# Drug review – Dabigatran for stroke prevention in atrial fibrillation

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# Drug review – Dabigatran for stroke prevention in atrial fibrillation

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**Summary:** The incidence of atrial fibrillation (AF) is growing at an increasing rate and presents major health problems due to its high association with stroke and systemic embolism. Antithrombotic therapy is highly effective for stroke prevention in AF using the vitamin K antagonist warfarin. However, this approach does not provide adequate therapy for all eligible patients due to the limitations and complications of using warfarin. Underuse of oral anticoagulant therapy has prompted the search for a safe and effective alternative to warfarin that does not require regular monitoring, and with improved safety and tolerability. New anticoagulants, such as dabigatran, a direct thrombin inhibitor, target specific steps in the coagulation cascade. Dabigatran demonstrates stable and predictable pharmacology with rapid dose-related anticoagulant activity following oral administration and conversion from its prodrug dabigatran etexilate. Dabigatran has been found to be an effective anticoagulant for the prevention of thomboembolic events following surgery for hip or knee replacement compared with subcutaneous enoxaparin, a low-molecular-weight heparin. Clinical data from Phase II and Phase III trials indicate that there are two therapeutic doses of dabigatran that are at least as effective as warfarin in stroke prevention in patients with AF and with similar or improved bleeding rates. Dabigatran provides convenient fixed-dose treatment without the need for monitoring, and has the potential to improve the management of venous and arterial thromboembolism. Dabigatran may provide an alternative and more cost-effective therapy to warfarin for stroke prevention in patients with AF.

## Introduction

### *Atrial fibrillation – a perspective*

Atrial fibrillation (AF) is the most common chronic clinical arrhythmia affecting over 6 million people in Europe[1] and nearly 2.5 million people in the USA.[2] Since AF often remains undiagnosed until it reaches a more serious state, its occurrence in the general population is probably higher than originally estimated. The prevalence of non-valvular AF is highly age-dependent and increases rapidly from age 60 onwards. It is associated with high mortality and morbidity rates from stroke and thromboembolism.[1–3] Those that survive stroke are usually severely disabled and more likely to suffer from recurrence of stroke with AF than stroke from other causes. This doubles the risk of death and increases the cost of care by 1.5-fold.[1]

AF is a common cause of arterial thrombosis due to disturbed blood flow in the fibrillating left atrium. If the thrombus embolises to the cerebral circulation it can block arterial blood flow causing ischaemic injury and stroke. AF may be considered as a marker for stroke, therefore effective anticoagulation is essential for stroke prevention. All cardiac impairments that reduce cerebral blood flow, such as coronary heart disease, cardiac failure and AF are established risk factors for stroke as well as hypertension. However, AF alone is a potent and significant risk factor for stroke and its impact on risk of stroke increases with age, independent of other risk factors, which tend to decrease with age.[4,5] In the original Framingham Heart Study, 5029 men and women, who were free of cardiovascular disease including stroke at study entry, were examined every 2 years for a 34-year follow-up period. AF appeared in 303 subjects and rates of AF increased with age up to 4% in the over-80 age group. AF increased the risk of stroke at all age groups by 4–5-fold. The proportion of stroke associated with AF was 14.7% increasing with age from 6.7% in the 50–59 age group up to 36.2% in the over-80 age group. A follow-up study looked at the impact of various risk factors for stroke in 5070 participants of the Framingham Study over a period of 34 years. In patients with AF the incidence of stroke increased by up to 5-fold and was often fatal.[5] The significance of AF on the outcome of ischaemic stroke was analysed in the long-term prospective follow-up of the original Framingham cohort over a period of 40 years. AF was associated with increased stroke severity and patients with AF were twice as likely to have a fatal stroke during that period.[6]

Analysis of pooled data from five US studies indicated that AF accounts for 15% of all strokes. The ATRIA study (AnTicoagulation and Risk Factors In Atrial Fibrillation) carried out in 2001 found that AF is likely

 

 

to increase by 2.5-fold affecting 5.6 million people by 2050, which reflects the growing proportion of elderly adults in the population. The study also found that prevalence of stroke increases with age from 0.1% under age 55 to 9% at age 80 and older.[7] However, the prevalence of AF may be increasing more rapidly than at first indicated and these findings may be an underestimate, according to projections made using a community-based study of changing trends in age-adjusted data of the incidence of AF.[8] This study suggests the incidence of AF may be in excess of 10 million in the US population by 2050, which emphasises the urgent need for primary prevention strategies for AF and its associated increased risk of stroke.[8]

## *Antithrombotic therapy for primary stroke prevention in atrial fibrillation*

Antithrombotic therapy as a strategy for stroke prevention, in patients with non-valvular AF who are at risk of stroke, has proved highly effective, reducing the incidence of stroke by up to 80%. This strategy provides the key to stroke prevention in high-risk patients and options for antithrombotic therapy include antiplatelet therapy and oral anticoagulants (OACs).[1,5,9]

Risk assessment schemes are used for stratification of patients into low, medium or high risk of stroke to help make decisions on the need for antithrombotic therapy and the most appropriate therapeutic regimen. Identification of patients who would benefit from antithrombotic therapy is also based on a balance between reducing risk of stroke and increased risk of bleeding. Although there are several schemes for stroke risk stratification, the absolute stroke rates vary widely within patient groups categorised as low or high risk.[10]

The CHADS2 score (Cardiac failure, Hypertension, Age > 75, Diabetes, prior Stroke/transient ischaemic attack) is a widely used risk assessment scheme that allocates a single point for each risk factor and 2 points for prior stroke/transient ischaemic attack. A score of 1 indicates moderate risk of stroke and a score of ≥ 2 indicates high risk.[11]

Analysis of pooled data from five randomised trials comparing warfarin and aspirin with placebo were used to help make predictions for high and low risk of stroke in patients with AF. Patients were identified as high risk if over 65, had a history of hypertension, previous stroke or transient ischaemic attack, and diabetes, and in this group there was a 68% reduction in risk of stroke with warfarin. Patients under 65 without these risk factors were at low risk of stroke even when not receiving treatment.[12]

Meta-analyses of pooled data from several randomised trials have been carried out to determine the efficacy and safety of antithrombotic therapy as a strategy for stroke prevention in AF. These analyses found that treatment with the vitamin K antagonist warfarin and the antiplatelet agent aspirin both reduced stroke in patients with AF, but in all studies warfarin was more effective than aspirin.[13] A further meta-analysis of pooled data from 29 trials with adjusted-dose warfarin reduced stroke by 64% (95% CI: 49–74%) compared with placebo, although risk of haemorrhage increased. This was more effective than aspirin, which reduced incidence of stroke by 22% (CI: 6–35%), although there was an increased risk of bleeding with warfarin.[14] To address whether reduced risk of stroke outweighs the increased risk of bleeding in elderly patients, the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study compared warfarin with aspirin in patients with AF over 75 years and found that warfarin was more effective than aspirin in stroke prevention than aspirin alone without increased risk of bleeding. This study supports the use of OAC in elderly patients, unless specifically contraindicated.[15]

Where warfarin is contraindicated or patients with AF are considered at low risk of stroke, antiplatelet agents such as clopidogrel and aspirin are used instead. The ACTIVE W (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) study compared antithrombotic therapy with clopidogrel added to aspirin with warfarin in patients that could tolerate warfarin, and confirmed that warfarin was more effective. However, this trial was stopped early since OAC therapy with warfarin was clearly superior to antiplatelet therapy.[16] The ACTIVE A study compared the efficacy of dual antiplatelet therapy using clopidogrel added to aspirin, with aspirin alone in patients who could not tolerate warfarin. The results demonstrated that this combination was more effective than aspirin alone, although there was increased risk of haemorrhage.[17]

Another advantage of OAC over antiplatelet therapy is that the absolute benefit of OAC increases with age since risk of stroke also increases with age. The relative efficacy of OAC in stroke prevention does not change with age, whereas relative efficacy of antiplatelet agents decreases with age.[18]

## *Guidelines for antithrombotic therapy*

The American College of Cardiology (ACC), the American Heart Association (AHA), Task Force on Practice Guidelines and the European Society of Cardiology (ESC) Committee for Practice Guidelines created a joint committee in 2006 to establish guidelines for optimum management of AF, including epidemiology, pathophysiology and antithrombotic strategies.[19] Similar guidelines have been proposed by the National Institute for Health and Clinical Excellence[9] (NICE) and the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC), recently updated in 2010.[1] Guidelines for management of AF focus on risk stratification, primary prevention and the use of antithrombotic therapy. Stroke risk assessment is applied to determine whether to use thromboprophylaxis and when to use antiplatelet or OAC therapy. A risk stratification algorithm is recommended by the 2006

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NICE guidelines to identify low-, moderate- or high-risk patients.[9] On this basis aspirin is used for low-risk patients, aspirin or OAC for medium-risk patients and the most effective anticoagulant for this purpose is warfarin. Warfarin is recommended for high-risk patients unless contraindicated, in which case aspirin is recommended. The 2010 guidelines developed by the Task Force for the Management of Atrial Fibrillation of the ESC recommends basing antithrombotic therapy on the presence or absence of risk factors using the CHADS2 stroke risk stratification scheme.[1] For patients with a CHADS2 score of ≥ 2, chronic OAC therapy with warfarin is recommended, dose adjusted to achieve an INR value in the range of 2.0–3.0, unless contraindicated. For patients with a CHADS2 score of 1 either OAC or aspirin is recommended. For patients with a CHADS2 score of 0–1, a more comprehensive risk assessment is recommended using other risk factors, including gender and vascular disease, to determine whether aspirin or no antithrombotic therapy should be used.

