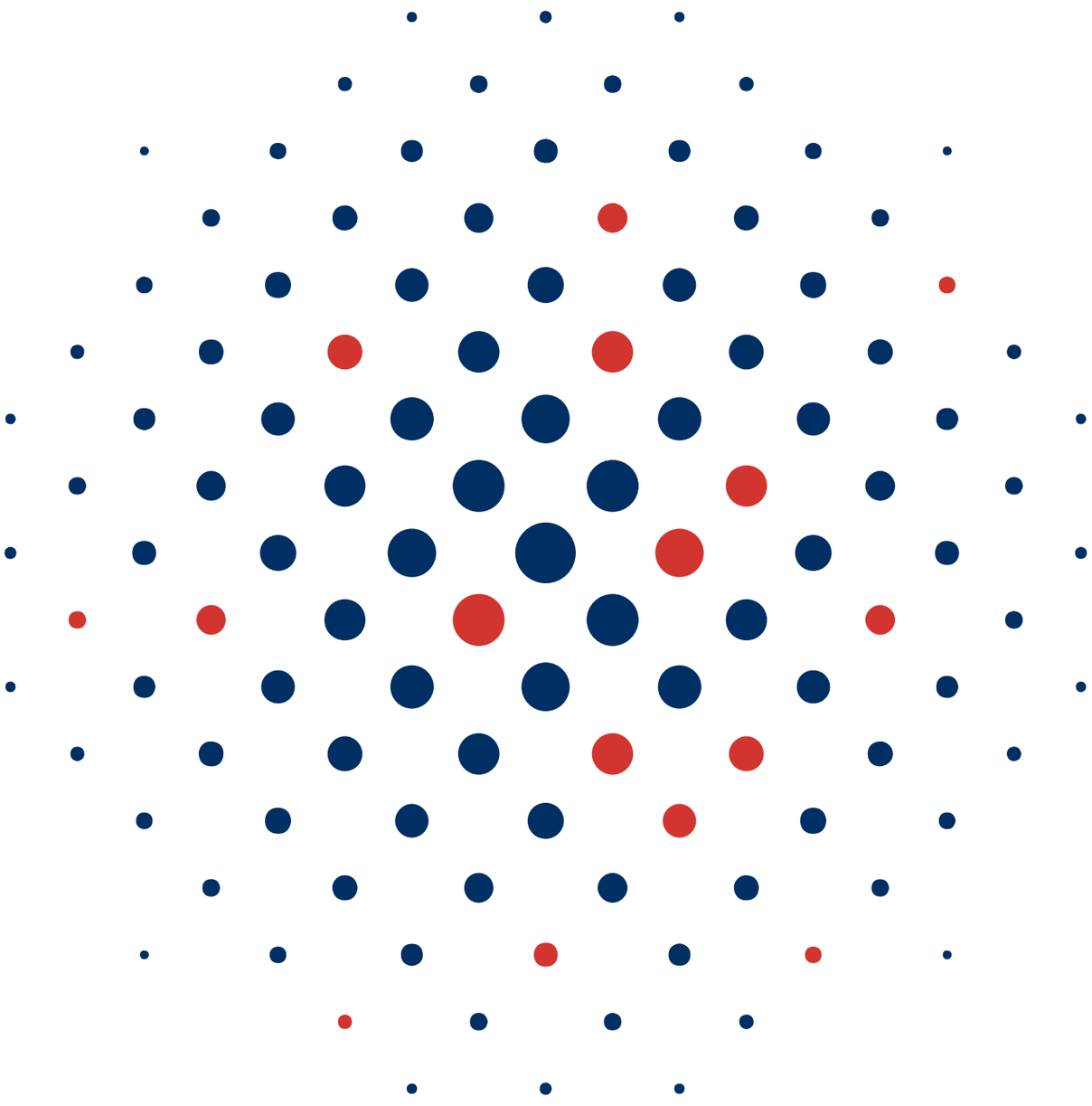
BANNE NÉMETH

Venous thrombosis following lower-leg cast immobilization and knee arthroscopy

From a population-based approach to individualized therapy



Stellingen behorende bij het proefschrift

Venous thrombosis following lower-leg cast immobilization and knee arthroscopy

From a population-based approach to individualized therapy

1. A prophylactic regimen of low-molecular-weight-heparin for eight days after knee arthroscopy or during the complete immobilization period in patients with casting of the lower leg is not effective for the prevention of symptomatic venous thromboembolism.
   -this thesis-
2. For patients with a history of venous thromboembolism who are undergoing surgery or are treated with a lower leg cast, the risk of recurrent venous thromboembolism is high.
   -this thesis-
3. Estimating the risk of venous thromboembolism risk following lower leg cast immobilization or following knee arthroscopy is feasible by using a risk prediction model.
   -this thesis-
4. A targeted approach, by identifying high-risk patients who may benefit from a higher dose or longer duration of thromboprophylactic therapy, is a promising next step to prevent symptomatic VTE following lower leg cast immobilization or knee arthroscopy.
   -this thesis-
5. The best treatment strategy to prevent symptomatic venous thromboembolism following lower leg cast immobilization or following knee arthroscopy is yet to be determined.
6. Prognostic models are meant to assist and not to replace clinicians' decisions. Accurate estimation of risks of outcomes can enhance informed decision making with the patient.
   -Adapted from PLoS Med 10(2): e1001381-
7. The first developed prediction model is not the last.
8. Voor de dagelijkse klinische praktijk is het essentieel dat onderzoeksresultaten op de juiste manier worden geïnterpreteerd en toegepast. Om dit te waarborgen is een intensievere samenwerking tussen epidemiologen en dokters aan te raden.
9. Allereerst, niet schaden. Geef geen tromboseprofylaxe wanneer dit niet effectief is.
   -Adapted from Eed van Hippocrates-
10. Een bloedstollende film is niet alleen maar eng.
    -Adapted from BMJ 2015;351:h6367-

Venous thrombosis following lower-leg cast immobilization and knee arthroscopy

From a population-based approach to individualized therapy

Banne Németh

Venous thrombosis following lower-leg cast immobilization and knee arthroscopy

From a population-based approach to individualized therapy

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 2 september 2020
klokke 16.15 uur

door

Banne Németh
geboren te Alphen aan den Rijn
in 1987

Colophon
The research described in this thesis was performed at the Department of Clinical Epidemiology and the Department of Orthopaedic Surgery, Leiden University Medical Center, Leiden, The Netherlands.

Cover: Antony Nguyen
Lay-out and print: Gildeprint

ISBN: 978-94-6402-463-0

Financial support by the Federatie van Nederlandse Trombosediensten, ChipSoft, Nederlandse Orthopaedische Vereniging, Anna Fonds, Pfizer, Daiichi Sankyo and Boehringer Ingelheim, for the publication of this thesis is gratefully acknowledged.

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Promotores
Prof. dr. S.C. Cannegieter
Prof. dr. R.G.H.H. Nelissen

Leden promotiecommissie
Prof. dr. F.R. Rosendaal
Prof. dr. R.W. Poolman
Prof. dr. H.R. Büller (Amsterdam UMC)
Prof. A.B. Pedersen (Aarhus University, Aarhus, Denmark)

TABLE OF CONTENTS

1

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.

REFERENCE LIST

1. I.A. Naess, S.C. Christiansen, P. Romundstad, S.C. Cannegieter, F.R. Rosendaal, J. Hammerstrom, Incidence and mortality of venous thrombosis: a population-based study. Journal of Thrombosis Haemostasis 5(4) (2007) 692-9.
2. Y. Falck-Ytter, C.W. Francis, N.A. Johanson, C. Curley, O.E. Dahl, S. Schulman, T.L. Ortel, S.G. Pauker, C.W. Colwell, Jr. Prevention of VTE in orthopaedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141(2 Suppl) (2012) e278S-e325S.
3. G. Bauer, Thrombosis following leg injuries. Acta chirurgica Scandinavica (90) (1944) 229-48.
4. B. Riou, C. Rothmann, N. Lecoules, E. Bouvat, J.-L. Bosson, P. Ravaud, C.M. Samama, M. Hamadouche. Incidence and risk factors for venous thromboembolism in patients with nonsurgical isolated lower limb injuries. The American Journal of Emergency Medicine 25(5) (2007) 502-508.
5. R.A. van Adrichem, J. Debeij, R.G. Nelissen, I.B. Schipper, F.R. Rosendaal, S.C. Cannegieter. Below-knee cast immobilization and the risk of venous thrombosis: results from a large population-based case-control study. Journal of Thrombosis Haemostasis 12(9) (2014) 1461-9.
6. S. Patil, J. Gandhi, I. Curzon, A.C. Hui. Incidence of deep-vein thrombosis in patients with fractures of the ankle treated in a plaster cast. The Journal of bone and joint surgery. British volume 89(10) (2007) 1340-3.
7. G. Abelseth, R.E. Buckley, G.E. Pineo, R. Hull, M.S. Rose. Incidence of deep-vein thrombosis in patients with fractures of the lower extremity distal to the hip. Journal of orthopaedic trauma 10(4) (1996) 230-5.
8. H.J. Kock, K.P. Schmit-Neuerburg, J. Hanke, G. Rudofsky, H. Hirche. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. Lancet 346(8973) (1995) 459-461.
9. M.R. Lassen, L.C. Borris, R.L. Nakov. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. The New England journal of medicine 347(10) (2002) 726-30.
10. L.J. Lapidus, S. Ponzer, A. Elvin, C. Levander, G. Larfars, S. Rosfors, E. de Bri. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. Acta orthopaedica 78(4) (2007) 528-35.
11. L.J. Lapidus, S. Rosfors, S. Ponzer, C. Levander, A. Elvin, G. Larfars, E. de Bri. Prolonged thromboprophylaxis with dalteparin after surgical treatment of achilles tendon rupture: a randomized, placebo-controlled study. Journal of orthopaedic trauma 21(1) (2007) 52-7.
12. P.S. Jorgensen, T. Warming, K. Hansen, C. Paltved, H. Vibeke Berg, R. Jensen, R. Kirchhoff-Jensen, L. Kjaer, N. Kerbouche, P. Leth-Espensen, E. Narvestad, S.W. Rasmussen, C. Sloth, C. Torholm, P. Wille-Jorgensen. Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study. Thrombosis research 105(6) (2002) 477-80.
13. P. Kujath, U. Spannagel, W. Habscheid. Incidence and prophylaxis of deep venous thrombosis in outpatients with injury of the lower limb. Haemostasis 23 Suppl 1 (1993) 20-26.
14. R.A. van Adrichem, R.G. Nelissen, I.B. Schipper, F.R. Rosendaal, S.C. Cannegieter. Risk of venous thrombosis after arthroscopy of the knee: results from a large population-based case-control study, Journal of thrombosis and haemostasis. 13(8) (2015) 1441-8.

15. G.B. Maletis, M.C. Inacio, S. Reynolds, T.T. Funahashi. Incidence of symptomatic venous thromboembolism after elective knee arthroscopy. The Journal of bone and joint surgery. American volume 94(8) (2012) 714-20.
16. A.J. Krych, P.L. Sousa, J.A. Morgan, B.A. Levy, M.J. Stuart, D.L. Dahm. Incidence and Risk Factor Analysis of Symptomatic Venous Thromboembolism After Knee Arthroscopy. Arthroscopy (2015) Nov;31(11):2112
17. T. Gaskill, M. Pullen, B. Bryant, N. Sicignano, A.M. Evans, M. DeMaio. The Prevalence of Symptomatic Deep Venous Thrombosis and Pulmonary Embolism After Anterior Cruciate Ligament Reconstruction. The American journal of sports medicine 43(11) (2015) 2714-9.
18. P. Roth. Thromboembolieprophylaxe bei ambulant durchgefuhrten arthroskopischen Meniskusoperationen. Orthop Praxis (1995) 345-348.
19. T. Wirth, B. Schneider, F. Misselwitz, M. Lomb, H. Tuylu, R. Egbring, P. Griss. Prevention of venous thromboembolism after knee arthroscopy with low-molecular weight heparin (reviparin): Results of a randomized controlled trial. Arthroscopy 17(4) (2001) 393-9.
20. M. Michot, D. Conen, D. Holtz, D. Erni, M.D. Zumstein, G.B. Ruflin, N. Renner. Prevention of deep-vein thrombosis in ambulatory arthroscopic knee surgery: A randomized trial of prophylaxis with low--molecular weight heparin. Arthroscopy 18(3) (2002) 257-63.
21. G. Camporese, E. Bernardi, P. Prandoni, F. Noventa, F. Verlato, P. Simioni, K. Ntita, G. Salmistraro, C. Frangos, F. Rossi, R. Cordova, F. Franz, P. Zucchetta, D. Kontothanassis, G.M. Andreozzi, K.S. Group. Low-molecular-weight heparin versus compression stockings for thromboprophylaxis after knee arthroscopy: a randomized trial. Annals of internal medicine 149(2) (2008) 73-82.
22. G. Canata, A. Chiey. Prevention of venous thromboembolism after ACL reconstruction: a prospective, randomized study. ISAKOS congress Vol. Poster 71–2003. (2003).
23. J. Ramos, C. Perrotta, G. Badariotti, G. Berenstein. Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy. The Cochrane database of systematic reviews (4) (2008) CD005259.

2

Thromboprophylaxis after knee arthroscopy and lower-leg casting

* van Adrichem RA, * Németh B, Algra A, le Cessie S, Rosendaal FR, Schipper IB, Nelissen RGHH, Cannegieter SC; POT-KAST and POT-CAST Group.

*N Engl J Med. 2017 Feb 9;376(6):515-525. *Authors contributed equally*

ABSTRACT

Background The use of thromboprophylaxis to prevent clinically apparent venous thromboembolism after knee arthroscopy or casting of the lower-leg is disputed. We compared the incidence of symptomatic venous thromboembolism after these procedures between patients who received anticoagulant therapy and those who received no anticoagulant therapy.

Methods We conducted two parallel, pragmatic, multicenter, 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. Patients were assigned to receive either a prophylactic dose of low-molecular-weight heparin (for the 8 days after arthroscopy in the POT-KAST trial or during the full period of immobilization due to casting in the POT-CAST trial) or no anticoagulant therapy. The primary outcomes were the cumulative incidences of symptomatic venous thromboembolism and major bleeding within 3 months after the procedure.

Results In the POT-KAST trial, 1543 patients underwent randomization, of whom 1451 were included in the intention-to-treat population. Venous thromboembolism occurred in 5 of the 731 patients (0.7%) in the treatment group and in 3 of the 720 patients (0.4%) in the control group (relative risk, 1.6; 95% confidence interval [CI], 0.4 to 6.8; absolute difference in risk, 0.3 percentage points; 95% CI, −0.6 to 1.2). Major bleeding occurred in 1 patient (0.1%) in the treatment group and in 1 (0.1%) in the control group (absolute difference in risk, 0 percentage points; 95% CI, −0.6 to 0.7). In the POT-CAST trial, 1519 patients underwent randomization, of whom 1435 were included in the intention-to-treat population. Venous thromboembolism occurred in 10 of the 719 patients (1.4%) in the treatment group and in 13 of the 716 patients (1.8%) in the control group (relative risk, 0.8; 95% CI, 0.3 to 1.7; absolute difference in risk, −0.4 percentage points; 95% CI, −1.8 to 1.0). No major bleeding events occurred. In both trials, the most common adverse event was infection.

Conclusions The results of our trials showed that prophylaxis with low-molecular-weight heparin for the 8 days after knee arthroscopy or during the full period of immobilization due to casting was not effective for the prevention of symptomatic venous thromboembolism. (Funded by the Netherlands Organization for Health Research and Development; POT-KAST and POT-CAST ClinicalTrials.gov numbers, NCT01542723 and NCT01542762, respectively.)

INTRODUCTION

Patients who undergo arthroscopic knee surgery and patients who are treated with casting of the lower-leg are at increased risk for venous thromboembolism (i.e., deep-vein thrombosis or pulmonary embolism).[1,2] Venous thromboembolism is an important health problem that is associated with considerable mortality, morbidity, and resource expenditure.[3-5] The use of pharmacologic thromboprophylaxis after most orthopaedic interventions is well established, because it strongly reduces the risk of thrombosis while only slightly increasing the risk of bleeding. [6-8] However, whether such prophylaxis is effective after arthroscopic knee surgery is uncertain, despite the fact that this procedure is the most commonly performed orthopaedic procedure worldwide (performed in more than 4 million patients per year).[7,9] It is also uncertain whether such prophylaxis is effective after casting of the lower-leg, a treatment for which the risk for venous thromboembolism has not been reliably estimated.[10-13] For both indications, several trials have been performed to evaluate the effectiveness of anticoagulant prophylaxis. However, an overall risk–benefit balance could not be established because of methodologic shortcomings; hence, there has been reluctance to establish international guidelines regarding the use of anticoagulant therapy for either of these indications.[7,8]

The Prevention of Thrombosis after Knee Arthroscopy (POT-KAST) and the Prevention of Thrombosis after Lower Leg Plaster Cast (POT-CAST) trials were designed to compare anticoagulant therapy (low-molecular-weight heparin) for the prevention of symptomatic venous thromboembolism with no anticoagulant therapy. We hypothesized that treatment with anticoagulants for the 8 days after knee arthroscopy (in POT-KAST) or during the complete period of immobilization due to casting of the lower-leg (in POT-CAST) would be effective in the prevention of symptomatic venous thromboembolism and that the benefit would outweigh the risk of bleeding.

METHODS

Trial Oversight and Design

In the two parallel, multicenter, randomized, controlled, open-label trials with blinded outcome evaluation, we used the same methods and design to evaluate the same intervention — anticoagulant therapy with low-molecular-weight heparin. The POT-KAST trial involved patients who underwent knee arthroscopy, and the POT-CAST trial involved patients who were treated with casting of the lower-leg. The two trials had a pragmatic design to maximize generalizability. The protocol (available with the full text of this article at NEJM.org), which contains both trial designs, was approved by the medical ethics committee at Leiden University Medical Center; no methodologic changes were made after approval. The trials were funded by the Netherlands Organization for Health Research and Development, which had no role in any aspect of the trials. The first two authors and the last author had full access to all data and vouch for the accuracy and completeness of the reported data and the fidelity of the trials to the protocol.

Participants

The trials were performed at 10 hospitals in the Netherlands (7 teaching hospitals, 2 private medical care clinics, and 1 academic medical center; see the *Supplementary Appendix*, available at NEJM.org). Patients 18 years of age or older who were scheduled to undergo knee arthroscopy for meniscectomy, diagnostic arthroscopy, removal of loose bodies, or other indications (see the *Supplementary Appendix*) were eligible for inclusion in the POT-KAST trial. Patients 18 years of age or older who presented to the emergency department and were treated for at least 1 week with casting of the lower-leg (with or without surgery before or after casting but without multiple traumatic injuries) were eligible for inclusion in the POT-CAST trial. Exclusion criteria for both trials were a history of venous thromboembolism, contraindications to low-molecular-weight heparin therapy, pregnancy, and current use of anticoagulant therapy for other indications (although use of antiplatelet drugs was allowed). In addition, patients who had insufficient knowledge of the Dutch language or insufficient mental or physical ability to fulfill trial requirements or those who had previously participated in either trial were not included. All participants provided written informed consent.

Procedures and Intervention

Eligible patients in the two trials were randomly assigned to receive either a prophylactic dose of low-molecular-weight heparin (treatment group) or no anticoagulant therapy (control group). In the POT-KAST trial, low-molecular-weight heparin was administered once daily for the 8 days after arthroscopy; the first dose was administered postoperatively

but before discharge on the day of surgery. In the POT-CAST trial, low-molecular weight heparin was administered for the full period of immobilization; the first dose was administered in the emergency department. In both trials, patients in the treatment group received nadroparin or dalteparin (according to the preference at the hospital), administered subcutaneously; a dose of 2850 IU of nadroparin or 2500 IU of dalteparin was used for patients who weighed 100 kg or less, and a double dose (in one daily injection) was used for patients who weighed more than 100 kg.

Patients received a brochure with information about the signs and symptoms of venous thromboembolism and were advised to seek medical care if such signs or symptoms developed. Follow-up started on the day of the procedure and continued for a total duration of 3 months, because after this period, the risk of venous thromboembolism returns to baseline.[1,2] Digital (online) or postal questionnaires on the occurrence of trial outcome events and adherence to the trial regimen were sent 2 weeks and 6 weeks after the start of follow-up in the POT-KAST trial and 3 weeks and 7 weeks after the start of follow-up in the POT-CAST trial. Patients were also asked to complete a questionnaire on risk factors for venous thromboembolism and hemorrhage within 1 week after enrollment in the trial. In addition, all patients were contacted by telephone after 3 months and were asked whether they had undergone examination for a suspected venous thromboembolism, whether any hospital visit had taken place, and whether they had adhered to the assigned regimen. If a patient did not respond, the patient's general practitioner was contacted to determine whether any trial outcome event or death had occurred. For all patients who did not respond, vital status was determined from the Dutch population register. When an outcome event was suspected to have occurred in a patient, detailed information was collected from the patient's electronic hospital files and radiology reports. Data were collected centrally in an online database management system.[14]

Randomization and Blinding

Eligible patients were randomly assigned to the treatment group or the control group in a 1:1 ratio. Block randomization with variable block sizes was used. Randomization was performed centrally with the use of ProMISe software (Leiden University Medical Center) by a data-management unit in the POT-KAST trial and by the treating physicians in the POT-CAST trial.[14] To ensure concealment of treatment assignment, the datamanagement unit, physicians, and researchers were unaware of the randomization scheme and block sizes. Randomization was stratified according to trial center; in the POT-CAST trial, randomization was further stratified according to nonsurgical or surgical treatment. Patients were aware of the treatment assignment.

Outcomes

The primary outcome was the cumulative incidence of symptomatic venous thromboembolism (i.e., deep-vein thrombosis or pulmonary embolism) within 3 months after the procedure. The primary safety outcome was the cumulative incidence of major bleeding.[15] The cumulative incidence of clinically relevant nonmajor bleeding was a secondary outcome, and all other cases of hemorrhage were recorded as minor bleeding. All possible primary and secondary outcome events were evaluated and assessed by an independent outcome adjudication committee whose members were unaware of the treatment assignments. The definitions of all outcomes and a list of the members of the outcome adjudication committee are provided in the *Supplementary Appendix*.

Statistical Analysis

In both trials, as the basis of our sample-size calculations, we assumed an incidence of symptomatic venous thromboembolism of 2% in the absence of treatment.[16-18] We calculated that a sample size of 625 patients in each group would provide 80% power to detect an 85% lower risk[16,18] of symptomatic venous thromboembolism in the treatment group than in the control group, at a two-sided alpha level of 0.05. To account for a maximum dropout rate of 15%, we aimed to include 750 patients in each group. For the primary safety outcome, we assumed a risk of major bleeding of 0.3%, which allowed us to determine an upper limit of the 95% confidence interval of approximately 1%.[19-21]

Prespecified interim analyses for safety purposes were performed when 50% and 75% of the target number of patients were enrolled in the trials, with the data reviewed by an independent data and safety monitoring board (a list of the members of the data and safety monitoring board and their tasks is provided in the *Supplementary Appendix*). It was determined that if an interim analysis showed that the intervention was clearly contraindicated because of an increased risk of major bleeding (upper limit of the 95% confidence interval, >1%), we would terminate the trial prematurely.

All analyses were performed according to the prespecified plan described in the protocol. Baseline characteristics were summarized as means with standard deviations or proportions, as appropriate. Data on outcome events were analyzed in the intention-to-treat population, which excluded patients who underwent randomization in error (i.e., they had not met the inclusion criteria or had met exclusion criteria). For the primary outcomes, cumulative incidences with 95% confidence intervals were estimated on the basis of binomial distribution in both groups. Incidences were compared by means of relative risks and absolute differences in risk with 95% confidence intervals. We calculated Wilson's confidence intervals for absolute differences in risk and asymptotic confidence intervals for relative risks. In a per-protocol analysis, we included only data from patients who had adhered to the trial regimen. Analyses were performed with the use of IBM SPSS Statistics software for Windows, version 23 (SPSS), and Stata software, version 14 (StataCorp).

RESULTS

POT-KAST Trial

Patients

From May 2012 through January 2016, a total of 6413 patients scheduled for knee arthroscopy were screened for eligibility, of whom 1543 were enrolled at eight centers in the Netherlands; 773 were randomly assigned to receive low-molecular weight heparin (treatment group), and 770 to receive no anticoagulant therapy (control group) (see the Supplementary Appendix). After randomization, 30 patients (10 in the treatment group and 20 in the control group) were excluded because they had not met the inclusion criteria or had met exclusion criteria. Of the remaining participants, 37 withdrew consent and 25 were lost to follow-up. A total of 731 patients in the treatment group and 720 in the control group were included in the intention-to-treat population. Baseline characteristics were similar in the two groups *(Table 1)*. In the overall cohort, 55.8% were men, the mean age was 48.5±12.5 years, 64.2% had an American Society of Anesthesiologists physical status classification of I (indicating no disease), and approximately half had the procedure performed while they were under general anesthesia *(Table 2)*. The majority of patients (1118 patients; 77.1%) underwent meniscectomy, 114 (7.9%) underwent diagnostic arthroscopy, 77 (5.3%) underwent removal of loose bodies, and 340 (23.4%) underwent another procedure (a patient could undergo multiple interventions; see the *Supplementary Appendix*).

Effectiveness Outcomes

In the treatment group, 12 patients had suspected primary outcome events, of whom 5 patients had confirmed events: 4 cases of deep-vein thrombosis and 1 case of pulmonary embolism. In the control group, 11 patients had suspected primary outcome events, of whom 3 patients had confirmed events: 2 cases of deep-vein thrombosis and 1 case of pulmonary embolism. In the intention- to-treat analysis, the cumulative incidence of symptomatic venous thromboembolism within 3 months after the procedure was 0.7% (95% confidence interval [CI], 0.2 to 1.6) in the treatment group and 0.4% (95% CI, 0.1 to 1.2) in the control group, representing a relative risk of 1.6 (95% CI, 0.4 to 6.8) and an absolute difference in risk of 0.3 percentage points (95% CI, −0.6 to 1.2) *(Table 3)*.

The per-protocol population included the 621 patients (85.0%) in the treatment group and the 706 patients (98.1%) in the control group who adhered to the trial regimen (see the *Supplementary Appendix*). In the per-protocol analysis, symptomatic venous thromboembolism was confirmed in 4 patients (0.6%) in the treatment group and in 3 (0.4%) in the control group (relative risk, 1.5; 95% CI, 0.3 to 6.7) (*Table 4*). The eighth patient with confirmed venous thromboembolism, who was in the treatment group, chose to take carbasalate calcium (80 mg) for 1 week instead of the trial drug.

Table 1: Baseline Characteristics of the Patients.

POT-KAST trial	**Treatment group * (n=731)**	**Control group (n=720)**
Male sex, n (%)	414/731 (56.6)	396/702 (55.0)
Mean age (SD), years	48.1 (12.8)	49.1 (12.3)
Mean BMI (SD), kg/m^2 †	27.1 (3.9)	26.8 (4.0)
Obese, n (%) †	163/717 (22.7)	137/710 (19.3)
ASA classification‡		
ASA 1, n (%)	438/692 (63.3)	449/689 (65.2)
ASA 2, n (%)	248/692 (35.8)	236/689 (32.8)
ASA 3, n (%)	6/692 (0.9)	4/689 (0.6)
Smoking, n (%)		
Current	131/716 (18.3)	140/706 (19.8)
Ever	247/716 (34.5)	244/706 (34.6)
Contraceptives use, n (% of women) ¶	94/308 (30.5)	83/320 (25.9)
Paid employment (%)	559/712 (78.5)	534/708 (75.4)
Cancer		
Within last year	6/714 (0.8)	6/707(0.8)
More than 1 year ago	27/714 (3.8)	23/707 (3.3)
Family history of venous thromboembolism (1st degree), n (%)	82/713 (11.5)	87/707 (12.3)

POT-CAST trial	**Treatment group * (n=719)**	**Control group (n=716)**
Male sex, n (%)	347/719 (48.3)	369/716 (51.5)
Mean age (SD), years	46.5 (16.5)	45.6 (16.4)
Mean BMI (SD), kg/m^2 †	26.0 (4.4)	25.7 (4.4)
Obese, n (%) †	113/665 (17.0)	91/670 (13.6)
Smoking, n (%)		
Current	173/663 (26.1)	178/665 (26.8)
Ever	188/665 (28.4)	178/665 (26.8)
Contraceptives use , n (% of women) ¶	86/348 (24.7)	69/326 (21.2)
Paid employment (%)	442/664 (66.6)	469/669 (70.1)

Table 1: Baseline Characteristics of the Patients.

Cancer**		
Within last year	8/674 (1.2)	9/674 (1.3)
More than 1 year ago	26/674 (3.9)	20/674 (3.0)
Family history of venous thromboembolism (1st degree), n (%)	60/564 (10.6)	52/555 (9.4)

* Low Molecular Weight Heparin, either Nadroparin or Dalteparin.
† BMI: body mass index in kg/m^2, Obese (BMI>30 kg/m^2). BMI data are missing for 14 patients in the treatment group and 10 patients in the control group.
‡ ASA classification: American Society of Anesthesiologists physical status classification system
¶ Any hormonal contraceptive us, e.g., oral contraceptives, intra-uterine devices.
** Nonmelanoma skin cancers are not included.

Safety Outcomes

Two patients had major bleeding (*Table 3*): 1 patient (0.1%) in the treatment group had hemarthrosis of the knee, and 1 patient (0.1%) in the control group had bleeding at the surgical site 2 days after the procedure and underwent reoperation (relative risk, 1.0; 95% CI, 0.1 to 15.7). Clinically relevant nonmajor bleeding occurred in 1 patient (0.1%) in the treatment group and in 3 (0.4%) in the control group (relative risk, 0.3; 95% CI, 0 to 3.1). Minor bleeding occurred in 69 patients (9.5%) in the treatment group and in 39 (5.4%) in the control group. No patients died during the follow-up period, including patients who were lost to follow-up. The most common adverse event was infection. (For more details, see the *Supplementary Appendix*.)

POT-CAST Trial

Patients

From March 2012 through January 2016, a total of 1519 patients treated with casting of the lower-leg were enrolled at eight trial centers; 761 were randomly assigned to the treatment group, and 758 to the control group. After randomization, 33 patients (14 in the treatment group and 19 in the control group) were excluded because they had not met the inclusion criteria or had met exclusion criteria. An additional 23 patients withdrew consent and 28 were lost to follow-up. A total of 719 patients in the treatment group and 716 in the control group were included in the intention- to-treat population.

Patient characteristics were well balanced between the groups; 49.9% of the patients were men, and the mean age was 46.0±16.5 years (*Table 1*). The majority of patients (1279 patients; 89.1%) needed casting because of a fracture (*Table 5*). Of the patients with a fracture, 532 (41.6%) had one or more broken metatarsal bones and 497 (38.9%) had an ankle fracture. Surgery was performed in 170 patients.

Table 2: Arthroscopy Outcomes in the POT-KAST Trial.

Surgery details	**Treatment group * (n=731)**	**Control group (n=720)**
Total duration operation in minutes, mean (SD)	26 (11)	26 (11)
Duration surgery in minutes, mean (SD)	16 (8)	15 (8)
Anesthesia		
General, n(%)	362/716 (50.6)	345/709 (48.7)
Spinal, n(%)	353/716 (49.3)	363/709 (51.2)
Epidural	1/716 (0.1)	1/709 (0.1)
Procedure: †		
Meniscectomy, n (%)	562/731 (76.9)	556/720 (77.2)
Removal of loose bodies, n(%)	41/731 (5.6)	36/720 (5.0)
Diagnostic arthroscopy, n (%)	56/731 (7.7)	58/720 (8.1)
Other‡ , n (%)	168/731 (23.0)	172/720 (23.9)
Tourniquet use , yes (%)	688/703 (97.9)	673/688 (97.8)

* Low Molecular Weight Heparin, either Nadroparin or Dalteparin.
† Does not add up to 100% as some patients had multiple interventions.
‡ Full list of other interventions listed in the Supplementary Appendix.

Effectiveness Outcomes

In the treatment group, 10 patients had symptomatic venous thromboembolism (6 had deep vein thrombosis, 3 had pulmonary embolism, and 1 had both), for a cumulative incidence of 1.4% (95% CI, 0.7 to 2.5). In the control group, 13 patients had symptomatic venous thromboembolism (8 had deep-vein thrombosis, 4 had pulmonary embolism, and 1 had both), for a cumulative incidence of 1.8% (95% CI, 1.0 to 3.1). The relative risk was 0.8 (95% CI, 0.3 to 1.7), and the absolute difference in risk was −0.4 percentage points (95% CI, −1.8 to 1.0) (*Table 3*). In addition, 1 patient in each group had a distal superficial venous thrombosis (which was not adjudicated to be an outcome event).

The per-protocol population included the 626 patients (87.1%) in the treatment group and the 662 patients (92.5%) in the control group who adhered to the trial regimen. In the per-protocol analysis, symptomatic venous thromboembolism occurred in 10 patients (1.6%) in the treatment group and in 12 (1.8%) in the control group (relative risk, 0.9; 95% CI, 0.4 to 2.0) (*Table 4*). The 13th patient with venous thromboembolism, who was in the control group, used nadroparin for the 4 weeks after surgery (patient's own initiative).

Table 3: Primary and secondary outcomes, Intention-to-treat analysis†.

POT-KAST trial	**Treatment group * n (%, 95%CI)**	**Control group n (%; 95%CI)**	**RR (95%CI)**	**RD (95%CI), percentage points**
Primary efficacy outcome				
DVT	4/731 (0.5; 0.1 to 1.4)	2/720 (0.3; 0.0 to 1.0)		0.3 (-0.5 to 1.1)
PE	1/731 (0.1; 0.0 to 0.8)	1/720 (0.1; 0.0 to 0.8)		0.0 (-0.6 to 0.7)
DVT and PE	0/731 (0.0; 0.0 to 0.5)	0/720 (0.0; 0.0 to 0.5)		0.0 (-0.5 to 0.5)
Total	5/731 (0.7; 0.2 to 1.6)	3/720 (0.4; 0.1 to 1.2)	1.6 (0.4 to 6.8)	0.3 (-0.6 to 1.2)
Primary safety outcome				
Major bleeding	1/731 (0.1; 0.0 to 0.8)	1/720 (0.1; 0.0 to 0.8)	1.0 (0.1 to 15.7)	0.0 (-0.6 to 0.7)
Secondary safety outcome				
CRNMB	1/731 (0.1; 0.0 to 0.8)	3/720 (0.4; 0.1 to 1.2)	0.3 (0.0 to 3.1)	-0.3 (-1.1 to 0.4)
POT-CAST trial	**Treatment group * n (%, 95%CI)**	**Control group n (%; 95%CI)**	**RR (95%CI)**	**RD (95%CI), percentage points**
Primary efficacy outcome				
DVT	6/719 (0.8; 0.3 to 1.8)	8/716 (1.1; 0.5 to 2.2)		-0.3 (-1.5 to 0.8)
PE	3/719 (0.4; 0.1 to 1.2)	4/716 (0.6; 0.2 to 1.4)		-0.1 (-1.1 to 0.7)
DVT and PE	1/719 (0.1; 0.0 to 0.8)	1/716 (0.1; 0.0 to 0.8)		0.0 (-0.7 to 0.7)
Total	10/719 (1.4; 0.7 to 2.5)	13/716 (1.8; 1.0 to 3.1)	0.8 (0.3 to 1.7)	-0.4 (-1.8 to 1.0)
Primary safety outcome				
Major bleeding	0/719 (0; 0 to 0.5)	0/716 (0; 0 to 0.5)	-	0.0 (-0.5 to 0.5)
Secondary safety outcome				
CLNMB	1/719 (0.1; 0.0 to 0.8)	0/716 (0; 0 to 0.5)	-	0.1 (-0.4 to 0.8)

* Low Molecular Weight Heparin, either Nadroparin or Dalteparin.
† DVT denotes Deep Vein Thrombosis, PE denotes Pulmonary Embolism, CRNMB denotes clinical relevant non-major bleeding, CI denotes Confidence Interval, RR denotes Relative Risk, RD denotes Risk Difference

Table 4: Primary and secondary outcomes, per-protocol analysis†.

POT-KAST trial	**Treatment group * n (%; 95%CI)**	**Control group n (%; 95%CI)**	**RR (95%CI)**	**RD (95%CI), percentage points**
Primary efficacy outcome				
DVT	4/621 (0.6; 0.2 to 1.6)	2/706 (0.3; 0.0 to 1.0)		0.4 (-0.5 to 1.4)
PE	0/621 (0.0; 0.0 to 0.6)	1/706 (0.1; 0.0 to 0.8)		-0.1 (-0.8 to 0.5)
DVT and PE	0/621 (0.0; 0.0 to 0.6)	0/706 (0.0; 0.0 to 0.5)		0.0 (-0.5 to 0.6)
Total	4/621 (0.6; 0.2 to 1.6)	3/706 (0.4; 0.1 to 1.2)	1.5 (0.3 to 6.7)	0.2 (-0.7 to 1.3)
Primary safety outcome				
Major bleeding	1/621 (0.2; 0.0 to 0.9)	1/706 (0.1; 0.0 to 0.8)	1.1 (0.1 to 18.1)	0.0 (-0.7 to 0.8)
Secondary safety outcome				
CRNMB	1/621 (0.2; 0.0 to 0.9)	3/706 (0.4; 0.1 to 1.2)	0.4 (0.0 to 3.6)	-0.3 (-1.1 to 0.5)
POT-CAST trial	**Treatment group * n (%; 95%CI)**	**Control group n (%; 95%CI)**	**RR (95%CI)**	**RD (95%CI), percentage points**
Primary efficacy outcome				
DVT	6/626 (1.0; 0.4 to 2.1)	7/662 (1.1; 0.4 to 2.2)		-0.1 (-1.3 to 1.1)
PE	3/626 (0.5; 0.1 to 1.4)	4/662 (0.6; 0.2 to 1.5)		-0.1 (-1.1 to 0.9)
DVT and PE	1/626 (0.2; 0.0 to 0.9)	1/662 (0.2; 0.0 to 0.8)		0.0 (-0.7 to 0.8)
Total	10/626 (1.6; 0.8 to 2.9)	12/662 (1.8; 0.9 to 3.1)	0.9 (0.4 to 2.0)	-0.2 (-1.8 to 1.3)
Primary safety outcome				
Major bleeding	0/626 (0; 0 to 0.6)	0/662 (0; 0 to 0.6)	-	0.0 (-0.6 to 0.6)
Secondary safety outcome				
CLNMB	1/626 (0.1; 0.0 to 0.9)	0/662 (0; 0 to 0.6)	-	0.2 (-0.2 to 0.5)

* Low Molecular Weight Heparin, either Nadroparin or Dalteparin.
† DVT denotes Deep Vein Thrombosis, PE denotes Pulmonary Embolism, CRNMB denotes clinical relevant non-major bleeding, CI denotes Confidence Interval, RR denotes Relative Risk, RD denotes Risk Difference

Table 5: Casting outcomes in the POT-CAST trial.

Outcome	Treatment group * (n=719)	Control group (n=716)
Duration cast in weeks, mean (SD)	4.9 (2.5)	4.9 (2.5)
Lower-leg cast indication, n/total n (%)		
Fracture	648/719 (90.1)	631/716 (88.1)
Achilles tendon rupture	40/719 (5.6)	54/716 (7.5)
Ankle distortion	18/719 (2.5)	17/716 (2.4)
Antalgic	6/719 (0.8)	3/716 (0.4)
Contusion	5/719 (0.7)	8/716 (1.1)
Other	2/719 (0.3)	3/716 (0.4)
Fracture type, n(%)‡		
Ankle	255/648 (39.4)	242/631 (38.4)
44-A type	60/229 (26.2)	44/217 (20.3)
44-B type	126/229 (55.0)	130/217 (59.9)
44-C type	29/229 (12.7)	29/217 (13.3)
Maisonneuve	2/29 (6.9)	4/29 (13.8)
Other†	14/229 (6.1)	14/217 (6.5)
Metatarsal	277/648 (42.7)	255/631 (40.4)
Calcaneus	31/648 (4.8)	25/631 (4.0)
Pilon tibial	2/648 (0.3)	1/631 (0.2)
Tibia and fibula shaft	1/648 (0.2)	2/631 (0.3)
Talus	21/648 (3.2)	29/631 (4.6)
Tarsal	42/648 (6.5)	56/631 (8.9)
Phalanx	11/648 (1.7)	12/631 (1.9)
Lisfranc	4/648 (0.6)	2/631 (0.3)
Other	4/648 (0.6)	7/631 (1.1)
Multiple fractures, n (%)	53/648 (8.4)	52/631 (8.4)
Surgery, n (%) §	91/719 (12.7)	79/716 (11.0)
Total duration operation in minutes, mean (SD)	75.2 (32.2)	78.5 (27.4)
Duration surgery in minutes, mean (SD)	50.2 (28.2)	50.9 (21.7)

(SD) denotes Standard Deviation,
* Low Molecular Weight Heparin, either Nadroparin or Dalteparin.
† Fractures not meeting criteria to be classified in either type.
‡ Primary fracture (in case multiple fractures were present).
§ The total duration of the operation was from the time the patient began receiving anesthesia to the time the patient left the operating room. Data are missing for 40 patients in the treatment group and 33 patients in the control group. The duration of surgery was from the time of incision to the time of wound closure. Data are missing for 36 patients in the treatment group and 29 patients in the control group.

Safety Outcomes

One clinically relevant nonmajor bleeding event occurred in 1 patient (0.1%) in the treatment group and in no patients in the control group, and no major bleeding events occurred. Minor bleeding was reported by 55 patients (7.6%) in the treatment group and by 49 (6.8%) in the control group. One patient in the control group died (see the *Supplementary Appendix* for more information and a sensitivity analysis including this event). No deaths occurred among the patients who were lost to follow-up. The most common adverse event was infection. (For more details, see the *Supplementary Appendix*.)

DISCUSSION

In two parallel trials, one involving patients who underwent knee arthroscopy (POT-KAST) and one involving patients who were treated with casting of the lower-leg (POT-CAST), we found that treatment with anticoagulants, either for the 8 days after arthroscopy or during the complete period of immobilization due to casting, was not effective for the prevention of symptomatic venous thromboembolism.

The results of the POT-KAST trial contradict the findings of a meta-analysis of four small randomized, controlled trials (each with 36 to 239 participants) that suggested a beneficial effect of anticoagulant therapy with respect to the risk of symptomatic venous thromboembolism in patients who had undergone knee arthroscopy, with a pooled relative risk for the comparison of low-molecular-weight heparin therapy with no anticoagulant therapy of 0.42 (95% CI, 0.06 to 3.14).[16] In a larger trial (approximately 650 participants in each group), in which the use of low-molecular- weight heparin for 7 days was compared with the use of compression stockings (control), venous thromboembolism occurred in 4 patients (0.6%) in the low-molecular-weight heparin group and in 14 patients (2.1%) in the control group (relative risk, 0.3; 95% CI, 0.1 to 0.9).[17] The same investigators compared rivaroxaban with placebo in 241 randomly assigned patients and found incidences of venous thromboembolism of 0.8% in the treatment group and 6.1% in the control group. [22] However, in both trials, all the participants underwent ultrasonographic screening for venous thromboembolism, at which time questions were asked about possible signs and symptoms. This clearly does not reflect the method for identification of symptomatic venous thromboembolism that is used in general clinical practice and has therefore led to overestimation of the incidences.[23]

With respect to patients with casting, six small trials (with a total of 1536 patients) have been performed that showed results that are contradictory to ours, with pooled odds ratios in favor of low-molecular-weight heparin for the prevention of asymptomatic venous thromboembolism (0.49; 95% CI, 0.34 to 0.72) and symptomatic venous thromboembolism (0.16; 95% CI, 0.05 to 0.56).[24] Nevertheless, in addition to not being powered for symptomatic events, these trials had severe methodologic weaknesses, such as high rates of lost to follow-up[10] and enrollment only of patients who had a high risk of venous thromboembolism.[12,13] Because of these limitations, the need for stronger evidence regarding thromboprophylaxis for each of these indications has been expressed in several reviews and guidelines.[7,16,25]

A strength of our trials was the pragmatic design, with conditions set to approximate general clinical practice as much as possible. We included a nonselected, wide variety of patients, and almost no restrictions were made regarding the indication for knee arthroscopy or

the indication for or duration of casting. The exclusion criteria were minimal and hence maximized the generalizability for clinical practice. Furthermore, an outcome adjudication committee whose members were unaware of the treatment assignments classified all events. The completeness of follow-up was high (98%), and few patients (1 to 2%) withdrew consent.

The trials had limitations that may explain our neutral findings. First, POT-KAST had limited power because the incidence of symptomatic venous thromboembolism was lower than expected (i.e., 0.6%). This incidence is in line with two recent observational studies that reported incidences of symptomatic venous thromboembolism of 0.3% (95% CI, 0.3 to 0.5) within 3 months after the procedure and 0.4% (95% CI, 0.2 to 0.5) within 6 weeks after the procedure, and in both studies, the vast majority of patients did not receive any anticoagulants.[26,27] Furthermore, a meta-analysis showed a pooled incidence of symptomatic venous thromboembolism of 0.6% (95% CI, 0.3 to 1.1) in 571,793 arthroscopic meniscectomy procedures.[28] In contrast, randomized trials have shown much higher incidences, ranging from 0.9% (95% CI, 0.3 to 2.1) to 5.3% (95% CI, 2.4 to 11.0), and our sample sizes were calculated on the basis of these data.[7,16,17] If we accept, on the basis of our own data and the results of the observational studies, that the true incidence is indeed close to 0.6%, such a low incidence indicates futility of thromboprophylaxis, since the number needed to treat would be huge regardless of the effect of anticoagulant therapy (i.e., with an absolute difference in risk of 0.3% [95% CI, −0.6 to 1.2] in favor of no treatment, the number needed to treat, as based on the lower limit of the 95% confidence interval, would be ≥167). Furthermore, in this situation, the harms introduced by anticoagulant treatment would most likely outweigh its benefits, as would the costs of pharmacologic treatment.

Second, a possible explanation for our null result is the rate of adherence to the trial regimen, which was 85% in the POT-KAST trial and 87% in the POT-CAST trial in the treatment groups. Nevertheless, among 110 patients in the POT-KAST trial and 93 in the POT-CAST trial who did not adhere to the trial regimen, 40 patients and 50 patients, respectively, still partially adhered. Furthermore, the results of the per-protocol analyses were similar to the results of the intention-to- treat analyses in both trials. It is important to note that these results represent daily practice, and better adherence rates would not be expected outside the context of a trial (a large observational study involving 4388 patients who had under- gone orthopaedic surgery showed an identical adherence rate of 87%).[29]

Third, a possible explanation for our findings is the nonblinded study design. For example, patients randomly assigned to receive no anticoagulant therapy could have contacted their physician earlier to report signs and symptoms of venous thromboembolism. In both

trials combined, venous thromboembolism was suspected in 29 patients in the treatment group and in 36 patients in the control group. Nevertheless, the diagnosis was confirmed at the same rate in both groups (i.e., in 15 patients [52%] and 16 patients [44%] in the treatment group and control group, respectively). It should be noted that we intentionally chose a nonblinded design to reflect general practice, because patients may have different thresholds for contacting their doctor depending on their type of treatment.

Fourth, a possible limitation is that the patients who declined to participate could have had a different risk of thrombosis than those who participated. However, in POT-KAST, the distributions of age and sex among patients who declined to participate were similar to those among patients who participated, which indicates no major differences in the risk of thrombosis.

Finally, the lack of effect of anticoagulant therapy may have been due to the dose, type, or duration of treatment. The nadroparin dose of 2850 IU may have been too low, despite the fact that this is the standard dose for thromboprophylaxis. Furthermore, it may be argued that use of a direct oral anticoagulant would have led to different results. However, a recent meta-analysis of five randomized trials that compared the use of direct oral anticoagulants with low-molecular-weight heparin in patients who received thromboprophylaxis after hip or knee surgery showed no difference between the two treatments in efficacy, which makes it unlikely that the use of direct oral anticoagulants would have led to different conclusions.[30] In addition, in the POT-KAST trial, all events occurred after the treatment period of 8 days. In 9 of the 23 patients in the POT-CAST trial who had venous thromboembolism, the condition developed after the cast had been removed; 6 of these 9 patients had been treated with low-molecular-weight heparin, a finding that may indicate a need for longer treatment.

We can conclude that routine thromboprophylaxis with the standard regimen is not effective after knee arthroscopy or lower-leg casting. In light of the high frequency of knee arthroscopy and casting worldwide, a considerable number of cases of venous thromboembolism will nevertheless occur, and any possible prevention of these events should still be pursued. A higher dose or longer duration of treatment is not to be recommended for all patients because the number needed to harm will decrease and may consequently outweigh the high number needed to treat (250 in the POT-CAST trial). Nevertheless, a regimen with an increased dose or duration might be effective if it is restricted to high-risk groups; it can be hypothesized that patients who have symptomatic venous thromboembolism during treatment have a high baseline risk and that casting or knee arthroscopy is a relatively small trigger that, when added to the baseline risk, leads to thrombosis.[31] We have previously found that patients who had symptomatic

venous thromboembolism after casting or knee arthroscopy indeed had (several) other risk factors.[1,2] Also, in both POT-KAST and POT-CAST, other risk factors were present in the patients who had venous thromboembolism during treatment, including older age, hormone use, and a family history of venous thromboembolism. A similar situation is possibly present in patients who undergo hip replacement; 2% of such patients have venous thromboembolism despite anticoagulant prophylaxis.[30] We therefore speculate that, for the patients at the highest risk, the routine prophylactic dose is insufficient. Risk prediction (which we previously found to be feasible[32,33]) and tailored thromboprophylactic strategies for high-risk patients should be a topic for further research in patients undergoing knee arthroscopy or treatment with casting.

In conclusion, a prophylactic regimen of low-molecular- weight heparin therapy for the 8 days after knee arthroscopy or during the complete period of immobilization in patients with casting of the lower-leg was not effective for the prevention of symptomatic venous thromboembolism.

REFERENCE LIST

1. van Adrichem RA, Nelissen RG, Schipper IB, Rosendaal FR, Cannegieter SC. Risk of venous thrombosis after arthroscopy of the knee: results from a large population- based case-control study. J Thromb Haemost 2015; 13: 1441-8.
2. van Adrichem RA, Debeij J, Nelissen RG, Schipper IB, Rosendaal FR, Cannegieter SC. Below-knee cast immobilization and the risk of venous thrombosis: results from a large population-based case-control study. J Thromb Haemost 2014; 12: 1461-9.
3. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007; 5: 692-9.
4. ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to the global disease burden. J Thromb Haemost 2014; 12: 1580-90.
5. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. J Thromb Thrombolysis 2009; 28: 465-76.
6. American Academy of Orthopaedic Surgeons. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty (http://www .orthoguidelines.org/ guideline-detail?id=1075).
7. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopaedic 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.
8. National Institute for Health and Care Excellence. Venous thromboembolism: reducing the risk for patients in hospital. NICE guideline CG92. 2010 (https://www.nice.org.uk/guidance/cg92).
9. American Academy of Orthopaedic Surgeons. Knee arthroscopy (http://orthoinfo.aaos .org/ topic.cfm?topic =a00299).
10. Jørgensen PS, Warming T, Hansen K, et al. Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study. Thromb Res 2002; 105: 477-80.
11. Kock HJ, Schmit-Neuerburg KP, Hanke J, Rudofsky G, Hirche H. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. Lancet 1995; 346: 459-61.
12. Lapidus LJ, Ponzer S, Elvin A, et al. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebocontrolled, double-blind study. Acta Orthop 2007; 78: 528-35.
13. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. N Engl J Med 2002; 347: 726-30.
14. ProMISe (Project Manager Internet Server). About ProMISe (https:/ / www .msbi .nl/ promise).
15. Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010; 8: 202-4.
16. Ramos J, Perrotta C, Badariotti G, Berenstein G. Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy. Cochrane Database Syst Rev 2008; 4: CD005259.
17. Camporese G, Bernardi E, Prandoni P, et al. Low-molecular-weight heparin versus compression stockings for thromboprophylaxis after knee arthroscopy: a randomized trial. Ann Intern Med 2008; 149: 73-82.
18. Testroote M, Stigter W, de Visser DC, Janzing H. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. Cochrane Database Syst Rev 2008; 4: CD006681.
19. Comp PC, Spiro TE, Friedman RJ, et al. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. J Bone Joint Surg Am 2001; 83-A: 336-45.
20. Lassen MR, Borris LC, Anderson BS, et al. Efficacy and safety of prolonged thromboprophylaxis with a low molecular weight heparin (dalteparin) after total hip arthroplasty — the Danish Prolonged Prophylaxis (DaPP) Study. Thromb Res 1998; 89: 281-7.
21. Sobieraj DM, Lee S, Coleman CI, et al. Prolonged versus standard-duration venous thromboprophylaxis in major orthopaedic surgery: a systematic review. Ann Intern Med 2012; 156: 720-7.
22. Camporese G, Bernardi E, Noventa F, et al. Efficacy of Rivaroxaban for thromboprophylaxis after Knee Arthroscopy (ERIKA): a phase II, multicentre, doubleblind, placebo-controlled randomised study. Thromb Haemost 2016; 116: 349-55.
23. Németh B, van Adrichem RA, Cannegieter SC. The ERIKA trial: still limited evidence on the efficacy of thromboprophylaxis after knee arthroscopy. Thromb Haemost 2016; 116: 1001.
24. Testroote M, Stigter WA, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. Cochrane Database Syst Rev 2014; 4: CD006681.
25. Bushnell BD, Anz AW, Bert JM. Venous thromboembolism in lower extremity arthroscopy. Arthroscopy 2008; 24: 604- 11.
26. Mauck KF, Froehling DA, Daniels PR, et al. Incidence of venous thromboembolism after elective knee arthroscopic surgery: a historical cohort study. J Thromb Haemost 2013; 11: 1279-86.
27. Krych AJ, Sousa PL, Morgan JA, Levy BA, Stuart MJ, Dahm DL. Incidence and risk factor analysis of symptomatic venous thromboembolism after knee arthroscopy. Arthroscopy 2015; 31: 2112-8.
28. Thorlund JB, Juhl CB, Roos EM, Lohmander LS. Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. BMJ 2015; 350: h2747.
29. Bergqvist D, Arcelus JI, Felicissimo P,ETHOS investigators. Post-discharge compliance to venous thromboembolism prophylaxis in high-risk orthopaedic surgery: results from the ETHOS registry. Thromb Haemost 2012; 107: 280-7.
30. Forster R, Stewart M. Anticoagulants (extended duration) for prevention of venous thromboembolism following total hip or knee replacement or hip fracture repair. Cochrane Database Syst Rev 2016; 3: CD004179.
31. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet 1999; 353: 1167-73.
32. Németh B, van Adrichem RA, van Hylckama Vlieg A, et al. Venous thrombosis risk after cast immobilization of the lower extremity: derivation and validation of a clinical prediction score, L-TRiP(cast), in three population-based case-control studies. PLoS Med 2015; 12(11): e1001899.
33. Németh B, van Adrichem RA, le Cessie S, et al. Prediction of venous thrombosis risk after arthroscopy of the knee. Presented at the International Society on Thrombosis and Haemostasis 2015 Congress, Toronto, June 20–25, 2015 (poster).

3

No indication for thromboprophylactic therapy following knee arthroscopy or lower-leg casting

Adapted from:

1. B. Németh et al. Thromb Haemost. 2016 Oct 28;116(5):1001

2. B. Németh et al. Injury. 2017 Dec;48(12):2887-2888

In this chapter we respond to two trials which studied the efficacy of thromboprophylaxis following 1. Knee arthroscopy and 2. Lower-leg cast immobilization. For both trials, we question the validity of the results and we point out our concerns with regards to the study outcome.

THE ERIKA TRIAL:
still limited evidence on the efficacy of thromboprophylaxis after knee arthroscopy

Németh B, van Adrichem RA, Cannegieter SC.
Thromb Haemost. 2016 Oct 28;116(5):1001.

Dear editor,
We read with great interest the recent article by Camporese and colleagues "Efficacy of Rivaroxaban for thromboprophylaxis after Knee Arthroscopy (ERIKA). A phase II, multicentre, double-blind, placebo-controlled randomised study".[1] This study considers a highly relevant clinical problem, i.e. whether or not to prescribe thromboprophylaxis in patients undergoing knee arthroscopy (KA). The authors conclude that a seven day course of 10-mg rivaroxaban reduced both symptomatic and asymptomatic venous thrombosis (VT) (absolute risk difference -5.3% [95%CI -11.4 to -0.8], number needed to treat (NNT)=19). In addition, it is stated that this treatment may be safely employed in this patient group.

