Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

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 Trial Report**	Boehringer Ingelheim
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Title of trial:	A Phase III randomised, parallel-group, double-blind, active controlled study to investigate the efficacy and safety of oral 220 mg dabigatran etexilate (110 mg on the day of surgery followed by 220 mg once daily) compared to subcutaneous 40 mg enoxaparin once daily for 28-35 days in prevention of venous thromboembolism in patients following primary elective total hip arthroplasty (RE-NOVATE II)
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre, multinational trial in 108 centres in 19 countries worldwide
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	The primary objective was to demonstrate non-inferiority of oral dabigatran 220 mg/day compared with subcutaneous (s.c.) enoxaparin 40 mg/day. Additional objectives included the collection of additional efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) data.
Methodology:	Randomised, parallel-group, double-blind, active-controlled (double-dummy) study of 220 mg oral dabigatran once daily (q.d.) compared with subcutaneous 40 mg enoxaparin q.d. with a planned duration of 28-35 days of treatment, including the day of surgery, or until a confirmed venous thromboembolism (VTE) event (deep vein thrombosis [DVT] or pulmonary embolism [PE]).

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No. of subjects:	
planned:	entered: 1920 patients (960 patients per treatment arm)
actual:	enrolled: 2167 entered: 2055 Dabigatran: entered: 1036 treated: 1010 analysed (for primary endpoint): 792 Enoxaparin: entered: 1019 treated: 1003 analysed (for primary endpoint): 786 For PK/PD analyses, trough and post-dose plasma samples were to be collected at discharge. The PK/PD population comprised 729 dabigatran patients.
Diagnosis and main criteria for inclusion:	Men and women aged ≥18 years undergoing primary elective unilateral total hip arthroplasty and providing written informed consent.
Test product:	Dabigatran etexilate mesilate
dose:	110 mg on the day of surgery, 220 mg daily thereafter
mode of admin.:	Oral
batch nos.:	Refer to Appendix 16.1.6
Reference therapy:	Enoxaparin
dose:	40 mg daily, initiated the day before surgery
mode of admin.:	s.c.
batch nos.:	Refer to Appendix 16.1.6
Duration of treatment:	28-35 days, including the day of surgery

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Criteria for evaluation:

Efficacy

Primary efficacy endpoint was the composite of total VTE events and all-cause mortality during the treatment period. Total VTE was defined as the composite incidence of asymptomatic DVT (detected by routine bilateral venography), symptomatic DVT, and symptomatic PE

Secondary efficacy endpoints:

1. The composite of major VTE (defined as proximal DVT and PE) and VTE-related mortality
2. Proximal DVT
3. Total DVT
4. Symptomatic DVT
5. PE
6. Death
7. The composite of total VTE and all-cause mortality during the follow-up period

Efficacy endpoints were based on events centrally adjudicated by an independent, external VTE Endpoint Adjudication Committee.

Clinical pharmacology:

PK: Trough and post-dose plasma concentrations of total dabigatran measured at steady state (Visit 5, discharge).

PD: Activated partial thromboplastin time (aPTT) and thrombin time (TT) at baseline (screening visit; Visit 1) and at Visit 5 (discharge).

Safety:

1. Incidence of bleeding events (based on events centrally adjudicated by an independent, external Bleeding Adjudication Committee)
   a. Major bleeding events (MBEs)
   b. MBEs and clinically relevant bleeding events (CRBEs)
   c. Any bleeding event (MBEs, CRBEs, minor bleeding events)
2. Volume of blood loss
3. Blood transfusions
4. Adverse events (AEs) (included VTE-related and bleeding events)
5. Discontinuation due to AEs
6. Laboratory measures
7. Physical examination

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Statistical methods:

The primary objective was to demonstrate non-inferiority of oral dabigatran compared with s.c. enoxaparin administered q.d. In a hierarchical testing procedure, if non-inferiority of dabigatran to enoxaparin was demonstrated, superiority of dabigatran over enoxaparin was investigated. The test of non-inferiority was based on the confidence interval (CI) method, i.e. non-inferiority was shown if the upper limit of the 95% CI for the risk difference was smaller than the pre-specified non-inferiority margin (7.7%).

