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ADIS DRUG EVALUATION

Dabigatran Etexilate: A Review of Its Use in the Treatment of Acute Venous Thromboembolism and Prevention of Venous Thromboembolism Recurrence

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Abstract Dabigatran etexilate (Pradaxa®, Prazaxa®) has recently been approved for the treatment of acute venous thromboembolism (VTE) and prevention of VTE recurrence. Dabigatran etexilate is an oral prodrug of dabigatran, a selective, reversible, competitive, direct thrombin inhibitor. Dabigatran etexilate has a wide therapeutic range that allows for fixed-dose administration without the need for routine monitoring, a requirement of standard vitamin K antagonist (VKA) therapy. In randomized phase III trials in patients with acute VTE (RE-COVER and RE-COVER II), long-term treatment with oral dabigatran etexilate 150 mg twice daily for 6 months after initial parenteral anticoagulation was noninferior to dose-adjusted warfarin with regard to the incidence of recurrent symptomatic VTE or related death. In randomized trials of patients with previously treated VTE, extended dabigatran etexilate treatment was noninferior to warfarin (RE-MEDY) and significantly more effective than placebo (RE-SONATE) with regard to the incidence of recurrent VTE or related death. Dabigatran etexilate was generally well tolerated, with a similar incidence of major bleeding to that with warfarin in individual studies (although pooled data showed a significantly lower incidence in patients with acute VTE), and significantly lower incidences of the combined endpoint of major or clinically relevant nonmajor bleeding and of any bleeding than with warfarin. However, in the RE-SONATE trial, dabigatran etexilate was associated with a higher risk of bleeding than placebo. In conclusion, dabigatran etexilate is a valuable treatment option for acute VTE and prevention of VTE recurrence, providing an effective and convenient alternative to standard VKA therapy with the potential for a lower overall rate of bleeding.

Dabigatran etexilate in acute venous thromboembolism (VTE) and prevention of VTE recurrence: a summary
Oral prodrug of dabigatran, a selective, reversible, competitive, direct thrombin inhibitor
Wide therapeutic range allows for fixed-dose regimen without routine anticoagulation monitoring
Noninferior to warfarin in preventing VTE recurrence in patients with acute or previously treated VTE
Significantly more effective than placebo in preventing VTE recurrence in patients with previously treated VTE
Similar incidence of major bleeding to that of warfarin in individual studies (although pooled data showed a significantly lower incidence in patients with acute VTE), and significantly lower incidences of the combined endpoint of major or clinically relevant nonmajor bleeding and of any bleeding
Associated with a higher risk of bleeding than placebo in patients with previously treated VTE

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1 Introduction

Venous thromboembolism (VTE), a disease term that includes both deep venous thrombosis (DVT) and pulmonary embolism (PE) [1], causes considerable worldwide morbidity and mortality [2]. DVT commonly occurs in the veins of the lower extremities and can potentially embolize, leading to pulmonary vasculature occlusion [1]. The annual incidence of VTE is 122 people per 100,000 person-years, with selected patient populations (e.g. cancer patients) having an increased rate of occurrence [1, 3]. An estimated 300,000–600,000 individuals are affected by VTE in the USA every year [2]. The estimated mortality rate of untreated VTE varies from <5 to 30 % depending on the presence of underlying risk factors (e.g. increased age, cardiac disease or thrombophilia) [4]. VTE can also lead to further complications, including an increased risk of recurrent VTE, post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension [5, 6].

Anticoagulation, the standard therapeutic approach for VTE, is comprised of three phases: an initial phase (lasting ≈7 days), long-term therapy (continued after initial treatment until ≈3 months) and extended anticoagulation (beyond 3 months with no scheduled end of treatment) [5]. The goals of long-term therapy are to complete treatment of the acute VTE episode and to prevent new episodes of VTE that are not related to the acute event. Extension of anticoagulation treatment beyond 3 months is suggested in patients with a high risk of VTE recurrence who have a low or moderate bleeding risk, with reassessment at regular intervals [5].

In patients with acute VTE, initial treatment with parenteral anticoagulation [i.e. unfractionated heparin, a low molecular weight heparin (LMWH) or fondaparinux sodium] is recommended [5]. Following initial therapy, long-term or extended anticoagulation with an oral vitamin K antagonist (VKA) is suggested in most patients [5]. Treatment with warfarin and other VKAs is associated with a number of limitations, including a narrow therapeutic range, dose response variability, slow onset and offset of action and multiple interactions with medications and food [7]. Therefore, patients on VKA therapy require frequent monitoring of anticoagulant activity and regular dosage adjustments to ensure the correct level of anticoagulation, which may be inconvenient and increase treatment costs. Other traditional anticoagulants, including unfractionated heparin, LMWHs and fondaparinux sodium, require intravenous or subcutaneous administration; thus, their use in the long-term or extended treatment of VTE in an outpatient setting is limited. While warfarin is the mainstay of oral anticoagulant therapy, its limitations have led to the development of alternative oral anticoagulants [7].