These statements raised some concern from our perspective and we would like to point out the following: First, the study found an overall symptomatic VT risk of 3.0% within 3-months following KA (0.8% versus 5.3% in the rivaroxaban and placebo controlled group respectively). All but one symptomatic events were diagnosed at day seven, just before ultrasonography. This risk is much higher than (recent) published numbers derived from very large observational studies. For example, a study from Portsmouth, USA, reported a cumulative incidence of 0.53% for symptomatic VT after 16.558 anterior cruciate ligament reconstructions,[2] while other studies showed an incidence of 0.3% within 4 weeks (12.595 patients),[3] and 0.4% within 35 days (4833 patients).[4] This strong discrepancy made us question the method that was used to classify events as symptomatic. The investigators actively asked patients about signs and symptoms of VT before ultrasonography, which was performed by a trained nurse blinded to treatment arm. One positive sign or symptom combined with a thrombus found during ultrasonography resulted in the classification of a symptomatic event. This method most likely does not represent the pattern of signs and symptoms that is present when patients seek medical advice during follow-up themselves, i.e. the truly symptomatic events. The severity of these symptomatic events is therefore questionable and it is not known how many of these events would have spontaneously dissolved or progressed to real symptomatic cases. Also, it is not stated how many patients without thrombus formation had signs or symptoms of VT just before ultrasonography (information that would clarify the frequency of the symptoms).

Second, the authors conclude that rivaroxaban can be safely administered for

thromboprophylaxis after KA. This statement cannot be made based on the low sample size of this study. In addition, the study was not powered to determine the balance between treatment benefits (reducing thrombosis) and risks (induce bleeding). As a result of these two points, the presented NNT of 19 is not informative: 1. the primary efficacy outcome includes asymptomatic events as well, which also contribute to the NNT. What knowledge do we gain if we treat x number of patients to prevent x number of asymptomatic events?, and 2. without a number needed to harm it is difficult to decide on the net benefit of treatment.

To conclude, we believe that the results from this study are valuable as they demonstrate a possible benefit of rivaroxaban on prevention of asymptomatic events. Nevertheless, the clinical consequences of this study are limited for practice as any conclusion on its efficacy or safety in patients undergoing KA is precluded due to the low number of patients in the study. We agree with the authors that a larger randomised trial is needed to verify these findings and to confirm efficacy of rivaroxaban or other anticoagulants for the prevention of symptomatic VT after KA.

Conflict of interest disclosure: The authors of this letter collaborate on a randomized controlled trial on the efficacy and safety of thromboprophylaxis after knee arthroscopy.

CAST IMMOBILIZATION OF THE LOWER-LEG:
no indication for thromboprophylactic therapy

Németh B & Cannegieter SC.
Injury. 2017 Dec;48(12):2887-2888

Dear editor,
We read the manuscript entitled "Nadroparin or fondaparinux versus no thromboprophylaxis in patients immobilised in a below-knee plaster cast (PROTECT): A randomised controlled trial" with great interest.[5]

In this recently published randomized controlled trial, adults with an ankle or foot fracture, who required below-knee cast immobilization for a minimum of four weeks, were randomly assigned to receive no therapy (control group) or to one of the intervention groups: daily subcutaneous self-injection of either nadroparin (2850 IE anti-Xa = 0.3 ml) or fondaparinux (2.5 mg = 0.5 ml) (1:1:1). The primary outcome was the occurrence of deep vein thrombosis (DVT) verified by duplex sonography and/or symptomatic pulmonary embolism verified by CT angiography.[5]

The authors conclude that thromboprophylaxis with nadroparin or fondaparinux significantly reduces the risk of a thromboembolic event and therefore they propose to routinely prescribe thromboprophylaxis in patients with an ankle or foot fracture who are conservatively treated in below-knee cast immobilisation.

The trial concerns an important field of research. However, in our opinion, the study findings are not a sufficient basis for the authors' conclusion, for several reasons. First, the primary outcome was mainly asymptomatic DVT which occurred in 14 patients (11/94 in the control group, 2/92 in the nadroparin group and 1/92 in the fondaparinux group). In total, only two patients developed a symptomatic event, i.e. pulmonary embolism (control group). This finding indeed suggests a protective effect of thromboprophylaxis for the prevention of asymptomatic events. However, the authors cannot simply extrapolate these findings to symptomatic venous thromboembolism (VTE), because of the limited sample size. In the PROTECT trial, a risk reduction for symptomatic VTE of 2.1% was found (i.e. risk in pooled treatment group 0/184 (0%) minus risk in control group 2/94 (2.1%)). From these numbers, we can calculate that the risk for a type I error (p-value) is 12%. Moreover, the probability of a type I error increases up to 50% if we do not pool both treatment arms (2-sided Fisher's exact p).

Second, screening for asymptomatic VTE does not reflect clinical practice and up till now, the clinical relevancy of asymptomatic DVT is questionable. In 2014, Chan and colleagues performed a large systematic review of high quality VTE prevention trials (mainly in orthopaedic surgery patients), in which they concluded there was very poor agreement between the efficacy of thromboprophylaxis on asymptomatic DVT versus symptomatic VTE. Therefore the authors stated that "asymptomatic DVT is not a reliable surrogate for symptomatic events".[6]

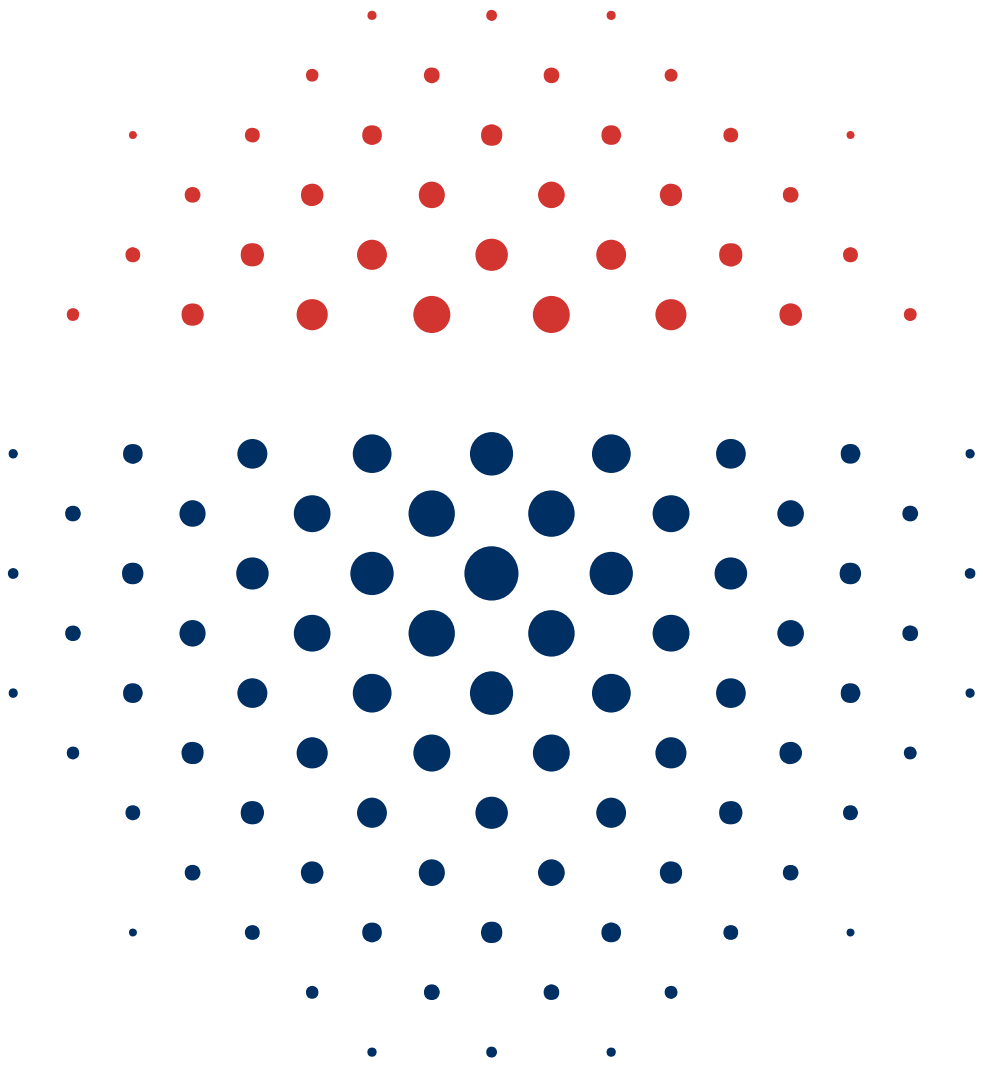
Third, of all 467 randomized patients, only 278 patients (60%) were included in the intention-to-treat analysis. A large proportion of excluded patients, did not undergo duplex sonography (59 patients) and therefore no information on the primary outcome was available in this group. This drop-out could have led to significant bias, for example, an under- or overestimation of the incidence of both asymptomatic and symptomatic VTE. We could speculate that those patients who did not undergo duplex sonography probably did not develop a symptomatic event, otherwise they would have been subjected to duplex sonography. Alternatively, some of these patients may have been hospitalized due to a pulmonary embolism, which would result in an underestimation of the incidence. These issues question the validity of the results, in particular those concerning symptomatic VTE because of the limited numbers.

The PROTECT conclusion contradicts with that of the POT-CAST trial which was recently published by our research group.[7] In the POT-CAST trial, 1519 patients treated with a lower-leg cast (both surgically and conservatively) for a minimum of 1 week, were randomized to receive either a prophylactic dose of low-molecular-weight-heparin for the complete duration of cast immobilization (treatment group) or no treatment (control group). Patients were followed for 3-months and only symptomatic VTE was considered as an outcome event. In the treatment group 10/719 (1.4%, 95%CI 0.7 to 2.5) patients developed symptomatic VTE versus 13/716 (1.8%, 95%CI 1.0 to 3.1) in the control group (risk difference -0.4%, 95%CI -1.8 to 1.0). No difference in major bleeding was observed. From this large, sufficiently powered trial we concluded that thromboprophylaxis was not effective to prevent symptomatic VTE in patients treated with lower-leg cast immobilization.[7] The PROTECT conclusion is not very helpful in advancing the field as physicians are now confronted with two contradictory messages. Considering the fact that the POT-CAST trial was 5 times larger, had wide inclusion criteria a 98% complete follow-up, treatment compliance of 87% and that it took only clinically relevant events into account, we urge physicians to discard the conclusion of the PROTECT trial and not to routinely treat all lower-leg cast patients with thromboprophylactic therapy, hence exposing their patients to its risk and burden.

However, we agree with the authors that VTE still is a substantial problem that occurs in about 1.5% of these patients. As the current strategy does not appear to work, a more feasible and efficient approach would be to target high-risk patients with higher dosage or longer duration of anticoagulation.[8] Further research should focus on these high risk patients in order to optimize thromboprophylactic therapy following lower-leg cast immobilization.

REFERENCE LIST

1. Camporese G, Bernardi E, Noventa F, Bosco M, Monteleone G, Santoro L, et al. Efficacy of Rivaroxaban for thromboprophylaxis after Knee Arthroscopy (ERIKA). A phase II, multicentre, double-blind, placebo-controlled randomised study. Thrombosis and haemostasis. 2016;116(2):349-55.
2. Gaskill T, Pullen M, Bryant B, Sicignano N, Evans AM, DeMaio M. The Prevalence of Symptomatic Deep Venous Thrombosis and Pulmonary Embolism After Anterior Cruciate Ligament Reconstruction. The American journal of sports medicine. 2015;43(11):2714-9.
3. Krych AJ, Sousa PL, Morgan JA, Levy BA, Stuart MJ, Dahm DL. Incidence and Risk Factor Analysis of Symptomatic Venous Thromboembolism After Knee Arthroscopy. Arthroscopy. 2015.
4. Mauck KF, Froehling DA, Daniels PR, Dahm DL, Ashrani AA, Crusan DJ, et al. Incidence of venous thromboembolism after elective knee arthroscopic surgery: a historical cohort study. Journal of thrombosis and haemostasis 2013;11(7):1279-86.
5. Bruntink MM, Groutars YM, Schipper IB, Breederveld RS, Tuinebreijer WE, Derksen RJ, et al. Nadroparin or fondaparinux versus no thromboprophylaxis in patients immobilised in a below-knee plaster cast (PROTECT): A randomised controlled trial. Injury. 2017;48(4):936-40.
6. Chan NC, Stehouwer AC, Hirsh J, Ginsberg JS, Alazzoni A, Coppens M, et al. Lack of consistency in the relationship between asymptomatic DVT detected by venography and symptomatic VTE in thromboprophylaxis trials. Thrombosis and haemostasis. 2015;114(5):1049-57.
7. van Adrichem RA, Németh B, Algra A, le Cessie S, Rosendaal FR, Schipper IB, et al. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. The New England journal of medicine. 2017;376(6):515-25.
8. Németh B, van Adrichem RA, van Hylckama Vlieg A, Bucciarelli P, Martinelli I, Baglin T, et al. Venous Thrombosis Risk after Cast Immobilization of the Lower Extremity: Derivation and Validation of a Clinical Prediction Score, L-TRiP(cast), in Three Population-Based Case-Control Studies. PLoS medicine. 2015;12(11):e1001899; discussion e.



4

High risk of recurrent venous thrombosis in patients with lower-leg cast immobilization

Németh B, Timp JF, van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC.

J Thromb Haemost. 2018 Nov;16(11):2218-2222.

ABSTRACT

Background Patients with lower-leg cast immobilization have a substantially increased risk to develop a first venous thrombosis (VT) while the risk in patients with a history of VT is as yet unknown.

Aims To estimate the risk of a recurrent thrombotic event after lower-leg cast immobilization in patients with a history of VT.

Methods This study is a case-control study nested within a cohort of 4597 patients with a first VT who were followed over time for recurrence from 1999-2010 (MEGA follow-up study). Participants completed a questionnaire on risk factors for recurrent thrombosis, including plaster cast in the first 3 months before a recurrence (cases) or a random 3 month-period during follow-up for participants without recurrence (controls). In total, 2723/4597 (59%) participants returned the questionnaire. Odds ratios (OR), adjusted for age and sex were calculated to compare risks of recurrence between subjects with and without cast.

Results 2525/2723 participants (93%) filled out information on plaster cast immobilization. Twenty (1.0%) controls and ten (2.2%) cases reported to have had lower-leg casting in the three months before control or recurrence date, for an adjusted OR of 2.4 (95% Confidence Interval 1.1-5.3). Thereafter we cross checked the data with these patients' medical records. Plaster cast application within 3-months was verified in seven (0.3%) controls versus six (1.3%) cases leading to an adjusted OR of 4.5 (95% CI: 1.5-14.0), for a corresponding cumulative incidence or 3.2%.

Conclusions Lower-leg cast immobilization increases the risk of recurrent VT in the 3 months after its application in patients with a history of VT.

INTRODUCTION

Patients who are treated with lower-leg cast immobilization have a substantially increased risk (about 1-2%) to develop Venous Thrombosis (VT) (i.e. deep vein thrombosis [DVT] and pulmonary embolism [PE]).[1, 2] However, the risk to develop a recurrent VT following cast immobilization in patients with a history of VT is as yet unknown. Knowledge on this risk can further support clinical policy regarding thromboprophylaxis treatment in these patients. Unfortunately, almost all large trials on this topic excluded patients with a history of VT so that precise risk estimations cannot be made.[3-8]

To date, multiple studies have focused on the prediction of a recurrent event (for both unprovoked and provoked recurrent events) by using risk factors that are present during the first venous thrombotic event. Yet, these risk assessment models lack discriminative ability which is not surprising, as prediction of a provoked recurrent event is challenging.[9] For optimal prophylactic strategies, identifying the risk for recurrence around periods with an increased thrombosis potential (such as cast immobilization) is crucial for the prevention of a provoked recurrent event. In this study we aimed to estimate the risk of a recurrent VT shortly after lower-leg cast immobilization in patients with a history of VT.

METHODS

Study population

We used data from the Multiple Environmental and Genetic Assessment follow up study (MEGA-follow up study). Details of this study have been published previously.[10] In short, the MEGA study is a population-based case-control study into the aetiology of VT. 4.956 consecutive patients with a first DVT, PE or both were recruited from six anticoagulation clinics in the Netherlands between 1999 and 2004. The diagnosis was confirmed by (Doppler) ultrasonography, ventilation-perfusion scan, angiography or spiral CT-scan. Control subjects were either partners of cases or recruited via random digit dialling.[11] Thereafter, the MEGA follow-up study was performed, details were also published previously.[12] 4731 cases who participated in the MEGA case-control study agreed to participate in the follow up study. Patients were followed over time to determine incidence rates for recurrent VT from 1999 until 2010. Between 2007 and 2009 the vital status of all patients was acquired from the central Dutch Population Register and the cause of death was obtained from the national register of death certificates. Recurrences were classified into certain and uncertain recurrences (information was obtained from questionnaires, hospital discharge letters, anticoagulation clinics and death certificates). For this analysis only certain recurrences were used. In addition, the MEGA follow-up database was linked to The Dutch Foundation for Pharmaceutical Statistics database, that provides information on all medical prescriptions from 95% of all public pharmacies in the Netherlands.[13] By doing so, medication usage (during the study period) for >90% of all participants in the study was objectively obtained. The MEGA follow-up study was approved by the Medical Ethics Committee of the Leiden University Medical Center and all participants gave informed consent.

Data collection

Participants were asked to complete a questionnaire on putative risk factors for recurrent VT by asking information on the period previous to the recurrent event or a random control period for participants who did not develop a recurrence. Plaster cast application of the lower extremities was identified with the question "Did you have plaster cast within 3 months previous to your second VT?". Plaster cast location and date were also recorded. For those patients who did not develop a recurrence the same question was asked, only the reference date was a 3-month period before a random control date.

Statistical analysis

We performed a nested case-control study within the MEGA follow-up study cohort. Patients with an uncertain recurrence diagnosis were excluded. Cases (patients with a recurrent VT) and controls (those without a recurrent VT) were identified at the end

of follow up. Finally, cases and controls who did not complete the questionnaire, or in whom information on plaster cast immobilization was missing were also excluded from the analysis. (*Figure 1*).

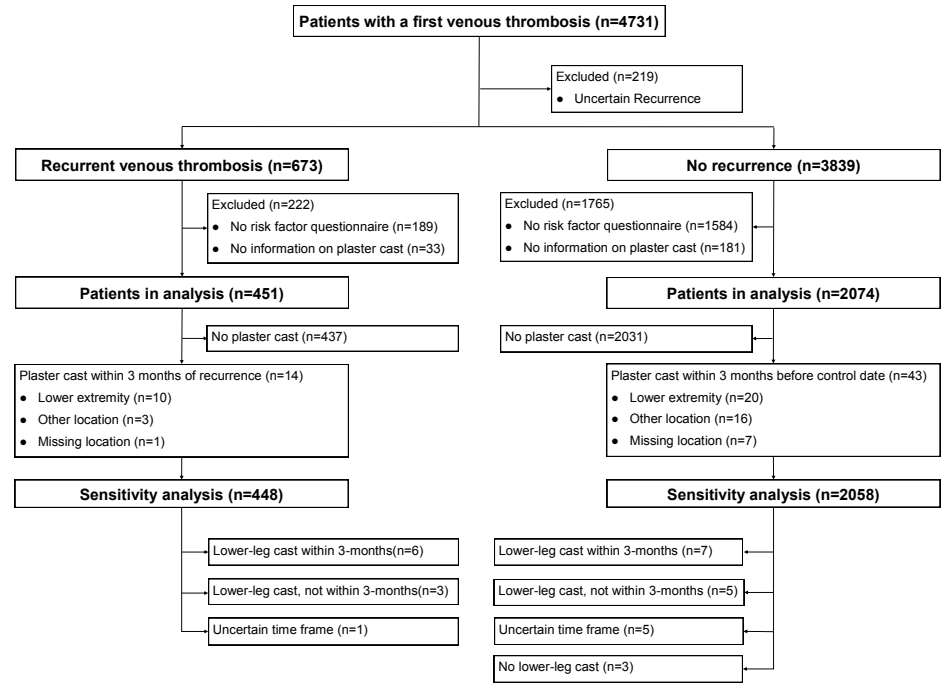


Figure 1: Study flow chart and number of patients included in the analyses.

To compare the risk of recurrence between subjects with and without plaster cast (all locations) we estimated the Relative Risk (RR) by calculating the Odds Ratio (OR) with the 95% Confidence Interval (95%CI). In addition, an OR (OR_{adj}) adjusted for age and sex was calculated using binary logistic regression. First, we calculated the OR for the development of recurrent VT for all types of cast immobilization. Subsequently, individuals with plaster cast of another location than lower-leg cast, or missing location, were excluded. Then we calculated the OR for recurrence for subjects with and without lower-leg cast. Finally, after verifying plaster date and recurrence date in the patients' records (to check the 3-month window of cast exposure previous to a patients VT or control date), we calculated the risk of recurrence between subjects with and without certain lower-leg cast (sensitivity analysis, *Figure 1*).

RESULTS AND DISCUSSION

4731 cases from the MEGA study agreed to participate in the MEGA follow-up study. After exclusion of participants with an uncertain recurrence (n=219), 673/4731 (14%) cases with a certain recurrence and 3839/4731 (81%) control subjects without recurrence were identified. 451 cases were included in the analysis after exclusion of cases with missing information on plaster cast (n=33) and cases who did not fill out the questionnaire on risk factors (n=189). Likewise, in 181 controls, information on plaster cast was missing and 1584 controls did not complete the questionnaire on risk factors, leaving 2074 controls for the analysis (*Figure 1*). The mean age of the study cohort was 47.7 years and 44.2% was male.

Of all cases, 14/451 subjects had any plaster cast within 3 months prior to their recurrent VT (10 lower-extremity, 3 other location, 1 missing location) and so did 43/2074 controls (20 lower extremity, 16 other location and 7 missing location, 3 months prior to the control date), for an OR of 1.5 (95%CI 0.8 - 2.8) (*Table 1*).

Table 1: The risk of recurrent venous thrombosis in individuals with lower-leg cast immobilization.

	Cases with cast	**Controls with cast**	**OR (95% CI)**	***OR_{adj} (95% CI)**
Original analysis				
All cast	14	43	1.5 (0.8-2.8)	1.6 (0.8-2.9)
Lower-leg cast	10	20	2.3 (1.1-5.0)	2.4 (1.1-5.3)
Sensitivity analysis†				
Certain lower-leg cast	6	7	4.0 (1.3-11.9)	4.5 (1.5-14.0)

*OR_{adj} denotes adjusted Odds Ratio for age and sex, CI denotes Confidence Interval
† Confirmed lower-leg cast within 3-month window from a patients' medical record

Subsequently, 4 cases and 23 controls were excluded because of a plaster cast location other than the lower extremities (i.e. arm, hand, finger and spine), or missing location, leaving subjects with or without plaster cast of the lower extremities only (10 cases and 20 controls with lower-leg cast). These patients had a 2.3-fold increased risk for developing a recurrent VT (95% CI 1.1 – 5.0), which hardly changed after adjustment for age and sex (OR_{adj} 2.4 (95%CI 1.1 – 5.3)) (*Table 1*). As these risks were self-reported we cross-checked the recurrence date and plaster date in the patients' medical records or discharge letter. By doing so, we were able to confirm cast of the lower-leg within 3 months prior to the recurrent VT/control period in 6/448 cases and 7/2058 controls. In most other patients the plaster cast date did not match the 3-month window before the recurrence

date. Therefore, these patients did have plaster cast, but not within the 3-month window. This further refinement resulted in a 4.0-fold increased risk for recurrent VT (95%CI 1.3 – 11.9) and adjusted for age and sex OR_{adj} 4.5 (95%CI 1.5 – 14.0) (*Table 1*). A corresponding cumulative incidence at 3 months of 3.2% can be derived from these numbers (28.1 recurrent VT cases per 1000 individuals per year (baseline) times 4.5 = 126.4/1000/year, thus 31.6/1000 (3.2%) recurrent events within 3 months following lower-leg cast immobilisation. By reviewing discharge letters and medical records it was showed that most cases and controls with a recurrence did not have a prescription of anticoagulation medication during plaster cast immobilization. However, this may be explained due to the fact that these prescriptions probably were issued at the hospital pharmacies (which were not linked to this database). Therefore, we cannot state for certain that these patients received prophylactic therapy.

Our results might be limited by misclassification of the plaster cast date i.e. unintendedly misclassifying a case or a control as having [or not having] a lower-leg cast within 3-months. Therefore, to verify our results, we performed a sensitivity analysis which showed that mainly controls had been misclassified (they did have a lower-leg cast, but not within 3-months). This refinement led to a 4.5-fold increased risk for VT. In addition, controls were sampled at the end of follow up and not matched on follow-up duration with cases. This approach may have led to an underestimation of the actual risk if controls, that were lost to follow up, for example died because of a lung embolism due to plaster cast immobilization although this is unlikely. Finally, it is unknown whether all patients received thromboprophylaxis during cast-immobilization. However, according to a recent survey study conducted in the Netherlands, thromboprophylactic therapy was always prescribed for patients with plaster cast immobilization of the lower-leg in 79% and 63% of patients by trauma surgeons and orthopaedic surgeons respectively, and if any risk factors were present (such as VT in patients history) in an additional 15% and 33% of patients, by trauma and orthopaedic surgeons respectively.[14] Therefore it is likely that almost all patients received thromboprophylactic therapy during immobilization.

Recently, van Adrichem et al reported that patients with cast immobilization of the lower-leg have a 32-fold risk for developing a first VT within 3 months.[1] The lower risk that we found (between 2.4 and 4.5-fold increased) for recurrent VT after plaster cast application might partly be explained by thromboprophylactic therapy, as patients with a history of VT have a high risk of developing a recurrence and therefore clinicians may be more willing to prescribe thromboprophylactic therapy than for a first event. Another explanation for this lower risk is the high baseline risk for recurrent VT as compared with the baseline risk for a first VT, also known as the "recurrence paradox".[15] Suppose that in absolute terms, the baseline risk for a first VT is 1 per 1000 individuals per year, thus 0.25 per 3-months[16].

Considering a relative risk of 32, this leads to an absolute risk for VT following lower-leg cast of about 8 per 1000 individuals within 3-months (thus 7.75 extra cases). Now, consider a population at risk for recurrent VT at an incidence rate of 30 per 1000 individuals per years, thus 7.5 per 3-months)[17]. The extra VT risk due to lower-leg cast immobilization would lead to 7.5 plus 7.75=15.25 cases per 1000 individuals within 3-month, thus a relative risk of 2.1 (15.25 divided by 7.5). Consequently, the relative risk for recurrence is lower compared with the risk of a first VT after cast immobilization.

For patients with a history of VT, most guidelines advise to asses VT and bleeding risk in circumstances of an increased risk (e.g. surgery, hospitalization etc.). Patients with a personal history of VT are considered to be at high risk for the development of a recurrence during these situations. Therefore all guidelines advise to give thromboprophylactic therapy in these situations, for example during cast immobilization.[18, 19] In our study, patients with a history of VT and casting of the lower-leg had a 4.5-fold increased risk, corresponding cumulative incidence at 3 months of 3.2%. Based on this high risk we carefully suggest that in patients with a history of VT and subsequent lower-leg cast immobilization, a prophylactic dosage might not be sufficient and therapeutic dosages should be considered on an individual patient basis. However, with the risk of bias and unknown information on prophylactic therapy in our study taken into account, our advice should be interpreted with caution. Also, an individual's bleeding risk has to be determined before such interventions can be applied. At any rate, antithrombotic medication is strongly advised for patients with cast immobilization of the lower-leg and a history of VT.

REFERENCE LIST

1. van Adrichem RA, Debeij J, Nelissen RG, Schipper IB, Rosendaal FR, Cannegieter SC. Below-knee cast immobilization and the risk of venous thrombosis: results from a large population-based case-control study. Journal of thrombosis and haemostasis 2014; 12: 1461-9.
2. Ettema HB, Kollen BJ, Verheyen CC, Buller HR. Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. Journal of thrombosis and haemostasis 2008; 6: 1093-8. 10.1111
3. Kock HJ, Schmit-Neuerburg KP, Hanke J, Rudofsky G, Hirche H. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. Lancet. 1995; 346: 459-61.
4. 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.
5. Lapidus LJ, Ponzer S, Elvin A, Levander C, Larfars G, Rosfors S, de Bri E. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. Acta orthopaedica. 2007; 78: 528-35.
6. Lapidus LJ, Rosfors S, Ponzer S, Levander C, Elvin A, Larfars G, de Bri E. Prolonged thromboprophylaxis with dalteparin after surgical treatment of achilles tendon rupture: a randomized, placebo-controlled study. Journal of orthopaedic trauma. 2007; 21: 52-7.
7. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. The New England journal of medicine. 2002; 347: 726-30.
8. van Adrichem RA, Németh B, Algra A, le Cessie S, Rosendaal FR, Schipper IB, Nelissen R, Cannegieter SC, Pot K, Group P-C. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. The New England journal of medicine. 2017; 376: 515-25.
9. Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. Lancet. 2010; 376: 2032-9. S0140-6736(10)60962-2
10. Timp JF, Lijfering WM, Flinterman LE, van H, V, Le CS, Rosendaal FR, Cannegieter SC. Predictive value of factor VIII levels for recurrent venous thrombosis: results from the MEGA follow-up study. Journal of thrombosis and haemostasis. 2015. 10.1111/jth.13113
11. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005; 293: 715-22.
12. Timp JF, Lijfering WM, Flinterman LE, van Hylckama Vlieg A, le Cessie S, Rosendaal FR, Cannegieter SC. Predictive value of factor VIII levels for recurrent venous thrombosis: results from the MEGA follow-up study. Journal of thrombosis and haemostasis 2015; 13: 1823-32.
13. SFK. Foundation for Pharmaceutical Statistics. 2015. https://www.sfk.nl/english
14. van Adrichem RA, van Oosten JP, Cannegieter SC, Schipper IB, Nelissen RG. Thromboprophylaxis for lower leg cast immobilisation and knee arthroscopy: a survey study. The Netherlands journal of medicine. 2015; 73: 23-9.
15. Cannegieter SC, Vlieg AH. Venous thrombosis: understanding the paradoxes of recurrence. Journal of Thrombosis and Haemostasis. 2013; 11: 161-9.
16. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. Journal of thrombosis and haemostasis 2007; 5: 692-9.

17. Christiansen SC, Lijfering WM, Helmerhorst FM, Rosendaal FR, Cannegieter SC. Sex difference in risk of recurrent venous thrombosis and the risk profile for a second event. Journal of thrombosis and haemostasis 2010; 8: 2159-68.
18. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ, American College of Chest Physicians Antithrombotic T, Prevention of Thrombosis P. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141: 7S-47S.
19. Nice Guidelines. Venous thromboembolism in adults admitted to hospital: reducing the risk. (NICE guideline CG92). 2010. https://www.nice.org.uk/guidance/cg92

5

Risk and risk factors associated with recurrent venous thromboembolism following surgery in patients with history of venous thromboembolism

Németh B, Lijfering WM, Nelissen RGHH, Schipper IB,
Rosendaal FR, le Cessie S, Cannegieter SC.

JAMA Netw Open. 2019 May 3;2(5):e193690.

ABSTRACT

Importance The size of the risk of recurrent venous thromboembolism (VTE) after surgery in patients with a history of VTE is not well known.

Objectives To estimate the risk of and to identify the factors associated with recurrent VTE in patients undergoing surgery who have a history of VTE.

Design, setting, and participants This population-based, follow-up cohort study includes patients with VTE who participated in the Multiple Environment and Genetic Assessment (MEGA) study. Original data were collected from March 1999 to April 2010. Data analysis began in June 1999 and ended in April 2010.

Exposures Surgery following a first VTE.

Main outcomes and measurements Kaplan-Meier analyses were used to estimate cumulative incidences of recurrent VTE. Cox regression with a time-dependent covariate (surgery) was used to calculate the hazard ratio (HR) for developing recurrent VTE after surgery compared with no surgery.

Results Overall, 3741 patients (mean [SD] age, 48.4 [12.8] years; 2020 [54.0%] women) with a history of VTE were included in the analysis, amounting to 18 899 person-years, with a median (interquartile range) follow-up of 5.7 (3.0-7.2) years. Of the 3741 patients, 580 (15.5%) underwent surgery and 601 (16.1%) developed a recurrent thrombotic event. The 1-month cumulative incidence of recurrent VTE for all surgery types was 2.1% (95%CI, 1.2%-3.6%), which increased to 3.3% (95% CI, 2.1%-5.1%) at 3 months and 4.6%(95%CI, 3.1%-6.6%) at 6 months. At 6 months, risk of recurrent VTE ranged from 2.3%to 9.3%, depending on surgery type. In addition to surgery type, factor V Leiden mutation (HR, 3.4; 95%CI, 1.6-7.4) and male sex (HR, 2.7; 95%CI, 1.3-5.8) were associated with increased risk of recurrent VTE.

Conclusions and relevance Surgery was associated with an increased risk of recurrent VTE in patients with a history of VTE; risk remained high for up to 6 months after the procedure. This study suggests that high-risk individuals may be identified based on surgery type, sex, and the presence of factor V Leiden mutation. These findings stress the need for revision of the current thromboprophylactic approach to prevent recurrence in these patients.

INTRODUCTION

Surgery is a major risk factor for the development of venous thromboembolism (VTE), encompassing both deep vein thrombosis and pulmonary embolism.[1] For this reason, routine thromboprophylaxis therapy is strongly recommended for high-risk individuals undergoing general surgery and for all patients who undergo major orthopaedic surgery, unless contraindicated.[1,2] Although the risk of developing a first VTE after surgery has been studied extensively, there are few studies that evaluate the size of the recurrence risk in patients with a history of VTE who undergo surgery. Several studies[3-5] showed an increased risk in patients with a history of VTE who underwent surgery compared with individuals without a history of VTE. Yet, to our knowledge, only a single study[6] addressed whether patients with a previous VTE are at increased risk after surgery compared with patients with VTE who did not undergo surgery. This is a more clinically relevant comparison because, if this is the case, additional thromboprophylactic measures are asked for. This study found a 3-fold increased risk of developing recurrence up to 92 days postdismissal.[6] However, the authors were not able to distinguish between various types of surgery, and more importantly, absolute risks could not be determined.

It is advised that clinicians assess an individual's thrombosis risk by using risk scores, such as the Caprini score,[4-7] to evaluate risk factors of VTE in all patients undergoing surgery. [1,8,9] Individuals with a history of VTE are almost always classified as being at moderate to high risk. Consequently, thromboprophylactic therapy is indicated for most of these patients (unless there is also a high risk of major bleeding) during hospitalization following surgery.[1,9] However, it is not clear if this treatment sufficiently lowers the risk among this high-risk group. Furthermore, risks may differ between individuals, depending on surgery type and other clinical or laboratory risk factors. For example, no differentiation is currently made with respect to the dosage or duration of thromboprophylaxis in patients at high risk.

Because these data are essential to guide physicians in thromboprophylaxis management following surgery, we set out to determine the size of the risk of recurrent VTE in patients with a history of VTE who undergo surgery. In addition, we identified factors associated with recurrence in these patients.

METHODS

Study design

For this study, data from the Multiple Environment and Genetic Assessment (MEGA) follow-up study were used, details of which have been published previously.[10-12] Briefly, the MEGA study is a large population-based case-control study of the etiology of VTE and includes 4956 individuals with VTE and 6297 control participants.[13] Unselected patients aged 18 to 70 years with a confirmed pulmonary embolism or deep vein thrombosis were recruited from 6 anticoagulation clinics in the Netherlands between March 1999 and August 2004. The trial protocol is available in *Supplement 1*. Subsequently, all patients with a first VTE who provided written informed consent to participate in the MEGA follow-up study were evaluated for recurrent VTE until April 2010. Initial information on the recurrent event was collected by means of a short questionnaire or telephone interview. Further detailed information about the recurrent event was retrieved from questionnaires, anticoagulation clinics, treating physicians, or cause of death statistics (vital status from the central Dutch Population Register).[12] Recurrent events were adjudicated as certain or uncertain recurrent events[10] to distinguish between genuinely new events and extensions of the first event. The decision rule for event classification is available in *eMethods* in *Supplement 2*. For the current analysis, only certain recurrent events were used to minimize misclassification. Patients with an uncertain event had a similar age and sex distribution (mean [SD] age, 50.1 [13.6] years; 107 (54.0%) women) compared with the study population.

All participants provided written informed consent. This study was approved by the Medical Ethical Committee of the Leiden University Medical Center in Leiden, the Netherlands. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Data collection and surgery exposure

After inclusion in the study, patients completed a questionnaire on putative risk factors of recurrent VTE, including age, sex, weight and height, and comorbidities. In 2011, participants of the MEGA study were linked to the Dutch Hospital Data registry.[14] This registry provides nationwide electronic coverage of data on all hospital admissions since 1995. For each admission, information on dates of admission and discharge, diagnoses, and surgical procedures is available (coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification). A previous study comparing a random sample of hospital admissions in the Dutch Hospital Data registry with information from hospital records[15] showed that 99% of the personal, admission, and discharge data and 84% of the principal diagnosis data were correctly encoded. Individuals with information

leading to more than 1 person (eg, twins) or to no one at all (eg, immigrants or visitors) were excluded. Of the 4956 MEGA participants with VTE, 4721 patients (95.3%) could be uniquely linked to the registry. We collected information on all surgical procedures and operations for which patients were hospitalized for 1 or more days. We defined major surgical procedures (in terms of VTE risk) as those with an estimated duration longer than 30 minutes and minor surgical procedures as those with an estimated duration shorter than 30 minutes. The association of cancer-related surgery with recurrence risk was also studied.

Statistical analysis

Patient demographic characteristics were listed as means with standard deviations or numbers with percentages, depending on data type. Since we were interested in the risk of recurrent VTE after anticoagulation therapy for the first VTE had been stopped, follow-up time was calculated from the stop date of anticoagulation treatment after a patient's first VTE until the end of study, death, recurrent event, or loss to follow-up, whichever occurred first. The window of exposure to surgical procedures during which an individual was at risk of VTE was defined as 3 months from the surgery date and later. The total follow-up time in which patients were not exposed to surgery was calculated as the total follow-up time minus surgery exposure time (*Figure 1*). Because it is unclear for how long the risk of recurrent VTE is increased after surgery, we varied the exposure time and considered 1-month, 3-month, 6-month, and 1-year windows as risk periods. For all analyses, we included only the first surgery exposure during follow-up, and patients were censored when they underwent a second surgery. As a sensitivity analysis, we did not censor these patients and also considered a second surgery as an exposure (*eTable 1 in Supplement 2*). Thus, patients could be exposed to multiple periods of increased risk (eg, first, second, and third surgery) during follow-up.

For the main outcome, we calculated the cumulative incidence of recurrent VTE over time for exposure to several types of surgery using life-table techniques (Kaplan-Meier). To compare with the cumulative incidence without surgery (ie, to show the excess recurrence risk after surgery), we estimated the expected cumulative recurrence risk for each patient who underwent surgery in the same period in the absence of surgery. These expected recurrence risks were obtained from a Kaplan-Meier curve of the total population, with follow-up time censored at time of surgery. A sensitivity analysis was performed with a landmark analysis for which we used the median time to surgery of 713 days. The risk of VTE in patients unexposed to surgery was calculated from this time point onwards.

Cox regression analysis with a time-dependent covariate (exposure time after surgery) was used to calculate hazard ratios (HRs) with 95%CIs for developing a recurrent VTE, adjusted for age and sex. In a restriction analysis, we excluded patients with a cancer diagnosis in

the 5 years before their first VTE. Likewise, patients who developed cancer during follow-up were excluded in a second restriction analysis. An additional Cox regression analysis was performed to identify factors associated with recurrence, in which we adjusted for time between VTE and surgery (ie, follow-up began on day of surgery). The association with recurrent VTE was assessed for 10 potential or established prognostic determinants of recurrent VTE, including increasing age, male sex, non-O blood type, factor V Leiden mutation, prothrombin 20210A mutation, pulmonary embolism or deep vein thrombosis as a first event, obesity, self-reported comorbidity,[16,17] provoked first venous thrombosis, and time elapsed since first VTE. We calculated HRs with 95%CIs for these factors and cumulative incidences for recurrence (Kaplan-Meier). There were no missing data for the main analysis; for the risk factor analysis, a complete case analysis was performed because some comorbidities were missing. All analyses were performed using SPSS software version 23.0 (IBM) and Stata Package SE version 14.0 (StataCorp).

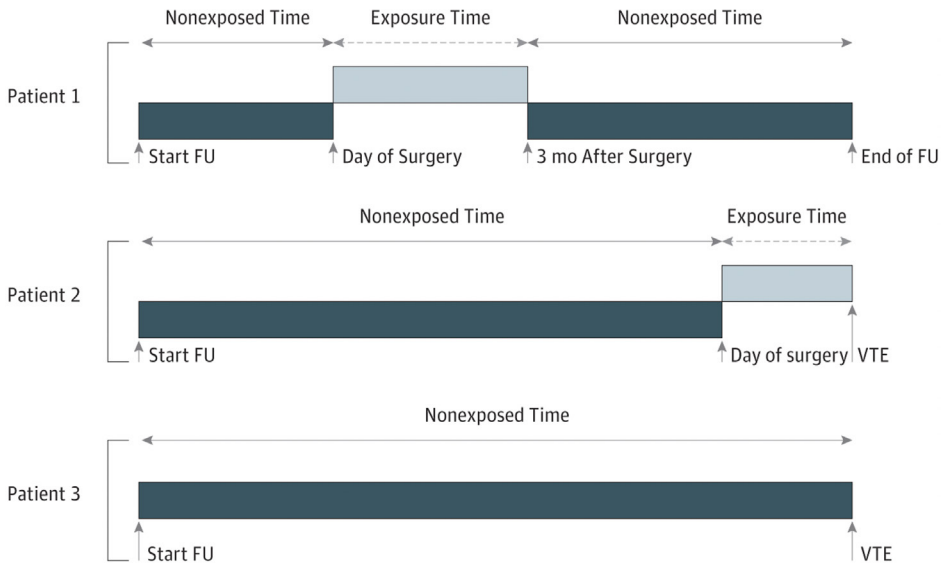


Figure 1: Visualization of Time-Dependent Analysis.
Exposure time denotes the time window of surgery exposure during which each individual was at risk of venous thromboembolism (VTE; 1 month, 3 months, 6 months, or 1 year). Three hypothetical patient pathways are presented. Patient 1 represents an individual who underwent surgery halfway through follow-up (FU) with no thrombotic event during exposure time. Patient 2 represents an individual who developed a thrombotic event within the surgery exposure time, and patient 3 represents an individual who had no surgery during FU but developed VTE.

RESULTS

Study population

Of the 4721 patients who could be linked to the Dutch Hospital Data registry, 371 did not consent to participate in the follow-up, resulting in 4350 total participants. In addition, 609 patients were excluded because they continued anticoagulation therapy after their first VTE throughout the follow-up period (*Figure 2*). Therefore, in total, 3741 patients were evaluated for a total of 18 899 person-years (median [IQR] follow-up, 5.7 [3.0-7.2] years). The mean (SD) age at start of follow-up (after first VTE) was 48.4 (12.8) years, and 2020 (54.0%) were women (*Table 1*). Overall, 601 patients (16.1%) developed a recurrent event. Most patients (2748 [82.9%]) had no major illnesses in their medical history at time of first VTE.

Surgical procedures

In total, 580 patients (15.5%) had undergone 1 or more operations (808 total operations during the complete follow-up period) (*eTable 2* in *Supplement 2*). Overall, 578 major operations and 230 minor operations were performed, of which 275 were orthopaedic and 533 non orthopaedic. A detailed overview of all surgical procedures (including type of surgery) that were included in the analysis is given in *eTable 3* in *Supplement 2*. Median (IQR) time to first surgery was 713 (252-1334) days.

VT recurrence risk

Of all 580 patients who underwent a surgical procedure during follow-up, 13 patients developed a recurrent event within 1 month, 21 patients within 3 months, 30 patients within 6 months, and 38 patients within 12 months after surgery (ie, 38 events total). The cumulative incidence of recurrent VTE at 1 month was 2.1% (95%CI, 1.2%-3.6%), which increased to 3.3% (95%CI, 2.1%-5.1%) at 3 months, 4.6% (95%CI, 3.1%-6.6%) at 6 months, and 6.3% (95%CI, 4.6%-8.7%) at 1 year (*Figure 3* and *eTable 4* in *Supplement 2*). At 6 months, risk ranged from 2.3% to 9.3%, depending on surgery type.

Table 1: General characteristics of patients included in the MEGA follow-up study.

General characteristics	
Study population, n	*3741*
Age, mean (SD)	48.4 (12.8)
Women, n (%)	2020, (54.0)
BMI, kg/m^2, mean (SD)	26.8 (14.0)*
Comorbidity	
No major illness†, n (%)	2748 (82.9)
Any major illness, n (%)	569 (17.1)
COPD	204 (6.2)
Liver disease	18 (0.5)
Kidney disease	35 (1.1)
Rheumatoid arthritis	111 (3.4)
Multiple sclerosis	16 (0.5)
Heart failure	46 (1.4)
Hemorrhagic stroke	23 (0.7)
Arterial thrombosis	197 (5.3)
Myocardial Infarction	94 (2.9)
Angina	47 (1.4)
Ischemic stroke	9 (0.3)
Transient ischemic attack	38 (1.2)
Peripheral vascular disease	41 (1.2)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease.

*Calculated as weight in kilograms divided by height in meters squared. Data missing for 326 patients.

† Percentages of total, any major illness missing for 424 patients.

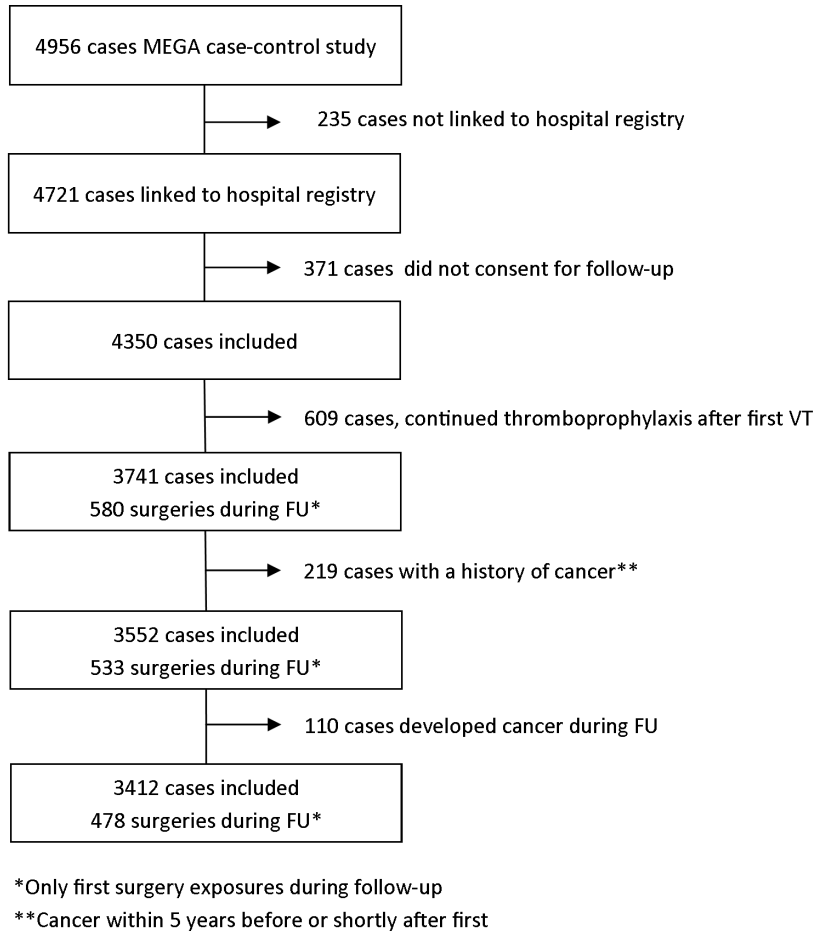


Figure 2: Study flowchart
FU denotes follow-up, VT denotes Venous Thrombosis

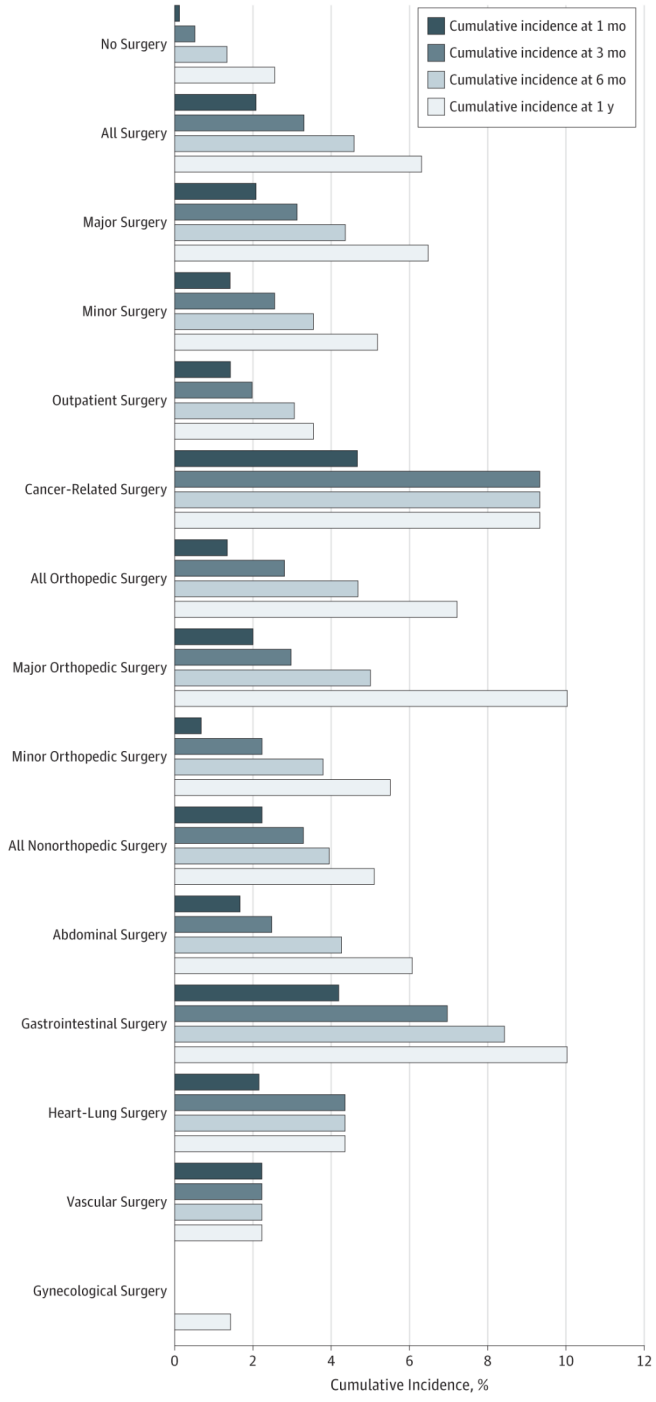


Figure 3: Absolute risk of recurrent venous thromboembolism after surgery in patients with a history of VTE.

The cumulative incidence of recurrence in patients unexposed to surgery was 0.8% (95%CI, 0.6%-1.1%) at 3 months. The landmark analysis yielded similar results. Recurrence risk was highest within the first month of surgery (HR, 6.8; 95%CI, 3.9-11.9) and remained increased up to approximately 6 months after surgery (HR, 1.7; 95%CI, 0.8-3.7) (*Table 2; eTable 5* in *Supplement 2*). Vascular and outpatient surgical procedures were associated with the lowest recurrence risk at 6 months (vascular: HR, 2.3; 95%CI, 0.6-8.8; outpatient: HR, 3.1; 95%CI, 1.4-6.7). Patients who had undergone gastrointestinal procedures (eg, esophagus, stomach, bowel, or rectal operations) had a high risk of recurrent VTE at 6 months (HR, 8.4; 95%CI, 4.0-17.8) (*Figure 2*). Non orthopaedic surgical procedures were associated with a higher risk of recurrence at 1 month (HR, 8.2; 95% CI, 4.4-15.3) compared with orthopaedic surgery (HR, 4.0; 95% CI, 1.3-12.4) (*Table 2*). Furthermore, patients who had undergone major surgery had a higher risk of recurrent VTE than those who had undergone minor surgery.

Cancer-related surgery

During follow-up, 110 patients developed cancer (*Figure 2*), of whom 55 underwent surgical procedures within our period of interest (44 first operations during follow-up and 11 second or third operations). The most commonly performed operations were related to breast cancer (n = 12), colon cancer (n = 7), or rectal cancer (n = 8). The absolute recurrence risk at 6 months after cancer-related surgery was 9.3% (95%CI, 3.6%-22.9%) (*Figure 3*). The risk of recurrent VTE in all patients who underwent surgery did not change when we excluded patients with a cancer diagnosis within 5 years before (or within 6 months following) their first VTE. Subsequent exclusion of patients who developed cancer during follow-up resulted in somewhat lower risks, most strongly pronounced in patients who underwent non orthopaedic surgery (patients who underwent non orthopaedic surgery: risk at 6 months, 4.0; 95%CI, 2.5-6.5; after exclusion of patients who developed cancer during follow-up: risk at 6 months, 3.2; 95%CI, 1.7 to 5.9; difference, −0.8%) (*eTable 6* in *Supplement 2*).

Predictors associated with recurrence

Factors associated with increased risk of VTE recurrence in patients who underwent surgery included factor V Leiden mutation (HR, 3.4; 95%CI, 1.6-7.4) and male sex (HR, 2.7; 95%CI, 1.3-5.8) (*Table 3*). Men with factor V Leiden who underwent surgery had an 8.5-fold increased risk of VTE recurrence compared with women without factor V Leiden who underwent surgery (cumulative incidence at 6 months: 18.0%; 95%CI, 9.0%-34.1%). For those with a first unprovoked VTE, recurrence risk was 6.7% (95%CI, 3.6%-12.6%), while patients with a first provoked VTE also had a high risk of recurrence (HR, 5.1; 95%CI, 3.4-7.7) at 6 months. For patients who underwent surgery 2 or more years after their first VTE, absolute recurrence risks were slightly lower in most risk groups (*Table 3*).

Table 2: Association of surgery with recurrence risk in patients with a history of VTE per time-window.

VTE recurrence risk ¶	no. operations	Person years	no. VTEs	0 to 1-month HR_{adj}± (95%CI)	1 to 3-months HR_{adj}± (95%CI)	3 to 6-months HR_{adj}± (95%CI)	6 to 12-months HR_{adj}± (95%CI)
Patients without surgery	0	18636	571	-	-	-	-
Surgery	580	263	30	6.8 (3.9 to 11.9)	2.5 (1.2 to 5.1)	1.7 (0.8 to 3.7)	1.3 (0.7 to 2.6)
Restriction analyses 1†	533	240	29	6.5 (3.5 to 11.8)	2.8 (1.4 to 5.6)	1.9 (0.9 to 4.1)	1.5 (0.8 to 2.9)
Restriction analyses 2†	478	219	24	5.8 (3.0 to 11.2)	1.9 (0.8 to 4.5)	2.1 (1.0 to 4.4)	1.6 (0.8 to 3.2)
Orthopaedic surgery	219	101	11	4.0 (1.3 to 12.4)	3.3 (1.2 to 8.8)	2.7 (1.0 to 7.3)	1.6 (0.6 to 4.3)
Restriction analyses 1†	207	95	11	4.2 (1.4 to 13.2)	3.4 (1.3 to 9.2)	2.9 (1.1 to 7.7)	1.7 (0.6 to 4.6)
Restriction analyses 2‡	200	92	11	4.3 (1.4 to 13.4)	3.5 (1.3 to 9.3)	2.9 (1.1 to 7.8)	1.8 (0.7 to 4.7)
Non-orthopaedic surgery	403	181	19	8.2 (4.4 to 15.3)	1.9 (0.7 to 5.1)	1.9 (0.8 to 4.7)	1.0 (0.4 to 2.6)
Restriction analyses 1†	368	165	18	7.4 (3.7 to 14.9)	2.2 (0.8 to 5.8)	2.2 (0.9 to 5.3)	1.1 (0.4 to 2.9)
Restriction analyses 2‡	317	145	13	6.4 (2.8 to 14.3)	0.6 (0.1 to 4.3)	2.5 (1.0 to 5.9)	1.2 (0.5 to 3.3)

Person years and no. of VTEs only shown for the complete period of increased risk (0-6 months). Note that numbers (person years, number of VTEs and number of operations) do not sum up to the total as the first-surgery can be all surgery types depending upon the risk group of interest.
* Separate time windows 0 to 1-month, 1 to 3-months, 3 to 6-months and 6 to 12-months, thus excluding previous risk periods.

¶ Only for first surgery exposure during follow-up, start follow-up is stop-date of anticoagulant therapy after first VTE.
± Hazard Ratio (HR_{adj}) adjusted for age & sex.
† Exclusion of patients with cancer diagnoses within 5 years before and 6 months after first VTE.
‡ Exclusion of patients with cancer diagnoses within 5 years before and 6 months after first VTE and additional exclusion of patients who developed cancer during follow-up.

Table 3: Factors associated with recurrent VTE parallel to surgery.

