Annals of Internal Medicine | ARTICLE

Low-Molecular-Weight Heparin versus Compression Stockings for Thromboprophylaxis after Knee Arthroscopy

A Randomized Trial

Giuseppe Camporese, MD; Enrico Bernardi, MD, PhD; Paolo Prandoni, MD, PhD; Franco Noventa, MD; Fabio Verlato, MD; Paolo Simioni, MD, PhD; Kadimashi Ntita, MD; Giovanna Salmistraro, MD; Christos Frangos, MD; Franco Rossi, MD; Rosamaria Cordova, MD; Francesca Franz, MD; Pietro Zucchetta, MD; Dimitrios Kontothanassis, MD; and Giuseppe Maria Andreozzi, MD, for the KANT (Knee Arthroscopy Nadroparin Thromboprophylaxis) Study Group*

Background: Knee arthroscopy, the most common orthopedic operation worldwide, carries a definite risk for deep venous thrombosis; however, postsurgical thromboprophylaxis is not routinely recommended.

Objective: To evaluate whether low-molecular-weight heparin (LMWH) better prevents deep venous thrombosis and does not cause more complications than graduated compression stockings in adults having knee arthroscopy.

Design: Assessor-blind, randomized, controlled trial.

Setting: The Department of Knee Surgery, Abano Terme Clinic, Abano Terme (knee surgery, random assignment, and bleeding event survey), and the Unit of Angiology, University Hospital of Padua, Padua (efficacy outcomes evaluation, follow-up, data management, and analysis), Italy.

Patients: 1761 consecutive patients undergoing knee arthroscopy between March 2002 and January 2006.

Intervention: Patients were randomly assigned to wear full-length graduated compression stocking for 7 days (660 patients) or to receive a once-daily subcutaneous injection of LMWH (nadroparin, 3800 anti-Xa IU) for 7 days (657 patients) or 14 days (444 patients). The data and safety monitoring board prematurely stopped the 14-day heparin group after the second interim analysis.

Measurements: Combined incidence of asymptomatic proximal deep venous thrombosis, symptomatic venous thromboembolism, and all-cause mortality (primary efficacy end point) and combined incidence of major and clinically relevant bleeding events (primary safety end point). All patients had bilateral whole-leg ultrasonography at the end of the allocated prophylactic regimen or earlier if indicated. All patients with normal findings were followed for 3 months, and none was lost to follow-up.

Results: The 3-month cumulative incidence of asymptomatic proximal deep venous thrombosis, symptomatic venous thromboembolism, and all-cause mortality was 3.2% (21 of 660 patients) in the stockings group, 0.9% (6 of 657 patients) in the 7-day LMWH group (absolute difference, 2.3 percentage points [95% CI, 0.7 to 4.0 percentage points]; $P = 0.005$), and 0.9% (4 of 444 patients) in the prematurely stopped 14-day LMWH group. The cumulative incidence of major or clinically relevant bleeding events was 0.3% (2 of 660 patients) in the stockings group, 0.9% (6 of 657 patients) in the 7-day LMWH group (absolute difference, −0.6 percentage point [CI, −1.5 to 0.2 percentage points]), and 0.5% (2 of 444 patients) in the 14-day LMWH group.

Limitations: The study was not double-blind or double-dummy. Almost half of the events making up the composite outcome measure were distal deep venous thromboses. Stockings were used instead of placebo because of local prophylaxis policies.

Conclusion: In patients undergoing knee arthroscopy, prophylactic LMWH for 1 week reduced a composite end point of asymptomatic proximal deep venous thrombosis, symptomatic venous thromboembolism, and all-cause mortality more than did graduated compression stockings.

Ann Intern Med. 2008;149:73-82. www.annals.org

For author affiliations, see end of text.

International Standard Randomized Controlled Trial Number: ISRCTN75056741.

* For additional KANT study investigators, see the **Appendix** (available at www.annals.org).

Knee arthroscopy is a minor orthopedic procedure that is regularly performed in an outpatient setting. Diagnostic arthroscopy and arthroscopy-assisted knee surgery are the most common orthopedic operations performed in the United States and Europe, with more than 3.5 million procedures per year globally (roughly 250 000 in Italy)—mostly in young patients (1, 2). Despite the frequency of knee arthroscopy, data on the associated risk for venous thromboembolism are scarce.

The incidence of objectively proven deep venous thrombosis after knee arthroscopy ranges from 0.6% to 18% without thromboprophylaxis (3–14), and no clear evidence of the efficacy of low-molecular-weight heparins (LMWHs) or other antithrombotic drugs is available in this setting (12). Although the latest American College of Chest Physicians (ACCP) Consensus Conference recommended against routine thromboprophylaxis for reasons other than early mobilization in this setting, the lack of information from adequate studies led to a relatively weak

See also:

Print

Editors' Notes 74
Editorial comment. 137
Summary for Patients. I-40

Web-Only

Appendix
Appendix Table
Conversion of graphics into slides

Context

Many experts do not recommend thromboprophylaxis after knee arthroscopy.

Contribution

In this trial, 1761 adults who had knee arthroscopy were randomly assigned to receive daily low-molecular-weight heparin (LMWH) or to wear a full-length graduated compression stocking on the operated leg for 1 week. Fewer than 1% of the patients in either group had important postsurgical bleeding complications. During a 3-month follow-up, fewer cases of asymptomatic proximal deep venous thrombosis, symptomatic venous thromboembolism, and death occurred in patients who received LMWH than in those who wore stockings (0.9% vs. 3.2%).

Caution

Many outcomes were distal deep venous thromboses.

Implication

Postsurgical prophylactic LMWH for 1 week may prevent some thromboses after knee arthroscopy.

—The Editors

(grade 2B) recommendation (15). Only 2 randomized clinical trials (16, 17) have investigated the efficacy and safety of LMWH for preventing thrombotic complications in these patients, with conflicting results.

We tested the efficacy and safety of graduated compression stockings for 7 days versus a 7- or 14-day LMWH regimen for venous thromboembolic prophylaxis in patients receiving knee arthroscopy in an outpatient setting.

METHODS

We designed this assessor-blind, randomized, controlled trial to verify whether LMWH better prevents deep venous thrombosis and does not cause more complications than graduated compression stockings in adults having knee arthroscopy. We conducted the study according to the principles contained in the Declaration of Helsinki. We recruited patients between March 2002 and January 2006 and completed follow-up in April 2006. The local ethics committee and institutional review board approved this trial. All patients gave written informed consent.

We randomly assigned patients to wear commercially available full-length graduated compression stockings (30 to 40 mm Hg at the ankle) on the operated leg for 7 days or to receive a daily subcutaneous injection of nadroparin (3800 anti-Xa IU) for either 7 or 14 days. We chose the duration of the LMWH prophylactic regimens on the basis of the latest ACCP Consensus Conference recommendations for knee arthroplasty (15). We originally designed the study as a 3-group trial that included the 14-day LMWH regimen (18, 19); however, the data and safety monitoring board stopped this group during a planned interim analysis, and the study continued as a 2-group trial (20).