The primary analysis was based on centrally adjudicated results of total VTE plus all-cause mortality. Point estimates by treatment group and the risk difference between groups (and the 95% CI) were determined. The analysis was based on the normal approximation of 2 independent binomial distributions without stratification. p-values were created using two Z-statistics pre-defined for non-inferiority and superiority. The same analyses were used for secondary endpoints, but no non-inferiority margin was defined for secondary endpoints: the composite of major VTE and VTE-related mortality, proximal DVT, and total DVT. For symptomatic DVT, PE, death, and the composite of total VTE and all-cause mortality during the follow-up period, the incidence and 95% CI (Clopper and Pearson) by treatment were calculated and compared using Fisher's exact test.

Plasma concentrations of total dabigatran were summarised descriptively. Safety data were summarised descriptively. The Cochran-Mantel-Haenszel test was used to compare categories of worst bleeding between treatments: (1) MBEs, all other bleeds, and no reported bleeding and (2) MBEs, CRBEs, and minor bleeding vs. no reported bleeding.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

In total, 2167 patients were enrolled and 2055 were randomised (dabigatran: 1036; enoxaparin: 1019), 2013 were treated (treated set [TS]; dabigatran: 1010; enoxaparin: 1003), and 1993 were treated and operated (dabigatran: 1001; enoxaparin: 992). A total of 89.9% completed treatment (dabigatran: 89.4%; enoxaparin: 90.3%). Overall, 10.1% of patients discontinued treatment prematurely, with similar rates of discontinuation in both groups (dabigatran: 10.6%; enoxaparin: 9.7%). The most common reason for discontinuing trial medication was the occurrence of an AE (dabigatran: 5.9%; enoxaparin: 5.3%).

The demographic and baseline characteristics were similar in the 2 treatment groups. Overall, the mean (SD) age was 62.0 (11.4) years. Most patients were white (90.4%) and the majority were from Western or Central Europe (69.3%). The mean (SD) BMI was 27.8 (4.8) kg/m^2. The majority had a creatinine clearance (CrCl) of ≥80 mL/min (65.9%) at screening. Not quite half the patients were male (48.2%). Baseline conditions (hypertension, diabetes mellitus, coronary artery disease, and heart failure) were reported at a similar frequency in both groups. Overall, hypertension was reported by 46.0% of all treated patients, diabetes mellitus by 8.3%, coronary artery disease by 5.9%, and heart failure by 2.4%.

Surgical characteristics for the total hip arthroplasty on Day 1 were similar in the 2 groups. Most patients had local anaesthesia (71.7%). Mean duration of surgery was 85.0 minutes. There were similar incidences of blood transfusions in both treatment groups (dabigatran: 24.6%; enoxaparin: 23.9%).

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Primary endpoint: In total, 61 (7.7%) dabigatran patients had 61 events during the treatment period that contributed to the composite primary endpoint compared with 69 (8.8%) enoxaparin patients with 70 events. The overwhelming contributing event of the primary endpoint was asymptomatic DVTs detected on routine venography at the end of the treatment period (dabigatran: 7.6%; enoxaparin: 7.9%). Symptomatic DVTs (dabigatran: 0.0%; enoxaparin: 0.5%), PEs (dabigatran: 0.1%; enoxaparin: 0.3%), and deaths (dabigatran: 0.0%; enoxaparin: 0.1%) during the treatment period were less frequent.

Proximal DVTs made up about 28% of DVTs (i.e. 17 of 60) in the dabigatran group, compared with 46% (31 of 66) in the enoxaparin group.

