

# Oral Thromboprophylaxis Following Total Hip or Knee Replacement: Review and Multicentre Experience with Dabigatran Etxilate

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**Abstract:** The risk of venous thromboembolism (VTE) in patients undergoing total knee or hip replacement surgery is high. As a result, thromboprophylaxis is highly recommended. While current thromboprophylactic agents, such as low molecular weight heparins (LMWH) and vitamin K antagonists, are safe and effective their use can be problematic. Therefore, there is a need for alternative anticoagulants that are as safe and effective as conventional agents, but are more convenient and easier to use. Dabigatran etexilate, a direct thrombin inhibitor, is one such anticoagulant. For VTE prevention following major orthopaedic surgery, dabigatran etexilate shows similar efficacy and safety to the LMWH enoxaparin, and is approved for use in more than 75 countries, including Europe and Canada. Here, we summarize and discuss the experiences of four German clinics that have recently introduced dabigatran etexilate into clinical practice. Overall, dabigatran etexilate was well received by patients, surgeons and nurses, and compared favourably with enoxaparin. Staff appreciated the oral, single-dose administration of dabigatran etexilate. Patient satisfaction was high, especially in those individuals who had previously used LMWHs. In this review, we also address a number of questions that were asked by patients or staff; this will be of relevance to orthopaedic surgeons and nurses. We conclude that, in these four German clinics, dabigatran etexilate offered an effective oral alternative to existing thromboprophylactic agents in patients undergoing major orthopaedic surgery.

**Keywords:** Anticoagulant, Dabigatran etexilate, Direct thrombin inhibitor, Hip replacement surgery, Knee replacement surgery, Thromboprophylaxis.

## INTRODUCTION

Despite the clear benefits of thromboprophylaxis, venous thromboembolism (VTE) remains one of the most common causes of re-hospitalization in orthopaedic surgery patients [1, 2]. Here, we briefly review current thromboprophylaxis and report the experience of four German clinics that have implemented prophylaxis with the recently introduced oral direct thrombin inhibitor dabigatran etexilate.

## THE NEED FOR THROMBOPROPHYLAXIS FOLLOWING ORTHOPAEDIC SURGERY

Patients undergoing primary or secondary elective total hip replacement (THR) or total knee replacement (TKR) surgery have a high risk of VTE, which presents as symptomatic deep vein thrombosis or pulmonary embolism [3]. VTE may also be asymptomatic but detectable by venography. Without thromboprophylaxis ~40–60% of these patients will develop objectively confirmed, hospital-acquired, asymptomatic, or symptomatic deep vein thrombosis [4]. Hence, since 1986, treatment with thromboprophylactic

agents has been recommended for patients undergoing major orthopaedic surgery [5]. Fatal pulmonary embolism occurs in 1 of every 300 patients following THR without thromboprophylaxis, although events are rare if guideline-recommended anticoagulants are administered [4].

Postoperative VTE is associated with considerable morbidity and mortality [6-9], and the ever-increasing number of THR and TKR procedures being performed could also increase the incidence of these VTE-related events [10-13]. Using statistical projections based on the increase in procedures between 1990 and 2003, it has been estimated that the demand for THR procedures in the USA could increase by 174% from 209,000 in 2005 to 572,000 by 2030; the demand for TKR procedures could increase by 673% from 450,000 in 2005 to 3.48 million by 2030 [12]. These estimates help to illustrate the scale of the current and future challenge of postoperative VTE prevention that also exists in Europe. In Germany, for instance, 223,000 THR and 157,000 TKR operations were conducted in 2008 [14]. Furthermore, it is predicted that in Germany and most other European countries, the number of primary and secondary total joint replacement surgeries will increase over the next few decades [14].

