

**Pharmacoeconomic implications of thromboprophylaxis with new oral anticoagulants after total hip or knee replacement in the United States**

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## **Abbreviations**

ACCP	American College of Chest Physicians
AF	Atrial fibrillation
bid	Twice daily
CTPH	Chronic thromboembolic pulmonary hypertension
DVT	Deep vein thrombosis
INR	International normalized ratio
LMWH	Low-molecular-weight heparin
od	Once daily
PE	Pulmonary embolism
PPPM	Per patient per month
PTS	Post-thrombotic syndrome
QALY	Quality-adjusted life-year
THR	Total hip replacement
TKR	Total knee replacement
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

## **Abstract**

**Introduction:** Adequate thromboprophylaxis after total hip or knee replacement (THR or TKR) is essential to reduce the incidence of venous thromboembolism (VTE) and its associated complications. Although effective, traditional anticoagulants are associated with a considerable economic burden, particularly when used outside the hospital setting. This article explores whether newer oral anticoagulants can reduce costs of VTE prophylaxis and therapy.

**Areas covered:** Cost associated with vitamin K antagonists; indirect costs associated with complicated or inconvenient anticoagulation regimens, nonadherence, and associated complications; potential of the newer oral anticoagulants, including direct thrombin inhibitors and direct factor Xa inhibitors, to produce indirect cost savings after THR or TKR through a potential reduction in VTE rates and administration and monitoring costs.

**Expert Opinion:** The use of new anticoagulants for VTE prophylaxis after THR or TKR can result in direct and indirect cost savings through improved efficacy by reducing VTE rates and decreased drug administration and monitoring costs compared with traditional anticoagulants. Future research will need to focus on cost analyses driven by clinical outcomes measured on the performance of these agents in actual clinical practice.

## **Article highlights**

- Patients undergoing total hip or knee replacement (THR/TKR) surgery are at risk for developing venous thromboembolism (VTE) if they do not receive appropriate thromboprophylaxis
- Taking into account costs of hospital stay and administration of parenteral agents, VTE is expensive to treat, both in hospital and post discharge, and its long-term consequences may amount to  $\geq 75\%$  of the cost of treating the initial event

- Traditional thromboprophylactic agents are effective in reducing VTE rates but have limitations that complicate management and add to the overall cost of anticoagulant care
- New oral anticoagulants have been proven efficacious and safe in clinical trials, have a predictable pharmacologic response, do not require routine coagulation monitoring, are administered orally, are more convenient to use outside the hospital setting, and may improve adherence to guideline recommendations
- The new oral anticoagulants have the potential to produce substantial direct and indirect cost savings through reduced VTE rates and reduced administration and monitoring costs compared with the currently available agents
- Potential reductions in the rate of VTE will lead to reduced direct and indirect costs relating to the treatment of VTE, the cost of further inpatient care or rehospitalization, and the cost of managing any associated long-term consequences

## **1.0 Introduction**

Patients undergoing total hip or knee replacement (THR or TKR) surgery are at increased risk of developing postoperative venous thromboembolism (VTE) [1]. Proximal deep vein thrombosis (DVT) occurs in approximately 5–36% of THR and TKR patients without thromboprophylaxis (as detected by venography) [2], and pulmonary embolism (PE) occurs in  $\leq 50\%$  of patients with proximal DVT [3]. Symptomatic PE is fatal in 10% of cases, usually within the first hour of developing symptoms, but often remains unidentified until autopsy due to the nonspecific nature of the symptoms [4]. VTE is also associated with complications such as post-thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension (CTPH), and an increased risk of recurrent events. However, appropriate and effective thromboprophylaxis can substantially reduce the incidence of postoperative VTE.

As such, VTE after THR or TKR has been classified by the US Centers for Medicaid & Medicare Services as a hospital-acquired condition, and hospitals will be required to pay the extra costs of treating these events should they occur [5]. This will provide added incentive for adherence to guideline recommendations for the prevention of postoperative VTE and will increase interest in the pharmacoeconomic burden of thromboprophylaxis in this setting. However, as VTE occurs at a mean of 27 days after THR and 16 days after TKR, duration of prophylaxis should be continued for up to 35 days after surgery which is well after patients have been discharged from the hospital.[2] This has important implications for patient management, because parenteral therapies are difficult to manage and patient compliance is problematic in the outpatient setting.

The currently used anticoagulants – mainly vitamin K antagonists (VKAs) and low-molecular-weight heparins (LMWHs) – although effective, are associated with a number of complexities that not only limit their use (e.g., monitoring of anticoagulation in patients receiving warfarin), but also increase the burden on healthcare resources. New oral anticoagulants that are recently approved or currently in development may help to address these limitations. These agents have the potential to reduce administration and monitoring costs compared with the currently available agents. They may also have the potential to reduce VTE rates and, consequently, to reduce direct and indirect costs associated with the treatment and management of VTE events and their complications.

This review will discuss the economic burden of VTE after THR and TKR and the healthcare resource requirements for thromboprophylaxis with the currently available anticoagulants. The impact of the new oral, targeted anticoagulants on VTE-related healthcare costs will also be examined.

## **2.0 The pharmacoeconomic burden of VTE**

In the United States, VTE imposes a considerable burden on the healthcare system, costing almost US\$500 million per annum, and the components of VTE (DVT and PE) are a major cause of disease and death [6]. Development of a thromboembolic event after THR or TKR imposes considerable direct and indirect costs at diagnosis and throughout long-term treatment. Once VTE is suspected, confirmatory diagnostic tests such as venography or ultrasound are required [7]. If it is confirmed, treatment with heparins or fondaparinux and a VKA is required; these agents are associated with administration costs and monitoring costs, respectively. The potential long-term consequences of VTE, such as recurrent thromboembolic events, PTS, and CTPH, can also be very costly [8,9].