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Efficacy / clinical pharmacology results (continued):

Dabigatran was non-inferior to enoxaparin. The risk difference between groups for the primary endpoint was -1.1% in favour of dabigatran, with a 95% CI of -3.8, 1.6 ($p<0.0001$). While dabigatran was numerically better than enoxaparin (i.e. there was a lower incidence of the primary endpoint than observed with enoxaparin), it was not statistically superior to enoxaparin ($p=0.4367$). All sensitivity analyses performed for the primary efficacy endpoint supported the non-inferiority result of the confirmatory analysis and demonstrated the robustness of the confirmatory analysis.

The incidences of total VTE and all-cause mortality varied substantially between geographical regions, from 18.7% of dabigatran patients in Asia to 5.2% in Western Europe ($p <0.0001$ for region in the univariate logistic regression analysis), but there was no interaction between region and treatment ($p=0.6644$). The findings of the primary analysis stratified by geographical region corroborated the confirmatory analysis, with a risk difference of -1.1% (CI -3.8, 1.6) in favour of dabigatran.

There was no consistent or marked effect of age, sex, weight, concomitant medications, or CrCl levels at baseline on the incidence of the primary endpoint. In the univariate analysis, patients administered general anaesthesia, patients with a history of hypertension, and patients with a history of diabetes were more at risk of having an event than patients in the respective complementary groups. However, there were no obvious interactions with treatment for any of these factors. In the multivariate logistic regression analysis, the age*treatment interaction in the final model ($p=0.1019$) suggests some effect of age but there was no clear direction of effect of age apparent in the subgroup analysis of incidence of the primary endpoint. In the final model, the odds ratio of dabigatran versus enoxaparin was 0.96 (CI 0.65, 1.41), which supports the confirmatory analysis.

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Efficacy / clinical pharmacology results (continued):

Secondary endpoints: All analyses of prespecified secondary endpoints were consistent with the confirmatory analysis. The incidence of major VTE and VTE-related death was 2.2% in the dabigatran group, which was lower than in the enoxaparin group (4.2%). The risk difference for major VTE and VTE-related mortality was consistent with the confirmatory analysis of the primary endpoint. The risk difference for dabigatran vs. enoxaparin for this endpoint was -1.9%, 95% CI -3.6, -0.2 (p=0.0293). Sensitivity and subgroup analyses of major VTE and VTE-related mortality were also consistent with the analyses of the primary endpoint. Since proximal DVT is the driving component for the composite endpoint of major VTEs and VTE-related mortality, the analyses of proximal DVT followed the same pattern as described for major VTEs and VTE-related mortality. The analysis of proximal DVTs resulted in a risk difference for dabigatran vs. enoxaparin of -1.8%, 95% CI -3.5, -0.1 (p=0.0358).

The population for the analysis of total DVT during the treatment period was very similar to the population included in the confirmatory analysis, the only distinction being the exclusion of patients who had a PE or who died during the treatment period (3 patients in total). A total of 7.6% of patients in the dabigatran group and 8.5 % of patients in the enoxaparin group were reported withDVTs. The analysis of total DVTs resulted in a risk difference for dabigatran vs. enoxaparin of -0.96%, 95% CI -3.65, 1.73 (p=0.4839).

There were no symptomatic DVTs reported for patients on dabigatran and the incidence was very low for the enoxaparin group (0.4%) (p=0.0612). The incidence of PEs was low and similar in both treatment groups (dabigatran: 0.1%; enoxaparin: 0.2%; p=0.6231). Only 1 patient died (enoxaparin group) during the treatment period.

Only 2 dabigatran patients and 4 enoxaparin patients had events during the follow-up period (dabigatran: 1 symptomatic DVT, 1 PE; enoxaparin: 1 asymptomatic DVT detected during a delayed venography, 2 PEs, and 1 death).

