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

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Summary and general discussion

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SUMMARY AND GENERAL DISCUSSION

The aim of this thesis was to investigate the effectiveness of thromboprophylaxis following lower-leg cast immobilization and knee arthroscopy for the prevention of Venous Thrombosis (VT). Moreover, we explored whether an individualized approach is a feasible strategy towards optimal VT prevention. In this chapter, we provide an overview of our main findings and give recommendations for future research directions.

Effectiveness of thromboprophylaxis

In **Chapter 2**, we present the results of two parallel, pragmatic, multicentre, randomized, controlled, open-label trials with blinded outcome evaluation: the POT-KAST trial, which included patients undergoing knee arthroscopy, and the POT-CAST trial, which included patients treated with casting of the lower-leg.[1] In these trials, in which 1543 (POT-KAST) and 1451 (POT-CAST) patients were included, we studied the incidence of symptomatic VT within 3-months after the procedure, so no screening for asymptomatic VTE was performed. In neither trial, comparing a prophylactic dose of a Low-Molecular-Weight-Heparin (LMWH) with no treatment, thromboprophylaxis was effective for the prevention of symptomatic VT (absolute risk difference in POT-KAST, 0.3 percentage points, 95% Confidence Interval (95%CI), −0.6 to 1.2 and absolute risk difference in POT-CAST −0.4 percentage points, 95%CI −1.8 to 1.0). Overall, in the knee arthroscopy trial, only 0.6% of patients developed a symptomatic VTE versus 1.6% in the lower-leg cast trial. In **Chapter 3**, the results of the POT-(K)CAST trials are emphasized. In two letters to the editor, the results of two other trials on thromboprophylaxis following lower-leg cast and knee arthroscopy are questioned.

Identification of high-risk groups

Since thromboprophylaxis lacked effectiveness in the entire population, the need for a different treatment strategy evolved. First, we explored whether high-risk patients could be identified based on classical risk factors for VT. In **Chapter 4**, using the MEGA (Multiple Environmental and Genetic Assessment) follow-up study[2], patients with a history of VT were followed over time for recurrence from 1999-2010. The Odds Ratio (OR), adjusted for age and sex was calculated to compare risks of recurrence between subjects with and without cast immobilization. It was found that cast application in patients with a history of VT was associated with a 4.5-fold risk of VT (95%CI 1.5 – 14.0), corresponding to a cumulative incidence of 3.2%. This study clearly showed that patients with a history of VT have a very high-risk for a recurrent event after cast application and that a different prophylactic approach (for example a higher dose) might be necessary.

Likewise, **Chapter 5** focussed on the risk of recurrent VT in patients with a history of VT who subsequently undergo various types of surgery. For this analysis, the MEGA follow-up study was linked to the Dutch Hospital Data registry. Kaplan-Meier analyses were used to calculate cumulative incidences of recurrent VT. In addition, Cox-regression with a time-dependent co-variate (surgery) was used to calculate the hazard ratio (HR) for developing recurrent VT after surgery. The 1-month cumulative incidence for recurrent VT for all surgery types was 2.1% (95%CI 1.2 to 3.6) which increased up to 3.3% (95%CI 2.1 to 5.1), 4.6% (95%CI 3.1 to 6.6) and 6.3% (95%CI 4.6 to 8.7) at 3-, 6- and 12-months, respectively. Considering these high-risks, it is doubtful whether the current practice is sufficiently effective for recurrence prevention in this high-risk group. Furthermore, we found that high-risk individuals can be identified based on the type of surgery and the presence of additional predictors (for example, the cumulative incidences at 6-months were 5.0% and 3.8% for respectively major and minor orthopaedic surgery). These results stress the need for anticoagulation treatment following surgery in all patients with a history of VT, the duration and dosage of which may need to be individualised.