## **2.1 The cost of treating VTE**

Initial therapy for VTE after THR or TKR accounts for a large proportion of the associated costs of this condition [10]. Development of VTE in hospital doubles the length of hospital stay after THR or TKR and results in a corresponding doubling of in-hospital costs [11]. The direct health plan cost of managing an initial episode of DVT is estimated to be US\$7712–10,804; for an initial PE event it is US\$9566–16,644 [12]. Overall costs for DVT plus PE, including skilled facility care, amount to US\$12,200 [13]. In a managed care database, patients with a thromboembolic event after THR or TKR incurred additional charges of up to nearly US\$18,000 compared with patients without an event [14]. However, most cases of VTE after THR or TKR occur after hospital discharge [14,15]. Patients undergoing major orthopaedic surgery who develop VTE after discharge incur additional direct costs of US\$5800 during the 3-month post-discharge period as compared with age- and procedure-matched controls [14].

Initial treatment of VTE typically involves anticoagulation with VKAs, an LMWH, or unfractionated heparin for at least 5 days and until the international normalized ratio (INR) is stable and above 2.0 [16]. Warfarin therapy is recommended for at least 3 months after the initial VTE event [17]. Both in-hospital and post-discharge costs must therefore be considered in calculating costs of treatment. The average direct cost of hospital stay for a patient with DVT without complications is approximately US\$3000 per patient, at an average cost of US\$820 per patient per day, including acute and subacute care [18]. This cost is considerably increased if a patient develops complications. An estimated 2.2% of patients treated for VTE are at risk of major bleeding [10]. Patients treated for DVT who experience a major bleed during the hospital stay have an increased average cost per stay of US\$11,189 as the result of an increased length of hospital stay (average 8.6 days) and higher daily cost (average US\$1460) [18]. A minor bleeding event increases the cost of a hospital stay for DVT by US\$2419.

Drug-induced thrombocytopenia adds US\$3118 to the cost of stay, and development of PE adds US\$3915 [18]. A retrospective cohort study of patients from two US managed care populations showed that after an incident in-hospital DVT event, patients received warfarin on an outpatient basis for an average of 6.2 months. The average duration of outpatient treatment with warfarin was 7.9 months after an in-hospital PE event and 8.0 months after DVT and PE. The average acquisition cost of warfarin therapy was estimated at US\$19.50 per patient per month (PPPM) [13]. These patients received an average of 13.5 INR tests (1.86 tests PPPM) at a cost of US\$84 (US\$12.50 PPPM), with nearly 30% requiring at least one office visit within a day of the INR test at a cost of US\$127 (US\$18.96 PPPM), potentially attributable to warfarin monitoring. In this study, 17% of patients with VTE received outpatient LMWH therapy at a cost of US\$50 per patient–day [13]. During the acute-care

period, the calculated cost of at-home LMWH therapy with administration by a registered nurse ranges from US\$1707 for once-daily to US\$2390 for twice-daily injections. The cost of self-injection is somewhat lower, ranging from US\$1415 for once-daily to US\$1734 for twice-daily injections. Injections given at a specialized anticoagulation clinic cost between US\$1520 for once-daily injections and US\$2015 for twice-daily injections [18].

## **2.2 The cost of complications associated with VTE**

The potential long-term consequences of VTE, such as recurrent VTE events and PTS, can further increase the economic burden associated with the disease. The risk of recurrent VTE persists for several years after an initial event, but recurrence is most common after 6–12 months. Risk estimates range between 6% at 3 months and 24% at 5 years [19]. The cost of hospital readmission for recurrent DVT is 21% greater than the cost for the initial DVT event, mainly due to the increased length of hospital stay (an average of 7.7 days for the initial admission compared with 8.7 days for readmission) [20].

PTS is a chronic condition that can develop in patients with DVT. It is characterized by pain, swelling, cramps, edema, and hyperpigmentation and is a cause of considerable morbidity [21]. Estimates of the rate of PTS after VTE vary considerably; the available literature demonstrates that PTS develops in 23–60% of patients in the 2 years following a DVT; approximately 10% of cases are considered to be severe [22]. Although the incidence may be difficult to assess, it is accepted that the cost of PTS is sizeable, depending on the severity of the condition. A literature-based model estimates the annual per-patient cost for mild-to-moderate PTS to be US\$839 in the first year and US\$341 in subsequent years. In this model, costs were determined by multiplying the amount of resources used by the unit price of those resources. For severe PTS characterized by ulceration, the cost is estimated to be US\$3817 in



the first year. The cost in subsequent years ranges from US\$933 to US\$3295, depending on whether ulcers are open or healed [23]. Long-term costs of treating PTS are estimated to add 75% to the cost of treating the initial DVT [19]. For patients with VTE, annualized mean total direct costs, including resource utilization, for those with PTS were 32% higher than for those who did not develop PTS (US\$47,596 compared with US\$35,929, adjusted for clinical and demographic factors) [8]. PTS is also associated with chronic venous insufficiency, which also requires treatment. Approximately 4% of patients with PE will develop CTPH within 2 years [9]. However, because CTPH is underdiagnosed, its real prevalence is unknown [9]. CTPH is associated with considerable morbidity and mortality [9], increasing the burden on healthcare services.

### **3.0 Thromboprophylaxis with currently available anticoagulants**

Routine thromboprophylaxis after THR or TKR, as recommended by the American College of Chest Physicians (ACCP), can substantially reduce the rate of postoperative VTE, helping to reduce the direct and indirect costs associated with treating VTE and its potential consequences. The anticoagulant regimens recommended by the ACCP are LMWHs, fondaparinux, dabigatran, apixaban, rivaroxaban, low-dose unfractionated heparin, aspirin, or VKAs for a minimum of 10 to 14 days and up to 35 days [2]. Because the current duration of a hospital stay is 4–5 days after THR or TKR [15], anticoagulation will thus be continued beyond the period of hospitalization for most patients. Costs for the currently recommended anticoagulants involve not only acquisition (fondaparinux, US\$30/day; enoxaparin once daily [od], US\$16/day; enoxaparin twice daily (bid), US\$24/day; warfarin, US\$0.30/tablet – based on 2003 costs) [24], but also the costs of administration (parenteral agents), and routine coagulation monitoring (for VKAs) must also be taken into account.