Based on the outcome of the RE-LY study a focused update of the ACC/AHA/ESC 2006 guidelines was published to give a specific focus on the use of dabigatran as an alternative to warfarin for the management of AF.[20] Individual recommendations in this publication, made in conjunction with the Heart Rhythm Society (HRS) are to be incorporated into future revisions and/or updates of the full guidelines. These guidelines recommend that dabigatran should be considered for patients with AF and at least one additional risk factor for stroke who would benefit from dabigatran instead of warfarin for anticoagulant therapy. Each patient should be considered individually for clinical suitability and ability to comply with twice-daily dosing, as well as other factors such as patient preferences and cost. High-risk AF patients who can tolerate warfarin and have excellent INR control may have little to gain by switching to dabigatran and could continue on warfarin anticoagulant therapy.[20]

## *Limitations and underuse of warfarin therapy*

Although oral anticoagulation therapy with warfarin for stroke prevention in AF has proved highly effective, using warfarin poses several problems for both patient and clinician. These include:

- slow onset of action
- risk of increased bleeding and major haemorrhage
- narrow therapeutic window
- variation in dose response between individuals and also variation in individual day-to-day dose response
- multiple drug interactions
- food interactions that require dietary restrictions.

These limitations result in unpredictable and variable results, the need for international normalised ratio (INR) control and the need for dose adjustments and continual monitoring for anticoagulant efficacy during long-term use.

The time in therapeutic range (TTR) and variation in INR control between centres can make all the difference in patient benefit from warfarin treatment, and studies suggest that there is considerable variation in both. In a *post-hoc* analysis of trial data, there was little patient benefit for stroke prevention in AF with warfarin compared with antiplatelet therapy below a target threshold of 58–64% TTR.[21]

The limitations associated with the use of warfarin make its use perceived as being inconvenient from the patient viewpoint and provide management issues from the clinician viewpoint, as well as creating uncertainty about patient benefit. There is increasing evidence for the underuse of warfarin in antithrombotic therapy and that these issues associated with using warfarin have contributed to a decline in the use of warfarin to approximately 50–60% of eligible patients.[22,23] This is of concern particularly with the emergence of the predicted increase in AF incidence in the ageing population.

In a review of 98 studies in which the current guidelines for stroke prevention in AF were applied, the rate of patient eligibility for treatment with OAC was compared with the actual rate of treatment, with under-treatment defined as less than 70%. In many of the studies reviewed, high-risk patients were under-treated with treatment levels as low as 60%, which highlights the need for new treatment options.[23]

## *The search for novel anticoagulants*

The need to identify safe and effective alternatives to warfarin for patients with AF has contributed to the search for new OACs that can be administered in fixed doses with predictable pharmacokinetics and without regular laboratory monitoring or dose adjustments.[11,22]

Trial design poses challenges for evaluating new antithrombotics. Placebo-controlled trials are ethical in low-risk patients but pose ethical problems in high-risk patients. Evaluating the superiority of a new drug to aspirin is a trial strategy that can be used as many high-risk patents will already be taking aspirin. Demonstrating non-inferiority to warfarin is an objective common to many trials for new drugs, since warfarin is currently the most effective antithrombotic drug used for stroke prevention in AF. This trial design is based on showing that the new drug is at least as effective as warfarin, and preferably superior.[22] Other factors to be considered in trial design include declining stroke rates in AF patients on warfarin and improved INR control. There is the potential for different treatment effects in warfarin-naïve and warfarin-experienced patients as patients who are already on warfarin are more likely to respond better in clinical trials for new anticoagulants as they are already responding well to warfarin, particularly with good INR control.

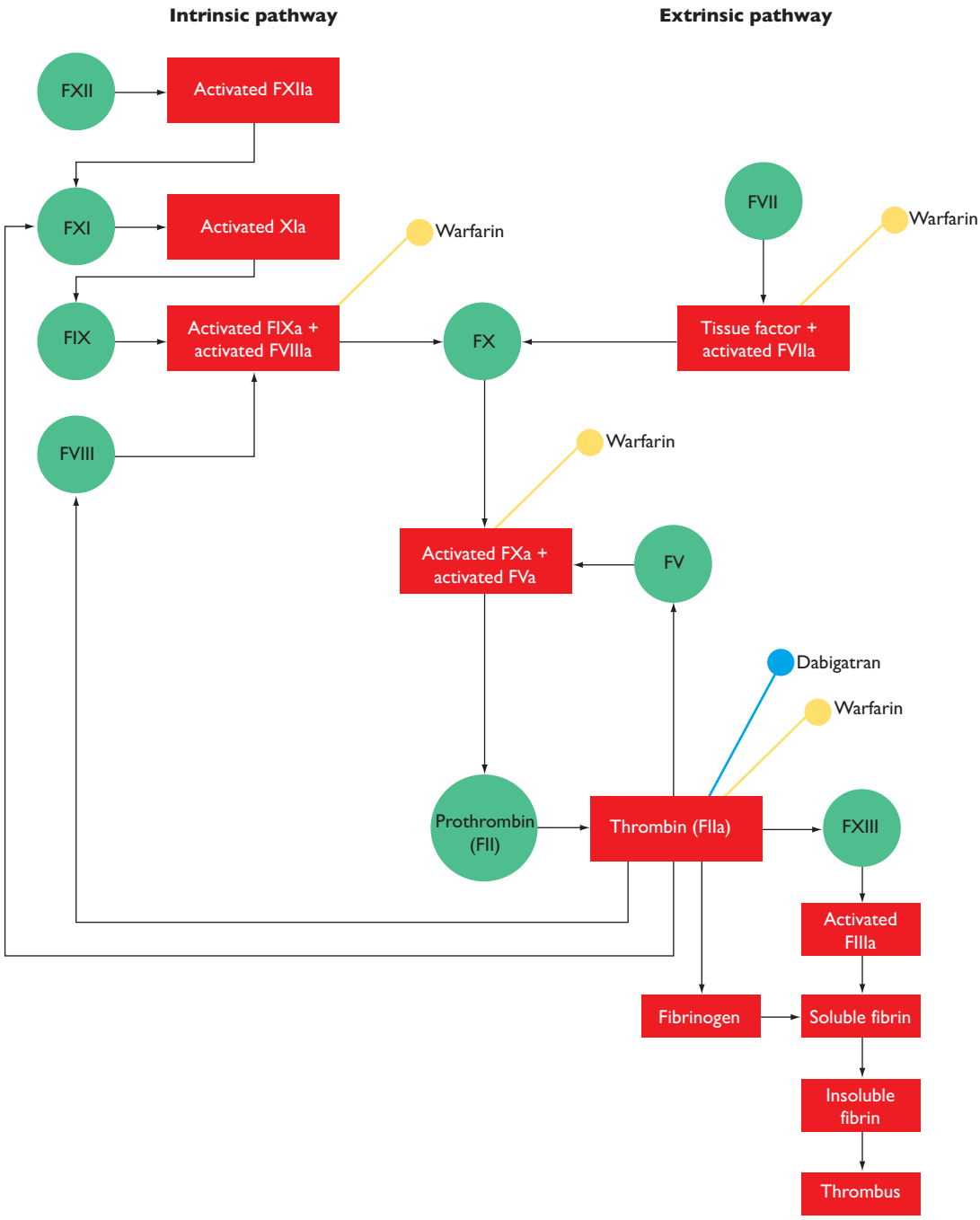
Conventional antithrombotics, such as the vitamin K antagonist warfarin, unfractionated heparin and low-molecular-weight heparin, act at more than one

point in the coagulation cascade, which contributes to their inconsistent effects and variable results between individuals. Vitamin K is an essential cofactor for several clotting factors, including II, VII, IX and X, and therefore the anticoagulant activity of warfarin is based on blocking the coagulation cascade at each of these points. The issue of anticoagulant non-specificity has been the focus of the search for novel anticoagulants which target single coagulation factors to prevent thrombus formation. The two emerging approaches that have met with success are drugs that directly inhibit Factor Xa (FXa), the point of primary amplification of the coagulation cascade, and Factor IIa or thrombin, which is involved further down the coagulation cascade (Figure 1).[24–30]

Indirect FXa inhibitors are synthetically derived pentasaccharides and include fondaparinux and idraparinux. They cannot be taken orally and are injected subcutaneously. When compared with warfarin, idraparinux was not inferior to warfarin in efficacy in stroke prevention in AF but had a significantly greater risk of bleeding (AMADEUS trial).[31] Several direct

Figure 1. Diagrammatic representation of the coagulation cascade showing the multiple targets of the vitamin K antagonist warfarin and the thrombin-specific target of the direct thrombin inhibitor dabigatran (adapted from Lassen and Laux,[29] and Maegdefessel *et al.*[28]).

