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Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting

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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.)

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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 orthopedic 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 orthopedic 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]

A Quick Take is available at NEJM.org

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 data-management 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.

Safety Outcomes

Two patients had major bleeding (Table 3): 1 patient (0.1%) in the treatment group had hemar-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	POT-KAST Trial		POT-CAST Trial	
	Treatment Group (N=731)	Control Group (N=720)	Treatment Group (N=719)	Control Group (N=716)
Male sex — no./total no. (%)	414/731 (56.6)	396/720 (55.0)	347/719 (48.3)	369/716 (51.5)
Age — yr	48.1±12.8	49.1±12.3	46.5±16.5	45.6±16.4
Body-mass index†	27.1±3.9	26.8±4.0	26.0±4.4	25.7±4.4
Obesity — no./total no. (%)†	163/717 (22.7)	137/710 (19.3)	113/665 (17.0)	91/670 (13.6)
American Society of Anesthesiologists classification — no./total no. (%)‡				
I	438/692 (63.3)	449/689 (65.2)		
II	248/692 (35.8)	236/689 (34.3)		
III	6/692 (0.9)	4/689 (0.6)		
Smoking — no./total no. (%)				
Current	131/716 (18.3)	140/706 (19.8)	173/663 (26.1)	178/665 (26.8)
Previous	247/716 (34.5)	244/706 (34.6)	188/665 (28.3)	178/665 (26.8)
Contraceptive use — no./total no. of women (%)§	94/308 (30.5)	83/320 (25.9)	86/348 (24.7)	69/326 (21.2)
Paid employment — no./total no. (%)	559/712 (78.5)	534/708 (75.4)	442/664 (66.6)	469/669 (70.1)
Cancer — no./total no. (%)¶				
≤1 yr before enrollment	6/714 (0.8)	6/707 (0.8)	8/674 (1.2)	9/674 (1.3)
>1 yr before enrollment	27/714 (3.8)	23/707 (3.3)	26/674 (3.9)	20/674 (3.0)
History of venous thromboembolism in first-degree relatives — no./total no. (%)	82/713 (11.5)	87/707 (12.3)	60/564 (10.6)	52/555 (9.4)

* Plus–minus values are means ±SD. The POT-KAST trial included patients who underwent knee arthroscopy, and the POT-CAST trial included patients who were treated with casting of the lower leg. The treatment groups were assigned to receive low-molecular-weight heparin (nadroparin or dalteparin). There were no statistically significant differences in baseline characteristics between the treatment and control groups in each trial.

† The body-mass index is the weight in kilograms divided by the square of the height in meters. A body-mass index of 30 or higher indicates obesity. In the POT-KAST trial, data are missing for 14 patients in the treatment group and 10 patients in the control group. In the POT-CAST trial, data are missing for 54 patients in the treatment group and 46 patients in the control group.

‡ An American Society of Anesthesiologists physical status classification of I indicates no disease, II mild systemic disease, and III severe systemic disease.

§ Contraceptive use includes the use of any hormonal contraceptive, including oral contraceptives and intrauterine devices.

¶ Nonmelanoma skin cancers are not included.

throsis 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.

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

Outcome	Treatment Group† (N=731)	Control Group (N=720)
Total duration — min‡	26±11	26±11
Duration of the surgery — min§	16±8	15±8
Type of anesthesia — no./total no. (%)		
General	362/716 (50.6)	345/709 (48.7)
Spinal	353/716 (49.3)	363/709 (51.2)
Epidural	1/716 (0.1)	1/709 (0.1)
Procedure — no./total no. (%)¶		
Meniscectomy	562/731 (76.9)	556/720 (77.2)
Removal of loose bodies	41/731 (5.6)	36/720 (5.0)
Diagnostic arthroscopy	56/731 (7.7)	58/720 (8.1)
Other	168/731 (23.0)	172/720 (23.9)
Tourniquet use — no./total no. (%)	688/703 (97.9)	673/688 (97.8)

* Plus–minus values are means ±SD.
† The treatment group was assigned to receive low-molecular-weight heparin (nadroparin or dalteparin).
‡ The total duration was from the time the patient began receiving anesthesia to the time the patient left the operating room. Data are missing for 189 patients in the treatment group and 188 patients in the control group.
§ The duration of the surgery was from the time of incision to the time of wound closure. Data are missing for 94 patients in the treatment group and 83 patients in the control group.
¶ The percentages do not sum to 100% because some patients had multiple interventions. A full list of other interventions is provided in the Supplementary Appendix.

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.

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).