The oral anticoagulant dabigatran etexilate (Pradaxa®, Prazaxa®) is a prodrug of dabigatran, a direct competitive thrombin inhibitor [8, 9]. Like other recently developed novel oral anticoagulants (e.g. factor Xa inhibitors), dabigatran etexilate has several advantages over warfarin, including a rapid onset and offset of action, comparatively few drug interactions and a wide therapeutic range [10]. While this allows for fixed-dose administration without the requirement for frequent monitoring, recent evidence suggests some patient populations (i.e. the elderly and those with reduced renal function) may benefit from anticoagulant monitoring and/or dosage adjustment [11]. Dabigatran etexilate has recently been approved in the USA and the EU for long-term treatment of acute VTE after parenteral anticoagulation and extended treatment for prevention of recurrent VTE [8, 9]. This article provides an overview of the pharmacology of dabigatran etexilate and reviews the therapeutic efficacy and tolerability data from recent clinical trials of the drug for its recently approved indication. Dabigatran etexilate is also indicated for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and primary VTE prevention in patients following elective total hip or knee replacement surgery [8, 9]; however, these indications are reviewed elsewhere [12–14] and are beyond the scope of this review.

2 Pharmacodynamic Properties

This section provides a brief overview of the pharmacodynamic properties of dabigatran etexilate (summarized in Table 1), which have been previously reviewed [12–16].

Dabigatran etexilate is a prodrug of dabigatran, the active moiety in plasma (see Sect. 3 for details on conversion) [8, 15, 17]. Dabigatran is a direct thrombin inhibitor [8], with a strong affinity for human thrombin and highly selective binding properties [18], binding free and clot-bound thrombin and inhibiting thrombus formation [8, 19]. Dabigatran is also an inhibitor of thrombin-induced platelet aggregation [18], tissue factor-induced thrombin generation [18] and tissue factor-induced platelet aggregation (Table 1) [15].

The anticoagulant effect of dabigatran etexilate can be assessed by several methods with varying reliability. The diluted thrombin time (dTT) assay response is linear over a large dabigatran concentration range, and as such this assay is being used increasingly to determine the effects of dabigatran etexilate when required [20]. The dTT test is commercially available as the Hemoclot® Thrombin Inhibitor assay [21]. While the thrombin time (TT) assay also has a linear relationship with dabigatran concentrations, the high sensitivity of this assay limits its clinical use [20]. The ecarin clotting time (ECT) assay also provides a

Table 1 Key pharmacodynamic properties of dabigatran[a]

Mechanism of action
Selective, reversible, competitive direct inhibitor of thrombin, a key enzyme in the coagulation cascade [8, 18]
Strong affinity for active site of human thrombin (Ki 4.5 nmol/L) [18, 19]
Highly selective for thrombin, with selectivity ratios of >700 to >10,000 for thrombin versus the majority of other enzymes in the coagulation cascade [18]
Antithrombotic effects
Inhibits thrombus formation by binding to free and clot-bound thrombin, thereby blocking the conversion of fibrinogen to fibrin [8, 19]
Potent inhibitor of thrombin-induced platelet aggregation in vitro (IC_{50} 10 nmol/L) [18]
Concentration-dependent inhibition of tissue factor-induced thrombin generation in human platelet-poor plasma (IC_{50} 0.56 μmol/L) [18]
Exhibits greater inhibitory effect on tissue factor-induced platelet aggregation (IC_{50} 35 nmol/L) than rivaroxaban (IC_{50} 312 nmol/L) and apixiban (IC_{50} 817 nmol/L) in platelet-rich plasma [15]
Effects on coagulation parameters
Prolongs coagulation parameters such as aPTT, INR, TT and ECT in a dose-dependent manner [17, 23]
The aPTT assay has a curvilinear relationship with plasma concentrations, with low sensitivity at concentrations <200 ng/mL and reaching a plateau at concentrations >400 ng/mL [17, 23]
The INR, TT and ECT assays all display a linear relationship with plasma concentrations [17, 23]; the dTT assay has linear response over a larger concentration range than the TT assay and is commercially available [20, 21]
Rapid onset of action without a time delay, with E_{max} for coagulation parameters occurring at the same time as C_{max} within 2 h of oral dabigatran etexilate administration, indicative of a direct inhibitory effect on thrombin in plasma [23]
Offset of action occurs in parallel with decline in plasma concentrations, with a rapid initial decrease in effect on coagulation parameters at 4–6 h after C_{max}, followed by slow terminal phase [23]
Small residual pharmacodynamic effects and low plasma concentrations at 24 h after last administration in healthy volunteers [23]

aPTT activated partial thromboplastin time, C_{max} maximum plasma concentration, *dTT* diluted thrombin time, *ECT* ecarin clotting time, E_{max} maximum effect, IC_{50} 50 % maximum inhibitory concentration, *INR* international normalized ratio, *Ki* dissociation constant, *TT* thrombin time

