FONDAPARINUX COMBINED WITH INTERMITTENT PNEUMATIC COMPRESSION VERSUS INTERMITTENT PNEUMATIC COMPRESSION ALONE FOR PREVENTION OF VENOUS THROMBOEMBOLISM AFTER ABDOMINAL SURGERY: A RANDOMIZED, DOUBLE-BLIND COMPARISON

Alexander G. Turpie,[1] M.D., F.R.C.P., Kenneth A. Bauer,[2] M.D., Joseph A. Caprini,[3] M.D., F.A.C.S., Philip C. Comp,[4] M.D., Michael Gent,[5] D.Sc. and James E Muntz,[6] M.D., on behalf of the APOLLO investigators*.

[1] *Department of Medicine, McMaster University, Hamilton, ON, Canada (*turpiea@mcmaster.ca);
[2] *Beth Israel Deaconess Medical Center and VA Boston Healthcare System, Harvard Medical School, Boston, MA, USA (*kbauer@bidmc.harvard.edu);
[3] *Northwestern University Feinberg School of Medicine, Chicago, IL, USA (*jcaprini2@aol.com);
[4] *University of Oklahoma College of Medicine, Oklahoma City, OK, USA (*philip-comp@ouhsc.edu);
[5] *Henderson Research Centre, McMaster University, Hamilton, ON, Canada (*gentm@mcmaster.ca);
[6] *Baylor College of Medicine, Houston, TX, USA (*jmuntz@tmh.tmc.edu)

Correspondence to:

Alexander G.G. TURPIE, M.D., F.R.C.P.
Department of Medicine
Hamilton Health Sciences Corporation –
General Division
237 Barton Street East, HAMILTON, Ontario
L8L 2X2, CANADA
Tel: 905 528 9946
Fax: 905 521 1551
e-mail: turpiea@mcmaster.ca

Date of revision: December 22, 2006

Word count of the manuscript text: 2898 words (not including abstract, tables, figures, and references) (<3500)

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

ABSTRACT (333 words)

Context: The benefit of combined mechanical and pharmacologic methods for venous thromboembolism prevention after abdominal surgery has not been clearly established.

Objective: To compare the efficacy and safety of fondaparinux in conjunction with intermittent pneumatic compression *versus* intermittent pneumatic compression alone in this context.

Design, Setting, and Patients: Randomized, double-blind, placebo-controlled, superiority trial of patients aged at least 40 years undergoing abdominal surgery, conducted in 50 US Centers from November 2001 to October 2004.

Interventions: Patients were randomized to receive either the anticoagulant fondaparinux 2.5 mg or placebo subcutaneously for 5 to 9 days, starting 6 to 8 hours postoperatively. All patients received intermittent pneumatic compression.

Main Outcome Measures: The primary efficacy outcome was the composite of deep-vein thrombosis detected by mandatory bilateral venography, or documented symptomatic deep-vein thrombosis or pulmonary embolism up to day 10. The main safety outcomes were major bleeding during the treatment period, and all-cause mortality. A blinded independent committee adjudicated all these outcomes. Follow-up lasted 32 days.

Results: Of the 1309 patients randomized, 842 (64.3%) were evaluable for the primary efficacy analysis. 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 to 87.3; P=0.004). Fondaparinux treated patients had a lower rate of proximal deep-vein thrombosis (0.2% compared to 1.7% among control patients, P=0.037). In the overall population, the rate of symptomatic venous thromboembolism was low in both groups (0.2%). Major bleeding occurred in 1.6% and 0.2% of fondaparinux- and placebo-treated patients,

respectively (P=0.006), with transfusions in 9.9% compared to 6.6% (P=0.033) in control patients. None of the major bleeds was fatal or involved a critical organ. By day 32, 8 patients (1.3%) receiving fondaparinux and 5 (0.8%) receiving placebo had died (P=0.42).

Conclusions: In patients undergoing abdominal surgery and receiving intermittent pneumatic compression, fondaparinux 2.5 mg reduced the primary endpoint of total asymptomatic and symptomatic venous thromboembolism rate by 69.8% compared to pneumatic compression alone, with significantly more bleeding relative to placebo.

