Dabigatran etexilate for the prevention of stroke in patients with nonvalvular atrial fibrillation



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Practice points

- Dabigatran etexilate is the first oral, direct thrombin inhibitor approved for the prevention of stroke and systemic embolization in patients with nonvalvular atrial fibrillation.
- Unlike warfarin, dabigatran has predictable pharmacokinetics, few drug and food interactions, and does not require monitoring. Dabigatran is renally cleared and therefore dose adjustments are necessary in patients with chronic kidney disease.
- In the RE-LY study, dabigatran orally dosed at 150 mg twice-daily was superior to adjusted-dose warfarin for the prevention of stroke due to nonvalvular atrial fibrillation, with a similar rate of bleeding, while dabigatran orally dosed at 110 mg twice-daily was noninferior to adjusted-dose warfarin, with a lower rate of bleeding.
- Dabigatran is the first oral anticoagulant alternative to warfarin approved for the prevention of stroke due to nonvalvular atrial fibrillation. Dabigatran is more effective than warfarin for this indication, has few drug and food interactions, and does not require routine monitoring. Whether dabigatran will maintain its early market lead will partially depend on its relative efficacy compared with other novel anticoagulants and on long-term safety data.

SUMMARY For patients with nonvalvular atrial fibrillation, dabigatran etexilate is a new oral direct thrombin inhibitor to prevent stroke and systemic embolization. Dabigatran has few drug or food interactions, and has predictable pharmacokinetics that obviate the need for routine monitoring. The efficacy of dabigatran was established in the RE-LY trial, which found that dabigatran 150 mg twice-daily was superior to dose-adjusted warfarin for the prevention of

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stroke in patients with nonvalvular atrial fibrillation, but with similar rates of bleeding. Dabigatran dosed at 110 mg twice-daily was noninferior to warfarin for the prevention of stroke, but had a lower risk of bleeding. There are few commercially available assays to monitor the effects of dabigatran and there is no known antidote that can complicate the management of emergent bleeding. For selected patients, dabigatran provides a net clinical benefit over warfarin, both in terms of morbidity, cost and patient satisfaction.

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting approximately 1% of the population. The prevalence of AF increases with age, ranging from 0.1% in individuals younger than 55 years of age to 9% in individuals aged 80 years and older [1]. However, these figures underestimate the true prevalence because many patients are only identified with long-term monitoring [2] or after presenting with complications [3].

AF is associated with significant morbidity, the most serious being systemic embolization and stroke, which, depending on patient risk factors, can be as high as 10% per year [1]. Patients with AF have a 50–90% increased risk of mortality, even after adjusting for pre-existing comorbid cardiovascular conditions [4].

For the last 60 years, coumarin-derived vitamin K antagonists (VKAs) have remained the gold standard for the prevention and treatment of thromboembolism in patients with AF.

VKAs are highly effective and reduce the risk of stroke by up to 60% [5], but their use is limited by a narrow therapeutic index, unpredictable pharmacokinetics, multiple drug and food interactions, and the requirement for frequent monitoring. As a result, up to 50% of patients taking VKAs are consistently outside their target international normalized ratio (INR) [6], and many more patients, for whom anticoagulation is indicated, are not treated at all. For these reasons, there has been intense interest in developing novel anticoagulants to replace VKAs.

In 2004, ximelagatran, the first oral direct thrombin inhibitor (DTI), was approved in several European countries for the prevention of venous thromboembolism in patients partaking in orthopedic studies [101]. Unlike warfarin, ximelagatran had the distinct advantage of fixed dosing without the need for monitoring. Subsequent studies demonstrated that ximelagatran was noninferior to warfarin for the prevention of stroke in patients with nonvalvular AF (NVAF) [7,8]. These data supported the hypothesis that thrombin inhibition was a viable target for long-term anticoagulation. However, ximelagatran was never approved for this indication after safety data emerged showing that it caused significant hepatotoxicity and the manufacturer ultimately withdrew it from the market in 2006.

