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ORIGINAL ARTICLE

Thromboprophylaxis with dabigatran after total hip arthroplasty in Indian patients: A subanalysis of a double-blind, double-dummy, randomized RE-NOVATE II study

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KEYWORDS
dabigatran etexilate;
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Summary *Objective:* In the Re-NOVATE II study, oral dabigatran provided thromboprophylaxis after total hip arthroplasty and improved compliance postdischarge in a global population. This article aims to identify trends (if any) in the Indian population.

Conflicts of interest: The authors declare that they have no financial or nonfinancial conflicts of interest related to the subject matter or materials discussed in the manuscript, except for Clemens Andreas who was an employee of Boehringer Ingelheim during the RE-NOVATE study.

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total hip arthroplasty;
venous
thromboembolism

Methods: In this prospective, double-blind, double-dummy study, patients scheduled for primary, unilateral, elective total hip arthroplasty were randomized to 220 mg oral dabigatran once daily, starting with a 110 mg half-dose, 1—4 hours after surgery, or subcutaneous enoxaparin 40 mg once daily, starting the evening before surgery. Each group received a placebo of the other study drug. The primary efficacy outcome was the composite of total venous thromboembolism (VTE) and all-cause mortality. Secondary outcome measures were composite of major VTE and VTE-related mortality during the treatment period. The major safety outcome was incidence of bleeding events.
Results: Of the 179 Indian patients randomized, 91 received oral dabigatran and 88 received subcutaneous enoxaparin for 28—35 days. Total VTE and all-cause mortality occurred in 18.7% of patients in the dabigatran group and 13.7% in the enoxaparin group [odds ratio = 1.4 (95% confidence interval 0.6, 3.5)]. Major VTE and VTE-related mortality was numerically lower in the dabigatran group (7.9%) compared with the enoxaparin group (9.9%). Safety outcomes were comparable between both groups.
Conclusion: Dabigatran is an effective oral alternative to enoxaparin for thromboprophylaxis as demonstrated by the RE-NOVATE II study global results. Data analyzed in Indian patients indicate comparable effects of dabigatran etexilate for major efficacy and safety outcomes.

1. Introduction

Total hip arthroplasty (THA) is an effective surgical intervention for relieving pain and improving physical function in osteoarthritis.[1] Severe osteoarthritis and hip fragility fractures due to osteoporosis are the main conditions requiring THA. In India, osteoarthritis, secondary to avascular necrosis and/or trauma to the hip joint as well as inflammatory arthritis are the commonest indications for THA. It is one of the most successful orthopedic procedures. The demand for THA is expected to continually increase.[2]

Venous thromboembolism (VTE) is a common complication of surgical procedures. Reduction in fibrinolytic activity postsurgery and the occurrence of Virchow's triad (venous stasis, abnormal coagulation, and intimal damage) due to general anesthesia leads to intravascular coagulation.[3] VTEs can present as deep vein thrombosis (DVT) or pulmonary embolism (PE). The reported incidence range of DVT in Indian patients after THA without thromboprophylaxis is 40—70%, proximal DVT is 10—20%, clinical DVT is 1—3%, nonfatal symptomatic pulmonary thromboembolism is 1—2%, and fatal pulmonary thromboembolism is 0.1—1%.[4] The incidence of DVT after THA without prophylaxis in Asian patients was similar to those reported in patients from western countries.[5]

Thromboprophylactic treatment is recommended for up to 35 days postsurgery as symptomatic VTEs can develop up to 3 months following surgery or asymptomatic DVTs can become symptomatic in this duration.[6] Low molecular weight heparins (LMWH) or vitamin K antagonists such as phenprocoumon, acenocoumarol, and warfarin are traditionally used for thromboprophylaxis. The LMWH are parenteral agents, and their administration is a challenge as most patients are discharged within a week postsurgery. Routine anticoagulant monitoring and dose adjustments are required for warfarin and other vitamin K antagonists.[7]

