## ORIGINAL ARTICLE

# Fondaparinux combined with intermittent pneumatic compression vs. intermittent pneumatic compression alone for prevention of venous thromboembolism after abdominal surgery: a randomized, double-blind comparison

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ON BEHALF OF THE APOLLO INVESTIGATORS***

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**Summary.** *Background:* The benefit of combined mechanical and pharmacologic methods for venous thromboembolism prevention after abdominal surgery has not been clearly established. *Objectives:* To compare the efficacy and safety of fondaparinux in conjunction with intermittent pneumatic compression vs. intermittent pneumatic compression alone in this context. *Patients and Methods:* This was a randomized, double-blind, placebo-controlled superiority trial. Patients aged at least 40 years undergoing abdominal surgery were randomized to receive either fondaparinux 2.5 mg or placebo s.c. for 5–9 days, starting 6–8 h postoperatively. All patients received intermittent pneumatic compression. The primary efficacy outcome was venous thromboembolism up to day 10. The main safety outcomes were major bleeding and all-cause mortality. Follow-up lasted 32 days. *Results:* Of the 1309 patients randomized, 842 (64.3%) were evaluable for efficacy. The venous thromboembolism rate was 1.7% (7/424) in the fondaparinux-treated patients and 5.3% (22/418) in the placebo-treated patients (odds ratio reduction 69.8%; 95% confidence interval 27.9–87.3; $P = 0.004$). Fondaparinux significantly reduced the proximal deep vein thrombosis rate from 1.7% (7/417) to 0.2% (1/424; $P = 0.037$). Major bleeds occurred in 1.6% (10/635) and 0.2% (1/650) of fondaparinux-treated and placebo-treated patients, respectively ($P = 0.006$), none being fatal or involving a critical organ. By day 32, eight patients (1.3%) receiving fondaparinux and five (0.8%) receiving placebo had died. *Conclusions:* In patients undergoing abdominal surgery and receiving intermittent pneumatic compression, fondaparinux 2.5 mg reduced the venous thromboembolism rate by 69.8% as compared to pneumatic compression alone, with a low bleeding risk as compared to placebo.

**Keywords**: abdominal surgery, clinical trial, fondaparinux, intermittent pneumatic compression, prevention, venous thromboembolism.

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***Investigators and Committees contributing to the study are listed in the Appendix.

## Introduction

In patients undergoing major abdominal surgery not receiving thromboprophylaxis, the observed rates of deep vein thrombosis range between 15% and 30%, and the risk of fatal pulmonary embolism is between 0.2% and 0.9% [1]. Numerous randomized clinical trials and meta-analyses have shown that low-dose unfractionated heparin and low molecular weight heparin reduce deep vein thrombosis rates by at least 60% [1–3]. However, this beneficial effect is associated with increased bleeding risk, particularly in certain categories of patients. In the most recent meta-analysis, unfractionated heparin and low molecular weight heparins were associated with major bleeding rates of 2.7% and 2.4%, respectively [3].

The main reason for using mechanical methods of thromboprophylaxis is to lower bleeding risk [1]. However, these methods have been poorly studied in comparison to anticoagulant-based regimens [1]. Therefore, the efficacy of intermittent pneumatic compression remains uncertain [4–9], although recent data tend to indicate that this method is

effective for preventing deep vein thrombosis, notably if combined with pharmacologic prophylaxis [10,11]. After high-risk abdominal surgery, it is currently recommended in patients with high bleeding risk or combined with anticoagulant agents [1]. However, the benefit of adding anticoagulant therapy to intermittent pneumatic compression has never been clearly established in this setting. The results of one previous study suggested that combining unfractionated heparin and intermittent pneumatic compression was more effective than each method used alone [12].

Once-daily fondaparinux 2.5 mg, starting at least 6 h postoperatively, proved more effective than low molecular weight heparin for preventing venous thromboembolism after major orthopedic surgery [13–16]. In patients undergoing major abdominal surgery, fondaparinux was at least as effective as low molecular weight heparin for venous thromboembolism prevention [17]. In these studies, the risk of clinically relevant bleeding in the fondaparinux groups was comparable to that observed in the low molecular weight heparin groups when fondaparinux was started 6 h or later after incision closure [15,17]. We therefore conducted a randomized, double-blind, placebo-controlled trial to compare the efficacy and safety of fondaparinux combined with intermittent pneumatic compression with those of intermittent pneumatic compression alone for venous thromboembolism prevention after abdominal surgery.