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## THROMBOPROPHYLACTIC AGENTS

Traditionally, thromboprophylaxis has been provided with low molecular weight heparins (LMWH) or vitamin K antagonists, such as phenprocoumon, acenocoumarol and warfarin. Although such medications are effective, there are several limitations associated with their use. LMWH are parenteral agents and, therefore, their administration can be problematic (especially outside the hospital environment) and may incur additional costs [15]. In addition, heparin-induced thrombocytopenia can occur with LMWH, although the risk is thought to be lower with LMWH than with unfractionated heparin [16]; the incidence of heparin-induced thrombocytopenia has been reported to be 0–0.9% in orthopaedic surgery patients treated with LMWH and 3–5% in those treated with unfractionated heparin [17]. The condition is associated with a risk of thrombotic events 30 times that of control populations and hence can result in considerable mortality and morbidity [17, 18]. Warfarin and other vitamin K antagonists, which have tended to be used more in the USA than in Europe, require routine anticoagulation monitoring and dose adjustment, and have numerous food and drug interactions [19]. Vitamin K antagonists do, however, have a relative price advantage over LMWH.

Due to these relative drawbacks of existing therapies, there is a need for new anticoagulants that are safe, effective and overcome these challenges [15]. Two new oral antithrombotics, dabigatran etexilate and rivaroxaban, have been approved and established in clinical use within Germany for exclusive use in primary THR and TKR.

### Dabigatran Etexilate

Dabigatran etexilate (Pradaxa<sup>®</sup>, Boehringer Ingelheim GmbH, Ingelheim, Germany) is a new, oral direct thrombin inhibitor. It is a prodrug that is rapidly converted into dabigatran, which has a half-life of 12–17 hours and is mainly (about 80%) excreted renally [15, 20]. Dabigatran works by binding to the active site of free and clot-bound thrombin; as a result, thrombin's enzymatic capacity is inhibited [21, 22].

Based on successful pivotal phase III clinical trials in orthopaedic patients [23–24], dabigatran etexilate (hereafter referred to as dabigatran) is now licensed in over 75 countries, including Europe [25] and Canada [26], for VTE prevention following THR and TKR surgery. Pivotal studies showed that dabigatran demonstrated similar efficacy and safety compared with the parenteral LMWH enoxaparin, as prophylaxis following major orthopaedic surgery [23, 24], although at high doses it may be associated with gastrointestinal bleeding and dyspepsia [27]. Therefore, dabigatran provides an oral alternative to the parenteral agents (LMWH and fondaparinux). Compared with the oral vitamin K antagonist warfarin, which is still recommended and used widely in the USA [4], dabigatran has the potential to provide a number of benefits, including no food interactions and few drug interactions, convenient oral administration, no risk of heparin-induced thrombocytopenia, and predictable anticoagulant effects that abrogate the need for regular anticoagulation monitoring [28].

## Clinical Experience with Dabigatran

As a direct result of the European pivotal studies, the recently published UK and German guidelines include the use of dabigatran or other anticoagulants such as LMWH [29]. Although dabigatran is used regularly within the German medical system, and is already advocated by a large number of clinical centres, no detailed clinical protocols or descriptions of its clinical use following THR and TKR have (to our knowledge) been described as yet. Therefore, it seems appropriate and relevant to review the use of dabigatran in clinical practice, comparing the pros and cons highlighted by this multicentre evaluation.

Representatives from four German centres have shared and discussed their clinics' experiences of introducing dabigatran into clinical practice and its routine use to date as thromboprophylaxis following primary TKA and THR, focusing on: number of patients treated and type of thromboprophylaxis provided at the centres; outcomes with dabigatran; patient satisfaction with dabigatran and staff opinion of dabigatran (Table 1). A distinct evaluation of the current use and its comparison with LMWH or warfarin included the following: efficacy; ease of use; time saving compared with subcutaneous application; patient advantages; patient satisfaction level; staff (nurse) satisfaction; occurrence of haematoma; pricing and overall complication rate. Any difficulties encountered, especially during the initial clinical implementation phase, were also recorded for each centre.