The need for parenteral administration and routine monitoring required with the traditional thromboprophylactic agents hampers compliance and recovery in patients with THA. The recently available oral anticoagulant dabigatran etexilate provides thromboprophylaxis when administered postoperatively and improves compliance postdischarge. Dabigatran etexilate is a small molecule prodrug of dabigatran, a competitive reversible, direct thrombin inhibitor. A Phase III (RE-NOVATE) study[8] has demonstrated the noninferiority of dabigatran 150 mg or 220 mg once daily (started after surgery) to subcutaneous LMWH enoxaparin 40 mg once daily (started before surgery) for the prevention of VTE and all-cause mortality after THA. Bleeding and adverse event (AE) rates with dabigatran were low and similar to enoxaparin. Dabigatran 220 mg once daily (starting with half a dose on the day of surgery) is now approved in more than 75 countries for thromboprophylaxis in patients undergoing THA. The efficacy and safety of 28—35 days of oral dabigatran thromboprophylaxis was further evaluated in a more diverse population from 19 countries, including India (RE-NOVATE II).[9] The aim of this article is to discuss data from the RE-NOVATE II study specific to the Indian patients who represent Asian ethnicity, and identify any trends in relation with the global findings (RE-NOVATE II)[9] published previously.

2. Methods

2.1. Study participants

Patients were recruited from March 2008 until May 2009. Patients of either sex, aged 18 years and above, undergoing primary unilateral elective total hip replacement surgery were included in the study. Exclusion criteria for the RE-NOVATE II[9] study were similar to those reported in previous studies[8,10,11] and aimed to ensure the patient safety.

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Patients with: (1) bleeding diathesis, thrombocytopenia, and hemorrhagic stroke; (2) excessive risk of bleeding as perceived by the investigator; (3) major surgery or trauma within 3 months of enrollment; (4) recent unstable cardiovascular disease; (5) active liver disease or alanine transaminase more than three times the upper limit of normal range; and (6) known severe renal insufficiency (with creatinine clearance $<$ 30 mL/min) were excluded. Patients treated with anticoagulants, clopidogrel, ticlopidine, abciximab, aspirin $>$ 162.5 mg/d, or nonsteroidal anti-inflammatory drugs within 7 days prior to hip replacement surgery or with anticipated need for these agents during the period were excluded from the trial. Patients who had spinal or epidural anesthesia for which more than three attempts (sticks) at placement were made, or in whom the placement was traumatic, were excluded from the study. Patients likely to need quinidine and verapamil during the study were excluded.

The study was approved by the respective Institutional Ethics Committees and conducted according to the Declaration of Helsinki. All patients signed informed consent form before participating in the study.

2.2. Study site

The study was conducted in 14 centers across India at the following hospitals: (1) All India Institute of Medical Sciences, Delhi; (2) Sushrut Hospital, Nagpur; (3) Yashoda Hospital, Secunderabad; (4) St. John's Medical College & Hospital, Bangalore; (5) Kasturba Medical College, Mangalore; (6) Center for Knee Surgery, Baroda; (7) Siddhi Nursing Home, Mumbai; (8) Krishna Institute of Medical Sciences, Hyderabad; (9) Shalby Hospitals Pvt. Ltd., Ahmedabad; (10) Vadodara Institute for Reconstructive Orthopedic Care, Vadodara; (11) M.S. Ramaiah Memorial Hospital, Bangalore; Jehangir Hospital, Pune; and (12) Fortis Hospital, Mohali.

2.3. Study design and treatment

This was a prospective, double-blind, double-dummy study. The patient, the investigator, their staff, and clinical monitors were unaware of the treatment assigned.

Patients were randomized into two groups for up to 3 days prior to surgery. A 40 mg subcutaneous injection of enoxaparin (enoxaparin arm) or a matching placebo (in the dabigatran arm) was started the evening before surgery. In the dabigatran arm, half a dose (one capsule) of dabigatran was administered orally 1—4 hours postsurgery. A full dose of dabigatran (2 $\times$ 110 mg capsules) was given the morning after surgery and onwards as once-daily dosing. In the enoxaparin arm, subcutaneous treatment was continued thereafter every 24 hours. All patients received a matching placebo of the other study drug (double-dummy) respectively. Treatment was continued for 28—35 days (including the day of surgery) or until a bilateral venography was performed to detect any asymptomatic DVT. If a confirmed VTE (DVT or PE) occurred before treatment completion, the treatment was continued up to a maximum of 42 days. Safety was assessed during the treatment period and the two follow-up visits (at 63 $\pm$ 7 days and 91 $\pm$ 7 days).