[a] Dabigatran is the active moiety of the prodrug dabigatran etexilate

specific measure of the effect of dabigatran [8]; however, this assay is currently not commercially available [20]. The activated partial thromboplastin time (aPTT) assay provides an approximation of the anticoagulant effect of dabigatran etexilate [8]; however, the relationship is not linear within the dabigatran plasma concentration range used clinically [22]. The prothrombin time (PT) or international normalized ratio (INR) assay is relatively insensitive to dabigatran activity, and is therefore unsuitable as the primary measure of dabigatran anticoagulant effect [22].

The maximum effect (E_{max}) of dabigatran etexilate on coagulation parameters occurs within 2 h of oral administration, while the decrease in pharmacodynamic effect after the last administration occurs in parallel with the decline in dabigatran plasma concentrations (Table 1) [23].

Dabigatran etexilate at therapeutic (150 mg) and supratherapeutic (600 mg) doses is not associated with corrected QT (QTc) interval prolongation or arrhythmogenic effects according to the results of a thorough QTc interval study in 40 healthy volunteers [24].

Pharmacodynamic interactions may occur between dabigatran etexilate and other drugs, including aspirin, ticagrelor, clopidogrel, nonsteroidal anti-inflammatories (NSAIDs), selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), that could potentially result in an increased risk of bleeding [8, 9].

3 Pharmacokinetic Properties

This section provides a brief overview of the pharmacokinetic properties of dabigatran etexilate, which have been previously reviewed [12–16].

Dabigatran is a highly liphophilic molecule that is not orally available, and is therefore administered as the prodrug dabigatran etexilate [16]. After absorption, dabigatran etexilate is converted to dabigatran, the active moiety in the plasma [12]. In a study of healthy volunteers, dabigatran exhibited a dose-proportional pharmacokinetic profile, with C_{max} and AUC increasing linearly with single doses of 10–400 mg [23]. Steady-state conditions were reached on day 3 of multiple dosing with dabigatran etexilate 50–400 mg [23].

The absolute oral bioavailability of dabigatran is ≈6.5 % [9, 23]. Dabigatran etexilate, which is a substrate of the P-glycoprotein (P-gp) transporter, is rapidly absorbed after oral administration. In healthy volunteers, the maximum dabigatran plasma concentration (C_{max}) occurred 2 h after administration in the fasted state [16]. While the time to C_{max} after dabigatran etexilate administration following a

meal was delayed by a further 2 h, there was no overall effect on bioavailability. Dabigatran etexilate may therefore be administered with or without food [8, 9].

Following absorption, dabigatran etexilate is rapidly metabolized by microsomal carboxylesterases to dabigatran [16, 23, 25]. Dabigatran undergoes conjugation with glucuronic acid to form four positional isomers of acylglucuronides, each accounting for <10 % of total plasma dabigatran [8, 9]. Dabigatran and its acylglucuronides have similar pharmacological activity [8, 23].

The volume of distribution of dabigatran (50–70 L) exceeds the volume of total body water, consistent with a moderate tissue distribution of dabigatran [8, 9]. Approximately 35 % of dabigatran is bound to human plasma proteins [8, 9].

Dabigatran is eliminated predominantly by renal excretion, with ≈80 % of an intravenous dabigatran dose being excreted unchanged in the urine [16]. In healthy volunteers, 85 % of an intravenous dose of radiolabelled dabigatran was recovered in the urine; however, after oral administration, 7 % of the administered dose was excreted in the urine and 86 % was recovered in the faeces, consistent with the low oral bioavailability of dabibatran etexilate [8, 16]. Dabigatran plasma concentrations decrease in a biexponential manner, with a rapid distribution phase, resulting in concentrations declining to <30 % of C_{max} within 4–6 h of administration, followed by prolonged elimination [16]. The mean terminal elimination half-life ($t_{½\beta}$) of dabigatran is 12–14 h in healthy volunteers [8, 9].

3.1 Special Populations

Renal insufficiency is associated with increased dabigatran exposure [8, 9]. In an open-label study, subjects with mild [creatinine clearance (CL_{CR}) >50 to ≤80 mL/min], moderate (CL_{CR} >30 to ≤ 50 mL/min) or severe (CL_{CR} ≤30 mL/min) renal impairment had 1.5-, 3.2- and 6.3-fold increases in dabigatran area under the plasma concentration–time curve from time zero to infinity (AUC_{∞}) values, respectively, compared with healthy subjects after oral dabigatran etexilate administration [26]. The dabigatran mean C_{max} also increased in proportion with the level of renal impairment, while the apparent volume of distribution during the terminal phase decreased [26]. Renal excretion of dabigatran, which was almost complete within 24 h in healthy subjects or those with mild renal impairment, required more than 96 h in subjects with severe renal impairment. The mean $t_{½\beta}$ of dabigatran in subjects with renal impairment was also prolonged, with severe renal impairment being associated with a doubling of the $t_{½\beta}$ compared with healthy subjects [26]. See Sect. 6 for dosage recommendations in patients with renal impairment.