Risk factor	Person Years	no. of VTEs	HR_{adj}¶ (95%CI) 0-6 months *In all surgical patients*	CI at-6 months (95%CI) *In all surgical patients*	CI at 6-months (95%CI) *In surgical patients with first VTE >2 years before surgery*
Sex					
Women	153	10	1 (ref)	3.1 (1.7 to 5.7)	1.8 (0.6 to 5.5)
Men	109	20	2.7 (1.3 to 5.8)	8.5 (5.6 to 12.8)	6.3 (2.4 to 12.7)
Age	na	na	1.0 (1.0 to 1.1)	na	na
ABO blood-type					
O	75	7	1 (ref)	4.3 (2.1 to 8.9)	1.3 (0.2 to 8.5)
XO	127	16	1.3 (0.5 to 3.2)	6.0 (3.7 to 9.5)	6.0 (3.1 to 11.7)
Non-O	39	5	1.3 (0.4 to 4.3)	6.3 (2.7 to 14.5)	Not estimable*
Factor V Leiden					
Absent	207	18	1 (ref)	4.2 (2.6 to 6.5)	2.3 (1.0 to 5.5)
Present	35	10	3.4 (1.6 to 7.4)	12.8 (7.1 to 22.5)	10.7 (4.2 to 26.0)

Table 3: Continued.

Risk factor	Person Years	no. of VTEs	HR_{adj}¶ (95%CI) 0-6 months *In all surgical patients*	CI at-6 months (95%CI) *In all surgical patients*	CI at 6-months (95%CI) *In surgical patients with first VTE >2 years before surgery*
Prothrombin mutation					
Absent	231	27	1 (ref)	5.5 (3.8 to 7.9)	3.7 (2.0 to 7.0)
Present	10	1	0.8 (0.2 to 4.5)	5.0 (0.7 to 30.5)	Not estimable*
First VTE					
DVT	183	20	1 (ref)	5.2 (3.4 to 7.9)	2.6 (1.1 to 6.2)
PE (±DVT)	79	10	1.2 (0.5 to 2.5)	5.9 (3.2 to 10.7)	5.9 (2.5 to 13.5)
Obese					
No	88	9	1 (ref)	5.0 (2.6 to 9.4)	2.2 (0.6 to 8.5)
Yes (BMI>25)	174	21	1.2 (0.5 to 2.5)	5.6 (3.4 to 8.5)	4.4 (2.2 to 8.6)
Comorbidity					
No	184	20	1 (ref)	5.1 (3.4 to 7.9)	3.1 (1.4 to 6.7)
Yes †	46	3	0.6 (0.2 to 2.1)	3.1 (1.0 to 9.3)	2.2 (0.3 to 14.5)
First VTE provoked					
No	62	9	1 (ref)	6.7 (3.6 to 12.6)	4.2 (1.4 to 12.4)
Yes**	195	21	0.7 (0.3 to 1.6)	5.1 (3.4 to 7.7)	3.6 (1.7 to 7.3)
Risk score: Sex and/or Factor V Leiden‡					
0 (Female and no FVL)	124	6	1(ref)	2.3 (1.1 to 5.1)	1.5 (0.4 to 5.8)
1 (Female and FVL)	18	3	3.5 (0.9 to 14.2)	7.6 (2.5 to 21.9)	5.3 (0.8 to 31.9)
2 (Male and no FVL)	83	12	2.8 (1.1 to 7.6)	6.8 (3.9 to 11.7)	3.7 (1.2 to 10.9)
3 (Male and FVL)	17	7	8.5 (2.8 to 25.2)	18.0 (9.0 to 34.1)	15.8 (5.4 to 41.4)
Time to surgery					
Within 1 year	84	12	1(ref)	6.8 (3.9 to 11.7)	Not applicable
1-2 years	51	8	1.1 (0.5 to 2.7)	7.1 (3.6 13.8)	Not applicable
>2 years	127	10	0.6 (0.2 to 1.3)	3.7 (2.0 to 6.8)	3.7 (2.0 to 6.8)

Abbreviations: DVT, deep vein thrombosis; FVL, factor V Leiden; HR, Hazard Ratio; 95%CI, 95% confidence interval; CI at 6- months, cumulative incidence which was calculated from the start of surgery onwards (for 6 months in total).

¶ Adjusted for time to surgery.

* Not estimable because no events occurred within this subgroup.

† Comorbidity denotes presence of any major illness as listed in *Table 1*.

** Provoked first VTE, defined as provoked by either cancer, surgery, immobilization, travel, pregnancy or hormone use.

‡ Hazard ratios shown for patients of whom information on factor V Leiden mutation was available.

DISCUSSION

Principal findings

This study demonstrated that patients with VTE who underwent subsequent surgery had a high risk of developing recurrent VTE up to 6 months after surgery, with an overall risk of 4.6% (range, 2.3%-9.3%, depending on surgery type). Cancer-related surgery, major orthopaedic, gastrointestinal, and heart-lung procedures were associated with the highest risks of recurrence, while the risks of outpatient and minor surgery were increased to a lesser extent. In addition, we showed that men and patients with factor V Leiden had a higher risk of developing recurrent VTE.

Comparison with previous studies

In 2015, a population-based case-cohort study[6] showed that patients who underwent surgery for which they were also hospitalized after their first VTE had a 6-fold increased risk of developing in-hospital recurrent VTE compared with patients with a history of VTE without surgery (HR, 5.9; 95%CI, 3.3-10.4).[6] This relative risk declined to 1.9 (95%CI, 1.1-3.2) within 3 months. While our results are generally in line with this study, we were able to estimate risks for different types of surgery, which showed substantial variation. In 2010, Bahl et al[4] performed a large cohort study in which 8216 patients who underwent general, vascular, and urologic surgery (excluding outpatient surgery) were retrospectively analyzed for the occurrence of VTE. In that study, 285 patients with a history of VTE (4.2%) developed recurrence within 30 days of surgery.[4] Our study showed similar rates for gastrointestinal and cancer-related surgery, but the 30-day risk of recurrence in all surgical patients was lower, at 2.1%. The study by Bahl et al collected data from medical records, which could have led to an underestimation of the number of patients with a history of VTE, hence leading to a higher absolute risk. It is well known that these registry studies have implicit drawbacks, such as misclassification, which tend to underestimate absolute risks.

Clinical implications and future research perspective

To our knowledge, this is the first study that gives detailed information on absolute recurrence risks of VTE following various types of surgery in combination with patient characteristics. Our results indicate that there is much heterogeneity in risk dependent on these factors. Given that VTE is the most preventable death in hospitals, and 60% of VTE cases occur during or following hospitalization,[18] it is important to acknowledge the high recurrence risks associated with surgery when a patient has a history of VTE.

Contemporary guidelines for surgical patients advise clinicians to provide thromboprophylaxis therapy after most procedures, although the treatment duration is debated. Frequently, a distinction is made between high- and low-risk surgical patients,

based on the procedure itself and a patient's comorbidities.[1,9] A history of VTE will almost always warrant thromboprophylactic therapy after any surgical intervention. For instance, according to the American College of Chest Physicians guideline on thromboprophylaxis in non orthopaedic surgical patients, virtually all patients with a history of VTE who undergo surgery are to be treated with thromboprophylaxis unless contraindicated (eg, high bleeding risk). Only young patients with a history of VTE who undergo minor surgery can be withheld from prophylactic therapy.[1] Similarly, in the UK guidelines on prevention of VTE (National Institute for Health and Care Excellence), it is advised to offer VTE prophylaxis for 5 to 7 days for all patients undergoing gastrointestinal, gynecological, thoracic, or urologic surgery who are at increased risk (which includes patients with a history of VTE).[9] Despite these recommendations, 4.6% of patients undergoing surgery developed a recurrent event within 6 months in our study. It is therefore highly doubtful that the current practice is sufficiently effective for recurrence prevention. Interestingly, the 1-month risk following non orthopaedic surgery was higher than following orthopaedic surgery (2.3% vs 1.4%), which may reflect different thromboprophylaxis strategies between these groups (ie, a more aggressive and longer duration of prophylaxis following orthopaedic surgery). [1,2] However, risk differences between these groups evened out after 6 months, since the risk in the orthopaedic group remained high. Our finding that the recurrence risk remained increased up to 6 months after the surgical intervention supports a policy with extended duration of thromboprophylactic therapy, not restricted to in-hospital prophylaxis. This should be tested in further trials. Furthermore, our study indicates that some patients are at additional high risk; for instance, the size of the risk is associated with the type of surgery as well as on patient characteristics, such as male sex and factor V Leiden mutation. Moreover, 7 of 39 men with factor V Leiden mutation (18%) developed recurrence within 6 months after surgery. Furthermore, we showed that patients who underwent surgery more than 2 years after their first VTE had a slightly lower (but still increased) risk of recurrence. Hence, high-risk patients—those who undergo major surgical procedures or those who have multiple risk factors and are undergoing low-risk procedures—may need prolonged anticoagulation therapy (or a higher dosage) following surgery to prevent recurrence. However, such advice should be carefully weighed against individual bleeding risks and warrants additional studies.

Strengths and limitations

The main strengths of our study are the time-dependent analysis in a large unselected sample of patients who underwent surgery (largest to date, to our knowledge), long follow-up period, and the objective classification of surgery. By handling surgery as a time-dependent covariate in our model, we could adjust for time to surgery from start of follow-up. In addition, patients contributed to both exposure and non exposure time

during follow-up, so all patients also functioned as their own control. Furthermore, the large sample size led to precise estimations of the actual recurrence risk of VTE, and the objective classification of surgery led to the elimination of recall bias.

Our study had limitations. One limitation of our study is that we did not have information on thromboprophylaxis therapy following the surgical intervention. However, a nationwide survey study among all surgical departments in the Netherlands[19] performed within the same time frame as our study showed that adherence to antithrombotic guidelines in surgical patients was 92%. (Dutch guidelines were comparable with the American College of Chest Physicians guidelines at the time of study.) Because all guidelines advise clinicians to provide thromboprophylaxis during hospitalization to high-risk surgical patients (ie, patients with a history of VTE), it is highly unlikely that patients did not receive thromboprophylaxis after surgery. Furthermore, according to the survey, 76% of all surgeons took additional antithrombotic measures into consideration (such as double-dose prophylactic therapy) when patients had obesity, a personal history of VTE, or older age. Still, some patients undergoing minor surgery might have been withheld thromboprophylaxis or could have decided not to use it. Although we are confident that thromboprophylaxis was applied according to the guidelines for most, it might be worthwhile to consider 2 extreme situations to assess the effect of complete use or complete nonuse of prophylaxis on our results. On the one hand, suppose that no single patient in our study who underwent surgery received thromboprophylactic therapy. Then, assuming a risk reduction of 50% by using thromboprophylaxis, the cumulative incidence at 6 months would still be high even if patients had received thromboprophylaxis, ie, 2.3% following any surgery (4.6% * 0.5; ie, half the 6-month incidence rate we found). On the other hand, assuming that doctors had fully complied with antithrombotic guidelines, which is most likely, the cumulative incidence following any surgery with thromboprophylaxis is 4.6% (as presented in this study), and it would have been 9.2% (i.e., 4.6% * 2) if no patients had received thromboprophylaxis. Therefore, it is clear that, at any rate of prophylaxis, patients with a history of VTE who undergo surgery have a high risk of developing a new thrombotic event, ie, within a range of 2.3% to 9.2%, depending on the type of surgery. This suggests that current thromboprophylactic measures for patients with a history of VTE are not sufficiently effective.

As a possible second limitation, we only adjusted for age and sex in the Cox regression. Of note, our primary goal was to show the absolute risk of VTE following surgery and not to show whether surgery is a causal (provoking) risk factor. The former aim has clinical meaning, whereas the causal role of surgery in VTE has been known for decades. Third, patients 70 years and younger were included in the MEGA study; thus, the generalizability of our study is limited to individuals in that age range. However, it is not to be expected

that the conclusions of this study would be different for older patients. Also, the highest-risk patients (ie, those receiving long-term anticoagulation therapy following their first VTE) were excluded from the analyses.

Conclusion

This study found that patients with a history of VTE who underwent surgery had a high recurrence risk of VTE, which remained increased up to 6 months after surgery. High-risk individuals may be identified based on the type of surgery and the presence of additional factors. Our results stress the need for a revision of the thromboprophylactic approach following surgery in patients with a history of VTE, the duration and dosage of which may need to be intensified and individualized.

REFERENCE LIST

1. Gould MK, Garcia DA,Wren SM, et al. Prevention of VTE in non orthopaedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2)(suppl):e227S-e277S.
2. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopaedic 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.
3. Allen D, Sale G. Lower limb joint replacement in patients with a history of venous thromboembolism. Bone Joint J. 2014;96-B(11):1515-1519.
4. Bahl V, Hu HM, Henke PK, Wakefield TW, Campbell DA Jr, Caprini JA. A validation study of a retrospective venous thromboembolism risk scoring method. Ann Surg. 2010;251(2):344-350.
5. Nelson DW, Simianu VV, Bastawrous AL, et al; Colorectal Writing Group for Surgical Care and Outcomes Assessment Program–Comparative Effectiveness Research Translation Network (SCOAP-CERTAIN) Collaborative. Thromboembolic complications and prophylaxis patterns in colorectal surgery. JAMA Surg. 2015;150(8):712-720.
6. Heit JA, Lahr BD, Ashrani AA, Petterson TM, Bailey KR. Predictors of venous thromboembolism recurrence, adjusted for treatments and interim exposures: a population-based case-cohort study. Thromb Res. 2015;136(2): 298-307.
7. Caprini JA. Thrombosis risk assessment as a guide to quality patient care. Dis Mon. 2005;51(2-3):70-78.
8. ISTH Steering Committee for World Thrombosis Day. Venous thromboembolism: a call for risk assessment in all hospitalised patients. Thromb Haemost. 2016;116(5):777-779.
9. National Institute for Health and Clinical Excellence. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. https://www.nice.org.uk/guidance/ng89. Accessed April 3, 2019.
10. Timp JF, Lijfering WM, Flinterman LE, et al. Predictive value of factor VIII levels for recurrent venous thrombosis: results from the MEGA follow-up study. J Thromb Haemost. 2015;13(10):1823-1832.
11. van Stralen KJ, Rosendaal FR, Doggen CJ. Minor injuries as a risk factor for venous thrombosis. Arch Intern Med. 2008;168(1):21-26.
12. Timp JF, Cannegieter SC, Tichelaar V, et al. Antibiotic use as a marker of acute infection and risk of first and recurrent venous thrombosis. Br J Haematol. 2017;176(6):961-970.
13. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293(6):715-722.
14. Roach RE, Lijfering WM, Flinterman LE, Rosendaal FR, Cannegieter SC. Increased risk of CVD after VT is determined by common etiologic factors. Blood. 2013;121(24):4948-4954.
15. de Bruin A, Kardaun J, Gast F, de Bruin E, van Sijl M, Verweij G. Record linkage of hospital discharge register with population register: experiences at Statistics Netherlands. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.527.8816&rep=rep1&type=pdf. Accessed April 3, 2019.
16. Ocak G, Vossen CY, Verduijn M, et al. Risk of venous thrombosis in patients with major illnesses: results from the MEGA study. J Thromb Haemost. 2013;11(1):116-123.
17. Németh B, van Adrichem RA, van Hylckama Vlieg A, et al. Venous thrombosis risk after cast immobilization of the lower extremity: derivation and validation of a clinical prediction score, L-TRiP(cast), in three population-based case-control studies. PLoS Med. 2015;12(11):e1001899.
18. Jha AK, Larizgoitia I, Audera-Lopez C, Prasopa-Plaizier N,Waters H, Bates DW. The global burden of unsafe medical care: analytic modelling of observational studies. BMJ Qual Saf. 2013;22(10):809-815.
19. Truijers M, Kranendonk SE, Nurmohamed MT. Thromboprophylaxis in general surgical practices in the year 2004: perioperative use during hospitalisation, during out-patient care and following plaster cast immobilisation. Ned Tijdschr Geneeskd. 2005;149(45):2511-2516.

6

Venous thrombosis risk after cast immobilization of the lower extremity: derivation and validation of a clinical Prediction Score, L-TRiP(cast), in three population-based case-control studies

Németh B, van Adrichem RA, van Hylckama Vlieg A, Bucciarelli p, Martiselli I, Baglin T, Rosendaal FR, le Cessie S, Cannegieter SC.

PLoS Med. 2015 Nov 10;12(11):e1001899

ABSTRACT

Background Guidelines and clinical practice vary considerably with respect to thrombosis prophylaxis during plaster cast immobilization of the lower extremity. Identifying patients at high risk for the development of venous thromboembolism (VTE) would provide a basis for considering individual thromboprophylaxis use and planning treatment studies.

The aims of this study were (1) to investigate the predictive value of genetic and environmental risk factors, levels of coagulation factors, and other biomarkers for the occurrence of VTE after cast immobilization of the lower extremity and (2) to develop a clinical prediction tool for the prediction of VTE in plaster cast patients.

Methods and Findings We used data from a large population-based case–control study (MEGA study, 4,446 cases with VTE, 6,118 controls without) designed to identify risk factors for a first VTE. Cases were recruited from six anticoagulation clinics in the Netherlands between 1999 and 2004; controls were their partners or individuals identified via random digit dialing. Identification of predictor variables to be included in the model was based on reported associations in the literature or on a relative risk (odds ratio) > 1.2 and $p \leq 0.25$ in the univariate analysis of all participants. Using multivariate logistic regression, a full prediction model was created. In addition to the full model (all variables), a restricted model (minimum number of predictors with a maximum predictive value) and a clinical model (environmental risk factors only, no blood draw or assays required) were created. To determine the discriminatory power in patients with cast immobilization (n = 230), the area under the curve (AUC) was calculated by means of a receiver operating characteristic. Validation was performed in two other case–control studies of the etiology of VTE: (1) the THE-VTE study, a two-center, population-based case–control study (conducted in Leiden, the Netherlands, and Cambridge, United Kingdom) with 784 cases and 523 controls included between March 2003 and December 2008 and (2) the Milan study, a population-based case–control study with 2,117 cases and 2,088 controls selected between December 1993 and December 2010 at the Thrombosis Center, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy.

The full model consisted of 32 predictors, including three genetic factors and six biomarkers. For this model, an AUC of 0.85 (95% CI 0.77–0.92) was found in individuals with plaster cast immobilization of the lower extremity. The AUC for the restricted model (containing 11 predictors, including two genetic factors and one biomarker) was 0.84 (95% CI 0.77–0.92). The clinical model (consisting of 14 environmental predictors) resulted in an AUC of 0.77 (95% CI 0.66–0.87). The clinical model was converted into a risk score, the L-TRiP(cast) score (Leiden–Thrombosis Risk Prediction for patients with cast immobilization score), which showed an AUC of 0.76 (95% CI 0.66–0.86). Validation in the THE-VTE study data resulted in an AUC of 0.77 (95% CI 0.58–0.96) for the L-TRiP(cast) score. Validation in the Milan study resulted in an AUC of 0.93 (95% CI 0.86–1.00) for the full model, an AUC of 0.92 (95% CI 0.76–0.87) for the restricted model, and an AUC of 0.96 (95% CI 0.92–0.99) for the clinical model. The L-TRiP(cast) score resulted in an AUC of 0.95 (95% CI 0.91–0.99).

Major limitations of this study were that information on thromboprophylaxis was not available for patients who had plaster cast immobilization of the lower extremity and that blood was drawn 3 mo after the thrombotic event.

Conclusions These results show that information on environmental risk factors, coagulation factors, and genetic determinants in patients with plaster casts leads to high accuracy in the prediction of VTE risk. In daily practice, the clinical model may be the preferred model as its factors are most easy to determine, while the model still has good predictive performance. These results may provide guidance for thromboprophylaxis and form the basis for a management study.

INTRODUCTION

The incidence of venous thromboembolism (VTE) is estimated to be 1–2 per 1,000 person-years and increases with age up to 1% per year in the elderly. An individual's lifetime risk for the development of VTE is about 11% [1–3]. Multiple genetic and environmental risk factors, including cast immobilization, have been identified in etiologic research. However, the presence of one risk factor is generally not sufficient for the development of a thrombotic event. Only when multiple risk factors have accumulated, some of which may interact in a synergistic way, and the "thrombotic threshold" is crossed will thrombosis occur [1]. Although we understand this mechanism in general, we cannot accurately predict which individuals will develop VTE [3]. Such knowledge would be of use, as it allows targeted thrombosis prevention.

Recently, Hippisley-Cox and Coupland developed a risk prediction algorithm to estimate future risk of VTE in the general population. This prediction model included 15 environmental risk factors and resulted in a receiver operating characteristic (ROC) area under the curve (AUC) statistic of 0.75 [4]. Earlier, the Padua prediction score included similar risk factors in a risk assessment model for VTE in hospitalized medical patients [5]. In addition to these prediction models, which included only environmental predictors, there have been a few studies that investigated the added value of biomarkers. Recently, de Haan et al. developed a risk model that incorporated thrombosis-associated single nucleotide polymorphisms (SNPs) combined with environmental risk factors, which reached an AUC statistic of 0.82 in the general population [6]. The role of factor VIII, D-dimer, prothrombin fragment 1 + 2, platelet count, and hemoglobin level in predicting VTE has mainly been studied in patients with cancer [7–9].

Using a prediction model for first VTE in the general population is not efficient considering the heterogeneity of the condition and the rarity of disease in the general population. However, in more homogeneous high risk groups, such as patients with cast immobilization, prediction of VTE can be useful and cost-effective. Our recent study showed an 8-fold increased risk of VTE in patients with below-knee cast immobilization [10]. In terms of absolute risk, VTE incidence rates reported in these patients vary strongly depending on study design and definition of the event (asymptomatic or symptomatic). A recent meta-analysis reported a rate of symptomatic VTE during cast immobilization that varied between 0% and 5.5% [11]. The risk of VTE during cast immobilization is probably not large enough to justify anticoagulant prophylaxis in all patients with plaster cast, as the bleeding risk will also be considerable (0.3% major bleeding) [12,13]. Therefore, it would be beneficial to identify those at high risk and to offer targeted, individualized therapy.

The purpose of this study was to investigate the predictive value of genetic and environmental risk factors, coagulation factors, and other biomarkers for the development of VTE after cast immobilization of the lower extremity. We developed several models: in addition to a full model, we also created a restricted model in which we tried to find the optimal balance between maximum predictive value and a minimum number of (all types of) predictor variables and a clinical model that contained only predictors that are easy to determine in clinical practice. Finally, we validated the models in two independent datasets.

METHODS

Study Design

For developing the model, data from a large population-based case–control study, the MEGA study (Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis) were used (S1 Analysis Plan). Details of this study have been published previously [14–16]. In short, 4,956 consecutive patients aged 18 to 70 y with a first deep vein thrombosis (DVT), pulmonary embolism (PE), or both were recruited from six anticoagulation clinics in the Netherlands between 1 March 1999 and 31 August 2004. The diagnosis of DVT or PE was confirmed by (Doppler) ultrasonography, ventilation/perfusion scan, angiography, or spiral CT scan. The control group (n = 6,297) consisted of partners of participating patients and other controls who were identified using a random digit dialing method; controls were frequency matched to cases with respect to sex and age. Approval for this study was obtained from the Medical Ethics Committee of the Leiden University Medical Center, and all participants provided written informed consent.

Data Collection and Laboratory Analysis

All participants completed a questionnaire on risk factors for VTE that included questions on (potential) risk factors such as trauma, immobilization (including plaster cast and location), (orthopaedic) surgery, current use of (any) medication, and comorbidity in the past year before the venous thrombotic event.

In patients and controls included from the start of the study until May 31, 2002, a blood sample was collected approximately 3 mo after discontinuation of oral anticoagulant therapy. In patients who were still on anticoagulant therapy 1 y after the event, blood was drawn during treatment. Detailed information on laboratory analyses of coagulation factors and hemorheologic and other markers can be found in S1 Laboratory Analyses. For patients and controls included after June 1, 2002, and for patients who were unable to visit the clinic, DNA was collected by means of buccal swabs sent by mail. The factor V Leiden (F5, rs6025) and prothrombin G20210A (F2, rs1799963) mutations were measured simultaneously by a multiplex polymerase chain reaction using the TaqMan assay [17]. ABO blood type was also analyzed using the TaqMan assay [18].

Model derivation

Development of the full prediction model.

All prediction models were developed using the whole MEGA study population, with the exclusion of 689 individuals with multi-trauma, plaster cast of the arm or back, plaster cast afterthe occurrence of thrombosis, or use of anticoagulation medication during blood collection. In total, 4,446 cases and 6,118 controls were included in the analysis. Multiple

imputation techniques were used for missing values. In the imputation step, skewed variables were transformed (five datasets were imputed, and results were pooled according to Rubin's rules) [19].

Because the subset of individuals with plaster cast was small (n = 230), we were not able to test our model without imputed data in this specific group. Too many patients were missing one or more variables, and logistic regression analyses were not possible. However, results were consistent in the entire MEGA study population with and without the imputed data. Moreover, we checked all imputed data for errors. Univariate regression for all predictors was similar in the entire MEGA population when we performed regression analyses with and without imputed data. Detailed information on missing data can be found in *Supplement 1 Data*.

Controls were frequency matched on age and sex, meaning that the age and sex distribution of the control group was similar to that of the patient group. The age and sex distribution of the control group was therefore different from that of the general population (e.g., relatively older age and more females). In order to use age and sex as predictor variables, we needed a control group in which the age and sex distribution reflected the general population. For this we weighted the control individuals (for age and sex) to the age and sex distribution of the Dutch population in 2001 (Statistics Netherlands). Weights were calculated by dividing the proportion of individuals in a certain age- and sex-specific stratum in the Dutch population by the stratum-specific proportion of individuals in the MEGA study control group. For example, in the Dutch population, 1.2% of all inhabitants aged 18 and 70 y (same age range as our study) were 30-y-old males. In the MEGA study, this proportion was 0.8%, giving these individuals in our study a weight of 1.5 (1.2% divided by 0.8%). This approach is called direct standardization. Using this approach, younger control individuals were assigned a weight above one, and older control individuals were assigned a weight below one (stratum-specific weights can be found in *Supplement 1 Weights*). This way we corrected for the "oversampling" of older control individuals (due to frequency matching) and created a control group with the same age and sex distribution as that of the Dutch population in 2001. We subsequently performed weighted logistic regression analyses incorporating age and sex as predictor variables in our prediction model.

Derivation process.

For the development of the derivation models, the whole MEGA study population was used rather than the plaster cast subgroup, to avoid overfitting in the derivation process. *Figure 1* shows a flowchart of the model derivation process. Identification of candidate predictor variables (see *Table 1*) was based on (1) reported associations with the occurrence of VTE in the literature and standardized and easy measurement or (2) finding an odds ratio (OR) >

1.2 (highest versus lowest category) and a *p*-value ≤ 0.25 between cases and controls in the overall MEGA study population using weighted logistic regression (*Fig 1, step 1*). Continuous predictors such as age and body mass index (BMI) were categorized, biomarker values were split into tertiles based on control individuals, and protein S and protein C antigen levels were dichotomized (< 65 versus ≥65 IU/dl). The variable "plaster cast" was classified as no plaster cast, complete leg cast, lower-leg cast, circular knee cast, or foot cast, resulting in discrimination between different locations (more/less immobilization). Related clinical factors with a similar OR in the multivariate model were combined into one variable. The variables rheumatoid arthritis, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and multiple sclerosis were combined into the variable "comorbidity"; previous heart attack and angina pectoris into "cardiovascular disease"; stroke and transient ischemic attack (TIA) into "cerebrovascular events"; and urinary tract infection/cystitis, pyelonephritis, arthritis, bursitis, inflammation of other body parts, and tropical diseases into "inflammatory disease."

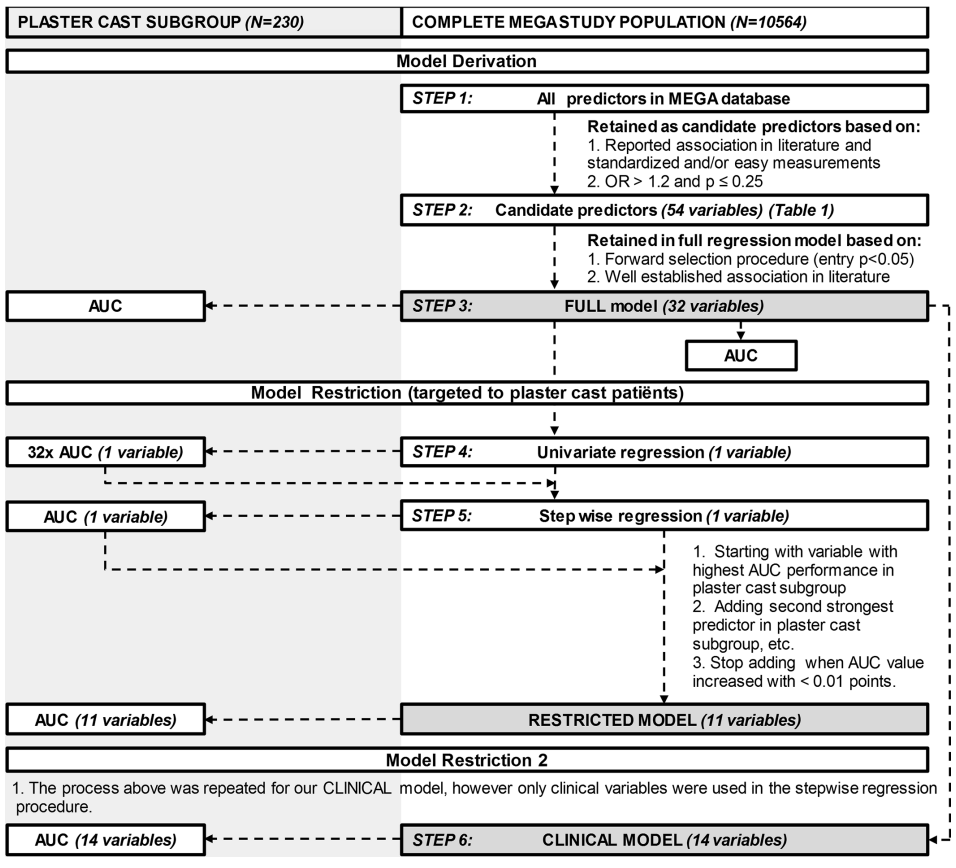


Figure 1. Flowchart of the prediction model derivation process.

Table 1: Candidate predictor variables.

Category	Candidate Predictor Variable
Environmental predictor variables	
	Age
	Sex
	Smoking
	Varicose veins
	Cancer within the past 5 y
	Congestive heart failure
	Comorbidity (rheumatoid arthritis, chronic kidney disease, COPD, multiple sclerosis)
	Cardiovascular disease (heart attack and angina pectoris)
	Cerebrovascular events (stroke and TIA)
	BMI
	Claudication
	Family history of VTE (first-degree relative)
	Hospital admission within the past 3 mo
	Bedridden within the past 3 mo
	Paralysis (partial)
	Surgery within the past 3 mo
	Current pregnancy or puerperium
	Current use of antipsychotic medication
	Current use of tamoxifen
	Current use of hormonal replacement therapy
	Current use of oral contraceptives
	Superficial vein thrombosis
	Plaster cast and location (no plaster cast, complete leg cast, lower leg cast, circular knee cast, or foot cast)
	Hepatitis
	Pneumonia
	Inflammatory disease (urinary tract infection/cystitis, pyelonephritis, arthritis, bursitis, inflammation of other body parts, and tropical diseases)

Table 1: Continued.

Category	Candidate Predictor Variable
Hemorheologic and coagulation predictor variables	
	Fibrinogen activity
	Factor VIII activity and antigen level
	Von Willebrand factor antigen level
	Factor IX antigen mean
	Protein S antigen mean
	Factor II activity
	Factor VII activity
	Factor X antigen level
	Protein C activity
	Factor XI activity
	Hematocrit
	White blood cell count
	Percentage/number lymphocytes
	Percentage/number monocytes
	Percentage/number granulocytes
	Red blood cell count
	Hemoglobin level
	Mean cell volume
	Mean cell hemoglobin
	Mean cell hemoglobin concentration
	Red cell distribution width
	Antithrombin activity
	Total homocysteine
	Total cysteine
	Methionine
Genetic predictor variables	
	Factor V Leiden mutation
	Prothrombin mutation
	Non-O blood type

The full prediction model was created using a forward selection procedure (entry $p < 0.05$) with the candidate biomarkers and genetic and clinical variables. Of all the variables that were not included in the model by this forward selection, some predictors were nevertheless retained in the full model because of a well-established reported association with the occurrence of VTE in the literature (*Fig 1, step 2*).

Calculating the discriminative value.

To determine the magnitude of discrimination of this model, an AUC (c-statistic) was calculated by means of a ROC, based on the predictions from the multiple logistic regression models. ROC curves were created both in the entire study population and in the plaster cast subgroup only, for which regression coefficients of the model developed in the total MEGA study population were used (*Fig 1, step 3*).

Model restriction

Models targeted to plaster cast patients: clinical and restricted models

From this full model, we developed two reduced sub-models specially targeted to plaster cast patients, i.e., the restricted model and the clinical model. For the development of the restricted model, we used as candidate variables the 32 variables included in our full model (including biomarkers and genetic variables). We performed a forward selection procedure. Models were fitted using all MEGA study individuals, but variables were selected based on the increase in AUC in the plaster cast subset of patients. This means that we started by fitting all 32 variables separately with a univariate logistic regression analysis using all MEGA study individuals. For each of the 32 predictors, we calculated the AUC in the subgroup of plaster cast patients (*Fig 1, step 4*). The variable corresponding to the highest AUC was then selected in the model (*Fig 1, step 5*). This procedure was repeated by subsequently adding the next strongest predictor until the AUC value in the plaster cast population increased by less than 0.01 points. Age and sex were forced (at first) in the model because of clinical importance. Variables were also selected based on their availability in our validation cohorts. For instance, when two variables performed the same in our plaster cast subgroup in the MEGA study, we chose to select the predictor that was also available in our validation cohorts. The model obtained in this way is the restricted model.

The clinical model was developed in the same way as the restricted model with the exception that only environmental predictor variables from the full model were used. Biomarkers and genetic variables were not included (*Fig 1, step 6*).

In this way we were able to develop models targeted to the plaster cast subpopulation, while the regression coefficients were stable because they were derived from the entire MEGA population [20].

Clinical risk score for plaster cast patients: the L-TRiP(cast) score

Additionally, we developed a risk score, the L-TRiP(cast) score (Leiden–Thrombosis Risk Prediction for patients with cast immobilization score), in which risk points are based on the regression coefficients (betas) for predictor variables in the clinical multivariate logistic model. We used the following scoring: $0.20 < \text{beta} \leq 0.75$, 1 point; $0.75 < \text{beta} \leq 1.25$, 2 points; $1.25 < \text{beta} \leq 1.75$, 3 points; $1.75 < \text{beta} \leq 2.25$, 4 points; $\text{beta} > 2.25$, 5 points. The L-TRiP(cast) score was the sum of these points across the predictor variables. The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated for different cutoff points of the L-TRiP(cast) score assuming an incidence of 2.5% for VTE in plaster cast patients, which is the reported incidence from a Cochrane meta-analysis [13].

Model validation

Validation was performed in two other case–control studies of the etiology of VTE: the THE-VTE study [21,22] and the Milan study [23] (both published in detail previously). The THE-VTE study is a two-center, population-based case–control study that was performed in Leiden, the Netherlands, and Cambridge, United Kingdom. Valid information on all environmental risk factors was available for all 784 cases and 523 controls who were enrolled in the study between March 2003 and December 2008. The Milan study is also a population-based case–control study: 2,117 cases and 2,088 controls were enrolled between December 1993 and December 2010 at the Thrombosis Center, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy. In addition to information on environmental risk factors, data on biomarkers and genetic predictors were collected in this study. In the Milan study, all genetic predictors and factor VIII activity were measured, and most environmental risk variables were known. Only Von Willebrand factor antigen level, red cell distribution width, percentage of monocytes, factor XI activity, and total cysteine were not available. In the Milan study, the following variables were not recorded: cancer within the past 5 y, comorbidity, cerebrovascular events, hospital admission within the past 3 mo, paralysis, pregnancy, superficial vein thrombosis, hepatitis, and pneumonia. The variable smoking was coded as yes/no, family history of VTE was coded as yes/no, and information on type of plaster cast of the lower extremity (i.e., complete versus lower-leg) was not available. For each individual, the different prognostic scores were calculated using the regression coefficients derived in the MEGA study.

Analyses were performed in IBM SPSS Statistics for Windows, version 20.0. The weighted analyses were performed in Stata, version 12.

RESULTS

Study Population

In the model derivation analysis, 4,446 cases and 6,118 controls were included. Of the cases, 2,606 (58.6%) were diagnosed with DVT, 1,452 (32.7%) had PE, and 388 (8.7%) had both. Plaster cast immobilization of the lower extremity was present in 194 patients and 36 control individuals, mainly due to traumatic events. Among these patients, 131 (67%) individuals developed DVT, 44 (23%) PE, and 19 (10%) both. The predictors that had the highest prevalence among cases were smoking, presence of varicose veins, being overweight, family history of thrombosis (first-degree relative), use of oral contraceptives, cancer in the past 5 y, and comorbidity. Frequencies of these variables in controls were much lower. Further baseline characteristics, including coagulation markers and genetic predictor variables, can be found in *S1 Table*.

Model Derivation

In univariate analyses, all 54 candidate predictor variables were significantly ($p < 0.25$) associated with the occurrence of VTE, with the exception of protein S antigen, percentage/number of lymphocytes and granulocytes, hemoglobin level, total homocysteine and antithrombin activity.

Out of these candidate predictors, 32 variables were retained in our full prediction model; these variables are listed in *Table 2*. The predictors cerebrovascular events, congestive heart failure, hepatitis, current use of tamoxifen, and non-O blood type were not significantly associated with VTE. Nevertheless, these were retained in the model because of a clear association with VTE in the literature. Factors most strongly associated with VTE, e.g., with the highest relative risk in this full model, were cancer within the past 5 y (OR 4.8, 95% CI 3.6–6.5), hospital admission within the past 3 mo (OR 3.6, 95% CI 2.7–4.7), current use of oral contraceptives (OR 7.3, 95% CI 6.0–8.8), pregnancy or puerperium (OR 6.1, 95% CI 4.0–9.5), complete leg plaster cast (OR 11.1, 95% CI 4.0–30.8), and factor V Leiden mutation (OR 5.7, 95% CI 1.6–19.7). *S2 Table* shows the univariate and multivariate ORs for the full logistic regression model in the MEGA study population. The predictive value of the full regression model resulted in an AUC of 0.85 (95% CI 0.77–0.92) in plaster cast patients and 0.88 (95% CI 0.87–0.89) in the entire MEGA population (*Table 3*).

Table 2: Overview of predictor variables in each model.

Category	Predictor Variable	Model		
		Full	Restricted	Clinical
Environmental predictor variables				
	Age	×	×	×
	Sex	×	×	×
	BMI	×	×	×
	Smoking	×		
	Varicose veins	×		
	Cancer within the past 5 y	×		×
	Congestive heart failure	×		
	Comorbidity (rheumatoid arthritis, chronic kidney disease, COPD, multiple sclerosis)	×		×
	Cerebrovascular events (stroke and TIA)	×		
	Family history of VTE (first-degree relative)	×	×	×
	Hospital admission within the past 3 mo	×		×
	Bedridden within the past 3 mo	×	×	×
	Paralysis (partial)	×		
	Surgery within the past 3 mo	×	×	×
	Pregnancy or puerperium	×		×
	Current use of antipsychotic medication	×		
	Current use of tamoxifen	×		
	Current use of hormonal replacement therapy	×		
	Current use of oral contraceptives	×	×	×
	Superficial vein thrombosis	×		×
	Hepatitis	×		
	Pneumonia	×		×
	Plaster cast and location (no plaster cast, complete leg cast, lower leg cast, circular knee cast, or foot cast)	×	×	×
Hemorheologic and coagulation predictor variables				
	Factor VIII activity	×	×	
	Von Willebrand factor antigen level	×		
	Factor XI activity	×		
	Percentage of monocytes	×		

Table 2: Continued.

Category	Predictor Variable	Model		
		Full	Restricted	Clinical
	Total cysteine	×		
	Red cell distribution width	×		
Genetic predictor variables				
	Factor V Leiden mutation	×		
	Prothrombin mutation	×	×	
	Non-O blood type	×	×	

Table 3: AUC values of the full, restricted, and clinical models, both in all individuals and in the plaster cast subgroup.

Model	All Individuals		Plaster Cast Subgroup	
	AUC	95% CI	AUC	95% CI
Full model	0.88	0.87–0.89	0.85	0.77–0.92
Restricted model			0.84	0.77–0.92
Clinical model			0.77	0.66–0.87
L-TRiP(cast) score			0.76	0.66–0.86

Restricted and Clinical Models

The AUC of our restricted model in plaster cast patients reached a maximum of 0.84 (95% CI 0.77–0.92) (*Table 3*). The restricted model comprised 11 predictor variables: age, sex, plaster cast and location, BMI, non-O blood type, current use of oral contraceptives, factor VIII activity, surgery within the past 3 mo, prothrombin mutation, family history of VTE (first-degree relative), and bedridden within the past 3 mo (see *Table 2*). *Fig 2* shows the AUC value after each addition of a predictor into the restricted model. The clinical model consisted of 14 environmental predictor variables (see *Table 2*). In plaster cast patients, this model reached an AUC of 0.77 (95% CI 0.66–0.87) (*Table 3*).

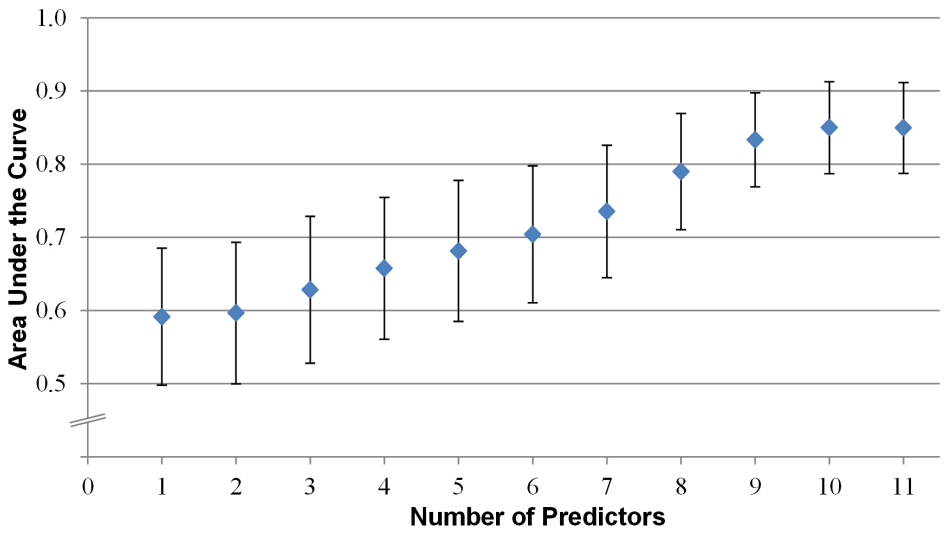


Figure 2: AUC value after addition of each predictor into the restricted model.
Vertical bars represent 95% CIs. Predictors: (1) age, (2) sex, (3) plaster cast and location, (4) prothrombin mutation, (5) current use of oral contraceptives, (6) family history of VTE (first-degree relative), (7) factor VIII activity, (8) bedridden within the past 3 mo, (9) surgery within the past 3 mo, (10) non-O blood type, (11) BMI.

L-TRiP(cast) Score

Based on the regression coefficients in the clinical logistic regression model, the L-TRiP(cast) score was developed (*Table 4*). For instance, a 40-y-old male who was admitted into the hospital within the past 3 mo receives 5 points (including 2 points for being older than 35 y and 1 point for male sex). If this person also has rheumatoid arthritis (1 point) and a plaster cast of the lower-leg (4 points), this results in a total of 10 points. In our plaster cast population, the score ranged between 4 and 20 points (out of a maximum of 29 points for men and 35 points for women). In all, 59.6% (n = 137) of the plaster cast patients had a score of at least 10 points. *Fig 3* shows the distribution of individual L-TRiP(cast) scores among cases and controls.

In the plaster cast patients, the L-TRiP(cast) score had an AUC of 0.76 (95% CI 0.66–0.86). Using a cutoff point of 10 points (59.6% of patients) to stratify individuals into high versus low risk categories, the sensitivity was 65.1%, and the specificity was 72.2%. Assuming an incidence of VTE of 2.5%, the positive predictive value of the test was 5.7%, and the negative predictive value was 98.8%. *Table 5* shows predictive values that were calculated for different cutoff points.

Table 4: L-TRiP(cast) score based on the clinical risk prediction model.

Environmental Predictor Variable	Point Value
Age ≥ 35 and < 55 y	2
Age ≥ 55 y	3
Male sex	1
Current use of oral contraceptives	4
Cancer within the past 5 y	3
Pregnancy or puerperium	3
BMI ≥ 25 and < 35 kg/m^2	1
BMI ≥ 35 kg/m^2	2
Pneumonia	3
Family history of VTE (first-degree relative)	2
Comorbidity (rheumatoid arthritis, chronic kidney disease, COPD, multiple sclerosis)	1
Hospital admission within the past 3 mo	2
Bedridden within the past 3 mo	2
Surgery within the past 3 mo	2
Superficial vein thrombosis	3
Plaster cast: complete leg	5
Plaster cast: circular knee cast (ankle free)	2
Plaster cast: foot	2
Plaster cast: lower-leg	4

This L-TRiP(cast) score was derived from the regression coefficients (betas) of the clinical prediction model: 0.20 < beta ≤ 0.75, 1 point; 0.75 < beta ≤ 1.25, 2 points; 1.25 < beta ≤ 1.75, 3 points; 1.75 < beta ≤ 2.25, 4 points; beta > 2.25, 5 points

Validation Cohorts

The characteristics of the THE-VTE study population, with 784 cases and 523 controls in our analyses, were similar to those of our derivation cohort. DVT was found in 460 (59%) cases, and PE (with or without DVT) in 325 (41%) cases. Plaster cast of the lower extremity was present in 32 (4.1%) cases and seven (1.3%) controls. In the Milan study, plaster cast of the lower extremity was seen in 143 (8.1%) cases and eight (0.4%) controls.

Table 5: Predictive performance of the L-TRiP(cast) score in plaster cast patients.

Cutoff Point	Percent Positive	Sensitivity	Specificity	Sensitivity + Specificity	Positive Predictive Value*	Negative Predictive Value*	Likelihood Positive	Likelihood Negative
2	100.0%	100.0%	0.0%	100.0%	2.5%	99.2%	1.0	0.3
3	100.0%	100.0%	0.1%	100.0%	2.5%	99.2%	1.0	0.3
4	99.9%	100.0%	0.1%	100.0%	2.5%	98.6%	1.0	0.5
5	99.3%	99.6%	2.0%	101.6%	2.5%	99.5%	1.0	0.2
6	96.5%	98.4%	14.2%	112.6%	2.9%	99.7%	1.1	0.1
7	92.1%	95.3%	26.2%	121.5%	3.2%	99.5%	1.3	0.2
8	87.8%	92.6%	39.7%	132.2%	3.8%	99.5%	1.5	0.2
9	74.7%	80.8%	60.8%	141.7%	5.0%	99.2%	2.1	0.3
10	59.6%	65.1%	72.2%	137.2%	5.7%	98.8%	2.3	0.5
11	44.4%	49.0%	82.0%	131.0%	6.5%	98.4%	2.7	1.0
12	31.2%	34.5%	88.3%	122.9%	7.1%	98.1%	3.0	0.7
13	21.7%	24.8%	96.3%	121.1%	14.7%	98.0%	6.7	0.8
14	14.3%	16.2%	96.6%	112.8%	10.9%	97.8%	4.7	0.9

*Presuming a prevalence of VTE in plaster cast patients of 2.5%.

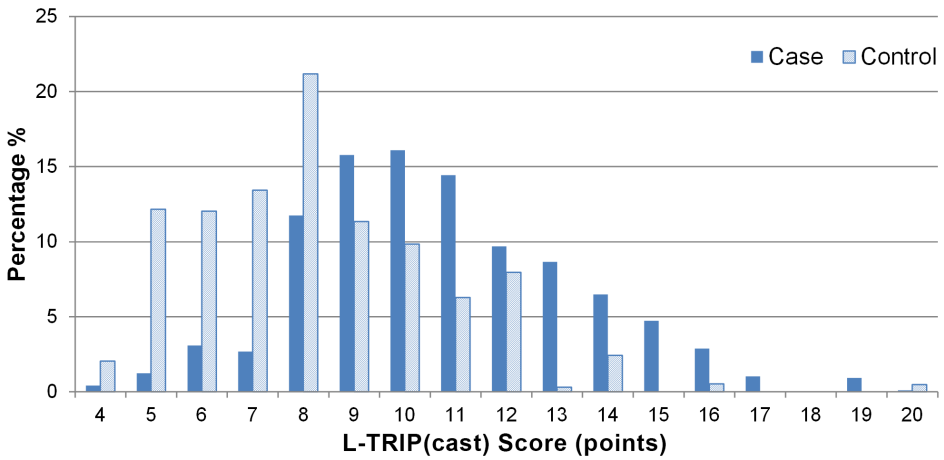


Figure 3: Distribution of individual L-TRiP(cast) scores in the plaster cast subgroup derived from study.

As discussed above, when selecting predictors for our restricted model, we selected variables based on availability in the validation cohorts without reducing the AUC performance. Because the MILAN study lacked data on Von Willebrand factor levels, monocyte percentage, varicose veins, and hospital admission within the past 3 mo (which were strong predictors in the derivation cohort), we adjusted our restricted model. These predictors were replaced with BMI, prothrombin mutation, non-O blood type, and bedridden within the past 3 mo. The predictive AUC value of this adjusted restricted model performed similarly to the unadjusted model in the MEGA study population. Therefore, we chose to continue using these predictors in our restricted model.

Results of the validation of the different prediction scores can be found in *Table 6*. The clinical model showed an AUC of 0.75 (95% CI 0.55–0.94) in plaster cast patients in the THE-VTE cohort. In the Milan study population, AUCs were 0.93 (95% CI 0.86–1.00), 0.92 (95% CI 0.87–0.98), and 0.96 (95% CI 0.92–0.99) for the full, restricted, and clinical models, respectively, in plaster cast patients. The L-TRiP(cast) score performed very well, with AUCs of 0.95 (95% CI 0.91–0.99) and 0.77 (95% CI 0.58–0.96) in the Milan study and the THE-VTE study, respectively.

Table 6: Validation results in plaster cast patients

Model or Prediction Score	AUC (95% CI)	
	THE-VTE Study	Milan Study
Full model	—	0.93 (0.86–1.00)
Restricted model	—	0.92 (0.87–0.98)
Clinical model	0.75 (0.55–0.94)	0.96 (0.92–0.99)
L-TRiP(cast) score	0.77 (0.58–0.96)	0.95 (0.91–0.99)

DISCUSSION

Summary of Key Findings

In this study we developed a prediction model for the occurrence of VTE in patients with plaster cast immobilization of the lower extremity. Due to the wide range of incidence rates that have been reported and a considerable bleeding risk secondary to anticoagulant prophylaxis, current guidelines on thromboprophylaxis are contradictory. A prediction model could help clinicians decide whether or not to prescribe thromboprophylaxis in individual patients [24,25].

The full model performed best in our derivation cohort, with an AUC of 0.85 (95% CI 0.77–0.92), and consisted of a mix of environmental risk factors, genetic risk factors, and biomarkers. However, as measurement of biomarkers and SNPs can be difficult, expensive, or take some time in clinical practice, we also developed two reduced versions of this full model: a restricted model and a clinical model. These models are more practical for clinical use and still showed good predictive characteristics, with an AUC of 0.84 (95% CI 0.77–0.92) and 0.77 (95% CI 0.66–0.87) for the restricted model (only one biomarker and two SNPs included) and the clinical model (no biomarkers or SNPs), respectively. In validation studies, the clinical and restricted models performed well in two validation populations. Of all the models, the clinical model performed best, with an AUC of 0.75 (95% CI 0.55–0.94) and 0.96 (95% CI 0.92–0.99) in the THE-VTE study and the Milan study, respectively.

Previous Prediction Models

Whereas other studies have examined risk factors and developed prediction models for thrombosis in the general population, this study focused particularly on the development of VTE in plaster cast patients. Considering the low risk of a first event and the heterogeneous etiology of VTE, it is not efficient to develop a prediction model for the general population. Instead, targeting a specific high risk group is much more likely to lead to a model that can be used in clinical practice to distinguish individuals in whom the expected risk is sufficiently high to warrant thromboprophylactic therapy [1]. For instance, location of the plaster cast (complete leg, lower-leg, etc.) was the most important predictive variable in our target group, giving specific information for these patients.

The predictive value of genetic and environmental risk factors for VTE has been described in previous studies [3,4,26]. Hippisley-Cox and Coupland reported an increased risk of VTE in the general population in association with overweight, COPD, varicose veins, congestive heart failure, chronic renal disease, cancer, inflammatory bowel disease, hospital admission within the past 6 mo, use of antipsychotic drugs, use of oral contraceptives, use

of hormone replacement therapy, use of tamoxifen, and smoking, which resulted in an AUC value of 0.75 (95% CI 0.74–0.76) in their validation cohort, which is in line with our results [4]. However, one very well established risk factor, i.e., immobilization, was not incorporated into this model. de Haan et al. recently found that multiple SNP testing had an additional predictive value in the prediction of VTE compared with a model with environmental variables only (also partially MEGA study data) [6]. They identified five common SNPs and incorporated these variables into a prediction model for the general population, together with environmental risk factors. This model had an AUC of 0.77 (95% CI 0.74–0.80) [6].

There have been only a few studies, predominantly in cancer-induced thrombosis, that have investigated the predictive role of biomarkers, such as high factor VIII and prothrombin fragment 1 + 2, in the prediction of VTE [7,9]. While other studies have focused on environmental risk factors, genetic risk factors, or biomarkers only, we incorporated all three types of predictor variables into our model. So far, this is the only prediction model for VTE to our knowledge that has combined all of these variables and that has focused on plaster cast patients.

Limitations of the Study

Although we incorporated genetic risk factors, environmental risk factors, and biomarkers in our model, we were not able to include age and sex as predictor variables at first, since the controls in our study were frequency matched on age and sex. To overcome this, control individuals were weighted to the age and sex distribution of the Dutch population, which made it possible to estimate the real effect of age and sex on the risk of VTE in our case–control study. We performed a sensitivity analysis with and without weighting of control individuals: the results for the weighted analyses were equal to those of the unweighted analyses in both the derivation and validation studies. This way, age and sex were incorporated into our models as predictor variables, making our risk score suitable for patients from 18 up to 70 y old. Another limitation of the study was that blood collection was performed after the occurrence of thrombosis. As a result, the levels of coagulation factors may have been a consequence of the thrombosis rather than a cause. However, increased levels of factor VIII and fibrinogen measured after the occurrence of thrombosis have been shown not to be due to acute phase reactions [27]. In fact, high factor VIII levels seem to be a permanent phenomenon, and repeated measurements of factor VIII show little variation [28,29]. A third limitation was that general information on anticoagulation therapy was available, but information on possible thromboprophylaxis during plaster cast was missing. Nonetheless, if we look at the results of a survey on thromboprophylaxis conducted in the Netherlands in 2002, which overlaps with the inclusion period of our study, 30% of orthopaedic surgeons provided thromboprophylaxis during lower-leg plaster

cast, and 88% during complete leg plaster cast [30]. Therefore, VTE risk may have been underestimated in this study. A fourth limitation of the study is that the relatively small number of individuals with plaster cast (n = 230) hinders development of a prediction model specifically targeted to this group. To overcome this issue and avoid overfitting, we first developed our model in the entire MEGA study population and then tested our full model in the plaster cast subgroup. Finally, using a c-statistic alone for building a prediction model may eliminate important risk factors. To overcome this, we first developed our full model based on clinical as well as statistical criteria. Candidate predictors were retained based on (1) a forward selection procedure or (2) well-established association in the literature. We used the c-statistic only to slim down our full model so that the same predictive power could be reached with fewer predictor variables.

Clinical Implications

Our study showed a good performance of the different prediction models in plaster cast patients. Although we found an added value of genetic variance and biomarker information in the prediction of VTE, the clinical model (with environmental factors only) performed only slightly less well than the full model, with a good discriminative statistic of 0.77 (95% CI 0.66–0.87) in the derivation data. Moreover, in our validation sets, the clinical model performed as well or even better than the full model, with an AUC of 0.75 (95% CI 0.55–0.94) and 0.96 (95% CI 0.92–0.99) in the THE-VTE study and the Milan study, respectively. Therefore, it is doubtful whether information on genetic variance and biomarkers will lead to higher accuracy in the prediction algorithm. In addition, genetic testing is currently not practical in the clinical setting and probably less cost-effective (due to the small prevalence of some genetic variants), and therefore the diagnostic value of these predictors might be limited.

