Randomized trial

Randomized clinical trial of postoperative fondaparinux *versus* perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery

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Background: **The aim of this study was to assess whether the synthetic factor Xa inhibitor fondaparinux reduced the risk of venous thromboembolism more efficiently than the low molecular weight heparin dalteparin in patients undergoing major abdominal surgery.**

Methods: **In a double-blind double-dummy randomized study, patients scheduled for major abdominal surgery under general anaesthesia received once-daily subcutaneous injections of fondaparinux 2·5 mg or dalteparin 5000 units for 5–9 days. Fondaparinux was started 6 h after surgery. The first two doses of dalteparin, 2500 units each, were given 2 h before surgery and 12 h after the preoperative administration. The primary outcome measure was a composite of deep vein thrombosis detected by bilateral venography and symptomatic, confirmed deep vein thrombosis or pulmonary embolism up until day 10. The main safety outcome measure was major bleeding during treatment.**

Results: **Among 2048 patients evaluable for efficacy, the rate of venous thromboembolism was 4·6 per cent (47 of 1027) with fondaparinux compared with 6·1 per cent (62 of 1021) with dalteparin, a relative risk reduction of 24·6 (95 per cent confidence interval −9·0 to 47·9) per cent ($P = 0·144$), which met the predetermined criterion for non-inferiority of fondaparinux. Major bleeding was observed in 49 (3·4 per cent) of 1433 patients given fondaparinux and 34 (2·4 per cent) of 1425 given dalteparin ($P = 0·122$).**

Conclusion: **Postoperative fondaparinux was at least as effective as perioperative dalteparin in patients undergoing high-risk abdominal surgery.**

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Introduction

Patients undergoing general surgery are at substantial risk of postoperative venous thromboembolism[1,2]. Without effective thromboprophylaxis, the reported incidences of deep vein thrombosis (DVT) and proximal DVT, as assessed by the fibrinogen uptake test, are 25 and 7 per cent, respectively, and those of pulmonary embolism (PE) and fatal PE are 1·6 and 0·9 per cent[1]. Low-dose unfractionated heparin and low molecular weight heparin (LMWH) reduce rates of DVT, as assessed by the fibrinogen uptake test, to 8 and 6 per cent, respectively[1]. In a recent meta-analysis of studies comparing these two agents, use of LMWH was associated with a significant 29 per cent relative risk reduction in clinically overt venous thromboembolism[3].

Fondaparinux is a new synthetic selective factor Xa inhibitor. In major orthopaedic surgery, fondaparinux administered subcutaneously at the once-daily dose of 2·5 mg starting after operation reduced the rate of venous thromboembolism by more than 50 per cent compared with the LMWH enoxaparin, without increasing the risk of clinically relevant bleeding[4–8].

This study was a randomized, double-blind, double-dummy trial to compare the efficacy and safety of fondaparinux with that of the LMWH dalteparin in the prevention of venous thromboembolism in high-risk patients undergoing abdominal surgery under general anaesthesia.

Patients and methods

Patients were eligible for the study if they were due to undergo abdominal surgery expected to last more than 45 min under general anaesthesia and were aged over 60 years, or aged over 40 years with one or more additional risk factors for thromboembolic complications. The qualifying risk factors included obesity (defined as a body mass index above 30·0 kg/m^2 for men and 28·6 kg/m^2 for women), a history of venous thromboembolism, congestive heart failure (New York Heart Association grade III or IV), chronic obstructive pulmonary disease, inflammatory bowel disease, or surgery for cancer.

Patients were excluded if they were having urological (except kidney), gynaecological, laparoscopic, vascular or emergency trauma surgery. Other main exclusion criteria were a life expectancy of less than 2 months, active bleeding, a documented bleeding disorder or thrombocytopenia, ulcerating or angiodysplastic gastrointestinal disease that was not the reason for the surgery, a haemorrhagic stroke or surgery to the brain, spine or eye within the previous 3 months, bacterial endocarditis or another contraindication to anticoagulant therapy, pregnancy, hypersensitivity to contrast media, or a serum creatinine concentration above 180 μmol/l in a well hydrated patient. Patients who received any type of anticoagulant or fibrinolytic therapy or dextran within 2 days of planned administration of the first study drug were also excluded.

