Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product:				
Name of active ingredient: Dabigatran etexilate mesilate		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 06 DEC 06	**Number:** U06-1618	**Study period (dates):** 03 DEC 04 - 25 JUL 06		

Title of study:	A phase III randomised, parallel-group, double-blind, active controlled study to investigate the efficacy and safety of two different dose regimens of orally administered dabigatran etexilate capsules [150 or 220 mg once daily starting with half dose (i.e. 75 or 110 mg) on the day of surgery] compared to subcutaneous enoxaparin 40 mg once daily for 28-35 days, in prevention of venous thromboembolism in patients with primary elective total hip replacement surgery RE-NOVATE (Extended thromboembolism prevention after hip surgery)
Investigator:	[redacted]
Study centers:	International, multi-centre study, cf. Appendix 16.1.4
Publication (reference):	Data of this study have not been published
Clinical phase:	III
Objectives:	To determine the comparative efficacy and safety of two different dose regimens of dabigatran etexilate administered orally (capsules), compared to enoxaparin 40 mg once a day subcutaneous, given for 28-35 days, for the prevention of venous thromboembolism in patients with primary elective total hip replacement surgery.
Methodology:	Randomised, parallel-group, double-blind, active-controlled (double-dummy) study of two different dose regimens of dabigatran etexilate compared with enoxaparin.
No. of subjects: **planned:** **actual:**	 entered: 3330 enrolled: 3613 entered: 3494 Treatment A: Dabigatran 220 mg entered: 1157 treated: 1146 analysed (for primary endpoint): 880 Treatment B: Dabigatran 150 mg entered: 1174 treated: 1163 analysed (for primary endpoint): 874 Treatment C: Enoxaparin entered: 1162 treated: 1154 analysed (for primary endpoint): 897
Diagnosis and main criteria for inclusion:	Patients with primary elective total hip replacement surgery who provided written informed consent.
Test product:	Dabigatran etexilate mesilate

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dose:	Regimen 1: 75 mg on the day of surgery, 150 mg once daily thereafter Regimen 2: 110 mg on the day of surgery, 220 mg once daily thereafter
mode of admin.:	Oral (p. o.)
batch no.:	Dabigatran etexilate 75 mg: 404323, 9040225 Dabigatran etexilate 110 mg: 404331, 9040226 Dabigatran-matching placebo capsules: 9040167, 9040224
Duration of treatment:	28-35 days (including day of surgery) [maximum up to day 42]
Reference therapy:	Enoxaparin
dose:	40 mg qd (to be started on the day before surgery)
mode of admin.:	Subcutaneous injection (s. c.)
batch no.:	Enoxaparin 40 mg: E 111, 4457, 49510 Enoxaparin-matching placebo syringes: refer to Section 9.4.2
Criteria for evaluation:	
Efficacy:	Primary efficacy endpoint: A composite endpoint consisting of total Venous Thromboembolic Events (VTE) and all-cause mortality during the treatment period. Total VTE was defined as the composite incidence of proximal and distal deep venous thrombosis (DVT), symptomatic DVT, and pulmonary embolism (PE). Secondary efficacy endpoints (during the treatment period): 1. Composite of major VTE (defined as proximal DVT and PE) and VTE-related mortality 2. Proximal DVT 3. Total DVT 4. Symptomatic DVT 5. Pulmonary Embolism (PE) 6. Death Additionally, a composite endpoint of total VTE and all-cause mortality during the follow-up period was evaluated.