Currently, the American College of Chest Physicians advises that pharmacologic thromboprophylaxis should not be used in patients with isolated lower-leg injuries requiring leg immobilization [12]. The UK National Institute for Health Care and Excellence guidelines recommend considering VTE prophylaxis after evaluating the risks and benefits in clinical discussion with the patient [31]. In addition, the British Society for Haematology recommends prophylaxis for patients at high risk of VTE associated with lower limb plaster cast [32]. Our L-TRiP(cast) score, based on the clinical model, classifies individuals with plaster cast of the lower extremity as high risk or low risk for VTE. This may give guidance to clinicians on prescribing thromboprophylaxis, in line with the latest guidelines. Defining a definite cutoff point is not straightforward. We cautiously suggest using a cutoff point of 9 points to classify individuals as being at high risk for VTE, in which case 74.7% of the people with plaster cast (cases and controls) in our study were identified as high risk. In this way, our risk score can identify a large proportion of people at risk; assuming an overall

incidence of VTE of 2.5% (or more with increasing age), the model in these patients has a positive predictive value for the development of VTE of 5.0% while only 0.8% of individuals who scored lower than 9 points will develop VTE. For recurrence, a ≥5.0% risk is considered as an indication for thromboprophylaxis [33], which outweighs the risk of major bleeding. For short term treatment (~6 wk for plaster cast), the bleeding risk is obviously much lower and is estimated at 0.5%. Furthermore, a higher sensitivity could be preferred over a higher specificity, as the burden of missing a VTE might be worse than the burden of overtreatment (i.e., prophylaxis without therapeutic consequences and bleeding complications). While an established cutoff is lacking, clinicians may determine the trade-off between thrombosis and bleeding risk using this decision rule, until additional results from other studies are available (ideally, a randomized controlled trial that compares thromboprophylaxis in all plaster cast patients, or never thromboprophylaxis, with the decision rule based on our L-TRiP[cast] score).

Conclusion

By using information on environmental risk factors, genetic risk factors, and biomarkers, we were able to develop models that predict the risk of VTE after cast immobilization of the lower extremity. The derivation models in this study show that determination of biomarkers and genetic variance leads to better accuracy in the prediction of VTE in plaster cast patients. However, the validation data show that the clinical model performs as well, or even better. The L-TRiP(cast) score may therefore be more efficient and can be used in the clinical setting. These results can give guidance in clinical decision-making until an unambiguous guideline for thromboprophylaxis therapy in these patients is available, so that not every patient needs to be exposed to the risk and burden of anticoagulant treatment.

REFERENCE LIST

1. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet. 1999;353:1167–1173.
2. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet. 2012;379:1835–1846.
3. Lijfering WM, Rosendaal FR, Cannegieter SC. Risk factors for venous thrombosis—current understanding from an epidemiological point of view. Br J Haematol. 2010;149:824–833.
4. Hippisley-Cox J, Coupland C. Development and validation of risk prediction algorithm (QThrombosis) to estimate future risk of venous thromboembolism: prospective cohort study. BMJ. 2011;343:d4656.
5. Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. 2010;8:2450–2457.
6. de Haan HG, Bezemer ID, Doggen CJ, Le Cessie S, Reitsma PH, Arellano AR, et al. Multiple SNP testing improves risk prediction of first venous thrombosis. Blood. 2012;120:656–663.
7. Ay C, Vormittag R, Dunkler D, Simanek R, Chiriac AL, Drach J, et al. D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. J Clin Oncol. 2009;27:4124–4129.
8. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111:4902–4907.
9. Vormittag R, Simanek R, Ay C, Dunkler D, Quehenberger P, Marosi C, et al. High factor VIII levels independently predict venous thromboembolism in cancer patients: the cancer and thrombosis study. Arterioscler Thromb Vasc Biol. 2009;29:2176–2181.
10. van Adrichem RA, Debeij J, Nelissen RG, Schipper IB, Rosendaal FR, Cannegieter SC. Below-knee cast immobilization and the risk of venous thrombosis: results from a large population-based case–control study. J Thromb Haemost. 2014;12:1461–1469.
11. Ettema HB, Kollen BJ, Verheyen CC, Buller HR. Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. J Thromb Haemost. 2008;6:1093–1098.
12. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopaedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e278S–e325S.
13. Testroote M, Stigter W, de Visser DC, Janzing H. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. Cochrane Database Syst Rev. 2008;2008:CD006681.
14. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293:715–722.
15. Bezemer ID, Doggen CJ, Vos HL, Rosendaal FR. No association between the common MTHFR 677C->T polymorphism and venous thrombosis: results from the MEGA study. Arch Intern Med. 2007;167:497–501.
16. Cannegieter SC, Doggen CJ, van Houwelingen HC, Rosendaal FR. Travel-related venous thrombosis: results from a large population-based case control study (MEGA study). PLoS Med. 2006;3:e307.

17. Gomez E, van der Poel SC, Jansen JH, van der Reijden BA, Lowenberg B. Rapid simultaneous screening of factor V Leiden and G20210A prothrombin variant by multiplex polymerase chain reaction on whole blood. Blood. 1998;91:2208–2209.
18. Ocak G, Vossen CY, Verduijn M, Dekker FW, Rosendaal FR, Cannegieter SC, et al. Risk of venous thrombosis in patients with major illnesses: results from the MEGA study. J Thromb Haemost. 2013;11:116–123.
19. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med. 1999;18:681–694.
20. Moons KG, Kengne AP, Grobbee DE, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: II. External validation, model updating, and impact assessment. Heart. 2012;98:691–698.
21. van Hylckama Vlieg A (2009) Thrombophilia, hypercoagulability, and environment, and the risk of venous thrombo-embolism (THE-VTE study) [abstract]. Abstract number 7:PP-MO-289. XXII Congress of the International Society on Thrombosis and Haemostasis; 11–16 July 2009; Boston, MA, US.
22. van Hylckama Vlieg A, Baglin CA, Luddington R, MacDonald S, Rosendaal FR, Baglin TP. The risk of a first and recurrent venous thrombosis associated with elevated D-dimer and thrombin potential; results of THE-VTE Study. J Thromb Haemost. 2015;13:1642–1652.
23. Ribeiro DD, Bucciarelli P, Braekkan SK, Lijfering WM, Passamonti SM, Brodin EE, et al. Seasonal variation of venous thrombosis: a consecutive case series within studies from Leiden, Milan and Tromso. J Thromb Haemost. 2012;10:1704–1707.
24. Nokes TJ, Keenan J. Thromboprophylaxis in patients with lower limb immobilisation—review of current status. Br J Haematol. 2009;146:361–368.
25. Struijk-Mulder MC, Ettema HB, Verheyen CC, Buller HR. Comparing consensus guidelines on thromboprophylaxis in orthopaedic surgery. J Thromb Haemost. 2010;8:678–683.
26. Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. Arch Intern Med. 2000;160:3415–3420.
27. Kamphuisen PW, Eikenboom JC, Vos HL, Pablo R, Sturk A, Bertina RM, et al. Increased levels of factor VIII and fibrinogen in patients with venous thrombosis are not caused by acute phase reactions. Thromb Haemost. 1999;81:680–683.
28. Kraaijenhagen RA, in't Anker PS, Koopman MM, Reitsma PH, Prins MH, van den Ende A, et al. High plasma concentration of factor VIIIc is a major risk factor for venous thromboembolism. Thromb Haemost. 2000;83:5–9.
29. O'Donnell J, Mumford AD, Manning RA, Laffan M. Elevation of FVIII:C in venous thromboembolism is persistent and independent of the acute phase response. Thromb Haemost. 2000;83:10–13.
30. Truijers M, Kranendonk SE, Nurmohamed MT. [Thromboprophylaxis in general surgical practices in the year 2004: perioperative use during hospitalisation, during out-patient care and following plaster cast immobilisation.] Ned Tijdschr Geneeskd. 2005;149:2511–2516.
31. National Institute for Health Care and Excellence. Venous thromboembolism in adults admitted to hospital: reducing the risk. NICE guidelines [CG92]. London: National Institute for Health Care and Excellence; 2010.
32. Baglin T, Barrowcliffe TW, Cohen A, Greaves M. Guidelines on the use and monitoring of heparin. Br J Haematol. 2006;133:19–34.

33. Kearon C, Iorio A, Palareti G. Risk of recurrent venous thromboembolism after stopping treatment in cohort studies: recommendation for acceptable rates and standardized reporting. J Thromb Haemost. 2010;8:2313–2315.

7

Venous thromboembolism risk stratification for patients with nonsurgical lower-limb trauma requiring immobilization: a consensus decision-making aid, clinical model designed using the Delphi method

Douillet D, Németh B, Penaloza A, Le Gal G, Moumneh T, Cannegieter SC, Roy PM.

PLoS One. 2019 Jun 20;14(6):e0217748.

ABSTRACT

Background Thromboprophylaxis for patients with non-surgical isolated lower-limb trauma requiring immobilization is a matter of debate. Our aim was to develop and validate a clinical risk- stratification model based on Trauma, Immobilization and Patients' characteristics (the TIP score).

Methods The TIP score criteria and the cut-off were selected by a consensus of 27 international experts using the Delphi method. Retrospective validation was performed in a population-based case-control study (MEGA study). The potential score's impact in anticoagulant treatment was assessed in a prospective single-center observational cohort study.

Findings After four successive rounds, 30 items constituting the TIP score were selected: thirteen items for trauma, three for immobilization and 14 for patient characteristics were selected, each rated on a scale of 1 to 3. In the validation database, the TIP score had an AUC of 0.77 (95% CI 0.70 to 0.85). Using the cut-off proposed by the experts (≥5) and assuming a prevalence of 1.8%, the TIP scores had a sensitivity, specificity and negative predictive values of 89.9%, 30.7% and 99.4% respectively. In the prospective cohort, 84.2% (165/196) of all the patients concerned who presented at the emergency department had a low VTE risk not requiring thromboprophylaxis according to their TIP scores. The 3-month rate of symptomatic VTE was 0.5% [95% CI 0.1–2.8].

Conclusion For patients with non-surgical lower-limb trauma and orthopaedic immobilization, the TIP score allows an individual VTE risk-assessment and shows promising results in guiding thromboprophylaxis.

BACKGROUND

Isolated lower-limb trauma requiring cast immobilization is a common condition with several thousand patient admissions into emergency departments each day. Approximately 120,000 patients were admitted into US emergency departments for lower-limb injury in 2009 according to the National Electronic Injury Surveillance System (NEISS) [1]. Those patients are at risk of venous thromboembolism (VTE) owing to the venous stasis secondary to immobilization, hypercoagulability and vascular trauma, and they may be able to benefit from thromboprophylaxis [2–4]. In a recent case-control study, patients with a below-knee cast immobilization had an eight-fold increased risk of VTE within one year following cast application (OR 8.3 [95% CI 5.3 to 12.9]) [5]. However, the benefits of preventive anticoagulation remain unclear. A recent meta-analysis by the Cochrane library assessing low molecular weight heparin (LMWH) for VTE prophylaxis in patients with lower-limb cast immobilization included eight randomized controlled trials and showed that LMWH reduced the rate of VTE. However, the quality of evidence was moderate, especially due to the risks of selection and attrition biases. Moreover, low-quality trials were pooled with high-quality trials, thus diluting the effect of higher-quality studies. Therefore, the authors suggested that future research might give more directives on specific thromboprophylaxis advice for different types of patient or patient groups [6].

Trauma patients are heterogeneous and represent a wide range of VTE risk: some high-risk patients may benefit from anticoagulant treatment whereas, for others, this risk may be too low to justify thromboprophylaxis. Several research reports have shown that the VTE risk depends on the type of trauma (e.g. simple sprain vs severe fracture) as well as on the type of orthopaedic immobilization (e.g. all lower-limb casting vs. below-knee brace) and on patient characteristics (e.g. young person with no medical history vs old person with a history of cancer and VTE), these different factors acting synergistically [5–8].

Our aim was to develop and validate a clinical risk-stratification model for patients with isolated non-surgical trauma of the lower limb requiring orthopaedic immobilization in order to guide physicians for thromboprophylaxis treatment based upon individual risk-assessments.

METHODS

Design

We used the Delphi method to reach an expert consensus on VTE risk factors in patients with non-surgical lower-limb trauma requiring cast immobilization, and to perform a clinical decision-making model: the TIP (Trauma, Immobilization, Patients) score [9–10]. A validation of this score was performed in a large population-based case-control study: MEGA study (*Figure 1*) and the TIP score's usability was assessed in a prospective cohort study.

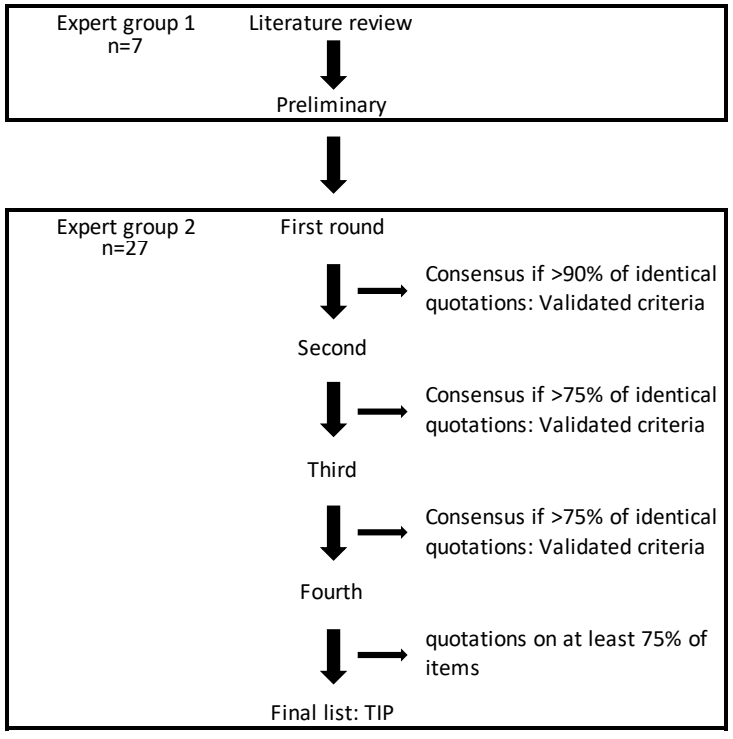


Figure 1: Study flow chart.

Development of the TIP score using the Delphi Method

Preliminary phase

An initial list of potential VTE risk factors for patients with lower-limb trauma of the knee or below the knee and requiring immobilization was compiled by the study's scientific committee. To this end, a comprehensive literature review was performed by the main investigators (DD and PMR). Publications were selected if they described VTE risk factors

in our sub-group of interest and/or in the general population. Criteria were classified into three categories: criteria relating to trauma, immobilization or patient characteristics. A preliminary list of 110 potential risk factors (41 for the type of trauma, 16 for the type of immobilization and 53 for patient characteristics) was compiled. The list was notified to the members of the scientific committee, who were encouraged to retrieve or modify the proposed criteria and to add other potential VTE risk factors. The scientific committee comprised seven experts. Finally, the first list was made up of 76 items (*S1 Table*).

Delphi Panel

The Delphi panel consisted of international multidisciplinary clinical experts (n = 27) whose eligibility was determined based upon their prior participation in collaborations and thromboembolic relevant publications indexed in PubMed/Medline. Unlike the principal investigator, members of the scientific committee were allowed to take part as experts. Anonymity of the panelists was assured throughout all Delphi rounds, i.e. the experts did not know who the other participants were, nor from whom answers, or commentaries had been obtained. With acceptance of the invitation, experts gave their informed consent to respect the rules of the Delphi Method, and to publication of the results (*Table 1*).

Data collection

Four rounds of expert consultations were performed between January and April 2017. The initial list of criteria was sent out to the experts as well as a list of references. Experts were asked to score each of the 76 items from 0 to 3. Zero was equivalent to "it is not a significant risk factor", 1 to "it is a low-risk factor", 2 to "it is an intermediate risk factor" and 3 to "it is a high-risk factor" for the onset of a thromboembolic event. The experts' comments and suggestions were relayed anonymously to the others at the next round. Criteria with an agreement between the experts >90% (absolute agreement) or >75% (strong agreement) were considered as validated. The others were subjected to a further round. From round to round, participants received the summary of results from the previous round and a questionnaire with an updated list of criteria. Questionnaires were sent out, and answers were collected electronically. The duration of each round was two weeks. To maximise participation, weekly e-mail reminders were sent to non-responders. On the final round, the experts were asked to group and simplify the criteria, which resulted in the final score named TIP score for trauma, immobilisation and patient. In addition, experts were asked to suggest a threshold value of VTE risk at which thromboprophylaxis should be administered.

Table 1: Delphi experts' characteristics.

Demographics	n=27	%
Gender		
Male	24	89
Female	3	11
State/territory		
Belgium	3	11
Canada	2	7
France	12	44
Monaco	1	4
Netherlands	3	11
Spain	1	4
Switzerland	2	7
Tunisia	1	4
United States	2	7
Expert category		
Anaesthesiology	1	4
Cardiology	1	4
Emergency medicine	10	37
Internal medicine	2	7
Orthopaedic surgery	3	11
Pulmonologist	4	15
Vascular medicine	5	19
Vascular surgery	1	4

Statistical analysis

Survey responses were summarized with descriptive statistics. Consensus (i.e., importance and agreement) was defined by examining the data distributions, mean and percentage of respondents rating. For the first round, criteria with a rate of agreement of over 90% were validated as absolute consensus. For the subsequent rounds, criteria with a rate of agreement of more than 75% were considered as a strong agreement. The study was considered positive if the agreement rate was greater than 75% for at least 75% of the items at the end of the fourth round. Data were analyzed using Microsoft Excel and the built-in tools from the SurveyMonkey website.

Validation of the TIP score

Study Design

Retrospective validation was performed in the MEGA study (Multiple Environmental and Genetic Assessment of risk-factors for venous thrombosis). Details of this study have been published previously [11–13]. In short, 4,956 consecutive patients aged 18 to 70 and with a first deep-vein thrombosis (DVT), pulmonary embolism (PE), or both, were recruited from six anticoagulation clinics in Netherlands between 1 March 1999 and 31 August 2004. The diagnosis of DVT or PE was confirmed by (Doppler) ultrasonography, ventilation/perfusion scan, angiography, or a spiral CT scan. The control group (n = 6,297) consisted of partners of participating patients and other controls who were identified using a random digit dialling method; controls were frequency-matched to cases with respect to sex and age. All participants completed a questionnaire on VTE risk-factors such as trauma, immobilisation (including plaster-cast and cast location), (orthopaedic) surgery, current use of medication, if any, and comorbidity in the past year before the VTE event.

Population

For this analysis, cases and controls (n = 230, 194 cases and 36 controls) with a leg-cast in the MEGA study were used. After excluding those participants who also underwent surgery as part of their treatment, 176 cases and 33 controls were retained in the analysis.

Statistical analysis

Since for some patients, information on a few risk-factors were missing; we performed a multiple imputation technique to obtain complete data (10 imputations, results pooled in accordance with Rubin's rules) [14]. Then the TIP score was calculated for each patient. Subsequently, the Area Under the Curve (AUC) was estimated by computing a Receiver Operating Characteristic. Sensitivity and specificity were calculated using the cut-off defined by the experts. Negative and positive predictive values were estimated assuming a prevalence of 1.8% [15].

We performed a sensitivity analysis, including only cases and controls in which the trauma component was known (n = 188, 163 cases, 25 controls). All validation analyses were performed in IBM SPSS Statistics for Windows, version 20.0 and Stata, version 12.

Ethics

Approval for this study was obtained from the Medical Ethics Committee of Leiden University's Medical Centre, and all participants gave their written informed consent.

Usefulness assessment

Study design

In order to assess the proportion of patients for which thromboprophylaxis should be considered if the TIP score were applied using the cut-off defined by the experts, we performed a prospective single-centre observational cohort study. Our other objectives were to compare thromboprophylaxis with current practice, and to assess the 3-month rate of symptomatic VTE, all causes of deaths and bleeding.

Population

All patients with a non-surgical lower-limb trauma requiring an immobilization who gave their informed consent were included in the Emergency Department of Angers University Hospital. Clinical characteristics, including criteria of the TIP score and thromboprophylaxis decision in current practice, were collected prospectively. The TIP score was calculated retrospectively. Missing data were considered to be normal or absent. Patients were interviewed by telephone at the end of a 3-month follow-up period. End-points were the occurrence of a symptomatic VTE (distal or proximal deep vein thrombosis, pulmonary embolism or unexplained sudden deaths for which PE could not be excluded), bleeding or death. All possible events were externally adjudicated by an independent adjudication committee.

Statistical analysis

Data were summarized as means and standard deviations or as numbers and percentages, depending on the data type. Proportions are given with their 95% confidence interval (CI). Comparative analyses were performed using McNemar's test, using $p<0.05$ for statistical significance.

Ethics

This study was approved by the Ethics Committee (ID-RCB: 2017-A00291-52) and declared on clinicaltrials.gov before inclusion of the first patient (NCT03089255).

RESULTS

Development of the TIP score using the Delphi Method

Four rounds were carried out, as defined a priori. The response-rate increased over successive rounds, 74% (20/27), 81% (22/27), 89% (24/27) and 93% (25/27), respectively. At the end of the rounds, all 76 criteria obtained a consensus considered at least as strong (>75%) (*S2 Table*). In the first round, two items obtained an absolute agreement (>90% identical answers) and were not submitted to the second round (n = 2/76; 2.6%). In the second round, 52 criteria were validated with an agreement rate >90% (n = 3/76; 3.9%) or >75% (n = 49/76; 64.5%). For the third round, 17 criteria reached a strong consensus >75% (n = 17/76; 22.4%). In the last round, a consensus was reached on the remaining five items (n = 5/76; 6.6%) (*S2 Table*).

The final score includes 30 criteria versus 76 on the first list. Eleven risk factors considered as not being clinically relevant were withdrawn: phalanx fracture(s), immobilization with plantar support, age less than 55 years, male sex, active smoking, known coronary artery disease, lower-limb arterial disease, liver failure, cirrhosis, diabetes, neuroleptic treatment. On the experts' proposal and in order to simplify the TIP score, 43 items were grouped together, resulting in 13 criteria (*S2 Table*). For example, BMI 25–35 kg/m2 and BMI >35 kg/m2 were consolidated into one criterion: BMI >30 kg/m2 scoring 1. Finally, four items were withdrawn. Known minor thrombophilia and other known hemostasis disorders were withdrawn because they were considered to be very rare in clinical practice in the absence of previous VTE. Quadriceps tendon rupture and distal femur fracture were left out because they were considered to require surgery most of the time, which did not correspond to the target population. For these regroupings or withdrawals, agreement rates ranged from 82% to 100% in the panel of experts.

The final TIP score includes 13 criteria for trauma, three criteria for immobilization, and 14 criteria for patient characteristics (*Table 2*). For trauma items, as for immobilization, a single item must be chosen (the item that corresponds to the highest score) whereas for the characteristics of the patient, the scores of each item must be summed up. For example, a 62-year-old patient with a personal history of VTE and cancer requiring rigid immobilization below the knee owing to severe ankle sprain with forefoot dislocation will have a TIP score of 9 (T:2; I:2, P:3+1+1). The final score was approved by 25/26 experts (96%). One expert suggested reducing the number of risk-factors in order to improve the score's clinical usability *(S1 Table)*.

Table 2: the TIP score.

	Criteria of the Trauma Immobilization Patient (TIP) score	Score
T	*Only one item can be selected*	
	Leg bones fracture (tibia and fibula)	3
	Proximal tibia fracture	
	Ankle bi- or tri-malleolar fracture	2
	One leg bone fracture (tibia or fibula)	
	Patellar fracture	
	Ankle or rear foot dislocation	
	Severe ankle sprain (grade 3) or knee sprain (with important oedema or haemarthrosis)	
	Achilles' tendon rupture	
	Ankle isolated malleolar fracture	1
	Tarsal bone(s) or forefoot fracture	
	Proximal tibiofibular, patellar, midfoot or forefoot dislocation	
	Moderate ankle sprain (grade 1 or 2) or knee sprain (without important oedema or hemarthrosis)	
	Major muscle injury	
I	*Only one item can be selected*	
	Rigid immobilization including the knee (resin or plaster)	3
	Rigid below the knee immobilization (resin or plaster)	2
	Semi-rigid immobilization without plant support	1
P	*Several items can be selected*	
	Known major thrombophilia* or a personal history of VTE †	3
	Age > 75 y	2
	Family history of VTE (first-degree relative)	2
	Active cancer or Myeloproliferative disorder	2
	Surgery within the past 3 months	2
	Pregnancy and Puerperium (less than 6 months)	2
	Oestrogen hormone therapy (<2y)	2
	Age > 55 y and < 75 y	1
	BMI > 30kg/m2 §	1
	History of cancer	1
	Chronic venous insufficiency	1

Table 2: Continued.

Criteria of the Trauma Immobilization Patient (TIP) score	Score
Bedridden within the past 3 months	1
or long travel/flight (> 6 hours)	
or unilateral or bilateral lower extremity paralysis	
Oestrogen hormone therapy (>2y)	1
Congestive heart failure NYHA > II ¶	1
or chronic respiratory failure	
or inflammatory bowel disease	
or chronic kidney disease (GFR<50mL/min) ¥	

*Known major thrombophilia: antithrombin deficiency, homozygous factor V Leiden, homozygote mutation on the prothrombin gene, multiple thrombophilia.
† Personal history of VTE: DVT or PE.
‡ Y: years
§ BMI: Body Mass Index
¶ NYHA: New York Heart Association's classification of cardiovascular disease
¥ GFR: Glomerular filtration rate

The experts were asked to decide intuitively on a TIP score threshold value above which a thromboprophylaxis would be required. With a participation rate of 85% (23/27), results ranged from 3 to 9 with a median of 4, meaning that only patients with a TIP score greater than 4 (≥5) should be considered for thromboprophylaxis.

Retrospective validation of the TIP score in the MEGA study

In the plaster-cast patients treated without surgery (n = 209; 176 patients and 33 control individuals), the TIP score ranged between 2 and 20 points (out of a maximum of 29 points for men and 35 for women). The TIP score had an AUC of 0.77 (95% CI 0.70 to 0.85). Using 5 points as a cut-off (0–4: low-risk i.e. negative, ≥5: high-risk i.e. positive), the sensitivity was 89.9% while the specificity was 30.7% (*Table 3*). Assuming a prevalence of 1.8%, the negative predictive value was 99.4% and the positive predictive value 2.32%. Using the Youden index, the optimal threshold value was 6 points with 71.9%, 64.9%, 99.3% and 3.76% for sensitivity, specificity, negative and positive predictive values, respectively (*Table 3*).

In the sensitivity analysis including only patients with information about their type of trauma, 188 patients were included (163 cases and 25 control individuals). The TIP score had an AUC 0.77 (95% CI 0.69 to 0.85).

Table 3: Predictive performance of the TIP score.

Cutpoint	Sensitivity	Specificity	PVV	NPV
3	100,0%	0,0%	1,8%	100,0%
4	98,5%	6,5%	1,9%	99,6%
5	89,9%	30,7%	2,3%	99,4%
6	74,9%	64,9%	3,8%	99,3%
7	53,9%	83,0%	5,5%	99,0%
8	32,8%	96,1%	13,3%	98,7%
9	16,6%	100,0%	100,0%	98,5%
10	7,3%	100,0%	100,0%	98,3%
11	3,2%	100,0%	100,0%	98,3%
12	0,8%	100,0%	100,0%	98,2%

Usefulness assessment of the TIP score in the prospective study

Between May and September 2017, 197 consecutive patients with a non-surgical lower-limb trauma were included in the prospective study. One surgical patient was secondarily excluded. Baseline characteristics are summarized in *Table 4*. The TIP score was <5 for 165 of 196 patients (84.2% [95% CI 78.6 to 88.8) and ≥5 for 31 patients (15.8% [95% CI 11.2 to 21.4]). In accordance with standard practice, 72/196 (36.7%) patients received anticoagulant treatment for thromboprophylaxis, 52/165 (31.5%) among patients with a TIP score <5 and 20/31 (64.5%) among patients with a TIP score ≥5. If the TIP score had been applied, the anticoagulation rate would have been reduced by -20.9%, ([95% CI -15.7 to -27], p<0.05). Six patients were lost to follow-up. One patient with a TIP score of = 5 did not receive thromboprophylaxis and developed proximal deep vein thrombosis one week after trauma and immobilization. The 3-month rate of symptomatic VTE was 0/160 (0%) [95% CI 0 to 2.3] in the sub-group of patients with a TIP score <5 and 1/30 (3.3%) [95% CI 0.6 to 16.7] in the sub-group of patients with a TIP score ≥5. No patient had major bleeding (0%, [95% CI 0.0 to 4.1%]), but three of 72 patients who received thromboprophylaxis had a non-major clinically relevant bleeding (4.2% [95% CI 1.4 to 11.6]).

Table 4: Patient characteristics of the prospective cohort.

Patients	N=196
Male sex __ no. (%) or means +/- SD	105 (53,3)
Age (yr) __means ± SD	37,5±16,2
Body-mass index __ means ± SD*	25,7 ±6
Personal history of venous thromboembolism __ no. (%)	9 (4,6)
History of venous thromboembolism in first-degree relatives __ no. (%)†	16 (8,2)
Active cancer __ no. (%)‡	2 (1)
History of cancer __ no. (%)§	5 (2,6)
Surgery < 3 months __ no.(%)	8 (4,1)
Recent bed rest __ no.(%)¶	6 (3,1)
Pregnancy __ no. (%)	2 (1)
Hormonal treatment __ no.(%)¥	29 (14.8)
Venous insufficiency __ no. (%)	10 (5,1)
Trauma	
Patellar fracture __ no./no. tot (%)	1 (0.5)
Knee sprain with oedema / haemarthrosis__ no. (%)	7 (3.6)
Knee sprain without oedema / haemarthrosis__ no. (%)	11 (5,6)
Major muscle injury__ no./no. tot (%)	3 (1.5)
Fracture of one leg bone (tibia or fibula) __ no. (%)	7 (3.6)
Ankle fracture: bi- and trimalleolar fracture__ no. (%)	9 (4.6)
Ankle fracture: isolated malleolar fracture__ no. (%)	2 (1)
Ankle sprain grade 3__ no. (%)	32 (16.3)
Ankle sprain grade 1 or 2 __ no. (%)	103 (52.6)
Achilles tendon rupture non-surgical__ no. (%)	1 (0.5)
Fracture one (or more) tarsal bone(s) or forefoot__ no. (%)	20 (10.2)
Immobilisation	
Rigid including knee (resin or plaster) __ no. (%)	0 (0)
Rigid below the knee (resin or plaster) __ no. (%)	54 (27.6)
Semi-rigid without plantar support__ no. (%)	122 (62.2)
Others immobilization__ no. (%)	20 (10.2)

DISCUSSION

Through a Delphi study involving an international multidisciplinary panel of experts and physicians, we classified thromboembolic risk-factors in patients with non-surgical lower-limb trauma requiring immobilization. A risk-stratification model based on trauma, immobilization and patient characteristics, i.e. the TIP score, was established. Validated retrospectively in a case-control study, the TIP score shows good prognostic performance (AUC 0.77). Using <5 as cut-off, the TIP score identified over 80% of patients as having a low risk of VTE, hence, no indication for thromboprophylaxis.

Current guidelines for thromboprophylaxis, and therefore also practices, differ widely among countries and centers, ranging from the absence of preventive anticoagulation to thromboprophylaxis for all patients for whom plantar support is not possible [16–19]. Both may be inappropriate. Indeed, recommendations for thromboprophylaxis are based mainly on small studies including heterogeneous and selected populations [20–24]. However, recently the largest multicenter randomized controlled trial performed thus far failed to demonstrate any beneficial effect of LMWH for VTE prevention in unselected patients with lower-limb casting [15]. Still, about 1.5%-2.0% of all patients develop VTE despite thromboprophylactic therapy [15]. Therefore, a new prophylactic strategy needs to be developed in order to prevent VTE in this large patient group. By using a risk-stratification model, low-risk patients can be withheld from thromboprophylaxis (and its downsides, i.e. bleeding, costs) whereas high-risk patients could benefit from treatment (i.e. prevent VTE), which should be of longer duration or higher dosage than the current strategy, as this is apparently not sufficient. For this purpose, the TIP score is a valuable and relevant decision-making aid.

Several methods can be used to develop a clinical decision-making aid model. In cases of heterogeneous and/or incomplete scientific data, the Delphi method is an appropriate and well-validated method [9–10]. It allows building a reliable model that is based upon scientific knowledge as well as clinical expertise. Our TIP score is the outcome of an international expert consensus that agreed on all the items presented through four successive rounds. With an AUC statistic of 0.77 (95% CI 0.70 to 0.85), the TIP score compares favorably with other risk-assessment models for VTE, such as the Qthrombosis for the general population (AUC of 0.75) [25], the Padua prediction score for hospitalized medical patients (AUC of 0.76) [26], or Trauma Embolic Scoring System (TESS) for severely injured patients (AUC of 0.71) [27]. Importantly, the TIP score appears to have at least similar performance to the L-TRiP (cast) score for patients with cast immobilisation developed from the MEGA-study [28]. Assessed, like the TIP score, in a sub-group of patients of the MEGA study with plaster-cast, the L-TRiP (cast) score has an AUC statistic of 0.76 (95% CI 0.66 to

0.86). Of note, many clinical variables of the L-TRIP (cast) score were incorporated by the experts into the TIP score. Nevertheless, the two scores have some relevant differences. For example, some items of the L-TRiP (cast) such as sex, pneumonia or superficial vein thrombosis were not considered by the experts as clinically relevant for decision-making at emergency departments. Conversely, the TIP score takes into account more variables, such as trauma and immobilisation characteristics, and apply to patients with semi-rigid immobilisation. Both the L-TRiP (cast) score and TIP score need prospective assessment and validation.

Our prospective observational study was the first stage of this process. Using the 5-point cut-off suggested by the expert, our results show that a large proportion of patients admitted into our emergency department for non-surgical lower-limb trauma requiring immobilization are classified as being a low-risk patient for VTE (<1%). Therefore, applying the TIP score could lead to a large decrease in the anticoagulation rate in some centers and countries. In a French national observational study, the overall rate of prophylactic treatment in non-surgical patients with lower-limb trauma and orthopaedic immobilization was 61% [29]. Such a large decrease in LMWH prescription would reduce the discomfort and iatrogenic risk of daily injections: 1.6% of anticoagulated patients experienced clinically-significant bleeding in our study. On the other hand, the TIP score allowed identification of 16% of at-risk patients who might benefit from anticoagulation. Of note, 45% of high-risk patients according to the TIP score did not receive thromboprophylaxis in our single-center study. Moreover, high-risk patients might be candidates for other and possibly more powerful treatments than LMWH. Despite LMWH prevention, 1.4% of unselected patients with plaster-cast developed symptomatic VTE in the POT-CAST study [13]. Fondaparinux was more effective than nadroparin for preventing VTE after below-knee injury requiring prolonged immobilization in patients with additional risk-factors in a randomized controlled study [30], and a direct oral anticoagulant could be a valuable option for further investigation.

Nevertheless, our study does have some limitations. Firstly, although eligible experts for the Delphi method were carefully recruited, selection bias could not be excluded, many of them having already collaborated. Nevertheless, the panel included a heterogeneous group of researchers and clinicians from various countries and continents, and such heterogeneity strengthens the consensus statement and practical applicability worldwide. The experts defined the threshold value justifying thromboprophylaxis using their 'gestalt', not on the predictive performance of the TIP score. Nonetheless, this threshold appears to optimize the sensitivity of the score as comparing to the value obtained using the Youden index. Moreover, our findings demonstrate that multidisciplinary physician teams are able to agree on clinically detailed guidelines to make decisions on VTE risk-stratification. Our final

score includes 30 criteria, which may be perceived as being a lot, a concern expressed by one expert. However, thanks to computerized clinical decision-support systems available on smartphones or other devices, this large number of criteria may not be disincentive. Indeed, such computerized decision-making aid systems have improved clinical practice at Emergency Departments [31]. Development of a computerized system for TIP scores is ongoing. Secondly, the MEGA study database contains a large number of patients. However, after selecting our population of interest the validation population remains modest (230 patients, 194 cases and 36 controls). Some data were missing, especially regarding trauma characteristics. Nevertheless, our sensitivity analysis confirmed that the results were similar both with and without imputation for missing data. Since the MEGA study is a case-control study, we had to apply a predefined prevalence (1.8% on the basis of the POT-CAST study) in order to calculate the predictive values of the TIP score. Finally, our observational prospective study was single-centre and not empowered to demonstrate the safety of TIP score implementation. Nevertheless, our results are encouraging and support further assessments.

In conclusion, for patients with non-surgical lower-limb trauma and orthopaedic immobilization, the TIP score, based on an international experts' consensus using the Delphi method, allows an individual VTE risk-assessment and shows promising results in terms of its safety and usefulness for guiding thromboprophylaxis. An implementation validation study is now required.

REFERENCE LIST

1. Lambers K, Ootes D, Ring D. Incidence of patients with lower extremity injuries presenting to US emergency departments by anatomic region, disease category, and age. Clin Orthop Relat Res. jan 2012;470(1):284 90.
2. Kujath P, Spannagel U, Habscheid W. Incidence and prophylaxis of deep venous thrombosis in outpatients with injury of the lower limb. Haemostasis. march 1993;23 Suppl 1:20 6.
3. Knudson MM, Morabito D, Paiement GD, Shackleford S. Use of low molecular weight heparin in preventing thromboembolism in trauma patients. J Trauma. sept 1996;41(3):446 59.
4. Kudsk KA, Fabian TC, Baum S, Gold RE, Mangiante E, Voeller G. Silent deep vein thrombosis in immobilized multiple trauma patients. Am J Surg. dec 1989;158(6):515 9.
5. van Adrichem RA, Debeij J, Nelissen RGHH, Schipper IB, Rosendaal FR, Cannegieter SC. Below-knee cast immobilization and the risk of venous thrombosis: results from a large population-based case-control study. J Thromb Haemost. sept 2014;12(9):1461 9.
6. Zee AAG, van Lieshout K, van der Heide M, et al. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilization. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD006681.
7. van Stralen KJ, Rosendaal FR, Doggen CJM. Minor injuries as a risk factor for venous thrombosis. Arch Intern Med. 14 jan 2008;168(1):21 6.
8. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet. 3 apr 1999;353(9159):1167 73.
9. Black N, Murphy M, Lamping D, McKee M, Sanderson C, Askham J, et al. Consensus development methods: a review of best practice in creating clinical guidelines. J Health Serv Res Policy. oct 1999;4(4):236 48.
10. Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol. apr 2014;67(4):401 9.
11. Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 9 feb 2005;293(6):715 22.
12. Bezemer ID, Doggen CJM, Vos HL, Rosendaal FR. No association between the common MTHFR 677C->T polymorphism and venous thrombosis: results from the MEGA study. Arch Intern Med. 12 march2007;167(5):497 501.
13. Cannegieter SC, Doggen CJM, van Houwelingen HC, Rosendaal FR. Travel-related venous thrombosis: results from a large population-based case control study (MEGA study). PLoS Med. aug 2006;3(8):e307.
14. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Med Res Methodol. 2009;9:57.
15. van Adrichem RA, Németh B, Algra A, le Cessie S, Rosendaal FR, Schipper IB, et al. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. New England Journal of Medicine. 9 feb 2017;376(6):515 25.
16. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopaedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. feb 2012;141(2 Suppl):e278S-e325S.

17. French Society of Anaesthesia and Intensive Care. Guidelines on perioperative venous thromboembolism prophylaxis. Update 2011. Short text. Ann Fr Anesth Reanim. 2011 dec;30(12):947-51 [erratum in: 2012 Jan;31(1):93].
18. National Institute for Clinical Excellence. Venous thromboembolism: reducing the risk. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. NICE guideline 92. National Institute for Clinical Excellence, 2010:50.
19. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. sept 2004;126(3 Suppl):338S-400S.
20. Lapidus LJ, Ponzer S, Elvin A, Levander C, Lärfars G, Rosfors S, et al. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. Acta Orthop. aug 2007;78(4):528 35.
21. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. N Engl J Med. 5 sept 2002;347(10):726 30.
22. Jørgensen PS, Warming T, Hansen K, Paltved C, Vibeke Berg H, Jensen R, et al. Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study. Thromb Res. 15 march 2002;105(6):477 80.
23. Testroote M, Stigter W, de Visser DC, Janzing H. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. Cochrane Database Syst Rev. 8 oct 2008;(4):CD006681.
24. Dalkey N, Helmer O. An Experimental Application of the DELPHI Method to the Use of Experts. Management Science. 1 apr 1963;9(3):458 67.
25. Hippisley-Cox J, Coupland C. Development and validation of risk prediction algorithm (QThrombosis) to estimate future risk of venous thromboembolism: prospective cohort study. BMJ. 16 aug 2011;343:d4656.
26. Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. nov 2010;8(11):2450 7.
27. Ho KM, Rao S, Rittenhouse KJ, Rogers FB. Use of the Trauma Embolic Scoring System (TESS) to predict symptomatic deep vein thrombosis and fatal and non-fatal pulmonary embolism in severely injured patients. Anaesth Intensive Care. nov 2014;42(6):709 14.
28. Németh B, Adrichem RAv, Hylckama Vlieg Av, Bucciarelli P, Martinelli I, Baglin T. Venous Thrombosis Risk after Cast Immobilization of the Lower Extremity: Derivation and Validation of a Clinical Prediction Score, L-TRiP(cast), in Three Population-Based Case–Control Studies. Sattar N, editor. PLoS Med. 2015 nov 10; 12(11):e1001899.
29. Riou B, Rothmann C, Lecoules N, Bouvat E, Bosson J-L, Ravaud P, et al. Incidence and risk factors for venous thromboembolism in patients with nonsurgical isolated lower limb injuries. Am J Emerg Med. june 2007;25(5):502 8.
30. Samama C-M, Gafsou B, Jeandel T, Laporte S, Steib A, Marret E, et al. [French Society of Anaesthesia and Intensive Care. Guidelines on perioperative venous thromboembolism prophylaxis. Update 2011.Short text]. Ann Fr Anesth Reanim. dec 2011;30(12):947 51.
31. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. BMJ. 2 apr 2005;330(7494):765.

8

Individualized thromboprophylaxis in patients with lower-leg cast immobilization - a validation and subgroup analysis in the POT-CAST trial

Németh B, van Adrichem RA, Nelissen RGHH, le Cessie S, Cannegieter SC.

Thromb Haemost. 2019 Sep;119(9):1508-1516.

ABSTRACT

Background A small subgroup of patients treated with lower-leg cast immobilization develops Venous Thromboembolism (VTE).

Objectives 1. Identify risk factors for VTE in patients with cast immobilization, 2. Assess the effectiveness of thromboprophylaxis in low- and high-risk groups, 3. Validate the performance of the L-TRiP(cast) score.

Methods Data from the POT-CAST trial were used. 1519 patients with lower-leg cast immobilization were randomized to a prophylactic dose of low-molecular-weight-heparin or no treatment. Primary outcome: symptomatic VTE within 3-months. Absolute risks (AR) were determined for low- and high-risk subgroups. For several risk factors, relative risks (RR) for VTE were estimated with corresponding 95%CIs. For validating the L-TRiP(cast) score, a discrimination and calibration analysis were performed.

Results Patients with a body mass index >30kg/m2 and those with a VTE in their family history had an increased VTE risk, RR 3.8, (95%CI 1.5 - 9.4) and RR 2.4 (95%CI 1.0 - 5.6), respectively. Concerning injury-specific risk factors, patients with an Achilles tendon rupture or those who were surgically treated had the highest risk of VTE, AR at 8.5% (95%CI 3.7 – 16.1) and AR 3.5% (95%CI 1.3 – 7.5), respectively. There were no subgroups in which thromboprophylaxis was effective for prevention of symptomatic VTE. The AUC for the L-TRiP(cast) score was 0.69 (95%CI 0.58 – 0.80).

Conclusions Thromboprophylaxis was not effective for VTE prevention following lower-leg cast immobilization in any risk category. Low- and high-risk individuals could be identified using the L-TRiP(cast) score. The best treatment strategy for these patients is yet to be determined.

INTRODUCTION

Patients treated with lower-leg cast immobilization still develop Venous Thromboembolism (VTE) (consisting of deep vein thrombosis [DVT] or pulmonary embolism [PE]) despite the administration of thromboprophylaxis.[1] Each year, approximately 3.5 million patients are treated with a lower-leg cast worldwide, therefore the burden of VTE is considerable with an estimated number of 56 000 VTEs due to this situation.[1]

In the POT-CAST trial (Prevention Of Thrombosis following lower-leg CAST immobilization), the overall risk of symptomatic VTE was 1.6% (n=1435) within 3-months following lower-leg cast immobilization. A prophylactic dose of low-molecular-weight-heparin (LMWH) (2850 IU once daily for patients <100kg, double dose >100kg, for the total duration of cast immobilization) was not effective for VTE prevention (absolute risk reduction -0.4%, 95% Confidence Interval (CI) -1.8 to 1.0).[2] Hence, new treatment strategies should be established in order to reduce the number of VTEs and to prevent chronic complications such as a post-thrombotic syndrome. A fairly simple approach would be to increase the duration or dose of thromboprophylaxis. However, if we would treat all patients, this may introduce an excess of bleeding events outweighing the number of prevented VTEs. Concomitantly, daily LMWH injections are unpleasant and associated with higher costs compared with no treatment. Therefore, individualized therapy might be a better strategy, in which thromboprophylaxis could be withheld in low-risk individuals whereas a higher dose could be administered in high-risk individuals.

To classify patients as high-risk individuals, some risk factors have been identified in previous studies. Besides classical risk factors like older age[3] and the use of oral contraceptives[4], cast-specific risk factors such as a non-weight bearing cast[5-7] or rigid immobilization[7,8] have been shown to be associated with increased VTE risk. In addition, injury-specific factors such as fracture[9,10] (versus soft tissue injury), severe injury[7] or traumatic injury increase thrombosis risk.[4] In addition to identification of risk factors in individuals, high-risk patients can be identified by use of a prognostic model for VTE risk, in which all such factors are combined. Previously, we developed and validated the L-TRiP(cast) score (Leiden-Thrombosis Risk Prediction) and showed that VTE risk prediction in lower-leg cast patients is feasible and leads to good discrimination. However due to the case-control setting, absolute risks could not be determined.[11] No other prediction models for VTE risk following lower-leg cast immobilization have been validated in this setting.

To explore whether individualized therapy is an option to improve prevention of VTE, we aimed to 1. Identify risk factors for VTE within the POT-CAST trial, 2. Assess the effectiveness of thromboprophylaxis within low- and high-risk groups and 3. Validate the performance of the L-TRiP(cast) score.

METHODS

Study Design

For this study we used data of the POT-CAST trial of which details have been published previously.[2] In short, the POT-CAST study is a pragmatic multicentre, randomized, controlled, open-label trial with blinded outcome evaluation designed to study the effectiveness of LMWH for the prevention of VTE following lower-leg (below the knee) cast immobilization. Patients with a traumatic injury of the leg or foot who were treated with a lower-leg cast for at least 1 week were eligible for inclusion. Those with a personal history of VTE or women who were pregnant were not allowed to participate. 1519 patients were randomized (1:1) to either a prophylactic dose of LMWH (2850IU administered subcutaneously, treatment group) or to no treatment (control group). The primary outcome was the occurrence of a symptomatic VTE within 3 months after inclusion and the primary safety outcome was the occurrence of major bleeding (according to the ISTH criteria[12]) within the same time frame. Patients were not screened for the occurrence of asymptomatic VTE.

Data Collection and Laboratory Analysis

Injury-specific data were collected upon inclusion and derived from an individuals' electronic patient record. In addition, patients were asked to complete a questionnaire (digital [online] or postal) on thrombotic risk factors (such as age, sex, use of oral contraceptives, cancer) shortly after inclusion in the trial. Furthermore, we collected data on the study outcomes, cast application (duration, complications) and treatment adherence using two additional questionnaires, and one final telephone interview, throughout follow-up.

Blood was drawn in vacuum tubes containing 0.105M sodium citrate in all patients upon presentation at the emergency department (before any administration of thromboprophylaxis). All blood samples were centrifuged at 2500g for 10 minutes at 18°C, thereafter, following aliquoting, the samples were stored at −80°C within 4 hours of venepuncture. We measured coagulant factor VIII, factor XI and Von Willebrand factor levels using the TOP analyser (Werfen Instrumentation Laboratory, Barcelona, Spain). DNA analysis for the FV Leiden mutation (rs6025) and the prothrombin G20210A mutation (rs1799963) was performed using a combined polymerase chain reaction method with the TaqMan assay. Blood group polymorphisms were determined by a 5' nuclease assay (Taqman; Applied Biosystems, Foster City, CA, USA) using a PCR reaction mix (Taqman Genotyping Master Mix, Applied Biosystems) and an allele-specific fluorescent probe equipped with a minor groove binding moiety (Applied Biosystems).

Statistical Analysis

After exclusion of patients who had not met the inclusion criteria (or had exclusion criteria), patients who were lost to follow-up or those who withdrew consent, 1435 patients were included in the intention-to-treat population and considered for the current analyses. We calculated absolute risks (AR) for several low- and high-risk subgroups by estimating the cumulative incidence for VTE within 3-months with corresponding 95%CI. In an intention-to-treat analysis, the effectiveness of LMWH for VTE prevention within subgroups was determined by comparing cumulative incidences between the treatment and control group which yielded absolute risk differences (RD) and relative risks (RR) with 95%CIs. For risk factor identification, a similar analysis was performed comparing the cumulative incidences between risk groups. All subgroup analyses were post-hoc analyses and not stated in the original study protocol. However, since the POT-CAST trial showed no effectiveness on a population level, targeting low- and high risk groups seems prompted.

For validation of the L-TRiP(cast) model we assessed discrimination and calibration. Discrimination is a statistic to assess how well a model can distinguish a case from a control (given a pair that consists of a case and control) whereas calibration shows the concordance between the observed risks and the risks as predicted by the model. For a small number of participants (12%), risk factor data were missing. Since only 23/1435 patients developed a VTE, we performed a multiple imputation technique to maintain power for the validation analysis (10 imputations, results were pooled according to Rubins' rules).[13] Following imputation, in a discrimination analysis, we calculated the L-TRiP(cast) score per individual, after which the absolute risk was estimated with corresponding 95%CI (per two points to account for the small event number). For each cut-off we calculated the sensitivity and specificity of the L-TRiP(cast) score and subsequently the Area Under the Curve (AUC) by modelling a Receiver Operating Characteristic (ROC) curve. Second, we fitted the L-TRiP(cast) score in a logistic regression model to obtain a new constant (baseline risk) as this lacked in the development of the L-TRiP(cast) score (because this model was developed using case-control data). Thereafter, we estimated the predicted risk for VTE per individual using the L-TRiP(cast) score which was compared with the observed risk and plotted in a calibration plot.[14]

Finally, we compared the performance of the L-TRiP(score) with two other models designed to predict VTE risk following cast-immobilization, i.e., the full and restricted model (all shown in *Supplement Table 1*). The full and restricted model were developed in addition to the L-TRiP(cast) score) to assess whether the inclusion of biomarkers improved predictive performance.[11] The full model consist of 32 predictors including 3 genetic and 6 biomarker predictors, whereas the restricted model consists of 11 predictors with 2 genetic and 1 biomarker predictors. While in the derivation data, the full and restricted model performed best, the L-TRiP(cast) score was developed to use in clinical practice (no need for blood sampling). For the full model, monocyte percentage, total cysteine and red cell distribution width were not available, but all other biomarkers/genetics (FVIII activity, FXI activity, vWF antigen level, prothrombin mutation, factor V Leiden mutation and ABO blood type) were measured. We compared AUC values and sensitivity and specificity statistics. As the full and restricted model included tertiles of coagulation factors levels (VWf, factor VIII and factor XI) that were based on population data, we checked whether updating the cut-offs of these tertiles to levels of the POT-CAST population improved performance. We expected coagulation factor levels to be increased after trauma, and anticipated on improved performance.

All analyses were performed with the use of IBM SPSS Statistics software for Windows, version 23 (SPSS), and Stata software, version 14 (StataCorp).

RESULTS

Study population and POT-CAST main result

Table 1 shows baseline characteristics of the POT-CAST trial. 1435 were included in the analyses, mean (SD) duration of cast immobilization was 4.9 (2.5) weeks. LMWH prophylaxis was not effective to prevent VTE within 3-months following lower-leg cast immobilization, either in the intention-to-treat or the per-protocol analysis. In the treatment group (LMWH prophylaxis) 10/719 patients developed VTE versus 13/716 patients in the control group (risk difference (RD) -0.4% (95%CI -1.8 to 1.0). No major bleeding occurred in either group.

Table 1: Characteristics of study population.

Patient characteristics §	**Treatment group*** **(n=719)**	**Control group** **(n=716)**
Male sex, no./total no. (%)	347/719 (48.3)	369/716 (51.5)
Mean age, years	46.5±16.5	45.6±16.4
Mean BMI, kg/m^2 †	26.0±4.4	25.7±4.4
Smoking, no./total no. (%)		
Current	173/663 (26.1)	178/665 (26.8)
Ever	188/663 (28.4)	178/665 (24.9)
Oral contraceptives use, no./total no. (% of women)	64/348 (18.4)	41/326 (12.6)
Paid employment (%)	442/664 (66.6)	469/469 (65.5)
Cancer		
Within last year	8/674 (1.2)	9/674 (1.3)
More than 1 year ago	26/674 (3.9)	20/674 (3.0)
Family history of venous thromboembolism, no./total no. (%) ‡	67/638 (10.6)	56/635 (9.4)

* Low Molecular Weight Heparin, either Nadroparin or Dalteparin.
§ Percentages of complete data, BMI data were missing for 112 patients
† BMI: body mass index in kilogram divided by the square of the height in meters.
‡ First degree relatives

Low- and high-risk groups

Table 2a shows absolute risks within all low- and high-risk groups. Men had a similar risk compared with (all) women (AR 1.9% [95%CI 1.1 – 3.3] versus 1.3% [95%CI 0.6 – 2.4]), for an RR of 1.6 (95%CI 0.7 - 3.7). Women using oral contraceptives had an exact similar risk as men (AR 1.9% [95%CI 0.2 – 6.7]). Patients with classical VTE risk factors such as a body mass index above 30 kg/m^2 or a positive family history of VTE had an increased risk of VTE, i.e., RR 3.8 (95%CI 1.5 - 9.4) and RR 2.4 (95%CI 1.0 - 5.6), respectively. Patients with cast immobilization for an Achilles tendon rupture developed VTE in 8.5% (95%CI 3.7-16.1), 4/21 (19.0%) patients who underwent surgery for Achilles tendon repair developed symptomatic VTE compared with 4/73 (5.5%) who were conservatively treated). Immobilization for fractures was associated with a lower risk than Achilles tendon ruptures (1.1% for metatarsal fractures and 1.2% for ankle fractures). Surgically treated injuries led to a higher VTE risk than conservatively treated injuries, AR 3.5% (95%CI 1.3 – 7.5) and 1.3% (95%CI 0.8 – 2.1), respectively (OR 2.7 [95%CI 1.0 - 6.9]). Patients with cast immobilization ≥ 6 weeks had a VTE risk of 1.5% (95%CI 0.7 – 2.7).

The effectiveness of LMWH in all subgroups is shown in *Table 2b*. There were no risk groups in which thromboprophylaxis significantly reduced symptomatic VTE. RRs between the treatment and control group ranged from 0.3 (95%CI 0.1 – 1.3) in women to 2.3 (95%CI 0.6 to 8.9) in patients with an Achilles tendon rupture. Overall, similar RDs were found (though with wide confidence intervals) as compared with the main RD in the entire trial population: RD -0.4 (95%CI -1.8 to 1.0).

Validation of the L-TRiP(cast) score

The L-TRiP(cast) model (score shown in *Table 3*) performed well with an AUC of 0.69 (95%CI 0.58 to 0.80) (*Table 4*). The Full model and Restricted model performed better with an AUC of 0.76 and 0.75 respectively. Updated coagulation factor tertiles (based on the tertile distribution in POT-CAST data) led to a further improvement of discriminative performance. *Table 5* shows sensitivity, specificity and absolute risk data for a range of L-TRiP(cast) scores. The absolute VTE risk increased with higher L-TRiP(cast) score. For example, patients with a risk score of 8-9 had a 1.6% risk while those with a score of 10 to 11 had a 2.8% risk for VTE. Using a cut-off score of at least 8, the sensitivity was 75% with a specificity of 46%. In the calibration plot (*Figure 1*), a good concordance between the observed and predicted probability for VTE is shown.