Study design

This was a double-blind double-dummy randomized trial. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and local regulations. The protocol was approved by independent ethics committees and written informed consent was obtained before randomization. Within 24 h before administration of the first study drug but at least 2 h before induction of anaesthesia, patients were randomized to receive once-daily subcutaneous injections of either fondaparinux 2·5 mg (Arixtra®; Sanofi-Synthelabo, Paris, France and NV Organon, Oss, The Netherlands) or dalteparin (Fragmin®; Pharmacia Corporation, Peapack, New Jersey, USA). The first fondaparinux injection was scheduled for 6 h after surgical closure. Dalteparin 2500 units was given 2 h before induction of anaesthesia and 12 h later. Thereafter, dalteparin was given at the once-daily dose of 5000 units. Patients given fondaparinux received a placebo injection 2 h before surgery and again 12 h later to correspond with the dalteparin dosing schedule. Patients given dalteparin received a placebo injection 6 h after surgery to correspond with the fondaparinux injection schedule. If epidural anaesthesia/analgesia was planned in conjunction with general anaesthesia, omission of the preoperative injection was recommended. If an epidural catheter was used after surgery, it was removed at least 2 h before the next injection. The scheduled duration of treatment was 5–9 days.

Patients were systematically examined for DVT with bilateral ascending contrast venography of the legs[9] between days 5 and 10 after surgery, but no more than one calendar day after the last injection of study drug. If DVT was suspected clinically before the planned day of venography, ultrasonography of the leg veins was performed, followed by bilateral venography if the result was positive. If the scan was negative, bilateral venography was performed on the scheduled day. Clinically suspected PE was confirmed by a high-probability lung scan[10], pulmonary angiography, helical computed tomography, or at autopsy. A non-high-probability lung scan defect plus confirmed DVT was considered as PE.

Follow-up was from the end of the study treatment until day 30 ± 2 when patients were contacted in person or by telephone. Patients were instructed to report any symptoms or signs of venous thromboembolism or bleeding and any other clinical event that occurred during follow-up. Extension of prophylaxis with non-study drug and treatment of venous thromboembolism arising during the study were left to the investigator's discretion.

Study drugs

Study medications were provided in 0·2-ml prefilled single-dose syringes of identical appearance, containing fondaparinux 2·5 mg or matching placebo (isotonic saline), or dalteparin 5000 or 2500 units (at concentrations of 25 000 and 12 500 units/ml respectively) or matching placebo. The use of aspirin, thienopyridines and non-steroidal anti-inflammatory drugs was discouraged during the study. Other antiplatelet agents, intermittent pneumatic leg compression, dextran, and anticoagulant or thrombolytic agents were prohibited. The use of graded-pressure elastic stockings was permitted and early mobilization was strongly recommended.

Outcome measures

The primary efficacy outcome was venous thromboembolism (asymptomatic and/or symptomatic DVT or PE or both) recorded until the time of the screening venography or day 10, whichever occurred first. Secondary efficacy outcomes were the individual events of total DVT, proximal DVT, distal DVT, symptomatic venous thromboembolism up to day 10, and symptomatic venous thromboembolism up to day 30 ± 2. Venography was considered positive if there was an intraluminal filling defect seen in two different views, or after repeated injection of the contrast medium; thrombi in the popliteal vein or above were considered 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.

The primary safety outcome was major bleeding detected between the first injection of study drug (dalteparin or placebo) and two calendar days after the last injection. Major bleeding was defined as fatal bleeding, bleeding that was retroperitoneal, intracranial, intraspinal or involved any other critical organ, bleeding leading to reoperation or intervention, and a bleeding index of 2·0 or more. The bleeding index was derived by adding the number of transfused units of packed red blood cells or whole blood to the difference in haemoglobin level measured in grams per decilitre before and after a bleeding event. Secondary safety outcomes were death, other reported bleeding, thrombocytopenia and any other adverse events.

Study outcome measures, including venography results, clinically suspected thromboembolic and bleeding events, and deaths, were adjudicated by a central independent committee that was unaware of the patients' treatment assignment and the local assessment.

Statistical analysis

The trial was initially designed to demonstrate whether fondaparinux was superior to dalteparin in preventing venous thromboembolism in high-risk elective abdominal surgery. Assuming a frequency of venous thromboembolism with dalteparin of at least 7 per cent[11,12], it was estimated that 1000 evaluable patients per treatment group would give a power of 75 per cent to detect a 40 per cent risk reduction predicted from previous fondaparinux trials in major joint surgery[8]. The target number of recruited patients was increased to 2900 to allow for the likely failure to obtain primary efficacy data in about 30 per cent of patients. A non-inferiority analysis was also planned; based on the previously observed odds ratio (OR) between LMWHs and placebo, it was calculated that an OR between fondaparinux and dalteparin with an upper limit of the 95 per cent confidence interval (c.i.) below 1·70 would indicate non-inferiority (defined as preserving at least 63 per cent of the LMWH effect compared with placebo)[3,13]. When it became apparent during the study that the overall rate of venous thromboembolism was lower than anticipated, the steering committee decided, before database lock and data unblinding, to perform the predefined non-inferiority analysis.