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Safety:	1. Incidence of bleeding events A. Major Bleeding Events (MBE) B. MBE and clinically relevant bleeding events C. Any bleeding events (major, clinically relevant and minor) 2. Volume of blood loss 3. Blood transfusion 4. Adverse events 5. Discontinuation due to adverse events 6. Laboratory measures 7. Physical examination All safety endpoints were assessed during the entire study phase.
Additional endpoint	Analysis of resource utilization for each treatment group, pre-specified as a tertiary endpoint, will be presented in a separate health economic report.
Statistical methods:	Non-inferiority testing with a minimum important difference of 7.7% in the rate of total VTE and all-cause mortality between dabigatran and enoxaparin. A hierarchical testing procedure was employed. This study aimed to show (1) non-inferiority of the high dabigatran dose regimen, (2) non-inferiority of the low dabigatran dose regimen, (3) superiority of the high dabigatran dose regimen, and (4) superiority of the low dabigatran dose regimen to enoxaparin in the primary efficacy endpoint. The overall significance level was controlled by a priori ordering of hypotheses. The planned sample size had at least 95% of power to claim non-inferiority with one-sided alpha=0.025. The calculation assumed equal rates between enoxaparin and dabigatran for the primary endpoint in the range of 14% to 20%, and that 35% of the venograms would be non-evaluable.

SUMMARY – CONCLUSIONS:

Efficacy results:

Overall, 3494 patients were randomised; 3463 patients were randomised and received treatment (safety set) and 3435 patients were randomised, treated, and underwent surgery (FAS-op); of these 2651 patients (dabigatran 220 mg: 880 patients, dabigatran 150 mg: 874 patients, enoxaparin: 897 patients) were evaluable for the primary endpoint (FAS); i.e. 77.2% of patients in the FAS-op population. Overall, the mean age was 63.9 years; almost all patients were white (99.4%), and 56.4% of patients were female. The majority of patients (57.2%) had normal kidney function (CrCl ≥80 mL/min), mild impairment (CrCl 50-80 mL/min) was observed in 34.1%, and moderate impairment (CrCl 30-50 mL/min) was seen in 6.0% of patients overall. The majority of patients had received spinal anaesthesia (69.0%) and both oral study drug (within 1- 4 hours post surgery, 85.0%) and subcutaneous injection (pre-surgery, 92.0%) were administered according to the protocol in almost all patients.

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Efficacy results: (continued)

The incidences of total VTE and all-cause mortality during the treatment period were 6.0% (dabigatran 220 mg), 8.6% (dabigatran 150 mg), and 6.7% (enoxaparin). The risk difference (95% CI) versus enoxaparin was -0.7% (-2.9, 1.6) in the dabigatran 220 mg group and +1.9% (-0.6, 4.4) in the dabigatran 150 mg group; the respective odds ratios (95% CI) were 0.9 (0.6, 1.3) and 1.3 (0.9, 1.9). Thus the incidences of total VTE and all-cause mortality in both dabigatran dose groups were within the pre-specified non-inferiority margin of 7.7%. The strongest contribution to the primary endpoint came from asymptomatic DVTs detected by venography with incidences of 4.5% (dabigatran 220 mg), 7.2% (dabigatran 150 mg), and 6.2% (enoxaparin). Symptomatic DVTs were rare events in all treatment groups; the incidences were 0.6% (dabigatran 220 mg), 1.0% (dabigatran 150 mg) and 0.1% (enoxaparin). In the dabigatran 220 mg group 5 patients had a non-fatal PE and 3 patients died, in the dabigatran 150 mg group no patient had a non-fatal PE and 3 patients died, and in the enoxaparin group 3 patients had a non-fatal PE and no patient died during the treatment period.

The analysis of total VTE and all-cause mortality by age category indicated a trend towards higher incidences of total VTE and all-cause mortality in older patients in the dabigatran 220 mg group and enoxaparin group while this was not apparent in the dabigatran 150 mg group. For gender, weight, and BMI no consistent trend was apparent in any treatment group. There was no indication of higher incidences of total VTE and all-cause mortality in patients with impaired kidney function. However, there was a trend towards reduced incidences of total VTE and all-cause mortality for patients with a low creatinine clearance for the dabigatran 220 mg group. In the dabigatran 150 mg group, this trend was only observed for mild renal impaired (CrCl 50 to 80 mL/min) compared with normal kidney function (CrCL >80 mL/min). Such a trend was not observed for the enoxaparin group.