Warfarin, although orally administered, has unpredictable pharmacokinetics and pharmacodynamics that are affected by various clinical and genetic factors and interactions with other drugs and foods [25]. Moreover, it has a narrow therapeutic window. Patients receiving warfarin therefore require regular INR testing to ensure that coagulation is maintained within a safe yet effective range. In the United States, monitoring requires regular visits to either a primary care physician or a specialized anticoagulation clinic. Patient self-testing is also an option; however, the uptake of this model of monitoring in the United States has been limited to date [26]. The cost of warfarin monitoring will differ among settings and regions, and it is therefore difficult to accurately assess the economic burden of warfarin use.

Most studies have been conducted in patients with atrial fibrillation (AF), who are often prescribed chronic warfarin therapy. In one such study, the mean cost of anticoagulation clinic care was US\$281 per patient after 1 year (average from three different sites) [27]. An additional analysis estimated the PPPM cost of a decentralized outpatient pharmacy anticoagulation service in patients with chronic AF receiving warfarin in a managed care setting. The average cost for pharmacist and laboratory monitoring as well as drugs was estimated to be US\$51.25 PPPM. This is distributed as US\$13.78 (27%) in personnel costs for monitoring pharmacists, US\$18.38 (36%) for laboratory tests, and US\$19.09 (37%) for anticoagulant drug costs (based on 2000 costs) [28].

Each visit to an anticoagulation clinic for INR testing can be reimbursed by the health system (e.g. Medicare) at a 'room fee' of US\$60 (based on 2003 data) [24]. The requirement for routine monitoring also imposes indirect costs on employers in terms of lost productivity. In addition to the healthcare resource required, the inconvenience of routine coagulation and dose adjustments means that management of anticoagulation is not straightforward and the

likelihood of complications is increased. The fact that patients receiving warfarin are frequently outside the therapeutic INR range [29] increases the risk of thrombosis or bleeding events, with associated direct and indirect cost implications.

Although thromboprophylaxis with LMWHs or fondaparinux does not require routine coagulation monitoring, when these agents are given outside of the hospital setting, their parenteral route of administration imposes additional costs. Administration by a nurse at home is the most costly method. Over the 6-month time period (acute care plus post-acute care management) after an initial DVT, LMWH injections administered at home by a registered nurse cost an estimated US\$2686 for once-daily injections and US\$3369 for twice-daily injections [18]. LMWH administration by the patient or a nonprofessional caregiver can save several hundreds of dollars per patient [18] but requires training by a nurse before the patient is discharged from the hospital. In addition, many patients – particularly elderly patients – are unable or unwilling to self-administer.

Despite the direct and indirect costs of prophylaxis after hospital discharge, routine prophylaxis has been shown to be cost effective compared with no prophylaxis or compared with treatment after diagnosis [30,31]. A literature-based study of thromboprophylaxis after THR revealed that the highest total expected costs (based on amounts reimbursed in the United States in 1995) were in patients who did not receive any prophylaxis and incurred costs of care associated with VTE events [32]. A similar conclusion was reached in a study comparing thromboprophylaxis approaches after THR or abdominal surgery, using a model based on VTE and bleeding rates in three review articles. Considering the costs of in-hospital care, routine prophylaxis was the least costly option, compared with no prophylaxis or selective treatment after diagnosis after DVT [33].

#### **4.0 The new oral target-specific anticoagulants**

In the development of new anticoagulants, attention has been focused on orally administered agents that do not require routine coagulation monitoring and dose adjustment. Both thrombin and factor Xa play a key role in the coagulation cascade and have been identified as viable targets for effective anticoagulation. In addition, as direct-acting agents, their pharmacologic response is more predictable than that of the indirect inhibitors such as LMWH and fondaparinux.

#### **4.1 Dabigatran etexilate: a direct thrombin inhibitor**

Dabigatran etexilate is an oral, direct thrombin inhibitor that has been investigated for the prevention of VTE after THR or TKR, the prevention of stroke in patients with AF, the treatment of acute VTE and secondary prevention of VTE. It has a low oral bioavailability (~6.5%) and is rapidly absorbed and converted to dabigatran, the active form [34]. Dabigatran has a half-life of 14–17 hours in patients undergoing THR or TKR [35], and approximately 80% is excreted unchanged by the kidneys [36]. It has a low potential for drug–drug interactions and a predictable anticoagulant effect, so it can be given in a fixed dose without the requirement for routine coagulation monitoring [34]. The phase III program investigating dabigatran for the prevention of VTE after THR or TKR comprised three randomized, double-blind trials: RE-NOVATE in patients undergoing THR [37], and RE-MODEL and RE-MOBILIZE in patients undergoing TKR [38,39]. The primary efficacy endpoint was the composite of total VTE (venographic or symptomatic DVT or symptomatic PE) and death. In the RE-NOVATE and RE-MODEL studies, dabigatran 150 mg or 220 mg od demonstrated noninferiority to enoxaparin 40 mg od for 28–35 days after THR and for 6–10 days after TKR, respectively [37,38]. In the RE-MOBILIZE study (TKR), dabigatran failed to meet the noninferiority criteria compared with enoxaparin 30 mg bid, the dosing regimen approved in

North America after TKR [39]. Dabigatran etexilate had a similar safety profile compared with enoxaparin in each of the studies.

#### **4.2 Rivaroxaban: a direct Factor Xa inhibitor**

Rivaroxaban is an oral, direct factor Xa inhibitor approved in the United States for the prophylaxis of DVT in patients undergoing THR or TKR. It selectively blocks the active site of factor Xa and does not require a cofactor (such as antithrombin III) for activity [40].

