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

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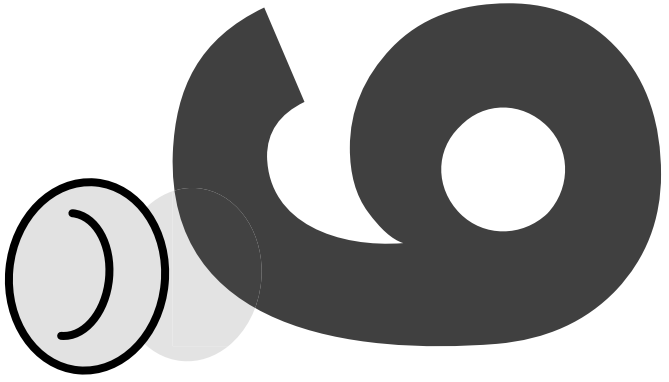

CHAPTER

Prevention of venous thromboembolism after knee arthroscopy: a randomized controlled trial

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Abstract

Background

The effectiveness of thromboprophylaxis for the prevention of venous thromboembolism (VTE) after knee arthroscopy is disputed. We contrasted anticoagulant therapy with no therapy for the prevention of symptomatic VTE following knee arthroscopy.

Methods

We conducted a pragmatic, multicenter, randomized, controlled, open label, blinded end-point trial in which patients were assigned to receive either low-molecular-weight-heparin (LMWH), 2850 IU (or 5700 IU in patients >100 kilograms) once daily, for 8 days post-operatively, or no therapy. The primary outcome was the occurrence of symptomatic VTE within three months following knee arthroscopy and the primary safety outcome was the occurrence of major bleeding in the same time period.

Results

6413 patients were screened for eligibility of whom 1543 were included in the study and 1451 analyzed in the intention-to-treat analysis. A venous thromboembolic event occurred in 5/731 (0.7%) patients assigned to LMWH and in 3/720 (0.4%) patients assigned to no therapy, for a relative risk (RR) with LMWH of 1.6; 95% confidence interval [CI] 0.4 to 6.8; (risk difference 0.3%; 95% CI -0.5 to 1.0). A major bleeding occurred in 1/731 (0.1%) patients in the LMWH and in 1/720 (0.1%) patients in the no-treatment group (RR 1.0; 95%CI [0.1 to 15.7]).

Conclusions

The POT-KAST trial showed that a prophylactic regimen of LMWH therapy for eight days was not effective for the prevention of symptomatic VTE in patients undergoing knee arthroscopy, which risk appeared to be low. These results do not support routine thromboprophylaxis in patients after knee arthroscopy.

Introduction

Patients who undergo arthroscopic knee surgery are at increased risk of developing venous thromboembolism (VTE) (i.e. deep vein thrombosis [DVT] or pulmonary embolism [PE]).[1] Venous thromboembolism is an important health-care problem, with considerable mortality, morbidity and resource expenditure.[2-4] For most orthopedic interventions, thrombosis prophylaxis with anticoagulant medication is well established, as it strongly reduces the risk of thrombosis, while the risk of bleeding is only slightly increased.[5-7] However, for arthroscopic knee surgery it is uncertain whether thrombosis prophylaxis is effective, despite it being the most commonly performed orthopedic procedure worldwide, with an estimated >4 million knee arthroscopies each year. [6,8]

To answer this question, six randomized controlled trials have previously been performed in these patients comparing anticoagulant treatment with no therapy.[9-11] However, these trials have not settled the question, since they used asymptomatic thrombosis as the primary outcome, generally chosen to reduce the required sample size. These trials were therefore underpowered to reach definite conclusions on the prevention of symptomatic events. Moreover, with the small sample sizes, side effects of the treatment were low in number and an overall risk-benefit balance could not be established. Due to this lack of evidence, international guidelines have been reluctant to advise in favor of or against anticoagulant treatment in these patients.[6,7]

The Prevention Of Thrombosis after Knee ArthroScopy Trial [POT-KAST] was designed to compare anticoagulant treatment (Low-Molecular-Weight-Heparin [LWMH]) with no therapy for the prevention of symptomatic VTE in patients who underwent arthroscopic knee surgery. We hypothesized that treatment with anticoagulants for 8 days post-operatively would be effective for the prevention of symptomatic VTE and that this benefit outweighed the bleeding risk.