Trial Registration:

- Name of the trial registry: APOLLO
- Registration number: NCT00038961
- URL of the registry: Clinicaltrials.gov

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 compared with anticoagulant-based regimens.[1] Therefore, the efficacy of intermittent pneumatic compression[4-9] remains uncertain, although recent data tend to indicate that this method is effective for preventing deep-vein thrombosis, notably if combined with pharmacological 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 hours postoperatively, proved more effective than and as safe as 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 without increasing bleeding risk.[17] We therefore conducted a

randomized, double-blind, placebo-controlled trial to compare the efficacy and safety of fondaparinux combined with intermittent pneumatic compression to intermittent pneumatic compression alone for venous thromboembolism prevention after abdominal surgery.

METHODS

Patients

Patients aged over 40 years, weighing over 50 kg, scheduled to undergo abdominal surgery expected to last longer than 45 minutes, 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 less than six months; clinical signs of deep-vein thrombosis and/or history of venous thromboembolism within the previous three 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 three months; bacterial endocarditis or other contraindication for anticoagulant therapy; planned indwelling intrathecal or epidural catheter for more than six hours 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 in a well-hydrated patient and platelet count below 100,000/mm^3. Finally, patients requiring anticoagulant therapy, or other pharmacological 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 4 and stratified by center), to receive once-daily subcutaneous injections of either fondaparinux 2.5 mg (fondaparinux

sodium, Arixtra®, GlaxoSmithKline) or placebo. The first injection was scheduled six to eight hours after surgical closure, provided that hemostasis was achieved, and the second injection 16 to 28 hours after the first. If an intrathecal or epidural catheter was used post-surgery, this was to be removed at least two hours before the first injection. During the on-study-drug period of 5 to 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 one calendar day after the last study drug injection. Clinically suspected pulmonary embolism was confirmed by a high-probability lung scan, a non-high-probability lung scan defect plus confirmed deep-vein thrombosis, pulmonary angiography, 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 ten 0.5 mL pre-filled, 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 GPIIb/IIIa receptor antagonist, concomitantly or within two calendar days before surgery, was prohibited, and that of aspirin and non-steroidal anti-inflammatory drugs 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 two 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 orthopaedic 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 six 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 once half 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 *versus* 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 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 (Figure 1). A total of 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 both among 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 compared with 5.3% (22/418) in patients randomized to placebo (odds ratio reduction: 69.8%; 95% confidence interval: 27.9 to 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 (Figure 2). Multiple logistic regression showed that venous thromboembolism rate increased with advancing age, longer duration of surgery, higher number of risk factors and previous history of VTE (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 to 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).

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 percent 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 showing 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.

In this study, the rate of venous thromboembolism in the intermittent pneumatic compression group was lower than expected, 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 pharmacological 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 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 agreement with previous studies in general[12] and cardiac surgery,[21]

and support current guidelines which 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% *versus* 40% in our study) and having two or more risk factors for venous thromboembolism (97% *versus* 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 antithrombotic 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 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 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.[3,15,22,23] 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 an acceptable bleeding risk compared with placebo. Overall, the APOLLO and PEGASUS[17] trials showed that once-daily 2.5 mg fondaparinux initiated six hours post-operatively should be added to the list of therapeutic strategies effective and safe for preventing thromboembolism after abdominal surgery.

AUTHOR CONTRIBUTIONS

Drs Turpie, Bauer, Caprini, Comp, Gent, and Muntz were members of the Steering Committee. They had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. They contributed to the conception and design of the study, the analysis and interpretation of the data, and critical revision of the manuscript for important intellectual content. Dr Turpie elaborated the first draft of the manuscript and all authors approved its final version. Drs Comp and Muntz were also recruiting investigators.

FINANCIAL DISCLOSURE

Drs Turpie, Bauer, Caprini, Comp, Gent, and Muntz have served as consultants or occasional speakers (sometimes for honoraria) for all companies involved in the development of antithrombotic agents.