Rivaroxaban has a rapid onset of action, reaching maximum plasma concentrations within 2–4 hours. It has been found to have predictable pharmacokinetic and pharmacodynamic properties and has a low potential for interactions with food or other medications, so it can be administered as a fixed dose without the requirement for routine coagulation monitoring. It has completed a large phase III investigative program in patients undergoing THR or TKR (RECORD, REgulation of Coagulation in ORthopaedic surgery to prevent Deep-vein thrombosis and pulmonary embolism), in which the primary efficacy endpoint was total VTE, the composite of any DVT, nonfatal PE, and all-cause mortality.

The RECORD1 study demonstrated that rivaroxaban 10 mg od was superior to enoxaparin 40 mg od for 30–35 days after THR [41]. RECORD3 and RECORD4 demonstrated the superior efficacy of rivaroxaban 10 mg od compared with 40 mg od and 30 mg bid, respectively, for 10–14 days after TKR [42,43]. The superiority of long-term thromboprophylaxis with rivaroxaban 10 mg od (28–35 days) compared with short-term thromboprophylaxis with enoxaparin 40 mg od (10–14 days) was demonstrated in the RECORD2 study [44]. In a pooled analysis of all four RECORD studies, rivaroxaban significantly reduced the composite of symptomatic VTE and all-cause mortality compared with enoxaparin regimens ( $P = 0.001$ )[45].

### **4.3 Apixaban: a direct Factor Xa inhibitor**

Apixaban is an oral, highly selective, direct factor Xa inhibitor. It is absorbed rapidly and has a mean terminal half-life of approximately 13 hours [46]. It has multiple elimination pathways, although renal excretion is an important route of apixaban elimination [46,47]. The primary efficacy endpoint in the ADVANCE-1, ADVANCE-2 (both TKR) and ADVANCE-3 (THR) studies with apixaban was the composite of symptomatic or asymptomatic DVT, nonfatal PE, and death by any cause during the treatment period. In ADVANCE-1, compared with enoxaparin 30 mg every 12 hours, apixaban 2.5 mg bid did not meet the prespecified statistical criteria for noninferiority for the primary efficacy endpoint [48]. The ADVANCE-2 study compared apixaban 2.5 mg bid with enoxaparin 40 mg od [49]. The primary efficacy endpoint occurred in 15.1% of patients in the apixaban group versus 24.4% in the enoxaparin group (absolute risk difference, -9.3%; one-sided  $P < 0.001$ ) [49]. The ADVANCE-3 study compared apixaban 2.5 mg bid with subcutaneous enoxaparin 40 mg od. The primary efficacy outcome occurred in 1.4% of patients in the apixaban group versus 3.9% in the enoxaparin group (absolute risk difference, -2.5%;  $P < 0.001$  for noninferiority and superiority) [50].

### **5.0 The pharmacoeconomic impact of the new target-specific oral anticoagulants**

The new anticoagulants have several advantages compared with agents such as LMWH and VKAs. First, their oral route of administration means that they are much more convenient to use compared with parenteral agents, such as the LMWHs, particularly if bid dosing is required. This will be particularly beneficial outside of the hospital setting because it will eliminate the need for nurse visits or for a nurse to train the patient to administer injections. After THR surgery, the median time to hospital discharge is 5 days. Approximately 85% of patients receiving thromboprophylaxis continue to receive it 5 days after surgery [15]. After TKR surgery, the median time to hospital discharge 4 days; approximately 90% of patients

continue to receive thromboprophylaxis 4 days post surgery [15]. These patients may be discharged into a healthcare facility, such as a skilled nursing facility or an inpatient rehabilitation facility. In a population-based study of patients undergoing primary or revision THR, 42% were discharged from the acute-care hospital directly to their homes, while 24% were discharged to a skilled nursing facility, intermediate care facility, or transitional care unit and 34% to a rehabilitation facility [51]. In each of these settings, extended use of VKAs is associated with a substantial economic burden due to the need for regular monitoring and dose adjustments. Use of parenteral agents can also contribute to the economic burden in these settings due to the nursing time required.

The fact that the new agents can be administered in a fixed, oral dose without the requirement for routine coagulation monitoring could help to improve adherence to guideline recommendations for thromboprophylaxis after THR or TKR. Furthermore, rivaroxaban and apixaban have demonstrated superiority compared with the LMWH enoxaparin, which suggests the potential to reduce the incidence of VTE with a similar safety profile compared with the established agents. Each of these advantages has potential pharmacoeconomic implications. (See Table 1) Although limited, pharmacoeconomic data are available for rivaroxaban and dabigatran; to date no comparable data are available for the direct factor Xa inhibitor apixaban.

### **5.1 Pharmacoeconomic analyses of dabigatran etexilate after THR or TKR**

Currently, although no available economic analysis indicates the potential impact of dabigatran in the US healthcare setting, analyses have been carried out from other national healthcare perspectives. Dabigatran has been compared with enoxaparin in two cost-effectiveness analyses in patients undergoing THR or TKR, from the perspective of the

Canadian Ministries of Health [52]. For patients undergoing THR, using results from the RE-NOVATE study, dabigatran 220 mg od was found to be cost saving compared with enoxaparin 40 mg od (for 28–35 days) [52]. Rates of VTE and bleeding were similar in both groups, but dabigatran was found to be less costly than enoxaparin, primarily because no nursing time is required for drug administration either in hospital or after discharge. Dabigatran thromboprophylaxis saved an estimated C\$593 over 10 weeks, C\$598 over 5 years, and C\$600 over patients' lifetimes after THR [52]. Compared with enoxaparin, dabigatran was also found to be cost saving in patients undergoing TKR, based on the results of the RE-MOBILIZE and RE-MODEL studies [52]. From the perspective of the Canadian Ministries of Health, dabigatran 220 mg od saved an estimated C\$420 compared with enoxaparin 30 mg bid over a 10-week period. Over 5 years and over patients' lifetimes, dabigatran was cost saving compared with enoxaparin 30 mg bid, but was less effective [52]. Compared with enoxaparin 40 mg od, dabigatran 40 mg od was cost saving by C\$11 over 10 weeks, C\$19 over 5 weeks, and C\$23 over patients' lifetimes [52]. Analyses from the UK National Health Service perspective indicate that dabigatran is cost saving compared with enoxaparin 40 mg od after THR or TKR [53]. More recently, the 150-mg od dabigatran dose has been shown to be cost saving in patients aged over 75 years and in patients with moderate renal impairment [54]. A budget impact model based on thromboprophylaxis costs in France estimated a cost saving of over 36,000 Euros per 1000 THR procedures [55].