In 2008, dabigatran etexilate, the second oral DTI, was approved in Europe for the prevention of venous thromboembolism following orthopedic surgery. In 2010, it was approved in the USA for the prevention of thromboembolism in patients with NVAF, followed by approval in Europe in 2011 [102,103].

Pharmacology

Hemostasis begins at the site of vessel injury with disruption of the endothelium, which exposes collagen and tissue factor to circulating blood. Platelets bind to collagen and collagen-bound von Willebrand factor leading to aggregation, activation and plug formation [9]. On the platelet surface, factor VIIa, phospholipids, calcium ions and factor X assemble to form the extrinsic tenase complex. This complex increases the efficiency of factor VIIa activating factors IX and X. Activated factor X (Xa) in turn assembles with activated factor V, phospholipids and calcium ions to form the prothrombinase complex, which cleaves prothrombin into soluble thrombin, the final enzyme in the clotting cascade [10].

Thrombin has a unique 3D structure characterized by a centrally located, negatively charged active site, which binds fibrinogen and cleaves it into fibrin. On either side of the active site are two positively charged domains designated exosites I and II. Exosite I serves as a fibrinogen docking site and orients the fibrinogen molecule correctly within the active site of thrombin. Exosite II is the binding site for heparin. Bound heparin exerts its anticoagulant effect by forming a ternary complex with circulating antithrombin that greatly accelerates the ability of antithrombin to inhibit thrombin [11–14]. Heparin can also form a bridge between thrombin and fibrin, forming a complex that is resistant to inhibition by the heparin–antithrombin complex. As such, heparin is relatively ineffective at inhibiting clot propagation [14].

Thrombin acts primarily by cleaving fibrinopeptides A and B from circulating fibrinogen. The resulting fibrin monomers polymerize and in the presence of thrombin-activated factor XIII, form a stable, insoluble fibrin clot. Thrombin has other procoagulant effects: it is a potent platelet activator, it stimulates endothelial cells, promotes chemotaxis of neutrophils to the site of injury and amplifies its own generation [12]. Thrombin activity is tightly regulated by endogenous anticoagulant feedback loops. The main pathway is initiated when thrombin binds to membrane-bound thrombomodulin. This complex catalyzes the conversion of protein C to its active form (APC), which in turns inhibits thrombin generation by degrading activated factors V and VIII [15,16].

The central role of thrombin in the coagulation cascade makes it an attractive target for anticoagulant therapy, but it was not until hirudin, the polypeptide responsible for the anticoagulant properties of the saliva of the leech (*Hirudo medicinalis*) was isolated that DTIs became available. Lepirudin, desirudin and bivalirudin are parental hirudin analogs. These direct thrombin inhibtors are bivalent with moieties that bind to both exosite I and the active site of thrombin. Argatroban, melagatran and dabigatran are univalent, reversible molecules that selectively bind to the active site of thrombin.

Dabigatran is a small-molecule, trisubstituted benzamidine derivative. It is highly charged due to two polar moieties: a negatively charged carboxylate and a positively charged amidinium, and as such has no oral bioavailability. This limitation was overcome by the development of the prodrug, dabigatran etexilate, which masks the polar moieties by esterification. *In vivo*, the esters are hydrolyzed, releasing the active dabigatran molecule into the circulation [17]. Dabigatran competitively inhibits thrombin by occupying the active site in a concentration-dependent manner [18].

Pharmacokinetics

Dabigatran etexilate is rapidly, but incompletely, absorbed, with only approximately 7% bioavailability (Table 1). Therefore, relatively high doses are required to achieve a therapeutic plasma concentration, but because the absorption is linear over a wide range of doses, the clinical response remains predictable [19]. The absorption of dabigatran etexilate is more consistent in an acidic environment. Therefore, the oral capsule was designed with dabigatrancoated pellets with a tartaric acid core that creates an acidic microenvironment independent of gastric pH [20]. The capsule should never be opened or crushed as this significantly increases the bioavailability and plasma drug levels. While pharmacokinetic studies have shown that antacids and H₂ blockers have no effect on the absorption of dabigatran, proton-pump inhibitors reduce both the area under the curve of dabigatran and the average maximum concentration. However, these changes have not been shown to be clinically relevant [20].