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FXa inhibitors have been developed, the most promising of which are rivaroxaban (ROCKET AF trial), apixaban (ARISTOTLE trial) and edoxaban (ENGAGE trial).[25,32]

The first of the new direct thrombin inhibitors (DTIs) approved in some countries in Europe (not the UK) for the prevention of venous thromboembolism (VTE) after major orthopaedic surgery (ximelagatran) was found to be non-inferior to warfarin for stroke prevention but was withdrawn due to liver toxicity (SPORTIF trial).[33] The next DTI to emerge was dabigatran, which has undergone extensive clinical trials for the prevention of VTE following major orthopaedic surgery and more recently for stroke prevention in AF. Many new antithrombotic drugs were first trialled for efficacy in VTE prevention in a perioperative setting for orthopaedic surgery[34,35] and the differences in their pharmacokinetic and pharmacodynamic (PD) parameters were compared as these parameters are likely to influence their use in clinical practice.[26]

The search for new antithrombotics was also driven by the need to find an alternative to heparin and low-molecular-weight heparin (LMWH) for the treatment and prevention of VTE. Heparin is associated with a high risk of bleeding and can only be administered parenterally by injection. LMWH is safer but these agents cannot be administered orally and administration can only be done in hospital.[36–40] There is a high risk of VTE following major orthopaedic surgery, such as in hip and knee replacements, and 40–60% of patients undergoing major orthopaedic surgery have serious VTE complications. Therefore effective thromboprophylaxis is essential for the prevention of VTE following orthopaedic surgery.[37,41,42]

### *Therapeutic potential of dabigatran*

The efficacy and safety of dabigatran has been studied extensively in a series of trials to determine its potential for antithrombotic therapy in primary prevention and treatment of a variety of thromboembolic diseases including VTE following orthopaedic surgery, acute VTE as well as stroke prevention in AF.[37,43–45]

The efficacy and safety of dabigatran was compared with conventional thromboprophylaxis therapy using enoxaparin in three large Phase III trials for the prevention of VTE in patients after total hip arthroplasty (RE-NOVATE trial)[46,47] or total knee arthroplasty[48,49] (RE-MODEL and RE-MOBILIZE trials) using either dabigatran 150 mg or 220 mg once daily. The RE-NOVATE and RE-MODEL trials found that dabigatran was at least as effective as enoxaparin and with a similar safety profile, demonstrating non-inferiority of dabigatran at both doses for primary and secondary outcomes, whereas the RE-MOBILIZE trial demonstrated non-inferiority for secondary outcomes only. In all three trials there was a similar safety profile between dabigatran and enoxaparin with similar incidence of bleeding in all groups.[50]

In a meta-analysis of RE-NOVATE, RE-MODEL and RE-MOBILIZE data, non-inferiority of dabigatran at 220 mg compared with enoxaparin was confirmed for the prevention of VTE in patients undergoing major orthopaedic surgery.[51] Another pooled analysis of these trials' data demonstrated that both doses of dabigatran were as effective as enoxaparin at reducing the risk of major VTE and VTE-related mortality and that they had a similar bleeding profile.[52] The findings of these studies led to the approval of dabigatran for thromboprophylaxis following hip or knee replacement surgery in Europe, Canada and the UK.[53]

Information obtained from these studies has demonstrated that dabigatran provides convenient fixed-dose treatment without the need for monitoring, and has the potential to change the management of venous and arterial thromboembolism.[54,55]

## Pharmacology

### *Chemistry*

Dabigatran, formerly known as the reference compound BIBR 953 ZW (β-alanine,*N*-[[2-[[[4-(aminoiminomethyl)phenyl]amino]methyl]-1-methyl-1*H*benzimidazol-5-yl]carbonyl]*N*-2-pyridinyl), is the major pharmacologically active metabolite of dabigatran etexilate, a small molecule prodrug, which does not exhibit any pharmacological activity. Dabigatran is not orally available due to its high polarity, but its prodrug dabigatran etexilate is rapidly absorbed after oral administration and converted via two intermediates (BIBR 951 and BIBR 1087) to dabigatran, by esterase-catalysed hydrolysis in plasma and in the liver, with trace amounts of minor metabolites (Figure 2).[56,57]

### *Mechanism of action*

Dabigatran is a potent direct thrombin inhibitor that inhibits both thrombin activity and generation. Its action is selective for thrombin and it has little effect on other serine proteases, interacting with the active site of thrombin in a manner that is competitive and reversible. Thrombin is a key enzyme in the coagulation cascade and is generated by the action of FXa on prothrombin (FII) converting it to thrombin (FIIa). Thrombin catalyses the conversion of soluble fibrinogen to fibrin, leading to thrombus formation. It also activates coagulation factors V, VIII and XI, which generates more thrombin and thus amplifies the cascade, as well as activating factor XIII, which promotes stabilisation of the clot by cross-linking fibrin.[58] Thrombin is also a potent agonist of platelet activation. Inhibition of thrombin by dabigatran prevents thrombus formation. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation (Figure 1).[59]

### *Anticoagulant activity*

The PD activity of dabigatran is assessed by measuring its anticoagulant activity on the following blood coagulation parameters:[60–63]


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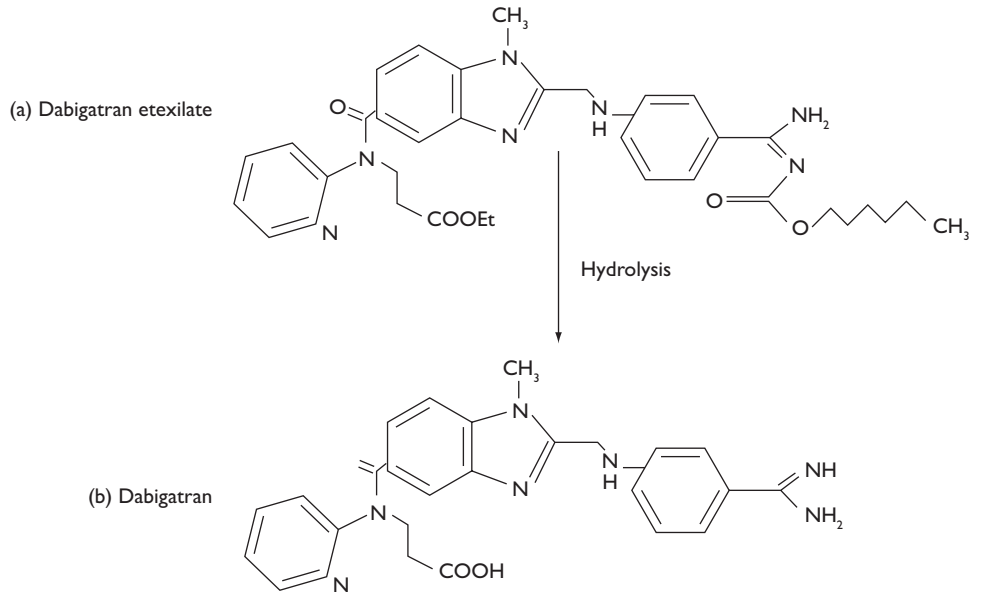
Figure 2. (a) Chemical structure of dabigatran etexilate and (b) its main metabolite dabigatran (taken from Baetz and Spinler[43]).