Setting and Participants

We conducted the study at the Department of Knee Surgery of the Abano Terme Clinic (where investigators selected and randomly assigned the patients and evaluated suspected bleeding events) and the Unit of Angiology of the University Hospital of Padua (where investigators assessed suspected thromboembolic events and handled data management and analysis). All consecutive outpatients scheduled at the Abano Terme Clinic for diagnostic arthroscopy or arthroscopy-assisted knee surgery for partial meniscectomy, cartilage shaving, cruciate ligament reconstruction, synovial resection, or combined surgical procedures were eligible for the study. We excluded patients who met any of the following criteria: younger than 18 years of age, pregnant, previous venous thromboembolism, active cancer, known thrombophilia, receiving mandatory anticoagulation, hypersensitive to LMWH, recent major bleeding event, severe renal or hepatic failure, anticipated poor adherence, geographic inaccessibility, or tourniquet thigh time greater than 1 hour. We included and randomly assigned all remaining patients who signed the written informed consent. We evaluated all included patients for the presence of known risk factors for venous thromboembolism (**Table 1**).

Arthroscopic Procedures

After the patients received selective subarachnoid anesthesia, a team of 6 experienced orthopedic surgeons performed the procedures by using a standard 2-portal technique. All patients were mobile and were discharged on the same day of the procedure. Patients who had cartilage shaving could not bear weight on the operated leg for the first 3 weeks after the operation and were invited to immediately start physiotherapy and rehabilitation; all other patients could bear weight on the operated leg as tolerated while on crutches. We recorded the type of surgical procedure and the tourniquet thigh time in each patient's file.

Randomization and Interventions

A research statistician generated a list of random assignments by using nQuery Advisor (Statistical Solution, Los Angeles, California) (21) with a block size of 10 participants and no stratification. We included the allocation sequence in consecutively numbered, sealed, opaque envelopes that were sequentially opened by the orthopedic surgeon after knee arthroscopy. Patients started wearing graduated compression stockings before weight bearing or received their first LMWH dose at the hospital 8 hours after the procedure. A trial nurse trained the patients to self-inject their medication subcutaneously or properly use their implements. All patients allocated to receive LMWH had complete blood counts done every 3 days starting from the fourth day of administration (22). We advised all patients to stop taking any antiplatelet agents 5 days before their operation and to resume this therapy 1 to 2 weeks

Table 1. **Demographic and Presurgical Baseline Characteristics**

Characteristic	7-d GCS (n = 660)	7-d LMWH (n = 657)	14-d LMWH (n = 444)*
Mean age (SD), *y*	42.3 (14.4)	41.9 (15.1)	42.5 (16.7)
Sex distribution, male:female	1.66:1	1.62:1	1.60:1
Mean body mass index (SD), kg/m^2	25.5 (3.8)	25.3 (4.1)	25.5 (4.5)
Smoker, *n (%)*	154 (23.3)	194 (29.5)	114 (25.7)
Use of hormonal compounds, *n (%)*	59 (8.9)	61 (9.2)	34 (7.6)
Family history of venous thromboembolism, *n (%)*	6 (0.9)	4 (0.6)	4 (0.9)
Mean tourniquet thigh time (SD), *min*	36 (19)	38 (17)	39 (21)
Type of anesthesia, *n*			
General	0	0	0
Locoregional	660	657	444
Type of surgical procedure, *n (%)*			
Anterior cruciate ligament reconstruction	229 (34.7)	223 (33.9)	146 (32.8)
Lateral and/or medial meniscectomy	251 (38.0)	254 (38.6)	199 (44.8)
Cartilage shaving	51 (7.7)	46 (7.0)	26 (5.8)
Anterior cruciate ligament reconstruction plus meniscectomy	20 (3.0)	43 (6.5)	20 (4.5)
Cartilage shaving plus meniscectomy	79 (11.9)	47 (7.1)	46 (10.3)
Other (e.g., loose body removal or synovial resection)	30 (4.5)	45 (6.8)	7 (1.5)

GCS = graduated compression stockings; LMWH = low-molecular-weight heparin.
* Stopped after the second interim analysis.

after the end of their prophylactic regimen. We also advised patients to take nonsteroidal anti-inflammatory drugs as needed for pain after surgery, unless contraindicated, but we did not monitor actual use.

Measurements and Outcomes

Efficacy

All patients had bilateral, whole-leg, color-coded Doppler ultrasonography at the end of prophylaxis (8 or 15 days) or earlier if clinically indicated. Four skilled physicians who were unaware of the patients' allocation group performed the ultrasonographies, which were evenly distributed among the physicians, during working hours at the Unit of Angiology of the University Hospital of Padua. A nurse instructed all patients to conceal their allocation from the operator and to cover their abdomen and avoid wearing graduated compression stockings on the day of ultrasonography.

Before ultrasonography, a nurse interviewed patients by using a standardized questionnaire to determine whether they had symptoms of deep venous thrombosis (calf swelling, pain, or tenderness; whole-leg swelling or edema; discoloration; or collateral superficial nonvaricose veins) or pulmonary embolism (syncope, chest pain, shortness of breath, palpitations, or hemoptysis) and whether they were adhering to the prophylactic regimen. Patients reporting 1 or more symptoms were considered symptomatic. Because patients receiving arthroscopy are usually only symptomatic at the knee, if at all, we attributed all new leg symptoms to a suspected thromboembolic event.

Assessment of Deep Venous Thrombosis

We performed ultrasonography according to a standardized protocol (23, 24) by using a Technos (ESAOTE Biomedica, Genoa, Italy) or a Sonos 5500 (Hewlett-Packard, Medical Products Group, Andover, Massachusetts) system, equipped with a 5- to 10-MHz broadband linear-array transducer.

We sequentially examined the proximal venous system (common, superficial, deep femoral, and popliteal to the trifurcation) with the patient supine and then examined the distal venous network (tibioperoneal and muscular) with the patient sitting. We did not routinely investigate the anterior tibial veins (25).

Vein incompressibility was the only diagnostic criterion for the proximal veins (25). We considered lack of intraluminal or reverse-flow color filling after augmentation maneuvers to be an additional criterion for the distal veins.

Assessment of Pulmonary Embolism

We confirmed suspected pulmonary embolism by performing a ventilation–perfusion lung scan; a high-probability result indicated pulmonary embolism and a near-normal or normal result excluded it. Patients with nondiagnostic scans received multidetector computed tomography (26–28). We diagnosed fatal pulmonary embolism on the basis of autopsy findings.

Safety

The orthopedic surgeon followed up with the patients during prophylaxis, assessed local or systemic bleeding events, and reviewed complete blood counts. Patients with local bleeding events were managed at the Abano Terme Clinic, whereas patients with systemic bleeding events or thrombocytopenia were admitted to the University Hospital of Padua (22).

End Points

The primary efficacy end point was the 3-month cumulative incidence of asymptomatic proximal deep venous thrombosis, symptomatic venous thromboembolism, and all-cause mortality (15, 29, 30). The primary safety end point was the 7- or 14-day cumulative incidence of major and clinically relevant nonmajor bleeding events. A major bleeding event was defined as a clinically overt hemorrhage associated with a hemoglobin decrease of at least 20 g/L or requiring transfusion of 2 or more units of packed red blood cells, a retroperitoneal or intracranial event, a bleeding event requiring reintervention, or a hemarthrosis with joint drainage of more than 450 mL. A clinically relevant nonmajor bleeding event was defined as a hemarthrosis with joint drainage of 100 to 450 mL that was not life-threatening and did not require reintervention.

The secondary efficacy end point was the primary efficacy end point plus the 3-month cumulative incidence of asymptomatic distal deep venous thrombosis. The secondary safety end point was the 7- or 14-day cumulative incidence of bleeding events.

An independent blinded adjudication committee that was unaware of the patients' allocation group, clinical status, or diagnostic findings reviewed all safety and efficacy events.

