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

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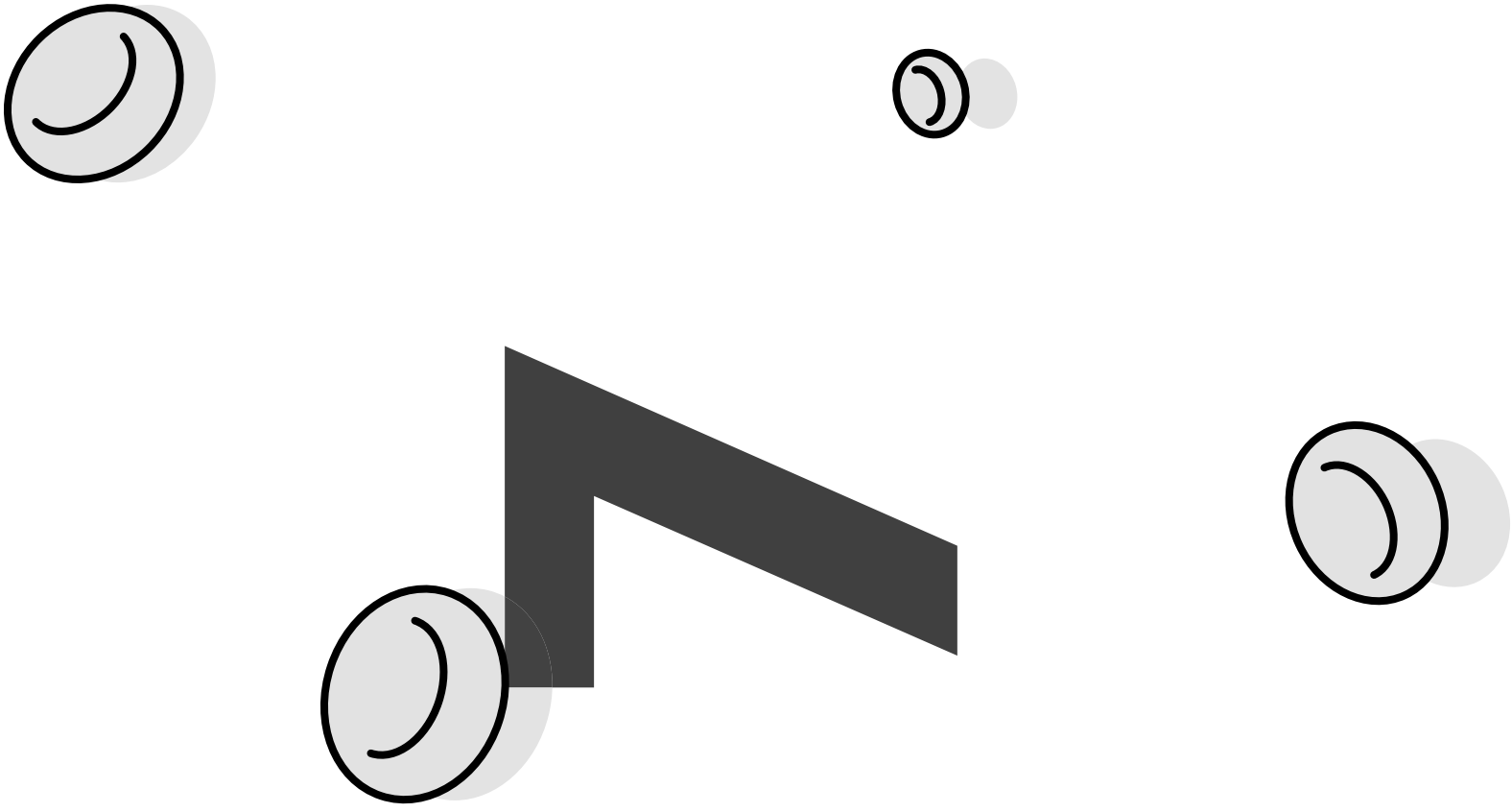
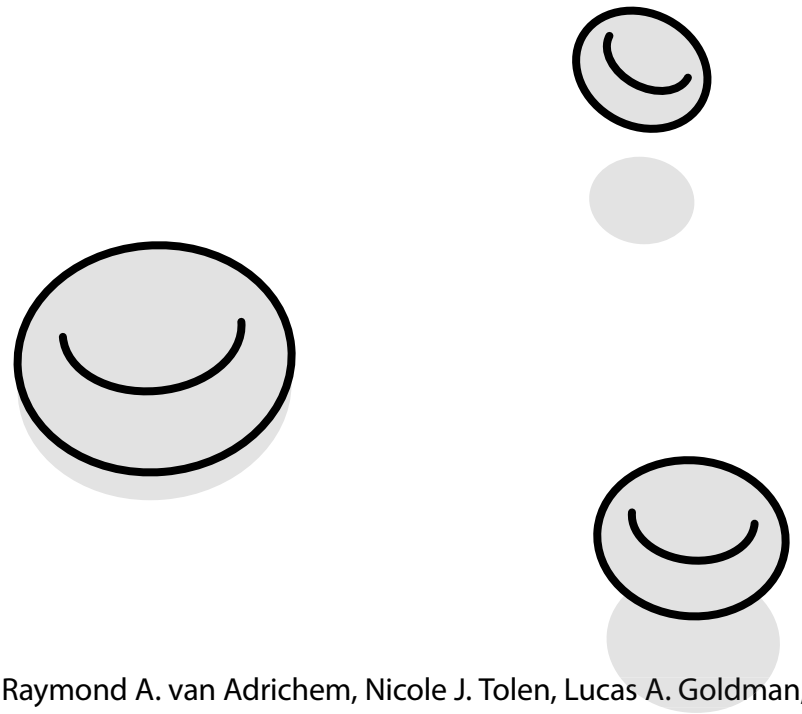