Table 2a Absolute VTE risk in subgroups of the POT-CAST trial.

	no. of patients*	no. of VTEs	Absolute VTE Risk % (95%CI)	Relative Risk (95%CI)†
Main outcomes				
Primary outcome: venous thromboembolism	1435	23	1.6 (1.0 - 2.4)	na
Primary safety outcome: major bleeding	1435	0	0 (0 - 0.3)	na
VTE risk factors				
Women	719/1435	9	1.3 (0.6 - 2.4)	ref
Men	717/1435	14	1.9 (1.1 - 3.3)	1.6 (0.7 - 3.7)
<55 years	697/1435	12	1.7 (0.8 - 3.0)	ref
≥55 years	461/1435	11	2.4 (1.2 - 4.2)	2.1 (0.9 - 4.9)
≥75 years	52/1435	0	0.0 (0.0 - 6.8)	na
Body Mass Index <30 kg/m²	1131/1335	12	1.1 (5.5 - 1.8)	ref
Body Mass Index ≥30 kg/m²	204/1335	8	3.9 (1.7 - 7.6)	3.8 (1.5 - 9.4)
No VTE in family history	1149/1273	15	1.3 (0.7 - 2.1)	ref
VTE in family history	123/1273	4	3.2 (0.9 - 8.1)	2.4 (1.0 - 5.6)
Use of oral contraceptives	105/1390	2	1.9 (0.2 - 6.7)	1.2 (0.2 - 5.3)
Injury specific factors ‡				
Metatarsal fractures	532/1435	6	1.1 (0.4 - 2.4)	ref
Ankle fractures	497/1435	6	1.2 (0.4 - 2.6)	1.0 (0.3 - 3.3)
Achilles tendon ruptures	94/1435	8	8.5 (3.7 - 16.1)	8.2 (2.8 - 24.1)
≥6 weeks cast immobilization	672/1435	10	1.5 (0.7 - 2.7)	0.9 (0.4 - 2.0)
Conservatively treated	1265/1435	17	1.3 (0.8 - 2.1)	ref
Surgically treated	170/1435	6	3.5 (1.3 - 7.5)	2.7 (1.0 - 6.9)

na denotes not applicable, ref denotes reference.
*Denominator indicates the number of patients in which subgroup data were available.
† Relative Risks for VTE for each risk factor.
‡ Relative Risk for ankle fractures or Achilles tendon ruptures versus metatarsal fractures.
≥6 weeks immobilization versus <6 weeks.

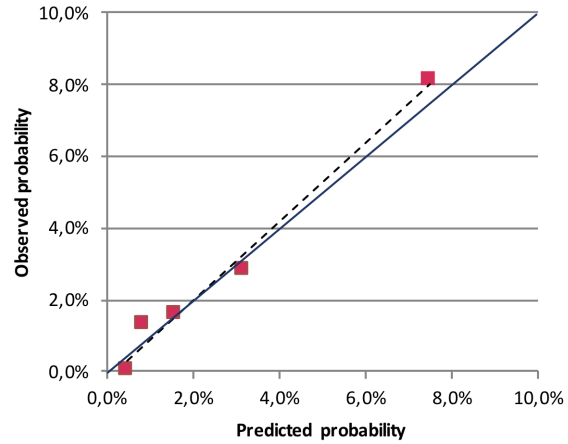


Figure 1: Calibration plot for the L-TRiP(cast) score.
Depicting the predicted versus the observed probability for venous thromboembolism (VTE) risk following cast immobilization. Dots represent risks for L-TRiP(cast) score categories 4–5, 6–7, 8–9, 10–11, and 12–17. Dashed line represents calibration line with slope 1.09.

Table 2b Efficacy of LMWH in subgroups of the POT-CAST trial.

	Treatment Group (n=719)			Control Group (n=716)			Efficacy	Efficacy
	no. of patients*	**no. of VTEs**	**Absolute Risk % (95%CI)**	**no. of patients***	**no. of VTEs**	**Absolute Risk % (95%CI)**	**Relative Risk (95%CI)**	**Absolute Risk Difference % (95%CI)**
Main outcomes								
Primary outcome: venous thromboembolism	719	13	1.4 (0.7 - 2.5)	716	10	1.8 (1.0 - 3.1)	0.8 (0.3 - 1.7)	-0.4 (-1.8 - 1.0)
Primary safety outcome: major bleeding	719	0	0 (0 - 0.8)	716	0	0 (0 - 0.5)	Not estimable	0 (-0.5 - 0.5)
VTE risk factors								
Women	372/719	2	0.5 (0.1 - 1.9)	347/716	7	2.0 (0.8 - 4.1)	0.3 (0.1 - 1.3)	-1.5 (-3.1 - 0.2)
Men	348/719	8	2.3 (1.0 - 4.5)	369/716	6	1.6 (0.6 - 3.5)	1.4 (0.5 - 4.0)	0.7 (-1.4 - 2.7)
<55 years	482/719	6	1.2 (0.5 - 2.7)	485/719	6	1.2 (0.5 - 2.7)	1.0 (0.3 - 3.1)	0.0 (-0.1 - 0.1)
≥55 years	237/719	4	1.7 (0.5 - 4.3)	224/716	7	3.1 (1.3 - 6.3)	0.5 (0.2 - 1.8)	-1.4 (-4.2 - 1.4)
≥75 years	28/719	0	0.0 (0.0 - 12.3)	24/716	0	0.0 (0.0 - 14.2)	Not estimable	Not estimable
Body Mass Index >30 kg/m^2	113/665	4	3.5 (1.0 - 8.8)	91/670	4	4.4 (1.2 - 10.9)	0.8 (0.2 - 3.1)	-0.9 (-6.3 - 4.6)
VTE in family history	67/638	2	3.0 (0.4 - 10.4)	56/635	2	3.6 (0.4 - 12.3)	0.8 (0.1 - 5.7)	-0.6 (-6.9 - 5.8)
Use of oral contraceptives	64/695	1	1.6 (0.0 - 8.4)	41/695	1	2.4 (0.1 - 12.9)	0.6 (0.0 - 10.0)	-0.9 (-6.5 - 4.7)
Injury specific factors								
Metatarsal fractures	277/719	2	0.7 (0.1 - 2.6)	255/716	4	1.6 (0.4 - 4.0)	0.5 (0.1 - 2.5)	-0.8 (-2.7 - 1.0)
Ankle fractures	255/719	3	1.2 (0.2 - 3.4)	242/716	3	1.2 (0.3 - 3.6)	0.9 (0.2 - 4.7)	-0.1 (-2.0 - 1.9)
Achilles tendon ruptures	40/719	5	12.5 (4.2 - 26.8)	54/716	3	5.6 (1.2 - 15.4)	2.3 (0.6 - 8.9)	6.9 (-5.0 - 18.9)
≥6 weeks cast immobilization	336/719	3	0.9 (0.2 - 2.6)	336/716	7	2.1 (0.8 - 4.2)	0.4 (0.1 - 1.6)	-1.2 (-3.0 - 0.6)
Conservatively treated	628/719	6	1.0 (0.4 - 2.1)	637/719	11	1.7 (0.9 - 3.1)	0.6 (0.2 - 1.5)	-0.8 (-2.0 - 0.5)
Surgically treated	91/719	4	4.4 (1.2 - 10.9)	79/716	2	2.5 (0.3 - 8.8)	1.7 (0.3 - 9.2)	1.9 (-3.6 - 7.3)

*Denominator indicates the number of patients in which subgroup data were available

Table 3: L-TRiP(cast) score.

Predictor variable	Point value
Age ≥ 35 and < 55 years	2
Age ≥ 55 years	3
Male sex	1
Current use of oral contraceptives	4
Cancer within the past 5 years	3
Pregnancy or puerperium	3
BMI ≥ 25 and < 35 kg/m^2	1
BMI ≥ 35 kg/m^2	2
Pneumonia	3
Family history of VTE (first-degree relative)	2
Comorbidity (rheumatoid arthritis, chronic kidney disease, COPD, multiple sclerosis)	1
Hospital admission within the past 3 months	2
Bedridden within the past 3 months	2
Surgery within the past 3 months	2
Superficial vein thrombosis	3
Plaster cast: Complete leg	5
Plaster cast: Circular knee cast (ankle free)	2
Plaster cast: Foot	2
Plaster cast: Lower-leg	4

Table 4: Validation of the L-TRiP(cast) score in the POT-CAST study.

Model	AUC	95% CI	Intercept	Beta
Full model	0.76	0.68 - 0.84	-8,466	0,727
*Coagulation factors updated**	0.78	0.70 - 0.86	-7,540	0,552
Restricted model	0.75	0.68 - 0.83	-7,552	0,661
*FVIII updated**	0.77	0.70 - 0.84	-7,345	0,669
L-TRiP(cast) score	0.69	0.58 - 0.80	-7,089	0,352

*Updated models: using biomarker tertiles based on POT-CAST data

Table 5: L-TRiP(cast) performance in the POT-CAST study.

L-TRiP(cast) score cutoff ≥	Sensitivity	Specificity	L-TRiP(cast) score	No VTE*	VTE*	Absolute Risk
4	100%	0%	4-5	214,20	0,00	0,0%
5	100%	3%				
6	100%	15%	6-7	437,70	5,70	1,3%
7	91%	27%				
8	75%	46%	8-9	546,50	8,70	1,6%
9	59%	71%				
10	37%	85%	10-11	164,30	4,60	2,8%
11	22%	92%				
12	17%	97%	12-17	49,30	4,00	8,1%
13	13%	99%				
14	4%	99%				
15	4%	100%				
16	4%	100%				
17	4%	100%				

*Pooled result, therefore absolute numbers include decimals

DISCUSSION

In this study we assessed the risk for VTE following cast immobilization of the lower-leg in several subgroups within the POT-CAST trial. Overall, 1.6% developed a symptomatic VTE within 3-months following cast-application. Patients with a BMI ≥30 kg/m^2 and those with a family history of VTE showed to have an increased risk for VTE. Some injury-specific risk factors were identified such as having an Achilles tendon rupture or undergoing surgical treatment. LMWH was not effective for symptomatic VTE prevention in any subgroup. In addition, we validated the L-TRiP(cast) score which showed good discrimination and calibration. The VTE risk in the lowest risk category was 0.0% (4-5 points) and 8.1% in the highest risk category (12-17 points) indicating that high risk individuals can be identified using this score.

In the POT-CAST trial we demonstrated a lack of effectiveness of thromboprophylaxis for the prevention of symptomatic VTE following cast immobilization. In contrast, a recent Cochrane review on this topic showed effectiveness of LMWH for prevention of VTE following cast immobilization.[15] However, in this review, the conclusion was downgraded due to risk of bias and imprecision of results. The authors concluded that "future research might give more directives on specific thromboprophylaxis advice for different patients or patient groups, based on patient and trauma characteristics". A similar advice followed from another meta-analysis on this topic.[16] As VTE still occurs in about 1-2% of individuals, a new preventive strategy is necessary. Such a strategy could be to identify high-risk individuals based on the assessment of one or more risk factors. However, due to the relatively low incidence of VTE following cast immobilization, differences in study outcomes (asymptomatic versus symptomatic VTE) and restricted inclusion criteria (for example exclusion of surgically treated patients or tendon ruptures) there is much variation in the literature on risk factors in these patients.[17] In 2007, Riou and colleagues performed an observational cohort study in which 3 698 patients with nonsurgical isolated lower-limb injuries were screened for the occurrence of asymptomatic VTE upon cast removal (incidence 6.4%).[7] It was found that age>50 years old, rigid immobilization, non-weight bearing cast and severe injury (classified as any injury with fracture or dislocation or a complete tendon rupture) were all associated with asymptomatic VTE. However, having a family history of VTE or a BMI>30 kg/m^2 was not associated with higher VTE risk. Of note, thromboprophylaxis was often administrated in high-risk individuals, which may have affected the association with asymptomatic VTE. In contrast, in the POT-CAST trial these classical risk factors for VTE were found to be associated with a higher VTE risk.[2] A similar result was shown in 1993 in one of the first trials on thromboprophylaxis following lower-leg cast immobilization.[9] According to this trial, patients who did not develop thrombosis had on average 1.24 risk factors as compared

with 1.96 in those patients who did. Moreover, patients who developed a thrombosis under thromboprophylaxis had an average of 2.7 risk factors. A similar pattern was found in more recent data from a large population-based case-control study.[4] Patients with additional risk factors next to lower-leg cast immobilization such as the use of oral contraceptives, obesity, Factor V Leiden mutation, Non-O blood type or having a traumatic injury had an increased symptomatic VTE risk.

Interestingly, in the POT-CAST data, patients with Achilles tendon rupture (ATR) had a remarkably high risk of VTE (8.5%, 95%CI 3.7-16.1) while thromboprophylaxis was not effective. Varying sizes of risk have been described in earlier studies: a cohort study that collected data on all ATR during 12 consecutive years from one centre (n=945) showed an incidence of 1.4% within 4-5 months from start of treatmen7[18], while in another prospective cohort study in 291 patients with ATR (managed with full weight bearing in a walker boot) the incidence of VTE events was 4.8%.[19] In another small retrospective study, prompted by the authors' observations in clinical practice on this association, the incidence of VTE was 6.8% in 88 patients who were surgically treated for an ATR.[20] The underlying mechanism for this high risk remains to be elucidated. The long duration of immobilization could contribute, however, patients with >6 weeks of cast immobilization for other indications did not have a higher VTE risk in the POT-CAST trial. Another possibility might be that ATRs are initially treated with a non-weight bearing cast, perhaps leading to extra stasis in the veins. Unfortunately, in the POT-CAST trial, no information was present on the presence or absence of weight-bearing casts.

Identifying patients at high-risk based on one or more risk factors does not necessarily result in accurate risk prediction, this was recently shown by a large systematic review on this topic.[17] Due to the high frequency of many risk factors, the majority of patients will be classified as high-risk patients because they have one or more risk factors. A score that integrates information on all risk factors should be more useful. For this reason, in this study, the earlier developed L-TRiP(cast) score was validated which showed promising results. The Full and Restricted model, both including biomarkers such as factor V Leiden mutation and FVIII activity reached a higher AUC than the score, indicating better discrimination. By updating tertiles of all coagulation factors included in both models risk prediction further improved. This indicated that the level of biomarkers (such as FVIII activity) measured upon presentation at the emergency department greatly contributes to risk prediction following injury. However, determining biomarkers in patients with lower-leg cast immobilization upon presentation at the emergency department is not straightforward and in addition, costly. Since the L-TRiP(cast) score performed well, this might be used by clinicians to identify high-risk individuals. Yet, as thromboprophylaxis lacked effectiveness in any high-risk group, and the risk for major bleeding was negligible, there is a need for

future studies on a more stringent prevention strategy (for example a longer duration, higher dosage or stronger anticoagulant) in these groups. These studies may determine which patients can be withheld from treatment and for whom thromboprophylaxis needs to be intensified (i.e. define low- and high-risk categories).

The main strength of the POT-CAST trial is its size, as the largest randomized study into the effectiveness of LMWH for VTE prevention following cast immobilization of the lower-leg. By using these data, we were able to calculate absolute risks for different subgroups. Additionally, follow up was almost complete (98%) and few data on risk factors were missing. Furthermore, in POT-CAST only clinically relevant symptomatic VTEs were considered as an endpoint, making results of this study worthwhile for clinical practice. The current analysis also may have some limitations. First, none of the subgroup analyses were predefined as the trial was not powered to perform such analyses. Yet, as the main trial outcome showed no effectiveness for VTE prevention, the need for risk factor and individual risk assessment increased, allowing us to perform these analyses. Second, the low number of VTEs (n=23) limited precision of incidence estimations and validation statistics, however, by using a near complete dataset with complete follow-up and low number of missing risk factors the loss of precision was reduced to a minimum. Third, in general, patients who participate in clinical trials are somewhat younger and healthier as compared to the target population. For the POT-CAST trial this doesn't seem to be the case. Compared with a large cohort on the incidence of VTE following isolated lower-leg immobilization[7], patients in POT-CAST were older and had a higher BMI, indicating no selection of healthy patients. Finally, patients with a history of VTE were not included in the POT-CAST trial, for which reason the results are not applicable to these patients. However, as the absolute risk of VTE in this population is high[21], one may argue that these patients need prophylaxis in all circumstances.

Conclusion

VTE risk following cast application is 1.6% within 3-months. Patients with additional classical VTE risk factors such as high body mass index or having a family history of VTE have a higher risk to develop symptomatic VTE. Furthermore, patients with an Achilles tendon rupture, or patients who are surgically treated have a high risk of VTE. LMWH was not effective in any of the risk groups for prevention of VTE. Low- and high risk individuals can be identified by using the L-TRiP(cast) score which showed good validation performance. Nevertheless, the best treatment strategy for these patients is yet to be determined.

REFERENCE LIST

1. Németh B, Cannegieter SC. Venous thrombosis following lower-leg cast immobilization and knee arthroscopy: From a population-based approach to individualized therapy. Thrombosis research. 2019;174:62-75.
2. van Adrichem RA, Németh B, Algra A, et al. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. N Engl J Med. 2017;376(6):515-525.
3. Knudson MM, Ikossi DG, Khaw L, Morabito D, Speetzen LS. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. Ann Surg. 2004;240(3):490-496; discussion 496-498.
4. van Adrichem RA, Debeij J, Nelissen RG, Schipper IB, Rosendaal FR, Cannegieter SC. Below-knee cast immobilization and the risk of venous thrombosis: results from a large population-based case-control study. Journal of thrombosis and haemostasis: 2014;12(9):1461-1469.
5. Kock HJ, Schmit-Neuerburg KP, Hanke J, Rudofsky G, Hirche H. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. Lancet. 1995;346(8973):459-461.
6. 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):52-57.
7. Riou B, Rothmann C, Lecoules N, et al. Incidence and risk factors for venous thromboembolism in patients with nonsurgical isolated lower limb injuries. The American Journal of Emergency Medicine. 2007;25(5):502-508.
8. 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):528-535.
9. 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 1:20-26.
10. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. N Engl J Med. 2002;347(10):726-730.
11. Németh B, van Adrichem RA, van Hylckama Vlieg A, et al. Venous Thrombosis Risk after Cast Immobilization of the Lower Extremity: Derivation and Validation of a Clinical Prediction Score, L-TRiP(cast), in Three Population-Based Case-Control Studies. PLoS Med. 2015;12(11):e1001899; discussion e1001899.
12. Schulman S, Angeras U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. Journal of thrombosis and haemostasis. 2010;8(1):202-204.
13. van BS, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. StatMed. 1999;18(6):681-694.
14. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology. 2010;21(1):128-138.
15. Zee AA, van Lieshout K, van der Heide M, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilization. Cochrane Database Syst Rev. 2017;8:Cd006681.

16. Hickey BA, Watson U, Cleves A, et al. Does thromboprophylaxis reduce symptomatic venous thromboembolism in patients with below knee cast treatment for foot and ankle trauma? A systematic review and meta-analysis. Foot and ankle surgery : official journal of the European Society of Foot and Ankle Surgeons. 2018;24(1):19-27.
17. Horner D, Pandor A, Goodacre S, Clowes M, Hunt BJ. Individual risk factors predictive of venous thromboembolism in patients with temporary lower limb immobilisation due to injury: a systematic review. Journal of thrombosis and haemostasis. 2019 Feb;17(2):329-344.
18. Heyes GJ, Tucker A, Michael AL, Wallace RG. The incidence of deep vein thrombosis and pulmonary embolism following cast immobilisation and early functional bracing of Tendo Achilles rupture without thromboprophylaxis. Eur J Trauma Emerg Surg. 2015;41(3):273-276.
19. Blanco JA, Slater G, Mangwani J. A Prospective Cohort Study of Symptomatic Venous Thromboembolic Events in Foot and Ankle Trauma: The Need for Stratification in Thromboprophylaxis? J Foot Ankle Surg. 2018;57(3):484-488.
20. Saragas NP, Ferrao PN, Saragas E, Jacobson BF. The impact of risk assessment on the implementation of venous thromboembolism prophylaxis in foot and ankle surgery. Foot and ankle surgery : official journal of the European Society of Foot and Ankle Surgeons. 2014;20(2):85-89.
21. Németh B, Timp JF, van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC. High risk of recurrent venous thrombosis in patients with lower-leg cast immobilization. Journal of thrombosis and haemostasis. 2018;16(11):2218-2222.

9

Venous thrombosis risk after arthroscopy of the knee: derivation and validation of the L-TRiP(ascopy) score

Németh B, van Adrichem RA, van Hylckama Vlieg A, Baglin T, Rosendaal FR, Nelissen RGHH, le Cessie S, Cannegieter SC.

Thromb Haemost. 2018 Oct;118(10):1823-1831

ABSTRACT

Patients at high risk for Venous Thrombosis (VT) following knee arthroscopy could potentially benefit from thromboprophylaxis. We explored the predictive values of environmental, genetic risk factors and levels of coagulation markers to integrate these into a prediction model. Using a population-based case-control study into the aetiology of VT we developed a *Complete* (all variables), *Screening* (easy to use in clinical practice) and *Clinical* (only environmental risk factors) model. The *Clinical* model was transformed into the *L-TRiP(ascopy)* score. Model validation was performed both internally and externally in another case-control study. 4943 cases and 6294 controls were maintained in the analyses, 107 cases and 26 controls had undergone knee arthroscopy. Twelve predictor variables (8 environmental, 3 haemorheological and 1 genetic) were selected from 52 candidates and incorporated into the *Complete* model (Area Under the Curve (AUC) of 0.81, 95%CI 0.76–0.86). The *Screening* model (9 predictors: environmental factors plus FVIII activity) reached an AUC of 0.76 (95%CI 0.64–0.88) and the *Clinical (and corresponding L-TRiP(ascopy)* model an AUC of 0.72 (95%CI 0.60 – 0.83). In the internal and external validation, the *Complete* model reached an AUC of 0.78 (95%CI 0.52–0.98) and 0.75 (95%CI 0.42-1.00), respectively, while the other models performed slightly less well.

INTRODUCTION

In general, orthopaedic surgery is associated with a high risk of venous thrombosis (VT), the composite of deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] This can be understood when we consider the long duration of surgery, the extensive tissue damage during hip or knee replacement and the associated immobilization. For general knee arthroscopy this is different: hardly any tissue damage occurs and the duration of the procedure is short (15-20 min). However, the risk of VT following arthroscopy of the knee is not negligible, with symptomatic incidence rates varying around 1%.[2-6] Knee arthroscopy is the most commonly performed orthopaedic procedure with worldwide 4 million arthroscopies carried out yearly.[7] Therefore, this will lead to high absolute numbers of, theoretically preventable, VT cases (40 000 VTs annually assuming a risk of 1%). In addition, numerous fatal cases after surgery have been described[8, 9], as can be expected based on a 30-day VT fatality rate of 3.0%.[10] Hence, on estimation 1 200 patients die yearly within 30 days after knee arthroscopy worldwide. Moreover, long term complications such as post-thrombotic syndrome affect about 40% of thrombosis patients. [11] Therefore the impact of VT is considerable, even in this generally young and healthy patient population.

Several studies have been performed to obtain more insight in the development of VT after arthroscopic knee surgery. Recently, we showed in the POT-KAST trial, a large Randomized Controlled Trial (1 451 patients) comparing Low Molecular Weight Heparin with no treatment, that there is no effectiveness for thromboprophylaxis following knee arthroscopic surgery, as the risk of VT was equal (~ 0.6%) in the treated and untreated group.[12]

Multiple high risk groups appear to exist: It was recently described that hospital admission before surgery was predictive of thrombosis (Hazard Ratio 14.1, 95% CI: 5.3–37.6). (3) Another study showed that patients undergoing anterior cruciate ligament (ACL) reconstruction had a higher VT risk compared with patients undergoing less invasive arthroscopic procedures.[13] Other risk factors, such as a history of malignancy[2], a history of VT[14], use oral contraceptives, being overweight or having a genetic predisposition (Factor V Leiden, non-O blood type, prothrombin 20210A mutation) have also been identified to elevate postoperative risk.[2, 15] Hence, it should theoretically be possible to distinguish between high or low risk of VT after knee arthroscopy by combining all information into one prediction model, instead of measuring single risk factor associations. If these groups can be targeted, the considerable morbidity and mortality due to VT after this procedure may yet be preventable.

The aim of this study was to investigate the combined predictive value of environmental and genetic risk factors, biomarkers and levels of coagulation markers on the development of VT in knee arthroscopy patients. We aimed to develop a prediction model to assist clinicians to decide whether or not to prescribe thromboprophylaxis in individual patients.

METHODS

Study design

For model development, data from a large population-based case-control study, the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA study) were used. Details of this study have been published previously.[16] In short, between 1999 and 2004, all consecutive patients aged 18 to 70 years with a first deep vein thrombosis, pulmonary embolism or both were recruited from six anticoagulation clinics in the Netherlands (n=4 956). The control-group (n=6 297) consisted of partners of participating patients and of other controls who were frequency matched with respect to sex and age and identified using a random digit dialling method. Approval for this study was obtained from the Medical Ethics Committee of the Leiden University Medical Center and all participants provided written informed consent.

Data collection and laboratory analysis

All participants completed a questionnaire, including potential risk factors for VT such as orthopaedic surgery, current use of medication and co-morbidity in the year before the venous thrombotic event. A blood sample was collected approximately three months after discontinuation of oral anticoagulant therapy for patients and controls included from the start of the study until May 31, 2002. Detailed information on laboratory analyses from coagulation and hemorheologic and other markers can be found in *Supplement 1*. In patients who were still on anticoagulant therapy one year after the event, blood was drawn during treatment. After June 1, 2002 and for participants who were unable to visit the clinic, DNA was collected by means of buccal swabs sent by mail. Factor V Leiden (F5, rs6025), prothrombin G20210A (F2, rs1799963) mutation and ABO-blood group were determined.

Model Derivation

The prediction model was developed using the data from the MEGA study population. Subjects with multiple orthopaedic surgeries or other operations in combination with a knee arthroscopy were excluded from analyses. To incorporate age and sex as predictor variables (because controls were frequency matched on age and sex) we weighted control subjects (for age and sex) to the age and sex distribution of the Dutch population in 2001 (Statistics Netherlands). Missing values were imputed (we imputed 5 datasets by multiple imputation and results were pooled according to Rubin's rules). Vitamin K dependent coagulation factors from patients who were still on anticoagulation treatment during blood collection were set as missing values and imputed as well. *Supplement 2* provides detailed information on missing data for risk factors incorporated in the prediction model.

We aimed to develop three models; a *Complete* model (all variables and highest discriminative ability), a *Screening* model (including a minimum number of all types of predictors with maximum discriminative performance to improve clinical usefulness) and a *Clinical* model (only environmental risk factors). Development of all models was based on a method we described in a previous study, using a multivariate logistic regression approach.[17] In short, candidate predictors were identified in the whole MEGA study population (n=11 237) (*step 1 and 2*) (*Figure 1*). Candidate predictors (already derived from our previous study) were entered in the *Complete* prediction model by hand, and a univariate logistic regression was conducted for all candidate predictors in the entire MEGA group (*step 3*). We started fitting our *Complete* model with the strongest predictor (based on highest Area Under the Curve [AUC] in the arthroscopy subgroup) (n=133). Further predictor selection was based on the variable that resulted in the strongest increase in AUC, in the knee arthroscopy subgroup (*step 4*) (addition of predictors was stopped when AUC increase was less than 0.01 points). Age and sex were forced in *all* models based on clinical importance. For calculating the AUC, a Receiver Operating Characteristic (ROC) was constructed. Model overfitting was prevented by conducting a ROC analysis in the arthroscopy subgroup only (using the beta coefficient derived from the logistic regression model calculated in the entire MEGA study population [n=11 237]) instead of conducting a regression in the small arthroscopy subgroup. Next to a *Complete* model, a *Screening* model was developed in a similar way *(step 5)*. Finally, we developed a *Clinical* model using environmental risk factors only *(step 6)*.

Risk Score

We developed a Risk Score, the Leiden-Thrombosis Risk Prediction(arthroscopy) score, [*L-TRiP(ascopy) score*] for VT risk following knee arthroscopy that was based on the beta coefficients for predictor variables in the *Clinical* model (using the following rule: if Beta was >0.25 and ≤0.75, this yielded 1 point, for; Beta>0.75 and ≤1.25=2 points; Beta>1.25 and ≤1.75=3 points; Beta>1.75 and ≤2.25=4 points; Beta>2.25 and ≤2.75=5 points; Beta>2.75=6 points). The *L-TRiP(ascopy) score* was the sum of these points. Assuming two overall prevalences of either 0.5% or 1.5% for VT in patients who undergo knee arthroscopy, we calculated sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and the negative likelihood ratio for different cut off points of the *L-TRiP(ascopy) score*.

Model validation

A bootstrapping procedure was performed to internally validate our results. Using the imputed dataset, we resampled our arthroscopy subgroup (1000 replications with replacement), after which all models were validated in this new population. In addition, THE VTE case-control study into the aetiology of VTE, which contains 784 cases and 523

controls (Leiden/Cambridge) was used for external validation of the *L-TRiP(ascopy) score*. Details of this study have been published previously.[18] For each subject in THE VTE study, prognostic scores were calculated using regression coefficients from the prediction models derived from the MEGA study.

All analyses were performed in IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. The weighted analyses were performed in Stata SE, version 14.

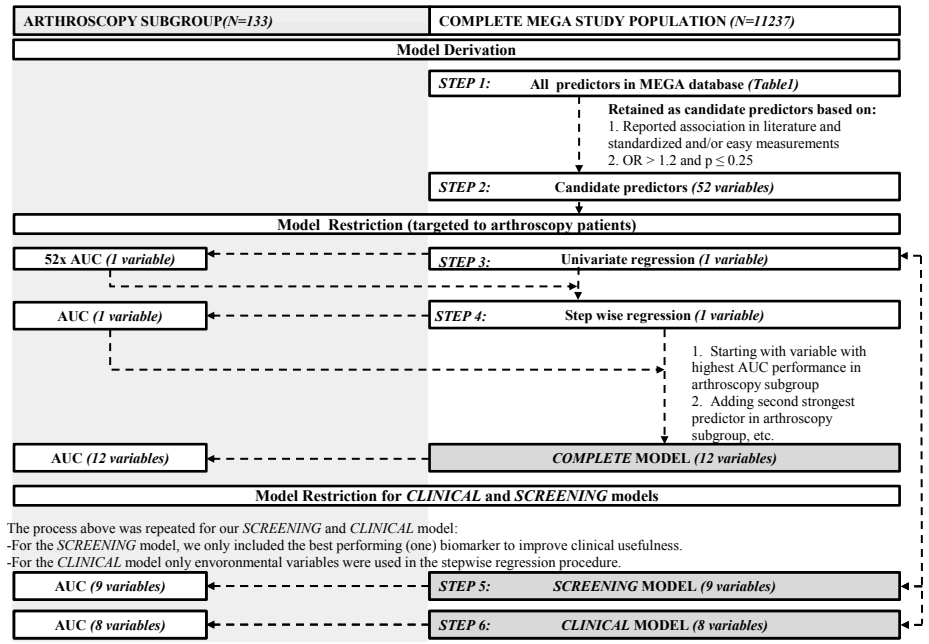


Figure 1: Flow-chart of the derivation process for development of the *L-TRiP(ascopy)* score.

RESULTS

Study population

4 943 cases and 6 294 controls were maintained in the analyses after exclusion of 13 participants who underwent multiple orthopaedic operations after the arthroscopy. Among all cases 2 881 (58%) had a DVT, 1618 (33%) a PE and 444 (9%) both. 107 cases and 26 controls had undergone knee arthroscopy within one year before thrombosis or index date, respectively (of whom most patients (~75%) within 3-months[19]). Thirteen of them (10%) underwent ligament reconstruction from the anterior cruciate ligament and/or posterior cruciate ligament. Compared with the complete MEGA study population, subjects who underwent knee arthroscopy were slightly younger (mean 44.6 years vs 47.7 years), and more often male (58% vs 46%).

Model derivation

52 candidate predictors were identified in the MEGA study population (*Table 1*). Strong predictors in both the total MEGA study population and arthroscopy subgroup were: family history of venous thrombosis, current use of oral contraceptives and having been bedridden within the past 3 months. Persons who underwent knee arthroscopy without ligament reconstruction had a 5-fold increased risk of developing VT, odds ratio (OR) 5.1, 95% confidence interval (95%CI 3.3 – 8.0), while those who had cruciate ligament reconstruction had an 18-fold increased risk (OR 17.5 [95%CI 2.3 – 134.8]), compared with subjects who did not have surgery.

Table 1: Candidate predictor variables.

Environmental predictor variables	
Age	Hospital admission within the past 3 months
Sex	Bedridden within the past 3 months
Smoking	Paralysis (partial)
Varicose veins	Surgery within the past 3 months
Cancer within the past 5 years	Current Pregnancy or puerperium
Congestive heart failure	Current use of antipsychotic medication
Comorbidity	Current use of tamoxifen
• Rheumatoid arthritis	Current use of hormonal replacement therapy
• Chronic kidney disease	Current use of oral contraceptives
• Chronic Obstructive Pulmonary Disease (COPD)	Thrombophlebitis
• Multiple Sclerosis (MS)	Hepatitis

Table 1: Continued.

Environmental predictor variables	
Cardiovascular events	Pneumonia
• Angina Pectoris (AP)	Inflammation
• Heart attack	• Urinary tract infection / Cystitis
Cerebrovascular events	• Pyelonephritis
• Stroke	• Arthritis
• Transient Ischemic Attack (TIA)	• Bursitis
Body Mass Index (BMI)	• Inflammation (other body parts)
Claudication	• Tropical diseases
Family history of VT	(Type of) Arthroscopy
Hemorheologic and coagulation predictor variables	
Fibrinogen activity	Percentage/number granulocytes
Factor VIII activity	Red Blood Cell Count (RBCC)
Von Willebrand Factor (vWF) (%)	Haemoglobin level
Factor II activity	Mean Cell Volume (MCV)
Factor VII activity	Mean Cell Haemoglobin (MCH)
Factor X antigen level	Mean Cell Haemoglobin Concentration (MCHC)
Protein C activity	Red cell Distribution With (RDW)
Factor XI activity	Antithrombin activity
Haematocrit	Total homocysteine
White Blood Cell Count (WBCC)	Total cysteine
Percentage/number lymphocytes	Methionine
Percentage/number monocytes	
Genetic predictor variables	
Factor V Leiden mutation	
Prothrombin mutation	
Non-O blood type	

Complete model

Twelve predictor variables (8 environmental risk factors, 3 hemorheologic factors and 1 genetic marker) were incorporated into the *Complete* prediction model. Risk factors included in the model were: age, sex, Von Willebrand Factor (vWF) activity, family history of VT, Factor V Leiden mutation (FV Leiden), having been bedridden within the past 3 months,

current use of oral contraceptives, (type) of knee arthroscopy, Factor VIII (FVIII) activity, presence of varicose veins, monocyte percentage and having congestive heart failure. This combination of risk factors resulted in an AUC of 0.81 (95%CI 0.70 – 0.93) (*Table 2*). *Fig 2* shows the AUC values of our *Complete* model after step-wise addition of these predictor variables.

Table 2: AUC values of the *Complete, Screening, Clinical model* and *L-TRiP(ascopy) score* in the MEGA and VTE study.

	MEGA study			**Internal validation**			**External validation: VTE study**		
Model	**AUC**	**95% CI**		**AUC**	**95% CI**		**AUC**	**95% CI**	
Complete model	0.81	0.70	0.93	0.78	0.67	0.89	0.75	0.42	1.00
Screening model	0.76	0.64	0.88	0.71	0.59	0.83	0.73	0.40	1.00
Clinical model	0.72	0.60	0.83	0.64	0.53	0.76	0.78	0.48	1.00
L-TRiP(ascopy) score	0.73	0.63	0.84	0.67	0.54	0.80	0.77	0.43	1.00

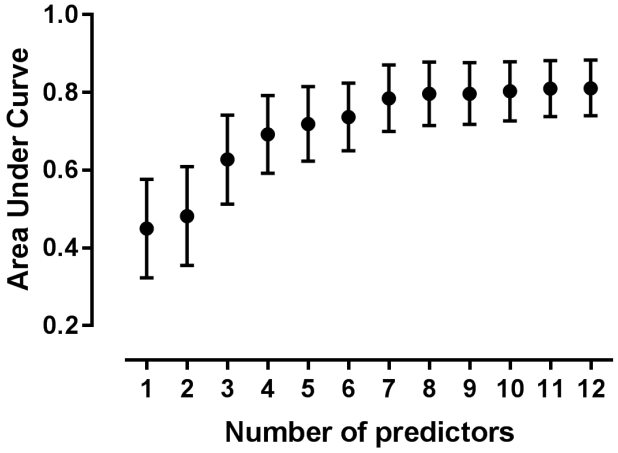


Figure 2: AUC values of the *Complete* model for step-wise addition of the following predictors: age, sex, von Willebrand Factor activity, family history of VT, Factor V Leiden mutation, being bedridden within the past 3 months, current use of oral contraceptives, (type) of knee arthroscopy, Factor VIII activity, presence of varicose veins, monocyte percentage and having congestive heart failure.

Screening model

Our *Screening* model consisted of nine predictors (all environmental risk factors of the Complete model plus FVIII activity) and reached an AUC of 0.76 (95%CI 0.64 – 0.88). Although vWF increased model performance more than FVIII (AUC increase of 0.02), FVIII was chosen over vWF as FVIII activity can be measured more easily in most clinics.

Clinical Model and L-TRiP(ascopy) score

The *Clinical* model resulted in an AUC of 0.72 (95%CI 0.60 – 0.83) and consisted of all eight environmental risk factors that were also included in the *Complete* and *Screening* model. The *L-TRiP(ascopy) score* (*Table 3*) derived from this model resulted in an AUC of 0.73 (95%CI 0.63 – 0.84). *Table 4* gives an overview of discriminative values for all cut-off points from the *L-TRiP(ascopy) score.* For example, a cut-off value of 7 results in a sensitivity and specificity of 77.8% and 40.2% respectively, to identify patients at high risk of developing VT. *Figure 3* shows the score distribution among cases and controls.

Table 3: L-TRiP(ascopy) score.

Risk Score	**Points**	**Original Beta**
Age >= 35 and <55	2	0.78
Age >55	3	1.48
Male sex	1	0.39
Current use of oral contraceptives	3	1.43
Family history of VT (1 family member)	2	0.82
Family history of VT (>=2 family members)	3	1.47
Bedridden within the past 3 months	3	1.38
Varicose Veins	1	0.68
Congestive heart failure	1	0.49
Knee arthroscopy	4	1.76
Ligament reconstruction	6	2.93

This score was derived from the regression coefficients (Beta) of the Clinical prediction Model. Beta>0.25 and ≤0.75=1; Beta>0.75 and ≤1.25=2; Beta>1.25 and ≤1.75=3; Beta>1.75 and ≤2.25=4; Beta>2.25 and ≤2.75=5; Beta>2.75=6

Table 4: L-TRiP(ascopy) score performance

Cutpoint	Sensitivity	Specificity	Sens+Spec	PVV*	NPV*	PVV**	NPV**	Likelihood+	Likelihood-
1	100.0%	0.0%	100.0%	1.50%	100.0%	0.50%	100.0%	1.0	0.0
2	100.0%	0.0%	100.0%	1.50%	100.0%	0.50%	100.0%	1.0	0.0
3	100.0%	0.0%	100.0%	1.50%	100.0%	0.50%	100.0%	1.0	0.0
4	100.0%	0.0%	100.0%	1.50%	100.0%	0.50%	100.0%	1.0	0.0
5	100.0%	0.0%	100.0%	1.50%	100.0%	0.50%	100.0%	1.0	0.0
6	92.3%	21.7%	114.1%	1.77%	99.5%	0.59%	99.8%	1.2	0.2
7	77.8%	40.2%	117.9%	1.94%	99.2%	0.65%	99.7%	1.5	0.2
8	68.8%	64.4%	133.2%	2.86%	99.3%	0.96%	99.8%	1.5	0.4
9	43.2%	84.9%	128.1%	4.17%	99.0%	1.42%	99.7%	1.8	0.4
10	29.0%	99.1%	128.0%	32.15%	98.9%	13.52%	99.6%	3.1	0.6
11	17.9%	100.0%	117.9%	100.00%	98.8%	100.00%	99.6%	29.9	0.6
12	7.1%	100.0%	107.1%	100.00%	98.6%	100.00%	99.5%	21.7	0.7
13	3.6%	100.0%	103.6%	100.00%	98.6%	100.00%	99.5%	∞	0.9
14	1.9%	100.0%	101.9%	100.00%	98.5%	100.00%	99.5%	∞	0.9

*Presuming a prevalence of VT in knee arthroscopy patients of 1.5%
**Presuming a prevalence of VT in knee arthroscopy patients of 0.5%

Internal and external validation

In the bootstrapped population the Complete and Screening models performed almost as good as in the derivation dataset, whereas the L-TRiP(ascopy) score and Clinical model performed somewhat less well (*Table 2*). The L-TRiP(ascopy) score resulted in an AUC of 0.67 (95%CI 0.54 – 0.80) while the complete model reached an AUC of 0.78 (95%CI 0.67-0.89).

The population study used for external validation consisted of 784 cases and 523 controls that were included in THE VTE study. 59% of all cases had DVT and 41% had PE with or without DVT. 30 cases and 3 controls had undergone knee arthroscopy within one year before VT. The *Complete* model resulted in an AUC of 0.75 (95%CI 0.52 – 0.98) and the *Screening* model yielded an AUC of 0.73 (95%CI 0.49 – 0.96). For our *Clinical* model and L-TRiP(ascopy) score the AUCs were 0.78 (95%CI 0.48 – 1.00) and 0.77 (95%CI 0.43 – 1.00), respectively. *Table 2* gives an overview of the predictive values for all models in both derivation and validation data.

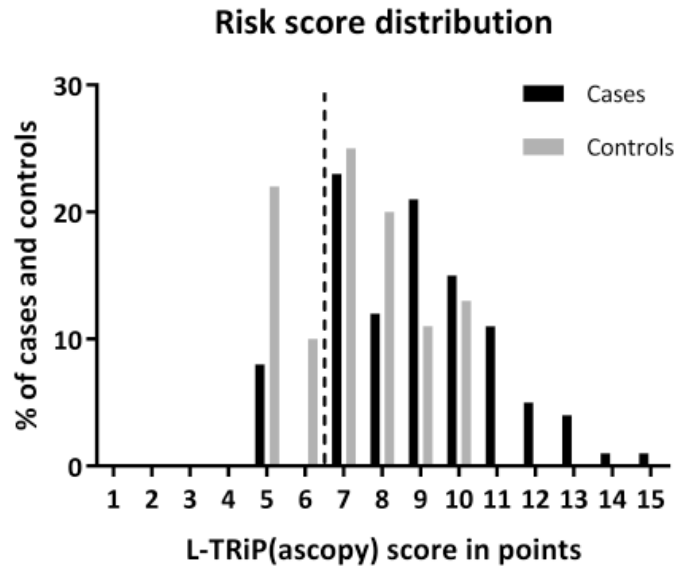


Figure 3: Risk score distribution among cases and controls for the *L-TRiP(ascopy)score*. Dashed black lines represent Cut-off values that correspond to a test sensitivity of 75%.

DISCUSSION

Summary of key findings

Patients who undergo knee arthroscopy have an increased risk of developing VT. We developed and validated a prediction model to identify patients at high risk for this complication. Because of the bleeding risk during thromboprophylactic therapy and the low risk of VT, risk stratification is likely to be beneficial, which can be achieved by using the *L-TRiP(ascopy) score*. Our results indicate that biomarker determination leads to more accurate risk prediction than limiting to clinical variables. However, for clinical practice a clinical model without additional biomarker testing can be preferred until larger validation studies show a strong added value of biomarker testing.

Risk factors for VT in knee arthroscopy patients

A recent cohort study of 12 595 patients found a symptomatic VT incidence of 0.34% (95% CI 0.25 – 0.46) at 4 weeks. Risk factors for VT were: a history of malignancy, a history of VT and the presence of two or more risk factors according to Delis (age>65, BMI>30, smoking, use of oral contraceptives or hormonal replacement therapy, chronic venous insufficiency, history of VT).[2] A similar incidence of 0.46% (95% CI 0.43 - 0.49) was found by Bohensky and colleagues, in a cohort study with 180 717 arthroscopies. [20] In this study only chronic kidney disease was found to be a clear risk factor for the development of VT while patients with cancer, peripheral vascular disease, chronic heart failure, cerebrovascular event, myocardial infarction, chronic lung disease, hemiplegia or diabetes were not at increased risk after arthroscopy. A study from New York reported on predictors of pulmonary embolism following a knee arthroscopy among 418 323 operations. The 30-day incidence was 2.8 per 10 000 knee arthroscopies and risk factors for the development of VTE were age>30, female sex, history of cancer and an operating time over 90 minutes. Type of surgery or presence of comorbidity was not associated with VT.[21] Another observational study with 4 833 patients undergoing arthroscopic surgery showed that only older age and hospitalization in the preceding 3 months were predictors of VT.[3]

All these studies had an observational design, and information bias cannot be ruled out: Data on comorbidities were collected using large hospital or nationwide databases. Data collection or reporting on putative risk factors may have been more rigorous for patients with VT than for those without, which could be an explanation for the contradicting results on different risk factors as shown by several of these studies. Also, logistic regression analyses in these studies were often underpowered because of the low incidence rate and scarce distribution of risk factors. In our study cases and controls were asked to complete questionnaires about their health one year prior to the VT date or a random control date,

respectively (this active approach reduced the risk of bias). The number of cases in our study used for the regression analysis (n=4 943) is much more than the total number of events in previous studies. Therefore, the predictive values of various risk factors, derived from all patients, are more accurate in our study. Furthermore, prediction of high risk patients in this population with a low incidence of VT is more valuable than identifying individual risk factors. Our goal was therefore not to estimate associations of single risk factors, but to combine all information for optimal individual risk stratification.

Specific aspects of the patient population that undergoes knee arthroscopy may also have contributed to the conflicting results that have been reported. In the study from New York, 92.3% of all patients had a Charlson/Deyo comorbidity score of 0, meaning that they had no history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, liver disease, diabetes mellitus, (para)plegia, renal disease or AIDS.(21) Similar patient characteristics were reported by Jameson, where 90% had a Charlson/Deyo score of 0 and the mean age was 45.9 years.[22] These studies illustrate that patients undergoing knee arthroscopy are in general young and healthy with only very few comorbidities. Consequently, while comorbidity is associated with VT risk in other situations, there is limited contribution of environmental risk factors to risk stratification in the arthroscopic population. A similar problem exists when using other prediction scores for VTE, for instance the Caprini score[23]. According to this score, patients who undergo arthroscopic surgery score 2 points, indicating a moderate risk for VTE. Consequently, all patients who undergo arthroscopy receive thromboprophylaxis and a further discrimination between low- and high-risk patients within a surgical subgroup (such as knee arthroscopy), cannot be made.

Given the young and healthy population with few environmental risk factors, we investigated the additional predictive value of biomarkers (that are easy to determine in a clinical setting). To our knowledge, this has not been done in knee arthroscopy patients for the development of VT to date. We found that addition of FVIII concentration (FVIII;C), vWF activity, Factor V Leiden mutation (FV Leiden) and monocyte percentage to our model increased the predictive value. However, to improve clinical usefulness we attempted to minimalize the number of biomarkers. Out of the biomarkers that were associated we chose to incorporate FVIII in the *Screening* model for practical reasons. The *Screening* model performed slightly better than the L-TRiP(ascopy) score, (AUC difference in derivation study 0.03 points, and 0.07 point in internal validation). Our external validation study was not powered sufficiently 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 convert the *Clinical* model in the L-TRiP(ascopy) score, rather than the *Screening* model as the

predictive value of adding a biomarker did not outweigh the hassle of measuring factor VIII (in terms of costs, and logistics in routine clinical care). However, it should be kept in mind that due to less discriminatory power, there will be overtreatment of controls (*Table 4*).

Limitations of the study

Our study lacked information on thromboprophylaxis therapy after knee arthroscopy for all individuals. However, in a survey study in the Netherlands which was performed during the same period as the inclusion period of our case-control study, 71% of all orthopaedic surgeons stated that they used a low-molecular-weight-heparin (LMWH) for prophylactic therapy in patients undergoing a knee arthroscopy in most cases. 91% of these surgeons only used a single-dose of LMWH.[24] This could have affected the actual risk in our patient population. Nevertheless, the therapeutic value of a single dose of LMWH is not known and probably limited. In addition, as we recently showed that thromboprophylaxis is not effective for VTE prevention following knee arthroscopy[12], the effect of prophylaxis on VTE development (and thus on model development) is negligible. Furthermore, the L-TRiP(ascopy) model was developed by identifying candidate predictors using all cases and controls from the MEGA study. Beta-coefficients and risk points in the final risk score were based on many patients, thereby preventing over-fitting. An additional internal validation showed similar performance statistics, indicating the robustness of model performance. Also, our validation cohort did not include sufficient numbers of patients (especially control subjects) with knee arthroscopy to obtain precise results. Validation results were therefore not very precise, however, all models performed promisingly and were in line with the derivation results. To account for this problem, an internal validation was performed to confirm our findings, which showed similar results. However, a larger validation study (and perhaps a cost-effectiveness study) is still needed to confirm our results and to determine if biomarkers are needed to improve risk prediction following knee arthroscopy.

Clinical implications

To date, there is no consensus on thromboprophylactic therapy for patients who underwent knee arthroscopy. However, we recently published a large randomized controlled trial (POT-KAST trial) that showed a lack of effectiveness for thromboprophylaxis for 8 days after knee arthroscopy (1451 patients).[12] In this trial, still 0.6% of patients developed a thrombotic event and these patients had several additional risk factors for VT. Our *L-TRiP(ascopy) score* can be a helpful tool to guide doctors in their decision on anticoagulant treatment for those patients at high risk for VT. Since we showed that a prophylactic dose of anticoagulant therapy does not prevent VT, other treatment regimens (such as a longer therapy duration or higher dosage) might be effective in those patients with an extremely high risk, but should also be restricted to this group, considering the high bleeding risk, which is currently about 0.5% major and clinically relevant non-major bleeding[12].

Increasing the duration and dosage of thromboprophylaxis will likely lead to a further increased bleeding risk. Since bleeding risk is already nearing VTE risk, it is crucial to identify only those patients with the highest VTE risk in order to optimize patient care. To accomplish this, a score with a high sensitivity and high specificity is desirable, in which case we would only treat those patients at high risk without giving treatment to patients who will not develop VT. The L-TRiP(ascopy) score can have a high sensitivity, for example, a cut off score of 7 or higher results in a sensitivity of 77.8%. However, the corresponding specificity is only 40.2%, which implies that many controls would also receive treatment, leading to unnecessary bleeding events and costs. Determining the right cut-off for risk discrimination is therefore not straightforward, especially because of the uncertainty in the specificity of our score, which is only based on 26 controls. Ideally, the absolute risks corresponding with our L-TRiP(ascopy) score should be calculated in a large prospective study so that the optimal cut-off can be determined.

Conclusion

Given the lack of effectiveness of thromboprophylactic therapy in all patients who undergo knee arthroscopy, an alternative strategy might be to identify those individuals at high risk of developing VT and provide stronger treatment for this group. We developed the *L-TRiP(ascopy) score* that may be suitable for this purpose. However, a larger validation study is needed to confirm our results and to determine a definite cut-off for high risk patients.

REFERENCE LIST

1. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl): 381S-453S.
2. Krych AJ, Sousa PL, Morgan JA, et al. Incidence and Risk Factor Analysis of Symptomatic Venous Thromboembolism After Knee Arthroscopy. Arthroscopy 2015.
3. Mauck KF, Froehling DA, Daniels PR, et al. Incidence of venous thromboembolism after elective knee arthroscopic surgery: a historical cohort study. Journal of thrombosis and haemostasis 2013; 11(7): 1279-86.
4. Ettema HB, Hoppener MR, Veeger NJ, et al. Low incidence of venographically detected deep vein thrombosis after knee arthroscopy without thromboprophylaxis: a prospective cohort study. Journal of thrombosis and haemostasis 2006; 4(6): 1411-3.
5. Camporese G, Bernardi E, Prandoni P, et al. Low-molecular-weight heparin versus compression stockings for thromboprophylaxis after knee arthroscopy: a randomized trial. Annals of internal medicine 2008; 149(2): 73-82.
6. Gaskill T, Pullen M, Bryant B, et al. The Prevalence of Symptomatic Deep Venous Thrombosis and Pulmonary Embolism After Anterior Cruciate Ligament Reconstruction. The American journal of sports medicine 2015; 43(11): 2714-9.
7. Surgeons AAoO. Knee arthroscopy. Available at: http://orthoinfo.aaos.org/topic.cfm?topic=a00299. Accessed 10/22/2015, 2015.
8. Eynon AM, James S, Leach P. Thromboembolic events after arthroscopic knee surgery. Arthroscopy 2004; 20 Suppl 2: 23-4.
9. Navarro-Sanz A, Fernandez-Ortega JF. Fatal pulmonary embolism after knee arthroscopy. The American journal of sports medicine 2004; 32(2): 525-8.
10. Naess IA, Christiansen SC, Romundstad P, et al. Incidence and mortality of venous thrombosis: a population-based study. Journal of thrombosis and haemostasis 2007; 5(4): 692-9.
11. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. Annals of internal medicine 2008; 149(10): 698-707.
12. van Adrichem RA, Németh B, Algra A, et al. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. The New England journal of medicine 2017; 376(6): 515-25.
13. Greene JW, Deshmukh AJ, Cushner FD. Thromboembolic complications in arthroscopic surgery. Sports medicine and arthroscopy review 2013; 21(2): 69-74.
14. van Adrichem RA, Debeij J, Nelissen RG, et al. Below-knee cast immobilization and the risk of venous thrombosis: results from a large population-based case-control study. Journal of thrombosis and haemostasis 2014; 12(9): 1461-9.
15. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopaedic 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.
16. Blom JW, Doggen CJ, Osanto S, et al. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005; 293(6): 715-22.

17. Németh B, van Adrichem RA, van Hylckama Vlieg A, et al. Venous Thrombosis Risk after Cast Immobilization of the Lower Extremity: Derivation and Validation of a Clinical Prediction Score, L-TRiP(cast), in Three Population-Based Case-Control Studies. PLoS medicine 2015; 12(11): e1001899; discussion e.
18. van Hylckama Vlieg A, Baglin CA, Luddington R, et al. The risk of a first and a recurrent venous thrombosis associated with an elevated D-dimer level and an elevated thrombin potential: results of the THE-VTE study. Journal of thrombosis and haemostasis 2015; 13(9): 1642-52.
19. 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. Journal of thrombosis and haemostasis 2015; 13(8): 1441-8.
20. Bohensky MA, deSteiger R, Kondogiannis C, et al. Adverse outcomes associated with elective knee arthroscopy: a population-based cohort study. Arthroscopy 2013; 29(4): 716-25.
21. Hetsroni I, Lyman S, Do H, et al. Symptomatic pulmonary embolism after outpatient arthroscopic procedures of the knee: the incidence and risk factors in 418,323 arthroscopies. The Journal of bone and joint surgery British volume 2011; 93(1): 47-51.
22. Jameson SS, Dowen D, James P, et al. The burden of arthroscopy of the knee: a contemporary analysis of data from the English NHS. The Journal of bone and joint surgery British volume 2011; 93(10): 1327-33.
23. Caprini JA. Thrombosis risk assessment as a guide to quality patient care. Disease-a-month : DM 2005; 51(2-3): 70-8.
24. Schonenberg D, van Meeteren M, Nelissen RG, et al. [Thrombosis prevention in orthopaedic surgery: clinical practice in the Netherlands in 2002]. Nederlands tijdschrift voor geneeskunde 2003; 147(38): 1856-60.

10

Predicting venous thromboembolism risk after immobilization of the lower-limb for trauma: update and validation of a clinical risk assessment model, the TRiP(cast) score

*B.Németh, *D. Douillet, S. le Cessie, A. Penaloza,
T. Moumneh, PM. Roy, S.C. Cannegieter
*Authors contributed equally

The Lancet - EClinicalMedicine. 2020 Feb 4;20:100270.

ABSTRACT

Background Patients with lower-limb trauma requiring immobilization have an increased risk of venous thromboembolism (VTE). While thromboprophylaxis for all patients seems not effective, targeted thromboprophylaxis in high risk patients may be an appropriate alternative. Therefore, we aimed to develop and validate a risk assessment model for VTE risk: the TRiP(cast) score (Thrombosis Risk Prediction following cast immobilization).

Methods In this prediction model study, for development, data were used from the MEGA study (case-control study into the aetiology of VTE) and for validation, data from the POT-CAST trial (randomized trial on the effectiveness of thromboprophylaxis following cast immobilization) were used. Model discrimination was calculated by estimating the Area Under the Curve (AUC). For model calibration, observed and predicted risks were assessed.

Findings The TRiP(cast) score includes 14 items; one item for trauma severity (or type), one for type of immobilization and 12 items related to patients' characteristics. Validation analyses showed an AUC of 0.74 (95%CI 0.61 to 0.87) in the complete dataset (n=1250) and 0.72 (95%CI 0.60-0.84) in the imputed data set (n=1435). The calibration plot shows the degree of agreement between the observed and predicted risks (intercept 0.0016 and slope 0.933). Using a cut-off score of 7 points in the POT-CAST trial (incidence 1.6%), the sensitivity, specificity, positive and negative predictive values were 76.1%, 51.2%, 2.5%, and 99.2%, respectively.

Interpretation The TRiP(cast) score provides a helpful tool in daily clinical practice to accurately stratify patients in high versus low-risk categories in order to guide thromboprophylaxis prescribing. To accommodate implementation in clinical practice a mobile phone application has been developed.

Funding source ZonMW VIMP grant:17110200011.

BACKGROUND

Patients with lower-limb injuries requiring immobilization, i.e. brace or casting, are at risk of venous thromboembolism (VTE). Approximately 2.0% of patients will develop VTE within 3-months following immobilization without the use of thromboprophylaxis such as low-molecular weight heparin (LMWH) [1–5]. However, applying a population-based approach by providing thromboprophylaxis for all patients is not effective (6). Therefore, an individualized approach, i.e. targeting individual patients based on the size of their VTE risk, might be an appropriate alternative. For instance, patients with a high risk may benefit from an intensified regimen of thromboprophylaxis whereas patients with a low risk can be (safely) withheld from treatment. By doing so, both thrombosis and bleeding risk can be reduced to a minimum. Because of the high prevalence of lower-limb trauma and the significant impact of VTE in terms of morbidity, mortality and resource expenditure, targeted thrombosis prevention will have a major impact on public health [7–11].