Follow-up Procedures and Monitoring

We treated patients with objectively documented venous thromboembolism according to standard protocols (31). We observed patients with normal ultrasonographic findings for 3 months and, when clinically indicated, instructed them to contact the study center for objective investigation.

We scheduled a final visit for each patient at day 91 and contacted by telephone those who did not attend the planned appointment. We interviewed patients about their health status, chest or leg symptoms, and history of hospital admissions by using a standardized questionnaire.

The members of the data and safety monitoring board joined us for 3 planned interim analyses to appraise data quality and verify the prespecified stopping rules. We made the following comparisons to determine the efficacy of the more invasive therapeutic protocol and the safety of the less invasive therapeutic protocol: 7-day LMWH versus graduated compression stockings, 14-day LMWH versus 7-day LMWH, and 14-day LMWH versus graduated compression stockings. A group was to stop receiving any prophylaxis found to be inferior in any comparison.

At the second interim analysis, the data and safety monitoring board officially discontinued therapy for the 14-day LMWH group because of concerns about potential safety issues related to a longer LMWH regimen. The trial continued as a 2-group study of graduated compression stockings versus a 7-day LMWH regimen.

Statistical Analysis

We estimated that, with a sample size of 554 participants in each of the 3 study groups, an overall chi-square test (2-sided, $\alpha = 0.05$) would have 80% power to detect a difference in the proportions of the primary efficacy end point. On the basis of the literature, we assumed that the proportions of patients with a primary end point condition would be 4%, 2%, and 1% in the 7-day graduated compression stockings, 7-day LMWH, and 14-day LMWH groups, respectively, characterized by an effect size (Δ^2) of 0.004927 (32, 33). Thus, assuming an 18% dropout rate, we would need at least 654 patients per group. Our study was underpowered to detect important differences in safety; these data are shown for descriptive purposes only.

We planned to conduct interim analyses at 40%, 65%, and 80% of the estimated sample size, with progressively augmented α levels of 0.0006, 0.0045, and 0.0125, resulting in a final α level of 0.025 (21).

Proportions are shown with their 95% CIs. We compared proportions by using a 2-tailed Fisher exact test.

We attempted a post hoc analysis to estimate the LMWH-related venous thromboembolic risk reduction by using univariate and multivariate logistic regression models, correcting for known risk factors for venous thromboembolism, as described in **Table 1**. For this analysis, we split the "surgical procedures" variable according to whether a meniscectomy was involved.

We performed all analyses with SPSS, version 15.0 (SPSS, Chicago, Illinois).

Role of the Funding Source

We did not receive external funding for this study.

RESULTS

Baseline Characteristics and Study Groups

We considered 2043 consecutive patients for this study. We excluded 282 patients on the basis of the predefined criteria and randomly assigned the remaining 1761 to wear graduated compression stockings (660 patients) or to receive LMWH for 7 days (657 patients) or 14 days (444 patients). The **Figure** depicts the study flow (34), and **Table 1** lists the demographic and clinical characteristics of the patients.

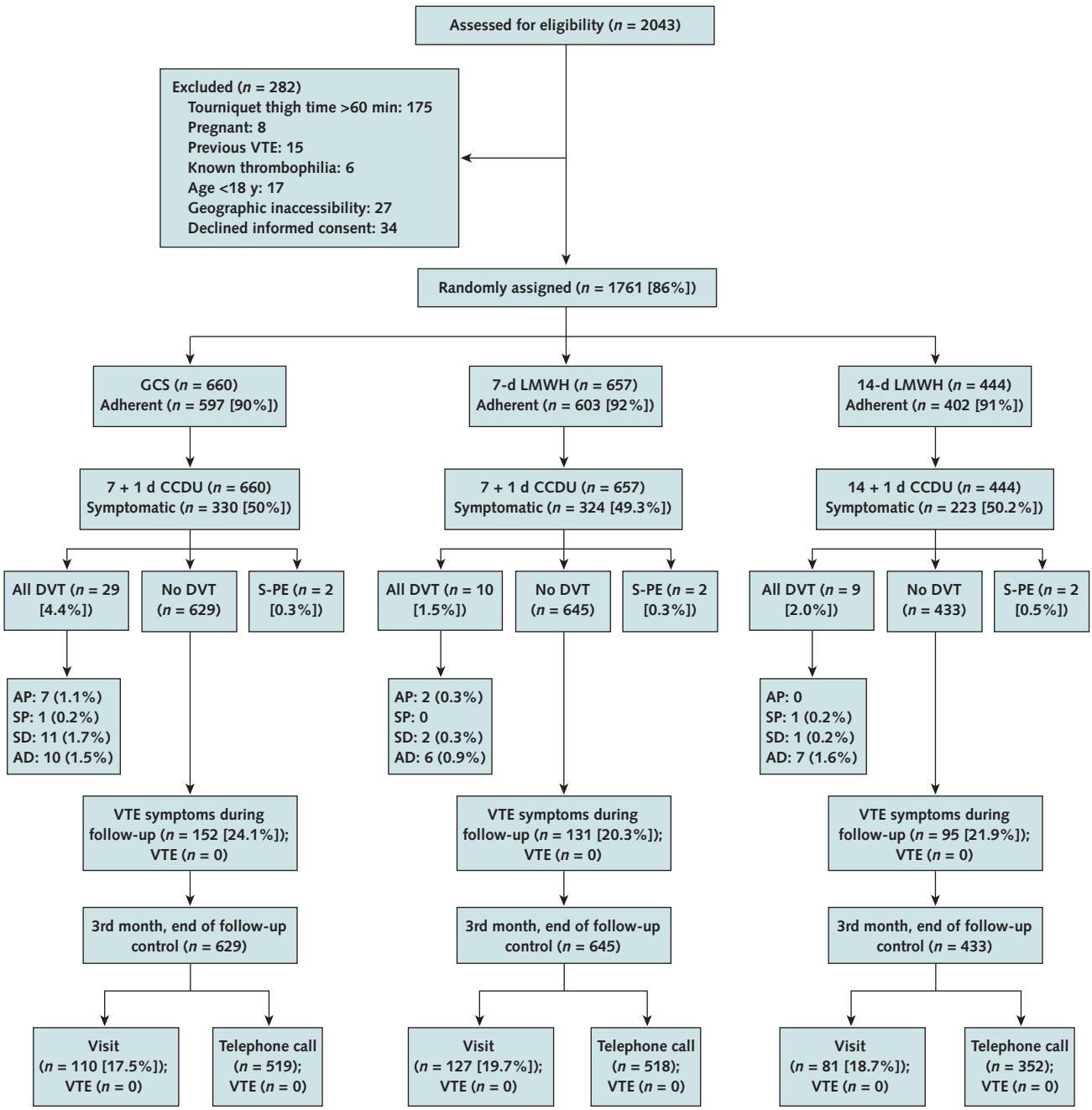
No patients crossed over among the 3 study groups. Of the 660 patients randomly assigned to the graduated compression stockings group, 597 (90.4%) completed the planned 7-day prophylactic regimen, compared with 603 of the 657 (91.7%) patients allocated to the 7-day LMWH group and 402 of the 444 (90.5%) patients allocated to the 14-day LMWH group.

The **Appendix Table** (available at www.annals.org) lists the results of the 2 interim analyses.