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Efficacy / clinical pharmacology results (continued):	PK and PD assessments: Trough and post-dose plasma concentrations of total dabigatran at steady state in the target population after oral administration of 220 mg dabigatran q.d. were 22.0 ng/mL and 70.8 ng/mL, respectively, with high inter-individual variability (gCV: 106 to 145%). The inter-quartile ranges were 13.0 to 35.7 ng/mL and 35.2 to 162 ng/mL, respectively. Plasma dabigatran concentration increased with increasing age and with decreasing CrCl. Plasma concentrations were also higher in females than in males. In total, 42 patients with evaluable PK samples had an event that contributed to the primary endpoint (i.e. 69% of patients with primary endpoint events). Note: Plasma samples were obtained at hospital discharge and not proximate to the diagnosis of VTE or bleeding events. The trough gMean dabigatran plasma concentration in patients with a total VTE and all-cause mortality event was 24% higher than that in patients without such an event. However, the inter-individual variability in both groups was very high (104 and 131%, respectively). The difference between subgroups for post-dose concentrations was much smaller. The number of patients with evaluable PK samples who experienced MBEs was very low (N=7; i.e. 50% of patients with MBEs). Increased post-dose dabigatran concentrations were associated with increased bleeding (31% higher in patients with any bleeding event than those in the patients without a bleeding event, but the inter-individual variability in both groups was very high; 111 and 148%, respectively). Patients with any bleeding event had longer post-dose aPTT and TT times compared with patients without any bleeding event. Visually, there appeared to be a non-linear correlation between plasma dabigatran concentration and aPTT and a linear correlation between plasma dabigatran concentration and TT, which were all determined at a central laboratory using a single standardised methodology (Hemoclot® direct thrombin inhibitor assay).
Safety results:	The median duration of exposure was identical in both treatment groups for both oral and s.c. trial medications (32.0 days). In both groups the majority of patients were treated for at least 28 days with oral medication (dabigatran: 89.5%; enoxaparin 89.7%) and s.c. medication (dabigatran: 89.1%; enoxaparin: 89.2%). Bleeding events: The incidence of MBEs was 1.4% for patients in the dabigatran group and 0.9% for patients in the enoxaparin group (p=0.4022). For any

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Safety results (continued):

bleeding event (major, clinically relevant, or minor), the incidence was 9.7% for patients in the dabigatran group compared with 8.3% for patients in the enoxaparin group (p=0.2626).

When analysed according to the worst severity of any bleeding event, similar percentages of patients in the dabigatran and enoxaparin groups had MBEs (1.4% vs. 0.9%), CRBEs (2.3% vs. 2.0%), and minor bleeding events (6.0% vs. 5.4%). Statistical testing did not indicate a difference between the dabigatran and enoxaparin groups for the incidence of bleeding events (p−value for the 4 categories of major,clinically relevant,minor, and none vs. enoxaparin: 0.2061). In both groups, most bleeding events occurred during surgery or in the immediate post-operative period. The incidence of MBEs with an onset after the first oral dose of trial medication was the same in both groups (0.8%).

In both groups, most MBEs were cases of clinically overt bleeding associated with a ≥20 g/L fall in haemoglobin or leading to transfusion of >2 units of packed cells or whole blood. No patient had a fatal MBE. One enoxaparin patient had a bleed (haematoma at the surgical site) that led to a re-operation. One dabigatran patient had a symptomatic bleed in a critical organ: vitral bleeding (preferred term: vitreous haemorrhage) in the right eye; visual acuity recovered, which was a moderate intensity, non-serious, event considered related to study medication.

Adverse events: The incidences of treatment-emergent AEs and serious AEs (SAEs) were comparable in the 2 treatment groups. The incidences by category of event and of the most common AEs are tabulated by treatment group below. The most frequently reported AEs in both treatment groups by system organ class (SOC) were gastrointestinal disorders (dabigatran: 35.8%; enoxaparin: 35.8%), followed by vascular disorders (dabigatran: 22.5%; enoxaparin: 20.9%). The most frequent AEs by preferred term were nausea, vomiting, and constipation (as tabulated below).