FUNDING/SUPPORT

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

ROLE OF THE SPONSOR

The study was supervised by a Steering Committee, including representatives of the Sponsor, Sanofi-Synthelabo, until GlaxoSmithKline acquisition of fondaparinux in September 2004, and thereafter GlaxoSmithKline. The Steering Committee was entirely responsible for the design, conduct, and analyses of the study. The committee comprised a majority of non-sponsor voting members. Two non-voting members of the committee were from the Sponsor, from Sanofi-Synthelabo until September 2004 (Dr Cariou [medical input in trial design and conduct] and Dr Destors [statistical input to trial design and data analysis]), and thereafter from GlaxoSmithKline

(Dr Okada [medical input] and Ms Hutchinson [statistical input in data analysis]). Administration of the study, including clinical trial supplies, was initially the responsibility of Sanofi-Synthelabo up to the acquisition of fondaparinux in September 2004. GlaxoSmithKline, centralized the data and was responsible for data management and data analyses under the direction of the Steering Committee. The Steering Committee had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The Sponsor provided administrative, technical and material support. The central Adjudication Committee and the Data Monitoring Committee were independent of the Sponsor.

APPENDIX

The members of the APOLLO group were: **Steering Committee:** A.G.G. Turpie (Chair), K.A. Bauer, J.A. Caprini, M. Gent, P.C. Comp, J.E. Muntz. The non-voting members from the Sponsor were R. Cariou and J.M. Destors from Sanofi-Synthelabo until September 2004 and thereafter, S. Okada and T. Hutchinson from GlaxoSmithKline. **Central Adjudication Committee:** M. Gent (Chair), C. Kearon, J. Weitz. **Data Monitoring Committee:** A. Planès (Chair), G.P. Clagett, G.E. Raskob, S. Vesely. **Participating centers:** N. Abramson, Jacksonville, FL; M. Cipolle, Allentown, PA; P.C. Comp, Oklahoma City, OK; J. Corbitt Jr., Atlantis, FL; G. Del Priore, NYU; N. Estes, Peoria, IL; R. Fisher, Richmond, VA; S. Freedman, Las Vegas, NV; M. Fusco, Melbourne, FL; S. Galandiuk, Louisville, KY; L. Galler, Somers Point, NJ; D. Green, Chicago, IL; W.T. Gregory, Portland, OR; J. Hunt, New Orleans, LA; G. Hunter, Galveston, TX; A. Jacobson, Loma Linda, CA; A. Jacocks, Oklahoma City, OK; W. Jeansonne, Mobile, AL; G. Johnson, Minneapolis, MN; E. Kalda, Sioux Falls, SD; J. Kapner, Scottsdale, AZ; D. Launer, Carlsbad, CA; M. Lavor, Tucson, AZ; D. Lawlor, Olathe, KS; E. Lee, Albany, NY; D. Lorch, Brandon, FL; M. Mancao, Pensacola, FL; B. Mills, Greenville, SC; J. Muntz, Houston, TX; Y. Niihara, Torrance, CA; J. O'Donnell, Lake Charles, LA; J. Portoghese, Orlando, FL; T.S. Ravikumar, Bronx, NY; T. Read, Pittsburgh, PA; R. Robertson, Little Rock, AR; R. Salloum, Rochester, NY; J. Savas, Richmond, VA; W.B. Shingleton, Jackson, MS; J. Snow, Sunrise, FL; T.V. Taylor, Houston, TX; B. Tortella, Philadelphia, PA; W.E. Tucker, Little Rock, AR; C. Van Way, Kansas City, MO; J. Vogler, Tampa, FL; R.B. Wait, Springfield, MA; K. Waxman, Santa Barbara, CA; L. Weireter, Norfolk, VA; R. White, Sacramento, CA; G. Wilson, Columbia, SC; B. Wittmer, Madisonville, KY

REFERENCES

1. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126:338S-400S.

2. Nicolaides AN. Prevention of venous thromboembolism. International Consensus Statement. Guidelines compiled in accordance with the scientific evidence. *Int Angiol.* 2001;20:1-37.

