

Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial

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Abstract

Objective To determine the efficacy and safety of the anticoagulant fondaparinux in older acute medical inpatients at moderate to high risk of venous thromboembolism.

Design Double blind randomised placebo controlled trial.

Setting 35 centres in eight countries.

Participants 849 medical patients aged 60 or more admitted to hospital for congestive heart failure, acute respiratory illness in the presence of chronic lung disease, or acute infectious or inflammatory disease and expected to remain in bed for at least four days.

Interventions 2.5 mg fondaparinux or placebo subcutaneously once daily for six to 14 days.

Outcome measure The primary efficacy outcome was venous thromboembolism detected by routine bilateral venography along with symptomatic venous thromboembolism up to day 15. Secondary outcomes were bleeding and death. Patients were followed up at one month.

Results 425 patients in the fondaparinux group and 414 patients in the placebo group were evaluable for safety analysis (10 were not treated). 644 patients (75.9%) were available for the primary efficacy analysis. Venous thromboembolism was detected in 5.6% (18/321) of patients treated with fondaparinux and 10.5% (34/323) of patients given placebo, a relative risk reduction of 46.7% (95% confidence interval 7.7% to 69.3%). Symptomatic venous thromboembolism occurred in five patients in the placebo group and none in the fondaparinux group ($P=0.029$). Major bleeding occurred in one patient (0.2%) in each group. At the end of follow-up, 14 patients in the fondaparinux group (3.3%) and 25 in the placebo group (6.0%) had died.

Conclusion Fondaparinux is effective in the prevention of asymptomatic and symptomatic venous thromboembolic events in older acute medical patients. The frequency of major bleeding was similar for both fondaparinux and placebo treated patients.

Introduction

Most patients who die from pulmonary embolism as a complication of being admitted to hospital are medical patients.¹ The baseline risk for venous thromboembolism and the effectiveness of thromboprophylaxis in these patients is uncertain, which has limited the systematic application of thromboprophylaxis in this population.²⁻⁶ So far only one placebo controlled study has been reported that used bilateral venography to evaluate the presence of venous thromboembolism.⁷

Fondaparinux, a synthetic, selective inhibitor of factor Xa, effectively reduces postoperative venous thromboembolism after orthopaedic surgery.⁸ We carried out a placebo controlled study of fondaparinux in acute medical patients to determine its efficacy and to document and understand the risk for thrombosis in this patient group.

Methods

We considered for inclusion in our study acutely ill patients with congestive heart failure class III/IV (New York Heart Association), acute respiratory illness in the presence of chronic lung disease, or diagnosed acute infections or inflammatory disorders such as arthritis. Patients had to be at least 60 years old and expected to remain in bed for at least four days. (See bmj.com for exclusion criteria.)

Patients were randomly assigned to either fondaparinux sodium (Arixtra; GlaxoSmithKline) or placebo, within 48 hours of admission to hospital. Study drugs were provided as prefilled single dose syringes to be given once daily subcutaneously. Each syringe contained either active drug (2.5 mg fondaparinux sodium in 0.5 ml saline) or placebo (0.5 ml isotonic saline). Treatment was scheduled until days 6 to 14, and the primary efficacy outcome was assessed up to day 15. Patients were examined for deep vein thrombosis

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BMJ 2006;332:325-7



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This is the abridged version of an article that was posted on bmj.com on 26 January 2006: <http://bmj.com/cgi/doi/10.1136/bmj.38733.466748.7C>

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by routine bilateral ascending venography of the legs between days 6 and 15 and no more than one calendar day after the last administration of study drug, or earlier if deep vein thrombosis was clinically suspected. Symptomatic pulmonary embolism was to be confirmed by a high probability lung scan, pulmonary angiography, or helical computed tomography, or at autopsy.⁹ In the absence of autopsy, death was classified due to pulmonary embolism if it occurred suddenly and was otherwise unexplained. Patients were followed up for one month: venous thromboembolism, bleeding, or death was recorded.

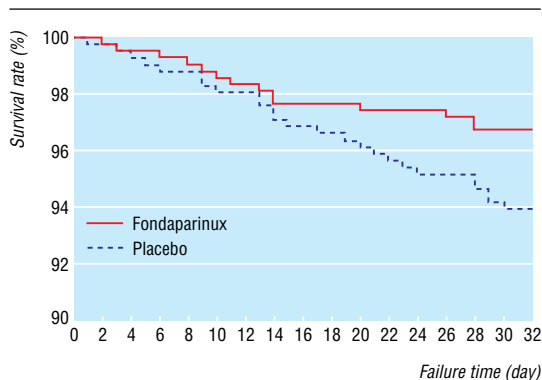
The primary efficacy outcome was the composite of deep vein thrombosis detected by routine bilateral venography on days 6 to 15, and symptomatic venous thromboembolism up to day 15.