With regard to the incidence of total VTE and all-cause mortality and its relation to the time of first oral administration, a trend towards lower incidences for earlier administration times was observed. This trend was not observed for the enoxaparin group. Patients who had general anaesthesia showed a higher event rate than patients who had non-general anaesthesia in all treatment groups.

The lowest incidence (95% CI) of major VTE and VTE-related death was observed in the dabigatran 220 mg with 3.1% (2.0, 4.2), followed by the enoxaparin group with 3.9% (2.7, 5.2), and then the dabigatran 150 mg group with 4.3% (2.9, 5.6).

There were no obvious trends for gender, weight, BMI in any treatment group. There appeared to be a relationship between the timing after surgery of the initial

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Efficacy results: (continued)	oral dose of dabigatran, but not enoxaparin, and the incidence of major VTE and VTE-related mortality, with earlier dabigatran dosing being associated with less major VTE and VTE-related mortality. Since the majority of events contributing to major VTEs and VTE-related mortality were proximal DVTs, the results for proximal DVTs were similar to the results of major VTE and VTE- related mortality. The lowest incidence was again observed in the dabigatran 220 mg group with 2.5%, followed by 3.6% for the enoxaparin group, and 4.0% for the dabigatran 150 mg group. The incidence of total VTE and all-cause mortality during the follow-up was very low; 1 (dabigatran 220 mg), 4 (dabigatran 150 mg), and 5 (enoxaparin) patients had an event.
Safety results:	The extent of exposure to study medication was similar in all treatment groups and the total exposure was 96.5 years (dabigatran 220 mg), 96.7 years (dabigatran 150 mg), and 97.4 years (enoxaparin). The incidences of major bleeding events (MBE) were similar in all treatment groups: During the treatment period, 23 patients (2.0%) in the dabigatran 220 mg group, 15 patients (1.3%) in the dabigatran 150 mg group, and 18 patients (1.6%) in the enoxaparin group had MBEs. A statistical test for treatment differences of the dabigatran groups versus enoxaparin yielded p-values of 0.4352 (dabigatran 220 mg) and 0.6037 (dabigatran 150 mg). No patient had an MBE before surgery in any treatment group. Most MBEs occurred on Day 1 during surgery (dabigatran 220 mg: 12 patients, dabigatran 150 mg: 5 patients, and enoxaparin: 7 patients) or in the post-operative period of Day 1 (dabigatran 220 mg: 2 patients, dabigatran 150 mg: 6 patients, and enoxaparin: 2 patients). No patient in any treatment group had an MBE later than 15 days post surgery. When analysed by worst bleeding, similar proportions of patients in all treatment groups had clinically-relevant bleeding events (CRBE) and minor bleeding events. In the dabigatran 220 mg group 48 patients (4.2%), in the dabigatran 150 mg group 55 patients (4.7%), and in the enoxaparin group 40 patients (3.5%) had clinically-relevant bleeding events; 6.1% (dabigatran 220 mg), 6.2% (dabigatran 150 mg), and 6.4% (enoxaparin) of patients had minor bleedings. Statistical testing did not indicate a difference between the dabigatran groups and the enoxaparin group. When MBEs CRBEs were combined, minimally higher incidences were apparent in the dabigatran groups (dabigatran 220 mg: 6.2%; dabigatran 150 mg: 6.0%) than in the enoxaparin group (5.0%). However, a statistical test for differences between the dabigatran groups and the enoxaparin group yielded p-

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Safety results: (continued)

values of 0.2229 (dabigatran 220 mg) and 0.2953 (dabigatran 150 mg).

An analysis of MBEs and CRBEs based on events shows that there were 76 bleeding events in 71 patients in the dabigatran 220 mg group, 76 bleeding events in 70 patients in the dabigatran 150 mg group, and 59 events in 58 patients.