## Methods

### Patients

Patients aged over 40 years, weighing over 50 kg and scheduled to undergo abdominal surgery expected to last longer than 45 min were eligible for the study.

Patients due to undergo vascular surgery, with evidence of leg ischemia caused by peripheral vascular disease, or unable to receive intermittent pneumatic compression or elastic stockings, were excluded. Pregnant women and women of childbearing age not using effective contraception were also excluded. Other exclusion criteria were: life-expectancy < 6 months; clinical signs of deep vein thrombosis and/or history of venous thromboembolism within the previous 3 months; active bleeding; documented congenital or acquired bleeding disorder; active ulcerative gastrointestinal disease, unless it was the reason for the present surgery; hemorrhagic stroke or surgery on the brain, spine or eyes within the previous 3 months; bacterial endocarditis or other contraindication for anticoagulant therapy; planned indwelling intrathecal or epidural catheter for more than 6 h after surgical closure; unusual difficulty in achieving epidural or spinal anesthesia (e.g. more than two attempts); known hypersensitivity to fondaparinux or iodinated contrast medium; current addictive disorders; serum creatinine concentration above 2.0 mg dL$^{-1}$ in a well-hydrated patient and platelet count below 100 000 mm$^{-3}$. Finally, patients requiring anticoagulant therapy, or other pharmacologic prophylaxis besides intermittent pneumatic compression, according to the investigator, were excluded.

### Study design

This was a randomized, double-blind, placebo-controlled study. The day of surgery was defined as day 1. Before anesthesia induction, patients were randomly assigned, using a centralized computer-generated schedule (1:1 randomization in blocks of four and stratified by center), to receive once-daily s.c. injections of either fondaparinux 2.5 mg (fondaparinux sodium, Arixtra, GlaxoSmithKline, Research Triangle Park, NC, USA) or placebo. The first injection was scheduled 6–8 h after surgical closure, provided that hemostasis was achieved, and the second injection 16–28 h after the first. If an intrathecal or epidural catheter was used postsurgery, this was to be removed at least 2 h before the first injection. During the on-study-drug period of 5–9 days, all patients were to receive venous thromboembolism prophylaxis with intermittent pneumatic compression using any type of device, except a foot pump, for a duration left to the investigator's discretion. The use of elastic stockings was left to the investigator's discretion. If the patient was discharged from hospital before completing the on-study-drug period, a visiting nurse administered the remaining trial injections.

In hospital, patients were examined daily for signs and symptoms of venous thromboembolism. Patients were systematically examined for lower extremity deep vein thrombosis by bilateral ascending contrast venography [18] between days 5 and 10, but no more than 1 calendar day after the last study drug injection. Clinically suspected pulmonary embolism was confirmed by a high-probability lung scan, by a non-high-probability lung scan defect plus confirmed deep vein thrombosis, by pulmonary angiography, by helical computed tomography, or at autopsy.

Patients underwent a follow-up visit in person, or were contacted by mail or telephone, between days 28 and 32. During follow-up, patients were instructed to report any symptoms or signs of venous thromboembolism or bleeding and any other clinical event occurring since treatment completion. After venography, fondaparinux was discontinued and investigators could extend prophylaxis during follow-up with any currently available therapy. If venous thromboembolism occurred during the study, treatment was at the investigator's discretion.

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 local institutional review boards, and written informed consent was obtained from all patients before randomization.

### Treatments

Study medications were packaged in boxes of identical appearance, one per patient, each containing 10 0.5-mL prefilled, single-dose syringes of identical appearance containing fondaparinux 2.5 mg or matching placebo (isotonic saline). The use of any type of anticoagulant, fibrinolytic agent, dextran, or glycoprotein IIb/IIIa receptor antagonist, concomitantly or within 2 calendar days before surgery, was

prohibited, and that of aspirin and non-steroidal anti-inflammatory drugs was discouraged.

### Outcome measures

The primary efficacy outcome was venous thromboembolism (defined as deep vein thrombosis detected by mandatory screening and/or documented symptomatic deep vein thrombosis or pulmonary embolism or both) up to day 10. Secondary efficacy outcomes were the individual components of the primary efficacy outcome up to day 10, the composite of any venous thromboembolism and death up to day 10 [19], symptomatic venous thromboembolism up to day 10 and day 32, the composite of symptomatic venous thromboembolism and death up to day 32, and the number of patients requiring treatment for acute venous thromboembolism.