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 se-

Table 3. Primary and Secondary Outcomes in the Intention-to-Treat Population.*

Outcome	POT-KAST Trial						POT-CAST Trial					
	Treatment Group (N=731)		Control Group (N=720)		Relative Risk (95% CI)	Absolute Difference in Risk (95% CI)	Treatment Group (N=719)		Control Group (N=716)		Relative Risk (95% CI)	Absolute Difference in Risk (95% CI)
	no. of patients	*% (95% CI)*	*no. of patients*	*% (95% CI)*		*percentage points*	*no. of patients*	*% (95% CI)*	*no. of patients*	*% (95% CI)*		*percentage points*
Primary outcome: thromboembolism	5	0.7 (0.2 to 1.6)	3	0.4 (0.1 to 1.2)	1.6 (0.4 to 6.8)	0.3 (−0.6 to 1.2)	10	1.4 (0.7 to 2.5)	13	1.8 (1.0 to 3.1)	0.8 (0.3 to 1.7)	−0.4 (−1.8 to 1.0)
Deep-vein thrombosis	4	0.5 (0.1 to 1.4)	2	0.3 (0 to 1.0)		0.3 (−0.5 to 1.1)	6	0.8 (0.3 to 1.8)	8	1.1 (0.5 to 2.2)		−0.3 (−1.5 to 0.8)
Pulmonary embolism	1	0.1 (0 to 0.8)	1	0.1 (0 to 0.8)		0 (−0.6 to 0.7)	3	0.4 (0.1 to 1.2)	4	0.6 (0.2 to 1.4)		−0.1 (−1.1 to 0.7)
Deep-vein thrombosis and pulmonary embolism	0	0 (0 to 0.5)	0	0 (0 to 0.5)		0 (−0.5 to 0.5)	1	0.1 (0 to 0.8)	1	0.1 (0 to 0.8)		0 (−0.7 to 0.7)
Primary safety outcome: major bleeding	1	0.1 (0 to 0.8)	1	0.1 (0 to 0.8)	1.0 (0.1 to 15.7)	0 (−0.6 to 0.7)	0	0 (0 to 0.5)	0	0 (0 to 0.5)	—	0 (−0.5 to 0.5)
Secondary safety outcome: clinically relevant nonmajor bleeding	1	0.1 (0 to 0.8)	3	0.4 (0.1 to 1.2)	0.3 (0 to 3.1)	−0.3 (−1.1 to 0.4)	1	0.1 (0 to 0.8)	0	0 (0 to 0.5)	—	0.1 (−0.4 to 0.8)

* The POT-KAST trial included patients who underwent knee arthroscopy, and the POT-CAST trial included patients who were treated with casting of the lower leg. The treatment groups were assigned to receive low-molecular-weight heparin (nadroparin or dalteparin).

Table 4. Primary and Secondary Outcomes in the Per-Protocol Population.*

Outcome	POT-KAST Trial					POT-CAST Trial				
	Treatment Group (N=621)		Control Group (N=706)	Relative Risk (95% CI)	Absolute Difference in Risk (95% CI)	Treatment Group (N=626)		Control Group (N=662)	Relative Risk (95% CI)	Absolute Difference in Risk (95% CI)
	no. of patients	*% (95% CI)*	*no. of patients*	*% (95% CI)*	*percentage points*	*no. of patients*	*% (95% CI)*	*no. of patients*	*% (95% CI)*	*percentage points*
Primary outcome: thromboembolism	4	0.6 (0.2 to 1.6)	3	0.4 (0.1 to 1.2)	1.5 (0.3 to 6.7)	0.2 (−0.7 to 1.3)	10	1.6 (0.8 to 2.9)	12	1.8 (0.9 to 3.1)	0.9 (0.4 to 2.0)	−0.2 (−1.8 to 1.3)
Deep-vein thrombosis	4	0.6 (0.2 to 1.6)	2	0.3 (0 to 1.0)		0.4 (−0.5 to 1.4)	6	1.0 (0.4 to 2.1)	7	1.1 (0.4 to 2.2)		−0.1 (−1.3 to 1.1)
Pulmonary embolism	0	0 (0 to 0.6)	1	0.1 (0 to 0.8)		−0.1 (−0.8 to 0.5)	3	0.5 (0.1 to 1.4)	4	0.6 (0.2 to 1.5)		−0.1 (−1.1 to 0.9)
Deep-vein thrombosis and pulmonary embolism	0	0 (0 to 0.6)	0	0 (0 to 0.5)		0 (−0.5 to 0.6)	1	0.2 (0 to 0.9)	1	0.2 (0 to 0.8)		0 (−0.7 to 0.8)
Primary safety outcome: major bleeding	1	0.2 (0 to 0.9)	1	0.1 (0 to 0.8)	1.1 (0.1 to 18.1)	0 (−0.7 to 0.8)	0	0 (0 to 0.6)	0	0 (0 to 0.6)	—	0 (−0.6 to 0.6)
Secondary safety outcome: clinically relevant nonmajor bleeding	1	0.2 (0 to 0.9)	3	0.4 (0.1 to 1.2)	0.4 (0 to 3.6)	−0.3 (−1.1 to 0.5)	1	0.1 (0 to 0.9)	0	0 (0 to 0.6)	—	0.2 (−0.2 to 0.5)

* The POT-KAST trial included patients who underwent knee arthroscopy, and the POT-CAST trial included patients who were treated with casting of the lower leg. The treatment groups were assigned to receive low-molecular-weight heparin (nadroparin or dalteparin).

vere methodologic weaknesses, such as high rates of loss 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

Table 5. Casting Outcomes in the POT-CAST Trial.*

Outcome	Treatment Group† (N=719)	Control Group (N=716)
Duration of casting — wk	4.9±2.5	4.9±2.5
Indication for casting — no./total no. (%)		
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 gait	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)
Type of primary fracture — no./total no. with fracture (%)		
Ankle	255/648 (39.4)	242/631 (38.4)
Infrasyndesmotic	60/229 (26.2)	44/217 (20.3)
Transsyndesmotic	126/229 (55.0)	130/217 (59.9)
Suprasyndesmotic	29/229 (12.7)	29/217 (13.4)
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 — no./total no. (%)	53/648 (8.2)	52/631 (8.2)
Surgery — no./total no. (%)	91/719 (12.7)	79/716 (11.0)
Total duration — min‡	75.2±32.2	78.5±27.4
Duration of the surgery — min§	50.2±28.2	50.9±21.7

* Plus–minus values are means ±SD.
† The treatment group was assigned to receive low-molecular-weight heparin (nadroparin or dalteparin).
‡ The total duration 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 the 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.

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 orthopedic 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.

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