The majority of major- or clinically relevant bleeding events occurred at the surgical site in all treatment groups: 50/76 (65.8%) in the dabigatran 220 mg group, 57/76 (75.0%) in the dabigatran 150 mg group, and 40/59 (67.8%) in the enoxaparin group.

The overall incidence of treatment-emergent adverse events was similar in all treatment groups with 76.7% (dabigatran 220 mg), 77.0% (dabigatran 150 mg), and 77.3% (enoxaparin) of patients. The majority of adverse events were of mild or moderate intensity, only 3.6% (dabigatran 220 mg), 4.0% (dabigatran 150 mg), and 2.9% (enoxaparin) of patients reported adverse events of severe intensity. The frequency of adverse events that led to discontinuation from the study was also similar in all treatment groups with 6.5% (dabigatran 220 mg), 7.6% (dabigatran 150 mg), and 5.7% (enoxaparin). In the opinion of the investigator, 8.6% (dabigatran 220 mg), 8.6% (dabigatran 150 mg), and 9.0% of patients experienced adverse events that were related to study drug. The proportion of patients who experienced serious adverse events was also similar in all treatment groups with 7.8% in the dabigatran 220 mg group, 7.8% in the dabigatran 150 mg group, and 7.1% in the enoxaparin group.

The most frequent adverse events were gastrointestinal disorders with similar frequencies in all treatment groups (dabigatran 220 mg: 44.2%; dabigatran 150 mg: 44.0%; enoxaparin: 44.8%). The second most frequent adverse events belonged to the system organ classes of injury, poisoning and procedural complications (dabigatran 220 mg: 24.0%; dabigatran 150 mg: 24.3%, enoxaparin: 23.1%).

The frequencies of adverse events tended to increase with age. Overall, 74.4%, 72.0%, and 73.6% of a patients younger than 65 years experienced adverse events compared with 80.2%, 86.5%, and 85.4% of patients above 75 years of age in the dabigatran 220 mg, the dabigatran 150 mg, and the enoxaparin groups, respectively. These differences were predominantly caused by higher incidences of gastrointestinal disorders and of adverse events belonging to the system organ class of injury, poisoning, and procedural complications.

All treatment groups showed a trend towards higher incidences of adverse events in patients with impaired renal function. The higher overall frequency of adverse events was mainly caused by higher incidences of gastrointestinal adverse events. There was no indication of higher incidences of gastrointestinal bleeding

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Safety results: (continued)

events in patients with moderately impaired renal function compared with patients with normal renal function.

Overall 10 patients, 3 patients in the dabigatran 220 mg group, 5 patients in the dabigatran 150 mg group, and 2 patients in the enoxaparin group died in the course of the study. Six patients, 3 in the dabigatran 220 mg group and 3 in the dabigatran 150 mg group, died in the treatment period which included the first 3 days after the last administration of study drug, 3 patients died in the post-treatment period, and 1 patient died in the post-study period.

In regard to clinical laboratory, no unexpected findings were observed for haematology parameters, electrolytes, and substrates. Liver enzyme elevations were rare events. The highest incidences of ALT elevations were observed in the immediate post-operative period in all treatment groups. By the first follow-up visit, most patients' ALT-levels had returned to normal values. The highest incidence of ALT-elevations was observed in the enoxaparin group. At any time post-baseline 9 patients (0.8%) in the dabigatran 220 mg, 18 patients (1.6%) in the dabigatran 150 mg group, and 20 patients (1.8%) in the enoxaparin group had ALT elevations above 5-times the upper limit of the normal range (ULN). A few patients had extremely high values: 1 patient in the dabigatran 150 mg group had ALT elevations above 20x ULN during Days 11-19 and 1 patient in the enoxaparin group had ALT elevations above 30x ULN during Days 20-56. In all patients with ALT elevations above 3x ULN had the ALT levels returned to within 10% of baseline or below 1.5x ULN at the end of the study.