The primary safety outcome was major bleeding detected during the treatment period (the interval between the first study drug injection and 2 days after the last injection). Major bleeding was defined as bleeding that was fatal, retroperitoneal, intracranial, or involved any other critical organ, led to intervention, or was associated with a bleeding index of 2.0 or more. The bleeding index was calculated as reported previously (see legend of Table 4) [13]. Death during the treatment period and up to day 32 was also assessed.

Study outcomes, including review of all venograms, bleeding and death, were adjudicated by a central independent committee, the members of which were unaware of the patients' treatment assignment and the local assessment.

### Statistical analysis

The trial was designed to demonstrate that fondaparinux was superior to placebo in preventing venous thromboembolism when both were used in conjunction with intermittent pneumatic compression. On the basis of previous fondaparinux trials in major orthopedic surgery [13], and assuming a frequency of venous thromboembolism with placebo of 12% [4,5,8,12,20], we estimated that 375 evaluable patients per treatment group, i.e. 750 in total, would give a power of 80% to detect a 50% odds ratio reduction with fondaparinux (two-sided Fisher's exact test, alpha = 0.05). The recruitment target was set at 1070 to allow for potential failure to obtain primary efficacy data in about 30% of patients. When it became apparent during the study that the overall rate of venous thromboembolism was lower than expected, the Steering Committee decided, before database lock and unblinding of data, to increase the enrollment period by 6 months to enroll approximately 240 additional patients.

The primary efficacy outcome analysis included data on all randomized patients who had an adequate venous thromboembolism assessment by day 10 (i.e. an evaluable venogram or adjudicated symptomatic venous thromboembolism; primary efficacy population). The efficacy analysis was also performed on the all-randomized population. Patients were analyzed as randomized in all efficacy analyses. The safety analysis was performed on data from patients who had received at least one dose of study medication. Patients were analyzed as treated in all safety analyses (as-treated population). A planned independent interim analysis was conducted when half of the 1070 patients initially targeted had been randomized and completed, so the trial could be stopped in the event of a major improvement in the primary efficacy outcome with fondaparinux. However, the Data and Safety Monitoring Board recommended continuing the study as planned.

The stopping guideline used an O'Brien and Fleming rule with critical values of 2.796 at the interim stage (alpha = 0.0052) and 1.977 at the final stage (alpha = 0.048), to maintain an overall two-sided significance level of 0.05 in the analysis of the primary efficacy outcome. The odds ratio (fondaparinux vs. placebo), 95.2% confidence interval and *P*-value were calculated. Treatment effect was also analyzed using a multiple logistic regression model incorporating several predefined baseline categorical covariates (gender, ethnic origin, age, obesity, type of surgery, cancer surgery, type of anesthesia, duration of surgery, number of venous thromboembolism risk factors, history of venous thromboembolism, and creatinine clearance). Furthermore, exploratory analyses were performed on the primary efficacy endpoint in predefined subgroups. For major bleeding, the two treatment groups were compared using a two-sided Fisher's exact test.

## Results

### Study population

Between November 2001 and October 2004, 1309 patients were randomized in 50 US centers to receive either fondaparinux or placebo (Fig. 1). In total, 1285 patients (98.2%) received at least one dose of study drug and were included in the safety analysis (as-treated patients). Of the 1309 randomized patients, 842 (64.3%) had an adequate evaluation of the primary efficacy outcome and were included in the efficacy analysis (primary efficacy population).

Demographic variables and risk factors at baseline, type of anesthesia, and type and duration of surgery were similar in the two groups among both randomized and treated patients (Tables 1 and 2) and among patients analyzed for primary efficacy (data not shown). The vast majority of patients (99.5%) received intermittent pneumatic compression, and 49.6% received elastic stockings. The median duration of prophylaxis was 6 days in both groups (range: 1–10 days). After completion of study drug administration, 1.4% (9/636) of fondaparinux-treated patients and 3.4% (22/649) of placebo-treated patient received extended prophylaxis with either heparins or vitamin K antagonists on the investigator's initiative.