CHAPTER

Venous thromboembolism prevention after anterior cruciate ligament reconstruction: compression stocking with and without low molecular weight heparin



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Abstract

Background

Evidence on the effectiveness of thromboprophylaxis in patients with anterior cruciate ligament reconstruction (ACL) is limited. Aim of this study was to establish the effect of low molecular weight heparin (LMWH) in addition to compression stockings after ACL reconstruction on venous thromboembolism (VTE) prevention.

Methods

Patients with ACL reconstruction between April 2011 and June 2013 in center A (compression stocking; n=441) and center B (compression stocking plus LMWH; n=936) were analyzed for the occurrence of VTE and bleeding events within three months. The clinics are located in the same geographical region and apply the same treatment protocol except for VTE prophylaxis. This observational design (e.g. an instrumental variable analysis) mimics a randomized trial. Cumulative incidences and risk differences (RD) with 95% confidence intervals (95CI) were calculated.

Results

One patient in center A (0.23%(95CI;0.01–1.41)) and four patients in center B (0.43%(95CI;0.12–1.14)) developed VTE, resulting in a RD of 0.20% (95CI;-0.41–0.81). In center A, five patients had a bleeding event (1.13%(95CI;0.41–2.71)) as did six patients in center B (0.64%(95CI;0.26–1.43)) resulting in a RD of -0.49% (95CI;-1.61–0.62).

Conclusion

Incidences of VTE and bleeding were low in both centers. No effect of routine LMWH could be demonstrated on the prevention of VTE after ACL reconstruction in addition to prophylaxis with compression stockings. Considering the burden from treatment with LMWH, routine treatment with LMWH after ACL reconstruction in addition to a compression stocking should not be recommended.

Introduction

Venous thromboembolism (VTE; the composite of deep vein thrombosis and pulmonary embolism) is a major public health problem.[1,2] A major risk factor for VTE is orthopedic surgery. Hence, thromboprophylaxis is recommended for most orthopedic procedures.[3-5] However, for knee arthroscopy, guidelines recommend not to use routine thromboprophylaxis, based on several small trials with a low incidence of symptomatic VTE in control groups.[3,4, 6-12] A recently published much larger trial confirmed this recommendation for regular knee arthroscopy.[13]

Since arthroscopic assisted ACL reconstruction is a more invasive procedure and has longer duration of surgery, the risk of VTE is estimated to be higher (i.e. 4% in 8 weeks).[14,15] The benefits of anticoagulant treatment may therefore outweigh the risk of postoperative bleeding as well as the burden for these patients. However, only two trials aimed to evaluate the effect of thromboprophylaxis after ACL reconstruction but they included small study populations (36 and 175 patients).[7,8] In addition, the later trial all focusses on short course vs extended prophylaxis.[8]In two other trials, patients with ACL reconstruction were included as a subset of patients with arthroscopic knee surgery (15 out of 241 patients and 681 out of 1761 patients), but patients with an ACL reconstruction were not analyzed separately.[6, 12] Furthermore in all studies the primary endpoint was the surrogate endpoint asymptomatic VTE. Unfortunately, the surrogate endpoint asymptomatic VTE is not representative of symptomatic VTE as no constant relationship was demonstrated between asymptomatic and symptomatic events in large VTE prevention trials.[16]

It is therefore currently unclear if thromboprophylaxis effectively reduces the risk of symptomatic VTE in these patients. This has resulted in variation in VTE prophylaxis policies in different centers that perform ACL reconstruction,[17] which variation provides a rare opportunity to study the effect of prophylactic Low Molecular Weight Heparin (LMWH) after ACL reconstruction in an observational setting that closely resembles a randomized trial, i.e., an instrumental variable analysis. An instrumental variable is a factor that affects the type of treatment a patient receives, but is not related to the patient's prognosis. Therefore, it mimics the randomization procedure in a randomized trial.[18-20]

In two clinics in The Netherlands, less than 10km apart, different VTE prophylaxis policies were used: in clinic A, virtually all patients received solely a compression stocking whilst in clinic B, all patients received both a compression stocking plus prophylactic LMWH. Similar patient populations were treated in these clinics, and the ACL reconstruction protocols were identical except for VTE prophylaxis.

In this setting, we aimed to study the effect of pharmacological thromboprophylaxis in addition to prophylaxis with compression stockings after arthroscopically assisted ACL reconstruction on prevention of VTE and the possibility of inducing bleeding events. The results of this study can aid clinicians in decision making on post-operative pharmacological prophylaxis after ACL reconstruction.