Predicting VT risk following lower-leg cast immobilization

In **Chapter 6** we developed the L-TRiP(cast) score for Leiden Thrombosis Risk Prediction following cast immobilization (using data from the MEGA study). This score, merely consisting of clinical risk factors (such as age, sex, use of oral contraceptives, body mass index, previous surgery or hospitalization, cast location [upper, lower- leg or foot cast]), reached an Area Under the Curve (AUC) of 0.76 (95%CI 0.66–0.86) in the derivation data and an AUC of 0.77 (95%CI 0.58–0.96) and 0.95 (95%CI 0.91–0.99) in two different validation data sets (both case-control studies). Although we found that the addition of biomarkers, such as coagulation Factor VIII activity, or genetic predictors like Factor V Leiden mutation, resulted in a better discrimination, the L-TRiP(cast) score was restricted to clinical predictors to enhance usefulness in clinical practice.

Thereafter, initiated by a French research group, we collaborated on the development of the TIP score, for Trauma, Immobilisation and Patient characteristics, also designed to predict VT risk following lower-limb cast immobilization. By using the Delphi method, 27 international experts developed the TIP score. In **Chapter 7**, the results of this score have been published. The main difference between the L-TRiP(score) and the TIP score is that trauma severity has been incorporated in the latter. We anticipated on improved performance since trauma severity has been shown to be associated with VT.[3-5] The discriminative performance of the TIP score in the MEGA study was good with an AUC of 0.77 (95%CI 0.70 to 0.85).

A validation of the L-TRIP(cast) score and a subgroup analysis in the POT-CAST trial was performed in **Chapter 8**. The overall risk of VT in the POT-CAST trial was 1.6%. Some high-risk groups were identified; patients with a body mass index >30kg/m2 had a risk of 3.9% while patients with a family history of VTE had a risk of 3.3%. In line with earlier observational studies[6-8], patients with a high-risk trauma were those with an Achilles tendon rupture (absolute risk 8.5%) or those surgically treated, for a risk of 3.5%. This indicates that VT risk greatly varies upon trauma type and severity. The AUC for the L-TRiP(cast) score was 0.69 (95%CI 0.58 – 0.80), indicating moderate discrimination.

The main aim of **Chapter 10** was to develop a combined and simplified score named TRiP(cast) score (note without the L-), merging and thereby updating the earlier developed TIP score and the L-TRiP(cast) score. We compared the performances of three different scores, the L-TRiP(cast), TIP and TRiP(cast), using data from the MEGA study. Subsequently, we externally validated the final TRiP(cast) score in the POT-CAST trial. The TRiP(cast) score performed well with an AUC of 0.74 (95%CI 0.61 to 0.87) in the complete dataset. Using a cut-off score of 7 points, the test sensitivity and specificity were 76.1% and 51.2%, respectively. The calibration plot in the POT-CAST data showed excellent concordance between the observed and predicted risk. To accommodate easy implementation in clinical practice, a mobile phone application was developed in three different languages by which an individual's risk for VT following lower-limb cast can be calculated.

Predicting VT risk following knee arthroscopy

For patients undergoing arthroscopic knee surgery, we developed the L-TRiP(ascopy) score to predict VT risk following this procedure (**Chapter 9**). Addition of biomarkers greatly improved discriminative performance, most likely due to the fact that patients who undergo arthroscopy are in general young and healthy and have only few co-morbidities.[9, 10] Consequently, there is limited contribution of clinical risk factors to risk stratification. In the bootstrapped population (internal validation), the AUC for the complete model (including for example factor VIII activity and Factor V Leiden mutation) was 0.78 versus 0.67 for the L-TRiP(ascopy) score (clinical predictors only). Our external validation study was not sufficiently powered to clearly show a beneficial effect of FVIII, and all models performed roughly similarly (AUC range, 0.75–0.78). Therefore, we finally opted to proceed with only clinical predictors, as in our opinion, the added predictive value of a biomarker did not outweigh the cumbersomeness of measuring FVIII (in terms of costs, and logistics in routine clinical care). A larger validation study is needed to confirm our results.