### Efficacy outcomes

In the primary efficacy population, the venous thromboembolism rate up to day 10 was 1.7% (7/424) in patients randomized to fondaparinux, as compared to 5.3% (22/418) in patients
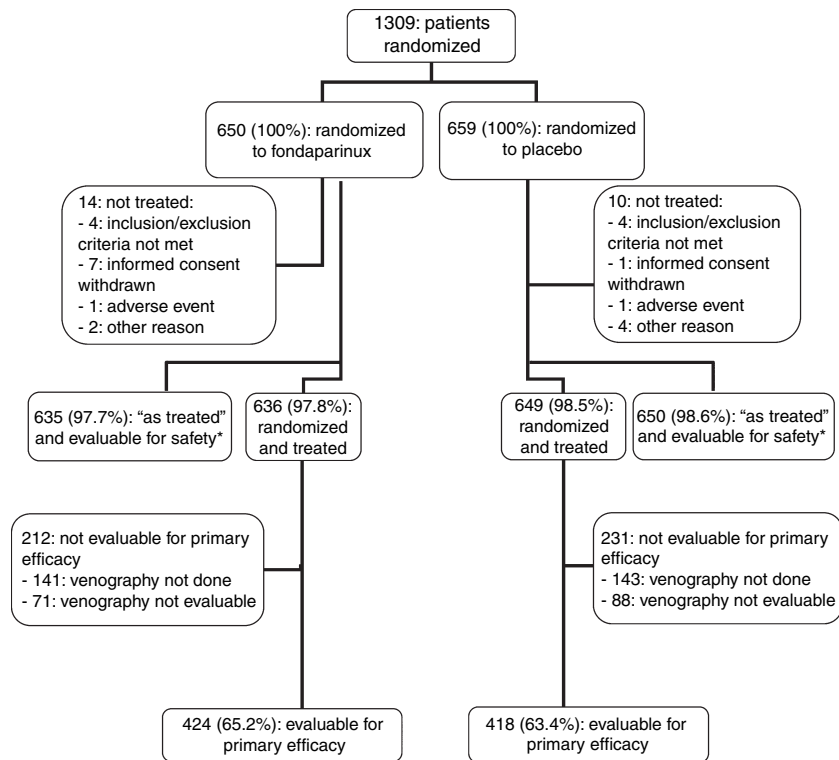
**Fig. 1.** Trial profile. *Three randomized patients were incorrectly given the opposite study drug to that assigned (two patients randomized to fondaparinux and one randomized to placebo). This resulted in one fewer patient in the fondaparinux group and one more patient in the placebo group than was randomized in the 'as-treated' population.

randomized to placebo (odds ratio reduction 69.8%; 95% confidence interval 27.9–87.3; $P = 0.004$). Comparable data were obtained in the all-randomized population (Table 3). Furthermore, fondaparinux reduced the proximal deep vein thrombosis rate by 86.2% ($P = 0.037$) and the rate of the composite of any venous thromboembolism or death by 62.8% ($P = 0.012$), but the two groups did not differ in terms of either symptomatic venous thromboembolism rate or death rate. The proportion of patients treated for venous thromboembolism following the qualifying assessment for venous thromboembolism, according to the local site, was 1.9% in the fondaparinux group (8/424) and 3.8% in the placebo group (16/418; $P = 0.101$). Overall, the superiority of fondaparinux over placebo as regards primary efficacy was consistent irrespective of gender, age, obesity, number of venous thromboembolism risk factors, duration of surgery, type of surgery, and whether or not patients underwent surgery for cancer (Fig. 2). Multiple logistic regression showed that the venous thromboembolism rate increased with advancing age, longer duration of surgery, higher number of risk factors, and previous history of venous thromboembolism (data not shown). When treatment effect was adjusted on these covariates, fondaparinux conferred an adjusted odds ratio reduction of 69.2% (95% confidence interval 26.2–87.1).

The rate of symptomatic venous thromboembolism was low and did not differ between groups. During study drug administration, one (0.2%) symptomatic adjudicated non-fatal pulmonary embolism occurred in each group. By the end of

follow-up (day 32), two (0.3%) and four (0.6%) symptomatic adjudicated venous thromboembolic events had occurred in the fondaparinux and placebo groups, respectively; fatal pulmonary embolism occurred in one (0.2%) patient in each group, and non-fatal pulmonary embolism in one (0.2%) and three (0.5%) patients in the fondaparinux and placebo group, respectively.

### Safety outcomes

The major bleeding rate during the treatment period was 1.6% (10/635) in the fondaparinux group and 0.2% (1/650) in the placebo group ($P = 0.006$) (Table 4). There was no fatal bleeding or bleeding in a critical organ. Most (8/10) of the major bleeds in the fondaparinux group occurred at the surgical site, five of these leading to permanent discontinuation of fondaparinux.