Efficacy

The 3-month cumulative incidence of the composite primary efficacy end point was 3.2% (21 of 660 patients)

Figure. **Study flow diagram.**



AD = asymptomatic distal; AP = asymptomatic proximal; CCDU = color-coded Doppler ultrasonography; DVT = deep venous thrombosis; GCS = graduated compression stockings; LMWH = low-molecular-weight heparin; S-PE = symptomatic nonfatal pulmonary embolism; SD = symptomatic distal; SP = symptomatic proximal; VTE = venous thromboembolism.

in the graduated compression stockings group, 0.9% (6 of 657 patients) in the 7-day LMWH group (absolute difference, 2.3 percentage points [95% CI, 0.7 to 4.0 percentage points]; $P = 0.005$), and 0.9% (4 of 444 patients) in the 14-day LMWH group. All deep venous thromboses occurred in the operated legs.

The 3-month cumulative incidence of the secondary efficacy outcome was 4.7% (31 of 660 patients) in the graduated compression stockings group, 1.8% (12 of 657 patients) in the 7-day LMWH group (absolute difference, 2.9 percentage points [CI, 1.0 to 4.9 percentage points]; $P = 0.005$), and 2.5% (11 of 444 patients) in the 14-day LMWH group.

All patients had ultrasonography at the end of prophy-

Table 2. **Efficacy and Safety Results at Eighth-Day Color-Coded Doppler Ultrasonography***

Variable	7-d GCS (n = 660), n (%)	7-d LMWH (n = 657), n (%)	14-d LMWH [95% CI] (n = 444), n (%)†	Absolute Difference (95% CI), 7-d GCS vs. 7-d LMWH, *percentage points*	*P* Value‡
Primary efficacy end point	21 (3.2)	6 (0.9)	4 (0.9 [0.4 to 2.3])	2.3 (0.7 to 4.0)	0.005
Death	0	0	0	0	
Symptomatic PE (nonfatal)	2 (0.3)	2 (0.3)	2 (0.5 [0.1 to 1.6])	0	
Asymptomatic proximal DVT	7 (1.1)	2 (0.3)	0	0.8 (−0.1 to 1.6)	
Symptomatic proximal DVT	1 (0.2)	0	1 (0.2 [0.0 to 1.3])	0.2 (−0.1 to 0.4)	
Symptomatic distal DVT	11 (1.7)	2 (0.3)	1 (0.2 [0.0 to 1.3])	1.4 (0.3 to 2.4)	
Secondary efficacy end point§	31 (4.7)	12 (1.8)	11 (2.5 [1.4 to 4.4])	2.9 (1.0 to 4.8)	0.005
Asymptomatic distal DVT	10 (1.5)	6 (0.9)	7 (1.6 [0.8 to 3.2])	0.6 (−0.6 to 1.8)	
Primary safety end point	2 (0.3)	6 (0.9)	2 (0.5 [0.1 to 1.6])	−0.6 (−1.5 to 0.2)	–
Major bleeding event	1 (0.2)‖	2 (0.3)¶	1 (0.2 [0.0 to 1.3])**	−0.2 (−0.7 to 0.4)	
Clinically relevant bleeding event	1 (0.2)††	4 (0.6)‡‡	1 (0.2 [0.0 to 1.3])§§	−0.5 (−1.4 to 0.3)	
Secondary safety end point‖‖	22 (3.3)	29 (4.4)	18 (4.1 [2.6 to 6.3])	−1.1 (−3.2 to 1.0)	–
Minor bleeding event	20 (3.0)	23 (3.5)	16 (3.6 [2.2 to 5.8])	−0.5 (−2.4 to 1.4)	

DVT = deep venous thrombosis; GCS = graduated compression stockings; LMWH = low-molecular-weight heparin; PE = pulmonary embolism.
* All events occurred in the operated leg.
† Stopped after the second interim analysis.
‡ We analyzed only data on the primary and secondary end points. Additional details are reported for descriptive purposes only. All *P* values are 2-tailed (Fisher exact test).
§ Secondary efficacy end point = primary efficacy end point + asymptomatic distal DVT.
‖ Large hematoma of the operated leg associated with a hemoglobin decrease of 39 g/L.
¶ Hemarthrosis requiring re-intervention with 600-mL blood joint drainage and large hematoma of the operated leg associated with a hemoglobin decrease of 25 g/L.
** Gastrointestinal hemorrhage requiring admission and transfusion of 3 units of packed red blood cells.
†† Hemarthrosis with 130-mL blood joint drainage.
‡‡ Hemarthroses with 170-, 200-, 270-, and 300-mL blood joint drainage.
§§ Hemarthrosis with 250-mL blood joint drainage.
‖‖ Secondary safety end point = primary safety end point + minor bleeding events.

laxis; diagnostic findings were conclusive (thrombosis confirmed or excluded) in all instances. No patients contacted our center with suspected venous thromboembolism before the end-of-prophylaxis visit.

We observed no differences in symptom location or number among patients with proximal or distal deep venous thrombosis. Of the 1761 patients attending the end-of-prophylaxis visit, 14 (0.8%) had suspected pulmonary embolism, which we objectively confirmed in 6 cases. Similarly, 877 (49.8%) patients had suspected deep venous thrombosis and we confirmed 16 cases (**Figure** and **Tables 2** and **3**).

We followed all patients with normal end-of-prophylaxis ultrasonography results for 3 months. During this period, 378 (28.7%) patients experienced new leg symptoms and had ultrasonography; all had normal results. One hundred fifty-two patients in the graduated compression stockings group reported symptoms (pain, 92; tenderness, 23; edema, 24; discoloration, 10; and nonvaricose collateral symptoms, 3), compared with 131 patients in the 7-day LMWH group (pain, 85; tenderness, 18; edema, 18; discoloration, 8; and nonvaricose collateral symptoms, 2) and 95 patients in the 14-day LMWH group (pain, 63; tenderness, 12; edema, 13; and discoloration, 7).

Of the 1707 patients we followed up, only 318 (18.6%) attended the end-of-follow-up visit (110 in the graduated compression stockings group, 127 in the 7-day LMWH group, and 81 in the 14-day LMWH group) and had ultrasonography; all had normal results. The remaining 1389, who were asymptomatic, declined the end-of-follow-up visit but consented to a standardized telephone interview. None reported symptoms of venous thromboembolism.

Overall, of the 1707 patients followed up, none died, was hospitalized, or was lost to follow-up.

Safety

At the end of prophylaxis, the incidence of major and clinically relevant bleeding events was 0.3% (2 of 660 pa-

Table 3. **Incidence of the Primary Efficacy End Point (*PEEP*)**

Type of Surgical Procedure	7-d GCS (n = 660)		7-d LMWH (n = 657)		Absolute Difference (95% CI), *percentage points*
	Patients, n	PEEP Incidence, n (%)	Patients, n	PEEP Incidence, n (%)	
Diagnostic arthroscopic procedures	29	0	36	0	0
Arthroscopy-assisted knee surgery	631	21 (3.3)	621	6 (0.96)	2.3 (0.8 to 4.0)
Meniscectomy involved	351	18 (5.1)	351	6 (1.7)	3.4 (0.7 to 6.1)
Meniscectomy not involved	280	3 (1.1)	270	0	1.1 (−0.1 to 2.8)

GCS = graduated compression stockings; LMWH = low-molecular-weight heparin.

tients) in the graduated compression stockings group, 0.9% (6 of 657 patients) in the 7-day LMWH group (absolute difference, −0.6 percentage point [CI, −1.5 to 0.2 percentage points]), and 0.5% (2 of 444 patients) in the 14-day LMWH group. The cumulative incidence of bleeding events at the end of prophylaxis was 3.3% (22 of 660 patients) in the graduated compression stockings group, 4.4% (29 of 657 patients) in the 7-day LMWH group, and 4.1% (18 of 444 patients) in the 14-day LMWH group.