The efficacy analysis included data from all randomized patients with adequate venous thromboembolism assessment (an evaluable venogram or adjudicated symptomatic venous thromboembolism). Safety analyses included data on all randomized patients who had received at least one dose of the study medication. Two-sided Fisher's exact test was used for binary variables. Normal approximation 95 per cent c.i. for risk reduction and the OR between fondaparinux and dalteparin were calculated.

The effect of risk factors for venous thromboembolism on the primary study outcome was evaluated by multivariable logistic regression analysis. Co-variates for logistic regression analysis were selected on the basis of their clinical plausibility. Treatment effect was adjusted for those risk factors that were identified at multivariate analysis. Efficacy and safety outcomes were analysed *post hoc* according to whether the first injection of active fondaparinux was administered before 6 h, at 6 h, or later after surgery. Two-sided $P < 0{\cdot}050$ was considered to indicate statistical significance.

Results

Between October 2001 and October 2002, 2927 patients in 131 hospitals in 22 countries were randomized to receive either fondaparinux or dalteparin (*Fig. 1*). A total of 2858 patients (97·6 per cent) received at least one dose of study drug and were included in the safety analysis; of these, 2048 patients (71·7 per cent) with an adequate evaluation of the primary efficacy outcome were included in the efficacy analysis.

Demographic variables and risk factors at baseline, type of anaesthesia, and type and duration of surgery were similar in the two groups of patients analysed for safety (*Tables 1* and *2*) and efficacy (data not shown). Nearly 70 per cent of treated patients were aged over 60 years. Other frequent risk factors for venous thromboembolism were obesity (22·3 per cent) and cancer surgery (67·9 per cent); 96·9 per cent of the patients had two or more risk factors. Colorectal surgery was the most common surgical procedure (56·2 per cent). A catheter

