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ORIGINAL ARTICLE

Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study

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Summary. *Background:* Patients undergoing major abdominal surgery carry a high risk of venous thromboembolism (VTE), but the optimal duration of postoperative thromboprophylaxis is unknown. *Objectives:* To evaluate the efficacy and safety of thromboprophylaxis with the low molecular weight heparin (dalteparin), administered for 28 days after major abdominal surgery compared to 7 days' treatment. *Patients/Methods:* A multicenter, prospective, assessor-blinded, open-label, randomized trial was performed in order to evaluate prolonged thromboprophylaxis after major abdominal surgery. In total, 590 patients were recruited, of whom 427 were randomized and received at least 1 day of study medication, and 343 reached an evaluable endpoint. The primary efficacy endpoint was objectively verified VTE occurring between 7 and 28 days after surgery. All patients underwent bilateral venography at day 28. *Results:* The cumulative incidence of VTE was reduced from 16.3% with short-term thromboprophylaxis (29/178 patients) to 7.3% after prolonged thromboprophylaxis (12/165) (relative risk reduction 55%; 95% confidence interval 15–76; $P = 0.012$). The number that needed to be treated to prevent one case of VTE was 12 (95% confidence interval 7–44). Bleeding events were not increased with prolonged compared with short-term thromboprophylaxis. *Conclusions:* Four-week administration of dalteparin, 5000 IU once daily, after major abdominal surgery significantly reduces the rate of VTE, without increasing the risk of bleeding, compared with 1 week of thromboprophylaxis.

Keywords: dalteparin, deep vein thrombosis, low molecular weight heparin, surgery, thromboembolism.

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Introduction

Patients undergoing major abdominal surgery are at risk of developing postoperative venous thromboembolism (VTE). Several methods to reduce the incidence of VTE have been implemented clinically, and thromboprophylaxis with low molecular weight heparin (LMWH) administered for the first postoperative week in general surgical patients has been shown to be efficacious [1].

Abdominal surgery leads to a hypercoagulable state, and an associated increased risk of deep vein thrombosis (DVT) [2]. The activation of the coagulation system persists for at least 14 days [3], and data suggest that patients remain in a hypercoagulable state for at least 1 month after orthopedic surgery [4]. Prospective cohort studies have reported the incidence of postoperative DVT to be as high as 25% [5,6], and an incidence of pulmonary embolism (PE) ranging from 0.13% to 0.63% in the 4–6 weeks after general surgery [7,8]. A small, randomized study of general surgical patients showed a non-significant reduction in the incidence of DVT, as assessed by bilateral venography 28 days after surgery, following 4 weeks vs. 1 week of thromboprophylaxis with LMWH [9]. A larger, double-blind multicenter study with a comparable design recently reported a significant reduction of DVT in patients with abdominal or pelvic cancer after prolongation of prophylactic administration with LMWH [10].

Meta-analyses have documented the efficacy of prolonged thromboprophylaxis with LMWH in patients undergoing elective hip or knee replacement [11]. The reduction of thromboembolic complications in these patients has not been limited to asymptomatic and venographically detected DVT, but includes a reduction of the incidence of symptomatic DVT [12].

The aim of the present prospective, assessor-blinded, randomized multicenter study was to evaluate the efficacy and safety of 4 weeks compared to 1 week of thromboprophylaxis with dalteparin, 5000 IU s.c. once daily, following

major abdominal surgery, and to determine the incidence of late thromboembolic complications.

Methods

This multicenter, prospective, randomized, open-label study was undertaken in surgical departments of university and large community hospitals in Denmark and Norway.

Patients were eligible for inclusion in the study provided they were hospitalized for major abdominal surgery, gave written informed consent to participate in the study, and were over 18 years old. Major surgery was defined as an open abdominal surgical intervention in the gastric tract, the biliary system, pancreas, or intestine, as well as explorative laparotomy. The duration of the planned surgical procedure was more than 1 h.

The exclusion criteria were severe peripheral arterial insufficiency (absence of a palpable pulsation in the dorsalis pedis artery), pregnancy, allergy to radiographic contrast medium, acid sulfite or LMWH, hepatic insufficiency, acute stroke within the last 3 months, gastrointestinal bleeding within the last month, hemorrhagic diathesis, anticoagulation treatment (including heparin, and vitamin K antagonists, but not antiplatelet treatment), treatment with dextran, psychosis or severe dementia, simultaneous participation in another clinical study, or previous participation in the present study.