## **5.2 Pharmacoeconomic analyses of rivaroxaban after THR or TKR**

The potential cost savings with rivaroxaban after THR or TKR have been evaluated in pharmacoeconomic analyses based on the RECORD data. The effect of improved efficacy with rivaroxaban and direct and indirect cost reductions associated with oral versus parenteral administration were assessed based on US healthcare costs. Based on the efficacy results of



the RECORD4 study in patients undergoing TKR, the impact of rivaroxaban 10 mg compared with enoxaparin 30 mg bid – the regimen most commonly used in North America – was assessed based on US healthcare costs [56]. As rivaroxaban was not yet approved in the United States at the time of the study, this analysis assumed a similar acquisition cost to enoxaparin 40 mg od (which is lower than the cost of the 30-mg bid regimen). Rivaroxaban was associated with a cost saving of US\$162 per patient for the duration of treatment, a saving driven primarily by the lower acquisition costs compared with enoxaparin 30 mg bid and reduced monitoring costs [56]. The reduced requirement for home nurse visits presents additional potential for cost savings [56].

The impact of rivaroxaban 10 mg od compared with enoxaparin 40 mg od after THR was evaluated based on the results of the RECORD1 study [57]. It was assumed that nurses spent 3 minutes per day administering enoxaparin and training patients to self-inject, and that the duration of hospital stay was 5 days. Assuming a nonsignificant difference in the incidence of symptomatic VTE, rivaroxaban was associated with a saving of US\$14.50 compared with enoxaparin. This saving was driven by reduced monitoring and administration costs, as well as the reduced incidence of VTE [57]. In a similar analysis based on the RECORD3 study after TKR, rivaroxaban was associated with a cost saving of US\$192 per patient (excluding drug costs), driven primarily by the reduced costs of hospitalization for symptomatic events [56]. Asymptomatic events were assumed to have no impact on healthcare costs [56]. These analyses excluded the potential healthcare cost savings due to a reduced incidence in the long-term sequelae of VTE, such as recurrent VTE or PTS, which, as discussed earlier, have a major impact on healthcare resources.

In patients undergoing THR, economic decision model analyses evaluated the long-term cost effectiveness of rivaroxaban compared with enoxaparin 40 mg od from the US perspective based on the individual RECORD1 and RECORD2 study results [56]. The model followed patients for 1 year after surgery. Efficacy and safety profiles during the study period were obtained from the published study results, and the incidence of VTE up to 90 days after surgery was extrapolated based on epidemiologic data [58,59]. Direct costs for treatment, major bleeding, and the duration of hospitalization were based on published data for the United States [20,60,61]. These analyses conservatively assumed that acquisition costs of rivaroxaban and enoxaparin 40 mg od were similar, and that no incremental nurse time or home visit costs were associated with subcutaneous enoxaparin injection [56]. In the 1-year economic model based on RECORD2, compared with short-duration (14 days) thromboprophylaxis with enoxaparin, extended-duration (35 days) thromboprophylaxis with rivaroxaban was associated with an incremental cost per symptomatic event avoided of US\$5945 [56]. In the 1-year economic model based on RECORD1, extended-duration thromboprophylaxis with both drugs resulted in a US\$82 cost saving with rivaroxaban, and a reduction of 6 symptomatic events per 1000 patients with rivaroxaban [56]. The main driver of these cost savings was the reduced cost of hospitalization for symptomatic events. Sensitivity analyses that included the indirect costs associated with home nursing time or time taken to train patients to self-administer enoxaparin further demonstrated that orally administered rivaroxaban has the potential to produce considerable cost savings compared with enoxaparin [56].

A more recent analysis evaluated the cost effectiveness of rivaroxaban compared with enoxaparin, from a U.S. payer's perspective using a decision-analytic model. [62] The model replicated short-term clinical outcomes from the phase III RECORD trials. The model also

included data on long-term complications from observational studies and direct medical costs for year 2010 over 1-year and 5-year time periods. Rivaroxaban was associated with cost savings of \$US 511.93 per patient and prevented an average of 0.0145 symptomatic VTE events per patient in THR and \$US 465.74 per patient and prevented an average 0.0193 symptomatic VTE events per patient in TKR. Additional sensitivity analysis showed cost savings ranging from \$US 133.96-629.57 for THR and \$US 293.01-848.68 in TKR patients and that the economic profile of rivaroxaban is further improved when the time horizon of the model is extended from 1 year to 5 years. [62]

Another study, conducted from the perspective of a Canadian healthcare system over a 5-year period, measured the cost effectiveness of VTE prevention after THR or TKR using rivaroxaban versus enoxaparin [63]. In patients undergoing THR, rivaroxaban was associated with 0.0061 fewer symptomatic VTE events, an increase in quality-adjusted life-years (QALYs; 0.0006) and cost savings of CN\$300 per patient. In patients undergoing TKR, rivaroxaban was associated with 0.0192 fewer symptomatic VTE events, a gain of 0.0018 QALYs, and a cost saving of CN\$129 per patient [63].

