trauma to the lower leg compared to non–traumatic indications. A further increased risk was found for patients with well-known genetic risk factors (factor V Leiden mutation and prothrombin G20210A mutation) and additional acquired risk factors (i.e. obesity and oral contraceptive use). The presence of a combination of these risk factors led to an even further increased risk.

Thrombosis risk after knee arthroscopy

In Chapter 3 the risk of VTE after knee arthroscopy is given. In the 3-months after the procedure a 16-fold increased risk compared to the general population was found. Once again, this risk was highest in the first weeks after knee arthroscopy, and no additional increased risk was found after three months. Different types of arthroscopic procedures showed different VTE risks, with a higher risk for anterior cruciate ligament reconstruction compared to less invasive procedures such as meniscal surgeries,

diagnostic arthroscopies or chondroplasties (i.e., a 17-fold increased risk vs a 5-fold increased risk in one year after the procedure). The combination of knee arthroscopy with the presence of well-known genetic and other acquired risk factors in patients (e.g. FV Leiden, Prothrombin G20210A mutation, non-O blood group, or oral contraceptives) resulted in an additionally increased risk. These distinct differences in the risk of VTE between individuals after knee arthroscopy and during lower leg cast immobilization was the basis for the identification of high-risk patients using prediction models in chapter 8 and 9.

Current treatment strategies

Because of the lack of solid evidence, national and international guidelines recommend against thromboprophylaxis after knee arthroscopy and during lower leg cast immobilization. [1-3] However, as shown in chapter 4, the vast majority of patients with lower leg cast immobilization in the Netherlands receives thrombosis prophylaxis with Low Molecular Weight Heparin (LMWH) (79% of trauma surgery and 63% of orthopedic surgery departments). In general, LMWH is given for the duration of immobilization (96% and 89% of trauma and orthopedic surgery departments respectively). With respect to knee arthroscopy, the decision to give prophylaxis depends on the type of arthroscopic knee surgery. Thrombosis prophylaxis is given to around one third of patients with a diagnostic arthroscopy, loose body removal surgery or partial meniscectomy. In contrast, if a more invasive procedure, such as an anterior cruciate ligament (ACL) reconstruction, is performed over 75% of patients are given prophylaxis. The duration of prophylactic treatment is also dependent on the type of arthroscopic knee surgery and varied between 1 day (most frequent) to 1 week (e.g. for diagnostic procedures, loose body removal and partial meniscectomy) and (most frequent) between 3 to 6 weeks after ACL reconstruction. The rationale for thromboprophylactic therapy was the assumption that the risk reduction for thrombosis outweighed the bleeding risk, the experience of clinicians that thromboprophylaxis is effective and that clinicians act in accordance with a department or hospital protocol. This widespread use of thrombosis prophylaxis in these patients despite clear-cut evidence for a beneficial effect shows that good quality research was needed to improve the quality of care for patients.

Effect of thrombosis prophylaxis during lower leg cast immobilization

The results of a large pragmatic randomized clinical trial studying the effect of low-molecular weight heparin (LMWH) on the prevention of symptomatic venous

thromboembolism compared to no treatment during cast immobilization is given in chapter 5. In total over 1500 patients were included, of which half were allocated to prophylactic treatment with LMWH and half to no treatment. The cumulative incidence of symptomatic VTE in three months for patients in the LMWH therapy group was 1.4% (95%CI: 0.7 – 2.5) vs 1.8% (95%CI: 1.0 – 3.0) in the no treatment group (RR 0.8 (95%CI: 0.3 – 1.7) and RD -0.4 (95%CI -1.8 – 1.0)). This corresponds to a high number needed to treat of 250 patients to prevent one symptomatic event. Therefore, we were unable to show a beneficial effect for prophylactic treatment with anticoagulants during the period of lower leg cast immobilization. With no major bleedings and only 1 clinically relevant non major bleeding in this study, treatment with prophylactic dosage of LMWH was relatively safe, however not beneficial. In addition, treatment with anticoagulants comes with additional costs and, in case of LMWH, with the burden of daily injections. Clinicians should therefore not routinely give thrombosis prophylaxis to patients treated with lower leg cast immobilization.

Effect of thrombosis prophylaxis after knee arthroscopy

In chapter 6 the results of the POT – KAST trial (prevention of thrombosis after knee arthroscopy) are given. In this large randomized trial, over 1500 patients who had knee arthroscopy were included of which half were allocated to thromboprophylaxis with LMWH for 8 days and half were allocated to no treatment. The cumulative VTE risk in three months in both groups was low: 0.7% (95%CI: 0.3 – 1.7) for treatment with LWMH and 0.4% (95%CI: 0.3 – 1.7) for no treatment. Therefore, no beneficial effect of prophylactic LMWH was found (RR 1.6 (95%CI: 0.4 – 6.8)). Treatment with a prophylactic dose of LMWH was relatively safe. In both groups 1 major bleeding event occurred and 1 clinically relevant non-major bleed occurred in the LMWH group compared to 3 events in the no-treatment group. Although treatment is relatively safe, because of a lack of beneficial effect we recommend that routine thrombosis prophylaxis should not be given after knee arthroscopy. Both in the trial in patients with lower leg cast immobilization and in the trial in patients who had knee arthroscopy, patients still developed VTE despite prophylactic treatment. A prophylactic dose of LMWH might not be sufficient for these patients. Providing a higher dose of LMWH to all patients is, however, expected not to be beneficial, as this would increase the bleeding risk. Therefore, instead of providing high dose prophylactic treatment to all patients, the aim of our future research will be on risk prediction in order to be able to identify high risk

groups and thus provide (higher or prolonged dose) thrombosis prophylaxis selectively to patients with an increased VTE risk.