To personalize thromboprophylaxis treatment in patients with lower-limb immobilization, two specific VTE risk assessment models (RAMs) have been developed [12,13]. Furthermore, two studies published a list of predictors in which case thromboprophylaxis should be considered [14]. In 2015, the Leiden-TRiP(cast) (for Leiden-Thrombosis Risk Prediction for patients with cast immobilization score) was developed in the Netherlands (13), using data from a large population-based case-control study [15]. It includes 19 items with scores ranging from 1 to 5 and was retrospectively validated in two independent datasets. Despite promising results, the Leiden-TRiP(cast) score has some weaknesses that impair its wide implementation. Mainly, it does not include trauma severity (which has been shown to be associated with VTE risk) and absolute risks for individual patients could not be obtained because of the case-control setting [16].

Hereafter, another RAM was developed for patients with lower-limb non-surgical trauma requiring brace or cast immobilization, e.g. the TIP score (for Trauma, Immobilization and Patients characteristics score) [17]. The TIP score was developed using a very different approach, i.e., via an international panel of experts and professionals using the Delphi consensus method. With at least a strong consensus (>75%), 13 items for trauma, 3 for immobilization and 14 for patient characteristics were selected. While the TIP score performed well, with a total of 30 items, the usability of this model in clinical practice is questionable.

Most clinical variables of the Leiden-TRiP(cast) score had also been incorporated by the experts in the TIP score. As both scores were very similar, this allowed us to select the best features of both scores and merge them together in a single new combined score: the TRiP(cast) score for "Thrombosis Risk Prediction for patients with cast immobilization".

Goals of this investigation

The main aim of this study was to develop and validate a new score, the TRiP(cast) score, to identify patients with lower-limb immobilization for trauma at low or high-risk for VTE.

METHODS

Study methods

Figure 1 shows the study flow-chart that presents all analyses which have been performed throughout the study. Two previous risk prediction models for VTE following cast immobilization (the Leiden-TRiP(cast) score and the TIP score) were used to create a final risk score entitled the TRiP(cast) score, note: without "Leiden". (*Step 1, Figure 1*). The Leiden-TRiP(cast) score was developed using data from the MEGA study whereas the TIP score was developed by a group of experts using the Delphi method. Following development, the TIP score was validated in the MEGA study [13]. Thereafter, score performances were compared by the AUC, sensitivity, and specificity. Both scores had a comparable discriminative value, and many similar predictors. The main difference was the Trauma component from the TIP which was lacking in the Leiden-TRiP(cast) score. Therefore, it was decided to merge both scores into one single score (*Step 2, Figure 1*). The performance of the final TRiP(cast) score was subsequently validated in both the MEGA study and, to obtain absolute risks, in the POT-CAST trial (Prevention of Thrombosis following CAST immobilization trial) (*Step 3, Figure 1*) [6].

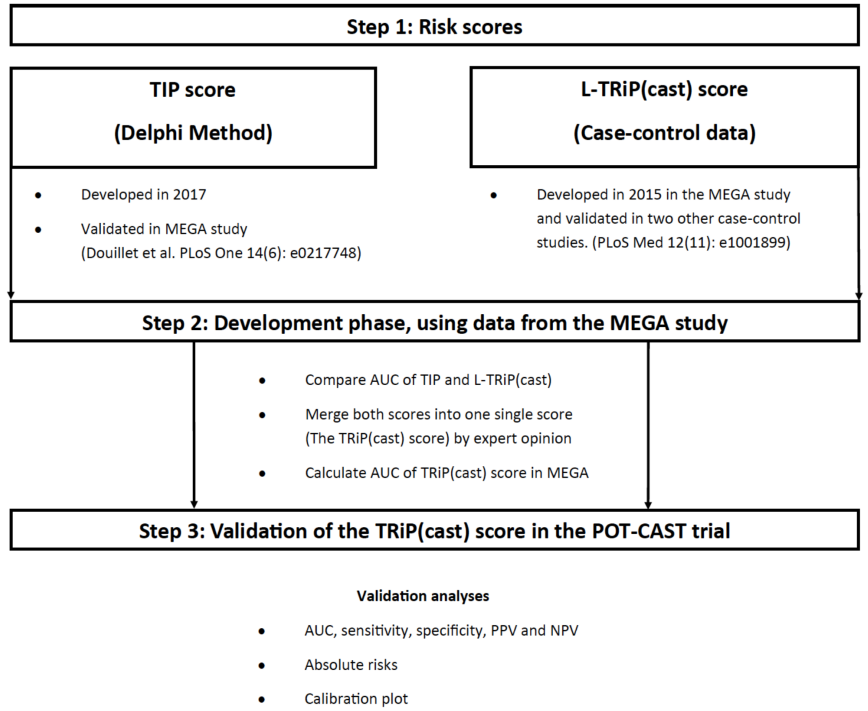


Figure 1: Flowchart of the TRiP(cast) score development and validation process.

Formation of the final TRiP(cast) score

Appendix Table 1 compares predictors included in the TIP and Leiden-TRiP(cast) scores. Both scores were merged in a single score (the TRiP(cast) score) focussing on optimal usability in clinical practice: predictors with a low prevalence (such as pneumonia or having a history of superficial vein thrombosis) were excluded from the final score. Risk points of the final TRiP(cast) score were based on that of the previous Leiden-TRiP(cast) score because these points were based on regression coefficients obtained from a multivariate logistic regression model whereas those of the TIP score had been determined by expert opinion (Delphi Method) and considered less accurate.

Primary study outcome measure

A prediction model which predicts the occurrence of symptomatic VTE within 3-months following cast immobilization for lower-limb trauma. As main outcome measures, model discrimination and calibration were assessed, please see the statistical analysis section for more details.

Study Design

The MEGA study

To assess the performances of all three scores, we used data from the MEGA study. Details of this study have been published previously [15,18,19]. In short, 4956 consecutive patients aged 18 to 70 years with a first deep vein thrombosis (DVT), pulmonary embolism (PE), or both were recruited from six anticoagulation clinics in the Netherlands between 1 March 1999 and 31 August 2004. The diagnosis of DVT or PE was confirmed by (Doppler) ultrasonography, ventilation/perfusion scan, angiography, or spiral CT scan. The control group (n=6297) consisted of partners from participating patients and other controls who were identified using a random digit dialling method; controls were frequency matched to cases with respect to sex and age. All participants completed a questionnaire on risk factors for VTE that included questions on (potential) risk factors such as trauma, immobilization (including cast immobilization and location), (orthopaedic) surgery, current use of (any) medication, and comorbidity in the past year before VTE.

The POT-CAST study

For external validation of the TRiP(cast) score, data of the POT-CAST trial were used of which details have been published previously [6]. In short, in the POT-CAST trial, patients with lower-leg injuries requiring cast immobilization were randomized to receive a prophylactic dose of LMWH or no therapy during cast immobilization. To study the effectiveness of LMWH, the occurrence of symptomatic VTE within 3 months was assessed by a blinded independent outcome adjudication committee. Between March 2012 and January 2016, patients admitted to the emergency department who were aged 18 years

or older were eligible for inclusion if cast immobilization of the lower-leg was indicated to treat their injury. Patients complying to one of the following criteria were excluded: history of VTE, current use of anticoagulant therapy (except antiplatelet medication), contra-indications for use of LMWH, pregnancy, mental or physical disability to fulfil study requirements or insufficient knowledge of the Dutch language. All participants completed a questionnaire on risk factors for VTE at the moment of inclusion.

Approval for both the MEGA and POT-CAST study was obtained from the Medical Ethics Committee of the Leiden University Medical Center, and all participants provided written informed consent.

Statistical analysis

Score comparison in the MEGA study

The performance of all scores was first assessed in the MEGA study. Twenty patients who underwent surgery (before or following cast-immobilization as part of their treatment) were excluded. This was done as the TIP score was originally developed for non-surgical patients only and all scores needed to be compared in the same data. In total, 179 cases and 31 controls who had cast immobilization of the lower-extremity were included. To assess model performance, the Area Under the Curve (AUC) with corresponding 95% Confidence Interval (95%CI) was estimated by means of a Receiver Operating Characteristic curve. Furthermore, the sensitivity, specificity and positive and negative predictive values (PPV and NPV) were calculated for a pre-defined cut-off (as stated in the original development papers) [13].

Validation of the final TRiP(cast) score in the POT-CAST trial

For the main external validation analysis of the TRiP(cast) score, we used data from all patients who were included in the intention-to-treat analysis of the POT-CAST trial (n=1435 patients) with a cast immobilization of the lower-leg. Demographics were summarized as means ± standard deviation or proportions as appropriate. To account for missing data, we used multiple imputation techniques. Ten imputations were performed, and results were pooled according to Rubin's rules [20]. The TRiP(cast) score was thereafter calculated in all patients.

To assess model discrimination, the AUC was estimated in both the complete cases (n=1250) and imputed data sets (n=1435). Furthermore, the sensitivity, specificity, PPV and NPV were calculated for several dichotomized cut-off scores. To obtain estimates of absolute risks, a logistic regression analysis with VTE as dependent variable and the TRiP(cast) score as a continuous independent variable was performed. The predicted risk for each individual was calculated as follows: predicted risk = exp(a+b*TRiP(cast)

score)/(1+exp[a+b*TRiP(cast) score]), with regression coefficients a and b of the logistic regression model. The predicted and observed risks for each risk score in the TRiP(cast) score were plotted against each other in a calibration plot, showing the concordance between the predicted and observed outcome. As the main aim of this study was to create and validate one final score, the Leiden-TRiP(cast) and TIP scores were not validated in the POT-CAST study. All analyses were performed in IBM SPSS Statistics for Windows, version 20.0 and Stata, version 12.

Sensitivity analyses

As the POT-CAST trial was an RCT with two different study arms (LMWH treatment and a non-treatment arm) the discriminative value (AUC) of the TRiP(cast) score was determined in both study arms separately to determine any possible treatment effect on predictive value (even though the POT-CAST trial showed non-effectiveness of LMWH). In addition, the effectiveness of LMWH was assessed in a low and high-risk group as defined by the TRiP(cast) score (low risk <7 points, high risk ≥7 points). We calculated relative risks with corresponding 95%CI by comparing cumulative incidences of symptomatic VTE between the treated and untreated groups.

Development of a computerized clinical decision support system

To allow easy application of the TRiP(cast) score in clinical practice, a mobile phone application was developed for IOS and Android mobile platforms.

Role of funding source

This research was funded by the Netherlands Organization for Health Research and Development, which had no role in any aspect of this study.

RESULTS

Development of the final TRiP(cast) score

The final TRiP(cast) score (*Table 1*), consisted of 3 components (Trauma, Immobilization and Patient characteristics). A total of 14 items were included in the score: 1 for trauma severity (or type of trauma), 1 for type of immobilization and 12 items related to patients' characteristics. Note that for trauma, if there are several (i.e. ankle distortion with significant muscle injury), only the highest trauma type determines the score of the trauma component. Each item can be scored on a scale of 1 to 4 and the sum of these scores results in the TRiP(cast) score. For instance, a 50-year-old male with a BMI of 30kg/m² receives 3 points (including 1 point for being older than 35 years old, 1 point for male sex and 1 point for having a BMI≥25 and <35kg/m²). If this patient has a bi-tri malleolar ankle fracture (2 points) requiring lower-leg cast (2 points), this results in a total of 7 points.

Table 1: TRiP(cast) score*.

Trauma †	Points
High-risk trauma Fibula and/or tibia shaft fracture Tibial plateau fracture Achilles tendon rupture	3
Intermediate risk trauma Bi or tri-malleolar ankle fracture Patellar fracture Ankle dislocation, Lisfranc injury Severe knee sprain (with oedema / haemarthrosis) Severe ankle sprain (grade 3)	2
Low-risk trauma Single malleolar ankle fracture Patellar dislocation (Meta)Tarsal bone(s) or forefoot fracture Non-severe knee sprain or ankle sprain (grade 1 or 2) Significant muscle injury	1

Table 1: Continued.

	Points
Immobilization ‡	
Upper-leg cast	3
Lower-leg cast	2
Foot cast (ankle free) or any semi-rigid without plantar support	1
Patient characteristics §	
Age ≥ 35 and <55 years	1
Age ≥ 55 and <75 years	2
Age ≥ 75 years	3
Male sex	1
Body Mass Index BMI ≥25 and <35 kg/m^2	1
Body Mass Index BMI ≥35kg/m^2	2
Family history of VTE (first-degree relative)	2
Personal history of VTE or known major thrombophilia	4
Current use of oral contraceptives or Estrogenic hormone therapy	4
Cancer within the past 5 years or active cancer	3
Pregnancy or puerperium	3
Immobilization (other) ||	
Hospital admission, bedridden or flight > 6 hours within 3 months	2
Lower limb paralysis	
Surgery within the past 3 months	2
Comorbidity	1
Heart failure, rheumatoid arthritis, chronic kidney disease,	
COPD, IBD	
Chronic venous insufficiency (varicose veins)	1

* Thrombosis Risk Prediction in patients with cast immobilization score
TRiP(cast) score is the sum of the Trauma, Immobilization and Patient components
† Trauma: Choose one, (the most severe trauma)
‡ Immobilization: Choose one
§ Patient: multiple points can be scored
|| Other immobility next to cast immobilization

Risk score performances in the MEGA study

In the MEGA study, the original AUC values for the Leiden-TRiP(cast) score and TIP score were 0.78 (95% CI 0.69–0.88) and 0.77 (95%CI 0.69-0.85), respectively. The AUC of the new TRiP(cast) score was 0.77 (95%CI 0.67-0.86) (*Table 2*).

Table 2: Performance of the L-TRiP(cast), TIP and TRiP(cast) score in the MEGA study.

	AUC*	**95% CI**	
L-TRiP(cast) score	0.78	0.69	0.88
TIP score	0.77	0.69	0.85
TRiP(cast) score	0.77	0.67	0.86

*AUC denotes Area Under the Curve, CI denotes Confidence Interval

POT-CAST (validation) population

Among the 1435 patients included in the POT-CAST study, the TRiP(cast) score could be calculated for 1250 patients (complete predictor data). Data were imputed for 185 patients. Patient characteristics are summarized in *Table 3*. In brief, 49.9% were males and the mean age was 46 ± 16.5 years. The median BMI was 25.8 ± 4.5 kg/m². Among all patients, 9.8% had a family history of VTE, 2.5% had active cancer or cancer history within 5 years and 9.5% received oral contraceptives or hormonal therapy. The majority of patients had a fracture: 1279/1435 (89.1%). Ninety-four patients had an Achilles tendon rupture (6.6%) and thirty-five patients had an ankle distortion (2.5%). 7.0%, 8.8% and 84.2% of patients were classified as having a high, intermediate or low-risk trauma, respectively. All patients were treated with lower-leg cast and immobilized for a mean duration of 4.9 weeks ± 2.5.

Of all 1435 patients, 23 patients developed symptomatic VTE (14 had DVT, 7 had a PE, and 2 patients both) for a cumulative incidence of 1.6% (95%CI 1.3 to 2.7).

TRiP(cast) score performance

The distribution of the TRiP(cast) score among patients with or without VTE is displayed in *Appendix figure 1*. The TRiP(cast) score performed well with an AUC of 0.74 (95%CI 0.61 to 0.87) in the complete dataset and an AUC of 0.72 (95%CI 0.60-0.84) in the imputed data set. *Table 4* shows test statistics for each dichotomized cut-off of the TRiP(cast) score. For example, using a cut-off score of 7 points to stratify individuals into a low versus high-risk category (low-risk 50.7% and 49.3% high risk), the sensitivity was 76.1% and the specificity was 51.2%. Based on an incidence of VTE of 1.6% (incidence in POT-CAST), the PPV of the test (cut-off >=7 points) was 2.5%, and the NPV 99.2%.

Table 3: POT-CAST trial – validation cohort characteristics.

	Total n=1435
Trauma	
High-risk trauma	100 (7.0)
Intermediate-risk trauma	127 (8.8)
Low-risk trauma	1208 (84.2)
Immobilization	
Duration of lower-leg cast in weeks, mean (SD)	4.9 (2.5)
Lower-leg cast indication, n (%)	
Fracture	1279 (89.1)
Achilles tendon rupture	94 (6.6)
Ankle distortion	35 (2.5)
Antalgic	9 (0.6)
Contusion	13 (0.9)
Other	5 (0.3)
Fracture type, n (%)	
Ankle	497 (34.6)
Metatarsal	532 (37.1)
Calcaneus	56 (3.9)
Pilon tibial	3 (0.2)
Tibia and fibula shaft	3 (0.2)
Talus	50 (3.5)
Tarsal	98 (6.8)
Phalanx	23 (1.6)
Lisfranc	6 (0.4)
Other *	11 (0.8)
Surgery, n (%) †	170 (11.8)
Patient characteristics ‡	
Mean age (SD), years	46.0 (16.5)
Male sex, n (%)	719 (49.9)
Mean BMI (SD), kg/m^2	25.8 (4.5)
Smoking, n (%)	
Current	173 (26.1)
Ever	188 (28.4)

Table 3: Continued.

	Total n=1435
Family history of venous thromboembolism (1st degree), n (%)	140.5 (9.8)
Personal history of VTE or known major thrombophilia	Not included
Current use of oral contraceptives or Estrogenic hormone therapy	137 (9.5)
Cancer within the past 5 years or active cancer	36 (2.5)
Pregnancy or puerperium	Not included
Immobilization (other)	134.5 (9.4)
Surgery within the past 3-months	232.6 (16.2)
Comorbidity	122.9 (8.6)
Varicose veins	222.2 (15.4)

SD : standard deviation, BMI : Body Mass Index
* Fractures not meeting criteria to be classified in either type.
† Surgery as part of lower-leg injury treatment
‡ As some patient data were imputed, the total n displays decimals due to imputation. Data were missing for the following characteristics: BMI in 100 patients, Smoking in 107 patients, Oral contraceptives use in 45 patients, Cancer in 87 patients, Family history of venous thromboembolism 316 patients.

Table 4: Performance of the TRiP(cast) score in the POT-CAST study.

	AUC (95%CI) in complete cases	**AUC (95%CI) in Imputed data**		
TRiP(cast) score	0.74 (0.61 - 0.87)	0.72 (0.60 - 0.84)		
*	**Sensitivity**	**Specificity**	**PPV†**	**NPV†**
Cutoff 4	100.0%	1.9%	1.6%	100.0%
Cutoff 5	95.7%	16.6%	1.8%	99.6%
Cutoff 6	85.7%	32.2%	2.0%	99.3%
Cutoff 7	76.1%	51.2%	2.5%	99.2%
Cutoff 8	64.8%	67.9%	3.2%	99.2%
Cutoff 9	53.0%	80.0%	4.1%	99.1%
Cutoff 10	45.7%	88.8%	6.2%	99.0%
Cutoff 11	31.7%	94.4%	8.5%	98.8%

* Cut-off represents the value at which the TRiP(cast) score was dichotomized to calculate model performance
AUC denotes Area under the Curve, PPV denotes positive predictive value, NPV denotes negative predictive value
† Based on a VTE prevalence of 1.6%

The predicted risk (absolute VTE risk) was calculated by exp(6.677015 + 0.3332203*TRiP(cast) score)/(1+ exp[6.677015 + 0.3332203*TRiP(cast) score]). The degree of concordance between the observed and predicted risk was estimated by a calibration line with an intercept of 0.0016 and slope of 0.933) (*Appendix Table 2*). *Figure 2* depicts the calibration plot in which this relationship can be observed.

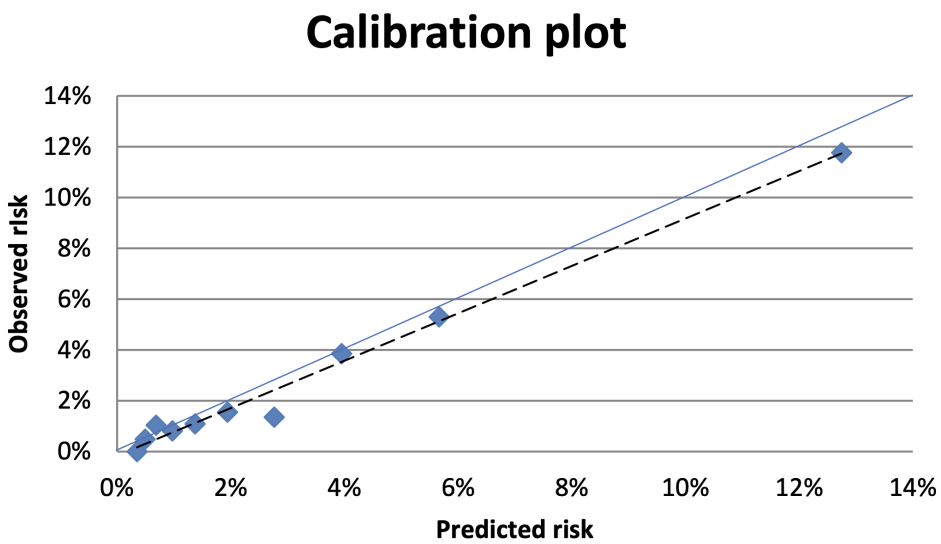


Figure 2: Calibration plot, showing the observed versus predicted risks for VTE for TRiP(cast) scores 3-12. TRiP(cast) scores ≥12 were summarized in a single dot due to a low number of events (3.0%) (observed risk 11.8% and predicted risk 12.8%). For values see *Appendix Table 2*.

Differentiation between a low and high-risk group for symptomatic VTE

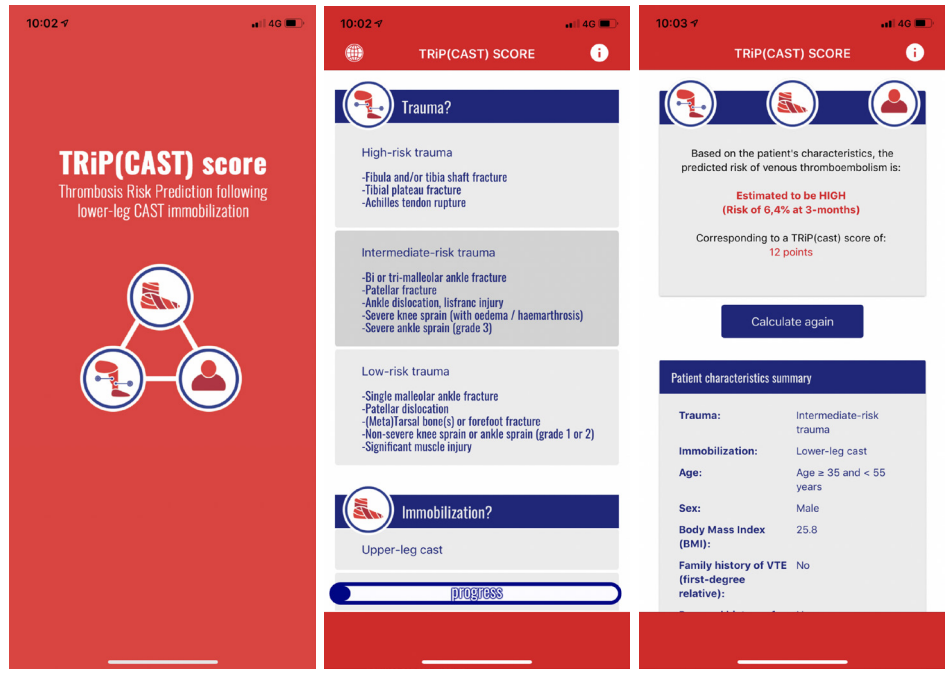
The AUC of the TRiP(cast) score in untreated patients in the POT-CAST trial (n=716) was 0.66 (95%CI 0.49-0.83) whereas for LMWH treated patients (n=719) the AUC was 0.80 (95%CI 0.67-0.94). 50.7% (n=728/1435) of all patients had a TRiP(cast) score of <7, and were classified as low-risk patients (mean observed symptomatic VTE risk of 0.8%) whereas 49.3% (n=707/1435) of patients had a TRiP(cast) score of ≥7, who were classified as high-risk (mean observed symptomatic VTE risk of 2.5%).

Across patients in the low-risk subgroup, 0.4% (1.3/360) of patients treated with LMWH developed symptomatic VTE as compared with 1.1% (4.2/367.8) in the untreated group, for a RR of 0.30 (95%CI 0.03 – 2.60) (absolute numbers represent mean values across 10 imputed datasets, hence, the non-integers). In the high-risk population, 2.4% (8.7/359)

of patients treated with LMWH versus 2.5% (8.8/348.2) of untreated patients developed VTE, so here LMWH was non-effective in reducing symptomatic VTE risk (RR 0.96, 95%CI 0.37-2.51).

Computerized clinical decision support systems

A mobile phone application (TRiP(cast) score © 2018) has been developed (screenshot in *Appendix Figure 2*) for IOS and Android mobile phone platforms which can be downloaded in the App store of Apple or Android, without costs and is available in three languages; English, Dutch and French. It calculates an individual's absolute predicted risk for VTE (using validation data from this paper) once all patient data have been entered in the application. Decisions on thromboprophylaxis can then be made accordingly.



Appendix Figure 2: Screenshots of the TRiP(cast) score © 2018 mobile phone application.

DISCUSSION

In order to facilitate individual VTE risk assessment and guide thromboprophylaxis in patients with lower-limb trauma and cast immobilization, we merged two existing RAMs into the combined TRiP(cast) score. The TRiP(cast) score exhibited good performance in the external validation with an AUC of 0.74 (95%CI 0.61 to 0.87) and the observed and predicted risk were in concordance (calibration slope 0.933). Using < 7 points as cut-off, the TRiP(cast) score allows identification of an important subgroup of patients with a low risk of symptomatic VTE (mean absolute risk of 0.8%) who may not require any thromboprophylactic treatment. Contrary, patients with a high-risk of VTE according to the TRiP(cast) score (≥ 7 points, mean absolute risk 2.5%) may require intensified or prolonged thromboprophylaxis.

Merging risk scores

The Leiden-TRiP(cast) and TIP scores were combined for several reasons. First, both scores overlapped on many items which allowed a simple transformation into the final TRiP(cast) score. Second, previous studies have shown that the effect of trauma on VTE risk varies widely according trauma severity and localization [3,16,21]. Whereas the Leiden-TRiP(cast) score lacks such important predictors on trauma severity, this is an important feature of the TIP score. Third, the Leiden-TRiP(cast) score has been validated in two other case-control studies and fewer risk items have to be scored which simplifies use in clinical practice (19 in Leiden-TRiP instead of 30 in the TIP score). Furthermore, the Leiden-TRiP(cast) score does not apply to brace immobilization and contains relatively uncommon items that have been collected using case-control questionnaire data such as pneumonia, or a history of superficial vein thrombosis. By merging the L-TRiP(cast) and TIP score we combined the strengths of both scores to increase the final score's discriminative ability, usability and simplicity. Hence, the combined TRiP(cast) score encompasses 14 items which are easily obtainable in current practice.

Strengths and limitations of the study

The main strength of this paper is that data of the POT-CAST trial were used, which were practically complete and reliable; due to the nature of the POT-CAST trial, trauma severity data have been prospectively collected by a physician and all data on patient characteristics were completed upon inclusion in the trial [6]. Absolute risks for symptomatic VTE were calculated with minimal loss-to follow-up and misclassification, which are common in large registry studies. The strength of the POT-CAST trial (i.e. pragmatic RCT design with non-selected patients and limited exclusion criteria) allowed us to calculate validation statistics in data mimicking clinical practice.

Nevertheless, some limitations have to be mentioned. Although the inclusion criteria of the POT-CAST trial were wide, some patient selection may still have been present. For instance, all patients had plaster cast, i.e. no brace. Patients with a history of VTE were not allowed to participate. However, as their VTE risk is certainly high, it may be reasoned that these patients do not need risk prediction at all, and should receive thromboprophylaxis in most circumstances. Furthermore, despite being the largest trial till date on this topic, few patients (23/1435) developed VTE which limits the accuracy of our validation statistics. The MEGA case-control study was also limited in terms of power. Yet, the predictive performance of the TRiP(cast) score (and previous TIP AND Leiden-TRiP scores) showed consistent results in both the MEGA and POT-CAST datasets indicating no overfitted prediction model. Another limitation might be the use of data imputation which can introduce misclassification (in this case of patient characteristics). However, model performance was good and hardly differed between the imputed and the complete dataset. Lastly, to optimize the TRiP(cast) score performance, 14 variables were maintained which might be considered as relatively many items have to be scored. To anticipate this, we developed a computerized clinical decision support systems (CCDSSs) using a mobile phone application. We believe this can be a helpful tool in clinical practice as entering and summation of the items is greatly facilitated. Furthermore, studies have highlighted that the use of CCDSSs increases the proportion of patients who receive adequate prophylaxis [22,23] and can be efficiently implemented in everyday clinical practice in emergency departments [24].

From a population-based approach to individualized therapy

Current guidelines for thromboprophylaxis and therefore practices vary widely among countries, ranging from the absence of preventive anticoagulation in the US [25] to thromboprophylaxis for all patients for whom plantar support is not possible in France [26]. This variation can be explained by the lack of convincing evidence when these guidelines were written. Some trials showed efficacy of thromboprophylaxis on asymptomatic VTE for patients following lower-limb cast immobilization [27–30]. However, the recent POT-CAST trial failed to demonstrate efficacy of LMWH versus no treatment on the 3-month cumulative incidence of symptomatic VTE with a relative risk of 0.8 (95%CI, 0.3 to 1.7) [6]. Contrary, a recent Cochrane systematic review and meta-analysis, including these RCTs, showed moderate-quality evidence in favour of thromboprophylaxis for patients with brace or casting [1]. Yet, concerning the methodological issues for many of these trials (e.g. doubtful classification of symptomatic events), inconsistency between the efficacy on asymptomatic vs symptomatic VTE, publication bias towards efficacy and high number needed to treat (250 based on POT-CAST), the quality of evidence was downgraded. The final conclusion of the authors was that future research should give more directives on specific advice for different patients or patients groups, based on patient and trauma characteristics. This goal has now come nearer with the TRiP(cast) score.

Clinical implications

To achieve a reduction in VTE risk as well as bleeding, individualized prophylaxis using the TRiP(cast) score might be an important step forward. Ultimately, patients with a high risk may need to receive a higher dosage or duration of thromboprophylaxis or a stronger anticoagulant, while those with a low risk (the majority), can be spared the burden and the costs of an intense treatment.

Individualized therapy will lead to three situations: adequate therapy, under- and over-prescription of anticoagulation. The former is true for all patients with a low- or high-risk who are correctly identified as such. However, as risk assessment is not 100% accurate there is a trade-off which results in under- and over-treatment. Under-prescription arises when high-risk patients are not classified as such, and therefore do not receive thromboprophylaxis (using a cut-off score of ≥7, with a corresponding sensitivity of 75%, this occurs in 25% of patients who will eventually develop VTE). Over-prescription occurs when low-risk patients are incorrectly classified as high-risk patients, again, using a cut-off of ≥7, 49% of patients receive overtreatment. Opposingly, 51% of patients with a low-risk are correctly withheld from the risks (bleeding) and downsides (costs) of thromboprophylaxis (a cut-off score of 7 was chosen as the absolute VTE risks for patients with a TRiP(cast) score<7 was lower than 1.0%). Another approach would be to identify three groups of patients, a low-middle- and high-risk group. In this case, low-risk patients do not require any treatment, middle-risk patients can receive the current dosage and duration of thromboprophylaxis while high-risk patients may need a prolonged and higher dosage of thromboprophylaxis. In this case, high-risk patients could be identified based on a TRiP(cast) score of ≥10 which results in an PPV of at least 6.2% (11% of patients).

This strategy is emphasized by the results from our sensitivity analyses in which we found a very limited suggestion for effectiveness for a prophylactic dose of LMWH in low-risk patients (RR 0.30, 95%CI 0.03 – 2.60) compared with no effectiveness in high-risk patients (RR 0.96 95%CI 0.37-2.51). This finding suggests that a prophylactic dose of LMWH is not sufficient to decrease the thrombosis potential to such an extent that it prevents symptomatic VTE in high-risk individuals.

As we found a different treatment effect across low and high-risk groups, consequently, the predictive value of the TRiP(cast) score was lower in untreated patients than in LMWH treated patients. This might indicate that the TRiP(cast) score particularly identifies high-risk patients despite thromboprophylaxis therapy. However, we have to stress that all these results should be interpreted with care based on the limited the sample size (wide confidence intervals) and hence, low number of patients who developed symptomatic VTE. Overall, the clinical implications of risk stratification and corresponding treatment options will be a

subject of debate and is dependent upon prioritizing the classification of low- or high-risk patients, and the trade-off between under- and over-treatment (i.e. the importance and weight of a false-negative versus false-positive classification).

Despite this study being validated in a large cohort of patients, the ultimate cut-off (in terms of VTE risk) and the corresponding optimal treatment need to be determined in a large management study (including decisions on more intensified treatment regimens). Especially, since the power of our validation study was for low and high-risk patient groups separately. At any rate, it is clear that the current situation needs improvement, as 2.0% of patients develop VTE despite thromboprophylaxis while at the same time a large proportion of this population is likely to be overtreated.

In conclusion, the TRiP(cast) score was developed and validated to predict VTE risk following lower-limb cast or brace immobilization. Thanks to a CCDSS (smartphone application), it can easily be implemented in future research and clinical practice to accurately stratify patients in risk categories and to help in decision making for individualized thromboprophylaxis.

REFERENCE LIST

1. Zee AA, van Lieshout K, van der Heide M, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilization. Database Syst Rev. 2017 Aug 6;8(8):CD006681.
2. Testroote M, Stigter W, de Visser DC, Janzing H. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD006681.
3. van Adrichem RA, Debeij J, Nelissen RGHH, Schipper IB, Rosendaal FR, Cannegieter SC. Below-knee cast immobilization and the risk of venous thrombosis: results from a large population-based case-control study. J Thromb Haemost. 2014 Sep;12(9):1461–9.
4. Ettema HB, Kollen BJ, Verheyen CCPM, Büller HR. Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. J Thromb Haemost. 2008 Jul;6(7):1093–8.
5. Hickey BA, Watson U, Cleves A, Alikhan R, Pugh N, Nokes L, et al. Does thromboprophylaxis reduce symptomatic venous thromboembolism in patients with below knee cast treatment for foot and ankle trauma? A systematic review and meta-analysis. Foot and Ankle Surgery. 2018 Feb;24(1):19–27.
6. van Adrichem RA, Németh B, Algra A, le Cessie S, Rosendaal FR, Schipper IB, et al. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. New England Journal of Medicine. 2017 Feb 9;376(6):515–25.
7. Lambers K, Ootes D, Ring D. Incidence of patients with lower extremity injuries presenting to US emergency departments by anatomic region, disease category, and age. Clin Orthop Relat Res. 2012 Jan;470(1):284–90.
8. Singer BR, McLauchlan GJ, Robinson CM, Christie J. Epidemiology of fractures in 15 000 adults: The influence of age and gender. The Journal of Bone and Joint Surgery. 1998 Mar 1;80(2):243–8.
9. Næss IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. Journal of Thrombosis and Haemostasis. 2007 Apr;5(4):692–9.
10. ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to the global disease burden. Journal of Thrombosis and Haemostasis. 2014 Oct;12(10):1580–90.
11. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. Journal of Thrombosis and Thrombolysis. 2009 Nov;28(4):465–76.
12. Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. 2010 Nov;8(11):2450–7.
13. Caprini JA. Individual Risk Assessment Is the Best Strategy for Thromboembolic Prophylaxis. Disease-a-Month. 2010 Oct;56(10):552–9.
14. Németh B, Adrichem RA van, Hylckama Vlieg A van, Bucciarelli P, Martinelli I, Baglin T, et al. Venous Thrombosis Risk after Cast Immobilization of the Lower Extremity: Derivation and Validation of a Clinical Prediction Score, L-TRiP(cast), in Three Population-Based Case–Control Studies. Sattar N, editor. PLOS Medicine. 2015 Nov 10;12(11):e1001899.
15. Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005 Feb 9;293(6):715–22.

16. Bezemer ID, Doggen CJM, Vos HL, Rosendaal FR. No association between the common MTHFR 677C->T polymorphism and venous thrombosis: results from the MEGA study. Arch Intern Med. 2007 Mar 12;167(5):497–501.
17. Cannegieter SC, Doggen CJM, van Houwelingen HC, Rosendaal FR. Travel-related venous thrombosis: results from a large population-based case control study (MEGA study). PLoS Med. 2006 Aug;3(8):e307.
18. van Stralen KJ. Minor Injuries as a Risk Factor for Venous Thrombosis. Archives of Internal Medicine. 2008 Jan 14;168(1):21.
19. Riou B, Rothmann C, Lecoules N, Bouvat E, Bosson J-L, Ravaud P, et al. Incidence and risk factors for venous thromboembolism in patients with nonsurgical isolated lower limb injuries. Am J Emerg Med. 2007 Jun;25(5):502–8.
20. Borab ZM, Lanni MA, Tecce MG, Pannucci CJ, Fischer JP. Use of Computerized Clinical Decision Support Systems to Prevent Venous Thromboembolism in Surgical Patients: A Systematic Review and Meta-analysis. JAMA Surgery. 2017 Jul 1;152(7):638.
21. Galanter WL, Thambi M, Rosencranz H, Shah B, Falck S, Lin F-J, et al. Effects of clinical decision support on venous thromboembolism risk assessment, prophylaxis, and prevention at a university teaching hospital. American Journal of Health-System Pharmacy. 2010 Aug 1;67(15):1265–73.
22. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopaedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e278S-e325S.
23. Samama C-M, Gafsou B, Jeandel T, Laporte S, Steib A, Marret E, et al. [French Society of Anaesthesia and Intensive Care. Guidelines on perioperative venous thromboembolism prophylaxis. Update 2011. Short text]. Ann Fr Anesth Reanim. 2011 Dec;30(12):947–51.
24. Kock H-J, Schmit-Neuerburg KP, Hanke J, Rudofsky G. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. The Lancet. 1995 Aug;346(8973):459–61.
25. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. N Engl J Med. 2002 Sep 5;347(10):726–30.
26. J Lapidus L, Ponzer S, Elvin A, Levander C, Lärfars G, Rosfors S, et al. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: A randomized placebo-controlled, double-blind study. Acta Orthopaedica. 2007 Jan;78(4):528–35.
27. Camporese G, Bernardi E, Noventa F, Bosco M, Monteleone G, Santoro L, et al. Efficacy of Rivaroxaban for thromboprophylaxis after Knee Arthroscopy (ERIKA): A phase II, multicentre, double-blind, placebo-controlled randomised study. Thrombosis and Haemostasis. 2016 Mar;116(08):349–55.
28. Bruntink MM, Groutars YME, Schipper IB, Breederveld RS, Tuinebreijer WE, Derksen RJ, et al. Nadroparin or fondaparinux versus no thromboprophylaxis in patients immobilised in a below-knee plaster cast (PROTECT): A randomised controlled trial. Injury. 2017 Apr;48(4):936–40.

11

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

B. Németh & S.C. Cannegieter

Thromb Res. 2019 Feb;174:62-75.

ABSTRACT

Venous thromboembolism (VTE) is a major complication following lower-leg cast immobilization and knee arthroscopic surgery. In this review, we aimed to give a comprehensive overview of the literature on the epidemiology, prevention and prediction of VTE in these patients.

First, the cumulative incidence of VTE was estimated by performing a meta-analysis in untreated patients only. In lower-leg cast patients with various injuries, asymptomatic VTE occurred in 18.0% (95%CI 12.9 to 23.1) and symptomatic VTE in 2.0% (95%CI 1.3 to 2.7). In knee-arthroscopy patients, asymptomatic VTE was seen in 5.9% (95%CI 3.9 to 7.9) versus a symptomatic rate of 0.6% (95%CI 0.4 to 0.7) following heterogeneous types of arthroscopic knee procedures.

Second, the efficacy of thromboprophylaxis was determined by performing a meta-analysis of all RCTs that have been performed till date. Following knee-arthroscopy, there was no clear benefit of thromboprophylaxis on the prevention of symptomatic VTE (RR 0.65, 95%CI 0.23 to 1.81), while in contrast, this seemed to prevent asymptomatic DVT. In lower-leg cast patients, thromboprophylaxis appeared to reduce symptomatic VTE (OR 0.31, 95%CI 0.13 to 0.73). However, the validity of these results may be questioned as many trials had several methodological weaknesses.

Concerning the bleeding risk (and costs) of thromboprophylaxis, treatment seems only prompted in high risk patients. Such patients could be identified based on individual risk factors such as higher age, obesity or presence of Factor V Leiden. In conclusion, we propose to use risk assessment models to identify patients at risk and to decide on individualised thromboprophylactic therapy, rather than one standard treatment for all patients.

INTRODUCTION

Patients with cast immobilization of the lower-leg or who undergo arthroscopic knee surgery are at increased risk for developing venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE). Many authors studied the occurrence of VTE following these healthcare interventions [1-5] and several clinical trials have been performed to explore whether thromboprophylaxis is effective for the prevention of VTE. [6, 7] However, regardless of all the evidence, guidelines are still ambivalent with regards to thromboprophylaxis advice.[8, 9] Recently, results from two large pragmatic randomized controlled trials (i.e. one in patients with lower-leg casting and one in patients who underwent knee arthroscopy) were published in which it was shown that thromboprophylaxis was not effective for symptomatic VTE reduction.[10] Contradictory findings in (most) previously published studies described a protective effect of thromboprophylaxis therapy.[6, 7]

In light of these recent findings, there is a necessity to integrate and translate all previously published and current research to clinical practice. For this reason, in this narrative review, we aimed to give a comprehensive overview of the literature on the epidemiology, prevention and prediction of VTE in lower-leg cast and knee arthroscopy patients.

First, the incidence of VTE following lower-leg cast immobilization and arthroscopic knee surgery was estimated. Therefore, we selected all cohort studies and clinical trials of moderate to high quality which were published till date with reliable incidence rates. We collected cumulative incidence data in all patients who did not receive thromboprophylaxis therapy (thus studies were excluded when data on thromboprophylaxis were not available). For this purpose the number of patients with a VTE and the size of the study population were extracted. Subsequently, a meta-analysis using a random effects model (using the method of DerSimonian and Laird) was performed to estimate the cumulative incidence for asymptomatic DVT and symptomatic VTE separately. Results were summarized in a forest plot showing the Estimated Proportion (ES) including 95% Confidence Interval (95%CI) of patients with a VTE in each study. Heterogeneity was assessed using the I^2 method. See *Supplement 1* for our search strategy.

Second, the efficacy of thromboprophylaxis is discussed including evidence from the most recent studies.[10-12] A meta-analysis using a random effects model (using the method of DerSimonian and Laird) was performed on the efficacy of thromboprophylaxis therapy, summarizing all clinical trials that have been performed up till now. We extracted the number of VTEs within each trial per study arm. In a forest plot we showed the Relative Risk (RR) including 95%CI for the effectiveness of thromboprophylaxis. This was done for the effectiveness on symptomatic and asymptomatic events separately. See *Supplement 1* for our search strategy.

Third, this review focusses on individualized preventive strategies. Therefore, we summarized all VTE risk factors that have been identified in knee arthroscopy and lower-leg cast patients. Additionally, we reviewed the literature for available risk prediction models that were able to assess VTE risk in these patient populations. Finally, future research perspectives are discussed, focusing on the mechanism of thrombus development following knee-arthroscopy and lower-leg casting.

Please see the table of contents below which clarifies the structure of this extensive review.

EPIDEMIOLOGY

In the general population, annually, 1.5 per 1000 patients will develop VTE, corresponding to an individual's lifetime risk after 45 years of age of about 8%.[13, 14] In this chapter we aimed to estimate the actual incidence of VTE following lower-leg cast immobilization without thromboprophylaxis. Subsequently, this was also done for patients who undergo knee arthroscopy. Thereafter the burden of VTE in both patients groups is described focussing on the impact of VTE on a population level.

Incidence of VTE following lower-leg cast immobilization

Patients with cast immobilization of the lower-leg have an increased risk for developing VTE which was already described in 1944. In that year, Gunnar Bauer showed that DVT was a very common complication (12% asymptomatic DVT) following leg injuries[15] and since then, a wide range of incidences of asymptomatic events have been published (*Figure 1*).

One of the first observational studies from Hjelmstedt and colleagues showed in 1968 that 46% of all patients with a tibial fracture developed an asymptomatic DVT (as diagnosed by phlebography).[16] Later, in 1975, a case series of six VTEs in four months was published in patients treated with cast immobilization of the lower extremities (within the Air Force orthopaedic service (USA).[27] Thereafter, multiple studies have shown an association between cast immobilization and the occurrence of VTE.[17, 28] To study whether VTE could be prevented, the first randomized controlled trial was performed in 1993.[1] 253 patients were randomized to receive a low-molecular-weight-heparin (LMWH) (126 patients) or no thromboprophylaxis (127 patients). In the control group, 21/127 (16.5%) patients developed asymptomatic VTE as compared with 6/127 (4.8%) patients in the LMWH group. A compression ultrasound was performed in all patients during plaster cast removal, and overall, only 9/253 (3.6%) patients had clinical symptoms of thrombosis. This study indicated for the first time that the frequency of asymptomatic events is much higher than that of symptomatic events, which was confirmed by another randomized controlled trial performed in 1995, that studied both the occurrence of symptomatic and asymptomatic VTE following cast immobilization for traumatic injury of the leg. In this study, lower rates were found; 4.3% of all 163 patients who received no prophylaxis developed an asymptomatic event as compared with 2.5% symptomatic events.[2]

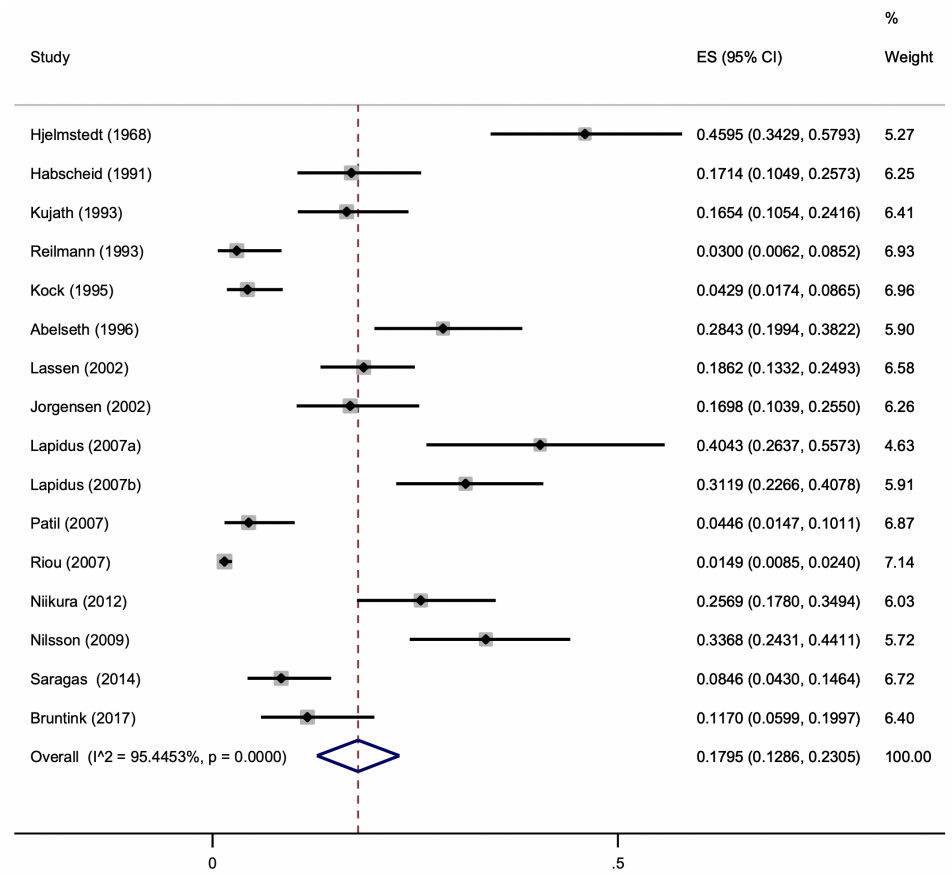


Figure 1: Incidence of asymptomatic VTE following lower-leg cast immobilization in patients without thromboprophylaxis.
ES denotes the estimated proportion of patients with a VTE in each study, thus the cumulative incidence. References: Hjelmstedt[16], Habscheid[17], Kujath[1], Reilmann[18], Kock[2], Abelseth[19], Lassen[20], Jorgensen[21], Lapidus[22], Lapidus[23], Patil[24], Niikura[25], Saragas[26], Bruntink[11].

In 2000, Giannadakis and colleagues reported a series of 178 patients with lower limb injuries who required cast immobilization at low-risk for VTE.[29] Only 1.1% (2 patients) developed a symptomatic VTE and the authors concluded that due to this low absolute risk there was no indication to give thromboprophylaxis. As a result of the wide variety of reported risks and lack of studies that used venography (the gold standard for DVT diagnosis) to measure asymptomatic VTE, a new randomized clinical trial was performed to study the efficacy of thromboprophylaxis following lower-leg cast immobilization.[21] Similar asymptomatic VTE rates were found as compared with some previous studies,[1, 17, 20] as in the untreated group 18/106 (17.0%) patients developed an asymptomatic VTE. However, no symptomatic events occurred, which was contradictive with incidences of symptomatic VTE from previous studies that ranged between 1.1%-3.2%.[2, 19, 20, 28, 29] Thereafter, two other trials were performed in 2007, one in patients who underwent surgical treatment for an Achilles tendon rupture[22] and one in patients who required ankle fracture surgery concomitant to cast immobilization.[23] In the ankle fracture study, 5.5% (6/109) of all patients in the untreated group developed a symptomatic VTE as compared with 31.2% (34/109) asymptomatic events. In the Achilles tendon rupture study, of all untreated patients, 6.4% (3/47) developed symptomatic VTE versus 40.4% (19/47) asymptomatic VTE. Contradictory, an observational study that was performed within the same year, studied the incidence of asymptomatic VTE in 100 low-risk (no prophylaxis) patients with a cast immobilization because of an ankle fracture.[24] The authors only found five (5%) asymptomatic events and no symptomatic VTEs were diagnosed.

In 2008, following many small venography or ultrasound studies on asymptomatic DVT, the first large observational study was published.[30] 1789 patients with cast immobilization of the leg received thromboprophylaxis therapy (and are therefore not included in our meta-analysis) of whom only 0.50% (9/1789) developed a symptomatic VTE. A similar large observational study was published in 2014 in which 1200 patients with a lower-limb fracture were followed for three months. However, in this study, thromboprophylaxis was not administered.[31] 98% of all patients had a complete follow-up and 82% was treated with cast immobilization. Seven patients (0.58%) developed a symptomatic VTE and it was concluded that symptomatic VTE is an infrequent complication after lower-leg fractures. A slightly higher, but still low incidence (1.4%) was found by Heyes and colleagues in 945 patients with an Achilles tendon rupture treated with cast immobilization.[32]

Combining all studies in a heterogeneous group of lower-leg cast patients who did not receive thromboprophylaxis, we found a pooled absolute risk for asymptomatic events of 18.0% (95%CI 12.9 to 23.1) and a symptomatic risk of 2.0% (95%CI 1.3 to 2.7) (within approximately 3-months) (*Figures 1 and 2*).

Both surgically and conservatively treated patients, as well as patients with ankle or foot fractures or Achilles tendon ruptures were included in the abovementioned studies. The pooled analyses confirm a large difference between the occurrence of asymptomatic and symptomatic VTE following leg-cast immobilization; on average, about 10% of all asymptomatic events seem to progress into clinical disease. Moreover, the wide range of reported incidences indicates considerable heterogeneity of included patients as well as heterogeneity in diagnostic methods (for asymptomatic events)[38]. In 2015, in a large population-based case-control study, van Adrichem and colleagues reported that the

increased VTE risk following cast immobilization of the lower extremity was only present up to 3 months, resulting in an odds ratio (OR) of 56.3 (95% confidence interval [CI] 17.9–177.3) as compared with patients without plaster cast.[39] Considering an absolute risk in the general population of 1.5 per 1000 persons[14] within one year (thus about 0.0375% within 3-months), cast immobilization leads to an absolute thrombosis risk of 2.1% within 3-months (i.e. 0.0375% multiplied by an OR of 56.3). A highly similar incidence (2.0% [95%CI 1.3 to 2.7%]) was found in our meta-analysis (*Figure 2*) indicating the precision of this estimation.

Incidence of VTE following knee arthroscopy

For decades it has been well known that major orthopaedic surgery is associated with a high VTE risk which could be explained by the invasiveness of the procedure, associated immobility and the presence of additional risk factors (i.e. comorbidities in an older population). Knee arthroscopic surgery is a less invasive procedure, most patients are young (few comorbidities) and in general, patients are mobilized within the same day following surgery. Nevertheless, patients who undergo arthroscopic knee surgery are considered to be at moderate or high risk for the development of VTE.[8] An early report of this complication was published in 1977, when McGinty and colleagues investigated whether it was better to perform a partial or complete meniscectomy in 128 patients who were hospitalized for approximately 4 days.[40] In this study, one symptomatic pulmonary embolism (0.78%) and eight cases of thrombophlebitis were described. 5 years later, Dandy and Carrol reported three cases of symptomatic DVT in 1168 arthroscopic knee procedures for an incidence of 0.3%.[41]

However, these studies were not designed to study the incidence of VTE and in 1989, authors from London published the first study on DVT incidence following elective knee surgery. 48 patients underwent knee arthroscopy of whom 2 (4.2%) developed an asymptomatic DVT as diagnosed by an ascending venography that was performed in all patients following surgery.[42] Similar incidences of asymptomatic VTE were described by Williams (3.5%)[43] and Wirth (4.1%)[44].(*Figure 3*)

Subsequently, in 1995 (Roth), the first randomized clinical trial on the efficacy of thromboprophylaxis was performed. In this study 144 patients undergoing elective arthroscopic knee surgery were randomized to receive LMWH for 4 days or no treatment. In the control group, 5/61 patients (8.2%) developed asymptomatic VTE of whom 1 patient (1.6%) was found to be symptomatic. Contradictory, much higher incidences were described in another study (Demers) which venographically assessed the incidence of VTE in 184 patients.[48] Here, asymptomatic VTE was found in 34 patients (18.5%) (33 DVT, 1 PE) and symptomatic VTE was reported in 20/184 (10.9%) patients.[48]

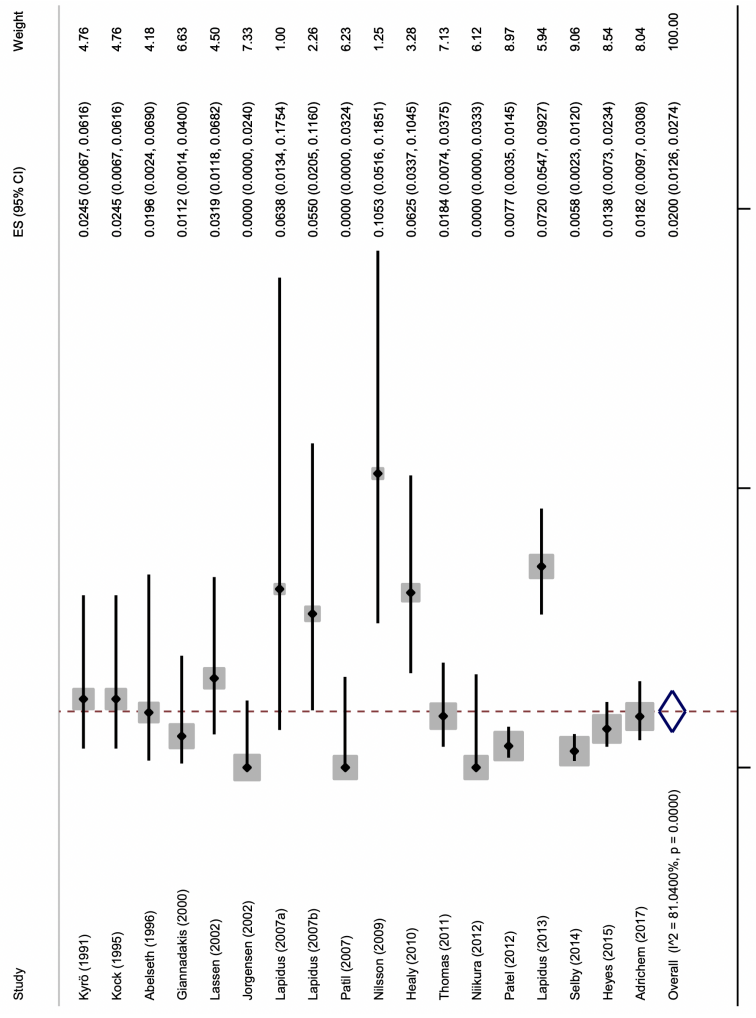


Figure 2: Incidence of symptomatic VTE following lower-leg cast in patients without thromboprophylaxis.
ES denotes the Estimated proportion of patients with a VTE in each study, thus the cumulative incidence. References: Kyrö[28], Kock[2], Abelseth[19], Giannadakis[29], Lassen[20], Jorgensen[21], Lapidus[22], Lapidus[23], Patil[24], Nilsson[33], Healy[34], Thomas[35], Niikura[25], Patel[36], Lapidus[37], Selby[31], Heyes[32], van Adrichem[10].