3. Mismetti P, Laporte S, Darmon JY, Buchmüller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg.* 2001;88:913-930.

4. Colditz GA, Tuden RL, Oster G. Rates of venous thrombosis after general surgery: combined results of randomised clinical trials. *Lancet.* 1986;2:143-146.

5. Clagett GP, Reisch JS. Prevention of VTE in general surgical patients: results of a meta-analysis. *Ann Surg.* 1988;208:227-240.

6. Vanek VW. Meta-analysis of effectiveness of intermittent pneumatic compression devices with a comparison of thigh-high to knee-high sleeves. *Am Surg.* 1998;64:1050–1058.

7. Moser G, Krahenbuhl B, Barroussel R. Mechanical versus pharmacological prevention of deep venous thrombosis. *Surg Gynecol Obstet.* 1981;152:448-450.

8. Nicolaides AN, Miles C, Hoare M. Intermittent sequential pneumatic compression of the legs and thrombo-embolism-deterrent stockings in the prevention of postoperative deep venous thrombosis. *Surgery.* 1983;94:21-25.

9. Muhe E. Intermittent sequential high-pressure compression of the leg: a new method for preventing deep venous thrombosis. *Am J Surg.* 1984;147:781-785.

10. Roderick P, Ferris G, Wilson K, et al. Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation,

dextran and regional anaesthesia as thromboprophylaxis. *Health Technol Assess.* 2005;9:iii-iv, ix-x, 1-78.

11. Urbankova J, Quiroz R, Kucher N, Goldhaber SZ. Intermittent pneumatic compression and deep vein thrombosis prevention. A meta-analysis in postoperative patients. *Thromb Haemost.* 2005;94:1181-1185.

12. Borow M, Goldson HJ. Prevention of postoperative deep vein thrombosis and pulmonary embolism with combined modalities. *Am Surg.* 1983;49:599-605.

13. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR, for the Steering Committees of the Pentasaccharide Orthopedic Prophylaxis Studies. Fondaparinux versus enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery. A meta-analysis of 4 randomized double-blind studies. *Arch Intern Med.* 2002;162:1833-1840.

14. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux and prevention of venous thromboembolism after orthopaedic surgery. *Lancet.* 2003;362:1582-1583.

15. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Efficacy and safety of fondaparinux in major orthopedic surgery according to the timing of its first administration. *Thromb Haemost.* 2003;90:364-366.

16. Turpie AGG. The design of venous thromboembolism prophylaxis trials: Fondaparinux is definitely more effective than enoxaparin in orthopaedic surgery. *Int J Clin Pract.* 2004;58:483-493.

17. Agnelli G, Bergqvist D, Cohen A, Gallus AS, Gent M; PEGASUS investigators. Randomized clinical trial of postoperative fondaparinux *versus* perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. *Br J Surg.* 2005;92:1212-1220.

18. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg.* 1972;104:134-144.

19. Committee for Proprietary Medicinal Products. Points to consider on clinical investigation of medicinal products for prophylaxis of intra- and post-operative venous thromboembolic risk. The European Agency for the Evaluation of Medicinal Products. London, 29 June 2000; CPMP/EWP/707/98.

20. Butson AR. Intermittent pneumatic calf compression for prevention of deep venous thrombosis in general abdominal surgery. *Am J Surg.* 1981;142:525–527.

21. Ramos R, Salem BI, De Pawlikowski MP, Coordes C, Eisenberg S, Leidenfrost R. The efficacy of pneumatic compression stockings in the prevention of pulmonary embolism after cardiac surgery. *Chest.* 1996;109:82-85.

22. Kearon C, Julian JA, Newman TE, Ginsberg JS. Noninvasive diagnosis of deep venous thrombosis. *Ann Intern Med.* 1998;128:663-677.

23. Davidson BL. What are the most reliable detection methods for deep vein thrombosis and pulmonary embolism to be used as endpoints in trials of venous thromboprophylaxis? *Haemostasis.* 1998;28 (Suppl 3):113-119.

24. Enoxacan Study Group. Efficacy and safety of enoxaparin *versus* unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. *Br J Surg.* 1997;84:1099-1103.