In elderly patients (aged ≥65 years), dabigatran exposure is increased compared with younger patients [9, 17]. In a study of healthy volunteers, elderly female and male subjects had a 1.7- and 2-fold increase, respectively, in dabigatran exposure compared with younger subjects [17]. This effect is likely to be caused by reduced renal function in the elderly compared with younger individuals [17]. See Sect. 6 for dosage recommendations in elderly patients.

The pharmacokinetic properties of dabigatran are not significantly affected by moderate hepatic impairment [8, 9]. However, the metabolism of dabigatran etexilate to active dabigatran is slower in patients with hepatic impairment than in healthy volunteers [27].

The prescribing information provides no recommendations for dosage adjustments based on ethnicity or gender [8, 9]. Similarly, dosage adjustments are generally not required based on weight; however, close clinical surveillance is recommended for patients weighing <50 kg [9].

3.2 Potential Drug Interactions

The prodrug dabigatran etexilate, but not dabigatran, is a substrate of the P-gp efflux transporter [8, 9]. Coadministration of dabigatran etexilate with P-gp inhibitors is expected to result in increased dabigatran exposure. For example, concomitant ketoconazole and dabigatran etexilate administration increased the dabigatran AUC by 153 % and the C_{max} by 149 % after multiple oral dosages of ketoconazole 400 mg daily [8, 9]. Close clinical monitoring is needed when dabigatran etexilate is coadministered with strong P-gp inhibitors, and in the EU, some of these agents are contraindicated (dronedarone, ketoconazole, ciclosporin and itraconazole) or not recommended (tacrolimus) in combination with dabigatran etexilate [9]. The EU summary of product characteristics recommends exercising caution during concomitant treatment with dabigatran etexilate and mild to moderate P-gp inhibitors, such as amiodarone, posaconazole, quinidine, clarithromycin, verapamil and ticagrelor, with dosage adjustments also required for verapamil [9]. In a study of healthy volunteers, coadministration of verapamil with dabigatran etexilate led to increased dabigatran bioavailability; however, the effects of the interaction could be minimized by administering dabigatran etexilate 2 h before verapamil [28]. In the USA, it is recommended that VTE patients with moderate renal impairment (CL_{CR} <50 mL/min) who are receiving P-gp inhibitor therapy avoid dabigatran etexilate treatment [8].

Concomitant administration of dabigatran etexilate and P-gp inducers, such as carbamazepine, phenytoin, St John's Wort and rifampicin, should be avoided due to reduced dabigatran exposure [8, 9]. In a study of healthy volunteers, dabigatran bioavailability was significantly reduced when a

single dose of dabigatran etexilate 150 mg was administered after treatment with rifampicin 600 mg once daily for 7 days [29]. Seven days after rifampicin discontinuation, dabigatran bioavailability had almost returned to baseline levels [29].

Ritonavir and other protease inhibitors can also affect P-gp transporters, either as inhibitors or inducers, and as clinical studies have not been performed with these combinations, concomitant administration with dabigatran etexilate is not recommended [9].

Concomitant administration of pantoprazole and dabigatran etexilate results in an ≈30 % decrease in the dabigatran AUC; however, during clinical trials of dabigatran etexilate with concomitant proton pump inhibitor treatment, there was no apparent reduction in dabigatran etexilate efficacy [8, 9].

Dabigatran etexilate and dabigatran are not metabolized by cytochrome P450 (CYP) enzymes and are not inhibitors or inducers of CYP enzyme activity [8, 9]. The pharmacokinetics of dabigatran showed no clinically relevant changes during concomitant administration of atorvastatin (metabolized by CYP3A4/5) [30] or diclofenac (metabolized by CYP2C9) [9] with dabigatran etexilate. Clopidogrel coadministration with dabigatran etexilate is associated with a slight increase in dabigatran exposure [8]; however, in a study of healthy volunteers, there were no significant effects on the pharmacokinetic properties of either agent at clinically relevant dosages [31]. Similarly, concomitant treatment with dabigatran etexilate and ranitidine, digoxin or enoxaparin sodium does not alter dabigatran exposure [8].

4 Therapeutic Efficacy

The therapeutic efficacy of dabigatran etexilate for long-term treatment of acute VTE (symptomatic proximal DVT or PE) (Sect. 4.1) and extended treatment for prevention of recurrent VTE (Sect. 4.2) was established in four large, randomized, double-blind, multinational, phase III trials (RE-COVER [32], RE-COVER II [33], RE-MEDY [34] and RE-SONATE [34]).