Subgroup Findings

Table 3 shows the distribution of the primary efficacy end point in the 2 study groups according to procedure type, classified by whether a meniscectomy was involved. The risk for venous thromboembolism associated with a 7-day LMWH regimen, compared with an equivalent graduated compression stockings regimen, was 0.28 (univariate logistic regression crude odds ratio; CI, 0.19 to 0.74; $P = 0.006$), which became 0.27 (adjusted odds ratio; CI, 0.11 to 0.69; $P = 0.006$) when corrected for meniscectomy-involved knee arthroscopy in multivariate analysis. Among the investigated variables (**Table 1**), only meniscectomy was independently associated with the development of the composite primary efficacy end point conditions (adjusted odds ratio, 7.3 [CI, 2.2 to 24.4]; $P = 0.001$), probably because our ability to adjust for many factors was limited by the small number of events.

Other Adverse Events

No patient discontinued the allocated intervention because of adverse events, although 63 (9.6%) patients in the graduated compression stockings group, 54 (8.3%) patients in the 7-day LMWH group, and 47 (10.6%) patients in the 14-day LMWH group declined to complete the prophylactic regimen.

None of the 1101 patients in the LMWH groups developed heparin-induced thrombocytopenia.

DISCUSSION

The latest ACCP Consensus Conference did not endorse routine thromboprophylaxis after knee arthroscopy because of the scarce evidence from adequate studies in this setting (15). This lack of evidence has also led most institutions worldwide to disregard thromboprophylaxis after knee arthroscopy (3, 4, 11, 35–38).

Our findings challenge this dominant view and instead suggest that a 7-day prophylactic regimen of LMWH lowers the incidence of clinically relevant venous thromboembolic events in patients undergoing knee arthroscopy by 2.3 percentage points (CI, 0.7 to 4.0 percentage points; $P = 0.005$; adjusted odds ratio, 0.27 [CI, 0.11 to 0.69]) versus graduated compression stockings, although a 14-day LMWH regimen does not further reduce venous thromboembolic events.

We used stronger graduated compression stockings (30 to 40 mm Hg at the ankle) than the common surgical hose used in the United States and Europe. Thus, because graduated compression stockings have been shown to reduce the incidence of venous thromboembolism by half in patients undergoing general or orthopedic surgery (39, 40), we speculate that the benefit conferred by LMWH would have been even greater had we compared LMWH with weaker stockings or placebo.

The cumulative incidence of major and clinically relevant bleeding events was 0.3% with graduated compression stockings and 0.9% with 7-day LMWH (absolute difference, −0.6 percentage point [CI, −1.5 to 0.2 percentage points]). We acknowledge that these figures are consistent with an absolute increase in the cumulative incidence of major and clinically relevant bleeding events of as much as 1.7%; however, we also emphasize that the difference is almost entirely accounted for by clinically relevant bleeding events, that is, non–life-threatening hemarthroses that did not require mandatory hospitalization, blood transfusion or reintervention. At most, they required drainage and delayed rehabilitation.

We searched MEDLINE through December 2007 by using the following search strategy: ([“knee arthroscopy” {all fields} OR arthroscopic knee surgery] AND [“deep venous thrombosis”{all fields} OR “deep-vein thrombosis”{all fields} OR “thrombophlebitis”{all fields}]). We retrieved only 3 randomized trials (13, 16, 17) that dealt with LMWH prophylaxis after knee arthroscopy. Marlovits and colleagues (13) identified a population at higher thromboembolic risk than our patient sample (41.2% in the placebo group) that included only patients undergoing anterior cruciate ligament reconstruction, and more than 50% of patients had a tourniquet thigh time longer than 2 hours. Michot and colleagues (17) included an intermediate-risk population (15.6% in the untreated group) with more than 70% meniscectomy-involved interventions. Wirth and colleagues (16) recruited patients at a moderate risk for venous thromboembolism (4.1% in the placebo group) that was similar to that of our patient sample (3.2% in the graduated compression stockings group), with about a 50% meniscectomy rate. Of interest, the event rate in the treatment group of the latter 2 studies was approximately 1%, similar to the rate in our study, indicating a substantially equivalent LMWH prophylactic effect. In contrast, the event rate in Marlovits and colleagues’ (13) active treatment group was 2- to 3-fold higher, probably because of the prolonged tourniquet thigh time.

To our knowledge, this is the largest randomized trial of venous thromboprophylaxis after knee arthroscopy (12). Nonetheless, a few potential limitations may limit the generalizability of the study results and deserve careful consideration.

First, our study was not double-blind and double-dummy because we could not afford the cost of “placebo” stockings and syringes for our nonsponsored trial. However, all clinical evaluations and diagnostic tests were per-

formed by physicians unaware of the patients' allocation group.

Second, we used ultrasonography to assess the incidence of deep venous thrombosis, potentially underestimating the actual incidence. However, according to a recent meta-analysis (41), ultrasonography is an appropriate screening method in low-risk populations, such as patients undergoing knee arthroscopy, because high specificity is required to avoid false-positive findings (12). Of note, no patients experienced symptomatic venous thromboembolism during the 3-month follow-up; we therefore believe that a gross underestimation of the true incidence of deep venous thrombosis in our population is unlikely. In addition, our results are similar to those of other published trials that used either venography (6, 7, 9, 14) or ultrasonography (3, 5, 8–12) as the reference test.

Third, because the 2 prophylactic regimens differed mainly in the incidence of distal deep venous thrombosis (1.7% in the graduated compression stockings group vs. 0.3% in the 7-day LMWH group; $P = 0.022$)—a condition for which physicians are uncertain about the need to look for or eventually treat (41–44)—one may disagree with the clinical relevance of our findings. However, we considered only symptomatic isolated distal deep venous thrombosis in the definition of our primary efficacy end point because the accuracy of ultrasonography in symptomatic patients is well documented (41, 45–52) and this policy was endorsed by both the ACCP (15) and the European Agency for the Evaluation of Medicinal Products (30). In addition, LMWHs, hirudin, and fondaparinux have been recently registered for clinical use based on the findings of several trials that used asymptomatic proximal and distal deep venous thrombosis as primary efficacy end points (29, 53–60).

Fourth, because we excluded patients who were having prolonged procedures or had risk factors for thromboembolism, we probably studied a very low-risk sample. Nonetheless, we observed a statistically significant and clinically important 2.3–percentage point higher absolute incidence of the composite primary efficacy end point in patients who wore graduated compression stockings than in patients who received LMWH for 7 days. It is possible that a higher risk population would have a greater need for adequate thromboprophylaxis. Of note, the slightly higher incidence of clinically relevant nonmajor bleeding events we observed in the 7-day LMWH group versus the graduated compression stockings group was accounted for by 4 hemarthroses of less than 300 mL of blood each.

Finally, we found that all deep venous thromboses occurred in the operated leg, which contrasts with findings reported in the literature on major knee surgery (a rate of venographic deep venous thrombosis incidence up to 20% in the contralateral nonoperated leg [61, 62]). No data are available from previous venographic studies (6, 7, 9) dealing with thromboprophylaxis after knee arthroscopy because, for ethical reasons, the investigators only obtained unilateral venography. Conversely, in agreement with our findings, no study that used ultrasonography as the reference test (3–5, 8, 16) detected deep venous thrombosis in the nonoperated leg.