All patients received standard thromboprophylaxis with once-daily s.c. dalteparin, 5000 IU, and wore graduated compression stockings for 7 days. The first dose of dalteparin was administered on the evening prior to surgery, or a reduced dose of 2500 IU was administered 2 h prior to surgery and repeated 12 h later.

Patients scheduled for abdominal surgery were enrolled in the study and randomly assigned to receive either no further treatment after day 7 (short-term thromboprophylaxis group) or prolonged administration of once-daily dalteparin, 5000 IU s.c., for a further 21 days (prolonged thromboprophylaxis group). All patients were randomized within the first 7 days. After discharge, the injections were administered by the patient ($n = 120$), a family member ($n = 4$), a visiting nurse ($n = 32$) or a staff nurse ($n = 9$). Randomization was by a computer-generated random allocation in blocks of 10, stratified by center. Allocation concealment was obtained by using consecutively numbered, opaque sealed envelopes, which contained details of the prophylactic regimen that the patient would receive. Compliance was checked by a review of the patient's drug chart, which was signed for every injection, and by counting used syringes returned on the day of venography. All the patients received written and oral information about the study medication and the venography procedure. The staff nurses taught patients who were allocated to prolonged thromboprophylaxis self-injection techniques.

The effect of short-term vs. prolonged thromboprophylaxis was evaluated by comparing the number of patients with thromboembolic events in the two groups. VTE was classified in three ways: (i) asymptomatic DVT detected by venography; (ii) symptomatic DVT or PE verified by objective means; or (iii) DVT or PE verified by autopsy.

Patients were assessed daily during admission by the medical staff for clinical signs of DVT or reported shortness of breath. In the case of clinically suspected DVT or PE, unilateral venography or ventilation/perfusion lung scintigraphy was performed, respectively. Patients with verified thromboembolic events were hospitalized and received appropriate anticoagulation treatment. Any deaths or serious events, defined as major bleeding, cardiopulmonary side effects, serious allergic reactions, or events resulting in hospitalization, prolongation of hospitalization or permanent disability were recorded.

Patients could withdraw their informed consent from the study at any time and for any reason with or without explanation. Patients could also be withdrawn from the study for any medical reason by the treating physician. As the incidence and the clinical significance of late thromboembolic complications following abdominal surgery have not yet been clarified, it was regarded as ethically justifiable to use a control group, which did not receive prolonged prophylaxis. The study complied with the Helsinki II Declaration and was approved by the Scientific Ethical Committee of Copenhagen (KF01-227/96), the Danish National Board of Health (5312-285-1996), the Danish Data Protection Agency (1996-1200-598) and the Ethics Committee in Norway (421/99.46.99).

The primary efficacy endpoint was VTE occurring beyond day 7 and up to day 28 after surgery, identified as symptomatic DVT verified by venography, symptomatic PE verified by ventilation/perfusion scan or spiral computerized tomography, VTE verified by autopsy, or asymptomatic DVT as assessed by venography.

The protocol called for a bilateral venography on day 28. The venography was performed according to a modified method of Rabinov and Paulin [13] with the examination couch at a 60° angle. The longest possible film was used, with division lengthwise into two or three parts. A tourniquet was applied proximally to the malleoli before injection of 50 mL of contrast medium. The contrast was injected before anterior/posterior exposures were taken. After injection of an additional 50 mL of contrast medium, pictures were obtained in a lateral projection. The venous system was examined from the ankle to the caval vein. All venograms were individually evaluated, at a single center, by two radiologists with a specific interest in venography (K.N. and H.H.). In case of disagreement, the radiologists met to re-evaluate the venograms in order to obtain a consensus. These radiologists were unaware of the personal data of the patients, the randomization group, the clinical outcome, and the date of the venography.

The criterion for a diagnosis of DVT was a constant intraluminal defect seen on at least two images. Filling defects in muscle veins or perforating veins were not considered to be DVT. Thrombi located in the popliteal vein or above were

regarded as proximal. A venogram was considered adequate if the entire deep venous system was visualized from the calf veins to the common iliac vein in both legs or a thrombus was found.