Overall, AST-elevations were substantially less frequent than ALT-elevations. The majority of AST-elevations occurred in the immediate post-operative period and returned to baseline in almost all patients.

Overall, elevations of total bilirubin levels were rare events. Even in the immediate post-operative period only very few patients in all treatment groups had elevated total bilirubin levels. One patient in the dabigatran 220 mg group and 2 patients in the dabigatran 150 mg group had total bilirubin elevations of more than 2x ULN at some time post baseline. One patient in the dabigatran 220 mg group and 1 patient in the dabigatran 150 mg group had both an elevation of total bilirubin above 2x ULN and an ALT-elevation of more than 3x ULN at some time post baseline. For both patients both parameters had returned to baseline at the end of the study.

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Conclusions:

With both dabigatran doses of 220 mg per day and 150 mg per day the pre-specified non-inferiority margin in comparison with enoxaparin for the primary endpoint, the incidence of total VTE and all-cause mortality, was reached. Overall, the incidence of the primary and the first secondary efficacy endpoint (major VTE and VTE-related mortality) were lower than anticipated for all treatment groups, suggestive of very effective VTE prophylaxis with any of the utilized treatment regimens. The incidence of total VTE and all-cause mortality was lowest in the dabigatran 220 mg group, intermediate in the enoxaparin group, and highest in the dabigatran 150 mg group. The ordering of the incidences of the secondary efficacy endpoints with incidences of at least 1% was consistent with those of the primary endpoint. The incidences of low-occurrence endpoints (symptomatic DVT, PE, and death, 0.0 to 0.8%) were not internally consistent (lowest incidence of PE in the dabigatran 150 mg group and lowest incidence of symptomatic DVTs in the enoxaparin group) suggesting chance variation in the observed incidences of these infrequent events. A slight propensity in the dabigatran 220 mg dose group towards higher incidences of bleeding events was observed compared with the dabigatran 150 mg group and the enoxaparin group. Thus, a dose-response relationship in the 2 dabigatran doses was observed with slightly greater efficacy but increased frequency of bleedings in the higher dose group; enoxaparin data were generally intermediate between those of both dabigatran treatment groups. It can be concluded that once daily dabigatran (150 mg and 220 mg) is non-inferior to enoxaparin 40 mg once daily when administered for 28-35 days in patients undergoing total hip replacement surgery. Generally, the safety profile was comparable in all 3 treatment groups.

Trial Synopsis – Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide disposition results and results of additional secondary endpoints, as summarised below.

Results for	**presented in**
Disposition of patients during treatment period	Table 15.1.1: 1
Composite of major VTEs and VTE-related mortality during treatment period	Table 15.2.2: 1
Proximal DVTs during treatment period	Table 15.2.3: 1
Composite of total VTE and all-cause mortality during the follow-up period.	Table 15.2.8: 1
Total DVTs during treatment period	Table 15.2.4: 1
Symptomatic DVT during treatment period	Table 15.2.5: 1
Pulmonary embolism (PE) during treatment period	Table 15.2.6: 1
Death during treatment period	Table 15.2.7: 1

