

Expanding horizons of anticoagulant therapy: Dabigatran etexilate a novel oral anticoagulant

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ABSTRACT

Thrombo-embolic disease is a major challenging clinical problem associated with significant mortality and morbidity. Anticoagulation with the existing heparin products and vitamin K antagonist (VKA) anticoagulants are still the mainstay of management. However, due to the risk of bleeding and well-documented drawbacks, the quest for a novel oral anticoagulant has led to the clinical development of dabigatran etexilate. Dabigatran etexilate is a direct thrombin (IIa) inhibitor which has recently been approved in India for prevention of venous thromboembolic events (VTE) in patients who have undergone major orthopaedic (total knee or hip replacement) surgery and for prevention of stroke, systemic embolism and reduction of vascular mortality in adult patients with atrial fibrillation. Thus dabigatran etexilate is a promising alternative to the current heparin products and VKAs in patients who require long-term oral anticoagulation.

Keywords: Dabigatran etexilate, Direct thrombin inhibitor, Novel anticoagulant, Stroke prevention, Atrial fibrillation, Venous thromboembolism, Orthopaedic surgery

INTRODUCTION

Anticoagulation is still the mainstay in the management of thrombo-embolic disorders. Advanced understanding of the cascade and molecular mechanisms of blood coagulation has led to the discovery of novel anticoagulants for the prevention and treatment of thrombo-embolic disorders in order to overcome the limitations of existing conventional heparin products and Vitamin K antagonists (VKA).^{1,2} These limitations include bleeding complications, narrow therapeutic index, inter-individual patient variability, multiple drug and food interactions, longer half-life, lower patient compliance and need for regular anticoagulation laboratory monitoring which limits the clinical effectiveness and safety of conventional anticoagulants.^{2,3}

Dabigatran etexilate a novel oral anticoagulant, which directly targets and inhibits thrombin, is the focus of research. Dabigatran has several advantages, which includes target specific action, better pharmacokinetic profile and predictable anticoagulant response, without the need for therapeutic monitoring.²⁻⁶ Dabigatran etexilate has been evaluated for its safety and efficacy in several large-scale clinical trials. This article highlights the pharmacology, clinical evidences and regulatory status of Dabigatran etexilate with current approved indications in India.

PHARMACOLOGY: DABIGATRAN ETEXILATE

*Chemical structure*²

Dabigatran etexilate is the orally active prodrug of the molecule “Dabigatran” (Figure 1). Dabigatran belongs to a new structural class of non-peptidic inhibitors employing a trisubstituted benzimidazole as the central scaffold and 4-amidinophenylalanine as a mimetic of arginine which exhibits a specific, competitive, and reversible inhibition of thrombin.^{2,4-6}

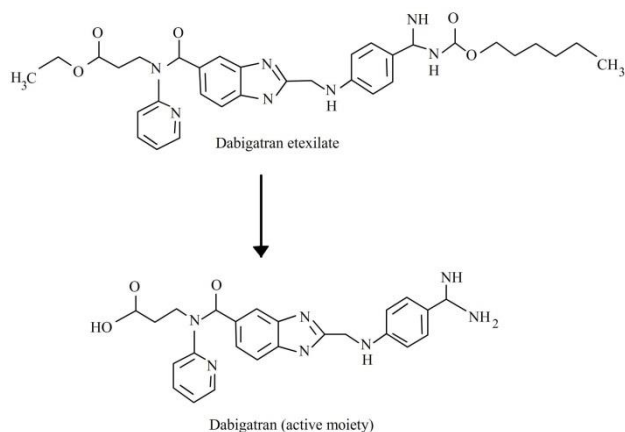


Figure 1: Chemical structure of dabigatran etexilate and its active moiety.

Mechanism of action

Thrombin plays a key central role in the blood coagulation cascade. Targeted inhibition of thrombin within the coagulation cascade not only attenuates fibrin formation, but also reduces thrombin generation and limits platelet activation. Dabigatran is a novel direct thrombin (IIa) inhibitor. It is a potent, non-peptidic molecule, competitive and reversible inhibitor of thrombin which exhibits a strong thrombin inhibitory activity as well as has a high selectivity to thrombin.^{5,6} It is effective in inhibiting both circulating and clot-bound thrombin.^{5,6} By inhibiting thrombin, Dabigatran prevents the conversion of fibrinogen into fibrin, positive feedback amplification of coagulation activation, cross-linking of fibrin monomers, platelet activation, and inhibition of fibrinolysis.⁷

Pharmacokinetics

Dabigatran etexilate is a prodrug that is rapidly converted to active moiety “Dabigatran”⁸ in the blood and liver with peak plasma levels and maximal anticoagulant effects achieved in 2-3 hours following oral administration. The half-life ($t_{1/2}$) of the drug ranges between 12-17 hours. The predictable pharmacokinetic profile of dabigatran supports a fixed-dose regimen without the need for routine coagulation. Dabigatran etexilate and dabigatran are neither metabolized by, nor induce or inhibit cytochrome P450 drug metabolizing enzymes.^{6,8}