Methods

Study oversight and design

The POT-KAST trial is a prospective, multicenter, randomized, controlled, open label, blinded endpoint trial comparing two treatment strategies, i.e., one by which the anticoagulant LMWH is administered versus one by which it is not, in patients who undergo knee arthroscopy. The POT-KAST study had a pragmatic design to maximize generalizability. The trial protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center; no methodological changes were made after approval. The trial was funded by The Netherlands Organization for Health Research and Development (project number 171102001) which had no role in the study design, analysis or preparation of the manuscript. The trial was registered at clinicaltrials.gov, number: NCT01542723. All authors of the study group vouch for the accuracy and completeness of the reported data.

Participants

The trial was performed in eight hospitals in the Netherlands (six teaching hospitals and two private medical care orthopedic focus clinics, Supplementary Appendix). All patients, aged 18 years or older, scheduled for knee arthroscopy for one of the following indications: meniscectomy, diagnostic arthroscopy or removal of loose bodies were eligible for inclusion. Exclusion criteria were a history of VTE, contra-indications to use of LMWH (e.g. previous allergic reaction), pregnancy and current use of anticoagulant therapy for other indications (either LMWH, vitamin K antagonists or direct oral anticoagulants). Furthermore, patients with insufficient knowledge of the Dutch language, mental or physical disability to fulfill study requirements and patients who had previously participated in the trial were not included. All participants provided written informed consent.

Study procedures and intervention

Eligible patients were randomly assigned to receive a prophylactic dosage of LMWH (type of LMWH according to the hospitals preference) once daily for 8 days post-operatively versus no treatment. The first dose was administered post-operatively on the day of surgery before discharge on the same day. Nadroparin 2850 IU subcutaneous or dalteparin 2500 IU subcutaneous was used for patients weighing less than 100kg, whereas patients over 100kg received a double dose.

Patients received an information leaflet for signs and symptoms of VTE and were advised to seek medical care if such symptoms arose. Follow-up started from the day of the procedure and the total duration was 3 months as after this period the risk is back to baseline.1 Digital (online) or postal questionnaires on study outcomes, study compliance and on study medication adherence were sent 2 and 6 weeks after start of follow-up. Additionally, all patients were contacted by telephone after 3 months and asked whether any study outcome had occurred, i.e., if they had undergone examination for a suspected VTE, whether any hospital visits had taken place and whether they had adhered to the assigned treatment. The patients were also requested to complete a questionnaire on risk factors for VTE and hemorrhage. In case of no response, patients' general practitioners were contacted to determine if any study outcome or death had occurred. For all unresponsive patients the vital status was acquired from the Dutch population register. Detailed information on study outcomes was collected from patients' electronic hospital files and radiology reports. Data were centrally collected in an online database management system.[9]

Randomization and blinding

Eligible patients were randomly allocated to the study arms in a 1:1 ratio. Block randomization with variable block sizes was used. The randomization was performed centrally (using Promise) by the data-management of the study.[9] To ensure concealment of treatment allocation the data management and researchers were unaware of the allocation scheme and block sizes. Randomization was stratified according to study center. Patients and caregivers were not blinded for the allocated treatment.

Study outcomes

The primary outcome was the occurrence of symptomatic venous thromboembolism, i.e. deep vein thrombosis, or pulmonary embolism. The primary safety outcome was the incidence of major bleeding.[10] Other clinically relevant non major bleeds (CRNMB) were considered as a secondary outcome (related to contact with a physician) and all other bleeds were registered as minor. All possible outcomes were evaluated and assessed by a blinded and independent outcome adjudication committee. All outcome definitions can be found in the Supplementary Appendix.

Sample size

We assumed an incidence of symptomatic VTE in the absence of treatment of 2% as the basis of our sample size calculations.[11,12] Based on a risk reduction of 85%[11], we calculated a sample size of 625 subjects in each arm (alpha 0.05, power 80%, two sided). To account for a maximum drop-out rate of 15%, we aimed to include 750 patients in each study arm. For our primary safety outcome, we assumed a risk of major bleeding of 0.3% which allowed us to determine an upper limit of the 95%CI of about 1%.[13-15]

Safety monitoring

A pre-specified interim analysis for safety purposes was planned and reviewed by an independent data safety monitoring board (DSMB) when 50% and 75% of the target number of patients was included. If at interim analysis the intervention would prove to be clearly contraindicated by means of an increased risk of major bleeding (upper limit of the 95%CI >1%), we considered to terminate the study prematurely.

