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A Benefit-Risk Assessment of Dabigatran in the Prevention of Venous Thromboembolism in Orthopaedic Surgery

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Contents

Abstract

Dabigatran etexilate is a novel orally administered anticoagulant that exerts its action through reversible direct thrombin inhibition. This anticoagulant has been approved for prophylaxis against venous thromboembolism (VTE) after hip or knee arthroplasty, and in a few countries also for atrial fibrillation. This article reviews the efficacy and safety of dabigatran for the prophylaxis of VTE-indication compared with data on the most common current regimen with low-molecular-weight heparin (LMWH), specifically enoxaparin.

Alternative prophylactic agents are also discussed. The results regarding efficacy and safety are very similar for dabigatran and LMWH. Bleeding and gastrointestinal reactions are the most frequently reported adverse events with a comparable incidence on LMWH and are probably the result of surgery and anaesthaesia. No adverse event that is specific for dabigatran has been observed in these studies, although dyspepsia has been reported as significantly more frequent than warfarin in long-term studies on other indications. The fact that dabigatran has no antidote has so far not been a problem in patients undergoing orthopaedic surgery. The use of the lower dose of dabigatran (150 mg) appears beneficial to reduce the risk of bleeding in patients over 75 years of age and in those with moderate renal impairment to avoid drug accumulation. The convenience of oral administration is an advantage for dabigatran over LMWH, particularly for extended prophylaxis up to 1 month after surgery. In conclusion, the benefit-risk profile of dabigatran is favourable for use as prophylaxis against VTE after major orthopaedic surgery with its convenient oral administration without need for laboratory monitoring and a low risk of bleeding or other adverse events.

Dabigatran is a novel anticoagulant that is a reversible competitive direct thrombin inhibitor, administered orally as the pro-drug dabigatran etexilate. The drug has a bioavailability of 6.5% and is converted by ubiquitous esterases to the active drug dabigatran with maximum serum concentration achieved 2 hours after ingestion.[1] Dabigatran is bound to plasma albumin to a proportion of 25–35% and 20% of the drug is glucuronidated but still fully active.[2] Dabigatran is distributed to all organs except for the CNS. The half-life of the active drug is 14–17 hours after multiple doses in patients with normal renal function,[2] but since the kidneys excrete about 80% of the drug, the half-life is prolonged in patients with renal impairment. A creatinine clearance below 30 mL/min has therefore been an exclusion criterion in all the clinical trials.

In 2008, the European Medicines Agency (EMA) granted marketing authorization for dabigatran in Europe and, at the time of writing, approval has been achieved in 65 countries. Dabigatran is currently only registered in Europe for thromboprophylaxis in orthopaedic surgery.[3] Recent studies have shown that dabigatran is as effective as warfarin for stroke prevention in patients with atrial fibrillation.[4] Approval for this indication has been achieved in the US and Canada and the drug is currently under review by the EMA for this indication. One phase III study has been reported for the treatment of venous thromboembolism (VTE).[5] The drug is marketed in Europe under the name Pradaxa® and in Canada as Pradax™.

Before the introduction of dabigatran, the available anticoagulants were unfractionated heparin, low-molecular-weight heparin (LMWH), the pentasaccharide fondaparinux and vitamin K antagonists (VKA), of which only VKA are administered orally whereas the other anticoagulants are given by subcutaneous injection for patients after orthopaedic surgery. The advantages of dabigatran are – in relation to warfarin – more rapid onset of action, fewer drug-drug and food-drug interactions, and no need for routine monitoring and dose adjustments, and – in relation to the other anticoagulants – the oral route of administration. After the introduction of dabigatran, another orally available agent, the factor Xa-inhibitor rivaroxaban has been approved in a large number of countries, albeit not yet in the US, for prevention of postoperative VTE.

Another pharmacological alternative used for prophylaxis against VTE after major orthopaedic surgery is aspirin (acetylsalicylic acid). The American Association of Orthopaedic Surgeons (AAOS) guidelines recommend aspirin as an equal alternative to the anticoagulants for patients at

standard risk of pulmonary embolism (PE).[6] Conversely, the American College of Chest Physicians (ACCP) guidelines recommend *against* the use of aspirin for prophylaxis against VTE after hip or knee arthroplasty.[7]

Non-pharmacological prophylactic tools against VTE are graduated compression stockings, intermittent pneumatic compression devices and venous foot pumps. These are considered inferior regarding efficacy; however, for patients with a high risk of bleeding this type of mechanical prophylaxis is recommended until that risk has decreased.[7] Studies with these devices are of low quality and there is evidence for important compliance problems.[8] In this review we will discuss the VTE disease targeted by the prophylaxis and we will position dabigatran against all the alternatives currently used but with emphasis on the comparator from the clinical trials, enoxaparin. Finally, the benefits of dabigatran will also be balanced against identified risks.