25. McLeod RS, Geerts WH, Sniderman KW, et al., and other investigators of the Canadian Colorectal Surgery DVT Prophylaxis Trial. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery. Results of the Canadian Colorectal DVT Prophylaxis Trial: a randomized, double-blind trial. *Ann Surg.* 2001;233:438–444.

26. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. *N Engl J Med.* 1988;318:1162-1173.

27. Leizorovicz A, Haugh MC, Chapuis F-R, Samama MM, Boissel JP. Low molecular weight heparin in prevention of postoperative thrombosis. *BMJ.* 1992;305:913-920.

28. Nurmohamed MT, Rosendaal FR, Büller HR, et al. Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery. *Lancet.* 1992;340:152-156.

29. Mismetti P, Laporte-Simitsidis S, Tardy B, et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. *Thromb Haemost.* 2000;83:14-19.

30. Mismetti P, Laporte S, Zufferey P, Epinat M, Decousus H, Cucherat M. Prevention of venous thromboembolism in orthopedic surgery with vitamin K antagonists: a meta-analysis. *J Thromb Haemost.* 2004;2:1058-1070.

31. Cohen AT, Bailey CS, Alikhan R, Cooper DJ. Extended thromboprophylaxis with low molecular weight heparin reduces symptomatic venous thromboembolism following lower limb arthroplasty. A meta-analysis. *Thromb Haemost.* 2001;85:940-941.

32. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomized trials. *Lancet.* 2001;358:9-15.

33. Hull RD, Pineo GF, Stein PD, et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med.* 2001;135:858-869.

34. Segers AEM, Prins MH, Lensing AWA, Buller HR. Is contrast venography a valid surrogate outcome measure in venous thromboembolism prevention studies? *J Thromb Haemost.* 2005;3:1099-1102.

FIGURE LEGENDS

Figure 1. Trial profile

*Three randomized subjects were incorrectly given the opposite study drug to that assigned. The first subject was randomized to placebo but given fondaparinux on days 4 and 5. The second subject was randomized to fondaparinux but given placebo. The third subject was randomized to fondaparinux but was given placebo on one day and was then withdrawn. This incorrect dosing resulted in one less subject in the fondaparinux group and one more subject in the placebo group in the "As Treated" population as compared to the "Treated" Population. The first two subjects (one in each treatment arm) were included in the Primary Efficacy Population as randomized rather than "As treated", and neither had venous thromboembolism. The third subject did not qualify for the Primary Efficacy Population, and consequently did not affect the primary efficacy analysis.

Figure 2. Relative efficacy of fondaparinux and placebo according to patient and surgical characteristics*

*Primary efficacy data set; there was no statistically significant heterogeneity of odds ratio between each subgroup of covariates (Breslow-Day test); †Men with body mass index $\geq$ 30 kg/m^2; women with body mass index $\geq$ 28.6 kg/m^2

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 – M/F	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 $\geq$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)
$\geq$2	210 (33.0)	224 (34.5)
Creatinine clearance, no. (%)		
< 30 mL/min	4 (0.6)	10 (1.6)
30 – 50 mL/min	53 (8.4)	38 (5.9)
50 – 80 mL/min	156 (24.7)	172 (26.7)
$\geq$ 80 mL/min	418 (66.2)	423 (65.8)

*Men with body mass index $\geq$ 30 kg/m^2; women with body mass index $\geq$ 28.6 kg/m^2

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 anesthesia induction to incision closure – median (range), hours : min	2:23 (0:45 - 14:05)	2:19 (0:45 - 17:16)
Time to first postoperative injection – median (range), hours : min	6:42	6:45
< 6 hours, no. (%)	24 (3.6)	25 (3.9)
6 to 8 hours, no. (%)	582 (91.5)	593 (91.4)
> 8 hours, no. (%)	30 (4.7)	31 (4.8)
Duration of treatment – no. (%)		
< 5 days	55 (8.6)	60 (9.2)
5 to 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)
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

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 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 two 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 less than 6 hours after skin closure, whereas for all other patients experiencing major bleeding, this first injection was administered 6 to 8 hours after skin closure; †the bleeding index was calculated as follows: [number of units of packed red blood cells or whole blood transfused] + [(pre-bleeding) - (post-bleeding) hemoglobin (g/dL) 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).