Dabigatran is not metabolized by the CYP450 system [21], and as such does not induce or inhibit the metabolism of drugs that are processed in this way.

However, dabigatran etexilate absorption is counteracted by efflux P-gp 1 transporters in the intestinal epithelium and medications that induce (e.g., rifampin) or inhibit (e.g., azoles or quinidine) these transporters, which can cause significant changes in the plasma concentration of dabigatran.

Dosing

The EMA approved dabigatran at a dose of 150 mg twice-daily for patients <80 years of age and 110 mg for patients \geq 80 years of age or those for whom the risk of bleeding is higher than that of stroke [104]. In the USA, the US FDA approved the 150 mg and not the 110 mg twicedaily dose based on their assessment that the higher dose resulted in a favorable risk-benefit ratio over all age groups. The FDA explained this decision by noting that although the risk of major hemorrhage was higher in elderly patients taking 150 mg rather than 110 mg (5.1 vs 4.4 per 100 patient-years), the risk of stroke was lower (1.4 vs 1.9 per 100 patient-years) and on the whole, the prevention of stroke was more important than the risk of hemorrhage [22].

The kidney is the main elimination pathway for dabigatran with over 80% excreted unchanged and, therefore, dose adjustments are necessary in patients with reduced creatinine clearance (CrCl). Patients with a CrCl

Table 1. Dabigatran versus warfarin.		
Properties	Dabigatran	Warfarin
Mechanism of action	Competitive, highly selective and reversible direct thrombin inhibitor	Vitamin K oxide reductase inhibitor
Metabolism	Esterase-mediated hydrolysis of dabigatran etexilate to dabigatran	CYP2C9, CYP1A2 and CYP3A4
Oral bioavailability	6-8%	>90%
Half-life	13 h (CrCl >80 ml/min) up to 27 h (CrCl 15–30 ml/min) [†]	36–44 h
Clearance	~80% renally; small fraction converted to pharmacologically active glucuronidated intermediates [‡]	Hepatic
Interactions	P-gp inhibitors (e.g., amiodarone, verapamil, ketoconazole, quinidine, and clarithromycin) increase plasma concentration; P-gp inducers (e.g., rifampicin and St John's wort) reduce plasma concentration	Inhibitors and inducers of CYP450
Administration	Daily	Daily
Monitoring	Ecarin clotting time, diluted thrombin time	INR
Reversal	Dialysis ~60% at 2 h, possibly neutralizing monoclonal antibodies (experimental) [§]	Prothrombin complex concentrates Fresh-frozen plasma vitamin K
[†] Data taken from [26]. [†] Data taken from [23]. [§] Data taken from [32]		

CrCl: Creatinine clearance; INR: International Normalized Ratio; P-gp: P-glycoprotein.

of <30 ml/min were excluded from the RE-LY study, the trial that served as the basis for dabigatran's approval. The FDA's recommended dosing for this population (75-mg orally twice-daily) was based on pharmacokinetic and pharmacodynamic data from a single study of 23 patients with varying degrees of renal failure who were administered a single dose of 150 mg of dabigatran etexilate [22,23]. These dosing recommendations were not approved in Canada or the UK, where dabigatran etexilate is contraindicated in patients with a CrCl of <30 ml/min. There are no specific dosing recommendations for patients with a CrCl of <15 ml/min or for those on renal replacement therapy.

The pharmacokinetics of dabigatran do not appear to be significantly affected by mild-to-moderate hepatic failure [20] and no dosing adjustments are recommended in this population.

Monitoring levels

Owing to its predictable dose response and wide therapeutic index, dabigatran does not require routine monitoring. However, there are a number of situations in which monitoring may be desired and these include:

- Assessing compliance with therapy;
- Evaluation and management of patients presenting with hemorrhage or thrombosis;
- Ensuring the absence of drug effect prior to an invasive procedure.