2.4. Outcome measures

The primary efficacy outcome was measured using bilateral venography and was the composite of total VTE (i.e., asymptomatic DVT detected with bilateral venography, symptomatic DVT confirmed with venography, venous compression ultrasound, or by autopsy, and PE confirmed with perfusion scintigraphy, chest X-ray, pulmonary angiography, spiral computed tomography or autopsy) and all-cause mortality during the treatment period. All-cause mortality was defined as the time from the first administration of the study drug until 3 days after the last administration. The important secondary outcome measures were composite of major VTE (defined as proximal DVT and/or PE) and VTE-related mortality during the treatment period. Other secondary outcomes during the treatment period were occurrence of total DVT (asymptomatic or symptomatic), proximal DVT (asymptomatic or symptomatic), symptomatic DVT, PE, and death. The secondary outcome measure during the follow-up period was the composite of total VTE and all-cause mortality.

The major safety outcome measures were the incidences of bleeding events (categorized as major, clinically relevant, or minor bleeding events), volume of blood loss, requirement for blood transfusions, occurrence of AEs, discontinuation of study treatment due to AEs, and abnormalities in laboratory safety parameters with particular focus on liver function tests. Definitions of bleeding events are as reported previously.[8,10,11]

A central and independent adjudication committee, who were blinded to the treatment allocation, objectively reviewed and interpreted all efficacy and safety parameters. The results of this review were used for analysis.

2.5. Randomization procedure

Randomization was stratified by center and prepared in blocks of four with the lowest number allocated sequentially. Treatment group assignment was concealed from the investigators, their staff, and the clinical monitors.

2.6. Analysis

The data on Indian population is presented in terms of descriptive statistics as numbers, percentages, two-sided 95% confidence interval (CI), median (range), mean, and standard deviation.

3. Results

3.1. Baseline data

Of the 195 patients enrolled in India, 179 patients were randomized to receive either oral dabigatran (N = 91) or enoxaparin (N = 88). Of the 179 patients, 168 (93.9%) received the study medications as per the study protocol. Ninety patients were treated and operated in the dabigatran group while the enoxaparin group consisted of 87 such patients. A total of 75 patients and 73 patients were evaluable for primary efficacy outcomes in the dabigatran

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and enoxaparin groups, respectively. The baseline demographic characteristics of the two randomized treatment groups are well balanced as described in Table 1. The surgical characteristics are described in Table 2.

3.2. Efficacy outcomes

Total VTE and all-cause mortality (primary endpoint) occurred in 18.7% (95% CI, 9.8%, 27.5%) of patients in the dabigatran group and 13.7% (95% CI, 5.8%, 21.6%) of patients in the enoxaparin group in Indian patients, resulting in an odds ratio over enoxaparin of 1.4 (95% CI, 0.6, 3.5). Asymptomatic DVT was the main contributor to the primary endpoint. Major VTE and VTE-related mortality (secondary endpoint) were low in the dabigatran group (7.9%) compared with the enoxaparin group (9.9%) as shown in Table 3. The percentage of patients with proximal DVTs during the treatment period was numerically lower in the dabigatran group than the enoxaparin group while the reverse was seen in cases of distal DVTs. No incidence of PE occurred in the Indian patients.

3.3. Safety outcomes

A major bleeding event occurred in one patient (1.1%) in the dabigatran group. It was not fatal and did not require treatment cessation or reoperation. No major bleeding events occurred in the enoxaparin-treated patients. The number of major or clinically relevant nonmajor bleeding events was low in both the treatment groups (Table 4).

The summary of AEs observed in the study is presented in Table 5. Patients in the enoxaparin group had a higher percentage of AEs and serious adverse events (SAEs) than those in the dabigatran group. In patients with SAEs, four patients (4.5%) had prolonged hospitalization in the enoxaparin group compared with one patient (1.1%) in the dabigatran group. The investigator evaluated that the drug-related AEs were higher in the enoxaparin group compared with the dabigatran group. Patients in the dabigatran group had no incidences of wound hemorrhage while the enoxaparin group had one such occurrence. The number of AEs leading to treatment discontinuation was similar in both treatment groups. Alanine transaminase elevation at any point of time after baseline was reported to be three times above the upper limit of normal range in 3.5% of patients in the enoxaparin group compared with 1.1% in the dabigatran group. The event of total bilirubin elevation was reported in 2.3% of patients with enoxaparin while none occurred within the dabigatran group.