Methods

Study population

All patients who had an arthroscopically assisted ACL reconstruction between 1 April 2011 and 1 June 2013 in two clinics for orthopedic surgery (Orthopedium, Delft, the Netherlands, (center A; compression stocking, additional LWMH only in a few high-risk patients) and Medinova Zestienhoven, Rotterdam, the Netherlands, (center B; compression. stocking and LMWH)) were included in this study. The patients were selected using the ACL reconstruction operation code and the ACL rupture diagnosis code in the clinics' database. Only patients with an American Society of Anesthesiologists (ASA) physical status classification score of 1 or 2 were operated in these clinics due to limited intensive care possibilities available. There were no exclusion criteria for this study. Description of the assumptions for an instrumental variable which would allow any difference in occurrence of thromboembolic events between the two centers to be attributed to the difference in pharmacological thromboprophylaxis are described in the supplement. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

Surgery and protocols

All arthroscopically assisted ACL reconstructions were performed in outpatient care. Surgery details and mobilization protocol can be found in the supplement. Clinical follow-up consisted of a visit to the outpatient clinic 14 days, 6 weeks and 3 months post-operatively in both clinics.

Thromboprophylaxis

In center A all patients received a compression stocking (foot to thigh) to wear day and night on the operated leg for six weeks. Post-operative pharmacological thromboprophylaxis was only rarely provided to patients the surgeon believed to be at high risk for VTE (nadroparin 2850 IE once daily <100kg or nadroparin 5700 IE once daily ≥ 100 kg for two weeks). The thromboprophylaxis protocol in center B consisted of a compression stocking (foot to thigh) to wear in the daytime on the operated leg for six weeks plus LMWH once daily for 15 days post-operatively (nadroparin 2850 IE <80 kg once daily or nadroparin 5700 IE ≥ 80 kg once daily).

Data collection

Data were collected from the patient records which consisted of charts, intake forms, anesthesia reports, surgery reports, computer log files and the clinics complication registries. Details on collected data can be found in the supplement.

Endpoints

The primary outcome was symptomatic VTE in the 3 months after ACL reconstruction (confirmed by compression ultrasound or spiral CT pulmonary angiogram). The primary safety outcome was bleeding (major bleeding or other clinically relevant non major bleeding) according to the definition of the International Society of Thrombosis and Haemostasis in the 3 months after the procedure[21]. The secondary safety outcome was surgical site infection (i.e. superficial incisional surgical site infection, deep incisional surgical site infection, organ/ space surgical site infection) according to the definition of the Centers for Disease control and Prevention[22].

Confirmation of events

All patients with a VTE event in the Netherlands were treated in outpatient anticoagulation clinics at the time. To ensure no thrombotic events were missed, our dataset was linked to the records of the anticoagulation clinics to determine if any of the patients from the two clinics had been treated for a VTE event in the three months after surgery.

Sample size

Assuming a 4% VTE risk after ACL reconstruction[8, 14] and a risk reduction of 75% with treatment with low molecular weight heparin[6, 23] a sample size of 424 patients in each

arm would be sufficient (alpha 0.05 and power 80%) in a classic prospective randomized controlled trial (RCT). Considering the similar situation in which the two centers of our instrumental variable analysis resemble the treatment arms of a trial and the difference in treatment received between arms is expected to be close to 100%, the same sample size calculation for an RCT is applicable here too.

Statistical analysis

After completing data collection, data were exported to a SPSS database (IBM SPSS Statistics 20.0, IBM, Armonk, New York, US). From patients with multiple reconstructions during the study period only the first reconstruction was included in the analysis. Demographic and baseline data were summarized as means with standard deviation for normally distributed data, as medians with ranges for skewed distributed data or as proportions for categorical data. Bleeding complications were categorized as major bleeding or other clinically relevant non major bleeding. Surgical site infections were categorized as superficial incisional surgical site infections, deep incisional surgical site infection, organ/space surgical site infections. Cumulative incidences with 95% confidence intervals (95CI) for VTE, bleeding and surgical site infections in the three months after the procedure were estimated for both patient cohorts and compared by estimating the risk difference (RD) and relative risk (RR) with 95%CIs.

Results

Baseline characteristics

Using the diagnosis and operation codes for ACL rupture and reconstruction, a total of 454 procedures were identified in center A (compression stocking) and 969 were identified in center B (compression stocking and LMWH). In total, 441 patients of center A and 936 patients from center B were included in the analysis (see figure 1 for flow chart). The demographics of these patients are shown in table 1.