Statistical analysis

All analyses followed the pre-specified plan as described in the study protocol. Baseline characteristics were summarized as means with standard deviations (SD) or proportions as appropriate. Data on outcome events were analyzed by the intention-to-treat principle, excluding patients who were inadvertently randomized since they had not met in-or exclusion criteria. For the primary outcome, cumulative incidences with 95% Confidence Intervals (CI) based on the binomial distribution in both groups for symptomatic VTE were estimated and compared by means of relative risks (RR) and risk differences (RD) with their 95%CIs. Similar analyses were performed for the safety outcomes. In a per-protocol analysis we included only those individuals who had adhered to the study protocol. Analyses were performed in IBM SPSS Statistics for Windows, version 23 and in Stata, version 14 SE.

Results

Study population

From May 2012 to January 2016, 6413 patients were screened for eligibility of whom 1543 were included at eight centers in The Netherlands (Figure 1). Of these randomized patients, 773 were allocated to LMWH therapy and 770 to no therapy. In total 30 patients were excluded after randomization because the original in- or exclusion criteria

turned out not to have been met (e.g., surgery cancellation, n=14). Of the remaining participants, 37 withdrew consent and 25 could not be reached for occurrence of an outcome event (vital status available), leading to a total of 731 patients allocated to LMWH versus 720 to no treatment who were included in the intention-to-treat analysis. Baseline characteristics were similar between groups (Table 1). 55.8% of all participants were men and mean age was 48.5 (SD 12.5) years. Most patients were classified as American Society of Anesthesiologists Class I (61.1%) and about half received general anesthesia (Table 2). The majority of patients underwent a meniscectomy (1118, 77%), followed by diagnostic arthroscopy (114, 8%). 340 (23%) other procedures were performed (multiple interventions possible, see Supplementary Appendix).

Table 1. *Characteristics of study population*

Patient characteristics §	**LMWH treatment* (n=731)**	**No treatment (n=720)**
Male sex, n (%)	414 (56.6)	396 (55.0)
Mean age ±SD, years	48.1±12.8	49.1±12.3
Mean BMI, kg/m^2 †	27.1±3.9	26.8±4.0
ASA classification‡		
ASA 1, n (%)	438 (63.3)	449 (62.4)
ASA 2, n (%)	248 (35.8)	236 (32.8)
ASA 3, n (%)	6 (0.9)	4 (0.6)
Smoking, n (%)		
Current	131 (18.3)	140 (19.8)
Ever	247 (34.5)	244 (34.6)
Contraceptives use, n (% of women)¶	94 (30.5)	83 (25.9)
Paid employment (%)	559 (78.5)	534 (75.4)
Cancer		
Within last year	6 (0.8)	6 (0.8)
More than 1 year ago	27 (3.8)	23 (3.3)
Family history of VTE (1st degree), n (%)	82 (11.5)	87 (12.3)

***** *Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

† *BMI: body mass index in kg/m^2*

‡ *ASA classification: American Society of Anesthesiologists physical status classification system*

¶ *Any hormonal contraceptive us, e.g., oral contraceptives, intra-uterine devices.*

§ *Data were missing for the following characteristics: BMI in 28 patients, ASA Classification in 70 patients, Smoking in 29 patients, Oral contraceptives use in 13 patients, Paid employment in 31 patients, Cancer in 30 patients, Family history of VTE in 31 patients.*