Figure 1. Trial profile

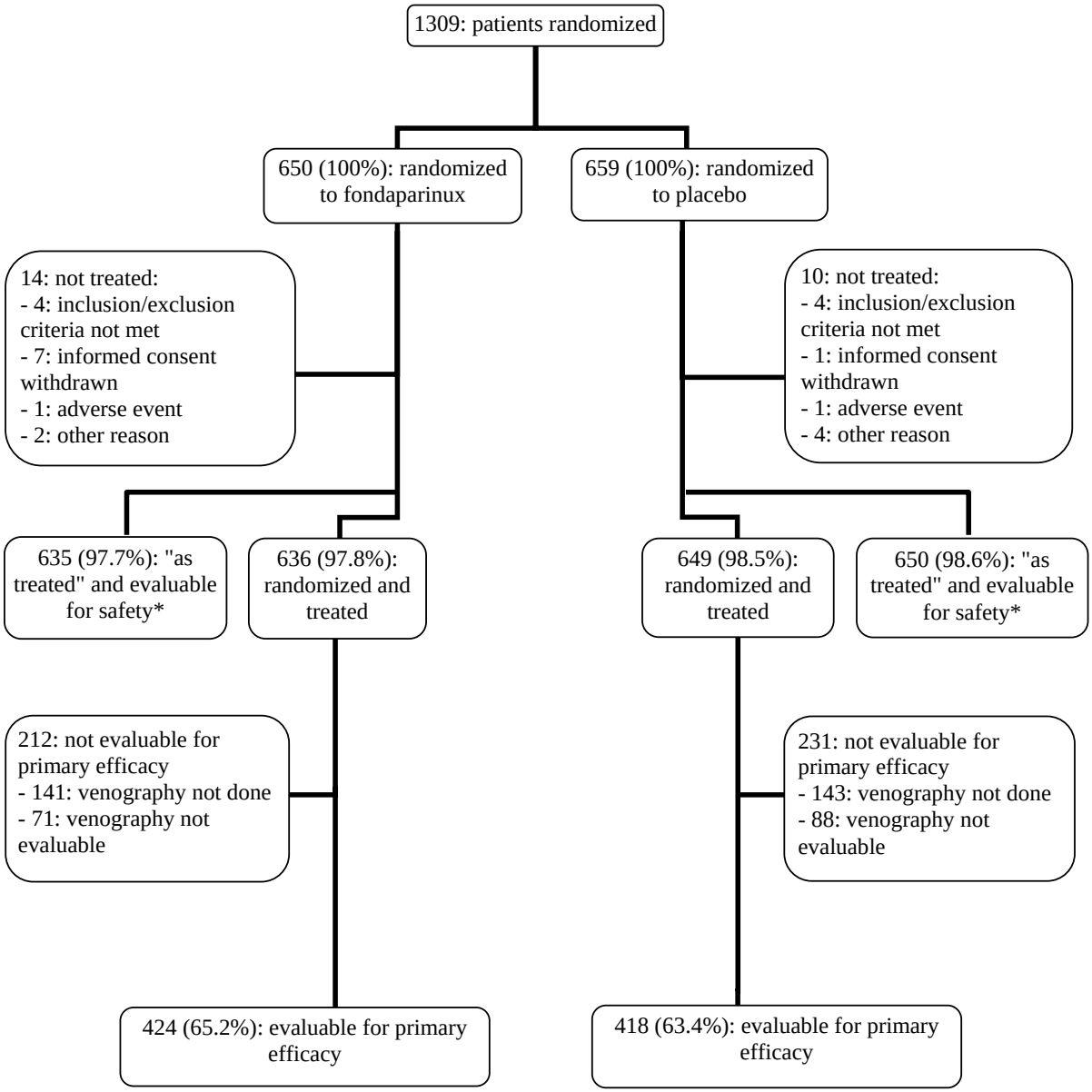

Figure 2. Relative efficacy of fondaparinux and placebo according to patient and surgical characteristics*