The incidence of other adverse events did not differ between groups. During the treatment period, the platelet count was below 100 000 mm$^{-3}$ in 0.7% (4/635) of fondaparinux-treated patients and 1.3% (7/650) of placebo-treated patients; decreased platelet count was reported by the investigator as an adverse event in two (0.3%) and seven (1.1%) patients in the fondaparinux and placebo groups, respectively. By day 32, eight patients (1.3%) in the fondaparinux group and five (0.8%) in the placebo group had died (Table 4). The causes of death were pulmonary embolism ($n = 2$, one in each group) and bleeding ($n = 3$, all in the fondaparinux group. Two of the bleeds resulting in death occurred 6 and 9 days after the study

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

| | Fondaparinux (n = 636) | Placebo (n = 649) |
|---|---|---|
| Age, median (range) (years) | 60 (40–93) | 59 (40–95) |
| Gender, male/female | 314/322 | 321/328 |
| Weight, mean (SD) (kg) | 84.6 (20.4) | 84.6 (20.4) |
| Body mass index, mean (SD) (kg m$^{-2}$) | 29.5 (7.3) | 29.6 (7.1) |
| Risk factor for venous thromboembolism, no. (%) | | |
| Age ≥ 75 years | 90 (14.2) | 100 (15.4) |
| Obesity* | 269 (42.4) | 270 (41.7) |
| History of venous thromboembolism | 16 (2.5) | 15 (2.3) |
| Congestive heart failure (NYHA grade III or IV) | 22 (3.5) | 29 (4.5) |
| Chronic obstructive pulmonary disease | 73 (11.5) | 83 (12.8) |
| Inflammatory bowel disease | 66 (10.4) | 58 (8.9) |
| Cancer surgery | 246 (38.7) | 262 (40.4) |
| No. of risk factors for venous thromboembolism, no. (%) | | |
| < 2 | 426 (67.0) | 425 (65.5) |
| ≥ 2 | 210 (33.0) | 224 (34.5) |
| Creatinine clearance, no. (%) | | |
| < 30 mL min$^{-1}$ | 4 (0.6) | 10 (1.6) |
| 30–50 mL min$^{-1}$ | 53 (8.4) | 38 (5.9) |
| 50–80 mL min$^{-1}$ | 156 (24.7) | 172 (26.7) |
| ≥ 80 mL min$^{-1}$ | 418 (66.2) | 423 (65.8) |

*Men with body mass index ≥ 30 kg m$^{-2}$; women with body mass index ≥ 28.6 kg m$^{-2}$.

drug was discontinued. The other death occurred 22 days after the study drug was discontinued in a patient who had repeated bleeding episodes starting on the first postoperative day). The other deaths ($n = 8$, four in each group) were not related to venous thromboembolism or bleeding. None of the deaths was considered to be related to study drug by the investigators.

## Discussion

Our study shows that in patients undergoing abdominal surgery, all receiving intermittent pneumatic compression, fondaparinux reduced the odds of venous thromboembolism by 69.8%, with a safety profile comparable to that seen with unfractionated or low molecular weight heparins in abdominal surgery thromboprophylaxis trials [3]. This reduction was consistent in all subgroups examined. Forty per cent of patients in our study population underwent surgery for cancer, a setting considered to carry the highest risk of venous thromboembolism in abdominal surgery [1]. In these patients, fondaparinux reduced the venous thromboembolism risk by 64%. This result is consistent with those of the PEGASUS study in high-risk patients undergoing major abdominal surgery, which showed that fondaparinux reduced the venous thromboembolism risk by 25.8% compared with low molecular weight heparin [17]. Thus, overall, fondaparinux thromboprophylaxis is effective in a wide variety of patients undergoing abdominal surgery.

**Table 2** Surgical and treatment characteristics of randomized and treated patients

| | Fondaparinux (n = 636) | Placebo (n = 649) |
|---|---|---|
| Type of surgery, no. (%)* | | |
| Gastrointestinal | 383 (60.2) | 389 (59.9) |
| Gynecologic | 62 (9.7) | 57 (8.8) |
| Urologic | 118 (18.6) | 112 (17.3) |
| Other | 255 (40.1) | 269 (41.4) |
| Type of anesthesia, no. (%) | | |
| General only | 626 (98.4) | 641 (98.8) |
| Spinal epidural | 10 (1.6) | 8 (1.2) |
| Use of catheter, no. (%) | 13 (2.0) | 7 (1.1) |
| Time between anesthesia induction and incision closure, median (range) (hours:min) | 2:23 (0:45–14:05) | 2:19 (0:45–17:16) |
| Time to first postoperative injection, median (hours:min) | 6:42 | 6:45 |
| < 6 h, no. (%) | 24 (3.6) | 25 (3.9) |
| 6–8 h, no. (%) | 582 (91.5) | 593 (91.4) |
| > 8 h, no. (%) | 30 (4.7) | 31 (4.8) |
| Duration of treatment, no. (%) | | |
| < 5 days | 55 (8.6) | 60 (9.2) |
| 5–9 days | 577 (90.7) | 584 (90.0) |
| > 9 days | 4 (0.6) | 5 (0.8) |
| Intermittent pneumatic compression, no. (%) | | |
| Knee-high | 312 (49.2) | 319 (49.2) |
| Thigh-high | 322 (50.6) | 325 (50.1) |
| Duration of intermittent pneumatic compression, median (range) (days) | | |
| Knee-high | 4.0 (1–32) | 4.0 (1–39) |
| Thigh-high | 4.0 (1–29) | 4.0 (1–33) |
| Elastic stockings, no. (%) | 316 (49.7) | 322 (49.6) |
| Physical therapy, no. (%) | 99 (15.6) | 116 (17.9) |
| Prohibited therapy†, no. (%) | 12 (1.9) | 5 (0.8) |
| Discouraged therapy‡, no. (%) | 112 (17.6) | 122 (18.8) |