The most frequent AEs leading to discontinuation were gastrointestinal disorders (1.8% of dabigatran patients; 2.0% of enoxaparin patients). The most frequently reported drug-related AEs were injury, poisoning and procedural complications (3.1% of dabigatran patients; 2.6% of enoxaparin patients), followed by gastrointestinal disorders (2.5% of dabigatran patients; 2.1% of enoxaparin patients). The most frequent of these AEs by preferred term are tabulated below.

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Safety results (continued):

Incidences (number [%] of patients) for categories of AEs and most frequently reported AEs during the treatment period

Category of AE	Dabigatran		Enoxaparin	
MedDRA preferred term	N	(%)	N	(%)
Number of patients	1010	(100.0)	1003	(100.0)
Any AE	684	(67.7)	696	(69.4)
Nausea	162	(16.0)	168	(16.7)
Vomiting	110	(10.9)	96	(9.6)
Constipation	100	(9.9)	104	(10.4)
Severe AEs	30	(3.0)	36	(3.6)
Investigator defined drug-related AEs	92	(9.1)	95	(9.5)
Traumatic haematoma	10	(1.0)	6	(0.6)
Alanine aminotransferase increased	9	(0.9)	6	(0.6)
Other significant AEs (ICH E3)[1]	46	(4.6)	36	(3.6)
AEs leading to disc. of trial drug[2]	60	(5.9)	52	(5.2)
Nausea	7	(0.7)	10	(1.0)
Hepatic enzyme increased	3	(0.3)	6	(0.6)
SAEs	57	(5.6)	59	(5.9)
Fatal	0	(0.0)	1	(0.1)
Immediately life-threatening	10	(1.0)	7	(0.7)
Disability/incapacity	1	(0.1)	1	(0.1)
Requiring hospitalisation	28	(2.8)	27	(2.7)
Prolonging hospitalisation	22	(2.2)	24	(2.4)
Congenital anomaly	0	(0.0)	0	(0.0)
Other	2	(0.2)	4	(0.4)
Most common SAEs				
DVT	4	(0.4)	10	(1.0)
Joint dislocation	4	(0.4)	3	(0.3)
Wound secretion	3	(0.3)	1	(0.1)
Femur fracture	2	(0.2)	3	(0.3)
Renal failure acute	0	(0.0)	4	(0.4)

[1] Any non-serious AEs that led to disc. or reduction in dose of trial medication.
[2] Any serious or non-serious AE that led to discontinuation of trial medication.

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Safety results (continued):

In total, 3 study patients (all enoxaparin group) are known to have died after providing informed consent. One patient died during the treatment period (on Day 3, 2 days after the last dose of trial medication) due to metabolic acidosis and acute renal failure, 1 patient died post-treatment (on Day 42, 7 days after the last dose of trial medication), with the AE reported only as "death", and 1 patient died after completion of study participation due to intestinal ischaemia (on Day 13, 13 days after the last dose of trial medication). None of the fatal AEs were considered to be related to trial medication. The most frequent SAEs were DVT, joint dislocation, and wound secretion (as tabulated above). In total, 6 dabigatran patients and 5 enoxaparin patients reported SAEs that were considered to be drug-related. On dabigatran, these were: rectal haemorrhage (2 patients), anaemia and haemarthrosis (both reported by the same patient), operative haemorrhage, post-procedural haemorrhage, and traumatic haematoma (each reported by 1 patient). On enoxaparin they were: abdominal distension, abdominal pain, constipation, nausea, vomiting (all reported by the same patient), anal haemorrhage, melaena (both reported by the same patient), acute renal failure and post-procedural haematoma (both reported by the same patient), and increased hepatic enzymes and wound haemorrhage (each reported by 1 patient). Three immediately life-threatening SAEs reported for dabigatran patients were considered to be drug related: rectal haemorrhage, operative haemorrhage, and post-procedural haemorrhage. One immediately life threatening event on enoxaparin was considered to be drug related: anal haemorrhage. In all 4 cases, the outcome was recovered.