Table 1 Demographic characteristics of treated patients.

Characteristics	Dabigatran[a]	Enoxaparin[a]
Treated patients (*N*)	91	88
Age (yr)	47.7 ± 14	50.9 ± 14.4
Female	35 (38.5%)	32 (36.4%)
Weight (kg)	61.8 ± 12.7	61.7 ± 13.1
Body mass index (kg/m^2)	23.6 ± 4.2	23.5 ± 5
Creatinine clearance (mL/min)	98.2 ± 34.4	94.2 ± 29.9

[a] Data expressed as mean ± standard deviation or number (percentage) of patients.

Table 2 Surgical characteristics.

Characteristics	Dabigatran[b]	Enoxaparin[b]
Treated and operated (*N*)	90	87
General anesthesia	6 (6.7%)	5 (5.7%)
Regional anesthesia	82 (91.1%)	82 (94.3%)
General and regional anesthesia	2 (2.2%)	0 (0.0%)
Duration of surgery (min)	90 (30–330)	95 (30–240)
Time from surgery to first oral or s.c. dose (h)	2.8 (1.3–21.4)	−12.6 (−37 to −9.5)
Duration of oral treatment[a] (d)	32 (3–45)	31 (2–43)
Duration of s.c. treatment (d)	32 (1–45)	31 (1–43)

s.c. = subcutaneous.
[a] Enoxaparin group received placebo capsules.
[b] Data expressed as number of patients (percentage) or median (range).

4. Discussion

DVT and PE are considered two of the most significant complications after THA, warranting thromboprophylaxis. The peak incidence of clinical DVT appears to occur 5–10 days after hip arthroplasty and continues to be diagnosed up to 6 weeks or 8 weeks after hospital discharge.[12] The American College of Chest Physicians

Table 3 Efficacy outcomes.

Characteristics	Dabigatran[a]	Enoxaparin[a]
Total VTE and all-cause mortality 95% CI	14/75 (18.7%) [9.8, 27.5]	10/73 (13.7%) [5.8, 21.6]
Asymptomatic DVT	14 (18.7%)	9 (12.3%)
Symptomatic DVT	0 (0%)	0 (0%)
Nonfatal PE	0 (0%)	0 (0%)
Death associated with VTE	0 (0%)	0 (0%)
Death not associated with VTE	0 (0%)	1 (1.4%)
Major VTE and VTE-related mortality 95% CI	6/76 (7.9%) [1.8, 14.0]	7/71 (9.9%) [2.9, 16.8]
Total DVT	14/75 (18.7%)	9/72 (12.5%)
Proximal DVT	6/76 (7.9%)	7/71 (9.9%)
Distal DVT	8/75 (10.7%)	2/73 (2.7%)
Symptomatic DVT	0 (0%)	0 (0%)
Symptomatic nonfatal PE	0 (0%)	0 (0%)
Death	0/90 (0%)	1/87 (1%)
Total VTE and all-cause mortality during follow-up	0/90 (0%)	1/87 (1%)

CI = confidence interval; DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.
[a] Data presented as number of patients who had an event/total number of patients (percentage), (95% CI).

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Table 4 Safety outcomes (bleeding events).

Characteristics	India	
	Dabigatran	Enoxaparin
Treated patients (*N*)	91	88
Major bleeding events (no. of patients, %) (95% CI)	1 (1.1%)[a] (0–6%)	0 (0%) (0–4.1%)
Fatal	0	0
In a critical organ[b]	0	0
>20 g/L fall in hemoglobin[c]	1	0
Leading to ≥ 2units transfusion[c]	1	0
Warranting treatment cessation	0	0
Leading to reoperation	0	0
Major or clinically relevant nonmajor bleeding events	2 (2.2%)	1 (1.1%)

CI = confidence interval.
[a] Occurred before administration of dabigatran.
[b] Symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding.
[c] In excess of what the investigator expected.