*Patients may have undergone more than one type of surgery.
†Any type of anticoagulant agents, dextran.
‡Aspirin and non-steroidal anti-inflammatory agents.

In this study, the rate of venous thromboembolism in the intermittent pneumatic compression group was lower than expected, and was close to that reported in other anticoagulant trials in general surgery [3]. This may reflect a greater than anticipated thromboprophylactic effect of intermittent pneumatic compression and/or the fact that patients with the highest risk of venous thromboembolism, requiring pharmacologic thromboprophylaxis according to the investigator, were excluded from the study. Moreover, the incidence of symptomatic events after day 11 may have been influenced by the administration of anticoagulant therapy to patients diagnosed with asymptomatic deep vein thrombosis in the first part of the study (16/418, 3.8%). Intermittent pneumatic compression is generally considered to be less effective than anticoagulant-based prophylaxis for venous thromboembolism prevention [1]. Our results confirm that the thromboprophylactic efficacy of intermittent pneumatic compression can be significantly increased by concomitant use of an anticoagulant agent, in

**Table 3** Venous thromboembolic events up to day 10

| | Fondaparinux n/N* (%) | Placebo n/N* (%) | P-value[†] | Odds ratio reduction[‡] (%) (95% CI*) |
|---|---|---|---|---|
| Primary efficacy population | | | | |
| Venous thromboembolism | 7/424 (1.7) | 22/418 (5.3) | 0.004 | 69.8 (27.9 to 87.3) |
| Any deep-vein thrombosis[¶] | 7/424 (1.7) | 22/418 (5.3) | 0.004 | 69.8 (28.5 to 87.2) |
| Any proximal deep-vein thrombosis[¶] | 1/424 (0.2) | 7/417 (1.7) | 0.037 | 86.2 (–13.0 to 98.3) |
| Distal deep-vein thrombosis only[||] | 6/424 (1.4) | 14/417 (3.4) | | |
| All-randomized population** | | | | |
| Venous thromboembolism | 7/650 (1.1) | 22/659 (3.3) | 0.008 | 68.5 (25.7 to 86.6) |
| Symptomatic venous thromboembolism | 1/650 (0.2) | 1/659 (0.2) | | |
| Deep vein thrombosis and non-fatal pulmonary embolism[††] | 1 (0.2) | 1 (0.2) | | |
| Fatal pulmonary embolism | 0 | 0 | | |
| Any venous thromboembolism and/or death | 9/650 (1.4) | 24/659 (3.6) | 0.012 | 62.8 (18.9 to 83.0) |

*$n$ is the number of patients experiencing events, and $N$ is the total number of patients assessed for this event; CI denotes confidence interval; for the primary efficacy analysis, 95% CI in fact denotes 95.2% confidence interval (see Methods).
[†]Two-sided Fisher's exact test.
[‡]Reduction in risk in the fondaparinux group as compared with the placebo group.
[¶]The number of patients with available data for this parameter could be lower than 842.
[||]Patients with distal deep vein thrombosis, but not evaluable for proximal deep vein thrombosis, were not counted.
**Patients without symptomatic venous thromboembolism and without venographic evaluation were considered not to have venous thromboembolism.
[††]No patients had symptomatic deep vein thrombosis only or symptomatic non-fatal pulmonary embolism only.