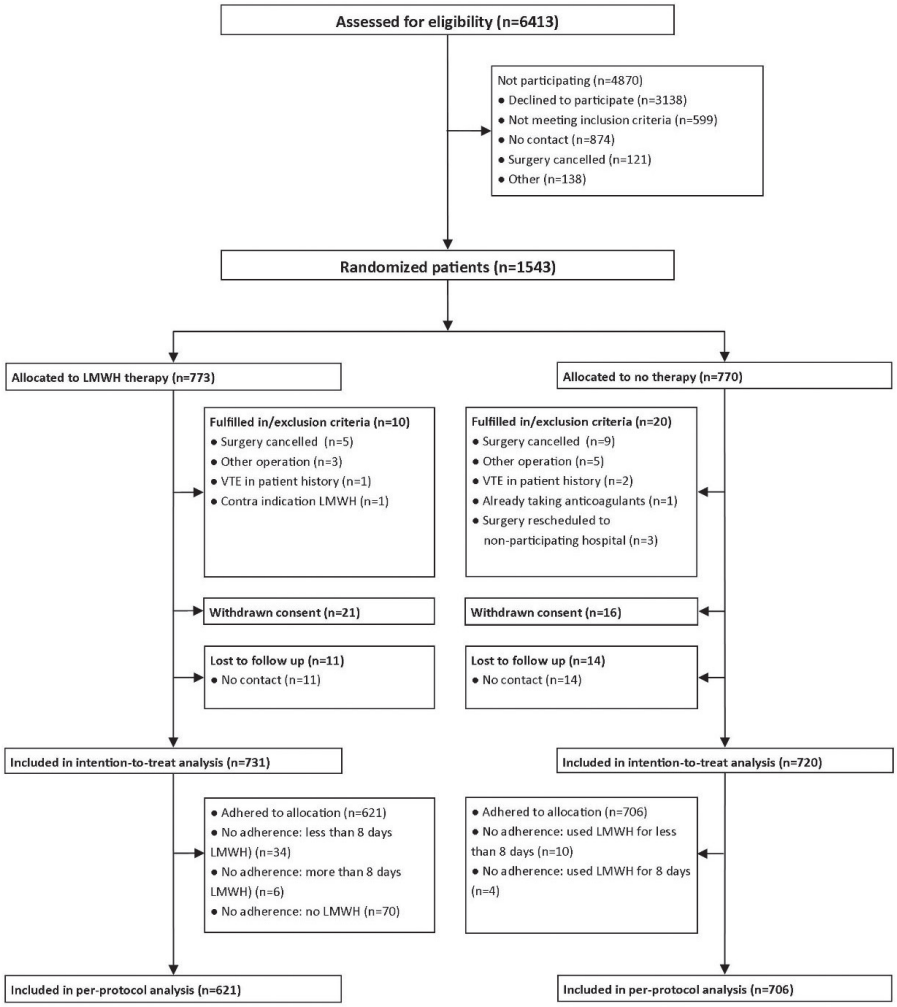

Figure 1. *Flow chart of patients*

Figure legend: Flow chart of patients enrolled, randomized and included in the intention-to-treat and per-protocol analysis.

Table 2. *Surgery details*

Surgery details §	LMWH* (n=731)	No treatment (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 (50.6)	345 (48.7)
Spinal, n(%)	353 (49.3)	363 (51.2)
Epidural	1 (0.1)	1 (0.1)
Procedure: †		
Meniscectomy, n (%)	562 (76.9)	556 (77.2)
Removal of loose bodies, n(%)	41 (5.6)	36 (5.0)
Diagnostic arthroscopy, n (%)	56 (7.7)	58 (8.1)
Other‡, n (%)	168 (23.0)	172 (23.9)
Tourniquet use, yes (%)	688 (97.9)	673 (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.*

§ *Data were missing for the following characteristics: Duration Operation and Surgery in 97 patients, Anesthesia in 26 patients, Tourniquet use in 60 patients.*

Effectiveness

Among patients randomized in the LMWH group, the primary outcome was suspected 12/731 times, out of which 4 DVTs and 1 PE were confirmed. In the no treatment group, 11/720 patients were investigated for VTE of whom 2 patients were diagnosed with DVT and 1 with PE. In the intention-to treat analysis, the cumulative incidence of VTE within 3 months was 0.7% (95%CI 0.2 to 1.6) in the LMWH and 0.4% (95%CI 0.1 to 1.2) in the no therapy group. This resulted in a RR for VTE of 1.6 (95%CI 0.4 to 6.8) for LMWH vs no treatment (RD 0.3%, 95%CI -0.5 to 1.0) (Table 3).

Table 3. *Primary outcomes, Intention-to-treat analysis†*

Outcome	LMWH* (n=731), n (%, 95%CI)	No treatment (n=720), n (%; 95%CI)	RR (95%CI)	RD (95%CI), percentage points
Primary outcome				
DVT	4 (0.5, 0.1 - 1.4)	2 (0.3, 0.0 - 1.0)	2.0 (0.4 - 10.7)	0.3 (-0.4 - 0.9)
PE	1 (0.1, 0.0 -0.8)	1 (0.1, 0.0 - 0.8)	1.0 (0.1 - 15.7)	0.0 (-0.4 - 0.4)
DVT and PE	0 (-)	0 (-)	-	-
Total	5 (0.7, 0.2 -1.6)	3 (0.4, 0.1 - 1.2)	1.6 (0.4 - 6.8)	0.3 (-0.5 - 1.0)
Primary safety outcome				
Major bleeding	1 (0.1, 0.0 - 0.8)	1 (0.1, 0.0 - 0.8)	1.0 (0.1 - 15.7)	0.0 (-0.4 - 0.4)
Secondary safety outcome				
Relevant minor bleeding	1 (0.1, 0.0 - 0.8)	3 (0.4, 0.1 - 1.2)	0.3 (0.0 - 3.1)	-0.3 (-0.8 - 0.3)