### *Number of Patients Treated and Thromboprophylaxis Provided*

Over 7,200 patients have been treated with dabigatran at the four centres; these are: Klinik für Gelenkersatz (Garmisch-Partenkirchen); ENDO-Klinik (Hamburg); OCM Klinik (Munich); Center for Endoprosthetic and Reconstructive Joint Surgery (Charité, Berlin). At the Klinik für Gelenkersatz, over 2,500 patients received dabigatran between April 2008 and September 2010. The ENDO-Klinik treated over 1,500 patients with dabigatran between January 2009 and March 2010, while dabigatran has been in clinical use at the OCM Klinik (Munich) since July 2008, and as of May 2010 over 2,600 patients had received the drug. At the Center for Endoprosthetic and Reconstructive Joint Surgery, dabigatran was prescribed to approximately 600 patients between April 2009 and September 2010. As the four centres used dabigatran during the same time period, this warranted a multicenter evaluation. Individual center patient numbers and methods of examination and evaluation are not detailed due to their heterogeneity. However, surgeons completed a standardized questionnaire to provide the results as described and detailed in the text and in Table 1.

Dabigatran was directly compared to enoxaparin, as enoxaparin was the standard treatment in all centers before the study. The criteria for choosing to prescribe dabigatran included: no contra-indications to therapy; no previous warfarin use; no severe bleeding disease; absence of a peridural catheter; the availability of a reduced dose for patients aged over 75 years, with renal insufficiency or receiving amiodarone therapy. The duration of treatment

**Table 1. Advantages and Disadvantages Associated with the Implementation and Use of Dabigatran in Clinical Practice, as Compared with low Molecular Weight Heparin**

	ENDO-Klinik	OCM Klinik	Center for Endoprosthesis and Reconstructive Joint Surgery	Klinik für Gelenkersatz
<b>Advantages</b>				
Good efficacy	•	•	• <sup>1</sup>	•
Comparable efficacy to enoxaparin				•
Ease of use/oral dosing/single application/fixed flexible dosing	•	•	• <sup>1</sup>	•
Time-saving		•		•
Can be taken by patients at home	•	•		•
High patient satisfaction levels	•	•		•
High staff satisfaction levels			•	• <sup>2</sup>
Lack of haematoma		•		•
No risk of heparin-induced thrombocytopenia	•	•		•
No need for regular monitoring of coagulation parameters	•	•		•
No increase in DVT in first 8 days post-surgery	•	•		•
No increase in complications such as severe bleeding or need for wound revision	•	•		•
Reduced dosage available				•
Good safety profile	•	•	•	•
Clarity of protocol			•	
Fair pricing			•	•
<b>Disadvantages</b>				
Time-consuming implementation	•	•		•
Limitations during spinal anaesthesia	•	•		•
Not suitable for use following DVT	•	•		•
No indication for treatment of DVT	•	•		•
Relative inaccuracy of laboratory coagulation parameters	•	•		•
No long-term experience	•	•		•
Severe nausea in some patients requiring change of therapy	•	•		•
Possible cost disadvantage	•			•
Large size of capsules				•

\*Either data provided by the clinic supports this statement or an author from the clinic stated that they agree with the statement.

<sup>1</sup>Very good; <sup>2</sup> Mostly.

DVT, deep vein thrombosis.

with dabigatran was in accordance with European guidelines: 28–35 days for THR patients and 10 days in TKR patients [25].

The alternative thromboprophylactic agents routinely prescribed in these clinics included enoxaparin (Clexane<sup>®</sup> [Sanofi Aventis, Paris, France]), heparin (Certoparin<sup>®</sup> [Novartis, Basel, Switzerland]) and fondaparinux (Arixtra<sup>®</sup> [GlaxoSmithKline, Brentford, UK]). Patients received these alternative medications if they exhibited the contraindications listed in the package insert for dabigatran. Switching from one therapy to another occurred for several reasons. Selected patients switched to dabigatran following the removal of the peridural catheter and occasionally due to recommendations from family doctors. A switch from dabigatran to enoxaparin was also necessary for selected

patients due to reports of nausea. While nausea is a common side effect of surgery/anaesthesia, switching of therapy was only needed in a small number of cases (fewer than 20 patients in the overall cohort). In addition, a small proportion of patients in three of the four centres reported a slight prolongation in wound secretion, which necessitated a switch to LMWH. However, an initial surveillance study including over 200 patients by the Endo-Klinik Hamburg did not show a significant prolongation of the incision or drainage wound when compared with LWMH.