The primary safety outcome was major bleeding (fatal, in a critical location, leading to surgical intervention, or overt and associated with a drop in haemoglobin concentration of ≥ 20 g/l or leading to transfusion of two or more units of red blood cells) during treatment and two days thereafter. Secondary safety outcomes were death and minor bleeding.

On the basis of the placebo controlled study that used venography, we expected a venous thromboembolism rate in the placebo group of between 10% and 14%.⁷ The primary efficacy analysis was carried out on all randomised patients with an available efficacy assessment up to day 15. The safety analyses included all patients who had received at least one dose of study drug. We carried out the analyses using a two sided Fisher's exact test and considered a P value of < 0.05 as statistically significant. We calculated relative risk reductions, with 95% confidence intervals. Incidences of the primary efficacy outcome were also calculated according to predefined categorical covariates (congestive heart failure, acute respiratory illness, or acute infectious or inflammatory disease separately). We compared survival rates using the log rank test.

Results

Between March 2002 and January 2003, 849 patients from 35 centres in eight countries were randomised to our study (see [bmj.com](#)). Four patients in the fondaparinux group and six in the placebo group were not treated. All treated patients received the allocated study treatment. Thus 425 patients in the fondaparinux



Survival estimates of older (≥ 60 years) acute medical patients treated with the anticoagulant fondaparinux or placebo. Log rank test on difference, $P=0.06$

Venous thromboembolic events in older (≥ 60 years) medical patients randomised to the anticoagulant fondaparinux or placebo. Values are numbers unless stated otherwise

Primary efficacy outcome	Fondaparinux group	Placebo group
Venous thromboembolic events:		
Any	18	29
Proximal deep vein thrombosis	5	7
Distal deep vein thrombosis	13	22
Symptomatic deep vein thrombosis	0	0
Non-fatal pulmonary embolism	0	0
Fatal pulmonary embolism	0	5
Total No (%)	18/321 (5.6)	34/323 (10.5)
No (%) of any symptomatic venous thromboembolism up to day 32:		
Symptomatic deep vein thrombosis	0	0
Non-fatal pulmonary embolism	1	4
Fatal pulmonary embolism	3	7
Total No (%)	4/429 (1)	11/420 (3)

group and 414 in the placebo group were evaluable for safety analysis. Treatment lasted for a median of 7 days (range 1-15 days) in the fondaparinux group and 7 days (range 1-13 days) in the placebo group. A total of 644 patients (75.9%) were available for the primary efficacy analysis. Baseline characteristics were similar between the two groups (see [bmj.com](#)).

Overall, 5.6% (18/321) of patients in the fondaparinux group and 10.5% (34/323) of patients in the placebo group had venous thromboembolism detected by routine bilateral venography and symptomatic venous thromboembolism up to day 15 (relative risk reduction 46.7%, 95% confidence interval 7.7% to 69.3%, $P=0.029$; table). Consistent reductions were shown in the incidence of total, proximal, and distal deep vein thrombosis. Five fatal cases of pulmonary emboli occurred during the study, all in the placebo group. Two of the five were confirmed by autopsy, the others were assumed to be due to pulmonary emboli.

The incidence of venous thromboembolism on venography and symptomatic venous thromboembolism was reduced in fondaparinux recipients with only congestive heart failure from 12.2% (10/82) to 9.0% (7/78), only acute respiratory illness from 5.5% (4/73) to 1.6% (1/63), only acute infectious or inflammatory disease from 11.4% (10/88) to 5.2% (4/77), and in patients with more than one reason for admission to hospital from 12.5% (10/80) to 5.8% (6/103).

Ten additional cases of pulmonary embolism occurred during follow-up (four in the fondaparinux group). Five were fatal (three in the fondaparinux group).

Major bleeding occurred in one patient in each group during the study, both related to overt bleeding and a drop in haemoglobin concentration of ≥ 20 g/l or transfusion of ≥ 2 units of blood (see [bmj.com](#)). Minor bleeds were observed in 11 patients (2.6%) in the fondaparinux group and four (1.0%) in the placebo group. At one month, 14 (3.3%) patients in the fondaparinux group and 25 (6.0%) in the placebo group had died ($P=0.06$) (figure and [bmj.com](#)).