The primary safety endpoint was the occurrence of hemorrhage between days 7 and 28. Bleeding was classified as major if: it resulted in death, a fall in hemoglobin concentration of ≥ 2 g dL^{-1}, or the transfusion of at least 2 units of blood; it was retroperitoneal, intracranial, or intraocular; it resulted in a serious or life-threatening clinical event; or surgical or medical intervention was required to stop or control the bleeding. Bleeding was classified as minor if it was overt and had some clinically important features (epistaxis, hematuria or cases of hematemesis not leading to endoscopy) but did not meet the criteria for major bleeding.

Patients were followed for a period of minimum of 2 months after venography with regard to readmittance to the hospital due to development of DVT or PE. If the patients died within the follow-up period, the hospital record and the death certificate were reviewed to assess the cause of mortality.

Statistical analyses

The incidence of VTE following abdominal surgery without prolonged thromboprophylaxis was estimated to be 15%. On the basis of the hypothesis of the study, it was assumed that there would be a 10% absolute risk reduction of DVT with prolonged thromboprophylaxis, equivalent to an incidence of 5% after prolonged prophylaxis. It was further assumed that 60% of the patients would be evaluable for primary efficacy endpoint, due to scheduling difficulties after major surgery. Thus, recruitment of 590 patients was required, with a type I error of 5% and an 80% power, based on a two-sided chi-squared test.

The chi-squared test was used for comparing binominal data, and the Mann–Whitney *U*-test for continuous data. The level of significance was taken as less than 0.05. For the estimation and interpretation of differences between the two groups in rates of VTE, 95% confidence intervals (CIs) were calculated. The statistical software used was SPSS for Windows, version 8.0 (SPSS Inc., Chicago, IL, USA).

The occurrence of VTE was analyzed on an intention-to-treat (ITT) basis, the population consisting of patients who fulfilled all the following criteria: underwent randomization; received at least one dose of study treatment or were randomized to short-term prophylaxis; and could be evaluated for DVT or PE. Patients who underwent unilateral venography with a normal result on day 28, or who died within the study period and in whom no VTE was found at autopsy, were considered not to have DVT or PE. Patients who died within the study period and had no autopsy performed were excluded from the ITT population. We also employed a broader analysis comprising all patients who underwent randomization. Patients who died without a subsequent autopsy or a sound endpoint were regarded as having no VTE in this analysis.

Results

Study population

Patients from five hospitals were recruited between January 1997 and June 2003. Of the 590 patients who met the inclusion criteria, 114 did not give informed consent to participate, 47 were too ill to continue the study after the surgical procedure, and two patients did not undergo surgery (Fig. 1). In total, 427 patients entered the randomized section of the study and received at least 1 day of study medication. Of these, 222 were randomized to short-term thromboprophylaxis and 205 to prolonged thromboprophylaxis; these patients constitute the safety population. Reasons for exclusion from the ITT population were refusal of venography, inadequate venography, oral anticoagulation, transferral, or death without autopsy, leaving an ITT population consisting of 178 patients in the short-term prophylaxis group and 165 in the prolonged prophylaxis group (Table 1). The total numbers of patients who dropped out of the study were 44 (19.8%) in the short-term group and 40 (19.5%) in the prolonged thromboprophylaxis group (Table 2). Patients in the ITT population had higher bodyweight ($P < 0.05$) as compared to the dropout group. This was attributed to a significantly higher rate of females dropping out ($P < 0.05$).

The patients in the two treatment arms were well matched for age, sex, weight, previous VTE, and previous cancer (Table 1). The types of surgical procedure were similar in the two groups, colorectal resection being the most common. More than half of the patients in each group underwent surgery for malignancy (60% and 56% of patients in the short-term and prolonged thromboprophylaxis groups, respectively). In the majority of patients, surgery for malignancy was curative (71% and 67%). The median duration of hospitalization was 9 days in both groups of patients.

In the short-term thromboprophylaxis group, 175 patients received all doses during the first 7 days with basic thromboprophylaxis, whereas three patients missed one or two injections. In the prolonged thromboprophylaxis group, all patients fully complied during the 7-day period of thromboprophylaxis. Prophylaxis was initiated the evening before surgery in 37 patients and 2 h prior to surgery in 306 patients. Four patients missed one or two injections, and three patients missed more than eight of the 21 prescribed doses in the extended prophylaxis period.

VTE events

The cumulative incidence of overall VTE between days 7 and 28 after major abdominal surgery was 16.3% (29 of 178 patients) in the short-term group and 7.3% (12 of 165 patients) in the prolonged thromboprophylaxis group ($P = 0.012$) (Table 3). This corresponds to a relative reduction in risk of 55% (95% CI 15–76) with 4 weeks compared to 1 week of thromboprophylaxis with dalteparin. The number that needed to be treated to prevent one case of overall VTE was 12 (95% CI 7–44).