The overall incidence of AEs was higher in both treatment groups in older patients (age ≥70 years: dabigatran 74.7%; enoxaparin 75.7%; age <70 years: 65.0% and 67.2%, respectively) and in female patients (female: dabigatran 71.7%; enoxaparin 72.5%; male: 63.1% and 66.3%, respectively). The incidence of AEs was not markedly higher in dabigatran patients with mild (70.9%) or moderate (67.5%) renal impairment than in those with normal renal function (66.4%). In the enoxaparin group, the incidence of AEs was higher in patients with moderate renal impairment (83.9%) than in patients with normal renal function (69.6%) or mild renal impairment (67.1%). In both treatment groups, the incidence of AEs was lower in Asian patients (dabigatran: 58.2%; enoxaparin: 61.4%) than in white patients (68.7% and 70.1%, respectively).

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Safety results (continued):

Safety laboratory data and vital signs: Three patients (all dabigatran group) had alanine transaminase (ALT) elevations above 3 x the upper limit of the normal range (ULN) in combination with elevated bilirubin values above 2 x ULN. One of these 3 patients experienced transient elevated LFTs on Day 6, which led to discontinuation of study medication on Day 9, and the event was resolved by Day 11. The remaining 2 patients both had underlying aetiologies to account for the elevations in ALT and bilirubin (viral hepatitis). In addition, very high ALT or AST (>10 x ULN) without associated elevation of bilirubin (to >2 x ULN) occurred in a total of 4 patients: 2 dabigatran patients and 2 enoxaparin patients. For each of these patients the maximal elevation was detected with the first post-operative laboratory sample. For both of the dabigatran patients the LFTs had almost completely normalised by the next time samples were drawn. Study medication was stopped due to the elevated LFTs in one of the enoxaparin patients. This patient's LFTs had returned to normal by about 7 weeks after surgery. The remaining patient, treated with enoxaparin had normalisation of LFTs at Day 26.

Most elevated LFTs occurred in the immediate post-operative period, during the first 10 days of treatment with trial medication, and most were transient. Elevated ALT levels were less frequent on dabigatran than on enoxaparin. The estimated cumulative incidence of an ALT value >3 x ULN from surgery up to Day 10 was 3.1% for dabigatran patients and to the end of the trial it was 3.6%. Corresponding figures for enoxaparin showed a slightly higher cumulative incidence: 5.0% to Day 10 and 5.4% to the end of the trial.

There were no unexpected changes in other laboratory parameters over the course of this trial. There were mean decreases in haematocrit and haemoglobin values in both groups, which were not unexpected in post-operative patients. There were no marked changes in mean platelet levels and no cases of thrombocytopenia.

There were no noteworthy changes in vital signs during this trial in either treatment group.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Pradaxa®		**EudraCT No.:** 2007-002630-11	
Name of active ingredient: Dabigatran etexilate mesilate, BIBR 1048 MS		**Page:** 14 of 14	**Synopsis No.:**
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Conclusions:	In summary, dabigatran was non-inferior to enoxaparin for the primary endpoint and superior to enoxaparin for the primary secondary endpoint. The superiority was driven by fewer proximal DVTs on dabigatran compared to enoxaparin. All secondary efficacy analyses were supportive of the primary and first secondary efficacy analyses. PK/PD data did not permit any definitive conclusions to be drawn about exposure and efficacy or bleeding. The safety profiles of dabigatran and enoxaparin were comparable in this study. The overall and individual incidences of bleeding events, AEs, including SAEs, and laboratory abnormalities were comparable between the 2 treatment groups, except that fewer dabigatran patients had elevated LFTs. Four to 5 weeks of prophylactic dabigatran treatment in patients undergoing elective hip replacement surgery was safe and well tolerated.