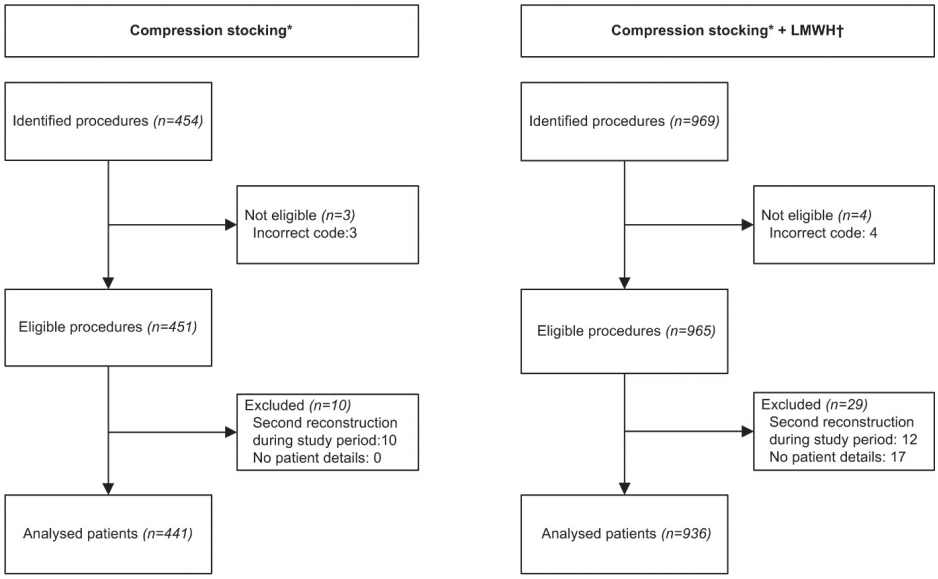

Figure 1. *Flow chart of patients*

Flow chart of patients identified in each clinic and included in the analysis.

**. Compression stocking foot to thigh*

†. Low molecular weight heparin

Table 1. *Characteristics of study population*

Patient characteristics	Compression stocking* (n=441)	Compression stocking* + LMWH†(N=936)
Male sex, n (%)	283 (64.2)	650 (69.4)
Median age, years (range)	29.0 (14.4 – 64.1)	26.9 (14.3 – 60.5)
Mean height, meters (SD)	1.78 (0.09)	1.79 (0.09)
Mean weight, kg (SD)	78.0 (13.0)	77.8 (12.2)
Median BMI‡, kg/m^2 (range)	24.1 (17.0 – 38.6)	24.2 (17.8 – 34.2)
BMI‡≥30, n (%)	24 (5.4)	29 (3.1)
ASA§ classification		
ASA§ 1, n (%)	375 (85.0)	690 (73.7)
ASA§ 2, n (%)	50 (11.3)	246 (26.3)
Left knee¶, n (%)	232 (52.6)	445 (47.5)
Smoking**, n (%)	95 (21.5)	248 (26.5)
Median units smoked daily, n (range)	10 (1 – 40)	10 (1 – 30)
Alcohol use††, n (%)	304 (68.9)	470 (50.2)
Median alcohol units weekly, n (range)	5 (1 – 40)	7 (1 – 28)
Pregnant during operation, n (%)	2 (0.5)	1 (0.1)
Recent surgery‡‡, n (%)	37 (8.4)	27 (2.9)
Non orthopedic surgery§§, n (%)	2 (0.5)	0 (0)
Orthopedic surgery¶¶, n (%)	35 (7.9)	26 (2.8)
Use of anticoagulants***, n (%)	0 (0)	2 (0.2)
Platelet inhibitors, n (%)	3 (0.7)	1 (0.1)
Hormonal replacement therapy	0 (0)	0 (0)
Previous episode of venous thrombosis†††, n (%)	3 (0.7)	14 (1.5)
Family history of venous thrombosis‡‡‡, n (%)	27 (6.1)	14 (1.5)
Orthopedic operation within 3 months after ACL§§§ reconstruction, n (%)	6 (1.4)	7 (0.7)
Comorbidities		
Hypertension, n (%)	17 (3.9)	20 (2.1)
Asthma, n (%)	21 (4.8)	56 (6.0)
DM¶¶¶ 1 or 2, n (%)	4 (0.9)	2 (0.2)
Thyroid disease****, n (%)	5 (1.1)	2 (0.2)
Chronic inflammatory disease††††, n (%)	0 (0.0)	5 (0.5)

Table 1. *Characteristics of study population (continued)*

Patient characteristics	Compression stocking* (n=441)	Compression stocking* + LMWH†(N=936)
Comorbidities (continued)		
Heart disease ‡‡‡‡, n (%)	4 (0.9)	4 (0.4)
TIA§§§§, n (%)	1 (0.2)	0 (0.0)
Malignancy, n (%), n (%)	1 (0.2)	2 (0.2)
Coagulation disorder ¶¶¶¶, n (%)	0 (0.0)	1 (0.0)
Varicose veins, n (%)	0 (0.0)	4 (0.4)
Hemolytic anemia, n (%)	0 (0.0)	1 (0.1)
Other*****, n (%)	22 (5.0)	35 (3.7)

* *Compression stocking foot to thigh*

† *LMWH: Low molecular weight heparin*

‡ *BMI: body mass index in kg/m^2. Of 5 patients in Center A no information on BMI was available.*

§ *ASA classification: American Society of Anesthesiologists physical status classification system. Of 16 patients in Center A the ASA classification could not be retrieved.*

¶ *Of 3 patients in center A the side of operation could not be retrieved*

** *Of 7 patients in center A smoking status could not be retrieved*

†† *Of 7 patients in center A Alcohol use could not be retrieved*

‡‡ *Surgery within 3 months before anterior cruciate ligament reconstruction. Of 7 patients in center A information on recent surgery could not be retrieved*