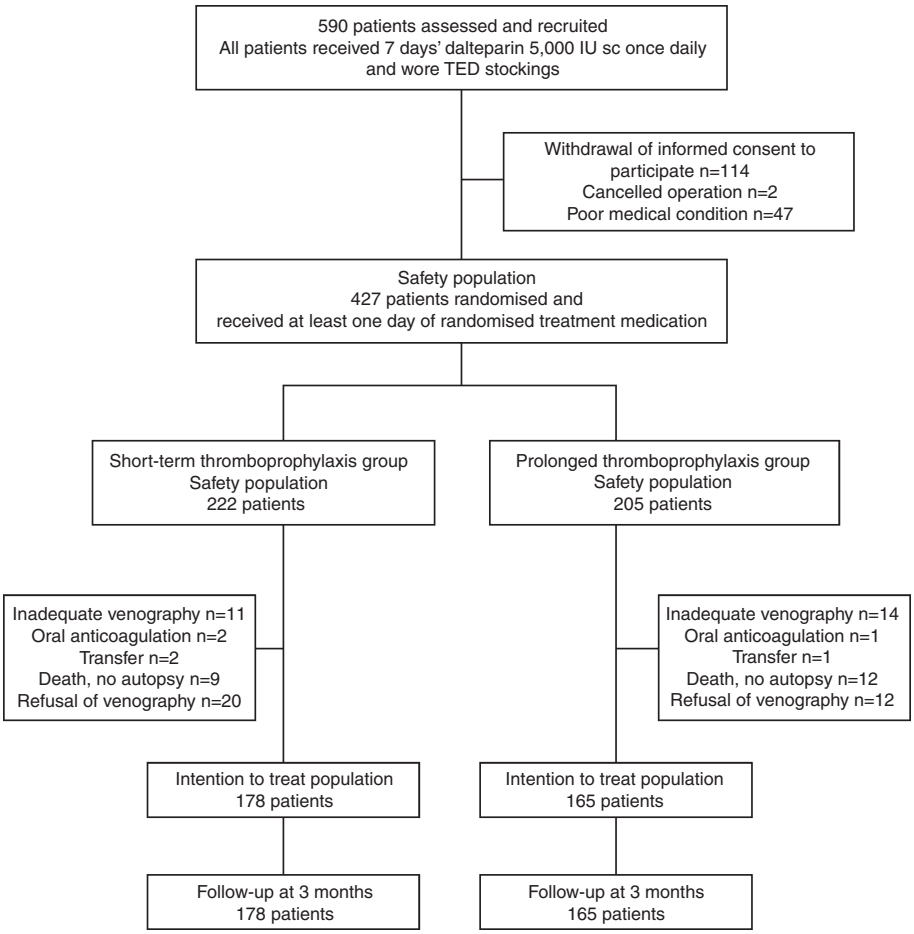

Fig. 1. Study population.

Table 1 Baseline characteristics: intention-to-treat population

	Short-term thromboprophylaxis ($n = 178$)	Prolonged thromboprophylaxis ($n = 165$)
Demographics		
Age (years), median (range)	67 (22–93)	67 (25–91)
Gender, F/M	83/95	86/79
Weight (kg), median (range)	72 (40–124)	71 (40–124)
Previous VTE, *n* (%)	9 (5.1)	6 (3.6)
Previous cancer, *n* (%)	14 (7.9)	11 (6.7)
Type of surgery, *n* (%)		
Colorectal	121 (68.0)	111 (67.3)
Gastric, biliary	20 (11.2)	24 (14.5)
Pancreatic	3 (1.7)	4 (2.4)
Other abdominal	34 (19.1)	26 (15.8)

Table 2 Baseline characteristics: dropout patients

	Short-term thromboprophylaxis ($n = 44$)	Prolonged thromboprophylaxis ($n = 40$)
Demographics		
Age (years) (range)	67 (33–86)	68 (36–89)
Gender, F/M	26/18	23/17
Weight (kg) (range)	69 (47–97)	66 (40–95)
Previous VTE, *n* (%)	3 (7)	3 (8)
Previous cancer, *n* (%)	8 (18)	3 (8)
Type of surgery, *n* (%)		
Colorectal	29 (64)	26 (65)
Gastric or biliary	6 (14)	6 (15)
Pancreatic	0	1 (3)
Other abdominal	9 (20)	7 (18)

The cumulative incidence of DVT (proximal or distal) during the randomized period was reduced from 14.9% in the short-term group to 7.3% in the prolonged thromboprophylaxis group ($P = 0.027$), a relative risk reduction of 51% (95% CI 6–74) (Table 3). The corresponding number that needed to be treated to prevent one case of DVT was 14 (95% CI 8–100).