## **6.0 Conclusions**

The currently available anticoagulants, such as LMWHs and warfarin, require either parenteral administration or regular coagulation monitoring, both of which contribute substantially to the economic burden of thromboprophylaxis after THR or TKR. A number of characteristics of newly introduced target-specific anticoagulants to the market could potentially lead to important direct and indirect cost savings. These include ease of use (once or twice daily oral administration; a rapid onset of action, obviating the need for early admission or delayed discharge; a wider therapeutic window, eliminating the need for dose

adjustment and costly complications of subtherapeutic and supratherapeutic INRs; limited interactions with food and other drugs; and proven efficacy in reducing thromboembolic events. Potential reductions in the rate of VTE will lead to reduced costs associated with the treatment of VTE, the need for further in-patient care or rehospitalization, as well as direct and indirect costs of managing any associated long-term consequences. Oral agents will eliminate the costs associated with injectable agents. The considerable resource burden of routine coagulation monitoring, the direct and indirect cost burden to patients attending clinics, and the indirect cost to employers in lost productivity will be reduced. In addition, the new oral agents may lead to better adherence to guidelines, with the potential to further reduce the rate of VTE and its long-term consequences. Healthcare providers will need to be comfortable with the new agents and to be aware of specific product characteristics that may make them more or less appropriate for individual patients. However, the promise of improved coagulation control without the need for anticoagulation clinics may make these newer agents very attractive to payers as well as to healthcare providers.

## **7.0 Expert Opinion**

While traditional anticoagulants (e.g. warfarin, low molecular weight heparins) used for thromboprophylaxis are effective in reducing VTE rates after THR and TKR, they have limitations that result in complex administration and management and add to the overall cost of care. Newer oral anticoagulants have shown the potential to produce direct and indirect cost savings through reduced VTE rates and related long-term complications, reduced administration, management, and monitoring costs, and improved quality adjusted life years when compared to traditional agents. While dabigatran is not approved in the US for VTE prevention after THR or TKR and economic analysis to indicate the potential impact of dabigatran in the US healthcare setting is lacking, such analyses have been carried out from

other national healthcare perspectives. Analyses from the perspective of the Canadian Ministries of Health and from the perspective of the UK National Health Service have shown dabigatran to be less costly than enoxaparin after THR or TKR. At the present time, rivaroxaban is the only agent among the novel oral anticoagulants approved in the US for VTE prevention after THR or TKR. Most of the economic data pertinent to rivaroxaban for this indication is derived from pharmacoeconomic analyses based on the data from the phase III RECORD trials and based on US healthcare costs. From the US payer's perspective, Rivaroxaban has been shown to be cost saving compared to both the higher (30mg bid – regimen approved in US for TKR) and lower doses (40mg qd) of enoxaparin with savings ranging from \$US 511.93 per patient in THR and \$US 465.74 per patient in TKR. Extrapolating the results from this economic model to the number of THAs and TKAs performed annually in the US (773,000 based on 2006 data) indicates that considerable cost savings (\$US 360,218,000 – 395,776,000) could be attained by use of rivaroxaban for thromboprophylaxis after surgery.

While the new agents have shown the potential to reduce the cost burden on the healthcare system, most of these data and cost estimates to date have been modeled based on clinical outcomes derived from the published phase III clinical trials. As trial conditions and populations often differ from real-world settings, future research will need to focus on cost analyses driven by clinical outcomes measured on the performance of these agents in actual clinical practice. Additionally, any clinical and economic comparisons among the various new anticoagulants are based on indirect data and conclusions for specific agent selection based on these data must be drawn with caution. Therefore, additional research is needed to determine the place and value of each specific new anticoagulant on the cost-benefit scale. In

this era of rapidly escalating costs in the US health care system, factoring in economics of anticoagulants to guide therapy decisions has never been more relevant.

**Declaration of Interest**

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## 8.0 References

1. Baser O, Supina D, Sengupta N et al. Clinical and cost outcomes of venous thromboembolism in Medicare patients undergoing total hip replacement or total knee replacement surgery. *Curr Med Res Opin* 2011;27:423-29
2. Falck-Ytter Y, Francis CW, Johanson N, et al. Prevention of VTE in Orthopedic Surgery Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(suppl):e278S–e325S
3. Tapson VF. Acute pulmonary embolism. *N Engl J Med* 2008;358:1037-52
4. Kearon C. Natural history of venous thromboembolism. *Circulation* 2003;107:I22-I30
5. Centers for Medicare & Medicaid Services. State Medicaid Director Letter. 2008. Available at: [www.cms.hhs.gov/SMDL/downloads/SMD073108.pdf](http://www.cms.hhs.gov/SMDL/downloads/SMD073108.pdf) [Last accessed 14 July 2012]
6. Nutescu E. Characteristics of novel anticoagulants and potential economic implications. *Am J Manag Care* 2011;17:S27-S32
7. Warwick D, Samama MM. The contrast between venographic and clinical endpoints in trials of thromboprophylaxis in hip replacement. *J Bone Joint Surg Br* 2000;82:480-82
8. MacDougall DA, Feliu AL, Boccuzzi SJ, Lin J. Economic burden of deep-vein thrombosis, pulmonary embolism, and post-thrombotic syndrome. *Am J Health Syst Pharm* 2006;63:S5-S15
9. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med* 2004;350:2257-64