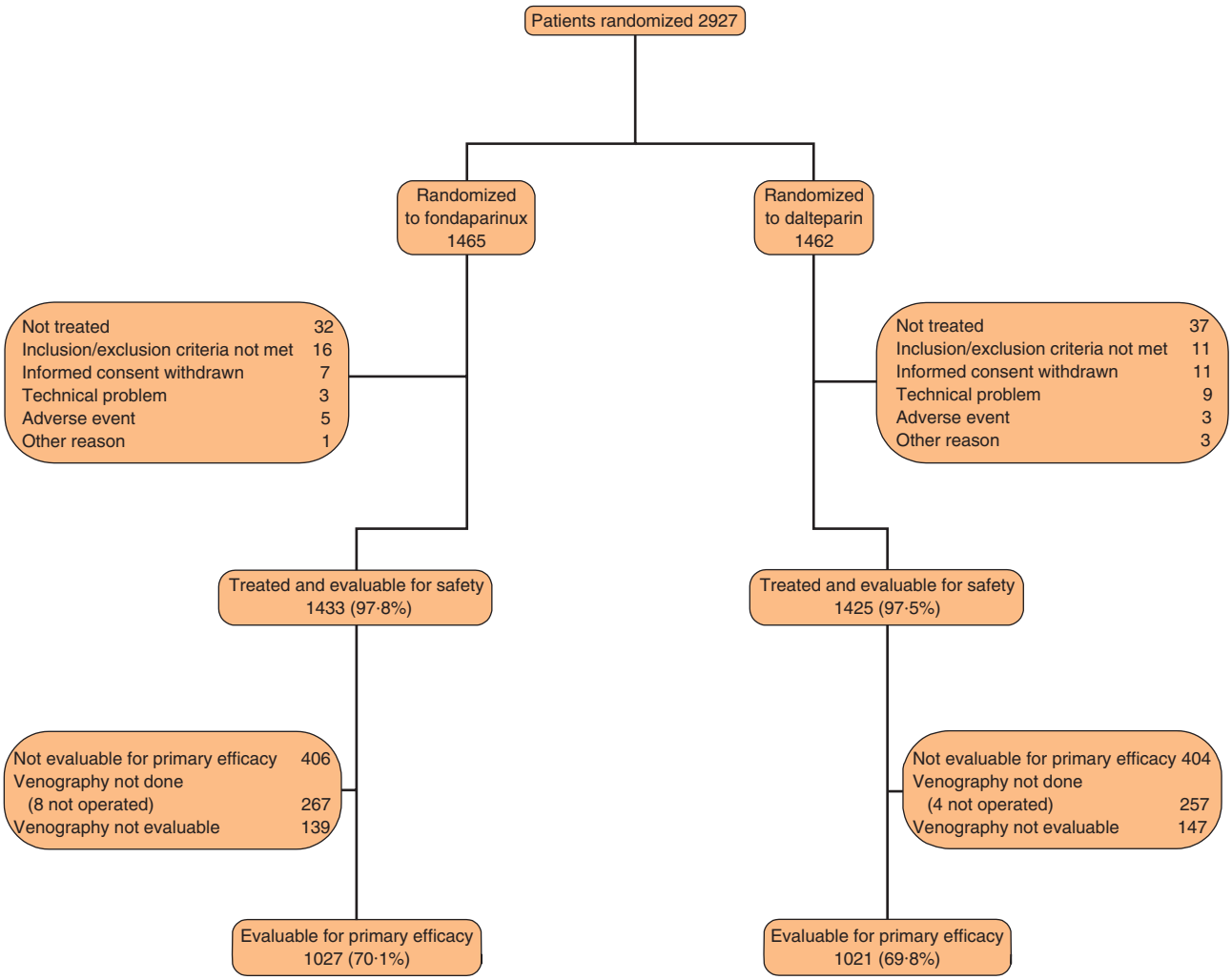

Fig. 1 Study profile

for epidural anaesthesia or analgesia (in conjunction with general anaesthesia) was used in 37·0 per cent of patients.

Dalteparin was started before operation in 68·6 per cent of patients. The preoperative dose was omitted mainly in patients who had combined epidural and general anaesthesia. The first dose of fondaparinux was given at least 6 h after surgery in 1139 (79·5 per cent) of treated and operated patients. The median duration of prophylaxis was 7 days in both groups.

Following the completion of study drug administration, 511 (35·7 per cent) of 1433 patients in the fondaparinux group and 521 (36·6 per cent) of 1425 in the dalteparin group received extended prophylaxis with either heparins or vitamin K antagonists on the investigator's initiative.

Efficacy outcomes

Venous thromboembolism was detected by screening venography or up to day 10 in 109 (5·3 per cent) of 2048 patients. The rate of venous thromboembolism was 4·6 per cent (47 of 1027) with fondaparinux compared with 6·1 per cent (62 of 1021) with dalteparin, a relative risk reduction of 24·6 (95 per cent c.i. −9·0 to 47·9) per cent ($P = 0·144$) (*Table 3*). The corresponding OR was 0·74, with an upper 95 per cent confidence limit of 1·09, below the predetermined criterion of 1·70 for non-inferiority.

Multivariable analysis showed that surgery for cancer (OR 1·75 (95 per cent c.i. 1·03 to 2·99)), duration of surgery (OR 1·36 (95 per cent c.i. 1·21 to 1·52) for each hour), body mass index (OR 1·08 (95 per cent c.i. 1·04 to 1·12) for each kg/m^2) and age (OR 1·05 (95 per cent c.i. 1·03 to 1·07) for each year) were risk factors for venous

Table 1 Baseline demographic and clinical characteristics of randomized and treated patients

	Fondaparinux ($n = 1433$)	Dalteparin ($n = 1425$)
Median (range) age (years)	66 (31–92)	65 (17–93)
Sex ratio (M : F)	788 : 645	796 : 629
Mean(s.d.) weight (kg)	74·2(16·6)	74·3(16·0)
Mean(s.d.) body mass index (kg/m^2)	26·3(5·3)	26·3(5·2)
Risk factor*		
Age > 60 years	1008 (70·3)	985 (69·1)
Men with body mass index > 30 kg/m^2	125 (16·1)	127 (16·1)
Women with body mass index > 28·6 kg/m^2	190 (29·8)	188 (30·1)
History of venous thromboembolism	52 (3·6)	53 (3·7)
Congestive heart failure (NYHA grade III or IV)	7 (0·5)	4 (0·3)
Chronic obstructive pulmonary disease	103 (7·2)	111 (7·8)
Inflammatory bowel disease	68 (4·7)	87 (6·1)
Cancer surgery	954 (66·6)	987 (69·3)
No. of risk factors†		
< 2	47 (3·3)	41 (2·9)
< 2	501 (35·0)	482 (33·8)
≥ 3	885 (61·8)	902 (63·3)

*Values in parentheses are percentages. †Including surgery of more than 45 min duration as a risk factor. NYHA, New York Heart Association.

thromboembolism independent of treatment group. The relative risk reduction after adjustment for these co-variates was 31·2 (95 per cent c.i. − 3·0 to 54·0) per cent in favour of fondaparinux. The relative efficacy of fondaparinux and dalteparin in the subgroups of patients with significant risk factors for venous thromboembolism is shown in *Table 4*.