The two most widely used measures of anticoagulation are the prothrombin time and the activated partial thromboplastin time (aPTT). The prothrombin time is insensitive to the effects of dabigatran at therapeutic levels and only becomes significantly prolonged at supratherapeutic concentrations; as such, it is not useful for monitoring dabigatran. The aPTT response to dabigatran is nonlinear and varies as a function of the plasma concentration. Both therapeutic and supratherapeutic levels of dabigatran may only mildly prolong the aPTT, while at very high doses (e.g., overdose), the dose–response curve flattens and the aPTT becomes increasingly insensitive to dabigatran levels [24]. In theory, the thrombin time (TT), which measures the activity of thrombin, would be well suited to monitoring the effects of dabigatran and, depending on the specific reagents and laboratory equipment, it can be used for this purpose. However, in most laboratories, the TT assay is too sensitive to measure anticoagulant activity at therapeutic drug levels [24]. For these reasons, the degree of prolongation of neither the aPTT or the TT provides an accurate quantitative measure of the anticoagulant effect of dabigatran. However, both assays are sufficiently sensitive to allow for a qualitative assessment of drug effect: a normal aPTT indicates the absence, or a very low level, of an anticoagulant effect of dabigatran and a normal TT essentially rules out an effect [25].

At present, there are two assays best suited to quantitative monitoring of the anticoagulant effect of dabigatran. These include the hemoclot thrombin inhibitor (HYPHEN BioMed, Neuvillesur-sur-Oise, France) and the ecarin clotting time. The hemoclot thrombin inhibitor is a diluted TT, which shows a linear relationship between the clotting time and dabigatran at therapeutic plasma concentrations [26]. The ecarin clotting time assay uses the snake venom ecarin to generate the thrombin intermediate meizothrombin. Meizothrombin is much less active than thrombin, but is completely neutralized by DTIs in a concentration-dependent manner [27]. Neither assay is yet widely available.

Reversal

As there is no specific antidote for dabigatran, clinicians have turned to therapies designed to reverse the effects of VKAs or to counteract bleeding in patients with factor deficiencies or inhibitors. These include fresh-frozen plasma, nonactivated and activated prothrombin complex concentrates, and recombinant activated factor VII. To date, there are conflicting data from *in vitro* studies and murine models of the efficacy of prothrombin-complex concentrates and recombinant activated factor VII for reversing the effects of dabigatran and no data to support their efficacy in humans [25,28–30].

Hemodialysis decreases the plasma concentration of dabigatran [23] and, while there are case reports supporting its use for the treatment of dabigatran-associated bleeding [31], in most clinical settings this intervention is challenging to execute in a timely manner. A monoclonal antibody (clone 22) has demonstrated the ability to neutralize the anticoagulant effect of dabigatran and may prove to be a useful reversal agent in the future [32].

Clinical evidence

The efficacy of dabigatran was evaluated in the RE-LY study. RE-LY was a large, multicenter, randomized controlled trial designed to test whether dabigatran was noninferior to warfarin for the prevention of stroke in patients with NVAF [33].

The investigators enrolled 18,113 participants at 951 clinical centers in 44 countries, who were randomly assigned to either dabigatran 110 or 150 mg twice-daily, or warfarin adjusted to an INR of 2–3. The comparison of warfarin and dabigatran was conducted in an open-label fashion, while the comparison of the two dabigatran doses was conducted in a double-blind fashion. The three arms were well matched for age, gender (64% male), CHADS₂ score (including prior stroke), prior VKA therapy and concomitant use of antiplatelet and antiarrhythmic medications. The median follow-up period was 2 years.

Inclusion criteria included documented NVAF and one or more of the following:

- Prior stroke;
- Left ventricular systolic dysfunction (left ventricular ejection <40%);
- Symptomatic heart failure;
- Ages ≥75 years or ages 65–74 years with coronary disease;
- Diabetes;
- Hypertension.

Exclusion criteria included:

- Prosthetic valve or hemodynamically relevant valvular disease;
- Stroke at <6 months prior to enrollment;
- Increased bleeding risk;
- CrCl of ≤30 ml/min;
- Alanine aminotransferease, aspartate aminotransferase or alkaline phosphatase more than twice the upper limit of normal, active, viral hepatitis;
- Pregnancy [34].