Table 15.1.1: 1 Patient disposition at the end of treatment

	Dabigatran 220mg	Dabigatran 150mg	Enoxaparin	Total
Enrolled				3613
Not entered randomised				119
Entered/ randomised	1157	1174	1162	3494
Not treated&	11	11	8	31
Treated	1146 (100.0)	1163 (100.0)	1154 (100.0)	3463 (100.0)
Completed treatment	1013 (88.4)	1012 (87.0)	1021 (88.5)	3046 (88.0)
Discontinued treatment	133 (11.6)	151 (13.0)	133 (11.5)	417 (12.0)
Reason for discontinued treatment				
AE: worsening of disease under study*	10 (0.9)	12 (1.0)	3 (0.3)	25 (0.7)
AE: worsening of other pre-existing disease	4 (0.3)	2 (0.2)	1 (0.1)	7 (0.2)
AE: other (including bleeding events)	63 (5.5)	75 (6.4)	64 (5.5)	202 (5.8)
Bleeding events~	11 (1.0)	6 (0.5)	7 (0.6)	24 (0.7)
Other than bleeding events§	52 (4.5)	69 (5.9)	57 (4.9)	178 (5.1)
Non compliant with protocol (investigator assessment)	8 (0.7)	11 (0.9)	11 (1.0)	30 (0.9)
Lost to follow-up	0 (0.0)	2 (0.2)	1 (0.1)	3 (0.1)
Consent withdrawn	25 (2.2)	20 (1.7)	22 (1.9)	67 (1.9)
Other	23 (2.0)	29 (2.5)	31 (2.7)	83 (2.4)
Deaths during treatment period^	3	3	0	6

*:I.e. symptomatic DVT or PE
The investigator terminated treatment prematurely due to DVT or PE, which was not centrally confirmed by the adjudication committees for 3 patients receiving Dabigatran220mg, 4 patients receiving Dabigatran150mg and 3 patients receiving Enoxaparin
~:Bleeding includes patients who discontinued due to any bleeding event which did or did not clinically require cessation of study drug
§:This line only counts patients who discontinued due to an other AE but who did not discontinue due to a bleeding
^:The date of death determines whether the patient is counted during treatment period or not
&:Patient [redacted] was randomized to Dabigatran 220mg [redacted]) by the investigator but never received any treatment. The investigator re-assigned the kit to patient [redacted]. Therefore, this patient is counted in the total column but not in the Dabigatran 220mg column

Source data: Appendix 16.2, Listing 1.1, 1.2, 1.3 safety\disp.sas 28NOV2006

Table 15.2.2: 1 Comparative analysis of major VTE and VTE related mortality during treatment period (FAS−major)

	Dabigatran 220mg	Dabigatran 150mg	Enoxaparin
FAS−mDVT	909	888	917
Incidence			
n	28	38	36
%	3.1	4.3	3.9
95% CI*	(2.0, 4.2)	(2.9, 5.6)	(2.7, 5.2)
Risk difference(%) vs. Enoxaparin			
estimate*	−0.8	0.4	
95% CI*	(−2.5, 0.8)	(−1.5, 2.2)	
p−value*	0.3256	0.7052	
Relative risk over Enoxaparin#			
estimate	0.78	1.09	
95% CI	(0.48, 1.27)	(0.70, 1.70)	
Odds ratio over Enoxaparin@			
estimate	0.8	1.1	
95% CI	(0.5, 1.3)	(0.7, 1.7)	

*: based on normal approximation of independent binomial distribution without stratification,
p−value is for testing no difference between two treatment groups
#: based on normal approximation of log relative risk without continuity correction
@: based on logistic regression including the main factor of treatment,
derived from contrast that compared the two treatments

Table 15.2.3: 1 Comparative analysis of proximal DVT during treatment period (FAS)

	Dabigatran 220mg	Dabigatran 150mg	Enoxaparin
FAS-pDVT	905	885	914
Incidence			
n	23	35	33
%	2.5	4.0	3.6
95% CI*	(1.5, 3.6)	(2.7, 5.2)	(2.4, 4.8)
Risk difference(%) vs. Enoxaparin			
estimate*	-1.1	0.3	
95% CI*	(-2.7, 0.5)	(-1.4, 2.1)	
p-value*	0.1863	0.7020	
Relative risk over Enoxaparin#			
estimate	0.70	1.10	
95% CI	(0.42, 1.19)	(0.69, 1.75)	
Odds ratio over Enoxaparin@			
estimate	0.7	1.1	
95% CI	(0.4, 1.2)	(0.7, 1.8)	

*: based on normal approximation of independent binomial distribution without stratification,
p-value is for testing no difference between two treatment groups
#: based on normal approximation of log relative risk without continuity correction
@: based on logistic regression including the main factor of treatment,
derived from contrast that compared the two treatments