The relative risk reduction of DVT from prolongation of thromboprophylaxis was comparable in patients receiving thromboprophylaxis the evening before surgery (60%) (95% CI 26–88) and in patients who received thromboprophylaxis 2 h before surgery (54%) (95% CI 2–78).

The cumulative incidence of proximal DVT decreased from 8.0% in the short-term group to 1.8% in the prolonged thromboprophylaxis group ($P = 0.009$), a relative risk

Table 3 Cumulative incidence of venous thromboembolism on day 28: intention-to-treat population

Venous thromboembolic event	Treatment group, *n* (%)		Relative risk reduction (95% CI) (%)	*P*
	Short-term thromboprophylaxis ($n = 178$)	Prolonged thromboprophylaxis ($n = 165$)		
Overall venous thromboembolism	29 (16.3)	12 (7.3)	55 (15–76)	0.012
Deep vein thrombosis	26 (14.9)*	12 (7.3)	51 (6–74)	0.027
Distal	13 (7.4)*	9 (5.5)	25 (−30–67)	0.28
Proximal	14 (8.0)*	3 (1.8)	77 (22–93)	0.009

*$n = 175$ as three patients with pulmonary embolism did not undergo venography. CI, confidence interval.

reduction of 77% (95% CI 22–93) (Table 3). The number that needed to be treated to prevent one case of proximal DVT was 17 (95% CI 10–59). In the robustness analysis including all randomized patients, the reduction of VTE incidence resulting from the prolongation of thromboprophylaxis was still highly significant ($P = 0.02$).

There were three symptomatic venous thromboembolic events, all due to non-fatal cases of PE found in the short-term group. Two of these cases were verified with ventilation/perfusion scans (high probability for PE) and one with a computed tomography scan (bilateral PE). No cases of symptomatic DVT were found during the first 7 days or during the study period. Autopsy revealed one case with DVT in the short-term group. No patients were readmitted to the hospital with symptomatic VTE during the 2-month follow-up period.

The kappa value for the evaluation of the venograms was 0.90 (95% CI 0.82–0.97), indicating a high interobserver agreement between the radiologists.

Safety outcomes

Major and minor bleeding events were not increased in the prolonged vs. the short-term thromboprophylaxis group. Major bleeding occurred in four (1.8%) patients in the short-term group and in one (0.5%) patient in the prolonged thromboprophylaxis group. All of these patients had upper gastrointestinal bleeding diagnosed by endoscopy. Minor bleeding occurred in two (0.9%) and three (1.5%) patients in the short-term and prolonged thromboprophylaxis groups, respectively. Hematoma at the injection site was found in 19 (9.3%) patients who received prolonged thromboprophylaxis. This parameter was irrelevant for patients in the short-term group, who received no injections after day 7. There were no cases of heparin-induced thrombocytopenia during this study.

During the study period, 10 (4.5%) patients in the control group and 16 (7.8%) in the prolonged prophylaxis group died ($P = 0.3$). Autopsy was performed in one and four of these cases, respectively. None of the patients who died without the completion of a subsequent autopsy had clinical signs of VTE or died suddenly to suggest PE as a contributing cause of death. Bleeding or hemorrhage caused none of the deaths. During the follow-up period, seven patients in the control group and four in the prolonged prophylaxis group died. None of the deaths was considered to be related to the study treatment (Table 4).

