Treatment A New Oral Direct Thrombin Inhibitor, Dabigatran Etexilate, Compared With Enoxaparin for Prevention of Thromboembolic Events Following Total Hip or Knee Replacement: the BISTRO II Randomized Trial

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INTRODUCTION

Background: Dabigatran etexilate is an oral direct thrombin inhibitor undergoing evaluation for the prevention of venous thromboembolism (VTE) following orthopedic surgery.

METHODS

This was a randomized, parallel-group, double-blind, active controlled study conducted at 60 centers in Europe and two centers in South Africa.

Treatment Schedule: On the day before surgery, patients were assigned randomly to five treatment groups, stratified by the study center and the surgical procedure (hip or knee replacement). Treatment was continued for a total of 6-10 days until mandatory bilateral venography was performed. Continued anticoagulation after this time was at the discretion of the investigator. Patients were assessed at a follow-up visit 4-6 weeks after surgery.

Patients were assigned to either oral dabigatran etexilate with doses of 50 and 150 mg twice daily, 300 mg once daily and 225 mg twice daily, or 40 mg of enoxaparin sc, once daily.

Outcomes: The primary efficacy outcome was the incidence of VTE, being symptomatic, or venographically detected DVT and/or PE detected during the treatment period. The primary safety outcome was major bleeding during the treatment period, defined as clinically overt bleeding associated with ≥20 gL-1 fall in hemoglobin; clinically overt leading to transfusion of ≥2 units packed cells or whole blood.

CONCLUSION

In this study, all doses of dabigatran etexilate commenced early in the postoperative period were effective in preventing VTE following major joint replacement surgery. This treatment effect was dose dependent and consistent in patients undergoing both THR and TKR. Bleeding was also dose dependent with higher doses of dabigatran etexilate showing an increase in all bleeding parameters. Evidence of a dose relationship for efficacy and safety therefore achieved the main objective of this study. A *post hoc* analysis of efficacy and bleeding according to timing of the first dose of dabigatran etexilate showed that VTE was lower among patients receiving their first dose within 2 h postoperatively without any associated increase in major or clinically significant bleeding. The three higher doses of dabigatran etexilate, commenced within 1-4 h postoperatively, were significantly more effective than enoxaparin (40 mg once daily) starting preoperatively, although appearing to result in an increase in bleeding events.

RESULTS

Of the 2039 patients enrolled, 1973 were randomized to either dabigatran etexilate (1576) of enoxaparin (397). Patient demographic and surgical characteristics were similar for all five treatment groups. Two-thirds of patients underwent THR (68%) and a third TKR (32%). The mean time interval between surgery and first dose of dabigatran etexilate was 2.6 h. The median duration of treatment was 7 days.

Efficacy Results: There was a significant dose dependent decrease in the frequency of VTE with increasing doses of dabigatran etexilate (*P*<0.0001). This occurred for both distal and proximal DVT, and among the two surgical groups

Safety Results: Major Bleeding occurred on the day of surgery [33 of 58 (57%)] with the majority at the surgical site [52 of 58 (90%]; no case of bleeding into a critical organ was observed. Four patients (one in each of the three highest dabigatran etexilate groups and one in the enoxaparin group) required reoperation due to bleeding. Clinically significant bleeding and the composite endpoint of major and clinically significant bleeding showed similar results compared with the primary safety outcome. Compared with enoxaparin, major bleeding was significantly lower in the 50 mg twice-daily group (0.3% vs. 2.0%, *P*=0.047), while showing a non-significant trend for increased bleeding in those receiving 150 mg twice daily (4.1%, *P*=0.10), 225 mg twice daily (3.8%, *P*=0.15) and 300 mg once daily (4.7%, *P*=0.051).

Adverse Events: A total of 98 patients reported 160 serious adverse events during the treatment period, 24 of whom were judged attributable to the study drug by the investigators (none in the 50 mg group, four in the 150 mg group, 12 in the 300 mg group, six in the 225 mg group, two in the enoxaparin group).

Table1. Efficacy outcomes during the treatment period

	Dabigatran etexilate groups				Enox	
	50 mg bid	150mg bid	300 mg qd	225 mg bid	40 mg qd	Total
Total population						
VTE evaluable patients*	302	282	283	297	300	1464
Patients with VTE (%)	86 (28.5)	49 (17.4)	47 (16.6)	39 (13.1)	72 (24.0)	293 (20.0)
(95% CI)	(23.5-33.9)	(13.1-22.3)	(12.5-21.5)	(9.5-17.5)	(19.3-29.2)	(18.0-22.2)
Patients with DVT (%)†	86 (28.5)	47 (16.8)	47 (16.6)	39 (13.1)	72 (24.0)	291 (19.9)
Proximal DVT	15 (5.0)	9 (3.3)	6 (2.1)	5 (1.7)	17 (5.6)	52 (3.6)
Distal DVT	79 (26.2)	43 (15.4)	43 (15.2)	36 (12.1)	67 (22.3)	268 (18.3)
Composite proximal DVT/PE	15 (5.0)	11 (4.0)	6 (2.1)	5 (1.7)	17 (5.6)	54 (3.7)
Total hip replacement						
VTE evaluable patients*	208	201	191	204	208	1012
Patients with VTE (%)	49 (23.6)	27 (13.4)	25 (13.1)	17 (8.3)	31 (14.9)	149 (14.7)
(95% CI)	(18.0-29.9)	(9.0-18.9)	(8.7-18.7)	(4.9-13.0)	(10.4-20.5)	(12.6-17.1)
Patients with DVT (%)†	49 (23.6)	26 (13.0)	25 (13.1)	17 (8.3)	31 (14.9)	148 (14.6)
Proximal DVT	12 (5.7)	8 (4.0)	3 (1.5)	4 (2.0)	11 (5.2)	38 (3.7)
Distal DVT	42 (20.2)	22 (11.0)	22 (11.6)	14 (6.9)	26 (12.5)	126 (12.5)
Composite proximal DVT/PE	12 (5.7)	9 (4.5)	3 (1.5)	4 (2.0)	11 (5.2)	39 (3.8)
Total knee replacement						
VTE evaluable patients*	94	81	92	93	92	452
Patients with VTE (%)	37 (39.4)	22 (27.2)	22 (23.9)	22 (23.7)	41 (44.6)	144 (31.9)
(95% CI)	(29.4-50.0)	(17.9-38.2)	(15.6-33.9)	(15.5-33.6)	(34.2-55.3)	(27.6-36.4)
Patients with DVT (%)†	37 (39.4)	21 (26.3)	22 (23.9)	22 (23.4)	41 (44.6)	143 (31.6)
Proximal DVT	3 (3.4)	1 (1.3)	3 (3.4)	1 (1.1)	6 (6.6)	14 (3.2)
Distal DVT	37 (39.4)	21 (26.3)	21 (22.8)	22 (23.4)	41 (44.6)	142 (31.4)
Composite proximal DVT/PE	3 (3.4)	2 (2.6)	3 (3.4)	1 (1.1)	6 (6.6)	15 (3.4)

bid, twice daily; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; qd, once daily; VTE, venous thromboembolism. *Evaluable patients for the total VTE population only. †Patients with more than one DVT are shown in both distal and proximal categories.