- Activated partial thromboplastin time (aPTT) represents the intrinsic coagulation pathway and measures the lag-time until thrombin generation and subsequent clot formation, using a contact activation trigger.
- Prothrombin time (PT) reported as the international normalised ratio (INR), represents the clotting time in the extrinsic pathway in the presence of an excess of tissue factor.
- Total thrombin time (TT) measures the activity of a direct thrombin inhibitor and time to clot formation that depends on the amount of thrombin and the concentration of thrombin inhibitor.
- Ecarin clotting time (ECT) uses the snake venom ecarin to convert prothrombin into the intermediate meizothrombin, which is inhibited by a direct thrombin inhibitor prolonging clot formation.

In a single-dose study of dabigatran in normal human male subjects, a close correlation between prolongation of blood coagulation assays and dabigatran plasma concentrations was demonstrated, using aPTT, PT, TT and ECT. The anticoagulant activity was still present in plasma at 8 hours post-administration for doses of 50 mg or higher. Increases in blood coagulation times following multiple doses of dabigatran also correlated with plasma concentration at steady state. There was a rapid onset of action with maximum effect seen within 2 hours of administration and there was no lag between maximum plasma concentration and maximum activity.[64]

Dabigatran conjugates with glucuronic acid in plasma to form pharmacologically active conjugates that account for approximately 20% of total dabigatran in plasma and exhibits direct thrombin inhibition of the same potency as non-conjugated dabigatran. The concentration of dabigatran in plasma after conjugate cleavage represents the total concentration of active thrombin inhibitor in the plasma. The pharmacokinetic/pharmacodynamic (PK/PD) correlation following alkaline cleavage of the glucuronide conjugates indicates that there are differences between PD assays in terms of sensitivity and precision. The TT assay exhibits a linear relationship with plasma concentration with a high level of sensitivity. The ECT assay displays a linear relationship with drug plasma concentrations in the clinically relevant drug concentration range and exhibits adequate sensitivity and precision. The TT and ECT assays are the most sensitive clotting assays followed by aPTT and PT.[64]

The PK/PD characteristics of dabigatran were evaluated in patients undergoing orthopaedic surgery using data from the BISTRO I study,[65] and results obtained confirmed the findings in normal healthy subjects.[66] The coagulation parameters assessed were aPTT and ECT, and the relationship between plasma concentration and anticoagulant activity was also determined. The aPTT model was less sensitive and non-linear up to 200 mg, then became linear. The ECT model was more sensitive and linear even at high plasma concentrations. Maximum prolongation of both aPTT and ECT occurred approximately 2 hours after oral administration of dabigatran and was dose related. Both models demonstrated that anticoagulant response varies with time after surgery with highest response immediately after surgery and declining with time. The effects of patient demographics (age, weight, gender, creatinine clearance) and treatment effects (fed/fasted condition, concomitant medications) on anticoagulant activity was also evaluated. Taking into consideration all variables, the inter- and intra-individual variation was found to be low.[66]

## *Reversibility*

Bleeding is the major adverse reaction of anticoagulants and there may be situations where it becomes necessary to reverse the anticoagulant effect to prevent excess bleeding, particularly pericardial, intraspinal or intracranial bleeds. Such situations include dosing errors, increased exposure due to renal impairment or due to emergency medical procedures. The anticoagulant effect of warfarin and heparins can be reversed with protamine sulphate and prothrombin supplementation, respectively. However, there are as yet no specific reversal agents for dabigatran to prevent severe bleeding. For patients undergoing elective surgery, discontinuation of dabigatran before surgery is recommended and its short half life and duration may help in reducing circulating levels. Assessment of the anticoagulated state using the appropriate coagulation assay is essential so that the correct interpretation can be made. PT (INR) is less sensitive than other assays; TT and ECT are the most sensitive and aPTT provides useful qualitative assessment, but is less sensitive at higher than therapeutic levels. Dabigatran overdose may be reversible using activated charcoal as it is lipophilic and can be completely removed from suspension in water and from plasma *in vitro* by activated charcoal.[67] Haemodialysis may be used to remove dabigatran from the blood as there is relatively low protein binding (< 35%) particularly in patients with renal impairment, based on a study in which dabigatran was given to patients with end stage renal disease and receiving haemodialysis. Preclinical studies have indicated that prolonged bleeding time may be reversed using recombinant activated factor VII or activated prothrombin complex.[68]

## *Pharmacokinetics*

Studies with normal healthy subjects and patient groups have shown that dabigatran has a predictable dose-related and linear PK profile. The PK of dabigatran in normal healthy male volunteers has a coefficient of variation of 30% and is also consistent across a broad range of different patient populations. It is unaffected by gender, body weight, ethnic origin, obesity and mild-to-moderate hepatic impairment.[60,66,69,70]

### Absorption, metabolism and distribution

Absorption of dabigatran was investigated following a single 150 mg dose of dabigatran etexilate in healthy volunteers and patients undergoing total hip replacement. Absorption was not affected by food but was enhanced by an acidic environment. Based on these finding dabigatran etexilate is administered in a capsule formulation as pellets with a tartaric acid core, so that absorption is not affected by individual variations in gastric acid. Absorption was moderately reduced when co-administered to patients with the proton pump inhibitor pantoprazole. Food prolonged the time to peak plasma concentration ($C_{max}$) by approximately 2 hours without influencing the $C_{max}$ or area under the curve (AUC). Peak absorption was delayed when administered 1–3 hours post-surgery but absorption was rapid and comparable to normal subjects.[71]

Absorption of dabigatran following surgery appears to be biphasic, with reduced absorption in the first 24 hours, which increases in following days. This may reflect changes in gastric motility and pH in the first 24 hours post-surgery leading to individual variability in drug exposure with reduced variability in the days following surgery.[72]

In a placebo-controlled study with 40 healthy male subjects, dabigatran etexilate was administered as single doses of 10–400 mg or multiple doses of 50–400 mg three times daily for 6 days. The dabigatran peak plasma concentration ($C_{max}$) was reached within 2 hours (mean $T_{max}$ 1.5–2 hours) of oral administration indicating rapid conversion of the prodrug dabigatran etexilate to its active metabolite. Conversion is effectively complete with little trace of inactive metabolites. Rapid absorption of a single dabigatran dose was consistent with previous studies, with a mean $T_{max}$ of 1.5–2 hours and the increase of $C_{max}$ and AUC was dose related. Following a single dose of 150 mg of dabigatran, the plasma concentration declined in a biphasic manner once $C_{max}$ was reached, followed by a rapid distribution phase, falling to 30% of $C_{max}$ within 4–6 hours of dosing. There was a prolonged elimination phase with a terminal half life ($t_{½}$) of approximately 7–9 hours and dabigatran was eliminated mainly unchanged by renal excretion. The PK profile obtained after multiple doses was similar. Dabigatran plasma concentrations reached steady state within 3 days and maximum plasma levels ($C_{max}$) reflected accumulation of dabigatran in plasma. Both $C_{max}$ and AUC were dose related. The half life ($t_{½}$) was 14–17 hours and was dose-independent (Table 1).[59,64]

### Bioavailability and elimination

The fate of radiolabelled dabigatran was investigated in 10 healthy male subjects who received either 200 mg of oral radiolabelled [$^{14}$C]-dabigatran or an i.v. infusion of 5 mg of [$^{14}$C]-dabigatran etexilate.[57] Radioactivity was measured in plasma, urine and faeces over 1 week. Peak plasma radioactivity was seen after 1.5 hours confirming previous findings of rapid absorption,[71] but absolute bioavailability was low (6–7%). Binding of dabigatran to plasma proteins was also low (35%) thereby reducing the risk of protein binding interactions. Dabigatran undergoes conjugation with activated glucuronic acid to yield pharmacologically active, but unstable, glucuronide conjugates, which account for approximately 20% of total dabigatran in plasma. It is eliminated unchanged predominantly by renal excretion (77%) with a further 4% accounted for by the glucuronide conjugates. Since renal function decreases with age, prolonged elimination is likely in the elderly. Incubation of radiolabelled plasma samples with human liver microsomes confirmed that dabigatran etexilate is metabolised primarily by esterases and demonstrated that dabigatran is not metabolised by

Table 1. Arithmetic mean PK parameters of dabigatran after single-dose oral administration (10–400 mg dabigatran etexilate) and after multiple-dose administration of 50–400 mg dabigatran etexilate three times daily (reproduced from Stangier *et al.*[64]).