Surgery was performed for cancer in 1941 (67·9 per cent) of 2858 randomized patients and in 1408 (68·8 per cent) of 2048 patients included in the efficacy analysis. In this subgroup, the rate of venous thromboembolism was 7·7 per cent (55 of 712) in the dalteparin group and 4·7 per cent (33 of 696) in the fondaparinux group, an observed relative risk reduction with fondaparinux of 38·6 (95 per cent c.i. 6·7 to 59·6) per cent. For non-cancer surgery, the rate of venous thromboembolism was 2·3 per cent (seven of 309) and 4·2 per cent (14 of 331) in dalteparin- and fondaparinux-treated patients respectively, an observed relative risk reduction with fondaparinux of − 86·7 (95 per cent c.i. − 356·5 to 23·6) per cent.

During the treatment interval, there were 11 symptomatic adjudicated venous thromboembolic events, six (0·4 per cent) in the fondaparinux group and five

Table 2 Surgical characteristics of treated and operated patients

	Fondaparinux ($n = 1425$)	Dalteparin ($n = 1421$)
Type of surgery†		
Colorectal surgery	798 (56·0)	802 (56·4)
Gastric and intestinal surgery	321 (22·5)	366 (25·8)
Cholecystectomy, hepatic or other biliary surgery	246 (17·3)	249 (17·5)
Other abdominal surgery	352 (24·7)	285 (20·1)
Type of anaesthesia		
General only	959 (67·3)	924 (65·0)
General and regional	461 (32·4)	493 (34·7)
Regional only	5 (0·4)	4 (0·3)
Use of epidural catheter	506 (35·5)	548 (38·6)
Time from incision to closure (h : min)*	2 : 30(0 : 23–11 : 00)	2 : 30(0 : 16–15 : 27)

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Patients may have had more than one type of operation.

Table 3 Venous thromboembolic events up to the first venogram or up to day 10, whichever occurred first

	Fondaparinux*	Dalteparin*	P**	Relative risk reduction (%)†
All VTE	47 of 1027 (4·6)	62 of 1021 (6·1)	0·144	24·6 (− 9·0, 47·9)
Any DVT	43 of 1024 (4·2)	59 of 1018 (5·8)	0·10	27·5 (− 6·3, 50·6)
Any proximal DVT‡	5 of 1076 (0·5)	5 of 1077 (0·5)	1·0	0·1 (− 244·7, 70·9)
Distal DVT only§	40 of 1025 (3·9)	54 of 1021 (5·3)	0·14	26·1 (− 10·1, 50·5)
Symptomatic VTE¶	6 of 1465 (0·4)	5 of 1462 (0·3)		
DVT	2 of 1465 (0·1)	2 of 1462 (0·1)		
Non-fatal PE	2 of 1465 (0·1)	0 of 1462 (0·0)		
Fatal PE	3 of 1465 (0·2)	3 of 1462 (0·2)		

Values in parentheses are *percentages or †95 per cent confidence intervals. ‡The number of patients available for adjudication for proximal DVT; §patients with distal deep-vein thrombosis (DVT), but not evaluable for proximal DVT were not counted; ¶data refer to all randomized patients; one patient in the fondaparinux group presented first with symptomatic DVT and subsequently fatal pulmonary embolism (PE). VTE, venous thromboembolism. **Fisher's exact test.