§§ *Surgery within 3 months before anterior cruciate ligament reconstruction, e.g. colonoscopy, endocervical curettage. Of 5 patients in center A no information on recent non-orthopedic surgery could be retrieved*

¶¶ *Orthopedic surgery within 3 months before anterior cruciate ligament reconstruction. e.g. diagnostic arthroscopy, meniscectomy, meniscal suture, arthroscopic debridement or lavage. Of 2 patients in Center A information on recent orthopedic surgery could not be retrieved*

*** *Of 4 patients in Center A information on the use of anticoagulants could not be retrieved*

††† *Either deep vein thrombosis or pulmonary embolism. Of 4 patients in Center A Information on a previous episode of venous thrombosis could not be retrieved.*

‡‡‡ *Either deep vein thrombosis or pulmonary embolism. Of 7 patients in Center A Information on family history of venous thrombosis could not be retrieved.*

§§§ *ACL: Anterior cruciate ligament reconstruction*

¶¶¶ *DM: diabetes mellitus*

**** *Either hyperthyroidism or hypothyroidism*

†††† *E.g. chronic inflammatory bowel disease*

‡‡‡‡ *Myocardial infarction and atrial fibrillation*

§§§§ *TIA: transient ischemic attack*

¶¶¶¶ *von Willebrand disease*

***** *E.g. hypercholesterolemia, migraine, attention deficit hyperactivity disorder.*

Surgical details

Mostly, the ACL reconstruction was performed under general anesthesia with the use of a thigh tourniquet and an autologous hamstring graft (table 2). In center A 19 patients (4.3%) were additionally treated with LMWH post-operatively because the surgeon believed they were at high risk of VTE (mainly previous episode of VTE (3 (0.7%)), family history of VTE (4 (0.9%)), obesity (5 (1.1%)), recent surgery (5 (1.1%))).

Table 2. *Surgery details*

Surgery details	**Compression stocking* (n=441)**	**Compression stocking* + LMWH† (N=936)**
Anesthesia‡:		
General, n(%)	365 (82.8)	923 (98.6)
Spinal, n(%)	68 (15.4)	13 (1.4)
Additional femoral block, n(%)	54 (19.0)	3 (0.3)
Procedure:		
Hamstring, n (%)	340 (77.1)	892 (95.3)
Bone-Patellar-tendon-bone, n(%)	77 (17.5)	31 (3.3)
Donor tendon, n(%)	24 (5.4)	13 (1.4)
Additional procedure:		
Meniscectomy, n(%)	99 (22.4)	351 (37.5)
Meniscal suture, n(%)	19 (4.3)	41 (4.4)
Microfracture, n(%)	2 (0.5)	2 (0.2)
Chondroplasty, n(%)	10 (2.3)	0 (0)
Tourniquet¶, yes (%)	421 (95.5)	934 (99.8)
Median tourniquet pressure, mmHg** (range)	300 (250 – 350)	300 (300 – 330)
Median tourniquet duration, minutes (range)	70 (30 – 140)	63 (39 – 140)

Table 2. *Surgery details (continued)*

Surgery details	Compression stocking* (n=441)	Compression stocking* + LMWH† (N=936)
ACL reconstruction rank ††		
Primary	435 (98.6)	934 (99.8)
Secondary	6 (1.4)	1 (0.1)
Tertiary	0 (0)	1 (0.1)
LMWH† after ACL†† reconstruction	19 (4.3)	934 (99.8)

** Compression stocking foot to thigh*

† LMWH: low molecular weight heparin

‡ Of 8 patients in center A information on type of anaesthesia could not be retrieved

§ Femoral block was used both in combination with general and spinal anaesthesia

¶ Of 7 patients in center A and 2 patients in center B information on tourniquet use could not be retrieved.

*** mmHg: millimeters of mercury*

†† ACL: anterior cruciate ligament

Venous thromboembolic events, bleeding and infections

The linkage with the database of the anticoagulation clinics was complete for 1057 (77%) patients, resulting in identification of one additional VTE event in center B and the confirmation of the other events.

Within three months after the procedure one VTE event occurred among the 441 patients in center A (compression stocking, cumulative incidence 0.23% (95CI; 0.01%–1.41%) (table 3). In two patients a diagnostic compression ultrasonography was conducted because of clinical suspicion of deep vein thrombosis, however, no thrombosis was diagnosed. In group B (compression stocking + LMWH) there were four events (cumulative incidence 0.43% (95CI; 0.12%–1.14%). The relative risk of VTE for patients treated with LMWH plus compression stocking compared to patients treated with a compression stocking alone was 1.9 (95CI; 0.2–11.8). The absolute risk difference was +0.20% (95CI; -0.41% – 0.81%). For further details of patients with a VTE see table 4.

Fewer bleeds were reported in the three months after the procedure in patients treated additionally with LMWH compared to compression stockings alone, (5 bleeds center A (1.13% (95CI; 0.41%–2.71%) and 6 in center B (0.64% (95CI; 0.26%–1.43%), RR 0.6 (95CI; 0.2–1.8)). Surgical site infections were reported more frequently in patients additionally treated with LMWH (1 in center A (0.23% (95CI; 0.01%–1.41%) and 9 in center B (0.96% (95CI; 0.48%–1.85%), RR 4.2 (95CI; 0.5–33.4). More details on major and minor bleeding and type of surgical site infection can be found in table 3.