| Parameter | Dose of dabigatran etexilate (mg) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Single-dose study | | | | | Multiple-dose study | | | |
| | 10 (n = 6) | 30 (n = 6) | 100 (n = 6) | 200 (n = 6) | 400 (n = 6) | 50 (n = 7–8) | 100 (n = 8) | 200 (n = 8) | 500 (n = 8) |
| $C_{max}$ (ng ml$^{-1}$) | 8.3 | 21.5 | 82.2 | 161.0 | 344.0 | 42.6 | 128.0 | 199.0 | 303.0 |
| (CV%) | (30.1) | (42.7) | (30.0) | (28.1) | (39.4) | (42.1) | (46.2) | (15.6) | (29.6) |
| $t_{max}$* (h) | 1.25 | 1.25 | 1.50 | 1.50 | 1.50 | 1.25 | 1.50 | 1.50 | 1.25 |
| $C_{max}$ (ng ml$^{-1}$) | – | – | – | – | – | 64.3 | 191.0 | 359.0 | 697.0 |
| (CV%) | | | | | | (34.6) | (20.5) | (14.6) | (33.0) |
| $C_{min,ss}$ (ng ml$^{-1}$) | – | – | – | – | – | 18.1 | 56.9 | 105.0 | 224.0 |
| (CV%) | | | | | | (31.1) | (33.2) | (21.4) | (33.7) |
| $t_{max,ss}$ (h) | – | – | – | – | – | 1.5 | 1.5 | 1.5 | 1.5 |
| $t_{½}$ (h) | – | – | 7.1 | 8.4 | 8.9 | 7.3 | 14.0 | 17.2 | 16.4 |
| (CV%) | | | (11.9) | (12.9) | (9.4) | (13.6) | (32.3) | (19.2) | (15.5) |
| $AUC_{(0,\infty)}$ (ng ml$^{-1}$ h) | – | – | 548 | 1110 | 2380 | – | – | – | – |
| (CV%) | | | (31.5) | (26.7) | (40.3) | | | | |
| $AUC_{(0,8\ h)}$ (ng ml$^{-1}$ h) | – | – | – | – | – | 165 | 552 | 821 | 1290 |
| (CV%) | | | | | | (33.7) | (45.3) | (16.5) | (32.4) |
| $AUC_{ss}$ (ng ml$^{-1}$ h) | – | – | – | – | – | 305 | 904 | 1620 | 3270 |
| (CV%) | – | – | – | – | – | (32.6) | (25.5) | (18.5) | (32.3) |
| $MRT_{tot}$ (h) | – | – | 8.7 | 9.6 | 10.3 | – | – | – | – |
| (CV%) | | | (11.3) | (15.3) | (10.2) | | | | |
| $MRT_{ss}$ (h) | – | – | – | – | – | 9.0 | 10.6 | 10.1 | 11.0 |
| (CV%) | | | | | | (12.8) | (11.0) | (7.67) | (10.7) |
| $CL_{tot}/F$ (ml min$^{-1}$) | – | – | 2430 | 2390 | 2410 | 2260 | 1480 | 1590 | 1660 |
| (CV%) | | | (23.7) | (26.6) | (39.2) | (33.9) | (28.4) | (17.4) | (28.8) |
| $V_z/F$ (l) | – | – | 1470 | 1720 | 1830 | 1430 | 1840 | 2390 | 2400 |
| (CV%) | | | (21.7) | (23.9) | (36.8) | (36.1) | (48.1) | (31.7) | (35.1) |

*Median values

the P450 isoenzyme system and does not inhibit P450-dependent reactions, suggesting that the likelihood of drug interactions with other drugs that are metabolised by this system is minimal.[57]

## *Special patient populations*

### Elderly subjects:

The PK profile of 36 healthy elderly subjects over 65 years was assessed to determine the effect of age and gender on exposure to dabigatran. After 6 days' twice-daily dosing with 150 mg of dabigatran etexilate, with one dose on day 7, $C_{max}$ was reached between 2–4 hours with plasma levels 1.7–2-fold higher in an elderly age group than in younger subjects. Exposure, as determined by mean AUC, was higher by 20–30% in female subjects, indicating gender-related differences in elderly female subjects, which were not considered clinically relevant. The anticoagulant activity of dabigatran correlated with the plasma concentration, without any time delay, confirming rapid absorption and metabolism to the active drug. The coefficient of variation between individuals was low (28%), confirming the predictable nature of dabigatran PK in elderly as well as younger subjects. The 40–60% increase in dabigatran exposure in elderly healthy subjects compared with younger healthy subjects is associated with age and attributed to changes in renal function and age-related reduction in creatinine clearance rates ($CL_{CR}$).[60,73]

### Renal impairment:

Variations in dabigatran exposure have been found in patient groups with normal or impaired renal function, and to eliminate this source of variation, patients with severe renal impairment have been excluded from study groups in Phase III trials with dabigatran. The effect of mild-to-severe renal impairment was investigated in 35 subjects aged between 18 and 75 years, divided into groups according to their creatinine clearance rates ($CL_{CR}$). Subjects included patients with end stage renal disease on haemodialysis and a group of healthy subjects with normal renal function. All subjects received a single dose of 150 mg of dabigatran and blood samples were collected at intervals of up to 96 hours post-dosing. Renal impairment did not cause delay in the rapid absorption of dabigatran, with a mean $T_{max}$ of 2–2.5 hours. The mean $C_{max}$ and exposure (AUC) to dabigatran increased proportionately to the degree of renal impairment 1.5-, 3.2- and 6.3-fold in patients with mild, moderate and severe renal impairment, respectively, compared with healthy subjects. In subjects on haemodialysis 62–68% of the dose was removed. Elimination was also prolonged with a doubling of the mean terminal half-life ($t_{½}$) from 14 to 28 hours in subjects with severe renal impairment. Overall recovery of dabigatran in urine was not affected by renal impairment but the percentage excreted as glucuronide conjugates increased in proportion to the degree of renal impairment compared with healthy

subjects. The PD parameters (aPTT and ECT) reflected the changes in PK properties of dabigatran in these study groups. Moderate-to-severe renal impairment resulted in significant accumulation, increased exposure and delayed renal clearance of dabigatran, in proportion to the degree of severity. Clarification of the effect of renal impairment on dabigatran PK may be useful for making dose adjustments, particularly since renal dysfunction is associated with increasing age.[74]

## Clinical efficacy

Dabigatran is a promising emerging therapeutic for thromboprophylaxis of stroke prevention in AF. Phase II and Phase III clinical trials have been completed for efficacy and tolerability of dabigatran in comparison with warfarin and other therapies.[45,55]

### *Outcome measures for stroke prevention in atrial fibrillation*

The primary study outcome measures for dabigatran in stroke prevention in AF are stroke (including haemorrhagic) or systemic embolism, defined as a sudden onset of neurological deficit consistent with the territory of a major cerebral artery and categorised as ischaemic, haemorrhagic or unspecified. Secondary study outcome measures are stroke (including haemorrhagic), systemic embolism and death. Other outcomes included myocardial infarction (MI), pulmonary embolism, transient ischaemic attack (TIA) and hospitalisation. The primary safety outcome was major haemorrhage.[75]

### *Therapeutic dose*

Dose escalating studies to determine the safe therapeutic range for clinical efficacy of dabigatran anticoagulant activity were originally carried out in patients undergoing orthopaedic surgery. These patients are at high risk of developing VTE post-surgery without thromboprophylaxis. In the BISTRO-I (Boehringer Ingelheim Study in Thrombosis) study, 289 patients received doses of oral dabigatran etexilate ranging from 12.5 to 300 mg twice daily or 150 mg once daily, or 300 mg once daily 4–8 hours after surgery for 6–10 days. The primary efficacy endpoint was the rate of VTE as defined by venographic deep-vein thrombosis, symptomatic DVT and pulmonary embolism during the treatment period. Increasing doses of dabigatran were associated with reduced incidence of DVT (20.8% and 6.1% with 12.5 mg and 300 mg, respectively) and none of the patients developed pulmonary embolism although no consistent dose-related response was seen.[65]

In the BISTRO II study, 1973 orthopaedic surgery patients were randomised to receive oral dabigatran etexilate at four different doses (50, 150 or 225 mg twice daily, or 300 mg once daily) given at the earlier time of 1–4 hours after surgery or subcutaneous enoxaparin given 12 hours before surgery. Using the same primary efficacy endpoint as BISTRO I, this study demonstrated a dose-related reduction in the incidence of VTE with increasing dose of dabigatran (28.5%, 17.4%, 13.1% and 16.6%, with 50, 150 and 225 mg twice daily, and 300 mg once daily, respectively $p < 0.001$). Compared with 24% incidence with enoxaparin, all doses of dabigatran were more effective; the 225 mg dabigatran group had the lowest incidence (13.1% $p = 0.0007$). Major bleeding incidence was lower than enoxaparin at lower doses of dabigatran but higher at the 150 mg and 300 mg doses.[76]