Table 4 Relative efficacy of fondaparinux and dalteparin according to patient and surgical characteristics

	Fondaparinux*	Dalteparin*	Relative risk reduction† (%)
Age (years)			
< 75	35 of 832 (4·2)	42 of 843 (5·0)	15·6 (– 30·9, 45·5)
≥ 75	12 of 195 (6·2)	20 of 178 (11·2)	45·2 (– 8·8, 75·4)
Sex			
M	27 of 575 (4·7)	30 of 570 (5·3)	10·8 (– 48·1, 46·3)
F	20 of 452 (4·4)	32 of 451 (7·1)	37·6 (– 7·4, 63·8)
Cancer surgery			
Yes	33 of 696 (4·7)	55 of 712 (7·7)	38·6 (6·7, 59·7)
No	14 of 331 (4·2)	7 of 309 (2·3)	– 86·7 (– 356·5, 23·6)
Duration of surgery‡			
< Median	19 of 517 (3·7)	14 of 492 (2·8)	29·2 (– 34·5, 154·7)
≥ Median	28 of 508 (5·5)	48 of 528 (9·1)	39·4 (4·9, 61·3)

Values in parentheses are *percentages or †95 per cent confidence intervals. ‡Data were missing for three patients, two in the fondaparinux group and one in the dalteparin group.

Table 5 Safety outcomes during the treatment interval (plus two calendar days after day of last injection of study treatment)

	Fondaparinux ($n = 1433$)	Dalteparin ($n = 1425$)
Major bleeding	49 (3·4)	34 (2·4)
Fatal bleeding	2 (0·1)	2 (0·1)
Bleeding in a critical organ	0 (0)	0 (0)
Bleeding leading to reoperation or intervention	29 (2·0)	14 (1·0)
Bleeding with return to operating theatre	19 (1·3)	12 (0·8)
Bleeding index > 2·0*	18 (1·3)	18 (1·3)
Other bleeding	31 (2·2)	23 (1·6)
Death from any cause	15 (1·0)	20 (1·4)

Values in parentheses are percentages. *The bleeding index was calculated as [no. of units of packed red blood cells or whole blood transfused] + [(prebleeding) – (postbleeding) haemoglobin concentration (g/dl)].

(0·4 per cent) in the dalteparin group, including three deaths deemed to have resulted from PE. By the end of follow-up (day 32), there were 12 (0·8 per cent) and 14 (1·0 per cent) symptomatic adjudicated venous thromboembolic events in the fondaparinux and dalteparin groups respectively, and death judged to be due to PE occurred in five (0·3 per cent) and nine (0·6 per cent) patients respectively. Non-fatal PE occurred in four patients (0·3 per cent) from the fondaparinux group and two (0·1 per cent) from the dalteparin group.

Safety outcomes

The incidence of major bleeding was 3·4 per cent (49 of 1433) with fondaparinux and 2·4 per cent (34 of 1425) with dalteparin ($P = 0·122$) (*Table 5*). In each group, there were two fatal bleeding episodes and no instances of non-fatal major bleeding into a critical organ. Most reoperations consisted of evacuation of wound haematoma. Forty-five major bleeding episodes led to permanent discontinuation of study treatment, 26 in the fondaparinux group and 19 in the dalteparin group. The overall results were consistent regardless of sex, age, body mass index, type of surgery, duration of surgery and creatinine clearance (data not shown). In patients undergoing surgery for cancer, major bleeding was reported in 32 (3·4 per cent) of 954 patients treated with fondaparinux and in 25 (2·5 per cent of 987 treated with dalteparin ($P = 0·355$).

The incidence of other adverse events was similar in the two groups. There were no epidural haematomas. The platelet count was lower than 100 000/mm^3 in 49 (3·4 per cent) of 1421 patients given fondaparinux and in 50 (3·5 per cent) of 1409 who had dalteparin.

During the study, 15 patients (1·0 per cent) in the fondaparinux group and 20 (1·4 per cent) in the dalteparin group died (*Table 5*). Corresponding figures for death by day 32 were 40 (2·8 per cent) and 55 (3·9 per cent).

Effect of timing of first fondaparinux injection

Major bleeding occurred in 32 (2·8 per cent) of 1139 patients who received their first fondaparinux injection at least 6 h after surgical closure and nine (3·4 per cent) of 263 who received fondaparinux closer to surgery. The corresponding figures for venous thromboembolism were 4·2 per cent (35 of 842) and 6·5 per cent (12 of 184).

Discussion

In patients undergoing high-risk general surgery postoperative administration of fondaparinux produced a 24·6 per cent relative risk reduction in the incidence of venous thromboembolism compared with perioperative administration of dalteparin. The difference in favour of fondaparinux increased to 31·2 per cent after adjusting for risk factors for venous thromboembolism identified by multivariate analysis. This risk reduction was not statistically significant but is consistent with previously reported results in major orthopaedic surgery. The predefined noninferiority analysis indicated that fondaparinux was at least as effective as dalteparin. It is of practical and clinical importance that these results were achieved with a postoperative dose regimen that would be preferred by most surgeons and anaesthetists.