***** *Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

† DVT denotes Deep Vein Thrombosis, PE denotes Pulmonary Embolism, CI denotes Confidence Interval, RR denotes Relative Risk, RD denotes Risk Difference

In the per-protocol analysis, 621/731 (85%) patients allocated to LMWH followed the study protocol compared with 706/720 (98%) patients who were allocated to the no treatment group (Figure 1). Here, VTE was confirmed in 4/621 (0.6%) patients using LMWH as compared with 3/706 (0.4%) patients in the no therapy group (RR 1.5, 95%CI 0.3 to 6.7) (Table 4). The 8th VTE case, who was assigned to LMWH, did not take LMWH but a regimen of 80mg carbasalate calcium for one week instead.

Table 4. *Primary outcomes, per-protocol analysis†*

Outcome	LMWH*(n=621), n (%; 95%CI)	No treatment (n=706), n (%; 95%CI)	RR (95%CI)	RD (95%CI), percentage points
Primary efficacy outcome				
DVT	4 (0.6, 0.2 - 1.6)	2 (0.3, 0.0 - 1.0)	2.3 (0.4 - 12.4)	0.4 (-0.4 - 1.1)
PE	0 (-)	1 (0.1, 0.0 - 0.8)	∞	-0.1 (-0.4 - 0.1)
DVT and PE	0 (-)	0 (-)	-	-
Total	4 (0.6, 0.2 - 1.6)	3 (0.4, 0.1 - 1.2)	1.5 (0.3 - 6.7)	0.2 (-0.6 - 1.0)
Primary safety outcome				
Major bleeding	1 (0.2, 0.0 - 0.9)	1 (0.1, 0.0 - 0.8)	1.1 (0.1 - 18.1)	0.0 (-0.4 - 0.4)
Secondary safety outcome				
Minor bleeding	1 (0.2, 0.0 - 0.9)	3 (0.4, 0.1 - 1.2)	0.4 (0.0 - 3.6)	-0.3 (-0.8 - 0.3)

***** *Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

† *DVT denotes Deep Vein Thrombosis, PE denotes Pulmonary Embolism, CI denotes Confidence Interval, RR denotes Relative Risk, RD denotes Risk Difference*

Safety outcome

Two major bleedings occurred during the study (Table 3). One patient (1/731; 0.1%) assigned to LMWH developed a hemarthrosis (knee) and one patient assigned to no treatment (1/720; 0.1%) developed a surgical site bleeding two days post-operatively requiring re-intervention (RR 1.0, 95%CI 0.1 to 15.7). A CRNMB occurred in 1/731 (0.1%) patients and in 3/720 (0.4%) patients in the treated and non-treated group respectively (RR 0.3, 95%CI 0.0 - 3.1). Minor bleeding occurred in 71/731 (9.7%) and in 43/720 (6.0%) patients in the treated and non-treated group respectively (Supplementary Appendix). No patients died within the follow-up period (also confirmed for all patients who were lost to follow-up).

Discussion

We found no beneficial effect of thromboprophylaxis (8 days LMWH post-operatively) on the prevention of symptomatic VTE after knee arthroscopy. In both groups one major bleeding occurred, demonstrating an overall neutral risk-benefit ratio for treatment with LMWH in patients undergoing knee arthroscopy.