The therapeutic dose range identified in trials with orthopaedic patients[65,76] provided the basis for a pilot study that was used to define the therapeutic dose for patients with AF. The Prevention of Embolic and Thrombotic Events in Patients with Persistent AF (PETRO) was a Phase II multicentre trial to determine a safe therapeutic dose range of dabigatran in patients with non-valvular AF and at high risk of thromboembolism.[77] A total of 502 patients with AF were randomised to receive 50, 150 or 300 mg of dabigatran twice daily alone or in combination with 81 or 325 mg of aspirin. The open-label comparator group received warfarin administered to achieve an international normalised ratio of 2–3. Warfarin pre-treatment was terminated at randomisation and levels were below INR 1.5 before the start of the study treatment, which continued for a period of 12 weeks. Blood and urine samples were taken at 1, 2, 4, 8 and 12 weeks. Study efficacy outcome was thromboembolic events but these were limited to the 50 mg dabigatran dose groups. The primary safety outcome of bleeding was limited to higher dabigatran doses (300 mg) with aspirin (Table 2). Plasma dabigatran levels increased in a linear fashion with increasing doses of dabigatran and correlated with increases in anticoagulant activity as measured by aPTT, although there was a flattening of response at higher doses. D-dimer (a fibrin degradation product) suppression also correlated with increasing levels of dabigatran, as a measure of long-term effects of anticoagulation. The clinical observations were therefore consistent with PK and PD measurements. There was an unexplained increase in urinary 11-dehydrothromboxane B2 (DTB2) that reflects an amount of platelet activation. No serious liver toxicity was found with any dose of dabigatran.[77]

In a long-term extension of the original PETRO study (PETRO-Ex), all patients on warfarin were discontinued from the study and the remaining 361 patients were initially maintained on the same doses of dabigatran, apart from the 50 mg twice-daily group who were switched to 150 mg once daily. There was a higher frequency of bleeding in the 300 mg twice-daily group and a higher frequency of thromboembolic events in the 150 mg once-daily group, and all patients in these groups were switched to either 300 mg once daily or 150 mg twice daily. Results from PETRO and PETRO-Ex were pooled and events expressed as the absolute number per 100 patient years. Thromboembolic events were lowest in the dabigatran 150 mg and 300 mg twice-daily groups but bleeding events were higher in the dabigatran 300 mg group. On the basis of these results, taking into consideration the balance between


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Table 2. Summary of data from the PETRO study showing major and clinically relevant bleeding episodes and thromboembolic events in each treatment group (taken from Ezekowitz *et al.*[77]).

| Dabigatran dose (mg twice daily) | Aspirin dose (mg) | No. of patients | Bleeding events | | | Thromboembolic events |
|---|---|---|---|---|---|---|
| | | | Major | Clinically relevant plus major | Total | |
| 50 | 0 | 59 | 0 | 0 | 2 (3.4%) | 1 (1.7%) |
| 50 | 81 | 21 | 0 | 1 (4.8%) | 2 (9.5%) | 1 (4.8%) |
| 50 | 325 | 27 | 0 | 1 (3.7%) | 3 (11.1%) | 0 |
| 150 | 0 | 100 | 0 | 9 (9%) | 15 (15%) | 0 |
| 150 | 81 | 36 | 0 | 2 (5.6%) | 8 (22.2%) | 0 |
| 150 | 325 | 33 | 0 | 2 (6.1%) | 7 (21.2%) | 0 |
| 300 | 0 | 105 | 0 | 6 (5.7%) | 14 (13.3%) | 0 |
| 300 | 81 | 34 | 1 (2.9%) | 5 (14.7%) | 11 (32.4%) | 0 |
| 300 | 325 | 30 | 3 (10%) | 6 (20%) | 14 (46.7%) | 0 |
| Warfarin once daily | 0 | 70 | 0 | 4 (5.7%) | 12 (17.1%) | 0 |

stroke and risk of bleeding, a dose of dabigatran between 100 and 150 mg was selected as providing well-tolerated and effective anticoagulant activity for further clinical studies.[78,79]

## *Efficacy for stroke prevention in atrial fibrillation compared with warfarin*

The RE-LY study (Randomised Evaluation of Long-Term Anticoagulation Therapy) was a Phase III, multicentre study comparing dabigatran and warfarin for long-term safety and efficacy in patients with AF and at least one risk factor for stroke. The purpose of the RE-LY study was to demonstrate non-inferiority of dabigatran compared to warfarin for stroke prevention in AF. The trial design was prospective, open-label and randomised with blinded evaluation of all events (PROBE). This design strategy allows patients to know whether they are taking warfarin or dabigatran but not the dose; however, the evaluation was considered sufficiently thorough to mitigate this. The study group of over 18,000 patients comprised 50% anticoagulant-naïve patients who had received no more than two months of warfarin treatment and 50% warfarin-experienced patients. The mean age was 71 years and the mean $CHADS_2$ score was 2.1. Patients received one of two doses of dabigatran (110 and 150 mg) twice daily or dose-adjusted warfarin (adjusted to an INR of 2–3) and were followed up at three-monthly intervals during the first year and at four-monthly intervals during the second year.[80] The primary efficacy outcome of the study was stroke or systemic embolism and occurred in 183 patients in the dabigatran 110 mg group, 134 patients in the 150 mg group and 202 patients in the warfarin group, and both doses of dabigatran were statistically non-inferior to warfarin ($p < 0.001$). The 150 mg dose of dabigatran was superior to warfarin (1.11% *vs* 1.71%, RR 0.65 [95% CI: 0.52–0.81], $p < 0.001$) (Figures 3 and 4, and Table 3).[75,81,82]

Rates of secondary outcomes with dabigatran were also non-inferior to warfarin, apart from risk of MI, which was found to be higher than warfarin with both doses of dabigatran. A re-analysis of the data was carried out to include additional events reported after the first publication, including silent MI evident by electrocardiography. The relative risk of MI with 110 mg dabigatran was 0.82% *vs* 0.64%, RR 1.29 (95% CI: 0.96–1.75, $p = 0.09$) and with 150 mg dabigatran was 0.81% *vs* 0.64%, RR 1.27 (95% CI: 0.94–1.71, $p = 0.12$). Neither were significantly different to warfarin.[82] Since warfarin is known to reduce the risk of MI, it may provide better protection against MI than dabigatran.

Bleeding is the major adverse event when using anticoagulants and the most life-threatening event is intracranial haemorrhage, especially haemorrhagic stroke. The primary safety outcome of the RE-LY study was major bleeding events. The rate of major bleeding events was significantly less in the dabigatran 110 mg group compared with warfarin (2.87% *vs* 3.57%, respectively) with a relative risk of 0.80 (95% CI: 0.70–0.93; $p = 0.003$), but was similar to warfarin in the dabigatran 150 mg group (3.32% *vs* 3.57% per year) with a relative risk of 0.93 (95% CI: 0.81–1.07; $p = 0.32$). The rate of intracranial bleeding was significantly less with dabigatran 110 mg (0.23%) and dabigatran 150 mg (0.30%) than with warfarin (0.74%) ($p < 0.001$). Gastrointestinal bleeding was the only safety outcome that occurred at a significantly higher rate with dabigatran 150 mg than with warfarin.[75,81,82]

When the net clinical benefit as a measure of overall benefit and risk was combined to include major vascular events, major bleeding and death, the outcome was similar between both doses of dabigatran reflecting the reduced risk of stroke at the higher dose of 150 mg and reduced risk of bleeding at the lower dose of 110 mg.[75]

### Efficacy in warfarin-naïve or warfarin-experienced patients

There was no significant difference in dabigatran efficacy in reducing relative risk of stroke or systemic embolism between patients who had been on long-term therapy with warfarin compared with patients who had not previously received warfarin therapy.[75]

 
 

Figure 3. Cumulative hazard rates for the primary outcome of stroke or systemic embolism, comparing dose adjusted warfarin with 150 mg dabigatran or 110 mg dabigatran (taken from Connolly *et al.*[75]).