1. Epidemiology of Postoperative Venous Thromboembolism (VTE)

The incidence of asymptomatic and symptomatic deep vein thrombosis (DVT) and of symptomatic PE after hip and knee joint replacement surgery has varied in different clinical trials, depending on the study design, duration of prophylaxis and the method used for screening or diagnosis of VTE. Without prophylaxis, the incidence of objectively verified (by venography) DVT after major orthopaedic surgery is approximately 40–60% (table I). This is of the same magnitude as in patients with major trauma or spinal cord injury.[7] Lower incidences are observed in general medical and surgical patients.[11] Orthopaedic patients are therefore considered as being at high risk for VTE. However, the vast majority of the DVTs do not appear to cause symptoms in the leg or symptomatic PE. A contemporary example is a Korean study of 300 patients with total hip replacement (THR) without any prophylaxis against VTE, in which there was venographic evidence of VTE in 72 patients, none of whom had symptoms.[12] The relationship between symptomatic and asymptomatic DVT is approximately 1 : 5 for THR and 1 : 21 for total knee replacement (TKR).[13]

Table I. Risk of venous thromboembolism in patients who received placebo as thromboprophylaxis[a]

Outcome	THR[9]	TKR[10]
Patients included (n)	10 929	3482
Proximal DVT	25 (21.4, 30.7)	NA
Distal DVT	22.4 (18.8, 26.6)	NA
Total DVT	48.5 (43.4, 53.7)	60.2 (55.7, 64.5)
Symptomatic PE	1.51 (0.81, 2.57)	0 (0.0, 10.9)
Fatal PE	0 (0.0, 0.43)	0 (0.0, 4.2)
Major bleeding	0.56 (0.15, 1.43)	NA
Minor bleeding	3.0 (1.1, 8.2)	NA

a Results are presented as percentages and 95% CI unless stated otherwise.

DVT = deep vein thrombosis; **NA** = not available; **PE** = pulmonary embolism; **THR** = total hip replacement; **TKR** = total knee replacement.

The incidences of total (asymptomatic and symptomatic) DVT, proximal DVT and symptomatic PE in meta-analyses of patients with THR or TKR without prophylaxis against VTE are summarized in table I. It is the symptomatic outcomes that are of most importance and against which the risk of bleeding has to be weighed.

Symptomatic VTE usually occurs after discharge from the hospital and this is the most common cause of emergency readmission after these surgical procedures.[14] In a population-based study, 67% of VTE events occurred within a month from discharge, both for medical and surgical index admissions.[15] After THR, DVT and PE occurred at a median of 21 and 34 days, respectively, and after TKR the median time to the presentation of DVT and PE was 20 and 12 days, respectively.[16]

The occurrence of VTE is often the result of synergism between several risk factors.[17] In orthopaedic patients the typical risk factors for VTE are surgical trauma, lower limb or pelvic fractures, immobilization after surgery, obesity and old age. Additional relatively common risk factors in the elderly population are congestive heart failure, respiratory failure and varicose veins. The risk for developing DVT is strongly related to the number of concomitant risk factors, ranging from 11% to 100% with one and five risk factors, respectively.[18]

Ethnicity as a risk factor has been debated. It was believed for many years that the risk of VTE

after major orthopaedic surgery is lower in Asian countries. In a prospective study of 200 Asian patients who underwent THR without prophylaxis, venography was positive in 52 (26%) patients with bilateral THR, whereas among patients with unilateral THR 20 (20%) were positive.[12] More recent studies have demonstrated that the risk in these populations is not significantly reduced compared with Caucasians and that prophylaxis is therefore indicated.[19,20]

2. Natural History of VTE

Postoperative DVT typically arises in the calf vein valve cusps, where the blood flow is slow.[21,22] The thrombotic process often starts already during surgery and in patients with hip fractures sometimes even before surgery. Fifty percent of the thrombi resolve spontaneously within 3 days but 10–20% extend proximally[7] and may cause PE, which may be asymptomatic or symptomatic.[22] With increasing proximity of the thrombus the risk of PE increases. The majority of patients with proximal symptomatic DVT and no chest symptom have evidence of PE on lung scans.[23-26] Although this has generally not been studied in patients with major joint surgery, data from lower extremity amputation surgery verify a much higher prevalence of perfusion defects on routine lung scanning than clinically suspected.[27] Approximately 75% of DVT after orthopaedic surgery is located in the operated leg.[28,29]