The rates of major bleeding observed with fondaparinux and dalteparin were within the range previously reported in trials of LMWH prophylaxis[3]. Fatal bleeding or bleeding into a critical organ was rare in both groups. The higher rate of bleeding with fondaparinux was due to an excess of bleeding episodes leading to intervention, one-third of these being evacuation or aspiration of a surgical haematoma at the bedside. Consistent with previous studies in orthopaedic surgery[14], the timing of the first fondaparinux injection appeared to influence the bleeding risk. The lower rate of major bleeding seen when fondaparinux was started 6 h or later after incision closure was achieved without loss of antithrombotic efficacy. An improved benefit-to-risk ratio when fondaparinux was given no sooner than 6 h after wound closure was seen previously in the fondaparinux trials in major orthopaedic surgery[14].

The population of patients undergoing general surgery was quite heterogeneous in terms of the risk for venous thromboembolism. This large study provides an update on risk factors for venous thromboembolism during effective prophylaxis; age, obesity, duration of surgery and cancer surgery were confirmed as risk factors. The subgroup analysis suggested that fondaparinux may more effective than dalteparin in patients at particularly high-risk for venous thromboembolism, including those with cancer, those having prolonged surgery and the elderly.

The rate of non-evaluable patients of 28·3 per cent was not completely unexpected in a clinical study in which the endpoint was assessed by venography. Indeed, this rate was anticipated in the sample size calculation. The rate of non-evaluability was only slightly higher than that observed in the orthopaedic surgery trials and could by explained by the general poor health of the patients included in this study. The effects on generalizability of this rate should not be relevant.

The preoperative dose of dalteparin was omitted in about 30 per cent of the patients. This was mainly due to the concomitant use of epidural anaesthesia and highlighted the concerns about giving preoperative thromboprophylaxis in these patients. However, it should be noted that no difference in efficacy was found when preoperative and postoperative start of LMWH prophylaxis was compared in patients undergoing major orthopaedic surgery[8]. Omission of the preoperative dose of dalteparin might have favoured dalteparin in terms of the rate of bleeding complications.

Recent discussion has questioned which efficacy outcome measure is most appropriate when evaluating new antithrombotic agents for the prevention of venous thromboembolism[15]. The present choice of a composite of symptomatic and asymptomatic events is validated by several overviews of clinical trial results[3,13,16–23]. These overviews found consistent risk reduction regardless of the outcome measure used in prophylaxis trials (from asymptomatic DVT to symptomatic venous thromboembolism)[8,16]. Importantly, this study included a large number of patients, had high-quality venography with a high evaluability rate, and had an independent central adjudication committee for venography and for all the other study endpoints.

When the trial was designed, only short-term prophylaxis was recommended after high-risk abdominal surgery by international guidelines and by health authorities in both Europe and North America[1,2]. Recently, antithrombotic prophylaxis extended to 4 weeks after abdominal surgery for cancer has been found to prevent late thrombotic events[17].

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Members of the PEGASUS group steering committee were G. Agnelli (Chair), D. Bergqvist, R. Cariou, A. T. Cohen, J. Egberts and A. S. Gallus. The adjudication committee comprised M. Gent (Chair) and members of the Hamilton Research Center group. The data monitoring committee comprised A. Leizorovicz (Chair), O. Dahl and N. Victor.

Patients were recruited from paticipating centres in the following countries. Argentina (131 patients, seven centres): S. Viñuales, Buenos Aires; A. De Bonis, Buenos Aires; J. M. Ceresetto, Buenos Aires; M. C. Gallo, Buenos Aires; F. Santini, Mar Del Plata; R. Grinspan, Buenos Aires; J. Bluguermann, Buenos Aires. Australia (155 patients, eight centres): S. Dunkley, Sydney; R. Baker, Perth; P. Thurlow, Melbourne; A. Curtin, Lismore; K. Narayan, Melbourne; T. Brighton, Melbourne; D. Coghlan, Adelaide; H. Salem, Melbourne. Austria (22 patients, two