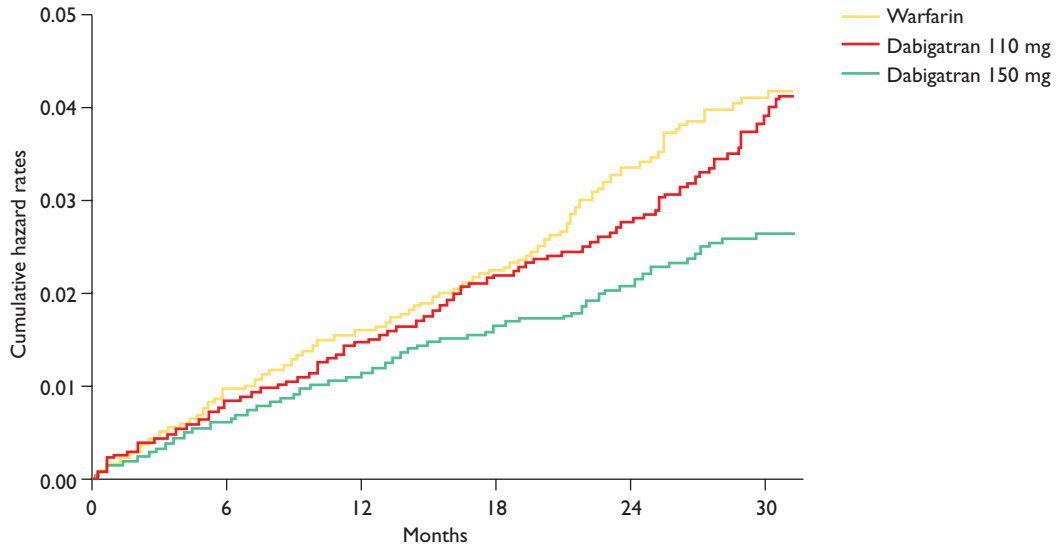


Figure 4. Relative risks of stroke or systemic embolism in the RE-LY trial, comparing warfarin with 150 mg dabigatran (D150) or 110 mg dabigatran (D110) (taken from Ezekowitz *et al.*[25], reproduced from Connolly[83]).

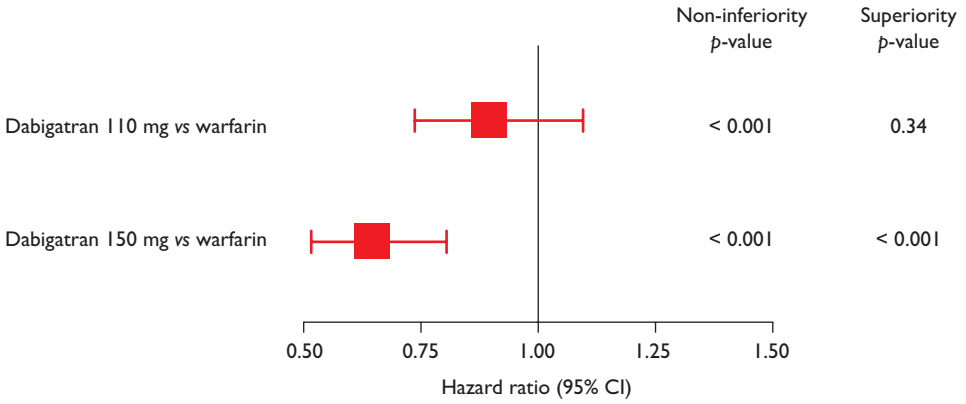


Table 3. Primary efficacy and safety outcomes and myocardial infarction, according to treatment groups (adapted from Connolly *et al.*[82]).

| Event | Dabigatran 110 mg (n = 6015) | | Dabigatran 150 mg (n = 6076) | | Warfarin (n = 6022) | | Dabigatran 110 mg *vs* warfarin | | Dabigatran 150 mg *vs* warfarin | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Number of patients | (%/yr) | Number of patients | (%/yr) | Number of patients | (%/yr) | Relative risk (95% CI) | P-value | Relative risk (95% CI) | P-value |
| Stroke or systemic embolism | 183 | 1.54 | 134 | 1.11 | 202 | 1.71 | 0.90 (0.74–1.10) | 0.30 | 0.65 (0.52–0.81) | < 0.001 |
| Major bleeding | 342 | 2.87 | 399 | 3.32 | 421 | 3.57 | 0.80 (0.70–0.93) | 0.003 | 0.93 (0.81–1.07) | 0.32 |
| Myocardial infarction | 98 | 0.82 | 97 | 0.81 | 75 | 0.64 | 1.29 (0.96–1.75) | 0.09 | 1.27 (0.94–1.71) | 0.12 |


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### Efficacy in subgroups of patients with previous stroke

Subgroups of patients in the RE-LY trial with AF and with or without previous stroke or TIA (provided the events did not occur within 2 weeks of enrolment), were re-evaluated for the same primary outcomes. In patients with previous stroke or TIA, which is the highest risk factor for stroke in patients with AF, there was a higher annual rate of stroke. The standard treatment for these high-risk patients is warfarin, although there is a National Institute for Health and Clinical Excellence (NICE) health technology appraisal in progress for dabigatran etexilate for the prevention of stroke in AF that is expected to be issued at the end of 2011.[83] Results of this sub-group analysis are consistent with the main results of the RE-LY study and demonstrated that the effects of warfarin and both doses of dabigatran were not significantly different between patient groups who had or had not suffered previous stroke or TIA for any of the outcomes of the RE-LY trial, apart from vascular death.[84]

### *Efficacy for stroke prevention in atrial fibrillation compared with antiplatelet therapy and placebo*

Many high-risk patients who are eligible for antithrombotic therapy with warfarin have not been receiving oral anticoagulant even if there are no contraindications for use. Instead these patients often receive antiplatelet therapy with aspirin or clopidogrel, which is recommended for low-risk patients. A network meta-analysis (NMA) was performed to indirectly compare the efficacy and safety data of published studies using dabigatran etexilate 110 mg or 150 mg, antiplatelet therapy (aspirin and clopidogrel) and placebo. Compared with placebo, dabigatran 150 mg twice daily reduced the risk of any stroke by 75%, by 63% compared with aspirin monotherapy and by 61% compared with aspirin plus clopidogrel. Dabigatran at both therapeutic doses (110 mg and 150 mg) reduced risk of any stroke with more efficacy than aspirin or clopidogrel without evidence of increased intracranial or extracranial haemorrhage. Also, relative risk estimates of dabigatran compared with dose-adjusted warfarin were consistent with trials in which direct comparisons were made.[85]*

### *Importance of INR control in clinical outcomes of anticoagulant therapy in atrial fibrillation*

Since efficacy and safety of warfarin therapy is strongly associated with TTR with an INR of 2–3, variations in TTR between individuals and treatment centre can affect outcomes for high-risk patients with AF who are eligible for antithrombotic therapy. The mean TTR for the warfarin patient group in the RE-LY trial was 64% which was similar to that of other trials and meta-analyses. The overall TTR was analysed in terms of the individual TTR (iTTR) and the centre TTR (cTTR) for primary and secondary outcomes of the RE-LY trial. Centres were grouped into four quartiles and outcomes compared by quartile, with cTTRs of < 57.1%, 57.1–65.5%, 65.5–72.6% and > 72.6%. Variation between individuals, centres and countries accounted for differences in quality of warfarin therapy. Clinical benefits of 150 mg dabigatran in reducing stroke and 110 mg in reducing bleeding compared with warfarin were consistent irrespective of the quality of INR control at each centre. For all vascular events, non-haemorrhagic events and mortality, advantages of dabigatran were greater at sites with poor INR control. Varying standards of care at different centres with respect to warfarin TTR did affect the interpretation of clinical outcomes and also the benefits of using dabigatran at those centres.[21,86]

### *Indirect comparisons of clinical efficacy between dabigatran and other antithrombotic therapy*

In an indirect comparison of antithrombotic therapies available at the time including drugs targeting specific coagulation factors, dabigatran appears to offer effective primary prevention in reducing the risk of stroke and systemic embolism compared with these drugs and compared with warfarin (Figure 5).[87]

## Safety and tolerability

### *Adverse events*

The adverse events reported in the RE-LY study are summarised in Table 4. This table also includes study-drug discontinuation rates and liver enzyme levels to represent liver function. Dyspepsia was the only adverse event that occurred more frequently in both dabigatran groups:11.8% and 11.3% with 110 mg and 150 mg, respectively, compared to 5.8% in the warfarin group ($p < 0.001$ for both comparisons). This may be explained by the use of tartaric acid in dabigatran capsules, which is added to maintain the low pH required to enhance absorption of dabigatran (Table 4).[75]

### *Study drug discontinuation*

Discontinuation rates in both the first and second year of the RE-LY trial were greater in both dabigatran groups than the warfarin group. Gastrointestinal symptoms led to greater study-drug discontinuation rates in both dabigatran groups at 2.2% and 2.1% for dabigatran 110 mg and 150 mg, respectively, compared with 0.6% in the warfarin group.[75]

### *Liver function*

No significant differences were seen in rates of increased liver enzyme concentrations (alanine aminotransferase and aspartate aminotransferase) between patients groups with AF who received dabigatran 110 mg or 150 mg compared with warfarin[75] or enoxaparin.[76]

*Absolute rates not available in publication.