The RE-COVER and RE-COVER II trials were identically designed, 6-month, double-dummy trials to determine the noninferiority of oral dabigatran etexilate to warfarin therapy in the long-term treatment of acute VTE after initial parenteral anticoagulation [32, 33]. Patients with acute, symptomatic and objectively verified proximal DVT of the legs or PE were eligible, and enrolled patients were assigned in a 1:1 ratio to receive a fixed dose of oral dabigatran etexilate 150 mg twice daily or an adjusted dose of warfarin. The warfarin dosage was adjusted to maintain an INR of 2.0–3.0. All patients initially received parenteral anticoagulation with either intravenous unfractionated heparin or subcutaneous LMWH for a mean of ≈10 days [32, 33].

The RE-MEDY trial was similarly designed, but evaluated the noninferiority of dabigatran etexilate to warfarin for extended treatment for prevention of recurrent VTE, including death related to VTE [34]. Patients who had completed ≥3 months of treatment for an objectively confirmed proximal DVT or PE with an approved anticoagulant were eligible, as well as patients who had received dabigatran etexilate as part of the RE-COVER or RE-COVER II trials. Patients were assigned in a 1:1 ratio to receive oral dabigatran etexilate 150 mg twice daily or warfarin. The dose of warfarin was adjusted to achieve an INR of 2.0–3.0. Previous anticoagulant therapy was stopped, and administration of the study drug was started when the INR was <2.3. The treatment duration was initially designed to be 18 months; however, due to a lower-than-projected event rate, the protocol was revised to increase the number of patients and extend the treatment period for patients already enrolled. Consequently, the planned treatment period was 6–36 months, with patients separated into three cohorts according to the duration of treatment (<18 months, 18 months or >18 months), and a meta-analysis was used to measure the primary endpoint at 18 months [34].

The RE-SONATE trial was designed to assess whether dabigatran etexilate was superior to placebo for the prevention of recurrent VTE throughout 6 months of extended treatment [34]. The patient inclusion criteria were identical to the RE-MEDY trial, the main difference in recruitment being that patients in the RE-SONATE trial were considered to have a lower risk for recurrent VTE than those in the RE-MEDY trial. Patients were assigned in a 1:1 ratio to receive a fixed dose of oral dabigatran etexilate 150 mg twice daily or placebo. Six months after recruitment of the first patient, the protocol was amended to extend the follow-up to 12 months after the final study treatment to assess the long-term risk of VTE recurrence [34].

All four trials enrolled patients aged ≥18 years from up to 33 countries [32–34]. Exclusion criteria were similar across all the trials and included renal impairment (estimated CL_{CR} ≤30 mL/min), active bleeding or a high risk of bleeding, active liver disease (aminotransferase levels of 2 or 3 times the upper limit of normal) and recent unstable cardiovascular disease [32–34]. In the trials evaluating the prevention of recurrent VTE, patients with symptomatic DVT or PE at study entry were also excluded [34].

The primary efficacy endpoint for all four trials was recurrent symptomatic and objectively confirmed (by central adjudication) VTE or death associated with VTE [32–34]. The RE-SONATE trial also included unexplained deaths in the primary efficacy outcome analysis [34].

Noninferiority was tested by comparing the upper limits of the 95 % confidence intervals (CI) for the hazard ratio (HR) and risk difference with predefined margins [32–34]. In each trial, efficacy was analysed according to the modified intention-to-treat principle, with exclusion of patients who did not receive any of the study drugs [32–34].

Secondary efficacy endpoints comprised components of the primary endpoint, including symptomatic DVT and symptomatic nonfatal PE for all trials, unexplained death for the RE-SONATE trial [34], and death related to VTE and all other deaths for the RE-COVER, RE-COVER II and RE-MEDY trials [32–34].

In each of the trials, the patients had a mean age of ≈55 years, 39–45 % of patients were female and most (78–95 %) were white [32–34].

4.1 Long-Term Treatment of Acute Venous Thromboembolism

Oral dabigatran etexilate was noninferior to warfarin in the long-term (6-month) treatment of acute VTE after initial parenteral anticoagulation with regard to the prevention of recurrent or fatal VTE in the RE-COVER and RE-COVER II trials [32, 33]. The noninferiority of dabigatran etexilate to warfarin was established as the HR and risk difference for this endpoint between the treatment groups met predefined criteria (Table 2) [32, 33]. Subsequent superiority testing found no significant difference between treatment groups in the RE-COVER trial [32].

A summary of the incidence of the secondary endpoints for both trials are shown in Table 3. While the incidence of events with regard to some secondary endpoints showed variation between trials, a pooled analysis from both RE-COVER trials showed that the incidence of each secondary endpoint did not significantly differ between treatment groups [33].