Table 3. *complications*

Complication	Compression stocking* (n=441), n (%; 95CI)	Compression stocking* + LMWH† (N=936), n (%; 95CI)	RR (95CI)‡	RD (95CI), percentage points §
Venous thrombosis	1 (0.23; 0.01 – 1.41)	4 (0.43; 0.12 – 1.14)	1.9 (0.2 – 11.8)	0.20 (-0.41 – 0.81)
DVT¶	0 (0.00 – 1.04)	2 (0.21; 0.01 – 0.83)	∞	0.21 (-0.08 – 0.51)
DVT¶ and PE**	1 (0.23; 0.01 – 1.41)	1 (0.11; 0.01 – 0.67)	0.5 (0.03 – 7.5)	- 0.12 (-0.61 – 0.37)
PE**	0 (0.00 – 1.04)	1(0.11; 0.01 – 0.67)	∞	0.11 (-0.10 – 0.32)
Deceased	0 (0.00 – 1.04)	0 (0.00; 0.00 – 0.49)	-	0
Bleeding event	5 (1.13; 0.41 – 2.71)	6 (0.64; 0.26 – 1.43)	0.6 (0.2 – 1.8)	- 0.49 (-1.61 – 0.62)
Major Bleed	2 (0.45; 0.01 – 1.75)	0 (0.00; 0.00 – 0.49)	0	-0.45 (-1.08 – 0.17)
Minor Bleed	3 (0.68; 0.13 – 2.08)	6 (0.64; 0.26 – 1.43)	0.9 (0.2 – 3.8)	-0.04 (-0.96 – 0.88)
Surgical site infection	1 (0.23; 0. 01 – 1.41)	9 (0.96; 0.48 – 1.85)	4.2 (0.5 – 33.4)	0.73 (-0.03 – 1.50)
Superficial	0 (0.00 – 1.04)	5 (0.53; 0.19 – 1.28)	∞	0.53 (0.07 – 1.00)
Deep	0 (0.00 – 1.04)	4 (0.43; 0.12 – 1.14)	∞	0.43 (0.01 – 0.85)
Space (joint)	1 (0.23; 0.01 – 1.41)	0 (0.00; 0.00 – 0.49)	0	-0.24 (-0.67 – 0.22)

* *Compression stocking foot to thigh. No patients who received additional treatment with LMWH in center A developed a complication.*

† *LMWH: low molecular weight heparin*

‡ *RR (95CI): relative risk with 95% confidence interval*

§ *RD (95CI): absolute risk difference in percentage points with 95% confidence interval*

¶ *DVT: deep vein thrombosis*

** *PE: pulmonary embolism*

Table 4. *Description of patients with a venous thrombotic event*

Patient	Patients details	Surgery details	Time to event (in days)	Type of event
Centre A				
- Male, 43 years old	ASA* 1, BMI† 26.5, no known additional risk factors, no medication use	ACL‡ reconstruction (hamstring graft) + meniscectomy, general anesthesia, tourniquet use	22	DVT§ + PE¶
Centre B				
- Male, 39 years old	ASA* 1, BMI† 26.6, no known additional risk factors, no medication use	ACL‡ reconstruction (hamstring graft), general anesthesia, tourniquet use	27	DVT§
- Male, 40 years old	ASA* 1, BMI† 21.9, 2 units of alcohol consumption daily, no other known additional risk factors, no medication use	ACL reconstruction (hamstring graft), general anesthesia, tourniquet use	40	DVT§
- Male 42 years old	ASA* 1, BMI† 28.0, 1 unit of alcohol consumption daily, no other known additional risk factors, no medication use	ACL‡ reconstruction (hamstring graft), general anesthesia, tourniquet use	19	DVT§ + PE¶
- Male 30 years old	ASA* 2, BMI† 23.6, smokes 20 cigarettes daily, 1 unit of alcohol consumption daily, allergic rhinitis, use of antihistamine.	ACL‡ reconstruction (hamstring graft) + meniscectomy, general anesthesia, tourniquet use	14	DVT§

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

† BMI: body mass index in kg/m²

‡ Anterior cruciate ligament

§ DVT: deep vein thrombosis

¶ PE: pulmonary embolism

Discussion

We found no reduced occurrence of symptomatic VTE with LMWH for 15 days in addition to a compression stocking for 6 weeks after ACL reconstruction (RR 1.9 (95CI; 0.2–11.8), comparing two centers with different VTE prophylaxis policies but otherwise identical treatment protocols and similar patient populations. Furthermore, the incidence of symptomatic VTE in both groups was low (0.23% vs 0.43%) and the corresponding absolute risk difference for treatment with LMWH was also low (RD +0.20% (95CI; -0.41%–0.81%)).