Effect of thrombosis prophylaxis after anterior cruciate ligament (ACL) reconstruction

Because ACL reconstruction is estimated to have a higher VTE risk than regular knee arthroscopy (see chapter 3), thrombosis prophylaxis in these patients has been studied separately. In chapter 7, the results of an instrumental variable analysis comparing two orthopedic surgery centers with different VTE prophylaxis policies but otherwise identical treatment protocols and similar patient populations (an observational study design of which the results can be interpreted as if it were a randomized clinical trial) is given. The additional effect of pharmacological thrombosis prophylaxis with LMWH to prophylaxis with a compression stocking on the incidence of VTE after an ACL reconstruction was studied. We found no difference in the occurrence of symptomatic VTE in these patients (RR 1.9 (95%CI; 0.2 – 11.8)). Furthermore, the incidence of symptomatic VTE in both groups was low (0.23% (95%CI; 0.01 – 1.41) vs 0.43% (95%CI; 0.12 – 1.14)). Therefore, we advise not to give thrombosis prophylaxis with LMWH, with its associated burden and risks, routinely to this generally young and healthy group of patients, in whom the VTE risk is very low. Once again, anticoagulant therapy might be beneficial in certain high-risk patients. Identifying high risk groups and selective treatment of these patients could reduce thrombosis morbidity and the risk of treatment complications.

Risk prediction and prevention of future events

Patients treated with lower leg cast immobilization or arthroscopy of the knee have an increased risk of venous thrombosis (chapter 2 and 3). However, as shown in chapter 5 and 6, a prophylactic dose of LMWH provided to all these patients did not decrease the risk of VTE. Selective treatment and identification of high-risk patients could therefore be beneficial. Consequently, the predictive value of genetic and environmental risk factors, coagulation factors and other biomarkers for the development of VTE during cast immobilization of the lower extremity (chapter 8) and after arthroscopy of the knee was studied (chapter 9). In addition, prediction models for the development of VTE in these patients were developed and validated (chapter 8 and 9).

Three risk prediction models were made for the development of VTE in patients with lower leg cast immobilization (chapter 8). A full model containing 32 predictors (including three genetic and six biomarkers), a restricted model (11 predictors, including two genetic and one biomarker) and a clinical model containing only environmental risk factors (14 predictors) which are easy to determine. All had good predictive value with an area under the curve (AUC) of the receiver operating characteristic (ROC) of 0.85 (95%CI: 0.77 – 0.92), 0.84 (95%CI: 0.77 – 0.92) and 0.77 (95%CI: 0.66 – 0.87) respectively. Validation of these prediction models in two other studies showed comparably good results. The clinical model was converted into a risk score based on points assigned to the regression coefficients of the predictor variables. With an AUC of 0.76 (95%CI: 0.66 – 0.86) results of the risk score were similar to the clinical model, external validation of the score showed comparable results.

In analogy to the development of prediction models for patients with lower leg cast immobilization, prediction models for the development of VTE after knee arthroscopy were developed (chapter 9). In addition to a full model and a restricted model (containing genetic risk factors and biomarkers), a clinical model with a corresponding risk score for daily clinical practise was developed. The clinical model included 8 environmental risk factors and resulted in an AUC of 0.72 (95%CI: 0.60 – 0.83). The corresponding risk score resulted in an AUC of 0.73 (95%CI: 0.63 – 0.84). External validation showed similar results.

Because the risk scores include only easy to determine environmental risk factors, these risk scores can provide guidance for the prescription of thrombosis prophylaxis in patients with lower leg cast immobilization and after arthroscopy of the knee in a clinical setting.

Conclusions, implications and future directives

Despite having an increased risk of venous thrombosis (chapter 2 and 3), the use of routine low dose LMWH as thrombosis prophylaxis did not decrease the risk of VTE in patients with lower leg cast immobilization nor in patients after arthroscopy of the knee (chapter 5 and 6). Because of this lack of a beneficial effect, we recommend no routine thrombosis prophylaxis with anticoagulants to these patients (chapter 5 and 6). Different treatment strategies, such as a higher dose of anticoagulant treatment or even longer duration of treatment might be beneficial in these patients. However, such

a policy will most likely also increase the risk of bleeding due to anticoagulant treatment. We have shown that the risk of VTE varies among patients based on the presence of additional acquired and genetic risk factors (chapter 2 and 3). Furthermore, these risk factors can be used in predicting the risk of VTE in these patients by means of prediction models (chapter 8 and 9). Hence, identification of high-risk patient can help to optimize prophylactic treatment: providing a higher dose or longer duration of anticoagulant treatment to patients with an additionally increased risk, whilst patients with a low risk will not be needlessly exposed to the burden and risk of anticoagulants. Our prediction models (Chapter 8 and 9) can give guidance in selecting these high-risk patients who can benefit from additional prophylactic therapy. The effect of selectively providing a higher dose or longer duration of treatment based on these prediction models, however, needs to be further investigated, ideally in a randomized trial comparing this strategy to no prophylactic therapy.

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