The noninferior efficacy of dabigatran etexilate versus warfarin in the long-term treatment of acute VTE demonstrated in RE-COVER and RE-COVER II trials was supported by the results of pooled analysis of data from both trials ($n = 5{,}107$) [33]. The incidence of recurrent VTE or related death throughout 6 months' treatment, subsequent to parenteral anticoagulation, was generally similar in dabigatran etexilate and warfarin treatment groups, and the predefined criteria for noninferiority were met (Table 2) [33].

Predefined subgroup analyses of the pooled data indicate that no dosage adjustment is required based on various baseline characteristics, including sex, race, body-mass-index (BMI), concomitant medications or pre-existing medical conditions. When age was analysed as a continuous variable, the difference in efficacy of dabigatran etexilate compared with warfarin was not statistically significant at any age [33]. Subgroup analysis of the pooled data also showed that dabigatran etexilate had similar

Table 2 Efficacy of dabigatran etexilate in the long-term treatment of acute venous thromboembolism and extended treatment for prevention of venous thromboembolism recurrence. Results from randomized, double-blind, multinational, phase III trials and pooled analysis

Study (duration)	Treatment regimen	No. of pts	VTE or related death[a] [pt no. (%)]	HR (95 % CI)[b]	Risk difference [% (95 % CI)][c]
Long-term treatment of acute VTE					
RE-COVER (6 months) [32]	DAB 150 mg bid	1,274	30 (2.4)	1.10 (0.65–1.84)**	0.4 (−0.8 to 1.5)**
	WAR[d]	1,265	27 (2.1)		
RE-COVER II (6 months) [33]	DAB 150 mg bid	1,279	30 (2.3)	1.08 (0.64–1.80)**	0.2 (−1.0 to 1.3)**
	WAR[d]	1,289	28 (2.2)		
Pooled analysis [33]	DAB 150 mg bid	2,553	60 (2.4)	1.09 (0.76–1.57)	
	WAR[d]	2,554	55 (2.2)		
Extended treatment for prevention of VTE recurrence					
RE-MEDY (6–36 months) [34]	DAB 150 mg bid	1,430	26 (1.8)	1.44 (0.78–2.64)*	0.38 (−0.50 to 1.25)**
	WAR[d]	1,426	18 (1.3)		
RE-SONATE (6 months) [34]	DAB 150 mg bid	681	3 (0.4)	0.08 (0.02–0.25)[†]	
	PL	662	37 (5.6)		

bid twice daily, *CI* confidence interval, *DAB* dabigatran etexilate, *HR* hazard ratio, *INR* international normalized ratio, *LMWH* low molecular weight heparin, *PL* placebo, *pts* patients, *VTE* venous thromboembolism (deep vein thrombosis + pulmonary embolism), *WAR* warfarin

* $p = 0.01$, ** $p < 0.001$ vs WAR for noninferiority, † $p < 0.001$ vs PL for superiority

[a] Primary efficacy endpoint

[b] Noninferiority was established as the upper limit of 95 % CI was <2.75 [32, 33] and <2.85 [34]

[c] Noninferiority was established as the upper limit of 95 % CI was <3.6 % [32, 33] and <2.8 % at 18 months [34]

[d] Adjusted to achieve an INR of 2.0–3.0

Table 3 Summary of secondary efficacy endpoints of dabigatran etexilate in the long-term treatment of acute venous thromboembolism and extended treatment for prevention of venous thromboembolism recurrence

Study (duration)	Treatment regimen	No. of pts	Symptomatic DVT [pt no. (%)]	Symptomatic nonfatal PE [pt no. (%)]	VTE-related death [pt no. (%)]	All deaths [pt no. (%)]
Long-term treatment of acute VTE						
RE-COVER (6 months) [32]	DAB 150 mg bid	1,274	16 (1.3)	13 (1.0)	1 (0.1)	21 (1.6)
	WAR[a]	1,265	18 (1.4)	7 (0.6)	3 (0.2)	21 (1.7)
	HR (95 % CI)		0.87 (0.44–1.71)	1.85 (0.74–4.64)	0.33 (0.03–3.15)	0.98 (0.53–1.79)
RE-COVER II (6 months) [33]	DAB 150 mg bid	1,279	25 (2.0)	7 (0.5)	3 (0.2)[b]	25 (2.0)
	WAR[a]	1,289	17 (1.3)	13 (1.0)	0 (0.0)	25 (1.9)
	HR (95 % CI)		1.48 (0.80–2.74)	0.54 (0.21–1.35)		0.98 (0.56–1.71)
Pooled analysis [33]	DAB 150 mg bid	2,553	40 (1.6)	18 (0.7)	2 (0.1)	46 (1.8)
	WAR[a]	2,554	34 (1.3)	18 (0.7)	3 (0.1)	46 (1.8)
	HR (95 % CI)					1.0 (0.67–1.51)
Extended treatment for prevention of VTE recurrence						
RE-MEDY (6–36 months) [34]	DAB 150 mg bid	1,430	17 (1.2)	10 (0.7)	1 (0.1)	17 (1.2)
	WAR[a]	1,426	13 (0.9)	5 (0.4)	1 (0.1)	19 (1.3)
	HR (95 % CI)		1.32 (0.64–2.71)	2.04 (0.70–5.98)	1.01 (0.06–16.2)	0.90 (0.47–1.72)
RE-SONATE (6 months) [34]	DAB 150 mg bid	681	2 (0.3)	1 (0.1)		0[c]
	PL	662	22 (3.3)	14 (2.1)		2 (0.3)[c]