We believe that withholding prophylaxis after knee arthroscopy exposes these predominantly young patients to a small but definite risk for venous thromboembolism (63, 64). The occurrence of a preventable venous thromboembolic event could lead to several consequences for these otherwise healthy young adults, including delayed postsurgical rehabilitation; impaired quality of life (65–67); and the risk for recurrent venous thromboembolism (68), the postthrombotic syndrome (69–71), or pulmonary embolism.

In conclusion, we observed a lower composite end point of asymptomatic proximal deep venous thrombosis, symptomatic venous thromboembolism, and all-cause mortality among patients having knee arthroscopy who received a prophylactic regimen of LMWH for 1 week than in those who wore graduated compression stockings for 1 week. This treatment effect was mainly evident in patients having meniscectomy-related procedures. Future research is needed to clarify the putative role of meniscectomy as a risk factor for venous thromboembolic complications after knee arthroscopy. Meanwhile, we recommend offering a short regimen of LMWH prophylaxis to all patients undergoing knee arthroscopy.

From the University Hospital of Padua, Padua; Hospital of Conegliano Veneto, Conegliano; Ferrara Day Surgery, Ferrara; and the Abano Terme Clinic, Abano Terme, Italy.

Acknowledgment: The authors thank Dr. Sabrina Perazzolo and Mr. Manuele Torelli for the creation of the database and data collection, Dr. Viviana Gialain for bibliographic search and for translating 2 papers from German to Italian, and Ms. Loretta Tasinato for the organization and planning of the visits of all the study patients. The authors also thank all the study patients, without whom this study would not have been possible.

Potential Financial Conflicts of Interest: None disclosed.

Reproducible Research Statement: *Study protocol:* Available by request from Dr. Camporese (e-mail, giuseppe.camporese@sanita.padova.it). *Statistical code and data set:* Not available.

Requests for Single Reprints: Giuseppe Camporese, MD, Unit of Angiology, University Hospital of Padua, Via Giustiniani 2,35128 Padua, Italy; e-mail, giuseppe.camporese@sanita.padova.it.

Current author addresses and author contributions are available at www.annals.org.

References

1. Italian National Health Service Registry, 2005. Rome: Ministero della Salute; 2008. Accessed at www.ministerosalute.it/dettaglio/phPrimoPianoNew.jsp on 27 May 2008.

2. **Hoppener MR, Ettema HB, Henny CP, Verheyen CC, Büller HR.** Low

incidence of deep vein thrombosis after knee arthroscopy without thromboprophylaxis: a prospective cohort study of 335 patients. Acta Orthop. 2006;77:767-71. [PMID: 17068708]

3. **Delis KT, Hunt N, Strachan RK, Nicolaides AN.** Incidence, natural history and risk factors of deep vein thrombosis in elective knee arthroscopy. Thromb Haemost. 2001;86:817-21. [PMID: 11583313]

4. **Williams JS Jr, Hulstyn MJ, Fadale PD, Lindy PB, Ehrlich MG, Cronan J, et al.** Incidence of deep vein thrombosis after arthroscopic knee surgery: a prospective study. Arthroscopy. 1995;11:701-5. [PMID: 8679032]

5. **Jaureguito JW, Greenwald AE, Wilcox JF, Paulos LE, Rosenberg TD.** The incidence of deep venous thrombosis after arthroscopic knee surgery. Am J Sports Med. 1999;27:707-10. [PMID: 10569354]

6. **Stringer MD, Steadman CA, Hedges AR, Thomas EM, Morley TR, Kakkar VV.** Deep vein thrombosis after elective knee surgery. An incidence study in 312 patients. J Bone Joint Surg Br. 1989;71:492-7. [PMID: 2785998]

7. **Demers C, Marcoux S, Ginsberg JS, Laroche F, Cloutier R, Poulin J.** Incidence of venographically proved deep vein thrombosis after knee arthroscopy. Arch Intern Med. 1998;158:47-50. [PMID: 9437378]

8. **Cullison TR, Muldoon MP, Gorman JD, Goff WB.** The incidence of deep venous thrombosis in anterior cruciate ligament reconstruction. Arthroscopy. 1996;12:657-9. [PMID: 9115551]

9. **Durica S, Raskob G, Johnson C, Janssen T, Jay G, Hargrove K, et al.** Incidence of deep-vein thrombosis after arthroscopic knee surgery [Abstract]. Thromb Haemost. 1997;77(Suppl):183.

10. **Ilahi OA, Reddy J, Ahmad I.** Deep venous thrombosis after knee arthroscopy: a meta-analysis. Arthroscopy. 2005;21:727-30. [PMID: 15944631]

11. **Dahl OE, Gudmundsen TE, Haukeland L.** Late occurring clinical deep vein thrombosis in joint-operated patients. Acta Orthop Scand. 2000;71:47-50. [PMID: 10743992]

12. **Ramos J, Perrotta C, Badariotti G, Berenstein G.** Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy. Cochrane Database Syst Rev. 2007:CD005259. [PMID: 17443578]

13. **Marlovits S, Striessnig G, Schuster R, Stocker R, Luxl M, Trattnig S, et al.** Extended-duration thromboprophylaxis with enoxaparin after arthroscopic surgery of the anterior cruciate ligament: a prospective, randomized, placebo-controlled study. Arthroscopy. 2007;23:696-702. [PMID: 17637403]

14. **Lombardi AV Jr, Berend KR, Tucker TL.** The incidence and prevention of symptomatic thromboembolic disease following unicompartmental knee arthroplasty. Orthopedics. 2007;30:46-8. [PMID: 17549868]

15. **Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al.** Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:338S-400S. [PMID: 15383478]

16. **Wirth T, Schneider B, Misselwitz F, Lomb M, Tüylü H, Egbring R, et al.** Prevention of venous thromboembolism after knee arthroscopy with low-molecular weight heparin (reviparin): results of a randomized controlled trial. Arthroscopy. 2001;17:393-9. [PMID: 11288011]

17. **Michot M, Conen D, Holtz D, Erni D, Zumstein MD, Ruflin GB, et al.** Prevention of deep-vein thrombosis in ambulatory arthroscopic knee surgery: A randomized trial of prophylaxis with low–molecular weight heparin. Arthroscopy. 2002;18:257-63. [PMID: 11877611]

18. **Camporese G, Ntita K, Rossi F, Bernardi E, Verlato F, Salmistraro G, et al. The KANT Study Group.** Different thromboprophylaxis approaches in patients undergoing knee arthroscopy (KANT Study): interim report of a prospective randomized study [Abstract]. J Thromb Haemost. 2003;1 (suppl. 1):P1888.

19. **Camporese G, Bernardi E, Ntita K, Verlato F, Salmistraro G, Cordova R, et al. The KANT Study Group.** Different thomboprophylaxis approaches in patients udergoing knee arthroscopy (KANT Study): a prospective randomized study, interim report [Abstract]. J Thromb Haemost. 2005;3 (Suppl 1);P1618.

20. **Camporese G, Bernardi E, Prandoni P, Verlato F, Cordova R, Simioni P, et al. The KANT Study Group.** Graduated compression stockings (GCS) versus low-molecular-weight heparin (LMWH) for prevention of deep vein thrombosis (DVT) after knee arthroscopy (KA). A randomized study [Abstract]. J Thromb Haemost. 2007;5 (Suppl 1):O-T-052.