**Table 4** Safety outcomes (as-treated population)

| | Fondaparinux (n = 635), no (%) | Placebo (n = 650), no (%) |
|---|---|---|
| Treatment period plus 2 calendar days after day of last injection of study drug treatment | | |
| Major bleeding | 10 (1.6) | 1 (0.2)* |
| Fatal bleeding | 0 | 0 |
| Bleeding in a critical organ | 0 | 0 |
| Bleeding at the surgical site leading to re-operation | 4 (0.6) | 0 |
| Bleeding at the surgical site leading to other intervention | 1 (0.2) | 0 |
| Bleeding at the surgical site with a bleeding index[†] ≥ 2.0 | 3 (0.5) | 1 (0.2) |
| Bleeding at a non-surgical site with a bleeding index[†] ≥ 2.0 | 2 (0.3) | 0 |
| Minor bleeding | 5 (0.8) | 3 (0.5)[‡] |
| Transfusions | 63 (9.9) | 43 (6.6)[||] |
| Death | 1 (0.2) | 2 (0.3) |
| Whole study period | | |
| Death[¶] | 8 (1.3) | 5 (0.8)** |
| Fatal pulmonary embolism | 1 (0.2) | 1 (0.2) |

*$P = 0.006$ (two-sided Fisher's exact test); for one patient in the fondaparinux group, the first injection of study treatment was administered < 6 h after skin closure, whereas for all other patients experiencing major bleeding, this first injection was administered 6–8 h after skin closure.
[†]The bleeding index was calculated as follows: (number of units of packed red blood cells or whole blood transfused) + [(prebleeding) – (postbleeding) hemoglobin (g dL$^{-1}$) values].
[‡]$P = 0.502$ (two-sided Fisher's exact test).
[¶]No death was associated with venous thromboembolism or bleeding.
[||]$P = 0.033$ (two-sided Fisher's exact test).
**$P = 0.42$ (two-sided Fisher's exact test).

agreement with previous studies in general [12] and cardiac surgery [21], and support current guidelines that recognize the efficacy of combination modalities [1]. The question of whether the combination of fondaparinux and intermittent pneumatic compression is more effective than fondaparinux alone remains unanswered, as it was not addressed in our study. The venous thromboembolism rate observed in the fondaparinux + intermittent pneumatic compression group of our study (1.7%) was lower than that observed in the fondaparinux group of the PEGASUS study in high-risk patients undergoing major abdominal surgery (4.7%) [17]. However, the patients included in the latter study were at higher risk for venous thromboembolism, as evidenced by the greater number of patients undergoing surgery for cancer (70% vs. 40% in our study) and having two or more risk factors for venous thromboembolism (97% vs. 34% in our study). Furthermore, the use of intermittent pneumatic compression was prohibited in the PEGASUS study.

