

## Review Article

# Efficacy and safety of dabigatran in prevention of venous thromboembolism in patients undergoing major orthopedic surgeries: a review

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## ABSTRACT

Thromboprophylaxis with anticoagulants can significantly reduce the risk of patients developing symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE) and VTE related mortality post major orthopedic surgeries like total hip and knee replacement surgeries. Dabigatran, a directly acting oral anticoagulant (DOAC) and direct thrombin inhibitor, is an available option for VTE prophylaxis having comparable efficacy to low molecular weight heparins (LMWH), other DOACs and Warfarin, once daily dosing, and comparable safety and bleeding risk to both LMWH and Aspirin. Dabigatran is currently the only DOAC with an available and marketed reversing agent. A review of Dabigatran's clinical efficacy and safety is presented here. Therefore, Dabigatran represents a balanced thromboprophylaxis option for VTE prevention in patients undergoing major orthopedic surgeries.

**Keywords:** Dabigatran, Thrombin, Direct oral anticoagulants, Total hip and knee replacement, THR, Anticoagulants, Venous thromboembolism, Deep vein thrombosis, Pulmonary embolism

## INTRODUCTION

Orthopedic surgeries are high risk factors for developing postoperative DVT and VTE.

In absence of thromboprophylaxis, confirmed DVT post lower limb orthopedic surgery is 40–60% with 10–14% progressing to symptomatic VTE, and around 5% showing PE, all usually seen post discharge from hospital.<sup>1</sup> One third are proximal DVTs seen more with hip surgeries with greater risk to embolize. The cumulative risk of venous thromboembolism lasted for up to three months (median 21–34 days) and one month (median 12–20 days) after hip and knee surgery respectively.<sup>2</sup>

Increased VTE risk post orthopedic surgeries can be due to immobilization, prolonged bed rest leading to venous stasis, surgical manipulations causing endothelial trauma and hyper-coagulable state, with presence of medical comorbidities increasing risk further.<sup>1,3</sup>

Contrary to perception, autopsy studies indicate similar incidence of PE in Asian and Western countries.<sup>4</sup> A multicentric study for the evaluation of patients at risk for venous thromboembolism in the acute hospital care setting (ENDORSE- cross-sectional survey in Asian countries: India, Thailand, Pakistan, and Bangladesh), reported similar VTE risk in surgical patients ranging from 44% to 62%, which was similar to the proportion, reported for all countries studied (overall: 64%; range: 44%–80%).<sup>5</sup>

With routine VTE prophylaxis in orthopaedic patients, fatal PE is uncommon, and the rates of symptomatic VTE within three months can be reduced to as low as 1-2%.<sup>3</sup> Pharmacoprophylaxis options for VTE prevention recommended include low molecular weight heparins (LMWH) LMWH, fondaparinux, direct (or newer/non-vitamin K) oral anticoagulants (DOACs/NOACs - dabigatran, apixaban, rivaroxaban), low dose unfractionated heparin (LDUH), adjusted-dose vitamin K antagonist (Warfarin), and aspirin (AAOS 2011<sup>6</sup> and ACCP 2012).<sup>7</sup>

Aspirin is not recommended to be used alone or as the only thromboprophylaxis agent in any patient group as other agents (LMWH, DOACs and warfarin) are more effective for prevention of VTE (ACCP 2008, SIGN 2010 updated 2015).<sup>8,9</sup> LMWH are conventionally first line anticoagulants in hospitalized patients, however being injectable, they do not represent a compliant option for patients once discharged from hospital. Warfarin has a slow onset and offset and is known to be associated especially in Asian populations with increased risk of intracranial hemorrhage (ICH), requires meticulous INR monitoring, and has associated high food-drug interactions.<sup>4,10</sup>

ACCP recommends that in patients undergoing major orthopaedic surgery who decline or are uncooperative with injections or a mechanical device like IPCD, the DOACs dabigatran or apixaban and if unavailable, rivaroxaban or adjusted-dose VKA should be used rather than alternative forms of prophylaxis.<sup>7</sup>

DOACs currently represent the most appropriate and balanced option for VTE risk reduction in patients discharged from hospital.