These results contradict previous findings from a meta-analysis on four small RCTs (included numbers: 36, 130, 122, 239) that suggested a beneficial effect on symptomatic VTE, with a pooled RR for LMWH vs no treatment of 0.42 (95%CI 0.06 – 3.14).[11] In a larger trial, where LMWH for 7 days was compared with use of compression stockings, including about 650 subjects in each arm, four symptomatic thrombotic events were detected in the LMWH group (0.6%) as compared with 14 in the control group (2.1%) [RR 0.3, 95%CI 0.1-0.9].[12] More recently, the same group compared rivaroxaban with placebo in 241 randomized patients and found incidences of 0.8% and 6.1% in the treated and untreated groups respectively.[16] However, in both trials all participants were subjected to ultrasonographic screening for VTE at which time questions were asked about possible signs and symptoms. This clearly does not reflect identification of VTE in general clinical practice, and has therefore led to overestimation of the incidences.[17] Due to the these limitations, the need for stronger evidence has been expressed in several reviews and guidelines.[6,11,18]

Strengths of the POT-KAST trial are the pragmatic design in which two treatment strategies were compared, with conditions set to approximate general clinical practice as much as possible. Furthermore, although this was an open label trial, a blinded outcome adjudication committee classified all events. Lastly, the completeness of follow-up was high (98%) and few patients withdrew consent (2%).

Limitations that may explain our negative findings are firstly limited power due to the incidence of symptomatic VTE that was lower than expected, i.e. 0.6%. This low incidence is in line with recent observational studies that reported a cumulative incidence of 0.3% (95%CI 0.3-0.5) for VTE within 3 months and 0.4% (95% CI, 0.2–0.5) within 6 weeks, where in both studies the vast majority of patients did not receive any form of anticoagulants.[19,20] Furthermore, a meta-analysis showed a pooled incidence for VTE of 0.6% (95%CI 0.3-1.1) in 571.793 arthroscopic meniscectomy procedures.[21] In contrast, in the randomized trials performed on this topic much higher incidences of 0.9% (95%CI

0.3-2.1) up to 5.3% (95%CI 2.4-11.0) have been reported, on which figures our samples size calculations have been based.[6,11,12] The lower risks from the more recent studies can possibly be attributed to introduction of fast-track mobilization programs directly after surgery instead of bedrest for a couple of days.[22,23] If we assume, based on our own data and that of the recent observational studies, that the true incidence is indeed close to 0.6%, such low incidence supports futility of prophylactic treatment with anticoagulants as the number needed to treat would be huge whatever the effect of anticoagulant therapy. Furthermore, in this situation the harms introduced by anticoagulant treatment will likely outweigh its benefits when we consider the incidence of minor bleedings (9.7% vs 6.0%) as well as the costs accompanying pharmacological treatment. A second possible explanation for our null result could be treatment compliance. Seventy patients (9.6%) allocated to LMWH did not use this therapy and 34 (4.7%) patients used LMWH for less than the full eight days. Yet, these figures represent daily practice situations,[24] which the study was designed to show (instead of pure drug efficacy). Moreover, the per-protocol analysis showed similar results as the intention-to-treat analysis. Another explanation for our findings might have been the nonblinded study design. For example, patients not randomized to LMWH could have contacted their physician earlier in case of signs and symptoms of VTE. However, a VTE was suspected at the same rate in both groups. Besides, non-blinding again reflects the general practice situation, where in 'real life' patients may also contact their doctor differently depending on their type of treatment. Lastly, the lack of effect may have been due to dosage, duration or type of anticoagulant treatment: the prophylactic dose of 2850 I.E. might have been too low, despite it being the standard dose for thromboprophylaxis. Raising this dosage implies a higher bleeding risk, thereby resulting in a lower number needed to harm, which would outweigh the number needed to treat. All events occurred after the treatment period of eight days. This might indicate a need for longer treatment, although this was opposed in an earlier trial that reported an increased bleeding risk and no additional benefit for 14 versus 7 days of treatment.[12] Finally, it may be argued that use of a Direct Oral Anticoagulant (DOAC) would have led to different results. A recent meta-analysis including 5 randomized trials where DOACs were compared with LMWH in patients who received thrombosis prophylaxis after hip or knee surgery showed no difference in efficacy, which makes it unlikely that DOAC use would have led to different conclusions in our study.[25] Furthermore, even if DOACs would be effective, the number needed to treat would still be too large to justify this treatment in all patients. A final possible limitation is that patients who declined to participate could have been different with

respect to thrombosis risk from those who did participate. However, they were of similar age and sex as included patients, indicating no major differences.