#### **Safety and Efficacy Outcomes with Dabigatran**

All advantages and disadvantages associated with the implementation of the new drug are summarized in Table 1. In general, the efficacy and safety of dabigatran were

deemed to be good or very good by the clinics and were thought to be comparable to the parenteral anticoagulants used. Since dabigatran is administered orally as a fixed dose, it was found to be easy to use. At three of the centres no notable safety complications with dabigatran were reported. However, one clinic reported rare cases of intestinal tract bleeding in patients receiving dabigatran, but a connection between the two was deemed questionable by the clinic.

### **Patient Satisfaction with Dabigatran**

Patient satisfaction with dabigatran in these clinical settings was high, and in some centres better patient comfort was reported with dabigatran. A number of questions were frequently asked by patients, including how dabigatran's efficacy compared to that of enoxaparin, and whether one dosing regimen was suitable for all. Satisfaction with dabigatran was particularly high in those patients with previous experience of LMWH; indeed, dabigatran's oral administration was preferable to the parenteral application of LMWH, which can be associated with abdominal haematomas.

However, some patients complained about the increasing number of oral medications that they needed to take postoperatively. The extra two capsules (2 x 110 mg), in addition to other necessary drugs, such as painkillers and anti-inflammatory medications, increase this burden. This is particularly a problem in the early postoperative phase, which is associated with limited oral receptiveness.

### **Staff Opinion of Dabigatran**

Although the implementation of the drug was initially time-consuming for nurses and clinical staff, the ease of use once implemented was rated as good. Staff appreciated the simple, independent and single daily dose application of dabigatran, all of which are likely to aid compliance. The fact that routine laboratory monitoring is not required was welcomed, as was the option of a reduced dose for specific patient groups.

Staff questioned the initiation and duration of dabigatran treatment and whether adjustment for body weight was necessary. It is recommended that dabigatran is initiated as a half dose 1–4 hours post-surgery if appropriate levels of haemostasis are achieved. However, if this is not possible, therapy should be started as a half dose later on during the day of surgery or as a full dose on the following day [30]. Studies show that delaying the initiation of 220 mg dabigatran does not affect efficacy [31].

As shown in a previous study, and confirmed with our nursing experience, the two main benefits of oral administration were removal of the threat of needle-stick injuries and of the need for patient education regarding LMWH self-administration in the rehabilitation phase [32]. However, it was also highlighted by the nurses that subcutaneous drugs, administered by the nurse, might be appropriate for some very elderly patients or patients with cognitive impairment.

### **SUMMARY**

Thromboprophylaxis is recommended following THR and TKR, and there has been a need for safe and effective but more convenient anticoagulant therapies. Dabigatran has

been licensed for this indication in over 75 countries, including Europe and Canada. Here, we have documented the experiences of four German clinics that have introduced dabigatran into routine clinical practice. This was an important exercise since the implementation of, and experiences with, a drug during trial conditions may differ from those in a clinical setting. This experience with over 7,200 patients should provide useful and relevant information for surgeons considering dabigatran for the indication discussed. Overall, dabigatran was viewed as an effective oral alternative for thromboprophylaxis following major orthopaedic surgery, and its discussed advantages are likely to improve patient adherence to anticoagulant therapy. To simplify general oral VTE prophylaxis for the orthopaedic surgeon, we propose that dabigatran should also be investigated for trauma or other elective surgical interventions involving the lower extremities.

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### **CONFLICT OF INTEREST**

The authors are paid consultants of Boehringer Ingelheim.

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