The long-term consequence of DVT is postthrombotic syndrome with chronic swelling of the leg, pain, hyperpigmentation, lipodermatosclerosis and in the most severe form, also venous ulcers. The syndrome is seen in 20–50% of patients after symptomatic DVT[30] but may also occur after asymptomatic thrombosis, although this has been poorly validated. PE is complicated in approximately 4% of the patients by development of chronic pulmonary hypertension after 2 years follow-up.[31]

3. Purpose and Outcome of Prevention

Patients undergoing major orthopaedic surgery, which includes THR, TKR and hip fracture surgery, receive in view of their particularly high risk for VTE, thromboprophylaxis increasingly often as standard in Europe and North America during the past two decades.[11,32-35] With the routine use of thromboprophylaxis, fatal PE is now uncommon.[14,33,36-42] Symptomatic VTE continues to be reported in 1.3–10% of patients within 3 months after surgery.[39,41-50] The opinion on the main purpose of prophylaxis differs between societies. Whereas ACCP traditionally has based the evaluation of effect on reduction of DVT, including also asymptomatic events, AAOS has focused on a reduction of PE. This explains the discrepancy in recommendation regarding aspirin, which does not reduce DVT after major orthopaedic surgery. On the other hand, it has been difficult to show that aspirin is worse than anticoagulants to prevent PE since those events are relatively few. This is understandable when one considers the calculations showing that in order to demonstrate a reduction of fatal PE from 0.8% to 0.4% a population of 20 000 is required.[51]

4. Low-Molecular-Weight Heparin: the Standard and Comparator

We will first focus on the effect of LMWH and specifically enoxaparin, which is the only agent dabigatran has been compared with in primary VTE prophylaxis. The first generation of randomized controlled trials provided prophylaxis for the period of hospitalization only, which at that time typically was for a week. Pooled results are shown in table II. The efficacy of LMWH could in these small studies only be demonstrated for any DVT and for proximal DVT.

Once it became routine to protect patients against VTE during the first week after surgery the continued high risk of thromboembolism had to be addressed. Meta-analyses of studies with prolonged prophylaxis in comparison with placebo demonstrated that LMWH reduces not only any DVT and proximal DVT but also symptomatic DVT in patients with THR but less convincingly in TKR, partly due to smaller numbers (table II). The prevention of VTE in orthopaedic patients has moved towards an extended duration of 1 month based on these results.[55-58]

Table II. Risk reduction for venous thromboembolism (VTE) with low-molecular-weight heparin (LMWH) vs placebo

Outcome	THR	TKR
Prophylaxis first 7–10 days[a,b]		
Evaluable patients (n)	190[52]	328[53,54]
Proximal DVT	0.62 (0.33, 1.14)	0.06 (0.01, 0.26)
Total DVT	0.55 (0.30, 1.00)	0.23 (0.14, 0.37)
Extended prophylaxis after the initial 7–10 days[a,c]		
Evaluable patients (n)	1577[55]	438[29]
Proximal DVT	0.25 (0.16, 0.39)	0.52 (0.23, 1.19)
Total DVT	0.30 (0.22, 0.40)	0.81 (0.50, 1.30)
Symptomatic VTE	0.32 (0.17, 0.59)	NA

a Results are presented as odds ratio and 95% CI unless stated otherwise.

b Symptomatic PE: THR 1 in each group; TKR 1 on LMWH, 2 on placebo; fatal PE: none; major bleeding: no difference.

c Fatal PE: THR none on LMWH, 2 on placebo; symptomatic PE: TKR none on LMWH, 2 on placebo. Major bleeding: THR none on LMWH, 1 on placebo; major bleeding: TKR none on LMWH, 1 on placebo.

DVT = deep vein thrombosis; **NA** = not available; **PE** = pulmonary embolism; **THR** = total hip replacement; **TKR** = total knee replacement.

The proponents of aspirin are concerned about an increase in the risk of bleeding by anticoagulants, outweighing the benefit of a reduction of symptomatic DVT while there is no evidence for a reduction of fatal PE. However, there seems to be a reduction of symptomatic PE with LMWH compared with placebo (0.36% vs 1.51%) but indeed also a statistically significant increase in the risk of major bleeding (3.46% vs 0.28%) in the meta-analysis of trials in THR.[9]

The prophylaxis with LMWH is generally tolerable and does not require laboratory monitoring, as opposed to VKA. A majority of the patients or family members can be taught subcutaneous self-injection technique but in some cases this is not feasible. Whenever the injections have to be given by healthcare professionals to patients at home, the cost-benefit becomes questionable and it is here the new oral agents play an important role.