Dabigatran is predominantly excreted unchanged via the kidneys (~80%) with the remainder eliminated via the bile⁷, thus reduced renal function results in elevated

plasma levels and prolonged half-life. Patients with mild renal impairment, do not require dose adjustment while in moderate renal impairment (creatinine clearance 30–50 mL/min), lower dose can be used. However it is absolutely contraindicated in patients with severe renal impairment (creatinine clearance less than 30 mL/min).^{6,8}

CLINICAL TRIAL EVIDENCES

1. Stroke prevention in atrial fibrillation

The clinical evidence for dabigatran etexilate in stroke prevention in atrial fibrillation (AF) has been established from landmark RE-LY⁹ trial. RE-LY was a phase III, multicenter, prospective, randomized, open-label, blinded, endpoint-adjudication trial in 18,113 patients with non-valvular AF at risk of stroke.⁹

RE-LY trial assessed the efficacy and safety of two fixed doses of dabigatran etexilate (110 or 150 mg twice a day), with adjusted-dose warfarin targeted international normalized ratio (INR) of 2 to 3.⁹ Dabigatran etexilate 110 mg twice a day was non-inferior to warfarin with respect to the primary end point of all stroke (ischemic or hemorrhagic) or systemic embolism, with event rates of 1.54% and 1.71% per year⁹, respectively (non-inferiority $P < 0.001$) and 1.11% per year with dabigatran etexilate 150 mg twice a day ($P < 0.001$ for superiority, $P < 0.001$ for non-inferiority).^{9,10,11} Dabigatran etexilate 150 mg twice a day was superior to warfarin for preventing stroke of all types, ischemic (25%) or hemorrhagic (74%) stroke, disabling or fatal stroke, and death (15%) from vascular causes.⁹⁻¹¹

The events of major bleeding were significantly lower with dabigatran etexilate 110 mg twice a day (2.87% per year, $P = 0.003$) compared with warfarin (3.57% per year), whereas the events of major bleeding with dabigatran etexilate, 150 mg twice a day (3.32% per year) was similar to warfarin.⁹⁻¹¹

Sub-analysis of RE-LY in Asian¹² population, also demonstrates consistently superior efficacy of dabigatran etexilate (150 mg) compared to warfarin.¹²

2. Secondary prevention in acute coronary syndrome

It has been evaluated in RE-DEEM¹³ study, phase II double-blind, placebo-controlled, dose-escalation study in patients with Acute Coronary Syndrome (ACS). Dabigatran etexilate in conjunction with (aspirin and clopidogrel) anti-platelet dual therapy significantly reduced coagulation activity in patients with recent myocardial infarction with a dose-dependent increase in bleeding events.¹³ Thus RE-DEEM study opened the doorway for a larger definitive phase 3 trial of dabigatran in prevention of recurrent events after ACS. It is uncertain whether a large phase 3 trial is being planned till date.

3. Primary prevention of venous thromboembolic (VTE) events

The clinical evidences for dabigatran etexilate in primary prevention of VTE in major orthopaedic surgery have been established from RENOVA¹⁴, REMODEL¹⁵, REMOBILIZE¹⁶ and RENOVA II¹⁷ trials. The REMOBILIZE trial indicated that dabigatran etexilate 150 mg or 220 mg once daily over 12-15 days of treatment, was not as effective to North American enoxaparin 30 mg twice daily regimen in preventing total VTE and all-cause mortality in patients undergoing unilateral Total Knee Replacement (TKR) surgery.^{16,18} However, the REMODEL study demonstrated that over 6-10 days of treatment, dabigatran etexilate 150 mg or 220 mg once daily was non-inferior to enoxaparin (40 mg once daily) for the prevention of VTE in patients undergoing TKR surgery.^{15,18} The incidence of major bleeding and overall adverse events did not differ significantly between either dose of dabigatran etexilate and enoxaparin.^{15,18} In RE-NOVATE trial, similar findings were documented in patients who underwent Total Hip Replacement (THR) surgery and used extended VTE prophylaxis (for 28-35 days).^{14,18} The RE-NOVATE II trial also demonstrated that extended prophylaxis with dabigatran etexilate 220 mg once daily was as effective as subcutaneous enoxaparin 40 mg once daily in reducing the risk of VTE after THR surgery, and superior to enoxaparin in reducing the risk of major VTE, with similar safety profiles.^{17,18}