Table 4 Causes of deaths occurring during the 3-month observation period

Cause of death	Short-term thromboprophylaxis ($n = 17$)	Prolonged thromboprophylaxis ($n = 20$)
Cancer	7	3
Anastomotic leakage	2	4
Cardiac insufficiency	4	5
Pulmonary insufficiency	1	1
Pneumonia	1	1
Multiorgan failure	2	5
Stroke	0	1
Gastrointestinal hemorrhage	1	0

Discussion

In this trial, late thromboembolic complications occurred in approximately one of six patients following major abdominal surgery, despite the use of 1 week of thromboprophylaxis. The present study demonstrates that the risk of developing VTE is significantly reduced by the extension of thromboprophylaxis with dalteparin, in recommended prophylactic doses, from 7 to 28 days. The number that needed to be treated to avoid one case of VTE was only 12, and prolonging the duration of thromboprophylaxis did not increase the risk of bleeding, with the exception of minor injection hematomas, in this patient population.

In a study of prolonged thromboprophylaxis following elective abdominal and non-cardiac thoracic surgery, a 52% (95% CI 14–198) relative risk reduction in thromboembolism was found, but the study was underpowered [9]. The ENOX-ACAN II study [10], which compared a 4-week and a 1-week regimen of the LMWH enoxaparin in patients undergoing elective curative surgery for abdominal or pelvic cancer, demonstrated a comparable 60% (95% CI 10–82) relative risk reduction in postoperative VTE with prolonged thromboprophylaxis.

The open-label design and the previous publications of preliminary results from our trial as symposia proceedings

[14,15] constitute a potential source of bias. However, these publications were not conventional interim reports, as they were based on the primary assessments of subsets of venograms made by local staff radiologists. Furthermore, the presentation of these data was not in conflict with the study plan. The inclusion of patients in the study continued to reach the total sample size as predefined in the protocol, irrespective of the presentation of the preliminary results. There were no significant differences regarding the baseline characteristics between patients included before and after publication of the preliminary results, suggesting no major bias due to selection. In the present article, the final interpretation of the venograms was based on the decisions of independent blinded radiologists as defined in the protocol. Despite the limitations of our study design, we therefore consider the conclusions robust.

To ensure that diagnostic bias was minimized, assessors of venograms were unaware of any patient data and group assignments. Venography is considered to be the 'gold standard' for establishing the diagnosis of DVT [16]. A number of authors argue that this procedure is not always technically possible, and that it overestimates the rate of clinically relevant DVT, as most cases of distal DVT are not symptomatic. However, even asymptomatic postoperative DVT is associated with a 59% relative risk increment of developing late post-thrombotic syndrome compared with patients without postoperative DVT [17]. Furthermore, a highly significant association was found between asymptomatic proximal DVT, detected by compression ultrasound, and 90-day mortality in medical patients [18]. This is in agreement with a large autopsy series reporting that fatal PE is seldom preceded by symptomatic DVT [19].

In order for venographically detected DVT to be a reliable parameter for clinical VTE, there should be an association between the two endpoints, as has been established in two meta-analyses of randomized studies of prolonged thromboprophylaxis after lower limb arthroplasty [11,20]. These meta-analyses showed a significant 50% reduction in the odds of symptomatic VTE, similar to that observed for venographically detected DVT. The use of asymptomatic endpoints in thromboprophylactic studies seems justified, as the study population would need to be at least 10 times as large to be able to show a reduction in mortality or symptomatic VTE.

The development of proximal DVT is associated with a high risk of clinical symptoms, including embolism. In the present trial, a significant reduction in the cumulative incidence of both overall and proximal DVT was observed with prolonged thromboprophylaxis.

In this multicenter study, fewer than 7% of the patients in either group had inadequate venography. Thus, we provide an accurate estimate of the cumulative incidence of DVT occurring up to 1 month following major abdominal surgery with and without prolonged prophylaxis.

The robustness of the study was tested by an analysis that included randomized patients without a sound VTE endpoint. This analysis also showed a highly significant reduction in VTE with prolonged thromboprophylaxis. The present trial was designed with wide inclusion criteria to limit selection bias. This was considered essential for a valid translation of the results into daily clinical practice. Overall, the proportion of non-evaluable patients in this trial was comparable to that in similar trials of patients undergoing surgery for malignant disease [10,21]. The conclusion of the present trial is not affected by the higher rate of female patients withdrawing before reaching an endpoint, as the beneficial effect from prolongation of prophylaxis was apparent for both genders. Therefore, it is considered that the results of this study are associated with a high level of external validity, despite the reported exclusion rates of patients.

This study is the first to show that administration of dalteparin 5000 IU once daily for 4 weeks after major abdominal surgery significantly reduces the rates of VTE complications without jeopardizing safety, when compared with 1 week of thromboprophylaxis.

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Disclosure of Conflict of Interests

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