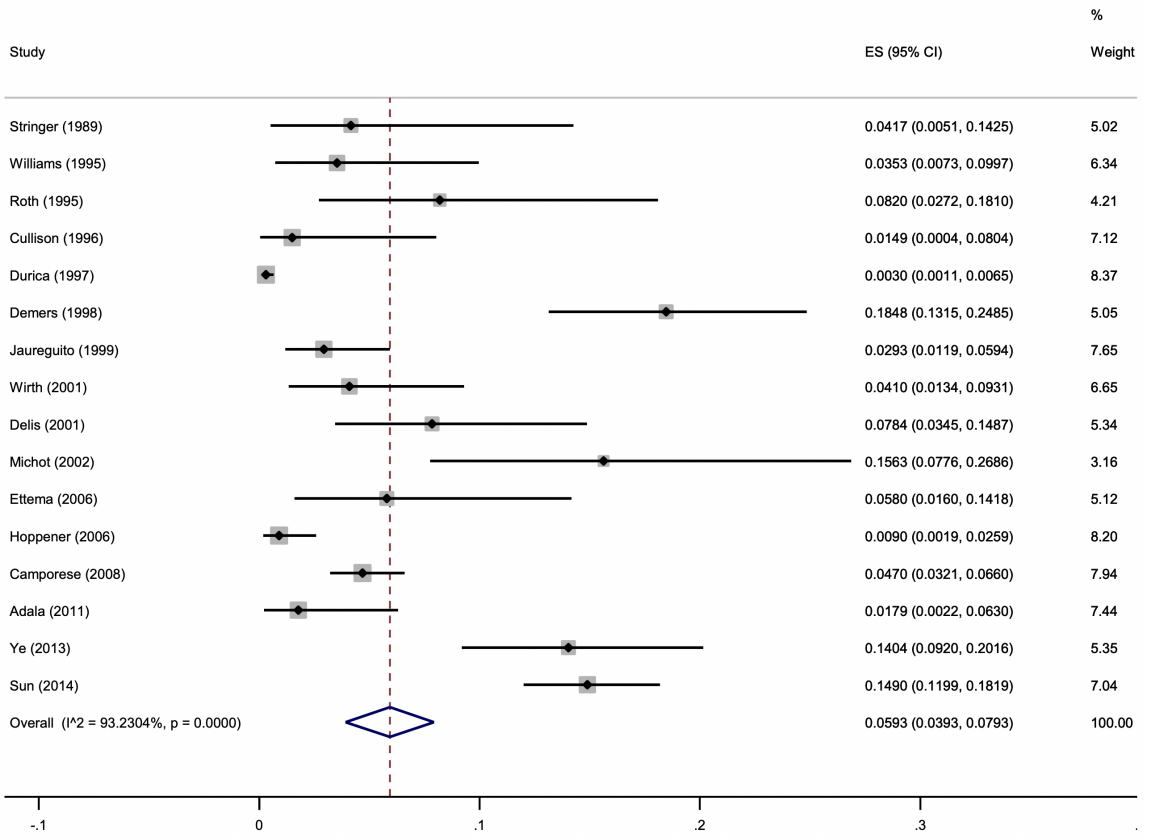


Figure 3: Incidence of asymptomatic VTE following knee arthroscopy in patients without thromboprophylaxis. ES denotes the Estimated proportion of patients with a VTE in each study, thus the cumulative incidence. References: Stringer[42], Williams[43], Roth[45], Cullison[46], Durica[47], Demers[48], Jaureguito[49], Wirth[44], Delis[50], Michot[51], Ettema[52], Hoppener[53], Camporese[54], Adala[55], Ye[56], Sun[57].

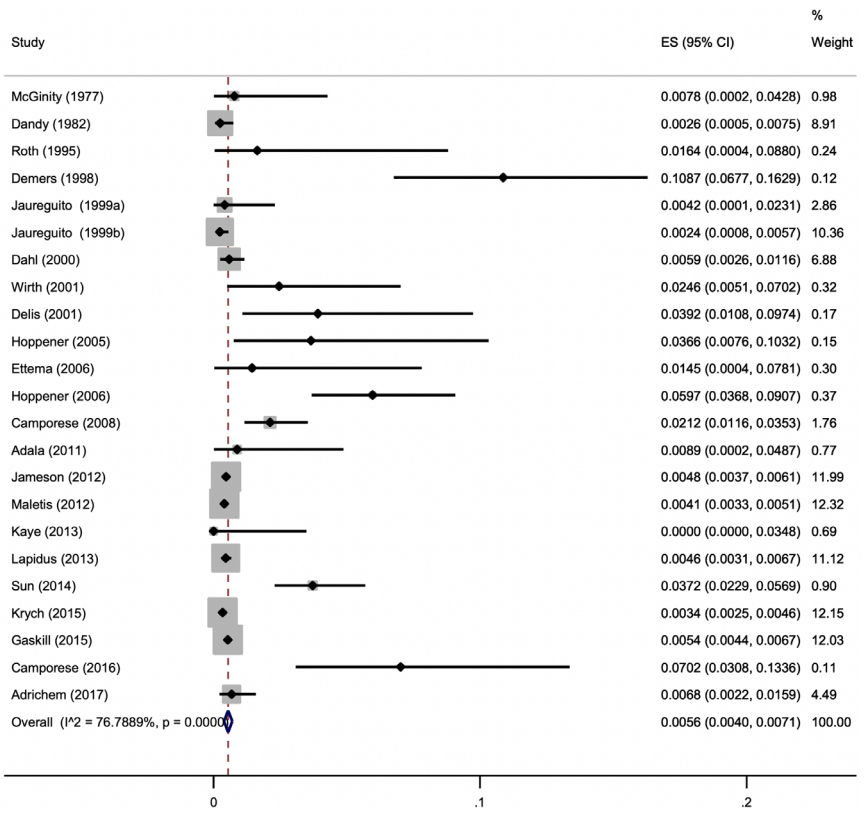


Figure 4: Incidence of symptomatic VTE following knee arthroscopy in patients without thromboprophylaxis.
ES denotes the Estimated proportion of patients with a VTE in each study, thus the cumulative incidence. References: McGinty[40], Dandy[41], Roth[45], Demers[48], Jaureguito[49], Jaureguito[49], Wirth[44], Delis[50], Hoppener[59], Ettema[52], Hoppener[53], Camporese[54], Adala[55], Jameson[58], Maletis[5], Kaye[60], Lapidus[37], Sun[57], Gaskill[4], Camporese[12], van Adrichem[10].

Possibly, more invasive procedures such as an anterior cruciate ligament [ACL] reconstruction or multiple performed procedures contributed to the higher risk as described by Demers and colleagues. Comparable results were shown by two other studies, both performed in 2014 that solely included patients who underwent cruciate ligament reconstruction. Asymptomatic VTE rates of 14.1%[56] and 14.9%[57] were observed. However, multiple large observational studies, including a wide range of knee arthroscopy types, showed low incidences for symptomatic VTE ranging from 0.3% to 0.5%.[4, 5, 37, 49, 58] As large retrospective registries were used to collect data on the occurrence of VTE, these studies are subject to information bias which could have resulted in an underestimation of the true incidence. Yet, the similar reported incidences in all of these studies suggest that VTE is not a frequent complication. (*Figure 4*)

Our meta-analysis shows that in patients undergoing knee arthroscopy, like in patients with lower-leg cast immobilization, asymptomatic VTE occurs about 10-times more than symptomatic VTE. Asymptomatic VTE was seen in 5.9% (95%CI 3.9-7.9) of all patients compared with a rate for symptomatic VTE of 0.6% (95%CI 0.4 to 0.8) following heterogeneous types of arthroscopic knee procedures in patients without chemical thromboprophylaxis (follow-up for most studies 3-months). In a large population-based case-control study, knee-arthroscopy was associated with a 16.2-fold risk for VTE within 3-months following surgery. Considering the absolute risk in the general population of about 1.5 per 1000 persons per year, this leads to an absolute risk for symptomatic VTE following arthroscopic knee surgery of 0.61% within 3-months. An almost identical incidence of symptomatic VTE was found in our meta-analysis (0.6%, 95%CI 0.4 to 0.8) which again indicates the robustness and precision of this estimate.

Burden of VTE following lower-leg cast and knee arthroscopy

It is estimated that each year, approximately 4 million knee arthroscopic procedures are performed worldwide[61], of which 40 000 in the Netherlands alone. For lower-leg cast, no accurate worldwide estimations are available. However, if we extrapolate the number of lower-leg cast applications in the Netherlands (35 000)[62] to the worldwide population, at least 3.5 million patients receive a lower-leg cast each year (for computational ease). Considering this high number of procedures, the burden of symptomatic VTE following these healthcare interventions in substantial. Assuming an incidence of symptomatic VTE following knee arthroscopy of 0.6% (derived from our meta-analysis), 24 800 patients will yearly develop VTE, worldwide. Likewise, assuming an incidence of symptomatic VTE following lower-leg cast of 2.0%, 70 000 patients will suffer from symptomatic VTE. Consequently, on a population level, knee arthroscopy and lower-leg cast immobilization are responsible for a population attributable fraction for VTE of 2.1% and 2.7%, respectively. This means that, of all patients who develop symptomatic VTE, a total of

4.8% is caused by leg-casting or knee arthroscopy. Furthermore, of all these patients, 11 945 patients are expected to die within 1-year following knee arthroscopy or cast-immobilization, (assuming a case-fatality rate for provoked non-cancer related VTE of 12.6%).[14] Hence, considering this high burden, it is of great importance to find the best strategy for VTE prevention in these situations.

PREVENTION

In this chapter, first the effectiveness of thromboprophylaxis in patients with lower-leg cast immobilization is discussed followed by the effectiveness following knee arthroscopy using data which have been published up to 2016. This has been done as all current guidelines and reviews are based on data up to 2016. Thereafter, we discuss all recent evidence (after 2016). Finally, we have updated results by performing our own meta-analyses on the effectiveness of thromboprophylaxis following lower-leg cast immobilization and knee arthroscopy.

The effectiveness of thromboprophylaxis following lower-leg cast immobilization

Several meta-analyses and reviews have been published regarding the effectiveness of thromboprophylaxis for the prevention of VTE following lower-leg cast immobilization.[3, 7, 63] In these meta-analyses, six randomized controlled trials were summarized of which the last one was published in 2007.[1, 2, 20-23] All trials allocated patients to either LMWH or no therapy (or placebo), however, a variety of leg-cast indications was eligible to be included (e.g. fracture, tendon ruptures, conservative or operative treatment etc.). Furthermore, all trials screened for the occurrence of *asymptomatic* DVT, either by compression ultrasound or venography. The first trial, performed in 1993, concerned 253 patients, aged >16 years, who were conservatively treated with a lower-leg cast for at least 7 days.[1] Patients were randomized between nadroparin or no treatment for 16 days. In the per-protocol analysis, after 53 post-randomization exclusions, 4.8% of all patients with prophylaxis, and 16.5% of patients without prophylaxis developed an asymptomatic DVT (defined by compression ultrasound) (risk reduction of 11.7% [95%CI 4.3% – 19.3%]). Kock et al. then published a RCT using similar inclusion criteria, in which 339 patients with a lower-leg cast were analysed.[2] Upon cast removal, a compression ultrasound and duplex scanning was performed and suspected asymptomatic events were confirmed with venography. In this trial, much lower incidences were found; 0% in the treated and 4.3% in the non-treated group developed an asymptomatic DVT (risk reduction 4.3% (95%CI 1.2% - 7.4%). Subsequently, in 2002 the first RCT using the gold standard (venography) was performed.[64] 95 patients with a planned cast immobilisation of the lower-leg for at least 3 weeks (both operated and non-operated) were eligible for inclusion and randomized between LMWH once daily or no therapy. A non-significant protective effect of prophylaxis was found (risk reduction (6.9%), RR 0.59, 95%CI 0.29 to 1.23) and no symptomatic VTE was observed. In the same year, another RCT included patients treated with cast immobilization for at least 5 weeks for either a fracture or Achilles tendon rupture (about half was treated surgically).[20] This was the first trial to use placebo injections instead of no therapy. 69 patients were excluded due to loss of follow up and in the per-protocol analysis, thromboprophylaxis prevented the development of asymptomatic DVT (RR 0.45, 95%CI 0.24 to 0.83). Furthermore, the authors observed a non-significant risk reduction

for symptomatic VTE (RR, 0.08, 95%CI 0.00 to 1.36). Finally, in 2007, Lapidus et al. performed two trials, one in patients immobilized for an Achilles tendon rupture and one in patients with a fracture.[22, 23] In the first trial, similar numbers of asymptomatic DVT were found in the treatment and control group (18/49 and 19/47, respectively),upon which the authors concluded that thromboprophylaxis was not effective. In the second trial, in patients with an ankle fracture, no significant effect of thromboprophylaxis was found for either asymptomatic or symptomatic VTE (RR 0.66; 95%CI 0.42-1.03 and OR 0.31: 95%CI 0.06-1.51, respectively).

Based on these six RCTs, several meta-analyses advise to prescribe thromboprophylaxis as the benefits (VTE prevention) outweigh the harms associated with treatment (bleeding, costs, patient burden). In a Cochrane review, a total of 1490 patients was included.[7] It was reported that thromboprophylaxis was effective for the prevention of *asymptomatic* VTE for a pooled RR of 0.49, 95%CI 0.34 to 0.72 (heterogeneity I^2 20%, p=0.29), which result was consistent for several subgroups (i.e. conservatively or operatively treated, fractures, soft-tissue injuries). Another meta-analysis which looked into several subgroups such as inclusion of the more methodologically sound trials revealed consistent results.[3] None of the meta-analyses showed an increased risk for major bleeding (major bleeding risk 0.3%[7]) associated with thromboprophylaxis therapy. However, despite these data, in the 2012 ACCP guidelines it was suggested to perform a large practical RCT which avoids screening for asymptomatic VTE due to a lack of compelling evidence.[8]

The effectiveness of thromboprophylaxis in patients following knee arthroscopy

In patients who had undergone knee-arthroscopy, 5 RCTs were performed to study the efficacy of thromboprophylaxis up until 2008.[44, 45, 51, 54, 65] In these trials, a variety of procedures such as a diagnostic arthroscopy, meniscectomy or ACL reconstruction were performed and all patients were screened for the occurrence of asymptomatic DVT, either by compression ultrasound or venography.

The first trial randomized 144 patients to LMWH for 4 days versus no treatment of whom 122 were included in the analysis.[45] 5/61 (8.2%) patients versus 1/61 (1.6%) patients developed an asymptomatic thrombotic event in the control and treated group respectively, while one symptomatic thrombosis occurred in both groups (1.6%). However, as all patients were over 60 years and no full weight bearing was allowed until the 5th day post-operative, results were less applicable to current clinical practice. In 2001, Wirth and colleagues found very similar results in elective knee arthroscopy patients with a mean age of 38 years.[44] 1/117 (0.9%) patients in the treatment group and 5/112 (4.5%) patients in the control group developed thrombosis. Whereas Roth included high risk patients,[45] Wirth focussed on low risk patients and excluded those patients with a history of VT, or those with three or

more risk factors (obesity, smoking, oral contraceptives and family history of thrombosis).[44] In 2002[51] and 2003[65], two more trials were performed into the efficacy of thromboprophylaxis. Michot randomized patients to a prophylactic dose of LMWH up to 30 days post-surgery versus no treatment. 1/66 (1.5%) patients in the LMWH group versus 10/64 (15.6%) patients in the control group developed an asymptomatic event, but no clinical events were seen. Canata and colleagues included patients scheduled for ACL reconstruction who were randomized for 6 days of LMWH therapy (n=18) versus no treatment (n=18). No asymptomatic or symptomatic events were diagnosed. Finally in 2008, the first large trial was performed by Camporese and colleagues.[54] In this assessor-blind RCT, 1761 patients were randomized to either full length graduated compression stockings for 7 days (n=660), LMWH for 7 days (n=657), or 14 days post-operatively (n=444). The 14-days LMWH group was stopped prematurely by the data safety monitoring board due to safety issues (no efficacy compared with 7-days and risk for major and minor bleeding of 4.1% [0.3% major]). In the compression stockings group, 21/660 (3.2%) patients developed the primary efficacy endpoint (death, symptomatic VTE and asymptomatic proximal DVT) versus 6/657 (0.9%) in the 7-day LMWH group (absolute risk difference -2.3% (95%CI 0.7 to 4.0). Asymptomatic distal DVT occurred in an additional 10/660 (1.5%) and 6/657 (0.9%) patients in the stocking and LMWH group respectively. From this trial is was concluded that 7-days of thromboprophylaxis reduced VTE significantly.

Overall, combining all trials results, the pooled risk for any VTE (both asymptomatic and/or symptomatic) was 5.6% (95%CI 2.7 to 8.5) in patients without, and 1.6% (95%CI 0.7 to 2.4) in patients with thromboprophylaxis. Multiple meta-analyses summarized the abovementioned data:[6, 66] A Cochrane review in 2008 concluded that thromboprophylaxis was effective for the prevention of asymptomatic VTE for a relative risk of 0.16 (95%CI 0.05 – 0.52). 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). Thereafter, Chapelle and colleagues summarized the abovementioned 5 RCTs plus an additional trial which studied whether extended LMWH therapy (20 days) was more effective for VTE prevention than short duration (in-hospital only) therapy.[67]. Not surprisingly, the authors found a comparable risk reduction on asymptomatic proximal DVT and any symptomatic VTE as the Cochrane review (RR 0.27, 95%CI 0.15-0.49).

Guidelines for VTE prevention following lower-leg immobilization and knee arthroscopy

Despite this great body of research, in both patient groups, guidelines have been reluctant to advice in favour or against the use of thromboprophylaxis in all patients treated with lower-leg cast immobilization or knee arthroscopy. Due to extensive heterogeneity of included patients, weak methodology and limited generalizability of some studies

(underpowered for symptomatic VTE[1, 2, 20, 22, 23, 44, 45, 51, 54, 64, 65], high rates of loss to follow-up[20, 23, 64], inclusion of high-risk patients only[20, 23, 65] and many post-randomization exclusions[1]), there is no clear evidence that thromboprophylaxis is effective for symptomatic VTE prevention. For instance, the American college of chest physicians guideline from 2012 (ACCP) suggests no prophylaxis rather than pharmacologic thromboprophylaxis in patients with isolated lower-leg injuries requiring leg immobilization or following knee arthroscopy.[8] Other guidelines such as the National Clinical Guideline Centre (UK) allows treatment of high-risk patients based on an individual approach by evaluating the risks and benefits based on clinical discussion with the patient.[9].

Recent evidence on the effectiveness of thromboprophylaxis

Thus far, in all trials that involved knee arthroscopy patients, LMWH was used as the preferred drug for thromboprophylaxis. In 2016, Camporese and colleagues performed an exploratory placebo controlled clinical trial aiming to evaluate the efficacy and safety of rivaroxaban (10 mg once daily) for VTE prevention in patients following knee arthroscopy.[12]. 122 patients were assigned to rivaroxaban and 119 to placebo, all patients were followed for 3-months. From this trial it was concluded that VTE could be prevented with rivaroxaban (absolute risk reduction of 5.3% [95 %CI −11.4 to −0.8]). However, this conclusion can be questioned as the classification of outcome events was not optimal, and furthermore, the trial was not powered to determine the balance between treatment benefits and risks.[68] Moreover, although it was shown that rivaroxaban had a protective effect on the composite endpoint of all-cause mortality, symptomatic VTE, and asymptomatic proximal DVT, this conclusion was mainly driven by the effect on asymptomatic proximal DVT.

Another recently published trial by Bruntink and colleagues (2017) in lower-leg cast patients, aimed to study the effect of LMWH or fondaparinux versus no therapy on the development of asymptomatic VTE.[11] The authors showed that LMWH significantly reduced the risk of a thromboembolic event, and therefore it was suggested to prescribe thromboprophylaxis in all patients. However, we found it difficult to translate these results to clinical practice. Of all 467 randomized patients only 278 (60%) were included in the analysis, likely resulting in a significant bias. Besides, the Protect trial only studied the occurrence of asymptomatic DVT which certainly does not reflect the true effect of thromboprophylaxis on symptomatic VTE reduction.

In 2017, we published 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.[10] In these trials, in which 1543 (POT-KAST) and

1451 (POT-CAST) patients were included, we compared the incidence of symptomatic VTE within 3-months after the procedure, and no screening for asymptomatic VTE was performed. In both trials, comparing a prophylactic dose of a LMWH with no treatment, thromboprophylaxis was not effective for the prevention of symptomatic VTE (absolute risk difference in POT-KAST, 0.3 percentage points, 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. Highly similar incidences for symptomatic VTE are found in the current meta-analysis in non-treated patients, i.e., for lower-leg cast 2.0% (95%CI 1.3 to 2.7) and knee-arthroscopy 0.6%, (95%CI 0.4 to 0.8) (*Figure 2 and Figure 4*), indicating high generalizability to clinical practice with regards to the risk population (since a similar incidence was found).

We believe a risk-benefit analysis cannot be made based on all previous trials that studied asymptomatic DVT as primary outcomes, not even if combined in a meta-analysis. In 2014, Chan and colleagues performed a large systematic review of high-quality VTE prevention trials (19 in orthopaedic patients, 5 in general surgery patients and 2 in medical patients) to examine the consistency of asymptomatic DVT to symptomatic VTE ratios within trials.[38] They found that the overall median rate for asymptomatic DVT versus symptomatic VTE was 14.5 with an extreme wide range from 2.75 to 103.86. Notably, there was poor agreement between the efficacy of thromboprophylaxis on asymptomatic DVT against symptomatic VTE. This implies that the effect of thromboprophylaxis (relative risk) on asymptomatic DVT is not consistent with the relative risk for symptomatic VTE. Consequently, decisions on the efficacy of thromboprophylaxis can only be based on trials powered for symptomatic endpoints. This viewpoint is also supported by the authors of the 9th edition of the ACCP guidelines on thromboprophylaxis.[8]

Since most guidelines and reviews (including meta-analyses on the effectiveness of thromboprophylaxis) have been performed using data which have been published up to 2016, an update is highly needed. Therefore, we summarized all data till date by performing a meta-analysis of all the abovementioned trials regardless of the methodological shortcomings. The results of these analyses will be discussed in the next section.

Updated effectiveness of thromboprophylaxis following lower-leg cast immobilization

In lower-leg cast patients, the effect of thromboprophylaxis on both asymptomatic DVT and symptomatic VTE was relatively similar. For symptomatic VTE, thromboprophylaxis reduced VTE risk: RR 0.31 (95%CI 0.13 – 0.73) (*Figure 5*). However, results from our POT-CAST trial completely opposed findings from 5 other trials. This might be explained

by the fact that identification of symptomatic events in those five trials was not optimal (i.e. not a true representation of an actual symptomatic VTE). For example, in one large trial, patients were asked about signs and symptoms of VTE before ultrasonography. One positive sign or symptom combined with a thrombus found during ultrasonography resulted in the classification of a symptomatic event. This method most likely does not represent the pattern of signs and symptoms that is present when patients seek medical advice during follow-up themselves, i.e. the truly symptomatic events.[68] This is illustrated by the high pooled incidence of symptomatic VTE in the untreated arms of 3.6% (25/703) in those 5 trials; i.e. more than of almost double as compared with the incidence in the POT-CAST trial (1.4%) or with the pooled incidence of symptomatic VTE estimated by our meta-analysis (2.0%), respectively. Another possibility is that results were overestimated due to some methodological weaknesses, for example, high rates of loss-to-follow up.[21] Furthermore, inclusion of high risk patients only (e.g. surgical patients only[37] or minimal cast duration of 5 weeks[20], could also have led to the protective effect of thromboprophylaxis on symptomatic VTE. In a recent Cochrane review on this topic a similar RR was described of (0.40, 95%CI 0.21 – 0.76) (note a slightly different RR was found compared with our own meta-analysis as this Cochrane review did not include a trial by Bruntink et al, 2017 [11]). Notably, there was no efficacy on the prevention of PE (RR 0.50, 95%CI 0.17 – 1.47), suggesting no effect on objectively confirmed symptomatic events. Although this result may be explained by a lack of power or heterogeneity of results.

In addition, a funnel plot of the RCTs shows a clear risk of publication bias towards effectiveness of thromboprophylaxis for VTE prevention (*Figure 6, left panel)*. No small trials with a negative effect (i.e. no effect) have been published while many small trials with a positive (i.e. protective effect) have. This is also true, although to a lesser extent, in RCTs in patients who underwent knee arthroscopy (*Figure 6, right panel*). Therefore, altogether, thus concerning the large difference between the efficacy on asymptomatic vs symptomatic VTE, issues regarding the classification of symptomatic events, publication bias towards efficacy, the high number needed to treat (250 based on POT-CAST) and the discomfort of daily injections and high costs, in our opinion there is no indication to provide thromboprophylaxis in all patients with lower-leg cast. However, as still about 2.0% of lower-leg cast patients develop symptomatic VTE, new preventive strategies are necessary to lower complication rates. Targeting high-risk populations could be such a preventive strategy. In this case, only high-risk patients are to be exposed to anticoagulants. In parallel, the optimal dosage and type of anticoagulants has to be determined. For example, a randomized trial that investigated the effectiveness of Fondaparinux 2.5mg once daily versus a LMWH 2850IE once daily in patients with lower-leg cast immobilization showed that Fondaparinux was much more effective than LMWH for VTE prevention.[70]

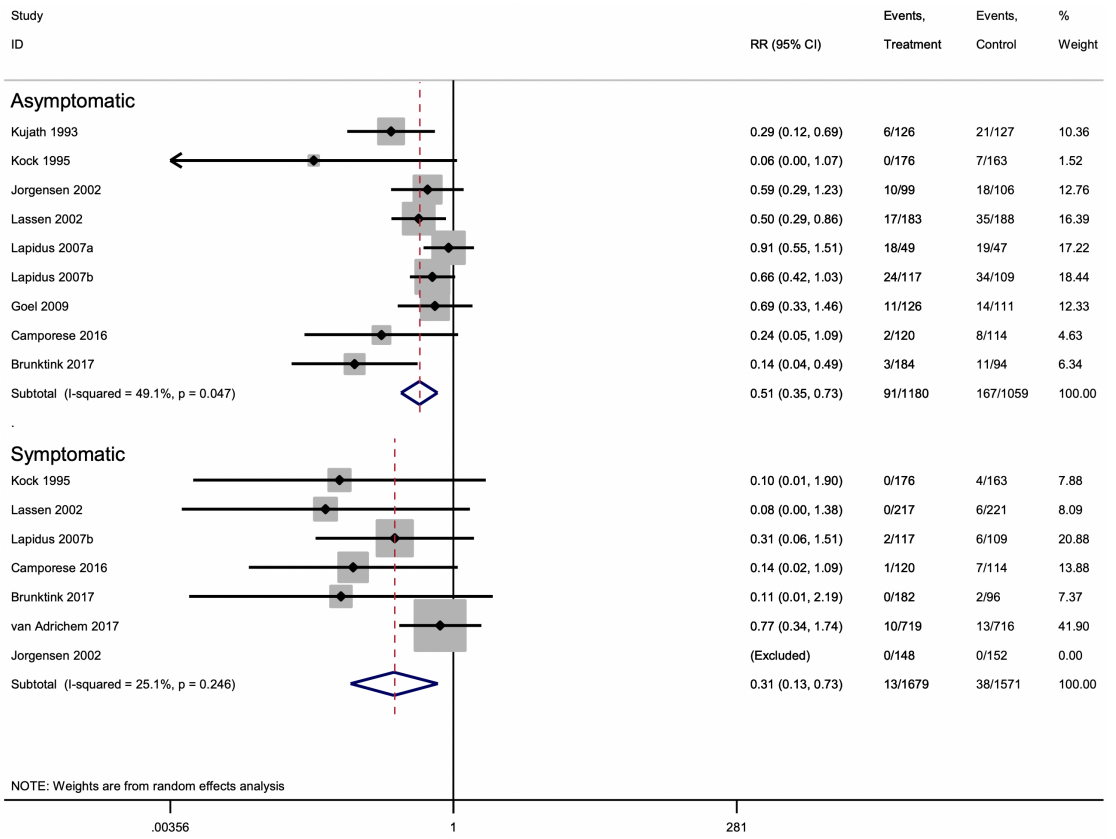


Figure 5: Effectiveness of thromboprophylaxis following lower-leg cast immobilization.
RR denotes Relative Risk. References: Kujath[1], Kock[2], Jorgensen[64], Lassen[20], Lapidus[22, 23], Goel[69], Caaporese[12], Bruntink[11], van Adrichem[10].

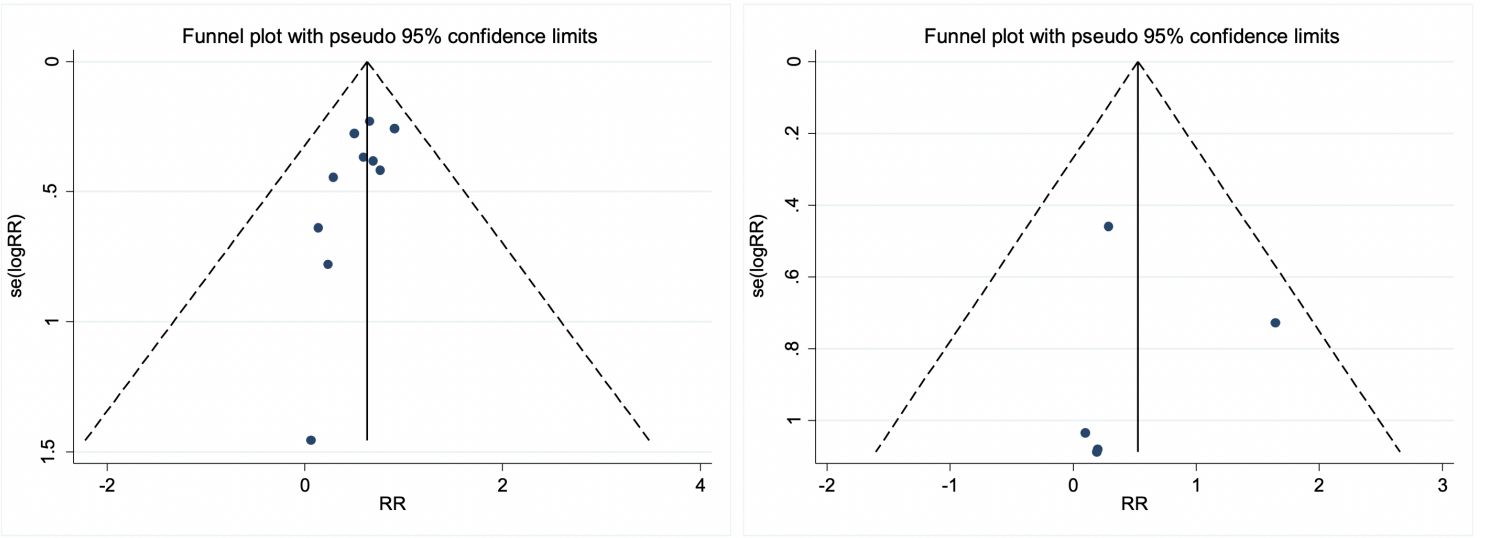


Figure 6: Funnel plot showing potential publication bias.
Funnel plot based on a meta-analysis of randomized controlled trials in patients with cast immobilization (left panel) and knee arthroscopy (right panel), note that for these analyses, symptomatic and asymptomatic endpoints are combined.

Updated effectiveness of thromboprophylaxis following knee arthroscopy

For knee arthroscopy, in light of all the previously discussed evidence, there is no clear benefit of thromboprophylaxis on the prevention of symptomatic VTE (RR 0.65, 95%CI 0.23-1.81), while conflictingly, this seems to prevent asymptomatic DVT (RR 0.23, 95%CI 0.11-0.47) (*Figure 7*). These results nicely demonstrate the poor agreement between the efficacy of thromboprophylaxis on symptomatic versus asymptomatic VTE as described by Chan and colleagues.[38] The neutral effect of thromboprophylaxis is mainly driven by two large trials, the KANT trial[54] and the POT-KAST trial[10] with contradictory findings. In our view, this could partially be explained by differences in inclusion criteria between trials. In both the KANT and POT-KAST trial, patients with a previous VTE were excluded. However, whereas the POT-KAST only included patients over 18 years, scheduled for meniscectomy, removal or loose bodies or diagnostic arthroscopies, the KANT trial also included patients who underwent anterior cruciate ligament reconstruction (39% of all patients in the control and 7-days LMWH study arm combined). Furthermore, in the KANT trial, patients were asked for signs and symptoms of VTE. Patients who reported to have 1 or more symptoms were considered symptomatic. In our view this method most likely does not represent the situation that is present when patients seek medical advice during follow-up themselves, i. e. the truly symptomatic events. The severity of these symptomatic events is therefore questionable and it is not known how many of these events would have spontaneously dissolved or progressed to real symptomatic cases.[68]

As a result of these different criteria and classification methods of symptomatic disease, the incidence of VTE differs considerably between trials; 0.6% (8/1450) in POT-KAST versus 1.4% (18/1317) in KANT. These findings might imply that high-risk patients, such as those undergoing ligament reconstruction, might actually benefit from treatment while low-risk patients can be safely withheld from thromboprophylaxis. Yet, in order to do so, high risk populations first need to be identified as such.

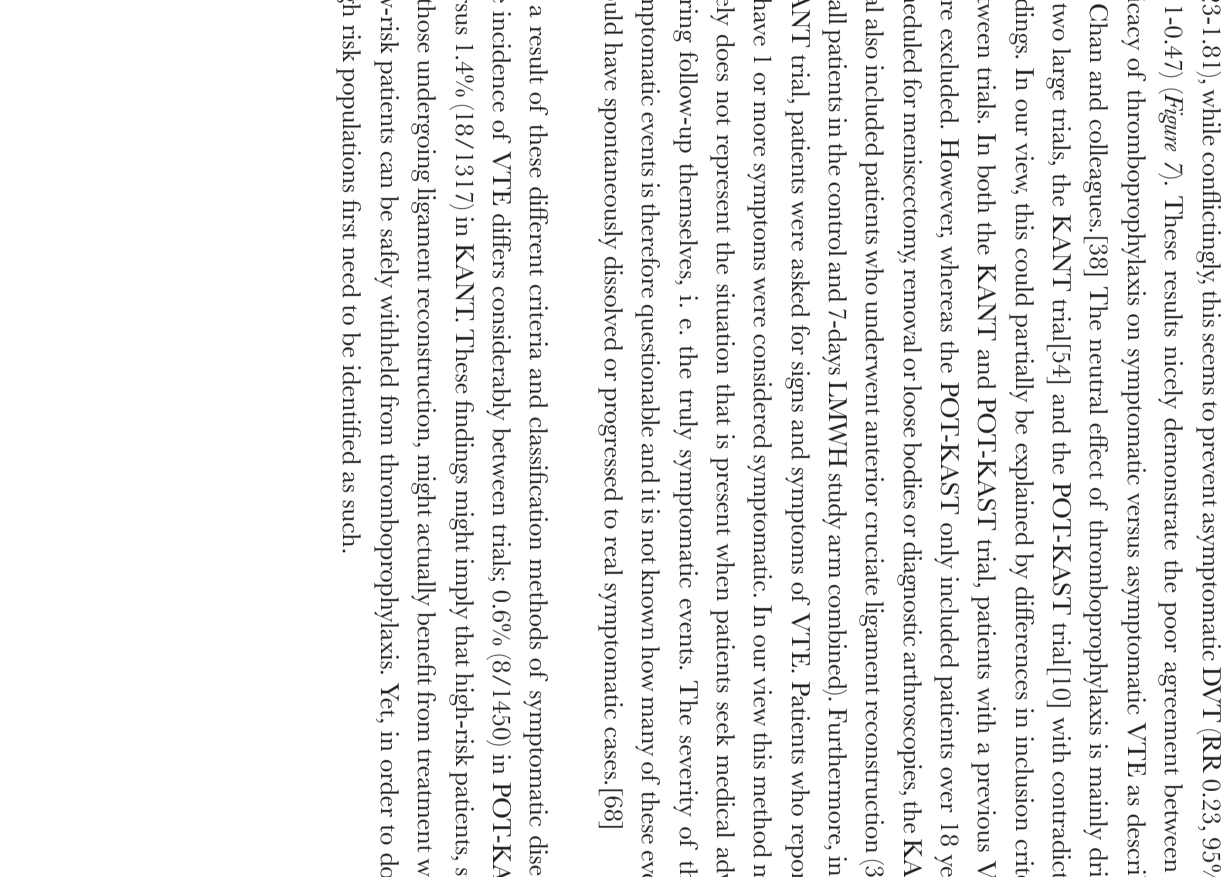


Figure 7: Effectiveness of thromboprophylaxis following knee arthroscopy.
RR denotes Relative Risk. References: Roth[45], Wirth[44], Michot[51], Camporese[54], Canata[65], van Adrichem[10].

PREDICTION

High quality epidemiological research performed over the past decades resulted in a long list of well-known risk factors for VTE.[71] Acquired risk factors such as increasing age, malignancy, obesity and comorbidity play a key role in the aetiology of VTE. Additionally, genetic factors such as Factor V Leiden mutation and blood group Non-O have contributed to our understanding in the development of VTE. Surgery, trauma and immobilization are recognized to be associated with the highest risk for VTE. Within this group of patients it is challenging to find those at the highest risk for VTE. In this chapter we aimed to give an overview of risk factors and risk assessment models (RAMs) that have been described to increase VTE risk within lower-leg cast or knee arthroscopy patients.

Risk factors for VTE in lower-leg cast patients

In cast patients, Kujath and colleagues showed already in 1993 that patients who developed thrombosis had 2.0 risk factors on average (mostly obesity and varicose veins) as compared with 1.2 risk factors in patients who did not develop thrombosis. [1] Moreover, patients who still developed thrombosis under treatment had an average of 2.7 risk factors. Healy and colleagues described that out of 13/208 patients who developed DVT following Achilles tendon ruptures, about half of all VTE patients had additional risk factors for VTE such as a positive family history, BMI > 30 kg/m2, significant medical comorbidity and planned long-distance travel. [34] A large observational study that enrolled 1200 patients stressed out that despite their large sample size, no risk factors could be identified because of the low incidence of VTE.[31] To overcome this problem, van Adrichem published results from a large population base case-control study, in which 143 cases with VTE and 23 controls, both with cast immobilization of the lower-extremity, were identified.[39] The study design and number of patients with a cast and VTE allowed the authors to study risk factors for VTE within lower-leg cast patients. Traumatic injuries were associated with higher thrombosis risks than non-traumatic injuries. Additionally, oral contraceptives (OR 18.2), obesity (OR 17.2), factor V Leiden mutation (OR 11.0), non-O blood group (20.9) showed to increase VTE risk (ORs for joint effect of cast + risk factor versus non-cast + no risk factor). Presence of multiple risk factors increased VTE risk in a dose response fashion. Several other risk factors were identified in multiple studies that we classified according to environmental, cast specific and injury specific factors (*Table 1*). For example, non-weight bearing cast was associated with a higher VTE risk in three studies[2, 22, 72] and VTE developed more often following fractures than after soft tissue injury.[1, 20]

Risk factors for VTE in knee arthroscopy patients

Despite the low VTE incidence (and thus low power for risk factor analyses) several studies did report risk factors for VTE (*Table 2*). Maletis and colleagues included 20 770 patients who underwent elective knee arthroscopy. Patients aged 50-years or older had

a 1.5-fold risk for VTE as compared with patients <50 years, furthermore, use of oral contraceptives doubled VTE risk.[5] Similarly, Gaskill and colleagues, showed that age (>35 years versus <35 years) increased VTE risk (OR 1.99)[4] Other risk factors could not be accurately identified. In 2015, van Adrichem performed a case-control study in which oral contraceptives, obesity, Factor V Leiden, and Non-O blood type were identified as risk factors for VTE within patients who underwent knee arthroscopic surgery.[75] Again, a dose-response relationship existed between the number of risk factors and the occurrence of VTE, a finding already described by Delis and colleagues in 2001 (though on asymptomatic DVT).[50] Four studies showed that for example, an increased operation time, the use of a thigh tourniquet or more invasive procedures (such as an ACL or PCL reconstruction) also increased VTE risk besides the presence of more classical VTE risk factors.

Table 1: Overview of VTE risk factors in lower-leg cast patients.

VTE risk factors in lower-leg cast patients	**Study**
Environmental	
Multiple risk factors	Kujath[1], van Adrichem[39]
Age >40 years*	Knudson[73]
Age >50 years	Riou[72]
Venous injury*	Knudson[73]
Charlson comorbidity index ≥1	Jameson[74]
Oral contraceptives	van Adrichem[39]
Obesity	van Adrichem[39]
Factor V Leiden mutation	van Adrichem[39]
Non-O blood group	van Adrichem[39]
Cast specific	
Non-weight baring cast	Kock[2], Lapidus 2007a[22], Riou[72]
Rigid immobilization	Lapidus 2007b[23], Riou[72]
Injury specific	
Fracture versus soft tissue injury	Kujath[1], Lassen 2002[20]
Major operation*	Knudson[73]
Severe injury	Riou[72]
Traumatic injury	van Adrichem[39]

*in 1602 trauma patients including lower-leg cast

Table 2: Overview of VTE risk factors in knee arthroscopy patients.

VTE risk factors in knee arthroscopy patients	Study
Environmental factors	
Increasing Age	Stringer[42], Hetsroni[76], Mauck[77], Maletis[5], Ye[56], Delis[50]
Female	Hetsroni[76], Ye[56]
Obesity (BMI>30)	Delis[50]
Varicose veins	Schippinger[78]
> 2 classical VTE risk factors	Delis[50], Krych[79]
Previous VTE	Delis[50], Krych[79]
Oral contraceptives	Delis[50], Maletis[5]
Hospitalization within 3 months before arthroscopy	Mauck[77]
Malignancy	Krych[79]
Surgery at high altitude	Cancienne[80]
Arthroscopy specific	
Operation time	Stringer[42], Jaureguito[49]
Tourniquet use	Demers 1998, Jaureguito[49]
Invasive procedures such as ACL or PCL reconstruction	Jaureguito[49], Gaskill[4]

Risk assessment models for VTE

As there is no compelling evidence that thromboprophylaxis prevents VTE in all lower-leg cast and knee arthroscopy patients, new preventive strategies have to be developed in order to prevent VTE. An appealing approach would be to use information on individual risk factors in order to fit these into a prediction model for VTE , as is done in many patients at risk for VTE, such as hospitalized medical or surgical patients. For example, surgical patients are at risk for VTE and the Caprini score has been developed to stratify these patients in a low, intermediate or high risk group. In this score, many risk factors are combined to achieve an accurate model which could be used in clinical practice for thromboprophylaxis decisions. Likewise, for medical patients, RAMs as the Geneva risk score[81], Padua prediction score[82] and Improve-7 score[83] aim to stratify patients in low or high risk groups for VTE.

For lower-leg cast patients, few attempts have been performed to develop a RAM. However, perhaps because of the high need for such a model, two recent papers were published that summarized the current evidence on RAMs for lower-leg cast patients.[84, 85] One

model, derived from the GEMNET (UK) guideline (for the use of thromboprophylaxis in ambulatory trauma patients requiring temporary limb immobilisation), suggests patients should receive prophylactic therapy if they have one or more permanent risk factor for VTE such as hormone therapy, personal history of VTE, or recent hospital admission. [86] (*Table 3*) Similar risk factors are described in the NICE guideline[9], though, in both guidelines, risk scores were not specifically developed (or validated) for lower-leg cast related VTE. Moreover, both guidelines only give a list of risk factors and if patients have one or more, thromboprophylaxis is indicated. So no actual individual risks can be calculated and no differentiation is made (regarding thrombosis risk) within those patients with one or more additional risk factors. In 2015, using a large population-based case-control study, we derived and validated a RAM, named the L-TRiP(cast) score (Leiden-Thrombosis Risk Prediction), developed to identify lower-leg cast patients at high risk for VTE.[87] The L-TRiP(cast) score consists of classical risk factors for VTE, but also includes the type of cast (degree of immobilization) which greatly improves discriminatory capabilities. Furthermore, it was shown that biomarkers (both genetic and coagulation factors) contributed to better model performance, however, these were not included in the model to increase clinical usefulness.

For knee arthroscopy, similarly, general RAMs for surgical patients (such as a list of risk factors as provided by the NICE guideline) can be used to identify high risk patients. As in patients with lower-leg cast, our group developed a RAM for VTE risk in knee-arthroscopy patients, named the L-TRiP(ascopy) score. Notably, the best model performance was achieved by adding factor VIII activity next to 8 environmental risk factors. However, again, to improve clinical usefulness and to reduce costs FVIII was not included in the final model.

For the L-TRiP(cast) score, thromboprophylaxis is suggested if cast immobilization patients score 9 points or more corresponding to a test sensitivity of 80.0%, specificity of 60.8% and false negative rate of 0.8%. For knee arthroscopy patients, it is proposed to provide thromboprophylaxis in case patients score 8 point or more (sensitivity 82.6%, specificity 45.2% and 0.2% false negatives). However, as both risk scores (L-TRiP(cast and scopy) were not validated in a prospective study (only in other case-control studies), there is no defined cut-off that corresponds to an absolute risk threshold on which thromboprophylaxis decisions can be made. Therefore, validation in a large cohort, and perhaps model refinement to ascertain the role of biomarker testing, is highly needed.

Table 3: Overview of risk assessment models for VTE in lower-leg cast and knee arthroscopy patients.

GEMNET guideline	NICE guideline		L-TRiP(cast) score	Risk points	L-TRiP(ascopy) score	Risk points
Age >60	Age over 60 years		Age ≥ 35 and < 55 y	*2*	Age ≥ 35 and < 55 y	*1*
			Age ≥ 55 y	*3*	Age ≥ 55 y	*2*
			Male sex	*1*	Male sex	*1*
Obesity (BMI >30)	Obesity (BMI over 30 kg/m2)		BMI ≥ 25 and < 35 kg/m2	*1*		
			BMI ≥ 35 kg/m2	*2*		
Active cancer	Active cancer or cancer treatment		Cancer within the past 5 y	*3*		
Current hormone therapy (contraceptive, hormone replacement, tamoxifen)	Use of hormone replacement therapy or oestrogen-containing contraceptive therapy		Current use of oral contraceptives	*4*	Current use of oral contraceptives	*3*
Pregnant or immediately post partum			Pregnancy or puerperium	*3*		
Extensive varicosities	Varicose veins with phlebitis		Superficial vein thrombosis	*3*	Varicose veins	*1*
Any serious medical comorbidity*	One or more significant medical comorbidities**		Comorbidity***	*1*		*1*
			Pneumonia	*3*	Congestive heart failure	*1*
Personal or first-degree relative VTE history	Personal history or a first degree relative with a history of VTE		Family history of VTE (first-degree relative)	*2*	Family history of VTE -1 family member -≥2 family members	*2* *3*
Known thrombophilia	Known thrombophilias				Factor VIII activity	
					<100	*0*
					>=100 and 124	*1*
					>124	*3*
Any recent hospital admission/major surgery			Hospital admission within the past 3 mo	*2*		
			Surgery within the past 3 mo	*2*		
	Critical care admission					
			Bedridden within the past 3 mo	*2*	Bedridden within the past 3 mo	*2*
Active smoker						
	Dehydration					
			Plaster cast: complete leg	*5*	Knee arthroscopy	*4*
			Plaster cast: circular knee cast (ankle free)	*2*	Ligament reconstruction	*6*
			Plaster cast: foot	*2*		
			Plaster cast: lower-leg	*4*		
Provide thromboprophylaxis when one or more risk factors are present	*Provide thromboprophylaxis when one or more risk factors are present*		*Calculate L-TRiP(cast) score, provide thromboprophylaxis if ≥ 9†*		*Calculate L-TRiP(ascopy) score, provide thromboprophylaxis if ≥ 8††*	

* Including cardiac failure/COPD/chronic renal failure or inflammatory bowel disease
** Including heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions
*** Including rheumatoid arthritis, chronic kidney disease, COPD, multiple sclerosis
† Test specifics: sensitivity 80.0%, specificity 60.8% and 0.8% false negatives
†† Test specifics: sensitivity 82.6%, specificity 45.2% and 0.2% false negatives

CONCLUSION AND FUTURE PERSPECTIVES

Symptomatic VTE is a common complication following lower-leg cast immobilization or arthroscopic knee surgery. In our meta-analyses on the incidence of VTE we found an incidence of 2.0% (95%CI 1.3 to 2.7) and 0.6%, (95%CI 0.4 to 0.8), for lower-leg cast and knee-arthroscopy patients, respectively

Unquestionably, the burden of VTE following lower-leg cast immobilization or arthroscopic knee surgery is substantial. In the past decades, we[10] and others[1, 2, 11, 12, 20, 22, 23, 44, 45, 51, 54, 64, 65, 69], have tried to reduce VTE burden using a population-based approach, namely, providing all patients with thromboprophylaxis therapy. Still, despite all research there is no convincing evidence that thromboprophylaxis reduces symptomatic VTE in the total patient group. As VTE nevertheless still occurs, new treatment methods have to be explored. Identifying and treating those patients with a high risk more intensively might be such a strategy, for which reason we suggest to move forward with a more individualized approach and adjust thromboprophylaxis therapy accordingly.

A targeted approach, identifying high-risk patients who can be treated possibly with a higher dose or longer duration of therapy, might be the next step to prevent VTE. The L-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.

Another approach would be to concentrate on the thrombosis 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 a patients' coagulation profile following a fracture could contribute to the development of new preventive or treatment 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 which 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.[88, 89] In our view, more extensive data on this matter could potentially be valuable for clinical management. For example, it is known that for each 10IU/dl increase of factor VIII concentration, an individual's thrombosis risk increases approximately 10%. Accordingly, we could speculate that

those patients who have a strong increase in coagulation factors (after lower-leg cast or knee arthroscopy) also have a higher risk for developing VTE. Future research has to point out whether determination of individual biomarkers is prompted to individualize prophylactic strategies. Additionally, new studies, preferably RCTs powered for symptomatic events, are necessary to study new thromboprophylactic strategies.

REFERENCE LIST

1. P. Kujath, U. Spannagel, W. Habscheid, Incidence and prophylaxis of deep venous thrombosis in outpatients with injury of the lower limb, Haemostasis 23 Suppl 1 (1993) 20-26.
2. H.J. Kock, K.P. Schmit-Neuerburg, J. Hanke, G. Rudofsky, H. Hirche, Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg, Lancet 346(8973) (1995) 459-461.
3. H.B. Ettema, B.J. Kollen, C.C. Verheyen, H.R. Buller, Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials, Journal of thrombosis and haemostasis: 6(7) (2008) 1093-8.
4. T. Gaskill, M. Pullen, B. Bryant, N. Sicignano, A.M. Evans, M. DeMaio, The Prevalence of Symptomatic Deep Venous Thrombosis and Pulmonary Embolism After Anterior Cruciate Ligament Reconstruction, The American journal of sports medicine 43(11) (2015) 2714-9.
5. G.B. Maletis, M.C. Inacio, S. Reynolds, T.T. Funahashi, Incidence of symptomatic venous thromboembolism after elective knee arthroscopy, The Journal of bone and joint surgery. American volume 94(8) (2012) 714-20.
6. J. Ramos, C. Perrotta, G. Badariotti, G. Berenstein, Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy, The Cochrane database of systematic reviews (4) (2008) CD005259.
7. M. Testroote, W.A. Stigter, L. Janssen, H.M. Janzing, Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization, The Cochrane database of systematic reviews (4) (2014) CD006681.
8. Y. Falck-Ytter, C.W. Francis, N.A. Johanson, C. Curley, O.E. Dahl, S. Schulman, T.L. Ortel, S.G. Pauker, C.W. Colwell, Jr., Prevention of VTE in orthopaedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Chest 141(2 Suppl) (2012) e278S-e325S.
9. NICE Guidelines. Venous thromboembolism in adults admitted to hospital: reducing the risk. (NICE guideline CG92), 2010.
10. R.A. van Adrichem, B. Németh, A. Algra, S. le Cessie, F.R. Rosendaal, I.B. Schipper, R. Nelissen, S.C. Cannegieter, K. Pot, P.-C. Group, Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting, The New England journal of medicine 376(6) (2017) 515-525.
11. M.M. Bruntink, Y.M. Groutars, I.B. Schipper, R.S. Breederveld, W.E. Tuinebreijer, R.J. Derksen, P. studygroup, Nadroparin or fondaparinux versus no thromboprophylaxis in patients immobilised in a below-knee plaster cast (PROTECT): A randomised controlled trial, Injury 48(4) (2017) 936-940.
12. G. Camporese, E. Bernardi, F. Noventa, M. Bosco, G. Monteleone, L. Santoro, C. Bortoluzzi, S. Freguja, M. Nardin, M. Marullo, G. Zanon, C. Mazzola, G. Damiani, P. Maniscalco, D. Imberti, C. Lodigiani, C. Becattini, C. Tonello, G. Agnelli, E.S. Group, Efficacy of Rivaroxaban for thromboprophylaxis after Knee Arthroscopy (ERIKA). A phase II, multicentre, double-blind, placebo-controlled randomised study, Thrombosis and haemostasis 116(2) (2016) 349-55.
13. E.J. Bell, P.L. Lutsey, S. Basu, M. Cushman, S.R. Heckbert, D.M. Lloyd-Jones, A.R. Folsom, Lifetime Risk of Venous Thromboembolism in Two Cohort Studies, The American journal of medicine 129(3) (2016) 339.e19-26.

14. I.A. Naess, S.C. Christiansen, P. Romundstad, S.C. Cannegieter, F.R. Rosendaal, J. Hammerstrom, Incidence and mortality of venous thrombosis: a population-based study, Journal of thrombosis and haemostasis 5(4) (2007) 692-9.
15. G. Bauer, Thrombosis following leg injuries, Acta chirurgica Scandinavica (90) (1944) 229-48.
16. A. Hjelmstedt, U. Bergvall, Incidence of thrombosis in patients with tibial fractures, Acta chirurgica Scandinavica 134(3) (1968) 209-18.
17. W. Habscheid, U. Spannagel, P. Kujath, G. Schindler, [Prevention of thrombosis with low molecular weight heparin in ambulatory patients with injury of the lower extremity: an ultrasound study], VASA. Supplementum 33 (1991) 222-3.
18. H. Reilmann, A.M. Weinberg, E.E. Forster, B. Happe, Prevention of thrombosis in ambulatory patients [in German], Orthopade (22) (1993) 117-120.
19. G. Abelseth, R.E. Buckley, G.E. Pineo, R. Hull, M.S. Rose, Incidence of deep-vein thrombosis in patients with fractures of the lower extremity distal to the hip, Journal of orthopaedic trauma 10(4) (1996) 230-5.
20. M.R. Lassen, L.C. Borris, R.L. Nakov, Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization, The New England journal of medicine 347(10) (2002) 726-30.
21. P.S. Jorgensen, T. Warming, K. Hansen, C. Paltved, B.H. Vibeke, R. Jensen, R. Kirchhoff-Jensen, L. Kjaer, N. Kerbouche, P. Leth-Espensen, E. Narvestad, S.W. Rasmussen, C. Sloth, C. Torholm, P. Wille-Jorgensen, Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study, Thromb.Res. 105(6) (2002) 477-480.
22. L.J. Lapidus, S. Rosfors, S. Ponzer, C. Levander, A. Elvin, G. Larfars, E. de Bri, Prolonged thromboprophylaxis with dalteparin after surgical treatment of achilles tendon rupture: a randomized, placebo-controlled study, Journal of orthopaedic trauma 21(1) (2007) 52-7.
23. L.J. Lapidus, S. Ponzer, A. Elvin, C. Levander, G. Larfars, S. Rosfors, E. de Bri, Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study, Acta orthopaedica 78(4) (2007) 528-35.
24. S. Patil, J. Gandhi, I. Curzon, A.C. Hui, Incidence of deep-vein thrombosis in patients with fractures of the ankle treated in a plaster cast, The Journal of bone and joint surgery. British volume 89(10) (2007) 1340-3.
25. T. Niikura, S.Y. Lee, K. Oe, A. Koh, T. Koga, Y. Dogaki, E. Okumachi, Y. Sakai, T. Akisue, R. Kuroda, M. Kurosaka, Incidence of venous thromboembolism in fractures around and below the knee with physical prophylaxis, Orthopedics 35(10) (2012) e1476-82.
26. N.P. Saragas, P.N. Ferrao, E. Saragas, B.F. Jacobson, The impact of risk assessment on the implementation of venous thromboembolism prophylaxis in foot and ankle surgery, Foot and ankle surgery : official journal of the European Society of Foot and Ankle Surgeons 20(2) (2014) 85-9.
27. L.J. Micheli, Thromboembolic complications of cast immobilization for injuries of the lower extremities, Clinical orthopaedics and related research (108) (1975) 191-5.
28. A. Kyro, T. Tunturi, A. Soukka, Conservative treatment of tibial fractures. Results in a series of 163 patients, Annales chirurgiae et gynaecologiae 80(3) (1991) 294-300.
29. K. Giannadakis, H. Gehling, H. Sitter, S. Achenbach, H. Hahne, L. Gotzen, [Is a general pharmacologic thromboembolism prophylaxis necessary in ambulatory treatment by plaster cast immobilization in lower limb injuries?], Der Unfallchirurg 103(6) (2000) 475-8.