4. Treatment and secondary prevention of venous thromboembolic events

The clinical evidences for dabigatran etexilate in the treatment of acute VTE have been established from RECOVER¹⁹ and RECOVER II²⁰ trials. RECOVER¹⁹ was a randomized, double-blind, non-inferiority trial of dabigatran etexilate 150 mg twice daily versus warfarin (target INR 2 to 3) in the treatment of acute VTE for 6 months. The trial reported that a fixed dose of dabigatran etexilate was as effective as warfarin in the treatment of acute VTE with hazard ratio in dabigatran for recurrent VTE 1.10 (95% CI, 0.65 to 1.84) and had similar safety profile to that of warfarin.^{18,19} RE-COVER II²⁰ as well documented and substantiated that, efficacy of dabigatran etexilate was non-inferior to warfarin with lower risk for major bleeding in the treatment of VTE for six months.^{18,20,21}

Recently RE-MEDY²² and RE-SONATE²², two paired randomized study also demonstrated the effectiveness of extended use of dabigatran in the treatment of VTE.^{22,23}

REGULATORY STATUS

U.S Food and Drug Administration (USFDA): On October 20, 2010, USFDA approved dabigatran etexilate 150 mg BID for prevention of stroke in patients with

AF.²⁴ It is not yet approved for the prevention and treatment of acute VTE in United States.

European Medicines Agency (EMA): On March 18, 2008, EMA approved dabigatran etexilate for the prevention of thromboembolic disease following hip or knee replacement surgery and in August 2011 approved it for prevention of stroke in non-valvular AF patients.²⁵ Currently, dabigatran etexilate is under process for approval in acute VTE and prevention of recurrent VTE.

Drug Controller General of India (DCGI): On December 2011, DCGI approved dabigatran etexilate for prevention of stroke in patients with AF.²⁶ Recently on 11th February 2013, it got approved for primary prevention of VTE after major orthopaedic surgery.²⁶

INDICATIONS

Approved indications in India are²⁶

1. Dabigatran etexilate is indicated for prevention of stroke, systemic embolism and reduction of vascular mortality in adult patients with AF.²⁶
2. Dabigatran etexilate is indicated for prevention of VTE events in patients who have undergone major orthopaedic (total knee or hip replacement) surgery.²⁶

DOSAGE AND ADMINISTRATION

Dose-Adults²⁷⁻³⁰

1. Prevention of stroke in AF: The recommended daily dose of Dabigatran etexilate is 300 mg taken orally as 150 mg hard capsules twice daily (75 mg twice a day for patients with moderate renal impairment 30-50 mL/min creatinine clearance).²⁷⁻³⁰

2. Prevention of VTE after major orthopaedic surgery: The recommended dose of Dabigatran etexilate is 220 mg once daily taken as 2 capsules of 110 mg. (Patients with moderate renal impairment have an increased risk for bleeding, the recommended dose is 150 mg once a day, taken as 2 capsules of 75 mg).²⁷⁻³⁰

A. Prevention of VTE following knee replacement surgery: Starting dose of 110 mg 1-4 hours after surgery and continued with 220 mg once daily thereafter for a total of 10 days.²⁷⁻³⁰

B. Prevention of VTE following hip replacement surgery: Starting dose of 110 mg 1-4 hours after surgery and continued with 220 mg once daily thereafter for a total of 28-35 days.²⁷⁻³⁰

ADVERSE EFFECTS

Most frequent adverse effects documented are bleeding and gastrointestinal events. The common adverse effects documented in clinical studies are anaemia, epistaxis, gastrointestinal haemorrhage, abdominal pain, diarrhoea,

dyspepsia, and nausea, hepatic function abnormal and urogenital haemorrhage.^{9,10,27-30}

CONTRAINDICATIONS

It is contraindicated in patients with known hypersensitivity to dabigatran or dabigatran etexilate, severe renal impairment with creatinine clearance less than 30ml/min, haemorrhagic manifestations with bleeding diathesis and concomitant treatment with ketoconazole (systemic).²⁷⁻³¹

DRUG INTERACTIONS

Dabigatran etexilate is a substrate of P-glycoprotein efflux transporter. Potent P-glycoprotein inhibitors (systemic ketoconazole amiodarone, and verapamil) increase the plasma concentration and potent P-glycoprotein inducers (rifampicin) reduces it plasma concentration.²⁷⁻³¹ Therefore dosage adjustments may be required.

SPECIAL POPULATION

It has been assigned Category C in pregnancy. There are no adequate and well-controlled studies in pregnancy, fertility and lactation.²⁷⁻³⁰

CONCLUSION

The current body of clinical evidences indicate that dabigatran etexilate is effective for the prevention and treatment of thrombo-embolic events in patients with acute venous thromboembolism, who are undergoing major orthopaedic (total knee or hip replacement) surgery, or who have atrial fibrillation and represents a giant step forward in the quest to replace conventional anticoagulants.

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