bid twice daily, *CI* confidence interval, *DAB* dabigatran etexilate, *DVT* deep venous thrombosis, *HR* hazard ratio, *INR* international normalized ratio, *LMWH* low molecular weight heparin, *PE* pulmonary embolism, *PL* placebo, *pts* patients, *VTE* venous thromboembolism (DVT + PE), *WAR* warfarin

[a] Adjusted to achieve an INR of 2.0–3.0

[b] Two deaths occurred during the period before DAB was started

[c] Unexplained deaths

efficacy to warfarin regardless of whether the index event was DVT alone or PE (reported in an abstract plus poster) [35]. Additionally, subgroup analysis of the pooled data from the RE-COVER trials demonstrated that VTE or VTE-related death were more likely to occur in patients with active cancer than in patients without cancer ($p < 0.0001$); however, dabigatran etexilate had similar efficacy to warfarin, irrespective of cancer status (reported in an abstract) [36].

4.2 Extended Treatment for Prevention of Recurrent Venous Thromboembolism

Extended treatment with dabigatran etexilate met the criteria for noninferiority to warfarin for prevention of recurrent or fatal VTE in the RE-MEDY trial, and significantly reduced the rate of recurrent VTE as compared with a placebo in the RE-SONATE trial [34].

In the RE-MEDY trial, recurrent VTE was confirmed in 1.8 % of patients receiving dabigatran etexilate and 1.3 % of patients receiving warfarin, and the HR for the time to the first primary outcome event and risk difference at 18 months met the predefined noninferiority criteria (Table 2) [34]. A summary of the incidence of secondary endpoints is shown in Table 3; the incidence of each secondary endpoint was not significantly different between treatment groups.

Subgroup analysis of data from the RE-MEDY trial demonstrated that the efficacy of dabigatran etexilate versus warfarin was similar regardless of the presence or absence of active cancer; however, the difference in the incidence of VTE or VTE-related death between patients with and without cancer did not reach significance ($p = 0.0580$) (reported in an abstract) [36].

In the RE-SONATE trial, recurrent or fatal VTE or unexplained death was confirmed in significantly fewer patients receiving dabigatran etexilate than placebo, with a 92 % relative risk reduction for symptomatic recurrent VTE with dabigatran etexilate compared with placebo (Table 2) [34]. Based on this finding, an estimated 38 patients would need to be treated for 1 year to prevent one episode of recurrent VTE [37]. In an extended 12-month follow-up period, which was completed for 98.5 % of patients ($n = 1,323$) receiving the study drug, the primary efficacy outcome event occurred during the total treatment period in 6.9 % of patients in the dabigatran etexilate group and 10.7 % of patients in the placebo group, with a HR of 0.61 (95 % CI, 0.42–0.88) [34]. When the individual

outcomes comprising the primary composite endpoint were evaluated in a secondary efficacy analysis, the incidence was numerically lower with dabigatran etexilate than with placebo, although levels of significance were not reported (Table 3) [34].

5 Tolerability

Dabigatran etexilate was generally well tolerated in phase III trials. For safety analyses in these trials, adverse events were included from the time of the first study drug intake until 6 days after the last study drug intake.

Adverse events leading to study drug discontinuation occurred in 9.0 % of patients receiving dabigatran etexilate and 6.8 % of patients receiving warfarin in the RE-COVER trial ($p = 0.05$) [32]. However, in the RE-COVER II and RE-MEDY trials the incidence of adverse events leading to discontinuation of the study drug was did not significantly differ between groups receiving dabigatran etexilate and warfarin [33, 34]. Similarly, the incidence of any adverse event did not significantly differ between the dabigatran etexilate and warfarin treatment groups in the RE-COVER, RE-COVER II and RE-MEDY trials [32–34]. For example, in RE-COVER II, 66.6 % of patients receiving dabigatran etexilate and 71.1 % of patients receiving warfarin experienced any adverse event [33].