**ORAL DIRECT THROMBIN INHIBITOR: DABIGATRAN**

Dabigatran is an oral direct thrombin inhibitor approved for VTE prophylaxis in orthopedic surgeries. Thrombin (IIa) is the key and central factor in the coagulation pathway. Table 1 shows mechanism of action of dabigatran as well as the dosing and treatment duration of dabigatran. Dabigatran acts on both free as well as fibrin bound thrombin as it has a different active binding site from the exosites used by fibrin and antithrombin, while LMWH act only on free thrombin.<sup>14</sup>

**Table 1: Dabigatran action and dosing.**

Dabigatran: mechanism of action <sup>11-13</sup>	Dose <sup>16</sup>	Duration
Inhibits the following actions of thrombin <ul style="list-style-type: none"> <li>• Conversion of fibrinogen to fibrin</li> <li>• Activation of Factor XIII which cross links fibrin</li> <li>• Feedback activation of factor V, VII and XI</li> <li>• Binding to thrombomodulin to activate protein C</li> <li>• Activation of platelet aggregation</li> <li>• Fibroblast proliferation<sup>18</sup></li> </ul>	VTE prophylaxis for Orthopedic surgeries: <ul style="list-style-type: none"> <li>• Once daily dose of 220 mg (2 capsules of 110mg).</li> <li>• Initiation, if within 1-4 hours of surgery is recommended with 1 capsule.</li> <li>• It can be taken irrespective of food and the capsule is to be swallowed intact.</li> </ul>	TKR: 10-14 days  THR: 28-35 days

Onset of Dabigatran action occurs in half to 1 hour with a half-life of 12-14 hours. It does not show CYP dependent metabolism and drug interactions so can be given even in moderate hepatic impairment, however interacts with Pgp inhibitors and due to majority renal clearance, should not be given if creatinine clearance falls below 30ml/min (<50 ml/min if concomitant Pgp inhibiting drugs are being co-administered). Dabigatran is contraindicated in patients with active pathological bleeding, mechanical or prosthetic valves and history of hypersensitivity to Dabigatran and does not have controlled studies in pregnancy or lactation to recommend its use.<sup>15,16</sup>

**CLINICAL EFFICACY AND SAFETY OF DABIGATRAN**

Three phase III studies compare Dabigatran to standard dose of Enoxaparin 40mg SC OD to assess VTE rate and bleeding risk in patients undergoing Hip and Knee replacement surgery (Table 2). Patients were treated for

6-10 days post TKR and 28-35 days post THR with a 3 month follow up period in all 3 studies. The REMODEL (TKR) and RENOVATE (THR) studies showed comparable efficacy and safety in VTE prevention and bleeding risk of Dabigatran doses to standard 40mg SC Enoxaparin.<sup>17,18</sup> In RENOVATE II, though the total VTE incidence as well as bleeds (major and clinically relevant non major - CRNM bleeds) were comparable to Enoxaparin 40mg OD, the rate of proximal DVT, major VTE and VTE related mortality was significantly lower than Enoxaparin (2.1 vs 3.9%; P=0.04 and 2.2 vs 4.2%; P=0.03 respectively).<sup>19</sup> This reduced risk of major VTE and VTE-related mortality was also seen in the Indian population sub-analyzed in RENOVATE II : 179 Indian patients (91 Dabigatran; 88 Enoxaparin : 7.9% vs 9.9%). This showed that in the normal clinical setting, Dabigatran was an effective and well tolerated option to LMWH in patients who had undergone THR and TKR and may offer greater convenience in the outpatient post discharged patients.<sup>20</sup>