recommend extended duration of thromboprophylaxis for 28–35 days postsurgery. With LMWH, extended thromboprophylaxis is significantly more effective in preventing VTE in orthopedic surgery patients than the recommended practice of 10 days.[13] Extended thromboprophylaxis with enoxaparin for 4 weeks [after THA/total knee arthroplasty (TKA)] has shown to significantly reduce the incidence of VTE significantly (0.5% vs. 3.27%) compared with short-term thromboprophylaxis (7–11 days) in Indian patients.[14] However, subcutaneous administration of LMWHs such as enoxaparin for up to 35 days could cause discomfort and also makes it difficult for patients to adhere to treatment postdischarge. A phase III trial (RE-NOVATE)[8] demonstrated that treatment with oral dabigatran 150 mg or 220 mg for 28–35 days was non inferior to subcutaneous enoxaparin 40 mg daily for the prevention of VTE and all-cause mortality after THA. Recently, switch-therapy modalities have been shown to provide clinicians an advantage of using enoxaparin safely during the hospitalization period and then switch to dabigatran for ease of administration during the outpatient period.[15]

Table 5 Other safety outcomes.

Characteristics	Dabigatran[a]	Enoxaparin[a]
Number of patients (*N*)	91	88
No. (%) with any adverse event	53 (58.2%)	54 (61.4%)
Serious adverse events	4 (4.4%)	8 (9.1%)
Fatal	0 (0%)	1 (1.1%)
Immediately life threatening	1 (1.1%)	1 (1.1%)
Disability/incapacity	0 (0%)	0 (0%)
Requiring hospitalization	2 (2.2%)	2 (2.3%)
Prolonging hospitalization	1 (1.1%)	4 (4.5%)
Congenital anomaly	0 (0%)	0 (0%)
Other	0 (0%)	2 (2.3%)
Severe adverse events	3 (3.3%)	3 (3.4%)
Drug-related adverse events (investigator evaluation)	3 (3.3%)	6 (6.8%)
Patients with wound hemorrhages	0 (0%)	1 (1.1%)
Leading to treatment discontinuation	3 (3.3%)	3 (3.4%)
ALT: > 3 × ULN anytime postbaseline	1/90 (1.1%)	3/86 (3.5%)
Total bilirubin: > 1.5 × ULN anytime postbaseline	0/90 (0%)	2/86 (2.3%)

ALT = alanine transaminase; ULN = upper limit of the normal range.
[a] Data expressed as number of patients (percentage).

Eriksson et al[9] have published the results of the efficacy and safety of oral dabigatran versus subcutaneous enoxaparin for thromboprophylaxis after primary THA in a diverse global population (RE-NOVATE II). As a part of this global study, 9% of total patients were enrolled in India. The mean age of Indian patients was lower than the mean age of the global population. The majority of the Indian patients were men (62.6%), whereas patients of both the sex equally participated in the global study. The mean body mass index of the Indian population was lower (23.6 ± 4.6 kg/m^2) compared with that of the global population (27.8 ± 4.8 kg/m^2). Surgical procedures mostly involved the use of regional anesthesia in both the Indian and global patients. The first dose of enoxaparin was administered presurgery (median 12.6 hours) and dabigatran was administered postsurgery (median 2.8 hours) in all the Indian patients, whereas in the global counterpart, enoxaparin and dabigatran were administered preoperatively as well as postoperatively depending on the local practice followed in that particular country and/or as per the investigator's judgment.

In the Indian population, the primary outcome (total VTE and all-cause mortality) occurred in 18.7% of patients in the dabigatran group and 13.7% of patients in the enoxaparin group [odds ratio for dabigatran over enoxaparin = 1.4 (95% CI 0.6, 3.5)]. In the global population, primary outcome occurred in 7.7% patients in the dabigatran group and 8.8% patients in the enoxaparin group with an absolute risk difference of 1.1% (95% CI, -3.8% to 1.6%). Dabigatran was found to be noninferior to enoxaparin ($p < 0.0001$) in RE-NOVATE II study. These observations are in line with the earlier RE-NOVATE study.[10] Furthermore, meta-analysis by Gomez-Outes et al[16] reported risk of symptomatic VTE with dabigatran (relative risk 0.71, CI 0.23 to 2.12) is similar and comparable to enoxaparin. Dabigatran is noninferior to warfarin for the prevention of recurrent and fatal VTE for up to 6 months.[17]