To our knowledge, only two randomized trials aimed to establish the effect of thromboprophylaxis with LMWH in patients with ACL reconstruction. Both trials included only small patient populations (36 and 175) and used asymptomatic VTE as the primary endpoint.[7,8] These studies were therefore largely underpowered and inconclusive for the clinically relevant endpoint, symptomatic VTE. Furthermore, the latter study addresses a different research question as it randomizes patients between short course vs extended thromboprophylaxis with LWMH[8]. In addition, in two trials addressing thromboprophylaxis after knee arthroscopy, also patients with an ACL reconstruction were included.[6, 12] However in one study, with only 6% of patients (15 out of 241) having an ACL reconstruction, the number of patients is limited.[12] In the other study the proportion of patients is much larger (39%(681 out of 1761 patients)), However in both trials patients with an ACL reconstruction were not analyzed separately.[6,12] Once more, asymptomatic VTE was used as the primary endpoint, limiting the ability to draw conclusions on the prevention of symptomatic VTE[16].

In the study on short course vs extended prophylaxis a much higher risk (4.4% in 3 to 4 weeks) of symptomatic VTE was found than in our study[8]. Patients in this study were hospitalized for 3 to 8 days after the reconstruction versus day-care surgery and direct mobilization in our study. The low incidence of VTE in our study is, however, in agreement with large database studies.[24, 25] The fact that all patients in our study were treated with a compression stocking may also have contributed to the low thrombosis risk found. The effect of compression stockings has been studied only on asymptomatic VTE in patients who had a total hip or knee arthroplasty. Here, the risk was reduced by compression stockings as shown in a meta-analysis of 6 trials (OR 0.47 (95CI; 0.32–0.68) for asymptomatic VTE and 0.44 (95CI; 0.12–1.58) for PE).[26]

In this study, preference in a center regarding prophylactic LMWH can be viewed as an instrumental variable, i.e. a factor that mimics randomization.[18, 20] In the supplement, we described the assumptions under which center preference for prophylactic LMWH would be a valid instrumental variable, i.e. when any difference in occurrence of VTE between the centers can be attributed to the difference in policy regarding LMWH. The first of these assumptions was clearly met with 95.8% of patients in center A treated with a compression stocking and 99.8% of patients in center B treated with compression stocking plus 15 days of LMWH. Although some confounders were unequally distributed between the centers (table 1), we expect the baseline risk of VTE (assumption 2) to be the same in both centers, because some risk factors for VTE were more frequent in center A, while others were more frequent in center B. On the whole, these risk factors are expected to balance each other out. With only five events in total, additional adjustments for unequally distributed confounders could not be made. Of note, a similar situation can occur in moderately sized randomized trials, where unequal distribution of prognostic factors can occur due to chance variation. Because pre-, per- and post-operative protocols were the same in both centers except for post-operative thromboprophylaxis, the assumption that center preference for LMWH may only affect VTE risk through LMWH administration (assumption 3) was also met. We are therefore confident we have provided a valid estimate of the treatment effect in the absence of a randomized trial. Regarding the low incidence of VTE, a regular trial, even using our most optimist effect of additional treatment with LMWH (e.g. a RR of 0.2 (lower level of the confidence interval), requires an unrealistically large number of 14.000 patients and should therefore be considered unfeasible (alpha 0.05 and power 80%). Therefore, we believe our study gives the most reliable results practical feasible considering pharmacologic thromboprophylaxis in patients with an ACL reconstruction.

As in all studies, including trials, some limitations need to be taken into account. Due to the limited intensive care possibilities in the clinics, only patients with an ASA classification of 1 or 2 were included in this study. This could potentially have implications for the generalizability of our results. However, the population of patients undergoing an ACL reconstruction consists in general of young, active and healthy persons. In a nationwide Danish study using the national knee ligament reconstruction registry, 94.5% of patients who received an ACL reconstruction had a Charlson comorbidity index of 0 (i.e. healthy patients , while only 0.2% of patients had an index of 3 or higher.[27] Therefore most likely only a few, if any, ASA 3 patients may have been referred to

another hospital so we believe this has had only a minor effect on the generalizability of our results.

Furthermore, results may have been influenced by a small difference in the compression stocking protocol between centers. In center A, patients were advised to wear their stocking for day and night, whereas in center B patients were advised to wear the stocking in daytime. However, a strong effect of this difference is unlikely as compression stockings are only effective in combination with muscle pump activity, which is clearly not present during the night. Additionally, a small proportion of patients (19 patients, 4.3%) were treated with LMWH in center A, due to a perceived high risk of VTE. Because these patients would have received LMWH in either center, our study provides no information on the effect of prophylactic LMWH in this high-risk subgroup. If we assume that these patients had an unusually high risk of 10% of developing VTE and if we assume that all events were prevented by the use of LMWH, 2 more cases of VTE would have been prevented. Adding these 2 extra cases to the results leads to a cumulative incidence of VTE in Centre A of 3/441= 0.68% (95CI; 0.13 – 2.08). With a corresponding RR of 0.63 (95CI; 0.18 – 2.20) and a RD of 0.25% (95CI; -0.62% - 1.13%), we still cannot show a clinically relevant and significant advantage of additional treatment with LMWH.