21. **O'Brien PC, Fleming TR.** A multiple testing procedure for clinical trials. Biometrics. 1979;35:549-56. [PMID: 497341]

22. **Warkentin TE, Greinacher A.** Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:311S-337S. [PMID: 15383477]

23. **Schellong SM, Schwarz T, Halbritter K, Beyer J, Siegert G, Oettler W, et al.** Complete compression ultrasonography of the leg veins as a single test for the diagnosis of deep vein thrombosis. Thromb Haemost. 2003;89:228-34. [PMID: 12574800]

24. **Schellong SM.** Complete compression ultrasound for the diagnosis of venous thromboembolism. Curr Opin Pulm Med. 2004;10:350-5. [PMID: 15316431]

25. **Cogo A, Lensing AW, Koopman MM, Piovella F, Siragusa S, Wells PS, et al.** Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. BMJ. 1998; 316:17-20. [PMID: 9451260]

26. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. JAMA. 1990;263:2753-9. [PMID: 2332918]

27. **Perrier A, Roy PM, Aujesky D, Chagnon I, Howarth N, Gourdier AL, et al.** Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. Am J Med. 2004;116:291-9. [PMID: 14984813]

28. **Roy PM, Colombet I, Durieux P, Chatellier G, Sors H, Meyer G.** Systematic review and meta-analysis of strategies for the diagnosis of suspected pulmonary embolism. BMJ. 2005;331:259. [PMID: 16052017]

29. **Turpie AG, Bauer KA, Eriksson BI, Lassen MR.** Superiority of fondaparinux over enoxaparin in preventing venous thromboembolism in major orthopedic surgery using different efficacy end points. Chest. 2004;126:501-8. [PMID: 15302737]

30. **Committee for Proprietary Medicinal Products.** Points to consider on clinical investigation of medicinal products for prophylaxis of intra- and post-operative venous thromboembolic risk. London: European Agency for the Evaluation of Medicinal Products; 2000. Accessed at www.emea.europa.eu/pdfs/human/ewp/070798en.pdf on 20 May 2008.

31. **Büller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE.** Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126: 401S-428S. [PMID: 15383479]

32. **Lachin JM.** Sample size determinants for r X c comparative trials. Biometrics. 1977;33:315-24. [PMID: 884194]

33. **Elashoff JD.** nQuery Advisor Version 6.0 User's Guide. Los Angeles: Statistical Solution; 2005.

34. **Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. CONSORT Group (Consolidated Standards of Reporting Trials).** The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med. 2001;134:663-94. [PMID: 11304107]

35. **Ettema HB, Hoppener MR, Henny CP, Büller HR, Verheyen CC.** Compliance of Dutch orthopedic departments with national guidelines on thromboprophylaxis. A survey of Dutch orthopedic thromboprohylaxis. Acta Orthop. 2005;76:99-103. [PMID: 15788316]

36. **Hoppener MR, Ettema HB, Henny CP, Verheyen CC, Büller HB.** Symptomatic deep vein thrombosis and immobilization after day-care arthroscopy of the knee [Letter]. J Thromb Haemost. 2005;3:185-7. [PMID: 15634289]

37. **Muntz JE.** The risk of venous thromboembolism in non-large-joint surgeries. Orthopedics. 2003;26:s237-42. [PMID: 12597232]

38. **Bergqvist D, Lowe G.** Venous thromboembolism in patients undergoing laparoscopic and arthroscopic surgery and in leg casts. Arch Intern Med. 2002; 162:2173-6. [PMID: 12390058]

39. **Amaragiri SV, Lees TA.** Elastic compression stockings for prevention of deep vein thrombosis. Cochrane Database Syst Rev. 2000:CD001484. [PMID: 10908501]

40. **Agu O, Hamilton G, Baker D.** Graduated compression stockings in the prevention of venous thromboembolism. Br J Surg. 1999;86:992-1004. [PMID: 10460633]

41. **Goodacre S, Sampson F, Thomas S, van Beek E, Sutton A.** Systematic review and meta-analysis of the diagnostic accuracy of ultrasonography for deep vein thrombosis. BMC Med Imaging. 2005;5:6. [PMID: 16202135]

42. **Righini M, Paris S, Le Gal G, Laroche JP, Perrier A, Bounameaux H.** Clinical relevance of distal deep vein thrombosis. Review of literature data. Thromb Haemost. 2006;95:56-64. [PMID: 16543962]

43. **Gaitini D.** Current approaches and controversial issues in the diagnosis of deep vein thrombosis via duplex Doppler ultrasound. J Clin Ultrasound. 2006; 34:289-97. [PMID: 16788961]

44. **Bounameaux H, Righini M, Perrier A.** Diagnosing deep vein thrombosis:

the case for compression ultrasonography limited to the proximal veins [Letter]. J Thromb Haemost. 2004;2:2260-1. [PMID: 15613044]
45. **Leizorovicz A, Kassai B, Becker F, Cucherat M.** The assessment of deep vein thromboses for therapeutic trials. Angiology. 2003;54:19-24. [PMID: 12593492]
46. **Labropoulos N, Webb KM, Kang SS, Mansour MA, Filliung DR, Size GP, et al.** Patterns and distribution of isolated calf deep vein thrombosis. J Vasc Surg. 1999;30:787-91. [PMID: 10550175]
47. **Atri M, Herba MJ, Reinhold C, Leclerc J, Ye S, Illescas FF, et al.** Accuracy of sonography in the evaluation of calf deep vein thrombosis in both postoperative surveillance and symptomatic patients. AJR Am J Roentgenol. 1996;166: 1361-7. [PMID: 8633448]
48. **Baxter GM, Duffy P, Partridge E.** Colour flow imaging of calf vein thrombosis. Clin Radiol. 1992;46:198-201. [PMID: 1395426]
49. **Schwarz T, Schmidt B, Schmidt B, Schellong SM.** Interobserver agreement of complete compression ultrasound for clinically suspected deep vein thrombosis. Clin Appl Thromb Hemost. 2002;8:45-9. [PMID: 11991239]
50. **Schellong SM, Schwarz T, Halbritter K, Beyer J, Siegert G, Oettler W, et al.** Complete compression ultrasonography of the leg veins as a single test for the diagnosis of deep vein thrombosis. Thromb Haemost. 2003;89:228-34. [PMID: 12574800]
51. **Stevens SM, Elliott CG, Chan KJ, Egger MJ, Ahmed KM.** Withholding anticoagulation after a negative result on duplex ultrasonography for suspected symptomatic deep venous thrombosis. Ann Intern Med. 2004;140:985-91. [PMID: 15197015]
52. **Elias A, Mallard L, Elias M, Alquier C, Guidolin F, Gauthier B, et al.** A single complete ultrasound investigation of the venous network for the diagnostic management of patients with a clinically suspected first episode of deep venous thrombosis of the lower limbs. Thromb Haemost. 2003;89:221-7. [PMID: 12574799]
53. **Schellong SM, Beyer J, Kakkar AK, Halbritter K, Eriksson BI, Turpie AG, et al.** Ultrasound screening for asymptomatic deep vein thrombosis after major orthopaedic surgery: the VENUS study. J Thromb Haemost. 2007;5:1431-7. [PMID: 17419763]
54. **Eriksson BI, Bauer KA, Lassen MR, Turpie AG. Steering Committee of the Pentasaccharide in Hip-Fracture Surgery Study.** Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med. 2001;345:1298-304. [PMID: 11794148]
55. **Bauer KA, Eriksson BI, Lassen MR, Turpie AG. Steering Committee of the Pentasaccharide in Major Knee Surgery Study.** Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med. 2001;345:1305-10. [PMID: 11794149]
56. **Lassen MR, Bauer KA, Eriksson BI, Turpie AG. European Pentasaccharide Elective Surgery Study (EPHESUS) Steering Committee.** Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet. 2002;359:1715-20. [PMID: 12049858]
57. **Turpie AG, Bauer KA, Eriksson BI, Lassen MR. PENTATHALON 2000 Study Steering Committee.** Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. Lancet. 2002;359:1721-6. [PMID: 12049860]
58. **Turpie AG, Bauer KA, Eriksson BI, Lassen MR.** Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. Arch Intern Med. 2002; 162:1833-40. [PMID: 12196081]
59. **Eriksson BI, Ekman S, Kalebo P, Zachrisson B, Bach D, Close P.** Prevention of deep-vein thrombosis after total hip replacement: direct thrombin inhibition with recombinant hirudin, CGP 39393. Lancet. 1996;347:635-9. [PMID: 8596376]
60. **Eriksson BI, Wille-Jørgensen P, Kälebo P, Mouret P, Rosencher N, Bösch P, et al.** A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. N Engl J Med. 1997;337:1329-35. [PMID: 9358126]
61. **Leclerc JR, Geerts WH, Desjardins L, Laflamme GH, L'Espérance B, Demers C, et al.** Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin. Ann Intern Med. 1996;124:619-26. [PMID: 8607589]
62. **Hull R, Raskob G, Pineo G, Rosenbloom D, Evans W, Mallory T, et al.** A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. N Engl J Med. 1993;329:1370-6. [PMID: 8413432]
63. **Rosendaal FR.** Thrombosis in the young: epidemiology and risk factors. A focus on venous thrombosis. Thromb Haemost. 1997;78:1-6. [PMID: 9198119]
64. **Heit JA.** The epidemiology of venous thromboembolism in the community: implications for prevention and management. J Thromb Thrombolysis. 2006;21: 23-9. [PMID: 16475038]
65. **Kahn SR, M'Lan CE, Lamping DL, Kurz X, Bérard A, Abenhaim L. The VEINES Study Group.** The influence of venous thromboembolism on quality of life and severity of chronic venous disease. J Thromb Haemost. 2004;2:2146-51. [PMID: 15613019]
66. **Kahn SR, Ducruet T, Lamping DL, Arsenault L, Miron MJ, Roussin A, et al.** Prospective evaluation of health-related quality of life in patients with deep venous thrombosis. Arch Intern Med. 2005;165:1173-8. [PMID: 15911732]
67. **van Korlaar IM, Vossen CY, Rosendaal FR, Bovill EG, Cushman M, Naud S, et al.** The impact of venous thrombosis on quality of life. Thromb Res. 2004;114:11-8. [PMID: 15262479]
68. **Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, et al.** The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica. 2007; 92:199-205. [PMID: 17296569]
69. **Kahn SR, Ginsberg JS.** Relationship between deep venous thrombosis and the postthrombotic syndrome. Arch Intern Med. 2004;164:17-26. [PMID: 14718318]
70. **Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, et al.** The long-term clinical course of acute deep venous thrombosis. Ann Intern Med. 1996;125:1-7. [PMID: 8644983]
71. **Brandjes DP, Büller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, et al.** Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet. 1997;349:759-62. [PMID: 9074574]