**Table 2: Dabigatran vs Enoxaparin studies (data in %: \*significant)**

Study	Total VTE		Symptomatic DVT		Symptomatic PE		Major VTE+ all cause mortality		Major bleed		CRNM bleed	
	Dabi	Enoxa	Dabi	Enoxa	Dabi	Enoxa	Dabi	Enoxa	Dabi	Enoxa	Dabi	Enoxa
<b>REMODEL<sup>17</sup></b> (2007) N=2086 TKR	40.5 (150mg) 36.4 (220mg)	37.7	0.4 (150mg) 0.1 (220mg)	1.2	0.1 (150mg) 0 (220mg)	0.1	3.8 (150mg) 2.6 (220mg)	3.5	1.3 (150mg) 1.5 (220mg)	1.3	6.8 (150mg) 5.9 (220mg)	5.3
<b>RENOVATE I<sup>18</sup></b> (2007) N=3463 THR	8.6 (150mg) 6.0 (220mg)	6.7	0.8 (150mg) 0.5 (220mg)	0.1	0.1 (150mg) 0.4 (220mg)	0.3	4.3 (150mg) 3.1 (220mg)	3.9	1.3 (150mg) 2.0 (220mg)	1.6	4.7 (150mg) 4.2 (220mg)	3.5
<b>RENOVATE II<sup>19</sup></b> (2011) N=2055; THR	7.7 (220mg)	8.8	0 (220mg)	0.4	0.1 (220mg)	0.2	2.2* (220mg)	4.2	1.4 (220mg)	0.9	2.3 (220mg)	2

Dabigatran and Warfarin have been compared in two studies (RECOVER and RECOVER II) to assess risk of VTE recurrence and bleeding risk in patients being treated for acute VTE.<sup>21</sup> In both studies, Dabigatran was found to have similar effects on VTE recurrence and a lower risk of bleeding compared with warfarin in 2 studies (RECOVER I,II: VTE Rate and deaths during 6 months of treatment : 2.4% vs 2.2% while major or CRNM bleeding rate: 5.3% vs 8.5%; total bleeding rate: 16.1% vs 22.2% for Dabigatran vs Warfarin with more than twice as many ICH cases in Warfarin group).<sup>21</sup>

Various metanalysis have also been published for DOACs. Comparable efficacy is seen among DOACs in treatment and prevention of recurrence of VTE however Dabigatran was associated with a significantly lower risk of 'major or CRNM bleed' compared with rivaroxaban and edoxaban.<sup>22</sup> and when compared with Enoxaparin, the relative risk of clinically relevant bleeding was higher with rivaroxaban (OR 1.25), and similar with Dabigatran (OR 1.12).<sup>23</sup>

When comparing apixaban, aspirin, Dabigatran, rivaroxaban, warfarin and placebo, the risk of the composite efficacy outcome (VTE and VTE-related death) seen on metanalysis was significantly lower with the DOACs and warfarin INR 2.0–3.0 compared with aspirin, with Dabigatran and apixaban being associated with comparable rate of major and CRNM bleeds to Aspirin and significantly lower than Warfarin, while rivaroxaban having higher and comparable rate of major and CRNM bleeds to Aspirin and Warfarin respectively.<sup>24</sup>

The efficacy and safety of DOACs in the geriatric population (10 RCTs included 25,031 elderly participants >75 years) showed that DOACs did not cause excess bleeding (9.3% vs 8.7%; OR = 1.07 for major/CRNM bleeds of Dabigatran versus conventional therapy: vitamin K antagonists, LMWH, aspirin, placebo) and were associated with equal or greater efficacy than conventional therapy.<sup>22</sup> (Overall DOACs resulted in a significantly lower risk of VTE or VTE-related death than conventional therapy (3.7% vs 7.0%; OR 0.45) in geriatric age group.

Dabigatran is the only DOAC to have a reversible agent currently available in the market: Idarucizumab. Idarucizumab in studies showed a median maximum 100% percentage reversal of Dabigatran (assessed by diluted thrombin time/ecarin clotting time) with a median time to the cessation of bleeding of 2.5 hours and a median time to surgery of 1.6 hours with 93% normal hemostasis.<sup>25</sup>

## CONCLUSION

The DOACs or NOACs (Newer Oral Anticoagulants) represent a more balanced, compliant, and effective approach for VTE preventions in patients undergoing

lower limb orthopedic surgery especially for patients discharged from hospital. Dabigatran in comparison to Enoxaparin (LMWH) has shown comparable efficacy with better risk reduction of proximal DVT, major VTE and VTE related mortality with the added advantage of oral dosing. Dabigatran efficacy is comparable to Warfarin as well as the other NOACs, and significantly better efficacy than Aspirin, in VTE prevention. Safety and bleeding risk of Dabigatran is similar to both LMWH and aspirin and lower than warfarin. Dabigatran has an effective available reversible agent. Therefore, Dabigatran can be a practical option for orthopedic surgeons for VTE prevention in patients undergoing lower limb orthopedic surgeries like TKR and THR.

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