centres): D. Depisch, Neustadt; H. Mischinger, Graz. Belgium (55 patients, three centres): M. Legrand, Huy; W. Ceelen, Ghent; G. Decker, Luxembourg. Brazil (119 patients, eight centres): J. Péricles Esteves, Salvador; J. M. Reis, São Paulo; P. E. Leães, Porto Alegre; S. Rasslan, São Paulo; L. Olivatto, Rio de Janeiro; E. Werneck, Rio de Janeiro; J. Mejia, Fortaleza; C. M. Neto, Curitiba. Canada (65 patients, seven centres): L. Desjardins, St Foy; E. Yeo, Toronto; J. P. Faucher, Greenfield Park; M. Rodger, Ottawa; D. Rolf, Kelowna; P. Blair, New Westminster; M. Mant, Edmonton. Chile (61 patients, two centres): A. Csendes, Santiago; L. Ibañez, Santiago. Czech Republic (321 patients, ten centres): S. Kubin, Karlovy Vary; V. Trebicky, Cesky Brod; J. Schwarz, Prague; J. Horak, Mlada Boleslav; V. Treska, Plzen; J. Faltyn, Prague; J. Adamkova, Prague; P. Opletal, Usti nad Labem; J. Wechsler, Brno; M. Ryska, Prague. Denmark (89 patients, three centres): S. Schulze, Glostrup; O. Thorlacius-Ussing, Aalborg; P. Wille-Jørgensen, Copenhagen. Finland (57 patients, two centres): M. Pääkkönen, Kuopio; J. Mäkelä, Oulu. France (236 patients, 14 centres): G. Janvier, Pessac; J.-L. Bourgain, Villejuif; B. Vallet, Lille; M. Carretier, Poitiers; N. Nathan Denizot, Limoges; M. Vergos, Saint-Mandé; P. Barsotti, Tours; Y. Munche, Lyon; M. Voitellier, Vichy; G. Angelvin, Avignon; P. Coriat, Paris; F. Bur, Metz; C. Meyer, Strasbourg; J.-P. Favre, Dijon. Germany (118 patients, six centres): T. Manger, Frankfurt/Oder; A. Encke, Frankfurt/Main; C. Mueller, Munich; W. E. Schmidt, Bochum; S. Schellong, Dresden; M. Buechler, Heidelberg. Hungary (214 patients, four centres): F. Jakab, Budapest; L. Harsányi, Budapest; L. Tóth, Siófok; Á. Altorjai, Székesfehérvár. Italy (413 patients, 15 centres): G. Liguori, Trieste; E. Ancona, Padua; W. Ageno, Varese; M. Silingardi, Reggio Emilia; A. Maffei Faccioli, Padua; M. Lise, Padua; P. Parise, Gubbio; R. Biffi, Milan; V. Di Carlo, Milan; D. Imberti, Piacenza; S. Testa, Cremona; A. Bartoli, Perugia; S. Bertoglio, Genoa; L. Gennari, Rozzano; O. Terranova, Padua. Norway (69 patients, three centres): J. H. Solhaug, Oslo; J. E. Grønbech, Trondheim; J. Kristinsson, Oslo. Poland (350 patients, nine centres): P. Andziak, Warsaw; R. Jaworski, Wroclaw; J. Wasiak, Lodz; K. Ziaja, Katowice; A. Jawien, Bydgoszcz; Z. Sledzinski, Gdansk; I. W. Krasnodebski, Warsaw; W. Witkiewicz, Wroclaw; G. Wallner, Lublin. South Africa (42 patients, four centres): R. Du Toit, Bloemfontein; B. Jacobson, Johannesburg; B. Warren, Cape Town; J. H. R. Becker, Pretoria. Spain (68 patients, seven centres): J. Marti Rague, Barcelona; J. M. Sanchez Ortega, Barcelona; E. Del Valle, Madrid; S. Lledo, Valencia; H. Ortiz, Pamplona; M. Monreal, Badalona; J. Garcia Valdecasas, Barcelona. Sweden (131 patients, three centres): K.-G. Ljungström, Danderyd; D. Bergqvist, Urban Karlbom, Lars Påhlman Uppsala; R. Andersson, Lund. Switzerland (58 patients, five centres): S. Martinoli, Lugano; M. Gillet, Lausanne; P.-A. Clavien, Zurich; P. Gertsch, Bellinzona; J. Lange, St Gallen. The Netherlands (137 patients, seven centres): C. G. B. M. Rupert, Heerenveen; M. M. W. Koopman, Amsterdam; E. H. Eddes, Deventer; M. Van Marwijk-Kooy, Zolle; P. De Ruiter, Alkmaar; I. R. O. Nováková, Nijmegen; J. Van der Meer, Groningen. UK (16 patients, two centres): A. Cohen, London.

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