Because patients were not routinely screened for VTE, events could have been missed since the symptoms of VTE may mimic those after an ACL reconstruction. However, this corresponds to daily clinical practice. Furthermore, the clinical relevance of detecting asymptomatic events is questionable and not recommended for trials addressing the effect of thromboprophylaxis.[3,16] Events could also have been missed in the clinics in case VTE was treated elsewhere, unknown to the orthopedic surgeons. However, to ensure a complete follow-up of all patients and to guarantee no VTE events were missed, our database was linked to the databases of the national anticoagulation clinics. This linkage was complete for 77% of patients and led to identification of only one additional event. We were unable to perform such a linkage to databases for bleeding events or surgical site infections. Although patients were seen at the outpatient clinic 14 days, 6 weeks and 3 months post-operatively for follow up, these events may have been underreported.

In this study we were unable to demonstrate a beneficial effect of 15 days of treatment with LMWH. A possible explanation for this finding is that patients in both groups were treated with a compression stocking, perhaps already maximally lowering the thrombosis risk. In addition, the reconstructive surgery in both clinics was performed in day-care setting and patients were mobilized immediately post-operatively, further reducing their thrombosis risk. Lastly, the population of patients undergoing an ACL reconstruction is a young, active and healthy population, therefore the baseline risk of VTE in these patients is in general already low.[2]

On the basis of our findings it is justified to assume that there is no beneficial effect of routinely adding LMWH to prophylaxis with a compression stocking and early mobilization in these patients, while there may be clear disadvantages related to this treatment, such as the costs involved, the burden of daily injections and the risk of bleeding complications. Although we did not find an increased risk of bleeding for treatment with LMWH, an increased bleeding risk has been demonstrated in previous studies (RR1.73 (95CI; 1.09–2.73).[6, 28] We did find a small increase in surgical site infections in the group treated with LMWH. A possible explanation is prolonged wound drainage caused by anticoagulants, which may have an effect on primary wound healing. The latter has been suggested after total joint arthroplasty surgery.[29-30]

Conclusion

We were unable to demonstrate any benefit of routine treatment with LMWH in patients receiving an ACL reconstruction in addition to VTE prophylaxis with a compression stocking and early mobilization. With respect to our results, we would advise not to provide thromboprophylaxis, with its associated burden and risks, routinely to this generally young and healthy group of patients, in whom the risk is very low. Nevertheless, we cannot exclude that anticoagulant therapy might be beneficial in certain high-risk patients. Identifying high risk groups and selective treatment of these patients should be the aim of future studies, thereby reducing thrombosis morbidity and the risk of treatment complications.

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Supplement material

Instrumental variable assumptions

In order to ascribe any difference between center A and center B in occurrence of venous thromboembolism or another outcome to prophylactic LMWH, a number of assumptions for instrumental variable analysis should be met. The centers must differ in their preference for type of treatment (assumption 1), the prognosis regarding VTE risk of the patients in the centers must be the same (assumption 2) and center preferences must not influence the VTE risk by other pathways than VTE prophylaxis (such as co-medication or mobilization protocol, assumption 3)[1,2]. Both clinics are specialized orthopedic clinics and are in the same geographical area (less than 10 kilometers apart). In addition, both clinics use the same surgical technique, pre-, per-, and post-operative protocols (including mobilization protocol), except for post-operative pharmacological thrombosis prophylaxis. All three assumptions for an instrumental variable are therefore expected to hold, which would allow any difference in occurrence of thromboembolic events between the two centers to be attributed to the difference in pharmacological thrombosis prophylaxis.

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Surgery protocol

Patients were given pre-operative 2gr cefazolin, 75mg diclofenac and 1 gr paracetamol (acetaminophen) all intravenously. The reconstruction was performed using a hamstring autograft (semitendinous-gracilis), bone-patellar tendon-bone autograft or a donor graft. Post-operative pain protocol consists of 10 ml levobupivacaine 5mg/ml and 10 ml 1% adrenaline 1:200.000 intra articular. Patients were post-operatively prescribed 5 days paracetamol(acetaminophen) 1gr 4 times daily, meloxicam 7,5mg 2 times daily and, if necessary, tramadol 50-100mg 3 times daily and ondansetron 4mg 1 time daily (all orally). Patients who received a donor graft ACL reconstruction received prophylactic antibiotic treatment (three times 1gr cefazolin over 24hours) and patients with an increased risk of complications (e.g. BMI>30, comorbidities or procedure performed with donor graft) stayed overnight. Patients were allowed to mobilize immediately after

surgery with crutches for 4-6 weeks and received a referral for physical therapy for 4-6 months which could be started seven days after surgery.

Details on data collection

All collected data were coded and registered in an Access database (Microsoft Access 2010, Microsoft corporation, Redmond, Washington, US). Surgical details, such as reconstruction technique (hamstring graft, bone-patellar tendon-bone, or allograft) and duration of surgery were recorded. We registered if the reconstruction was a primary reconstruction, a second (or third) reconstruction or a revision of a previous (still intact, however unstable) ACL reconstruction and if there were any concomitant procedures performed (such as a meniscectomy or meniscal suture). Besides all the operation procedures, data such as location of residence, age, sex, BMI, alcohol use and smoking, medication use, co-existing diseases, medical history (including surgery three months prior to the reconstruction), follow-up information and postoperative complications were also recorded.