The primary outcome was the composite of ischemic or hemorrhagic stroke, or systemic embolization, which occurred at a rate of 1.53% per year in the group receiving 110 mg of dabigatran, 1.11% per year in the group receiving 150 mg of dabigatran and 1.69% per year in the group receiving adjusted-dose warfarin. Both doses of dabigatran were noninferior to warfarin for the primary outcome and the 150-mg dose was superior to warfarin (relative risk [RR]: 0.66; 95% CI: 0.53–0.82 for superiority). There was no difference between either dose of dabigatran and warfarin in the rates of death, including from vascular causes.

The rate of ischemic stroke was significantly lower in the group that received 150 mg of dabigatran (0.92%) than in those receiving either 110 mg of dabigatran (1.34%) or warfarin (1.2%). When compared with warfarin, the number needed to treat to prevent one ischemic stroke with 150 mg of dabigatran was 357 patients.

The rate of hemorrhagic stroke was also significantly lower in both the 150 (0.10%) and 110 mg (0.12%) of dabigatran groups; compared with the group receiving warfarin (0.38%). The number to treat with dabigatran rather than warfarin to prevent one hemorrhagic stroke was approximately 370 patients [35].

The primary safety outcome was major hemorrhage (defined as a reduction in the hemoglobin level of at least 20 g\l transfusion of at least two units of blood or symptomatic bleeding in a critical area or organ), which occurred at a lower rate in the group receiving 110 mg of dabigatran than in both those receiving warfarin (RR: 0.80; 95% CI: 0.69-0.93) and 150 mg of dabigatran (RR: 1.16; CI: 1.00–1.34; p = 0.052). Dabigatran 150 mg was similar to warfarin in the rate of major hemorrhage. Gastrointestinal bleeding (both life threatening and nonlife threatening) was significantly higher in those receiving 150 mg of dabigatran than in those receiving 110 mg (RR: 1.36; 95% CI: 1.09-1.70) and in those receiving warfarin (RR: 1.50; 95% CI: 1.19-1.89). When restricted to life-threatening and/or intracranial bleeding, both doses of dabigatran were superior to warfarin.

There was no significant difference in the incidence of hepatobiliary disorders or elevations in alanine aminotransferease, aspartate aminotransferase or bilirubin between either dose of dabigatran and warfarin. Gastrointestinal side effects, including dyspepsia and abdominal pain, were twice as common in those receiving either dose of dabigatran (11–12%) compared with those receiving warfarin (5.8%) and contributed to the higher dropout rate in the group receiving dabigatran [35].

The most concerning finding of RE-LY was the fact that the incidence of myocardial infarction was higher in those receiving 110 (RR: 1.35; 95% CI: 0.98–1.87) and 150 mg (RR: 1.38; 95% CI: 1.00–1.91) of dabigatran than in those receiving warfarin. These findings were somewhat attenuated after the investigators reported 32 previously unidentified myocardial infarctions (four symptomatic, 28 silent), but there remained a nonsignificant 27% increased risk [36].

In a meta-analysis of seven randomized control trials (including RE-LY) of dabigatran for the prevention of thromboembolism in AF and the prevention and treatment of venous thromboembolism, dabigatran was associated with a 33% increased risk of myocardial infarction and acute coronary syndromes when compared with warfarin, enoxaparin and placebo [37]. However, it is important to note that the increased risk reported in this study was largely influenced by the results of the RE-LY study, which accounted for 59% of the cohort and 74% of the events. Indeed, when the analysis is restricted to the six other studies, excluding RE-LY, the summary odds ratio was 1.12 (95% CI: 0.66-1.9), and no longer statistically significant [38,39].

Ongoing surveillance data will help determine if the increased rates of myocardial infarction observed in the RE-LY trial reflect a true drug effect or whether they occurred by chance. Depending on patient-specific factors, the lower rates of stroke and systemic embolism with the 150-mg dose, and the lower risk of intracranial hemorrhage with the 110-mg dose of dabigatran may outweigh the increased risk of myocardial infarction.