10. Edelsberg J, Ollendorf D, Oster G. Venous thromboembolism following major orthopedic surgery: review of epidemiology and economics. *Am J Health Syst Pharm* 2001;58(suppl 2):S4-S13
11. Ollendorf DA, Vera-Llonch M, Oster G. Cost of venous thromboembolism following major orthopedic surgery in hospitalized patients. *Am J Health Syst Pharm* 2002;59:1750-54
12. Dobesh PP. Economic burden of venous thromboembolism in hospitalized patients. *Pharmacotherapy* 2009;29:943-53
13. Bullano MF, Willey V, Hauch O, et al. Longitudinal evaluation of health plan cost per venous thromboembolism or bleed event in patients with a prior venous thromboembolism event during hospitalization. *J Manag Care Pharm* 2005;11:663-73
14. Oster G, Ollendorf DA, Vera-Llonch M, et al. Economic consequences of venous thromboembolism following major orthopedic surgery. *Ann Pharmacother* 2004;38:377-82
15. \*Warwick D, Friedman RJ, Agnelli G, et al. Insufficient duration of venous thromboembolism prophylaxis after total hip or knee replacement when compared with the time course of thromboembolic events: findings from the Global Orthopaedic Registry. *J Bone Joint Surg Br* 2007;89:799-807. Data from >15,000 registry patients showing that the majority of VTE events occur after hospital discharge and that worldwide, patients are not receiving prophylaxis for a sufficient period of time after discharge.
16. Buller HR, Sohne M, Middeldorp S. Treatment of venous thromboembolism. *J Thromb Haemost* 2005;3:1554-60

17. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis. American College of Chest Physicians evidence-based clinical practice guidelines (9th edition). Chest 2012;141 (suppl):e419S-e494S
18. O'Brien JA, Caro JJ. Direct medical cost of managing deep vein thrombosis according to the occurrence of complications. Pharmacoeconomics 2002;20:603-15
19. Sullivan SD, Kahn SR, Davidson BL et al. Measuring the outcomes and pharmacoeconomic consequences of venous thromboembolism prophylaxis in major orthopaedic surgery. Pharmacoeconomics 2003;21:477-96
20. Spyropoulos A, Lin J. Direct medical costs of venous thromboembolism and subsequent hospital readmission rates: an administrative claims analysis from 30 managed care organizations. J Manag Care Pharm 2007;13:475-86
21. Kahn SR. The post-thrombotic syndrome: the forgotten morbidity of deep venous thrombosis. J Thromb Thrombolysis 2006;21:41-48
22. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. J Thromb Thrombolysis 2009;28:465-76
23. Caprini JA, Botteman MF, Stephens JM et al. Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. Value Health 2003;6:59-74
24. Davidson BL, Sullivan SD, Kahn SR et al. The economics of venous thromboembolism prophylaxis: a primer for clinicians. Chest 2003;124:393S-396S

25. Ageno W, Gallus AS, Wittkowsky A, et al. Oral Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, American College of Chest Physicians evidence-based clinical practice guidelines (9th edition). Chest 2012;141(suppl):e44S-e88S
26. Nutescu EA, Bathija S, Sharp LK, et al. Anticoagulation patient self-monitoring in the United States: considerations for clinical practice adoption. Pharmacotherapy 2011;31:1232-49
27. Menzin J, Boulanger L, Hauch O, et al. Quality of anticoagulation control and costs of monitoring warfarin therapy among patients with atrial fibrillation in clinic settings: a multi-site managed-care study. Ann Pharmacother 2005;39:446-51
28. Anderson RJ. Cost analysis of a managed care decentralized outpatient pharmacy anticoagulation service. J Manag Care Pharm 2004;10:159-65
29. \*van Walraven C, Jennings A, Oake N, et al. Effect of study setting on anticoagulation control: a systematic review and metaregression. Chest 2006;129:1155-66. A metaregression of the published literature reveals that patients receiving warfarin therapy in community practice spend significantly less time in therapeutic range than do patients attending anticoagulation clinics or in clinical trials.
30. Lieberman JR, Hsu WK. Prevention of venous thromboembolic disease after total hip and knee arthroplasty. J Bone Joint Surg Am 2005;87:2097-112
31. Matzsch T. Thromboprophylaxis with low-molecular-weight heparin: economic considerations. Haemostasis 2000;30(suppl 2):141-45

32. Menzin J, Colditz GA, Regan MM, et al. Cost-effectiveness of enoxaparin vs low-dose warfarin in the prevention of deep-vein thrombosis after total hip replacement surgery. *Arch Intern Med* 1995;155:757-64
33. Bergqvist D, Lindgren B, Mätzsch T. Comparison of the cost of preventing postoperative deep vein thrombosis with either unfractionated or low molecular weight heparin. *Br J Surg* 1996;83:1548-52
34. Stangier J, Clemens A. Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. *Clin Appl Thromb Hemost* 2009;15(suppl 1):9S-16S
35. Boehringer Ingelheim International GmbH. Pradaxa (dabigatran etexilate) summary of product characteristics. 2010. Available at: [www.medicines.org.uk/emc/medicine/20760](http://www.medicines.org.uk/emc/medicine/20760) [Last accessed 14 July 2011]
36. \*Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor Xa inhibitors in development. *Clin Pharmacokinet* 2009;48:1-22. A pharmacodynamic and pharmacokinetic profile of the new oral anticoagulants shows that they can be given in fixed doses without the need for routine coagulation monitoring.
37. \*\*Eriksson BI, Dahl OE, Rosenthal N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;370:949-56. The RE-NOVATE trial showed dabigatran to be as effective as enoxaparin in patients after total hip replacement, with a similar safety profile.

38. \*\*Eriksson BI, Dahl OE, Rosencher N, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007;5:2178-85. In RE-MODEL, in 2076 patients undergoing total knee replacement, dabigatran 220 or 250 mg was at least as effective as enoxaparin for the prevention of VTE and had a similar safety profile.
39. \*\*The RE-MOBILIZE Writing Committee. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* 2009;24:1-9. In RE-MOBILIZE, at doses of 150 or 220 mg once daily, dabigatran was less effective than enoxaparin 30 mg bid, the North American regimen.
40. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2011
41. \*\*Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008;358:2765-75. In RECORD1, 10 mg of enoxaparin once daily was significantly more effective than 40 mg of enoxaparin once daily in preventing a composite of deep vein thrombosis, pulmonary embolism, or death from any cause at 36 days post total hip replacement surgery, with a similar safety profile.
42. \*\*Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776-86. In the RECORD3 trial, rivaroxaban was superior to enoxaparin for thromboprophylaxis after total knee replacement surgery, with similar rates of bleeding.