A systematic review by Singh et al[18] reported an overall 30-day mortality rate of 0.3% across all type of arthroplasties in 28 out of 80 studies. In our study, major VTE and VTE-related mortality were low in both the arms (7.9% dabigatran and 9.9% enoxaparin) in Indian patients. Fewer patients were diagnosed with proximal DVT in the dabigatran group (7.9% India and 2.1% global population) compared with the enoxaparin group (9.9% India and 3.9% global population). However, in the Indian patients, distal DVTs were more often reported in the dabigatran group (10.7%) compared with the enoxaparin group (2.7%); whereas in the global population 5.4% and 4.5% of the

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patients had distal DVTs in the dabigatran and enoxaparin groups respectively.

Distal DVTs (associated with calf veins) are less serious than the proximal DVTs as thrombi in calf veins are generally small and have little chance of embolization. Distal DVTs are therefore not usually associated with clinical disability or other complications. Distal DVTs may be at risk of embolization if they extend proximally.[19] PE occurs frequently in Indian patients with symptomatic DVT.[20] In a prospective study conducted in New Delhi, the overall incidence of VTE was reported to be 6.12% and that of PE was 0.6% among patients undergoing major orthopedic surgeries (THA, TKA, and proximal femur fracture fixation).[21] However, our study did not report any incidence of PE in the Indian subpopulation, while three cases were reported in the global population.

Anticoagulants prevent VTE or PE after THA/TKA; nonetheless, risk of bleeding associated with their use can be fatal. The risk of gastrointestinal bleeding related to dabigatran is similar to warfarin.[22] Also, dabigatran and enoxaparin pose a similar risk of clinically significant bleeding, major bleeding, and clinically relevant nonmajor bleeding.[16] Assessed using the same bleeding criteria, the incidence of major bleeding events for dabigatran 220 mg was comparatively lower in the Indian population (1.1%) compared with the global population in RE-NOVATE II and RE-NOVATE (1.4% and 2.0%) studies. Only one patient had a major bleeding event prior to the administration of dabigatran as evidenced by a fall in hemoglobin level ($>$20 g/L) leading to blood transfusion ($\geq$2 units).

The occurrence of all AEs in the Indian population was slightly lower (58.2% dabigatran group and 61.4% enoxaparin group) than the global population (67% dabigatran group and 69% enoxaparin group). Occurrence of SAEs was more frequent in the enoxaparin (9.1%) group compared with the dabigatran (4.4%) group in the Indian patients. As per the investigator's evaluation, a higher number of drug-related AEs were reported in the enoxaparin group (6.8%) than the dabigatran group (3.3%) in the Indian patients, whereas in the global population, drug-related AEs were similar in both the groups. Negligible risk of hepatic dysfunction with dabigatran was observed in previously reported phase III hip and knee arthroplasty studies, as well as other studies in which dabigatran was administered for up to 18 months. The current Indian data, as well as the data in the previous studies do not report a clinically significant difference in the safety profiles of dabigatran and enoxaparin.[8,10,11,23,24]

The global results from the RE-NOVATE II study demonstrate that dabigatran is an effective oral alternative to enoxaparin for thromboprophylaxis. Analysis of data in a limited group of Indian patients treated for the prevention of VTE after THA indicate comparable effects of dabigatran etexilate regarding its major efficacy and safety outcomes. However, the data need to be interpreted with caution due to the limited number of Indian patients (n = 179).

The sample size for the Indian population was not sufficiently powered to compare the two drugs. Descriptive statistics used in this study, however, helped us to understand the general trends seen in the Indian population compared with the global population.

Dabigatran offers an effective oral alternative to existing thromboprophylactic agents in patients undergoing major orthopedic surgery.[7] Oral administration enables ease of use while drug–drug/food–drug interactions require dose adjustment. This adds to the practical advantage of oral dabigatran over the vitamin K antagonists and injectable heparins, which are inconvenient for administration posthospital discharge, especially in a clinical situation where an extended thromboprophylaxis is required.

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