From a population-based approach to individualized therapy

In **Chapter 11**, we aimed to give a comprehensive overview of the literature on the epidemiology, prevention and prediction of VT following lower-leg cast immobilization and knee arthroscopy. First, a meta-analysis on the incidence of VT in untreated patients was performed. In lower-leg cast patients asymptomatic VT occurred in 18.0% (95%CI 12.9 to 23.1) and symptomatic VT in 2.0% (95%CI 1.3 to 2.7). In knee-arthroscopy patients, asymptomatic VT was seen in 5.9% (95%CI 3.9 to 7.9), while only 0.6% (95%CI 0.4 to 0.7) of patients had symptomatic VT. The wide range of reported incidences indicates considerable heterogeneity of included patients as well as heterogeneity in diagnostic methods (for asymptomatic events).

Second, we conducted an updated meta-analysis on the effectiveness of prophylaxis in both patient groups. For lower-leg cast patients, thromboprophylaxis seemed to reduce symptomatic VT risk: Relative Risk (RR) 0.31 (95%CI 0.13 – 0.73) while for knee arthroscopy patients there was no clear benefit (RR 0.65, 95%CI 0.23-1.81). In this chapter, we concluded that thromboprophylaxis using a population-based approach was not effective. Therefore, we focussed on individual risk prediction as a logical next step. Risk factors and several risk prediction models for VT in both patients groups (such as risk scores included in the GEMNET[12] and NICE guidelines[13]) were summarized.

Future research perspectives

To further understand which patients are at risk for VT, we suggest to focus on the thrombosis and thromboembolic mechanism. While lower-leg cast and knee arthroscopy patients have a clear VTE risk, the underlying mechanisms for this increased thrombotic tendency, and eventually, development of VTE in these patients, are not well known. For example, knowledge on the reaction of a patients' coagulation system following a fracture could contribute to the development of new preventive strategies. In fact, it is actually unknown whether the fracture itself, the subsequent cast immobilization or both, significantly increase VTE risk. As there are no studies that explore the effect of fractures or the severity of lower-leg injury on coagulation factors, this could be a topic for further investigations. Likewise, in patients undergoing knee arthroscopy, little data are available on the effect of such surgery on a patients' coagulation profile. Some studies suggest that a thigh tourniquet contributes significantly to thrombus formation.[14, 15] In our view, more extensive data on this matter could potentially be valuable for clinical management.

Finally, this thesis will set the basis for the design of the POT-(K)CAST 2.0 trial in which patients are stratified in low- and high-risk categories. Patients will be randomized between a population-based approach versus individualized therapy (i.e. low-risk patients can be withheld from thromboprophylaxis while high-risk patients will need to receive a higher-

dose of thromboprophylaxis and/or a longer duration of therapy). However, before such a trial can be designed, the ideal cut-off point for high- and low risk groups for the development of symptomatic VT, in terms of sensitivity and specificity, has to be established.

Conclusion

In this thesis we conclude that by using a population-based approach, thromboprophylaxis was not effective for symptomatic VT prevention following lower-leg cast immobilization and knee arthroscopy. Due to many methodological shortcomings in most trials (i.e. concerning the large difference between the efficacy on asymptomatic vs symptomatic VTE, issues regarding the classification of symptomatic events[11] (as discussed in *Chapter 3*, publication bias towards efficacy, the high number needed to treat) and the discomfort of daily injections and high costs. In our opinion there is no indication for thromboprophylaxis in all patients with lower-leg cast or those undergoing knee arthroscopy. However, as still about 2.0% of lower-leg cast and 0.6% of knee arthroscopy patients develop symptomatic VTE, new strategies on VTE prevention are necessary to lower this complication rate. It was concluded that a targeted approach, by identifying high-risk patients who possibly have to be treated with a higher dose or longer duration of therapy, might be the next step towards VT prevention. The TRiP(cast) and L-TRiP(ascopy) risk scores could be used for this purpose. However, to make sure the benefits of anticoagulant treatment outweigh the risks, further studies are needed to determine the optimal dose, duration and timing of therapy. Ultimately, such studies can help phycisians to decide on individualized thromboprophylactic strategies.

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