Discussion

Daily subcutaneous injections of 2.5 mg fondaparinux for 6-14 days almost halved the rate of venous thromboembolism in older (≥ 60 years) acute medical

patients admitted to hospital and requiring bed rest for heart, lung, or infectious or inflammatory disorders. No patients in the fondaparinux group and five in the placebo group had symptomatic fatal or non-fatal pulmonary embolism. This reduction in venous thromboembolism was achieved with a minimal risk of major bleeding complications.

The relative risk reduction with fondaparinux we found is consistent with findings of the high dosage low molecular weight heparin group in the study that used venography.⁷ These results add to the efficacy data supporting the general applicability of fondaparinux in the prevention as well as treatment of venous thromboembolism.^{8,9}

Thrombosis risks are well known after surgical interventions, but when our study was designed few recent studies had evaluated this risk in older people admitted to hospital with other acute or chronic conditions. Guidelines are available on prophylaxis in high risk inpatients but a need for universal prophylaxis has not been shown.¹⁰ No simple and easily applied selection criteria exist, and audits of general medical inpatients indicate that thrombosis prevention is not systematically applied or well grounded on risk factor assessment.^{2,5,11}

Clinical events are not rare in medical patients (around 10% of deaths are due to pulmonary embolism^{12,13}) but are in thromboprophylaxis studies.^{7,14} Clinical events are rare in this type of study as venography is a sensitive and specific screening tool.

Venography is able to diagnose a higher frequency of deep vein thrombosis and smaller thrombi. Earlier and more accurate diagnosis has advantages for patients, with therapy starting before disease progression. As a result, clinical venous thromboembolism is rare in patients in whom venography studies are undertaken. We have concluded in favour of fondaparinux for two reasons, firstly because the surrogate end point of venographic deep vein thrombosis is strongly correlated to clinical deep vein thrombosis, clinical pulmonary embolism,¹¹ and fatal pulmonary embolism.¹⁵ Secondly, we found a significant reduction in the clinical secondary end point of fatal pulmonary embolism. Similar conclusions have been made in other studies on the basis of surrogate end points^{11,15} and by the American College of Chest Physicians.¹⁰

We believed that our study could best contribute to the improvement of clinical practice if we applied simple and easily generalisable patient selection criteria to general medical inpatients, without further risk factor assessment. Since these criteria differed from those applied by others, we depended on a placebo group to measure baseline risk and risk reduction by active therapy.^{7,11} Investigators excluded patients prescribed or thought to need thromboprophylaxis. This might explain why the 10.5% thromboembolism rate at baseline was below the 20% and 15% in other studies.^{7,10}

Two thirds of the clinically apparent events and half of the fatal pulmonary emboli were observed after the initial 6-14 day study period. This is similar to the observation in one trial and supports the need to evaluate extended prophylaxis in medical patients.⁷ Our results when added to those obtained with low molecular weight heparins^{7,10} establish the value of thromboprophylaxis in older medical inpatients at moderate to high risk of venous thromboembolism. The challenge now is to translate shown efficacy into effectiveness.

What is already known on this topic

Most patients who die from pulmonary embolism as a complication of being admitted to hospital are medical patients

The effectiveness of thromboprophylaxis in these patients is uncertain

What this study adds

Fondaparinux is effective in the prevention of venous thromboembolism in acutely ill older (≥ 60 years) medical patients

Contributors: See bmj.com.

Funding: Sanofi-Synthelabo (France) and NV Organon (Netherlands) sponsored the study and carried out on-site monitoring of all participants. The steering committee had the final responsibility for the study protocol, case report forms, statistical analysis plan, progress of the study and analysis, as well as the reporting of the data. The sponsors had an opportunity to comment on the manuscripts before submission, but the final version was the sole responsibility of the authors.

Competing interests: ATC, BLD, ASG, MRL, WT, and AGGT participated as investigators, consultants, or both for NV Organon and Sanofi-Synthelabo. JFME and AWAL are employees of NV Organon. BLD has served as an investigator or consultant for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, and Pharmacia. ASG has served as an investigator, consultant, or advisory board member for Bristol-Myers Squibb, AstraZeneca, Aventis, Bayer, and Progen. MRL has served as an investigator and advisory board member for AstraZeneca, Bristol-Myers Squibb, Mitsubishi Pharma Europe, Yamanouchi Pharma, and Bayer. AGGT is a consultant for Bristol-Myers Squibb.

Ethical approval: The institutional review boards of each centre approved the protocol.

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(Accepted 17 November 2005)

doi 10.1136/bmj.38733.466748.7C