5. Dabigatran: an Oral Alternative

5.1 Dose-Finding Studies

Dabigatran etexilate has been evaluated in major orthopaedic surgery in two dose-finding studies and four phase III clinical trials but one of the latter has not been published in full. In the phase II trials (BISTRO [Boehringer Ingelheim Study in ThROmbosis] I and BISTRO II)[59,60] daily doses of dabigatran of 50–600 mg once daily or as two daily doses were started 1–8 hours postoperatively. There was a significant dose-response for both efficacy (evaluated as total venographic DVT or proximal or distal DVT) and safety (evaluated as major bleeding or any bleeding).[60] There were no major bleedings in BISTRO I, but the number of patients in each dose group was only about 30. In BISTRO II, which had almost 400 patients per dose group, the incidence of major bleeding was 0.3% on 50 mg twice daily, increasing to 3.8% to 4.7% with daily doses between 300 mg and 450 mg.[60] The latter risk of major bleeding is considered high.

Elevations of liver enzymes ALT and AST were mild and with a lower incidence with dabigatran compared with enoxaparin (1.5% and 3.1%, respectively). There were no patients with combined elevations of aminotransferases and bilirubin. These observations are important in view of the liver-related adverse effects of the previous oral thrombin inhibitor, ximelagatran.[61] Drug-related thrombocytopaenia was not observed and other adverse events were similar between dabigatran and enoxaparin.

5.2 Phase III Trials

Two doses were brought forward to the phase III clinical trials, 150 mg and 220 mg, both given once daily. The first dose was reduced to half (75 mg or 110 mg) and given 1–4 hours postoperatively and compared with enoxaparin 40 mg once daily started the evening before surgery in the studies outside of North America (RE-NOVATE and RE-MODEL),[62,63] whereas dabigatran was started 6–12 hours postoperatively and compared with enoxaparin 30 mg twice daily started 12–24 hours after surgery in the North American study (RE-MOBILIZE).[64] Subsequently, a fourth trial in THR was performed world-wide with enoxaparin 40 mg once daily as the comparator.[65] The duration of treatment was 6–10 days in RE-MODEL, 12–15 days in

RE-MOBILIZE and 28–35 days in RE-NOVATE studies, and patients were followed for 3 months in all the trials. The studies had a double-blind, double-dummy design.

Two of the studies addressed TKR (RE-MODEL and RE-MOBILIZE), whereas patients with THR were recruited to RE-NOVATE and RE-NOVATE II. In all studies, the primary outcomes for efficacy and for safety were total VTE plus all-cause mortality and major bleeding, respectively. The main characteristics and these outcomes are summarized in table III. Whereas the three trials comparing dabigatran with the 'European' dose of enoxaparin (40 mg once daily) met the non-inferiority criteria,[62,63,65] RE-MOBILIZE with 30 mg enoxaparin twice daily failed in this respect. Major bleeding was not statistically different between the treatment alternatives in any study, although in RE-MOBILIZE the incidence of major bleeds was 0.6% in each of the dabigatran groups compared with 1.4% in the enoxaparin group. Overall, the results did not indicate any statistically significant differences between efficacy outcomes or risk of bleeding between the two doses of dabigatran and enoxaparin. This has also been confirmed in a formal meta-analysis[66] and a pooled analysis[67] of RE-NOVATE, RE-MODEL and RE-MOBILIZE.

6. Risk Evaluation

6.1 Bleeding and Other Adverse Effects

The phase II studies gave important information about increased risk of bleeding with high doses (≥300 mg daily) and with the selection of the 150 mg and 220 mg doses there was no increase of bleeding compared with LMWH.

Other reported events related to safety were details regarding major bleeding (requirement for reoperation, localization to critical organ, fatality or requirement for blood transfusions), wound infections, cardiovascular events (during treatment and during follow-up) and liver toxicity (ALT elevations alone and in combination with bilirubin elevations). Those pooled results for the fully published phase III trials are summarized in table IV and again there are no statistically significant differences between dabigatran 220 mg once daily and enoxaparin (dabigatran 150 mg once daily not shown). The incidence of myocardial infarction in the atrial fibrillation study[4] was higher with dabigatran than warfarin (0.7% vs 0.5%). In a study on VTE (RE-COVER) the number of myocardial infarctions was very small and no further conclusion is possible.[5]

Adverse events leading to discontinuation of study drug or serious adverse events did not differ between the treatments. In the orthopaedic studies, there was no report of any dabigatran-specific adverse event.

The most common adverse events (incidence ≥10%) were nausea, vomiting, constipation and pyrexia, which are expected in patients immediately after major surgery. These events occurred equally often with the three treatment alternatives. In the phase III clinical trials with dabigatran versus warfarin in stroke prophylaxis for patients with atrial fibrillation[4] and in the treatment of acute VTE[5] a dabigatran-related increase in the incidence of dyspepsia was reported.