Reports of serious bleeding associated with dabigatran etexilate have raised concerns about its safety in elderly patients and in those with low body weight [40,41]. Postmarketing surveillance of adverse bleeding events has prompted warnings from the EMA, the Medicines and Healthcare products Regulatory Agency and the FDA [42,104,105]. The manufacturer has also made several amendments to the prescribing information recommending increased vigilance in these populations [106].

Cost-effectiveness

Dabigatran is significantly more expensive than warfarin, but it is also more effective; whether this increased cost is offset by a corresponding decrease in healthcare expenditures required for the management of patients with ischemic and hemorrhagic stroke is of obvious interest.

In an industry-sponsored, cost–effectiveness Markov model simulating treatment patterns and costs reflective of the Canadian provincial healthcare system, when compared with actual prescribing patterns (defined as warfarin-eligible patients with suboptimal INR control, on aspirin or on no treatment), the present authors found that in patients at moderate risk of stroke (mean CHADS₂ score of 2.1), dabigatran was significantly more cost-effective than usual care [43].

In a similar analysis using costs reflective of the National Health Service in the UK, when compared with patients taking warfarin, dabigatran 150 mg twice-daily was determined to be cost-effective only for patients with a CHADS₂ score of \geq 3 or in those patients that could not maintain a therapeutic INR. The authors found that dabigatran 110 mg twice-daily was not cost-effective in any subgroup [44].

Several cost–effectiveness studies have been performed using data from the USA. In one analysis, dabigatran was only cost-effective in patients older than 65 years of age with a CHADS₂ score of ≥ 1 [45]. In a second analysis, warfarin was found to be more cost-effective than dabigatran for patients with a CHADS₂ score of ≥ 1 , unless there was an increased risk of hemorrhage or the percentage of time the INR was in therapeutic range was <57%. For patients with a CHADS₂ score of ≥ 3 , dabigatran was more cost-effective than warfarin unless the therapeutic range was >73% [46]. Neither model identified a subgroup for which the 110-mg dosing regimen was cost-effective.

Conclusion & future perspective

Dabigatran is the first oral DTI approved for the prevention of thromboembolism due to NVAF. The efficacy data for dabigatran is compelling: in the RE-LY study, both the 110 and 150 mg twice-daily regimens were noninferior to warfarin for the prevention of stroke and the 150-mg dose was superior. The 110-mg dose caused less major bleeding and the 150-mg dose caused a similar rate of bleeding to warfarin. When combined with a predictable dose–response that obviates the need for monitoring and fewer drug and food interactions, dabigatran has significant advantages over VKAs for the prevention of stroke in patients with NVAF.

However, several issues remain, which may dampen enthusiasm for this drug going forward. First, for many patients, gastrointestinal side effects will prevent them from tolerating dabigatran; second, there is no antidote for dabigatran, which presents a major challenge for the management of patients who develop hemorrhagic complications; and third, there are lingering concerns about the possibility that dabigatran is associated with an increased risk of myocardial infarction.

Dabigatran's early market penetration may provide an early advantage, but as other alternatives to warfarin become available, prescribing patterns will shift. Indeed, rivaroxaban - the first oral direct factor Xa inhibitor - is already in use in Europe, Canada and the USA. Rivaroxaban was approved based on the results of the ROCKETAF trial, which, similar to RE-LY, compared rivaroxaban with adjusted-dose warfarin for the prevention of stroke in NVAF [107]. The study showed that oncedaily rivaroxaban was noninferior to warfarin in a higher risk population (mean CHADS, score of 3.5 vs 2.1 in RE-LY), with similar rates of major bleeding, but lower rates of fatal and intracranial bleeding [47]. More recently, the ARISTOTLE trial found that apixaban - the second oral direct factor Xa inhibitor - was superior to warfarin in preventing stroke, had a lower rate of bleeding and an 11% reduction in mortality [48].

As the first non-VKA oral anticoagulant approved for the prevention of stroke in patients with NVAF, dabigatran remains a major therapeutic milestone. It is particularly attractive for patients who are unable to maintain a therapeutic INR or for whom VKA therapy is too burdensome and, therefore, compliance is low. Moreover, for certain risk groups, dabigatran may provide a net clinical benefit over warfarin, both in terms of morbidity and cost.

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