Currently, the ACCP guidelines cautiously suggest no thromboprophylaxis in patients undergoing knee arthroscopy without a history of VTE and that screening for asymptomatic VTE should be avoided. We agree that this guideline should be followed in all patients without a history of VTE. In an earlier study we demonstrated that in patients who develop VTE after knee arthroscopy, several other risk factors for VTE were present.[1] We therefore believe there might be an indication for identifying high risk patients to tailor individualized thromboprophylactic strategies. For those patients at high risk for VTE, higher dosage and/or longer treatment might be warranted, while in all others treatment can be safely withheld. This should obviously be the topic of further study.

In conclusion, a prophylactic regimen of LMWH therapy for eight days is not effective for the prevention of VTE in patients undergoing knee arthroscopy. Clinicians should not routinely prescribe thromboprophylaxis in these patients.

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Supplementary appendix

Participating study centers (all located in the Netherlands)

Alrijne Hospital, Leiderdorp
Groene Hart Hospital, Gouda
Haga Hospital, The Hague
Isala Hospital, Zwolle
Medical Center Haaglanden Hospital, The Hague
Orthopedium Clinic, Delft
Park Medical Center, Rotterdam
Reinier de Graaf Hospital, Delft

Primary and Secondary Outcome definitions

Primary study outcomes

The primary efficacy outcome is symptomatic venous thrombosis, i.e., deep venous thrombosis (DVT) or fatal or non-fatal pulmonary embolism (PE).

The following definitions are applied to confirm a suspected episode of symptomatic PE/DVT:

1. DVT: abnormal compression ultrasound
2. PE: an intraluminal filling defect in segmental or more proximal branches on spiral CT scan or a perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan or detected at autopsy.

The primary safety outcome is major bleeding, defined according to the guidelines of the ISTH[1]:

a) fatal bleeding, or
b) symptomatic bleeding in a critical area or organ, or
c) extra surgical site bleeding causing a fall in hemoglobin level of 1.24 mmol/L (2.0 g/dl) or more, or leading to transfusion of one or more units of whole blood or red cells, or
d) surgical site bleeding that requires a second intervention or a hemarthrosis interfering with rehabilitation, or surgical site bleeding that needs blood transfusion.

Secondary study outcomes

Other clinically relevant bleeding, defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, (temporary) cessation of study treatment, or associated with discomfort such as pain, or impairment of activities of daily life.

[1] Schulman S, Angeras 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(1):202-204.

Table. *Full list of other interventions during knee arthroscopy*

Interventions*	**Total no.**
Debridement (e.g. shaving cartilage, scar tissue)	180
Meniscal suture	24
Micro fracturing, drilling	19
Excision cyclops lesion	32
Partial synovectomy	22
Debridement synovitis	9
Needling meniscus	1
Biopsy	2
Knee arthroscopy both knees	1
Resection Cyst	21
Simple arthrotomy	2
Split or resection plica	21
Other	6

**Some patients had multiple interventions during surgery*

Table. *POT-KAST - Location of thrombotic event*

Study center	LMWH Total no.	No treatment Total no.	Total no.
Pulmonary Embolism			
Peripheral			
Central			
Multiple	1	1	2
Deep Vein Thrombosis			
Proximal	2	2	4
Distal	2		2

Table. *POT-KAST - List of bleedings events*

Bleeding type	LMWH Total no.	No therapy Total no.
Major bleeding †		
Surgical site bleeding, 2 days post-operative needing re-intervention		1
Hemarthrosis operated knee	1	
Total	1	1
Clinically relevant bleeding ‡		
Hematoma knee after fall on knee		1
Hematoma knee		2
Rectal bleeding	1	
Total	1	3

Table. *POT-KAST - List of bleedings events (continued)*

Bleeding type	LMWH Total no.	No therapy Total no.
Minor bleeding §		
Knee	8	1
Rectal bleeding	1	4
Menstruation (heavier than normal)	2	1
Throat	1	0
Anal bleeding	2	0
Head, arm	2	1
Leg, foot	1	0
Unknown	1	1
Total	18	7
Nose bleeding §	25	17
Hematoma >3cm §	26	15
Spontaneous hematoma >3cm*	17	8
Hematoma on head or trunk >3cm*	10	4
Grand Total	71	43

† *defined according to the ISTH guidelines (JTH 2010;8:202-4)*

‡ *defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, (temporary) cessation of study treatment, or associated with discomfort such as pain, or impairment of activities of daily life.*

§ *defined as other bleeding not meeting the criteria for major or clinically relevant bleeding, no contact with a physician.*

**Does not add up as patients could have both conditions.*