Table III. Main outcomes of the phase III trials with dabigatran in orthopaedic surgery[62-65]

Study	n	Primary efficacy[a,b]	Symptomatic DVT[b]	Symptomatic PE[b]	Major bleeding[b]	CRNMB[b]
RE-MODEL	2076	40.5/36.4/37.7	0.4/0.1/1.2	0.1/0/0.1	1.3/1.5/1.3	6.8/5.9/5.3
RE-MOBILIZE	2596	33.7/31.1/25.3	0.5/0.2/0.2	0/0.2/0.2	0.6/0.6/1.4	2.5/2.7/2.4
RE-NOVATE	3463	8.6/6.0/6.7	0.8/0.5/0.1	0.1/0.4/0.3	1.3/2.0/1.6	4.7/4.2/3.5
RE-NOVATE II	2055	NA/7.7/8.8	NA	NA	NA/1.4/0.9	NA

a Primary efficacy outcome was the combination of total venous thromboembolism and all-cause mortality.

b The numbers represent incidence (%) with dabigatran 150 mg once daily or 220 mg once daily or enoxaparin (i.e. 150/220/enoxaparin). In RE-NOVATE II dabigatran 150 mg was not used.

CRNMB = clinically relevant non-major bleeding; **DVT** = deep vein thrombosis; **NA** = not available yet; **PE** = pulmonary embolism.

Table IV. Comparison of safety-related parameters between dabigatran 220 mg daily and enoxaparin 40 mg once daily or 30 mg twice daily in the phase III trials in orthopaedic surgery[62-64]

Event	Dabigatran (n = 2682[a]) [n (%)]	Enoxaparin (n = 2716[a]) [n (%)]
Bleeding leading to reoperation	5 (0.2)	5 (0.2)
Bleeding with transfusion of at least 2 units	33 (1.2)	33 (1.2)
Bleeding leading to fall in Hb ≥20 g/L	29 (1.1)	32 (1.2)
Fatal bleeding	1 (0)	0 (0)
Bleeding in critical organ	1 (0)	0 (0)
Wound infection during study period	30 (1.1)	37 (1.4)
Cardiovascular event on treatment	9 (0.3)	17 (0.6)
Cardiovascular event after treatment	1 (0.0)	7 (0.3)
ALT ≥3 × ULN	58 (2.2)	95 (3.6)
ALT ≥3 × ULN + bilirubin ≥2 × ULN	3 (0.1)	2 (0.1)
Adverse event leading to discontinuation	148 (5.5)	152 (5.6)
Serious adverse events[b]	179 (6.7)	170 (6.3)

a The denominators apply to the bleeding outcomes but were lower for the other outcomes. None of the differences are statistically significant. There are no data on long-term joint function.

b A serious adverse event was defined as any adverse event that was leading to death, was immediately life threatening, resulted in persistent or significant disability or incapacity, required or prolonged hospitalization, was a congenital anomaly or birth defect, or was to be deemed serious for any other reason representing a significant hazard comparable to the other criteria.

Hb = haemoglobin; **ULN** = upper limit of normal.

This was statistically significant in both of these long-term treatment trials. This adverse event was only reported specifically in RE-NOVATE and there the incidence was low (1–2%) without any statistically significant difference between treatments.[62]

In the EMA CHMP Assessment Report for Pradaxa®, it is mentioned that a slight increase, although not statistically significant, of hypokalaemia (1.2%, 1.6% and 0.9%), of peripheral oedema (7.3%, 6.4% and 5.9%) and of wound secretion (6.9%, 7.0% and 4.7%) was seen in the dabigatran 150 mg and 220 mg groups compared with enoxaparin, respectively.[68] We submitted an enquiry to the EMA for postmarketing pharmacovigilance data on adverse events but we were only referred to the *Summary of Product Characteristics* and the *European Public Assessment Report*, which did not provide additional data. Eudravigilance is not available to the public.

We have performed a literature search in MEDLINE, EMBASE and CINAHL using the search term 'dabigatran' without limitations (April 2010, updated January 2011) but we have not found any reports on adverse events except for one case report on alveolar bleeding in a patient treated with dabigatran after orthopaedic surgery.[69]

Teratogenic effects have been studied in rats and rabbits and there was a slight morphogenesis effect in rat fetuses at doses of dabigatran of 200 mg/kg.[70] There was no mutagenic or tumorigenic effect in preclinical studies. Women with childbearing potential should be instructed to avoid pregnancy during treatment with dabigatran.