30. R. Otero-Fernandez, A. Gomez-Outes, J. Martinez-Gonzalez, E. Rocha, J. Fontcuberta, P. Bemiparin Cooperative Study Group in Orthopaedic, Evaluation of the effectiveness and safety of bemiparin in a large population of orthopaedic patients in a normal clinical practice, Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 14(1) (2008) 75-83.
31. R. Selby, W.H. Geerts, H.J. Kreder, M.A. Crowther, L. Kaus, F. Sealey, Symptomatic venous thromboembolism uncommon without thromboprophylaxis after isolated lower-limb fracture: the knee-to-ankle fracture (KAF) cohort study, The Journal of bone and joint surgery. American volume 96(10) (2014) e83.
32. G.J. Heyes, A. Tucker, A.L. Michael, R.G. Wallace, The incidence of deep vein thrombosis and pulmonary embolism following cast immobilisation and early functional bracing of Tendo Achilles rupture without thromboprophylaxis, European journal of trauma and emergency surgery : official publication of the European Trauma Society 41(3) (2015) 273-6.
33. K. Nilsson-Helander, A. Thurin, J. Karlsson, B.I. Eriksson, High incidence of deep venous thrombosis after Achilles tendon rupture: a prospective study, Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA 17(10) (2009) 1234-8.
34. B. Healy, R. Beasley, M. Weatherall, Venous thromboembolism following prolonged cast immobilisation for injury to the tendo Achillis, The Journal of bone and joint surgery. British volume 92(5) (2010) 646-50.
35. S. Thomas, M. Van Kampen, Should orthopaedic outpatients with lower limb casts be given deep vein thrombosis prophylaxis?, Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 17(4) (2011) 405-7.
36. A. Patel, B. Ogawa, T. Charlton, D. Thordarson, Incidence of deep vein thrombosis and pulmonary embolism after Achilles tendon rupture, Clinical orthopaedics and related research 470(1) (2012) 270-4.
37. L.J. Lapidus, S. Ponzer, H. Pettersson, E. de Bri, Symptomatic venous thromboembolism and mortality in orthopaedic surgery - an observational study of 45 968 consecutive procedures, BMC musculoskeletal disorders 14 (2013) 177.
38. N.C. Chan, A.C. Stehouwer, J. Hirsh, J.S. Ginsberg, A. Alazzoni, M. Coppens, G.â. Guyatt, J.W. Eikelboom, Lack of consistency in the relationship between asymptomatic DVT detected by venography and symptomatic VTE in thromboprophylaxis trials, Thrombosis and haemostasis 114(5) (2015) 1049-1057.
39. R.A. van Adrichem, J. Debeij, R.G. Nelissen, I.B. Schipper, F.R. Rosendaal, S.C. Cannegieter, Below-knee cast immobilization and the risk of venous thrombosis: results from a large population-based case-control study, Journal of thrombosis and haemostasis 12(9) (2014) 1461-9.
40. J.B. McGinity, L.F. Geuss, R.A. Marvin, Partial or total meniscectomy: a comparative analysis, The Journal of bone and joint surgery. American volume 59(6) (1977) 763-6.
41. D.J. Dandy, P.F. O'Carroll, Arthroscopic surgery of the knee, British medical journal (Clinical research ed.) 285(6350) (1982) 1256-8.
42. M.D. Stringer, C.A. Steadman, A.R. Hedges, E.M. Thomas, T.R. Morley, V.V. Kakkar, Deep vein thrombosis after elective knee surgery. An incidence study in 312 patients, The Journal of bone and joint surgery. British volume 71(3) (1989) 492-7.
43. J.S. Williams, Jr., M.J. Hulstyn, P.D. Fadale, P.B. Lindy, M.G. Ehrlich, J. Cronan, G. Dorfman, Incidence of deep vein thrombosis after arthroscopic knee surgery: a prospective study, Arthroscopy 11(6) (1995) 701-5.

44. T. Wirth, B. Schneider, F. Misselwitz, M. Lomb, H. Tuylu, R. Egbring, P. Griss, Prevention of venous thromboembolism after knee arthroscopy with low-molecular weight heparin (reviparin): Results of a randomized controlled trial, Arthroscopy 17(4) (2001) 393-9.
45. P. Roth, Thromboembolieprophylaxe bei ambulant durchgefuhrten arthroskopischen Meniskusoperationen, Orthop Praxis (1995) 345-348.
46. T.R. Cullison, M.P. Muldoon, J.D. Gorman, W.B. Goff, The incidence of deep venous thrombosis in anterior cruciate ligament reconstruction, Arthroscopy 12(6) (1996) 657-9.
47. S. Durica, G. Raskob, C. Johnson, Incidence of deep vein thrombosis after arthroscopic knee surgery, Thrombosis and haemostasis (79) (1997) 183.
48. C. Demers, S. Marcoux, J.S. Ginsberg, F. Laroche, R. Cloutier, J. Poulin, Incidence of venographically proved deep vein thrombosis after knee arthroscopy, Archives of internal medicine 158(1) (1998) 47-50.
49. J.W. Jaureguito, A.E. Greenwald, J.F. Wilcox, L.E. Paulos, T.D. Rosenberg, The incidence of deep venous thrombosis after arthroscopic knee surgery, The American journal of sports medicine 27(6) (1999) 707-10.
50. K.T. Delis, N. Hunt, R.K. Strachan, A.N. Nicolaides, Incidence, natural history and risk factors of deep vein thrombosis in elective knee arthroscopy, Thrombosis and haemostasis 86(3) (2001) 817-21.
51. M. Michot, D. Conen, D. Holtz, D. Erni, M.D. Zumstein, G.B. Ruflin, N. Renner, Prevention of deep-vein thrombosis in ambulatory arthroscopic knee surgery: A randomized trial of prophylaxis with low--molecular weight heparin, Arthroscopy 18(3) (2002) 257-63.
52. H.B. Ettema, M.R. Hoppener, N.J. Veeger, H.R. Buller, J. van der Meer, Low incidence of venographically detected deep vein thrombosis after knee arthroscopy without thromboprophylaxis: a prospective cohort study, J.Thromb.Haemost. 4(6) (2006) 1411-1413.
53. M.R. Hoppener, H.B. Ettema, C.P. Henny, C.C. Verheyen, H.R. Buller, Low incidence of deep vein thrombosis after knee arthroscopy without thromboprophylaxis: a prospective cohort study of 335 patients, Acta Orthop. 77(5) (2006) 767-771.
54. G. Camporese, E. Bernardi, P. Prandoni, F. Noventa, F. Verlato, P. Simioni, K. Ntita, G. Salmistraro, C. Frangos, F. Rossi, R. Cordova, F. Franz, P. Zucchetta, D. Kontothanassis, G.M. Andreozzi, K.S. Group, Low-molecular-weight heparin versus compression stockings for thromboprophylaxis after knee arthroscopy: a randomized trial, Annals of internal medicine 149(2) (2008) 73-82.
55. R. Adala, A. Anand, G. Kodikal, Deep vein thrombosis and thromboprophylaxis in arthroscopic anterior cruciate ligament reconstruction, Indian journal of orthopaedics 45(5) (2011) 450-3.
56. S. Ye, C. Dongyang, X. Zhihong, S. Dongquan, D. Jin, Q. Jianghui, Q. Jizhen, Y. Pu, H. Huacheng, S. Wei, J. Qing, The incidence of deep venous thrombosis after arthroscopically assisted anterior cruciate ligament reconstruction, Arthroscopy 29(4) (2013) 742-7.
57. Y. Sun, D. Chen, Z. Xu, D. Shi, J. Dai, J. Qin, Q. Jiang, Incidence of symptomatic and asymptomatic venous thromboembolism after elective knee arthroscopic surgery: a retrospective study with routinely applied venography, Arthroscopy 30(7) (2014) 818-22.
58. S.S. Jameson, D. Dowen, P. James, I. Serrano-Pedraza, M.R. Reed, D. Deehan, Complications following anterior cruciate ligament reconstruction in the English NHS, The Knee 19(1) (2012) 14-9.
59. M.R. Hoppener, H.B. Ettema, C.P. Henny, C.C. Verheyen, H.B. Buller, Symptomatic deep vein thrombosis and immobilization after day-care arthroscopy of the knee, Journal of thrombosis and haemostasis 3(1) (2005) 185-7.

60. I.D. Kaye, D.N. Patel, E.J. Strauss, M.J. Alaia, G. Garofolo, A. Martinez, L.M. Jazrawi, Prevention of Venous Thromboembolism after Arthroscopic Knee Surgery in a Low-Risk Population with the Use of Aspirin. A Randomized Trial, Bulletin of the Hospital for Joint Disease (2013) 73(4) (2015) 243-8.
61. AAOS, Knee arthroscopy http://orthoinfo.aaos.org/topic.cfm?topic=a00299. (Accessed 10/14/2016 2016).
62. VeiligheidNL, Injury information system, Central Bureau of Statistics, The Netherlands, 2006-2015. http://www.veiligheid.nl.
63. D. Bergqvist, G. Lowe, Venous thromboembolism in patients undergoing laparoscopic and arthroscopic surgery and in leg casts, Archives of internal medicine 162(19) (2002) 2173-6.
64. P.S. Jorgensen, T. Warming, K. Hansen, C. Paltved, H. Vibeke Berg, R. Jensen, R. Kirchhoff-Jensen, L. Kjaer, N. Kerbouche, P. Leth-Espensen, E. Narvestad, S.W. Rasmussen, C. Sloth, C. Torholm, P. Wille-Jorgensen, Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study, Thrombosis research 105(6) (2002) 477-80.
65. G. Canata, A. Chiey, Prevention of venous thromboembolism after ACL reconstruction: a prospective, randomized study., ISAKOS congress Vol. Poster 71–2003. (2003).
66. C. Chapelle, N. Rosencher, P. Jacques Zufferey, P. Mismetti, M. Cucherat, S. Laporte, Prevention of venous thromboembolic events with low-molecular-weight heparin in the non-major orthopaedic setting: meta-analysis of randomized controlled trials, Arthroscopy 30(8) (2014) 987-96.
67. S. Marlovits, G. Striessnig, R. Schuster, R. Stocker, M. Luxl, S. Trattnig, V. Vecsei, Extended-duration thromboprophylaxis with enoxaparin after arthroscopic surgery of the anterior cruciate ligament: a prospective, randomized, placebo-controlled study, Arthroscopy 23(7) (2007) 696-702.
68. B. Németh, R.A. van Adrichem, S.C. Cannegieter, The ERIKA trial: still limited evidence on the efficacy of thromboprophylaxis after knee arthroscopy, Thrombosis and haemostasis 116(5) (2016) 1001.
69. D.P. Goel, R. Buckley, G. deVries, G. Abelseth, A. Ni, R. Gray, Prophylaxis of deep-vein thrombosis in fractures below the knee: a prospective randomised controlled trial, The Journal of bone and joint surgery. British volume 91(3) (2009) 388-94.
70. C.M. Samama, N. Lecoules, G. Kierzek, Y.E. Claessens, B. Riou, N. Rosencher, P. Mismetti, A. Sautet, M.T. Barrellier, K. Apartsin, M. Jonas, J.R. Caeiro, A.H. van der Veen, P.M. Roy, Comparison of fondaparinux with low molecular weight heparin for venous thromboembolism prevention in patients requiring rigid or semi-rigid immobilization for isolated non-surgical below-knee injury, Journal of thrombosis and haemostasis 11(10) (2013) 1833-43.
71. W.M. Lijfering, F.R. Rosendaal, S.C. Cannegieter, Risk factors for venous thrombosis - current understanding from an epidemiological point of view, British journal of haematology 149(6) (2010) 824-33.
72. B. Riou, C. Rothmann, N. Lecoules, E. Bouvat, J.-L. Bosson, P. Ravaud, C.M. Samama, M. Hamadouche, Incidence and risk factors for venous thromboembolism in patients with nonsurgical isolated lower limb injuries, The American Journal of Emergency Medicine 25(5) (2007) 502-508.
73. M.M. Knudson, D.G. Ikossi, L. Khaw, D. Morabito, L.S. Speetzen, Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank, Annals of surgery 240(3) (2004) 490-6; discussion 496-8.

74. S.S. Jameson, K.S. Rankin, N.L. Desira, P. James, S.D. Muller, M.R. Reed, A. Rangan, Pulmonary embolism following ankle fractures treated without an operation - an analysis using National Health Service data, Injury 45(8) (2014) 1256-61.
75. R.A. van Adrichem, R.G. Nelissen, I.B. Schipper, F.R. Rosendaal, S.C. Cannegieter, Risk of venous thrombosis after arthroscopy of the knee: results from a large population-based case-control study, Journal of thrombosis and haemostasis 13(8) (2015) 1441-8.
76. I. Hetsroni, S. Lyman, H. Do, G. Mann, R.G. Marx, Symptomatic pulmonary embolism after outpatient arthroscopic procedures of the knee: the incidence and risk factors in 418,323 arthroscopies, The Journal of bone and joint surgery. British volume 93(1) (2011) 47-51.
77. K.F. Mauck, D.A. Froehling, P.R. Daniels, D.L. Dahm, A.A. Ashrani, D.J. Crusan, T.M. Petterson, K.R. Bailey, J.A. Heit, Incidence of venous thromboembolism after elective knee arthroscopic surgery: a historical cohort study, Journal of thrombosis and haemostasis 11(7) (2013) 1279-86.
78. G. Schippinger, G.H. Wirnsberger, A. Obernosterer, K. Babinski, Thromboembolic complications after arthroscopic knee surgery. Incidence and risk factors in 101 patients, Acta orthopaedica Scandinavica 69(2) (1998) 144-6.
79. A.J. Krych, P.L. Sousa, J.A. Morgan, B.A. Levy, M.J. Stuart, D.L. Dahm, Incidence and Risk Factor Analysis of Symptomatic Venous Thromboembolism After Knee Arthroscopy, Arthroscopy (2015).
80. J.M. Cancienne, D.R. Diduch, B.C. Werner, High Altitude Is an Independent Risk Factor for Postoperative Symptomatic Venous Thromboembolism After Knee Arthroscopy: A Matched Case-Control Study of Medicare Patients, Arthroscopy 33(2) (2017) 422-427.
81. M. Nendaz, D. Spirk, N. Kucher, D. Aujesky, D. Hayoz, J.H. Beer, M. Husmann, B. Frauchiger, W. Korte, W.A. Wuillemin, K. Jager, M. Righini, H. Bounameaux, Multicentre validation of the Geneva Risk Score for hospitalised medical patients at risk of venous thromboembolism. Explicit ASsessment of Thromboembolic RIsk and Prophylaxis for Medical PATients in SwitzErland (ESTIMATE), Thrombosis and haemostasis 111(3) (2014) 531-8.
82. S. Barbar, F. Noventa, V. Rossetto, A. Ferrari, B. Brandolin, M. Perlati, B.E. De, D. Tormene, A. Pagnan, P. Prandoni, A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score, J Thromb Haemost. 8(11) (2010) 2450-2457.
83. A.C. Spyropoulos, F.A. Anderson, Jr., G. FitzGerald, H. Decousus, M. Pini, B.H. Chong, R.B. Zotz, J.F. Bergmann, V. Tapson, J.B. Froehlich, M. Monreal, G.J. Merli, R. Pavanello, A.G.G. Turpie, M. Nakamura, F. Piovella, A.K. Kakkar, F.A. Spencer, Predictive and associative models to identify hospitalized medical patients at risk for VTE, Chest 140(3) (2011) 706-714.
84. U. Watson, B.A. Hickey, H.M. Jones, A. Perera, A critical evaluation of venous thromboembolism risk assessment models used in patients with lower limb cast immobilisation, Foot and ankle surgery : official journal of the European Society of Foot and Ankle Surgeons 22(3) (2016) 191-5.
85. M.H.S. Weisman, J.R. Holmes, T.A. Irwin, P.G. Talusan, Venous Thromboembolic Prophylaxis in Foot and Ankle Surgery: A Review of Current Literature and Practice, Foot & ankle specialist 10(4) (2017) 343-351.
86. C. Roberts, D. Horner, G. Coleman, L. Maitland, T. Curl-Roper, R. Smith, E. Wood, K. Mackway-Jones, Guidelines in Emergency Medicine Network (GEMNet): guideline for the use of thromboprophylaxis in ambulatory trauma patients requiring temporary limb immobilisation, Emergency Medicine Journal 30(11) (2013) 968-982.

87. B. Németh, R.A. van Adrichem, A. van Hylckama Vlieg, P. Bucciarelli, I. Martinelli, T. Baglin, F.R. Rosendaal, S. le Cessie, S.C. Cannegieter, Venous Thrombosis Risk after Cast Immobilization of the Lower Extremity: Derivation and Validation of a Clinical Prediction Score, L-TRiP(cast), in Three Population-Based Case-Control Studies, PLoS medicine 12(11) (2015) e1001899; discussion e1001899.
88. P. Aglietti, A. Baldini, L.M. Vena, R. Abbate, S. Fedi, M. Falciani, Effect of tourniquet use on activation of coagulation in total knee replacement, Clin.Orthop.Relat Res. (371) (2000) 169-177.
89. S.F. Hughes, B.D. Hendricks, D.R. Edwards, J.F. Middleton, Tourniquet-applied upper limb orthopaedic surgery results in increased inflammation and changes to leukocyte, coagulation and endothelial markers, PLoS One 5(7) (2010) e11846.

12

Summary and general discussion

Partially adapted from Németh & Cannegieter,
Thromb Res. 2019 Feb;174:62-75. (Chapter 11)

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.

REFERENCE LIST

1. van Adrichem RA, Németh B, Algra A, le Cessie S, Rosendaal FR, Schipper IB, et al. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. The New England journal of medicine. 2017;376(6):515-25.
2. Timp JF, Lijfering WM, Flinterman LE, van Hylckama Vlieg A, le Cessie S, Rosendaal FR, et al. Predictive value of factor VIII levels for recurrent venous thrombosis: results from the MEGA follow-up study. Journal of thrombosis and haemostasis : JTH. 2015;13(10):1823-32.
3. Riou B, Rothmann C, Lecoules N, Bouvat E, Bosson J-L, Ravaud P, et al. Incidence and risk factors for venous thromboembolism in patients with nonsurgical isolated lower limb injuries. The American Journal of Emergency Medicine. 2007;25(5):502-8.
4. 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.
5. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. The New England journal of medicine. 2002;347(10):726-30.
6. Knudson MM, Ikossi DG, Khaw L, Morabito D, Speetzen LS. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. Annals of surgery. 2004;240(3):490-6; discussion 6-8.
7. Blanco JA, Slater G, Mangwani J. A Prospective Cohort Study of Symptomatic Venous Thromboembolic Events in Foot and Ankle Trauma: The Need for Stratification in Thromboprophylaxis? J Foot Ankle Surg. 2018;57(3):484-8.
8. Lapidus LJ, Ponzer S, Pettersson H, de Bri E. Symptomatic venous thromboembolism and mortality in orthopaedic surgery - an observational study of 45 968 consecutive procedures. BMC musculoskeletal disorders. 2013;14:177.
9. Hetsroni I, Lyman S, Do H, Mann G, Marx RG. Symptomatic pulmonary embolism after outpatient arthroscopic procedures of the knee: the incidence and risk factors in 418,323 arthroscopies. The Journal of bone and joint surgery British volume. 2011;93(1):47-51.
10. Jameson SS, Dowen D, James P, Serrano-Pedraza I, Reed MR, Deehan DJ. The burden of arthroscopy of the knee: a contemporary analysis of data from the English NHS. The Journal of bone and joint surgery British volume. 2011;93(10):1327-33.
11. Chan NC, Stehouwer AC, Hirsh J, Ginsberg JS, Alazzoni A, Coppens M, et al. Lack of consistency in the relationship between asymptomatic DVT detected by venography and symptomatic VTE in thromboprophylaxis trials. Thrombosis and haemostasis. 2015;114(5):1049-57.
12. Roberts C, Horner D, Coleman G, Maitland L, Curl-Roper T, Smith R, et al. Guidelines in Emergency Medicine Network (GEMNet): guideline for the use of thromboprophylaxis in ambulatory trauma patients requiring temporary limb immobilisation. Emergency Medicine Journal. 2013;30(11):968-82.
13. Guidelines N. Venous thromboembolism in adults admitted to hospital: reducing the risk. (NICE guideline CG92). 2010.
14. Aglietti P, Baldini A, Vena LM, Abbate R, Fedi S, Falciani M. Effect of tourniquet use on activation of coagulation in total knee replacement. ClinOrthopRelat Res. 2000(371):169-77.
15. Hughes SF, Hendricks BD, Edwards DR, Middleton JF. Tourniquet-applied upper limb orthopaedic surgery results in increased inflammation and changes to leukocyte, coagulation and endothelial markers. PLoS One. 2010;5(7):e11846.

APPENDICES

NEDERLANDSE SAMENVATTING

NEDERLANDSE SAMENVATTING

Veneuze trombose

Bloedstolling is een fysiologisch proces dat een bloeding stelpt wanneer vaatschade optreedt. Doordat er een bloedstolsel vormt op de plek waar de vaatwand is beschadigd, blijft de normale bloeddoorstroming gehandhaafd. Het ontstaan van een bloedstolsel (coagulatie) en de afbraak hiervan (fibrinolyse) zijn mechanistisch sterk met elkaar verbonden waardoor er in de normale situatie een balans ontstaat tussen stolselvorming en stolselafbraak. Wanneer deze balans wordt verstoord kan er een veneuze trombose (VT) of een bloeding ontstaan. VT is een veneuze stollingsziekte die zich meestal uit als een trombosebeen of een longembolie. Daarbij ontstaat een bloedstolsel in respectievelijk, één of meerdere diepe aders van het been of de slagaders van de longen. In de algemene populatie ontwikkelen ongeveer 1.5 per 1000 personen per jaar deze ziekte. Een VT kan leiden tot ernstige complicaties zoals een post-trombotisch syndroom, chronische trombo-embolische pulmonale hypertensie of zelfs overlijden.

Orthopedische chirurgie is een belangrijke oorzaak van VT, wat gedeeltelijk kan worden verklaard door de forse weefselschade die ontstaat tijdens de operatie en de postoperatieve (relatieve) immobilisatie. Om postoperatieve VT te voorkomen is tromboseprofylaxe voor de meeste orthopedische patiënten geïndiceerd. Deze tromboseprofylaxe bestaat in het algemeen uit het gebruik van een bloedverdunner, vaak in relatief lage dosering gedurende enige tijd na de operatie. Terwijl er geen twijfel bestaat over de effectiviteit van tromboseprofylaxe na grote orthopedische ingrepen (bijvoorbeeld een totale heup- of knievervanging of wervelkolomoperaties) is niet goed bekend of patiënten met onderbeengips of patiënten die een kijkoperatie van de knie ondergaan ook baat hebben bij een behandeling met tromboseprofylaxe. Dit komt omdat het niet duidelijk is of de baten (een kleiner risico op trombose) opwegen tegen de kosten; een behandeling met tromboseprofylaxe verhoogt namelijk het risico op het ontstaan van bloedingen, tevens is dit kostbaar en het kan pijn en ongemak met zich mee brengen (bijvoorbeeld door dagelijkse injecties).

In dit proefschrift wordt onderzoek beschreven naar de effectiviteit en veiligheid van tromboseprofylaxe voor patiënten met onderbeengips en voor patiënten die een kijkoperatie van de knie hebben ondergaan. Tevens is bestudeerd of het individualiseren van tromboseprofylaxe een goede strategie zou kunnen zijn om VT te voorkomen. In dit hoofdstuk worden de bevindingen uit dit proefschrift samengevat.

Effectiviteit van tromboseprofylaxe

In **hoofdstuk 2** worden de resultaten besproken van twee parallelle, pragmatische, multicenter, gerandomiseerde, gecontroleerde, open-label trials met een geblindeerde uitkomst: de POT-KAST trial, waarin patiënten werden geïncludeerd die een kijkoperatie van de knie ondergaan hadden en de POT-CAST trial, waarin patiënten met onderbeengips werden geïncludeerd. In totaal werden 1543 patiënten geïncludeerd in de POT-KAST trial en 1451 in de POT-CAST trial. In de studies werd geloot tussen het gebruik van een profylactische dosering met een laag-moleculair-gewicht-heparine en geen therapie. Indien patiënten profylaxe kregen werd dit direct na de kijkoperatie, of het aanbrengen van onderbeengips gestart, de andere helft kreeg geen profylaxe. Vervolgens werden alle patiënten nauwkeurig gevolgd. In beide trials werd de cumulatieve incidentie van VT bepaald binnen 3 maanden na inclusie. Er werd niet gescreend op het ontstaan van asymptomatische trombose. In geen van beide trials was tromboseprofylaxe effectief om VT te voorkomen (absoluut risicoverschil 0.3%, 95% betrouwbaarheidsinterval (BI) -0.6% tot 1.2% in POTCAST en -0.4%, 95%BI -1.8% tot 1.0% in POT-KAST). In totaal ontwikkelden 0.6% van alle patiënten in de POT-KAST trial een VT tegenover 1.6% in de POT-CAST trial. In **hoofdstuk 3** worden de resultaten van de POT-(K)CAST trial benadrukt. In een tweetal brieven aan de editor trekken we de conclusies van twee andere trials in twijfel waarin wordt gesteld dat tromboseprofylaxe wel effectief is om VT te voorkomen na onderbeengips en na een kijkoperatie van de knie.

Identificatie van hoog-risico groepen

In de POT-(K)CAST trials hebben we aangetoond dat tromboseprofylaxe niet effectief is voor de gehele patiëntenpopulatie. Omdat in absolute zin veel patiënten VT krijgen is het noodzakelijk een nieuwe behandelstrategie te ontwikkelen om VT te voorkomen. Eerst hebben we onderzocht of hoog-risicopatiënten kunnen worden geïdentificeerd aan de hand van klassieke risicofactoren voor VT. In **hoofdstuk 4** werd onderzocht of patiënten met een voorgeschiedenis van VT die vervolgens werden behandeld met onderbeengips immobilisatie een verhoogd risico hebben op trombose. Door gebruik te maken van informatie uit de MEGA studie, werden patiënten met een voorgeschiedenis van VT gevolgd om te onderzoeken of zij nogmaals een VT ontwikkelden (recidief VT). De odds ratio voor het ontwikkelen van een recidief VT werd geschat door het risico op een recidief te vergelijken tussen een groep patiënten die werden behandeld met gipsimmobilisatie en een recidief (cases) en een groep patiënten met gipsimmobilisatie zonder recidief (controles). Dit onderzoek toonde aan dat patiënten met een voorgeschiedenis van VT, die daarna werden behandeld met gipsimmobilisatie van het been, een 4.5-voudig verhoogd risico (95%BI 1.5 tot 14.0) hadden op het ontwikkelen van een recidief VT ten opzichte van patiënten met een voorgeschiedenis van VT zonder gipsimmobilisatie. Dit komt overeen

met een absoluut risico van ongeveer 3.2% binnen drie maanden. Aan de hand van deze resultaten kon worden geconcludeerd dat het risico in deze populatie hoog is en dat er mogelijk een strikte tromboseprofylaxe strategie dient te worden toegepast om een recidief VT te voorkomen (bijvoorbeeld een hogere dosering).

In **hoofdstuk 5** worden de resultaten beschreven van een soortgelijk onderzoek. In dit onderzoek werd het risico op een recidief VT geschat voor patiënten met een voorgeschiedenis van VT die vervolgens werden geopereerd. Voor deze analyse werden data van de MEGA studie gekoppeld aan gegevens van de Nederlandse ziekenhuis registratie van het Centraal Bureau voor de Statistiek (met informatie over alle ziekenhuisopnames en operaties). Een Kaplan-Meier curve werd gebruikt om het absolute risico op een recidief te schatten. Daarnaast werd door middel van een Cox-regressie analyse, met een tijdsafhankelijke co-variabele (chirurgie), de Hazard-Ratio (HR) voor recidief VT geschat. Het absolute risico voor recidief VT na chirurgie voor patiënten met een voorgeschiedenis van VT was 2.1% (95%BI 1.2 tot 3.6) na 1-maand en steeg door tot 3.3% (95%BI 2.1 tot 5.1), 4.6% (95%BI 3.1 tot 6.6) en 6.3% (95%BI 4.6 tot 8.7) na 3-, 6- en 12-maanden, respectievelijk. Door deze hoge risico's is het twijfelachtig of het huidige tromboseprofylaxe beleid bij deze patiënten wel voldoende is om een recidief VT te voorkomen. Tevens werd gevonden dat hoog-risicopatiënten kunnen worden geïdentificeerd op basis van zowel het type chirurgie (ter illustratie, het absolute risico na 6-maanden was 5.0% vergeleken met 3.8% na respectievelijk grote en kleinere ingrepen) als de aanwezigheid van patiënt-afhankelijke factoren zoals bijvoorbeeld een Factor V Leiden mutatie. De resultaten uit deze studie ondersteunen de gedachte dat voor deze patiënten een strikt tromboseprofylaxe beleid moet worden ingesteld, waarvan de optimale duur en dosering van bloedverdunners nog moet worden onderzocht.

Voorspellen van VT risico na onderbeengipsimmobilisatie

In **hoofdstuk 6** wordt beschreven hoe met behulp van gegevens uit de eerder genoemde MEGA studie, de L-TRiP cast (Leiden Thrombosis Risk Prediction following cast immobilization) score werd ontwikkeld. Deze score schat de kans op VT voor patiënten die worden behandeld met onderbeengips en bestaat hoofdzakelijk uit klinische variabelen zoals leeftijd, geslacht, gebruik van anticonceptiepil, body mass index, locatie van gips (boven of onderbeengips), etc. De Area Under the Curve (AUC) was 0.76 (95%BI 0.66 tot 0.86) in de derivatie studie en 0.77 (95%BI 0.58 tot 0.96) en 0.95 (95%BI 0.91 tot 0.99) in twee onafhankelijke validatie studies (beide case-controle studies). De toevoeging van genetische informatie en biomarkers zoals aanwezigheid van de factor V Leiden mutatie of waarden van stollingsfactor VIII resulteerde in een nog nauwkeuriger voorspelling. Echter, vanwege de focus op klinische toepasbaarheid en reeds goede voorspellende waarde van alleen klinische voorspellers werden deze niet geïncludeerd in de definitieve L-TRiP(cast) score.

Na de TRiP(cast) score te hebben ontwikkeld, werden wij benaderd om bij te dragen aan de ontwikkeling van de TIP score, (Trauma, Immobilisatie en Patiënt), in samenwerking met een Franse onderzoeksgroep. Met behulp van de Delphi-methode werden 27 experts gevraagd om een score te ontwikkelen om het VT risico in te schatten voor patiënten die behandeld worden met onderbeengips. De resultaten hiervan staan beschreven in **hoofdstuk 7**. De TRiP(cast) en TIP score verschillen doordat in de TIP score zowel de ernst als het type trauma (de reden voor het gips) is opgenomen, informatie die niet aanwezig was voor de TRiP(cast) score. We anticipeerden op een nauwkeuriger voorspelling omdat de ernst en het type trauma geassocieerd zijn met het ontwikkelen van VT. De voorspellende waarde van de TIP score was goed, met een AUC van 0.77 (95%BI 0.70 tot 0.85) in de MEGA studie.

Een externe validatie van de L-TRiP(cast) score en subgroep analyse van de POT-CAST trial wordt beschreven in **hoofdstuk 8**. Het risico op een VT na onderbeengips immobilisatie was 1.6% in de POT-CAST trial. Een aantal groepen met een hoog risico werd geïdentificeerd; patiënten met een body mass index van >30kg/m^2 hadden een risico van 3.9% en patiënten met een familiegeschiedenis van VT (1^e graads) van 3.3%. Zoals meerdere malen beschreven in eerdere studies, hadden patiënten met een achillespeesruptuur een hoger tromboserisico in vergelijking met patiënten die andere soorten letsel hadden (het absoluut risico na 3 maanden was 8.5%). Ook patiënten die chirurgie ondergingen als onderdeel van de behandeling van een fractuur of peesletsel hadden een hoog risico (3.5%). Dit wijst erop dat het VT risico sterk afhankelijk is van de chirurgische behandeling en het type letsel. De AUC voor de L-TRiP(cast) score was 0.69 (95%BI 0.58 – 0.80), wat een matig tot goede voorspellende waarde indiceert.

In **hoofdstuk 10** richtten we ons op het ontwikkelen van één simpele, en daarmee gebruiksvriendelijke, score genaamd de TRiP(cast) score (zonder voorafgaande L-) door het samenvoegen van de L-TRiP(cast) en TIP score. De voorspellende waarde van de drie verschillende scores werd vergeleken met behulp van data uit de MEGA studie. Vervolgens werd de uiteindelijke TRiP(cast) score gevalideerd in de POT-CAST trial welke een AUC van 0.74 (95%BI 0.61 - 0.87) liet zien. Uitgaande van een afkapwaarde van 7 punten was de sensitiviteit en specificiteit van de score 76.1% en 51.2%, respectievelijk. De calibratie plot toonde een nagenoeg perfecte samenhang tussen het voorspelde en geobserveerde risico op VT. Om een gemakkelijke implementatie in de klinische praktijk te bewerkstelligen werd een mobiele telefoon applicatie (app*) ontwikkeld en beschikbaar gesteld in drie verschillende talen. Met behulp van de applicatie kan het tromboserisico van een individu met gipsimmobilisatie van het been worden geschat.

* https://apps.apple.com/sr/app/trip-cast-score/id1438610930?l=nl
https://play.google.com/store/apps/details?id=com.everywhereim.tripcast&hl=nl

Voorspellen van VT risico na een kijkoperatie van de knie

Voor patiënten die een kijkoperatie van de knie ondergaan werd eveneens een voorspellingsmodel voor het VT-risico ontwikkeld, de L-TRiP(ascopy) score (**hoofdstuk 9**). Toevoeging van biomarkers zoals factor VIII activiteit resulteerde ook hier in een verbetering van de nauwkeurigheid en zelfs meer dan bij de eerder genoemde score voor patiënten met onderbeengips. Dit kan voornamelijk worden verklaard doordat patiënten die een artroscopie van de knie ondergaan, in het algemeen jong zijn zonder veel comorbiditeit. Derhalve dragen klinische factoren maar in een beperkte mate bij aan de accuratesse van het voorspelmodel. Bij interne validatie (bootstrap analyse), was de AUC voor de complete score (inclusief genetische informatie en biomarkers), 0.78. In een externe validatie studie kon echter, vanwege een lage power, geen uitsluitsel worden gegeven over de toegevoegde waarde van biomarkers (AUC range 0.75-0.78 voor modellen met en zonder biomarkers). Vanwege deze validatie resultaten en de logistieke uitdagingen en kosten van bijvoorbeeld Factor VIII bepaling in de klinische praktijk, is besloten af te zien van toevoeging van biomarkers in het voorspellingsmodel. Een groter validatieonderzoek moet uitsluitsel geven of de toevoeging van biomarkers in het risicomodel, de nauwkeurigheid om VT te voorspellen vergroot en ook kosteneffectief is.

Van een populatie gerichte aanpak naar geïndividualiseerde therapie

In **hoofdstuk 11** wordt een omvangrijke samenvatting gegeven van de literatuur over de epidemiologie, preventie en predictie van VT bij patiënten met onderbeengipsimmobilisatie en patiënten die een knie artroscopie ondergaan. Middels een meta-analyse werd de incidentie van VT in onbehandelde (dus zonder tromboseprofylaxe) patiënten geschat. Voor patiënten die worden behandeld met onderbeengips zonder tromboseprofylaxe is de cumulatieve incidentie van asymptomatische trombose 18.0% (95%CI 12.9 tot 23.1) en van symptomatische VT 2.0% (95%CI 1.3 tot 2.7). Voor patiënten die een knie artroscopie ondergaan zonder tromboseprofylaxe is de cumulatieve incidentie van asymptomatische trombose 5.9% (95%CI 3.9 tot 7.9), terwijl de cumulatieve incidentie van symptomatische trombose, evenals voor patiënten met gips, ongeveer een 10-voud kleiner werd geschat, namelijk 0.6% (95%CI 0.4 tot 0.7). De grote variabiliteit van geschatte incidenties binnen alle studies geeft aan dat er een sterke heterogeniteit is van patiënten en diagnostische methode (aangaande diagnose van asymptomatische VT).

Tevens is er een aanvullende meta-analyse verricht naar de effectiviteit van tromboseprofylaxe in beide patiëntpopulaties. Voor patiënten met onderbeengips lijkt tromboseprofylaxe het risico op trombose te verminderen, relatief risico (RR) 0.31 (95%BI 0.13 – 0.73), terwijl voor patiënten met een knie arthroscopie er geen duidelijk verschil was (RR 0.65, 95%BI 0.23-1.81). Echter, gezien verschillende methodologische tekortkomingen en misclassificatie van symptomatische VT in meerdere trials, concluderen we in dit hoofdstuk dat een populatiegerichte aanpak niet effectief is voor preventie van VT. Derhalve dient de focus te worden gelegd op geïndividualiseerde behandeling middels identificatie van laag- en hoog-risicopatiënten.

Toekomstvisie

Om beter te begrijpen welke patiënten VT ontwikkelen stel ik voor om de onderliggende pathofysiologie in deze patiëntpopulatie te onderzoeken. Ondanks dat we weten dat patiënten met onderbeengips en patiënten die een knie artroscopie ondergaan een verhoogd risico hebben op het ontwikkelen van VT, zijn de onderliggende mechanismen niet goed in kaart gebracht. Kennis over de reactie van het stollingssysteem op een onderbeenfractuur zou kunnen bijdragen aan nieuwe behandelstrategieën, zo is het bijvoorbeeld onduidelijk of de fractuur zelf, de gipsbehandeling of beide bijdragen aan het verhoogde risico op VT. Omdat er geen studies zijn gedaan naar het effect van fracturen of de ernst van weefselschade op het stollingssysteem (en individuele stollingsfactoren) is dit een onderwerp waar we ons verder op zullen richten. Studies naar de onderliggende pathofysiologie zijn eveneens afwezig voor patiënten die een kijkoperatie van de knie hebben ondergaan. Er zijn wel studies die aantonen dat applicatie van een tourniquet (een apparaat wat gebruikt wordt om de bloedtoevoer naar het been te stoppen) invloed heeft op de formatie van een stolsel. Derhalve zou toekomstig onderzoek zich kunnen richten op de vraag of de applicatie van een tourniquet ten grondslag ligt aan het verhoogde risico op trombose na een kijkoperatie van de knie.

Dit proefschrift zal de basis vormen voor het ontwerp van de POT-(K)CAST 2.0 trial waarbij patiënten een behandeling met tromboseprofylaxe krijgen op basis van hun risico (laag of hoog) middels risicostratificatie. Patiënten worden gerandomiseerd tussen een populatiegerichte aanpak en een geïndividualiseerde behandeling (bij patiënten met een laag risico kan tromboseprofylaxe worden onthouden, terwijl hoog risicopatiënten een hogere dosering en langere duur van profylaxe krijgen). Echter, voordat een dergelijk onderzoek kan plaatsvinden moet de sensitiviteit en specificiteit van het toe te passen risicostratificatie model worden vastgesteld na een prospectieve studie.

Conclusie

In dit proefschrift hebben we geconcludeerd dat tromboseprofylaxe niet effectief is om VT te voorkomen bij patiënten met onderbeengips en bij patiënten die een kijkoperatie van de knie ondergaan. Door meerdere methodologische tekortkomingen, misclassificatie, publicatie bias en het ongemak en de kosten gepaard gaande met tromboseprofylaxe, is er geen plek voor een populatiegerichte aanpak. Echter, ongeveer 2.0% en 0.6% van alle patiënten met respectievelijk, onderbeengips en na een kijkoperatie van de knie ontwikkelt symptomatische VT. Daarom is een nieuwe behandelstrategie nodig om deze ziekte te voorkomen. Het identificeren van hoog risicopatiënten is een veelbelovende stap voorwaarts om VT te voorkomen. In dit proefschrift hebben we laten zien dat het goed mogelijk is hoog risicopatiënten te identificeren. Een volgende stap is te onderzoeken op welke manier deze hoog risicopatiënten moeten worden behandeld (bijvoorbeeld door een hogere dosering of langere therapieduur). De in dit proefschrift ontwikkelde TRiP(cast) en TRIP(ascopie) score kunnen gebruikt worden voor dit doel. Op basis daarvan kunnen toekomstige studies aantonen wat de beste behandeling is voor het voorkomen van VT na onderbeengips en na een kijkoperatie van de knie.

APPENDICES

DANKWOORD

DANKWOORD

Ten eerste bedank ik alle patiënten die vrijwillig hebben deelgenomen aan de POT-(K) CAST trial.

Prof. dr Cannegieter, beste Suzanne, in 2014 begon ik als student onder jouw supervisie. Ik wil je bedanken voor de onvoorstelbaar leerzame en leuke periode als promovendus. Je gaf me alle ruimte om nieuwsgierig te zijn en mezelf te ontwikkelen tot klinisch onderzoeker.

Prof. dr Nelissen, beste Rob, jouw enthousiasme voor de orthopedie en wetenschap werkt aanstekelijk. Waar ik aan het begin van mijn promotie nog dacht chirurg te worden, heb je me, bewust of onbewust, richting de orthopedie "gedreven". Heel veel dank!

Prof. dr Rosendaal, beste Frits, wat begon als een idee tijdens de jaarlijkse 'Schier' cursus monde uit in een geweldig project; de Fear Factor trial. Dank.

Beste Raymond, bedankt voor het vertrouwen dat je me gaf om het POT-(K)CAST stokje over te nemen.

Beste POT-(K)CAST crew, zonder jullie geen proefschrift! Enorm bedankt voor de prettige samenwerking.

Dear Delphine and Pierre-Marie, thank you for a wonderful collaboration.

Dear Roopen, Lara and Martin, many thanks for the possibility you've given me to work in London for several months. I look forward to expand our collaboration.

Dear Anthony, many thanks for designing my thesis cover.

Paranimf, Dr. Scheres, beste Luuk, een fijnere collega op kamer 101 had ik me niet kunnen wensen. Ik ben trots op ons bloedstollende avontuur!

Paranimf, drs. Rijkeé, beste Mattie, de berg op fietsen is ons ding. Ik hoop dat we hier in de toekomst weer meer tijd voor kunnen vinden. Bedankt voor onze vriendschap!

Goudse mannen, Frank, Ron, René, Peer, Vincent, Pieter Stijn & Laurens, jullie lieten me kennismaken met de "echte orthopedie". Daar ben ik jullie dankbaar voor, het was een top jaar.

Collega's van de Epi en Ortho, hartelijk dank voor de geweldige tijd. Beste Willem, bedankt voor je begeleiding en adviezen.

Lieve Pap, Eline, Mam en Jo, ik voel me bevoorrecht met de steun en betrokkenheid van zoveel lieve ouders. Zusje, we delen een gezamenlijke passie voor de gezondheidszorg. Dank dat je er altijd voor me bent.

Lieve Maaike, het leven is niet half zo leuk zonder jou. Je humor en zorgzaamheid maken mij elke dag blij. Ons Londen avontuur was te gek, ik hoop dat er nog vele mogen volgen. Lieve Juul, wat zijn dochters toch gaaf! Je bent samen met mama, het beste wat me ooit is overkomen.

APPENDICES

LIST OF PUBLICATIONS

LIST OF PUBLICATIONS

Last update 21 July 2020

Publications in (intern)national journals

Medische zorg in vluchtelingenkamp Moria
Kooistra J, Vrielink F, Németh B
Huisarts Wet. 2020, 23 juni

Evidence-based guidelines for thromboprophylaxis in patients with lower limb trauma requiring immobilization: an urgent, unmet need.
Douillet D, Penaloza A, Horner D, Savary D, Hugli O, Németh B, Chocron R, Tazarourte K, Roy PM.
Eur J Emerg Med. 2020 Aug;27(4):245-246.

Development and validation of a clinical risk assessment model to predict venous thromboembolism risk after immobilization for lower-limb trauma: the TRiP(cast) score
*Németh B, *Douillet D, le Cessie S, Penaloza A, Moumneh T, Roy PM, Cannegieter SC.
*The Lancet - EClinicalMedicine. 2020 Feb 4;20:100270. *Authors contributed equally.*

Thromboprophylaxis in temporary lower limb immobilization: Extrapolate with care.
Czuprynska J, Németh B, Roberts LN, Cannegieter SC, Arya R.
J Thromb Haemost. 2020 Feb;18(2):518-519.

No Evidence for Effective Prevention of Venous Thromboembolism With Low-Molecular-Weight Heparin After Anterior Cruciate Ligament Reconstruction: Letter to the Editor.
van Adrichem RA, Németh B, Nelissen RGHH, Cannegieter SC.
Am J Sports Med. 2020 Jan;48(1):NP1-NP2.

Individualized Thromboprophylaxis in Patients with Lower-Leg Cast Immobilization-A Validation and Subgroup Analysis in the POT-CAST Trial.
Németh B, van Adrichem R, Nelissen R, le Cessie S, Cannegieter SC.
Thromb Haemost. 2019 Sep;119(9):1508-1516.

Clinical outcomes of postcarotid endarterectomy hypertension.
Ngo HTN, Németh B, Wever JJ, Veger HTC, Mairuhu ATA, de Laat KF, Statius van Eps RG.
J Vasc Surg. 2019 Jul 4. pii: S0741-5214(19)31226-1.

Venous thromboembolism risk stratification for patients with lower limb trauma and cast or brace immobilization.
Douillet D, Németh B, Penaloza A, Le Gal G, Moumneh T, Cannegieter SC, Roy PM.
PLoS One. 2019 Jun 20;14(6):e0217748.

Space Medicine in the Era of Civilian Spaceflight.
Roberts LN, Németh B, Arya R.
N Engl J Med. 2019 Jun 20;380(25):e50.

Risk and Risk Factors Associated With Recurrent Venous Thromboembolism Following Surgery in Patients With History of Venous Thromboembolism.
Németh B, Lijfering WM, Nelissen RGHH, Schipper IB, Rosendaal FR, le Cessie S, Cannegieter SC.
Pending revisions
JAMA Netw Open. 2019 May 3;2(5):e193690.

Venous thrombosis following lower-leg cast immobilization and knee arthroscopy: From a population-based approach to individualized therapy.
Németh B, Cannegieter SC.
Thromb Res. 2019 Feb;174:62-75.

Validation of risk assessment models for venous thrombosis in hospitalized medical patients.
Cobben MRR, Németh B, Lijfering WM, Cannegieter SC
Res Pract Thromb Haemost. 2019;3:217–225.

High risk of recurrent venous thrombosis in patients with lower-leg cast immobilization.
Németh B, Timp JF, van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC.
J Thromb Haemost. 2018 Nov;16(11):2218-2222.

Venous Thrombosis Risk after Arthroscopy of the Knee: Derivation and Validation of the L-TRiP(ascopy) Score.
Németh B, van Adrichem RA, van Hylckama Vlieg A, Baglin T, Rosendaal FR, Nelissen RGHH, le Cessie S, Cannegieter SC.
Thromb Haemost. 2018 Oct;118(10):1823-1831.

Severe infrarenal atheroma load in open aortic aneurysm repair is not a risk factor for postoperative Acute Kidney Injury.
Ooms S, Németh B, Wever JJ, Knippenberg B, van Overhagen H, Statius van Eps RG.
Ann Vasc Surg. 2018 2018 Nov;53:70-77.

Cast immobilization of the lower-leg: No indication for thromboprophylactic therapy.
Németh B, Cannegieter SC.
Injury. 2017 Dec;48(12):2887-2888.

Determinants of Acute Kidney Injury and Renal Function Decline After Endovascular Abdominal Aortic Aneurysm Repair.
Statius van Eps RG, Németh B, Mairuhu RTA, Wever JJ, Veger HTC, van Overhagen H, van Dijk LC, Knippenberg B.
Eur J Vasc Endovasc Surg. 2017 Dec;54(6):712-720.

Higher incidence rates than previously known in tenosynovial giant cell tumors.
Mastboom MJL, Verspoor FGM, Verschoor AJ, Uittenbogaard D, Németh B, Mastboom WJB, Bovée JVMG, Dijkstra PDS, Schreuder HWB, Gelderblom H, Van de Sande MAJ; TGCT study group.
Acta Orthop. 2017 Aug 8:1-7.

Healthcare and disease burden among refugees in long-stay refugee camps at Lesbos, Greece.
Hermans MPJ, Kooistra J, Cannegieter SC, Rosendaal FR, Mook-Kanamori DO, Németh B.
Eur J Epidemiol. 32, 851–854 (2017)

Thromboprophylaxis after hospital discharge in acutely ill medical patients: need for trials in patients who are at high risk of venous thrombosis.
Németh B, Lijfering WM, Cannegieter SC.
J Thorac Dis. 2017 Apr;9(4):950-952.

Risk of Cerebral Venous Thrombosis in Obese Women.
Zuurbier SM, Arnold M, Middeldorp S, Broeg-Morvay A, Silvis SM, Heldner MR, Meisterernst J, Németh B, Meulendijks ER, Stam J, Cannegieter SC, Coutinho JM.
JAMA Neurol. 2016 May 1;73(5):579-84.

Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting.
van Adrichem RA*, Németh B*, Algra A, le Cessie S, Rosendaal FR, Schipper IB, Nelissen RGHH, Cannegieter SC; POT-KAST and POT-CAST Group.
*N Engl J Med. 2017 Feb 9;376(6):515-525. *Authors contributed equally.*

The ERIKA trial: still limited evidence on the efficacy of thromboprophylaxis after knee arthroscopy.
Németh B, van Adrichem RA, Cannegieter SC.
Thromb Haemost. 2016 Oct 28;116(5):1001.

Confounding by Indication: Letter to the Editor.
Németh B, Cannegieter SC.
Am J Sports Med. 2016 Apr;44(4):NP12.

Bloodcurdling movies and measures of coagulation: Fear Factor crossover trial.
Németh B*, Scheres LJ*, Lijfering WM, Rosendaal FR.
*BMJ. 2015 Dec 16;351:h6367. *Authors contributed equally.*

Venous Thrombosis Risk after Cast Immobilization of the Lower Extremity: Derivation and Validation of a Clinical Prediction Score, L-TRiP(cast), in Three Population-Based Case-Control Studies.
Németh B, van Adrichem RA, van Hylckama Vlieg A, Bucciarelli P, Martinelli I, Baglin T, Rosendaal FR, le Cessie S, Cannegieter SC.
PLoS Med. 2015 Nov 10;12(11):e1001899

Publications submitted to international journals
Preventing VTE following total hip and knee arthroplasty: is prediction the future?
Banne Németh, Rob Nelissen, Roopen Arya, Suzanne Cannegieter
Pending revisions at J Thromb Haemost.

DO'S and DON'TS in prediction research: a practical guide
Banne Németh, Suzanne Cannegieter, Maarten van Smeden
Pending revisions at Res Pract Thromb Haemost.

Presentations
INVITED
Best evidence for current thromboprophylaxis strategies following total hip and knee arthroplasty.
EFFORT (European Federation of National Associations of Orthopaedics and Traumatology), Lisbon, 7 June 2019, Lisbon, Portugal

Anticoagulation following Total Hip Arthroplasty, is prediction the Future?
European Hip Society, 20-09-2018, The Hague, The Netherlands

Keynote lecture: Anticoagulation in orthopaedic surgery, is prediction the future?
NOV annual congress, 03-02-2017, 's-Hertogenbosch, The Netherlands

Venous thrombosis in patients following knee arthroscopy or lower-leg cast immobilization, results from the POT-(K)CAST trial
LUMC TOP Research seminar: 16 May 2017, Leiden, The Netherlands

Invited lecture: Prediction of Venous Thrombosis Risk after Lower Leg Cast Immobilization and Arthroscopic Knee Surgery
ISTH SSC congress, 26 May 2016, Montpellier, France

OTHER
Poster, High risk of recurrent venous thrombosis in patients with lower-leg cast immobilization.
ISTH SSC Dublin, Ireland, 2018

Poster, Validation of risk assessment models for venous thrombosis in hospitalized medical patients.
ISTH Berlin, Germany, 2017

Presentation, Prevention Of Venous Thromboembolism After Knee Arthroscopy: A Randomised Clinical Trial
EFFORT Vienna, Austria, 31-05-2017

Presentation, Prevention Of Venous Thromboembolism After Lower Leg Cast Immobilisation: A Randomised Clinical Trial
EFFORT Vienna, Austria, 31-05-2017

A

Poster, Venous Thrombosis Risk after Cast Immobilization of the Lower Extremity: Derivation and Validation of a Clinical Prediction Score, L-TriP(cast), in Three Population-Based Case-Control Studies.
ISTH, Toronto, Canada, 2015

Presentation, Thromboprophylaxis for below-knee cast immobilization: A survey study
ECTES, Amsterdam, The Netherlands, 11-05-2015

Presentation, Prediction models for venous thrombosis risk after cast immobilization of the lower extremity.
ECTES, Amsterdam, The Netherlands, 12-05-2015

Guidelines contributions

Dutch guideline on thromboprophylaxis following lower-leg cast immobilisation and knee arthroscopy
Leading author, responsible for update of the following guidelines:
Available at:
https://richtlijnendatabase.nl/richtlijn/antitrombotisch_beleid/preventie_vte/tromboseprofylaxe_bij_gipsimmobilisatie_been.html
https://richtlijnendatabase.nl/richtlijn/antitrombotisch_beleid/preventie_vte/tromboseprofylaxe_bij_artroscopie_van_de_knie.html

Public (news)items

POT-(K)CAST studie: Prevention of Thrombosis after Knee arthroscopy or CAST immobilization
Tijdschrift voor Trombose en Antistolling, 45e jaargang, Nummer 1, 2017
(Dutch magazine for patients on thrombosis and anticoagulation)

Leiden University Medical Center press release
Bloedverdunners niet effectief tegen trombose bij onderbeengips of na kijkoperatie knie
5 December 2016, https://www.lumc.nl/over-het-lumc/nieuws/2016/december/publicatie-nejm-bloedverdunners/?setlanguage=English&setcountry=en

Leiden University Medical Center press release
Nieuw model voorspelt tromboserisico gipsbeen
13 November 2015, https://www.lumc.nl/over-het-lumc/nieuws/2015/november/Nieuw-model-voorspelt-tromboserisico-bij-gipsbeen/

International newspapers, news items on study in BMJ 2015 (Bloodcurdling movies and measures of coagulation: Fear Factor crossover trial. Németh B et al. BMJ. 2015 Dec 16;351:h6367)
Several news items and interviews for newspapers; The Guardian (UK), The Wall Street Journal (US), The Telegraaf (NL), De Standaard (BE), Metro (INT), Trouw (NL), FOX news (US), RTL Nieuws (NL).

Nominee for the VGZ zinnige zorg award 2018
Including informative film on our research project https://www.youtube.com/watch?v=GjtERFGpcrQ

APPENDICES

CURRICULUM VITAE

CURRICULUM VITAE

Banne Németh was born on December 6th, 1987 in Alphen aan den Rijn, the Netherlands. He completed higher education (HAVO) in 2004 and pre-university education (VWO) in 2006 at the Scala College. Thereafter, he studied Aerospace Engineering for one year at the Technical University in Delft. In 2007, Banne started medical school at the Leiden University Medical Center. During his studies, he was active in various student boards and in 2009-2010 he was full-time chairman of the Medical Student Faculty Board. During this period, he developed a great interest in epidemiological research, and after his third year in medical school, Banne started a research project at the department of Clinical Epidemiology under the supervision of Prof. dr Suzanne Cannegieter.

After obtaining his MD in 2014, Banne was appointed as a PhD student at the departments of Clinical Epidemiology and Orthopaedic Surgery, under the supervision of Prof. dr Suzanne Cannegieter and Prof. dr Rob Nelissen. During his PhD, he focused on prevention and prediction of venous thrombosis following lower-leg cast immobilization and knee arthroscopy. Banne presented his research at several (inter)national meetings. He was invited to give a keynote lecture on prediction of venous thrombosis following orthopaedic surgery at the annual Netherlands Orthopaedic Society and at the European Hip Society meetings.

In 2017, Banne started as a resident in Orthopaedic Surgery at the Groene Hart Hospital in Gouda, under the supervision of dr. Ron Onstenk. After one year, he worked as a visiting researcher in the United Kingdom at King's College London and the University of Surrey under the supervision of Prof. dr. Roopen Arya and dr. Martin Whyte, studying the prediction of venous thrombosis following total hip and knee arthroplasty.

In 2019 Banne started his residency in Orthopaedic Surgery at the Leiden University Medical Center, HAGA Hospital and Haaglanden Medical Center. At the same time, he will continue to work as a clinical epidemiologist, focusing on prevention and prediction of complications (venous thrombosis in particular) following orthopaedic surgery.

Banne lives happily together with Maaike and their daughter Juul in The Hague, The Netherlands.