 
 

Figure 5. Indirect comparison of relative effects of placebo or no therapy, antiplatelet therapy with aspirin, dual antiplatelet therapy with aspirin and clopidogrel, and with OACs ximelagatran and dabigatran compared with warfarin in reducing risk of stroke and systemic embolism among patients with AF in clinical trials (after Hankey and Eikelboom[87], reproduced from Medi *et al.*[11] and Weber *et al.*[44]).

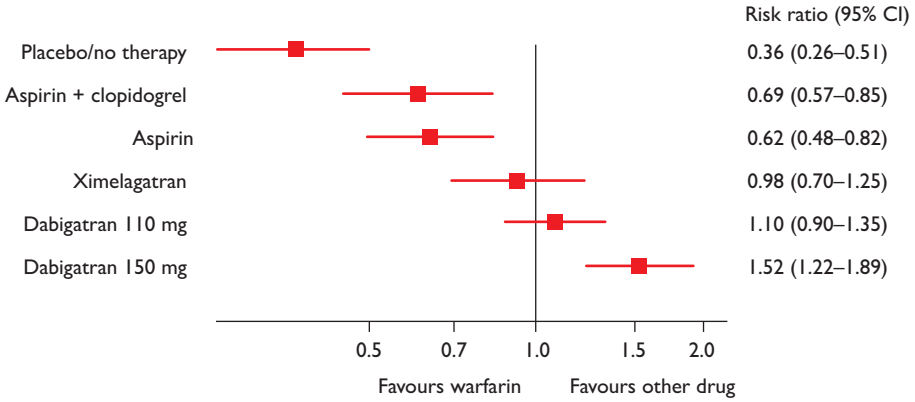


Table 4. Study-drug discontinuation, adverse events and liver function according to treatment groups in the RE-LY study (taken from Connolly *et al.*[75]). Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of the normal range.

| Variable | Dabigatran, 110 mg (n = 6015) Number of patients (%) | Dabigatran, 150 mg (n = 6076) Number of patients (%) | Warfarin (n = 6022) Number of patients (%) |
|---|---|---|---|
| Study-drug discontinuation | | | |
| Discontinued at 1 year | 862 (15) | 935 (16) | 608 (10) |
| Discontinued at 2 years | 1161 (21) | 1211 (21) | 902 (17) |
| Reason for discontinuation | | | |
| Patient's decision | 440 (7.3) | 474 (7.8) | 375 (6.2) |
| Outcome event | 192 (3.2) | 164 (2.7) | 130 (2.2) |
| Serious adverse event | 163 (2.7) | 166 (2.7) | 105 (1.7) |
| Gastrointestinal symptoms | 134 (2.2) | 130 (2.1) | 38 (0.6) |
| Gastrointestinal bleeding | 58 (1.0) | 80 (1.3) | 54 (0.9) |
| Adverse events | | | |
| Dyspepsia | 707 (11.8) | 688 (11.3) | 348 (5.8) |
| Dizziness | 486 (8.1) | 506 (8.3) | 568 (9.4) |
| Dyspnoea | 557 (9.3) | 580 (9.5) | 586 (9.7) |
| Peripheral oedema | 473 (7.9) | 478 (7.9) | 468 (7.8) |
| Fatigue | 399 (6.6) | 401 (6.6) | 372 (6.2) |
| Cough | 344 (5.7) | 348 (5.7) | 364 (6.0) |
| Chest pain | 312 (5.2) | 377 (6.2) | 357 (5.9) |
| Back pain | 316 (5.3) | 324 (5.2) | 337 (5.6) |
| Arthralgia | 270 (4.5) | 335 (5.5) | 346 (5.7) |
| Nasopharyngitis | 337 (5.6) | 330 (5.4) | 336 (5.6) |
| Diarrhoea | 377 (6.3) | 397 (6.5) | 346 (5.7) |
| Atrial fibrillation | 330 (5.5) | 357 (5.9) | 349 (5.8) |
| Urinary tract infection | 273 (4.5) | 289 (4.8) | 335 (5.6) |
| Upper respiratory tract infection | 288 (4.8) | 285 (4.7) | 323 (5.2) |
| Liver function | | | |
| ALT or AST > 3 × ULN | 124 (2.1) | 117 (1.9) | 132 (2.2) |
| ALT or AST > 3 × ULN with concurrent bilirubin > 2 × ULN | 13 (0.2) | 13 (0.2) | 21 (0.3) |
| Hepatobiliary disorder | | | |
| Serious adverse event | 33 (0.5) | 34 (0.6) | 33 (0.5) |
| Non-serious adverse event | 101 (1.7) | 109 (1.8) | 112 (1.9) |


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### *Drug interactions*

Dabigatran is not metabolised by cytochrome P450 isoenzymes, which suggests that there is minimal potential for interaction of dabigatran with drugs that are metabolised by the P450 system. *In vivo* drug interaction studies were carried out with the HMG-CoA reductase inhibitor atorvastatin,[88] a substrate of CYP3A4 and a substrate/inhibitor of P-glycoprotein (P-gp), the NSAID diclofenac,[89] a substrate of CYP2C9 and uridine glucuronosyltransferase (UGT) 2B7 also a substrate and weak inhibitor of UGT1A, and the cardiac glycoside digoxin[90] a substrate of P-gp. No interactions with these three drugs were observed, and there were no relevant effects on the PD or PK of dabigatran. This lack of interaction is also advantageous in the case of differential enzyme expression of P450 between individuals.[57]

## Pharmacoeconomics

The drug dabigatran etexilate may cost more than conventional anticoagulants like warfarin and enoxaparin; however, dabigatran may be more economic due to the convenience of oral administration, no requirement for coagulation monitoring or dose adjustments and improved tolerability. Overall costs of using dabigatran etexilate were evaluated compared with enoxaparin in elderly patients with renal impairment for prevention of VTE following total hip- or knee-replacement surgery. The findings indicated that dabigatran etexilate was cost-saving with comparable safety and efficacy profiles.[91]

The cost-effectiveness of doses of 110 mg and 150 mg dabigatran was evaluated compared with adjusted-dose warfarin for stroke prevention in patients over 65 with AF. A Markov decision model was used to evaluate data from the RE-LY trial to measure quality-adjusted life-years (QALYs), costs (in 2008 U.S. dollars) and incremental cost-effectiveness ratios (ICERs). Under base-case conditions, the quality-adjusted life expectancy was 10.28, 10.70 and 10.84 QALYs with warfarin, 110 mg dabigatran and 150 mg dabigatran, respectively. In patients at higher risk of stroke ($CHADS_2$ score ≥ 2), the ICER of dabigatran compared with warfarin was improved. This evaluation demonstrated that dabigatran could be a cost-effective alternative to adjusted-dose warfarin for stroke prevention in patients > 65 years with non-valvular AF at increased risk for stroke ($CHADS_2$ score ≥ 1 or equivalent).[92]

**Key points:**

- Dabigatran is an oral anticoagulant that targets a single point of the coagulation cascade and is a specific inhibitor of thrombin activity and generation.
- Dabigatran has a predictable PK profile with a clear correlation between plasma concentration and anticoagulant activity, rapid onset of action and can be administered at a fixed dose without the need for coagulation monitoring.
- Dabigatran is not metabolised by cytochrome P450 isoenzymes and therefore has a low potential for drug–drug interactions; also it has no food interactions.
- There are two therapeutic doses (110 mg and 150 mg) for stroke reduction in AF that allow for dose tailoring, if required.
- In comparison with warfarin, dabigatran at the higher dose of 150 mg has superior efficacy for stroke reduction but is similar for risk of bleeding. At the lower dose of 110 mg dabigatran has similar efficacy for stroke reduction but is superior in reducing the risk of bleeding.
- Patients with renal impairment, which is common with increasing age, benefit from dabigatran anticoagulation therapy for AF, but are at risk of increased exposure and therefore dose-adjustment may be required in these patients.
- There is no evidence of liver toxicity with dabigatran at any dose.
- The adverse event profile of dabigatran is similar to warfarin with the exception of increased gastrointestinal problems.
- Dabigatran may fulfil a therapeutic need for an effective alternative to warfarin for stroke prevention in AF.

 
 

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