The primary assessment for efficacy was based on bilateral venography, the reference method for evaluating new anti-thrombotic agents in patients undergoing surgery [19,22,23]. The proportion of patients evaluable for efficacy was 64%, a percentage comparable to those usually reported in large multicenter trials using venography in general surgery [17,24,25]. Importantly, the distribution of patients unevaluable for primary efficacy was well balanced between the two groups. The rate of symptomatic venous thromboembolism events was low and did not differ between the two groups. However, our study was not designed to detect a difference in symptomatic venous thromboembolism. Several meta-analyses of data from trials in various clinical settings, including general surgery, have consistently shown an association between decrease in
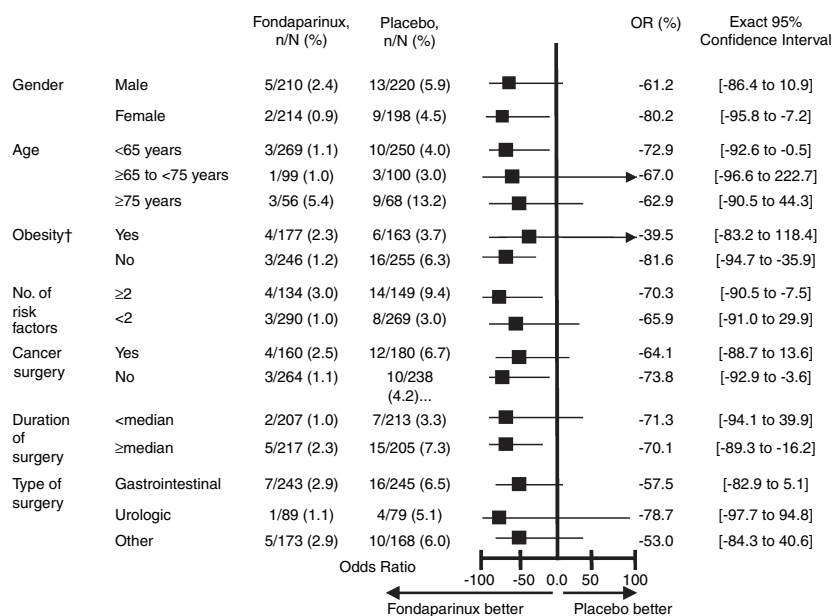
| | | Fondaparinux, n/N (%) | Placebo, n/N (%) | | OR (%) | Exact 95% Confidence Interval |
|---|---|---|---|---|---|---|
| Gender | Male | 5/210 (2.4) | 13/220 (5.9) | | -61.2 | [-86.4 to 10.9] |
| | Female | 2/214 (0.9) | 9/198 (4.5) | | -80.2 | [-95.8 to -7.2] |
| Age | <65 years | 3/269 (1.1) | 10/250 (4.0) | | -72.9 | [-92.6 to -0.5] |
| | ≥65 to <75 years | 1/99 (1.0) | 3/100 (3.0) | | -67.0 | [-96.6 to 222.7] |
| | ≥75 years | 3/56 (5.4) | 9/68 (13.2) | | -62.9 | [-90.5 to 44.3] |
| Obesity† | Yes | 4/177 (2.3) | 6/163 (3.7) | | -39.5 | [-83.2 to 118.4] |
| | No | 3/246 (1.2) | 16/255 (6.3) | | -81.6 | [-94.7 to -35.9] |
| No. of risk factors | ≥2 | 4/134 (3.0) | 14/149 (9.4) | | -70.3 | [-90.5 to -7.5] |
| | <2 | 3/290 (1.0) | 8/269 (3.0) | | -65.9 | [-91.0 to 29.9] |
| Cancer surgery | Yes | 4/160 (2.5) | 12/180 (6.7) | | -64.1 | [-88.7 to 13.6] |
| | No | 3/264 (1.1) | 10/238 (4.2)... | | -73.8 | [-92.9 to -3.6] |
| Duration of surgery | <median | 2/207 (1.0) | 7/213 (3.3) | | -71.3 | [-94.1 to 39.9] |
| | ≥median | 5/217 (2.3) | 15/205 (7.3) | | -70.1 | [-89.3 to -16.2] |
| Type of surgery | Gastrointestinal | 7/243 (2.9) | 16/245 (6.5) | | -57.5 | [-82.9 to 5.1] |
| | Urologic | 1/89 (1.1) | 4/79 (5.1) | | -78.7 | [-97.7 to 94.8] |
| | Other | 5/173 (2.9) | 10/168 (6.0) | | -53.0 | [-84.3 to 40.6] |

Odds Ratio: -100 -50 0.0 50 100

← Fondaparinux better    Placebo better →

**Fig. 2.** Relative efficacy of fondaparinux and placebo according to patient and surgical characteristics. *Primary efficacy dataset; there was no statistically significant heterogeneity of odds ratio between each subgroup of covariates (Breslow–Day test). †Men with body mass index ≥ 30 kg m$^{-2}$; women with body mass index ≥ 28.6 kg m$^{-2}$.

asymptomatic deep vein thrombosis and decrease in symptomatic events with the use of antithrombotic agents [3,26–33], supporting the view that asymptomatic deep vein thrombosis is a valid surrogate outcome measure in venous thromboembolism studies [34]. It is worth noting that, in our study, fondaparinux reduced by 86% the rate of proximal deep vein thromboses, which are more prone to embolize than calf vein thrombi.

Fondaparinux significantly increased the risk of major bleeding as compared with placebo. However, none of these episodes was fatal or involved a critical organ, and most occurred at the surgical site. Furthermore, the 1.6% rate of major bleeding observed with fondaparinux in our study is in the lower range of those reported in meta-analyses or recent trials on anticoagulant agents in the same setting [3,17,24,25]. We therefore conclude that, in patients undergoing major abdominal surgery and receiving thromboprophylaxis with intermittent pneumatic compression, fondaparinux significantly reduced the venous thromboembolism rate, with a low bleeding risk as compared to placebo. Overall, the APOLLO and PEGASUS [17] trials showed that once-daily 2.5-mg fondaparinux initiated 6 h postoperatively should be added to the list of therapeutic strategies that are effective and safe for preventing venous thromboembolism after abdominal surgery.

## Disclosure of Conflict of Interests

This study was funded initially by Sanofi-Synthelabo and then by GlaxoSmithKline.

## Appendix

The members of the APOLLO group were as follows.

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