Table 15.2.8: 1 Summary of total VTE and all-cause mortality during the follow up* period (FAS-op)

	Dabigatran 220mg	Dabigatran 150mg	Enoxaparin
Treated and operated (FAS-op)	1137	1156	1142
Any data available during the follow-up*	1106	1117	1108
Number of patients observed for:			
<20 days	10	9	10
20 to 40 days	43	50	43
41 to 60 days	512	546	547
>60 days	541	512	508
Incidence	1	4	5
asymptomatic DVT°	0	1	3
symptomatic DVT	1	1	0
PE	0	0	1
death	0	2	1

*: includes the period from the end of treatment period to the end of study
°: asymptomatic DVT detected by delayed routine venography

Note: patients were counted only once in the most severe category in subcategories of DVT, PE and death

Table 15.2.4: 1 Comparative analysis of total DVT during treatment period (FAS-tDVT)

	Dabigatran 220mg	Dabigatran 150mg	Enoxaparin
FAS-tDVT	874	871	894
Incidence			
n	46	72	57
%	5.3	8.3	6.4
95% CI*	(3.8, 6.7)	(6.4, 10.1)	(4.8, 8.0)
Risk difference(%) vs. Enoxaparin			
estimate*	-1.1	1.9	
95% CI*	(-3.3, 1.1)	(-0.5, 4.3)	
p-value*	0.3173	0.1274	
Relative risk over Enoxaparin#			
estimate	0.83	1.30	
95% CI	(0.57, 1.20)	(0.93, 1.81)	
Odds ratio over Enoxaparin@			
estimate	0.8	1.3	
95% CI	(0.5, 1.2)	(0.9, 1.9)	

*: based on normal approximation of independent binomial distribution without stratification,
p-value is for testing no difference between two treatment groups
#: based on normal approximation of log relative risk without continuity correction
@: based on logistic regression including the main factor of treatment,
derived from contrast that compared the two treatments

Table 15.2.5: 1 Comparative analysis of symptomatic DVT during the treatment period (FAS-op)

	Dabigatran 220mg	Dabigatran 150mg	Enoxaparin
FAS-op	1137	1156	1142
Incidence			
n	6	9	1
%	0.5	0.8	0.1
95% CI*	(0.2, 1.1)	(0.4, 1.5)	(0.0, 0.5)
Comparison vs. Enoxaparin			
p-value*	0.0694	0.0212	
Comparison vs. Dabigatran 150mg			
p-value*	0.6062		

*: exact 95% CI by Clopper and Pearson, p-value based on Fisher's exact test

Table 15.2.6: 1 Comparative analysis of PE during the treatment period (FAS-op)

	Dabigatran 220mg	Dabigatran 150mg	Enoxaparin
FAS-op	1137	1156	1142
Incidence			
n	5	1	3
%	0.4	0.1	0.3
95% CI*	(0.1, 1.0)	(0.0, 0.5)	(0.1, 0.8)
Comparison vs. Enoxaparin			
p-value*	0.5062	0.3717	
Comparison vs. Dabigatran 150mg			
p-value*	0.1215		

*: exact 95% CI by Clopper and Pearson, p-value based on Fisher's exact test

Table 15.2.7: 1 Comparative analysis of death during the treatment period (FAS–op)

	Dabigatran 220mg	Dabigatran 150mg	Enoxaparin
FAS–op	1137	1156	1142
Incidence			
n	3	3	0
%	0.3	0.3	0.0
95% CI*	(0.1, 0.8)	(0.1, 0.8)	[0.0, 0.3)
Comparison vs. Enoxaparin			
p–value*	0.1240	0.2497	
Comparison vs. Dabigatran 150mg			
p–value*	1.0000		

*: exact 95% CI by Clopper and Pearson, p–value based on Fisher’s exact test