43. \*\*Turpie AG, Lassen MR, Davidson BL, et al. RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet* 2009;373:1673-80. Oral rivaroxaban 10 mg once daily for 10–14 days was significantly superior to enoxaparin 20 mg bid for the prevention of venous thromboembolism after total knee replacement surgery.
44. \*\*Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008;372:31-9. In RECORD2, in more than 2500 patients undergoing total hip replacement surgery, extended thromboprophylaxis with rivaroxaban (31–39 days) was significantly more effective for prevention of venous thromboembolism than enoxaparin 40 mg once daily for 10–14 days.
45. Turpie AGG, Lassen MR, Eriksson BI, et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. *Thromb Haemost* 2011;105:444-53
46. Raghavan N, Frost CE, Yu Z, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. *Drug Metab Dispos* 2009;37:74-81
47. Carreiro J, Ansell J. Apixaban, an oral direct Factor Xa inhibitor: awaiting the verdict. *Expert Opin Investig Drugs* 2008;17:1937-45
48. \*\*Lassen MR, Raskob GE, Gallus A, et al. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med* 2009;361:594-604. When compared with 30 mg enoxaparin bid for prevention of venous thromboembolism after

total knee replacement, 2.5 mg apixaban bid failed to meet the criteria for non-inferiority but was associated with lower rates of clinically relevant bleeding.

49. \*\*Lassen MR, Raskob GE, Gallus A, et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet* 2010;375:807-15. In ADVANCE-2, apixaban 2.5 mg bid was more effective than 40 mg/d enoxaparin in preventing venous thromboembolism in patients undergoing total knee replacement surgery, with a similar incidence of bleeding.
50. \*\*Lassen MR, Gallus A, Raskob GE, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med* 2010;363:2487-98. In ADVANCE-3, apixaban was associated with lower rates of venous thromboembolism in more than 5000 total hip replacement patients, compared with enoxaparin.
51. de Pablo P, Losina E, Phillips CB, et al. Determinants of discharge destination following elective total hip replacement. *Arthritis Rheum* 2004;51:1009-17
52. Bradley-Kennedy C, Wolowacz SE, Roskell NS, Plumb JM. Cost-effectiveness of dabigatran etexilate in Canada for the primary prevention of venous thromboembolism in patients undergoing total hip replacement surgery. *J Thromb Haemost* 2009;7:786
53. Wolowacz SE, Roskell NS, Maciver F, et al. Economic evaluation of dabigatran etexilate for the prevention of venous thromboembolism after total knee and hip replacement surgery. *Clin Ther* 2009;31:194-212
54. Wolowacz SE, Roskell NS, Plumb JM, et al. Economic evaluation of dabigatran etexilate for the prevention of venous thromboembolism in patients aged over 75 years or with moderate renal impairment undergoing total knee or hip replacement. *Thromb Haemost* 2010;103:360-71

55. Bouee S, Zufferey P, Fagnani F. Budget impact analysis of Pradaxa thromboprophylaxis after total hip or total knee replacement. *Therapie* 2009;64:249-57
56. Kwong LM. Cost-effectiveness of rivaroxaban after total hip or total knee arthroplasty. *Am J Manag Care* 2011;17:S22-S26
57. Friedman R, Lees M, Sengupta N, Haas S. Rivaroxaban for prevention of venous thromboembolism after total hip replacement: impact on healthcare costs based on the RECORD1 study [abstract]. *J Bone Joint Surg Br.* 2008;92B(suppl 2):288
58. Kwong LM, Diamantopoulos A, Forster F, et al. Will rivaroxaban be cost-effective for prevention of venous thromboembolism after total hip replacement in US patients? *Blood (ASH Annual Meeting Abstracts)* 2008;112:Abstract 1290
59. Quinlan DJ, Eikelboom JW, Dahl OE, et al. Association between asymptomatic deep-vein thrombosis detected by venography and symptomatic venous thromboembolism in patients undergoing elective hip or knee surgery. *J Thromb Haemost* 2007;5:1438-43
60. McGarry LJ, Thompson D, Weinstein MC, Goldhaber SZ. Cost effectiveness of thromboprophylaxis with a low-molecular-weight heparin versus unfractionated heparin in acutely ill medical inpatients. *Am J Manag Care* 2004;10:632-42
- 61 . \*Friedman RJ, Gallus AS, Cushner FD, et al. Physician compliance with guidelines for deep-vein thrombosis prevention in total hip and knee arthroplasty. *Curr Med Res Opin* 2008;24:87-97. Three-month data from 8160 patients with total hip replacement showed that a large proportion did not receive thromboprophylaxis in accordance with American College of Chest Physicians guidelines.
62. Duran A, Sengupta N, Diamantopoulos A, Forster F, Kwong L, Lees M. Cost effectiveness of rivaroxaban versus enoxaparin for prevention of post-surgical venous



thromboembolism from a U.S. payer's perspective. *Pharmacoeconomics*. 2012;30(2):87-101.

- 63 . Diamantopoulos A, Lees M, Wells PS, et al. Cost-effectiveness of rivaroxaban versus enoxaparin for the prevention of postsurgical venous thromboembolism in Canada. *Thromb Haemost* 2010;104:760-70

**Table 1: Potential Resource Utilisation Benefits of New Oral Anticoagulants**

- Decreased incidence of VTE vs LMWH
- Decreased costs of hospitalizations for symptomatic VTE vs LMWH
- Decrease time to train patient on SC injection technique vs LMWH
- Decrease monitoring costs vs warfarin (INR)
- Decrease nursing time in-house or after discharge for drug administration vs LMWH (SC)
- Decrease requirement for nursing home visits vs warfarin and/or LMWH
- Increased quality adjusted life years vs LMWH