6.2 Dose Reduction in Subsets of the Studied Population

The renal function gradually deteriorates with age,[71] partly due to anatomical changes (e.g. nephrosclerosis, decrease in kidney size, decrease in proximal tubular length, thickening of the basement membrane around Bowman's Capsule, decrease in number of glomeruli and glomerular volume) and partly because of functional changes (decreased blood flow and altered tubular function). This is important since the elimination of dabigatran is largely dependent on renal excretion and some subsets of the population might be

at an increased risk for accumulation of dabigatran leading to an increased risk for serious bleeding complications. This was addressed by Dahl et al.,[72] who compared the efficacy and safety of dabigatran 220 mg or 150 mg with enoxaparin 40 mg in a subgroup analysis of pooled data from two studies, RE-MODEL[63] and RE-NOVATE.[62] The lower dose of 150 mg once daily had a favourable bleeding profile with similar efficacy as enoxaparin for thromboprophylaxis in patients older than 75 years.[72]

A similar argument applies to patients with renal impairment regardless of their age. A creatinine clearance of <30 mL/min was an exclusion criterion in all studies on dabigatran. An *ad hoc* analysis of the safety and efficacy of dabigatran, 150 mg versus 220 mg, in patients with moderate renal impairment (calculated creatinine clearance ≥30 and <50 mL/min), who were included in RE-MODEL[63] and RE-NOVATE[62] studies (n = 337), showed similar efficacy with lower bleeding rates in the 150 mg group compared with enoxaparin 40 mg. Consequently, the lower dose of dabigatran, 150 mg, is recommended after orthopaedic surgery in patients with moderate renal impairment.[73]

In the pooled analysis of three studies, a pattern emerged with a trend to better effect of dabigatran in women and better effect of enoxaparin in men, albeit not statistically significant.[67] The effect of dabigatran was consistent across all ages, bodyweights and levels of renal function. The risk of bleeding increased with lower creatinine clearance (≥30 to <50 mL/min) in both the dabigatran and enoxaparin groups and also with increasing age, mainly in the enoxaparin group.[67]

7. Strength of Evidence

The development programme for dabigatran on the indication of thromboprophylaxis in major orthopaedic surgery is sufficiently large to identify common adverse events and perform a comparison with enoxaparin. In four published trials with LMWH as the active control, 5419 patients were treated with dabigatran 150 mg or 220 mg and 1168 received higher doses, whereas 389 were treated with lower doses.[60,62,63,64] Based on these data, it can be stated that the incidence of bleeding, which is the only causally related risk identified in the orthopaedic trial programme, is not more common with dabigatran than with the standard regimen with LMWH. Meta-analyses on the safety of LMWH have, in turn, not shown any statistically significant increase of major bleeding with LMWH versus placebo in the extended prophylaxis (table II).[55,57] Therefore, most of the major bleeds are probably more strongly related to the surgical procedure rather than to LMWH.

8. Preventability, Predictability and Reversibility of Adverse Effects

Bleeding occurs normally in any major surgery. Major bleeding may occur due to technical difficulties, abnormal anatomy, in association with revision arthroplasty and in the presence of infections or pre-existing haemostatic disorders. Some of these factors are known in advance and an appropriate medical history should reveal important congenital coagulation abnormalities. In patients with increased risk of bleeding, it may be possible to reduce the risk of postoperative bleeding by delaying the first dose of dabigatran until the following morning or until there is no evidence of excess bleeding.

Dabigatran has a several-fold longer half-life than LMWH and therefore bleeding may continue longer even when the drug is withheld. There was, however, no evidence in the clinical trials of more serious consequences of bleeding in patients treated with dabigatran compared with LMWH, for example, in terms of bleeding leading to reoperation (table IV).[67]

Effective and selective agents are available for the reversal of the anticoagulant effect of heparin (protamine sulphate), LMWH (recombinant factor VIIa) and warfarin (prothrombin complex concentrates). A specific agent for reversal of dabigatran is not available, which can be a concern in case of major haemorrhage. The only method to eliminate the effect of dabigatran is by haemodialysis, although there are preliminary data indicating that active charcoal may be effective.[74] There was no indication of higher morbidity or

mortality with dabigatran compared with warfarin in the long-term treatment studies.[4,5]

9. Health-Economic Impact

In general, extended-duration prophylaxis, mostly used after THR, seems to be cost effective and when results are based on reduction of asymptomatic VTE, fondaparinux dominates over LMWHs, as concluded in a review of the literature.[75]

An evidence review group report regarding the clinical effectiveness and cost effectiveness of dabigatran after elective hip or knee surgery was based on the submission of the manufacturer to the National Institute of Clinical Excellence (NICE) in the UK. The analysis demonstrated that in an indirect comparison with fondaparinux, dabigatran was less cost effective in both types of surgery, although the incremental cost was small and the authors admitted several weaknesses in the modelling process.[76] In the full technology appraisal by NICE of dabigatran for prevention of VTE, the drug was assessed to be as cost effective as fondaparinux or LMWH.[77] In the full guideline from NICE, rivaroxaban was found to be more cost effective than either of LMWH and dabigatran for the extended prophylaxis after THR, whereas dabigatran and fondaparinux were the most cost-effective alternatives after TKR in most of the analyses.[78]