Current Author Addresses: Drs. Camporese, Verlato, Salmistraro, Cordova, Franz, and Andreozzi: Unit of Angiology, University Hospital of Padua, Via Giustiniani 2, 35128 Padua, Italy.
Dr. Bernardi: Department of Emergency and Accident Medicine, Hospital of Conegliano, Via Brigata Possagno 4, 31015 Conegliano (TV), Italy
Drs. Prandoni and Simioni: Department of Medical and Surgical Sciences, University Hospital of Padua, Via Giustiniani 2, 35128 Padua, Italy.
Dr. Noventa: Department of Clinical and Experimental Medicine, Clinical Epidemiology Group, University Hospital of Padua, Via Giustiniani 2, 35128 Padua, Italy.
Drs. Ntita, Frangos, and Rossi: Department of Knee Surgery, Abano Terme Clinic, Piazza Colombo 1, Abano Terme, Italy.
Dr. Zucchetta: Unit of Nuclear Medicine, University Hospital of Padua, Via Giustiniani 2, 35128 Padua, Italy.
Dr. Kontothanassis: Italian Phlebologic Institute at Ferrara Day Surgery, Via Verga 17, 44100 Ferrara, Italy.

Author Contributions: Conception and design: G. Camporese, E. Bernardi.
Analysis and interpretation of the data: G. Camporese, E. Bernardi, F. Noventa, F. Verlato.
Drafting of the article: G. Camporese, E. Bernardi, P. Prandoni, F. Noventa, F. Verlato.
Critical revision of the article for important intellectual content: G. Camporese, E. Bernardi, P. Prandoni, F. Noventa, F. Verlato, P. Simioni, G.M. Andreozzi.
Final approval of the article: G. Camporese, E. Bernardi, P. Prandoni, F. Noventa, F. Verlato, P. Simioni, K. Ntita, G. Salmistraro, C. Frangos, F. Rossi, R. Cordova, F. Franz, P. Zucchetta, D. Kontothanassis, G.M. Andreozzi.
Provision of study materials or patients: G. Camporese, K. Ntita, G. Salmistraro, C. Frangos, F. Rossi, R. Cordova, F. Franz, P. Zucchetta, D. Kontothanassis.
Statistical expertise: E. Bernardi, F. Noventa.
Collection and assembly of data: G. Camporese, E. Bernardi, F. Verlato, K. Ntita, G. Salmistraro, C. Frangos, F. Rossi, R. Cordova, F. Franz, P. Zucchetta, D. Kontothanassis.

Appendix: Additional KANT Study Investigators

University Hospital of Padua

Unit of Angiology: *Physicians:* Drs. C. Chiarion, R. Martini, M. Nardi, and L. Zotta. *Nurses:* E. Baracco, M. Bettella, M.L. Cappelletto, M. Facchinato, C. Fiorese, M.B. Galvan, F. Nalin, A. Romanato, R. Salmaso, O.M. Scarpazza, B. Scarso, C. Tonello, G. Ughini, and P. Zulian.

Department of Surgical and Medical Sciences: Drs. S. Gavasso, M. Perlati, V. Rossetto, G. Tognin, and P. Zerbinati.

Department of Nuclear Medicine: Professor F. Bui, and Dr. M.C. Marzola.

Abano Terme Clinic

Department of Knee Surgery: Drs. M. Cesana, R. Nardacchione, and M. Sanavio.

Appendix Table. **Efficacy and Safety Results at First and Second Interim Analyses**

Variable	7-d GCS, *n (%)*	7-d LMWH, *n (%)*	14-d LMWH, *n (%)*	Absolute Difference (95% CI), *percentage points*	
				7-d GCS vs. 7-d LMWH	7-d LMWH vs. 14-d LMWH
First interim analysis (40% sample)	260	265	261	–	–
Primary efficacy end point	5 (1.9)	3 (1.1)	2 (0.8)	0.8 (−1.3 to 2.9)	0.4 (−1.3 to 2.0)
Primary safety end point	0	1 (0.4)	1 (0.4)	−0.4 (−1.1 to 0.4)	0
Second interim analysis (65% sample)	446	443	444	–	–
Primary efficacy end point	16 (3.6)	4 (0.9)	4 (0.9)	2.7 (0.7 to 4.6)	0.002 (−1.2 to 1.2)
Primary safety end point	1 (0.2)	2 (0.4)	2 (0.4)	−0.2 (−1.0 to 0.5)	0

GCS = graduated compression stockings; LMWH = low-molecular-weight heparin.