In another analysis from the Irish health-payer perspective, the oral factor Xa-inhibitor rivaroxaban was more cost effective than dabigatran, which in turn was more cost effective than enoxaparin.[79]

In a British analysis performed together with representatives from the manufacturer and based on the cost year 2008, prophylaxis with dabigatran after THR was estimated at £137 for drug and administration, compared with £237 for enoxaparin, whereas the difference was smaller in TKR.[80]

Finally, in a German managerial pharmacoeconomic analysis, the use of dabigatran, compared with LMWHs, was associated with an economic advantage of €2.43 and €1.40 per day according to costs in 2006 at an acute-care hospital and at a rehabilitation hospital, respectively.[81]

10. Alternative Therapies

The comparisons between dabigatran and LMWH have already been discussed in sections 5.1, 5.2 and 6.1. The direct cost of these two alternatives is similar in most countries. Table V summarizes possible alternatives in situations when dabigatran is perceived as suboptimal.

10.1 Fondaparinux

Fondaparinux has shown superior efficacy in comparison with LMWH in the prevention of DVT among patients with THR, TKR or hip fracture surgery in several large clinical trials.[38] This was driven by a reduction of asymptomatic DVT, whereas the incidence of symptomatic VTE was the same as with LMWH. However, major bleeding was significantly more common in the fondaparinux group, although a subgroup analysis indicated that this could be ameliorated by delaying the first dose of fondaparinux until after 6 hours from end of surgery.[82] The incidence of major bleeding with delayed start was 2.1% compared with 1.7% with LMWH, a difference that was not statistically significant. The price of fondaparinux is in many countries approximately twice that of LMWH. In the absence of any direct comparisons between fondaparinux

Table V. Alternative prophylactic methods when dabigatran 220 mg daily is suboptimal[a]

Poor compliance	Expected lack of efficacy	High risk of bleeding	Severe renal dysfunction
LMWH	Rivaroxaban	Dabigatran 150 mg daily	Unfractionated heparin
Fondaparinux 2.5 mg	Fondaparinux 2.5 mg	Delayed start dabigatran	Vitamin K antagonists
		Mechanical methods	Fondaparinux 1.5 mg

a These suggestions are based on indirect comparisons or studies on subpopulations.

LMWH = low-molecular-weight heparin.

and dabigatran it is hard to speculate on differences in benefit-risk profile. An obvious difference is the subcutaneous injection route of administration with fondaparinux, raising the same problem as with LMWH for a subset of patients who are unable to manage this at home. A reduced dose of fondaparinux, 1.5 mg daily, is currently being studied in patients with severe renal failure (ClinicalTrials.gov NCT00927602 and another trial has been completed, NCT00555438).

10.2 Vitamin K Antagonists

Adjusted-dose oral VKA is commonly used as thromboprophylaxis in North America for major orthopaedic surgery.[83] Although warfarin reduces the incidence of symptomatic VTE compared with placebo it is inferior to LMWH during the first 5–7 days, due to the delayed onset of effect.[84] Combining VKA with a mechanical prophylactic method during this period can compensate for the initial lack of effect. There are reports of a significant increase in wound haematoma rates with VKA.[9,32,84] This is probably related to the unpredictable pharmacodynamics of VKA as a result of a large number of drug-drug interactions as well as some food-drug interactions. Patients developing postoperative infection requiring antibacterial therapy, or postoperative congestive heart failure with impaired liver function are at increased risk of being exposed to an excess effect of VKA. Postoperative laboratory monitoring of VKA is necessary but becomes a practical problem for some patients after discharge from the hospital. There are no direct comparisons of VKA with dabigatran in major orthopaedic surgery, only in atrial fibrillation[4] and in the treatment of VTE.[5] The most important difference between VKA and dabigatran is the eliminated need for laboratory monitoring and dose adjustments with the latter.

10.3 Oral Factor Xa Inhibitors

Rivaroxaban was more effective than enoxaparin for the prevention of VTE after TKR or THR in four phase III trials (the RECORD [REgulation of Coagulation in ORthopedic surgery to prevent Deep venous thrombosis and pulmonary embolism] programme),[85-88] regarding the primary outcome (any VTE plus all-cause mortality) and in two of the studies also for symptomatic VTE.[86,87] There were few major bleeding events, but the definition in these trials did not include surgical wound bleeding as major, unless it led to re-operation or death. In two pooled analyses, each one of dabigatran and rivaroxaban were compared with enoxaparin regarding the outcomes symptomatic VTE plus all-cause mortality for efficacy and major plus clinically relevant non-major bleeding for safety.[89] Enoxaparin had, compared with dabigatran 220 mg daily, similar efficacy (odds ratio [OR] 0.76; 95% CI 0.44, 1.31) and safety (OR 0.90; 95% CI 0.71, 1.15). On the other hand, enoxaparin, compared with rivaroxaban, was less effective (OR 2.04; 95% CI 1.32, 3.17) but was associated with a lower risk for bleeding (OR 0.79; 95% CI 0.62, 0.99).

A second orally available anti-Xa inhibitor, apixaban, has also completed its phase III programme (the ADVANCE [Apixaban Dosed Orally Versus Anticoagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism]) in orthopaedic surgery with favourable results compared with enoxaparin, but it has not been approved anywhere yet.[90-92]

10.4 Other Alternatives

Unfractionated heparin is more effective than placebo but less effective than the above-mentioned alternatives and is therefore no longer recommended in the ACCP guidelines.[7] The differences in opinion in North America regarding aspirin have been discussed in the introductory paragraphs of this review, but in Europe this is not considered an alternative (with the exception of Scotland).[93]

The mechanical thromboprophylaxis methods – graduated compression stockings, intermittent pneumatic compression and venous foot pumps – reduce the risk of DVT, but they appear to have limited efficacy compared with the anticoagulants for preventing proximal DVT in THR.[84,94-96] For patients with TKR, intermittent pneumatic compression has demonstrated good efficacy in five small studies,[97-101] but the method is not

always well tolerated by the patients, thereby reducing the compliance and making outpatient prophylaxis impossible. The other mechanical methods appear to be less effective.[7] For patients with such a high risk of bleeding that anticoagulants are considered contraindicated, one of the mechanical methods should be used.

11. Benefit-Risk Evaluation

VTE is a serious complication when it is symptomatic, which occurs in 2–4% of patients without any thromboprophylaxis after elective lower-limb arthroplasty. Fatal PE is, however, very rare in THR or TKR.

Dabigatran has similar benefit to LMWH, which provides approximately 70% risk reduction for symptomatic VTE after THR but less after TKR. Additional benefit from dabigatran is the oral route of administration (in relation to LMWH or to fondaparinux) and the elimination of laboratory monitoring and dose adjustments (in relation to warfarin).

The main risk with any anticoagulant is bleeding but with appropriate timing of dabigatran in relation to surgery and reduction of the first dose by 50% the risk of major bleeding is approximately 1%, which is similar to LMWH and to placebo. No other adverse event, specifically related to dabigatran has been observed in association with thromboprophylaxis after major orthopaedic surgery. Long-term studies on dabigatran have not found any evidence of liver toxicity.[4,5]

The overall benefit of dabigatran compared with the current standard of LMWH is the convenience for the patients during the prolonged prophylaxis at home. The benefit of dabigatran increases with the duration of treatment, such as after THR and eventually also after TKR if hospitals and physicians decide to change practice, and can then translate into decreased costs for society.

12. Conclusions

Major orthopaedic surgery is associated with a high risk for VTE, mainly manifested asymptomatic DVT but also with a substantial incidence of symptomatic VTE diagnosed after discharge from the hospital. Dabigatran has not been compared with placebo in this setting but there is evidence for a significant reduction of any DVT, proximal DVT and, in case of THR, also of symptomatic DVT with LMWH compared to placebo with a significant increase of major bleeding. When dabigatran in turn was compared with the LMWH enoxaparin, the overall efficacy was similar in a pooled analysis and also when compared with the 'European' dose of enoxaparin 40 mg once daily but it was inferior to 30 mg enoxaparin twice daily. The risk of bleeding was similar for dabigatran and enoxaparin 40 mg daily. There were no specific adverse events that were more common in patients treated with dabigatran in the orthopaedic studies. The main advantage of dabigatran is that it is administered orally and as such is an anticoagulant that does not require laboratory monitoring or dose adjustments, as opposed to VKA. Although the lack of a specific antidote against dabigatran is of potential concern, it has not had any appreciable influence on the safety results in any of the clinical trials. Therefore, the benefit-risk ratio of dabigatran can be considered as favourable in the prevention of VTE after major orthopaedic surgery, particularly when extended treatment for 30–35 days after surgery is required. Studies should also be performed in patients with hip fractures, where the risk of pulmonary embolism is even higher than in elective arthroplasty. Another indication of interest is spinal fractures with neurological deficit, where extended prophylaxis against VTE also is recommended. The optimal management of dabigatran-associated major bleeding also deserves further studies.

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