There was a higher incidence of acute coronary syndrome [including myocardial infarction (MI) and unstable angina] in the dabigatran etexilate treatment group (0.9 %) than in the warfarin treatment group (0.2 %) in the RE-MEDY trial ($p = 0.02$) [34]. However, in the RE-COVER and RE-COVER II trials, the difference in the incidence of acute coronary syndrome, including MI, between the two treatment groups did not reach significance [32, 33].

Of those adverse events that occurred in ≥3 % of patients throughout 6 months of treatment in the RE-COVER trial, dyspepsia was the only event to occur in significantly more patients in the dabigatran etexilate group than in the warfarin group (Fig. 1) [32]. In the RE-COVER II trial, dyspepsia occurred in 1.0 versus 0.2 % of patients, respectively [33].

5.1 Bleeding Events

Major bleeding was defined as clinically overt bleeding that was associated with a decrease in haemoglobin of ≥20 g/L, required transfusion of ≥2 units of red cells, involved a critical organ, or was fatal [32–34]. Other bleeding events were categorized as either clinically relevant nonmajor (CRNM) or nuisance bleeding. CRNM bleeding occurred when ≥1 of the following criteria were met: spontaneous skin haematoma of ≥25 cm, spontaneous nose bleed for >5 min, macroscopic haematuria (either spontaneous or lasting >24 h if associated with an intervention), spontaneous rectal bleeding, gingival bleeding for >5 min, bleeding leading to hospitalization and/or requiring surgery, bleeding requiring transfusion of <2 units of whole blood or red cells, or any other bleeding event considered clinically relevant by investigator [32–34].

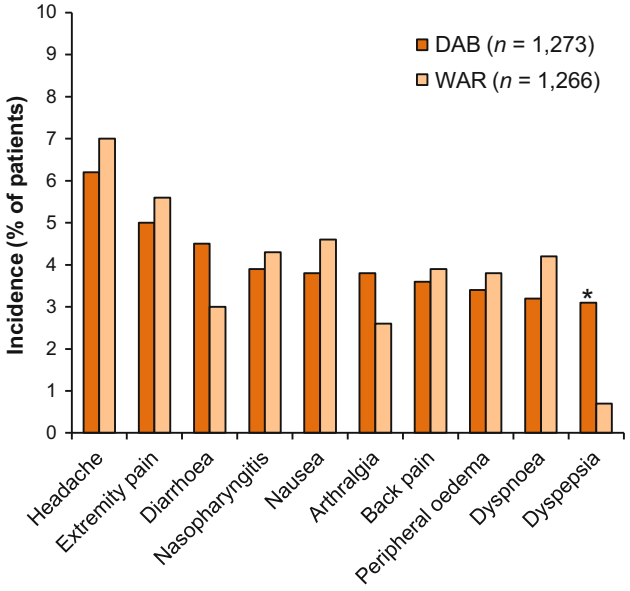

Fig. 1 Tolerability of oral dabigatran etexilate during long-term treatment of acute venous thromboembolism [32]. Nonbleeding adverse events with ≥3 % incidence during the RE-COVER trial. *DAB* dabigatran etexilate, *WAR* warfarin. *$p < 0.001$

The incidence of major bleeding was not significantly different between groups receiving dabigatran etexilate or warfarin in all three trials comparing these agents [32–34]. However, in all trials, dabigatran etexilate was associated with a significantly lower incidence of the combined endpoint of major or CRNM bleeding and of any bleeding than warfarin (Table 4) [32–34]. The sites of major bleeding varied between studies, but in the two RE-COVER trials and the RE-MEDY trial, the most frequently specified sites were gastrointestinal (GI) and intracranial [32–34], and urogenital in the RE-COVER trials [32, 33]. For example, in the dabigatran etexilate and warfarin groups in the RE-COVER trial, there were 9 (0.7 %) versus 5 (0.4 %) major GI bleeding events, 5 (0.4 %) versus 6 (0.5 %) major urogenital bleeding events, and 0 versus 3 (0.2 %) major intracranial bleeding events [32]. In the RE-COVER and RE-COVER II trials, the incidence of any GI bleeding was numerically higher with dabigatran etexilate than warfarin, while the incidence of any bleeding at other common sites (e.g. nasal, urogenital and intramuscular) was numerically higher with warfarin than dabigatran etexilate [32, 33]. The incidence of any bleeding at the different sites in the RE-COVER II trial is illustrated in Fig. 2.

Table 4 Bleeding events in patients during study treatment with oral dabigatran etexilate, warfarin or placebo

Study (duration)	Treatment regimen	No. of pts	Major bleeding [pt no. (%)]	Major or CRNM bleeding [pt no. (%)]	Any bleeding [pt no. (%)]
Long-term treatment of acute VTE					
RE-COVER (6 months) [32]	DAB 150 mg bid	1,273[a]	20 (1.6)	71 (5.6)	205 (16.1)
	WAR[b]	1,266[a]	24 (1.9)	111 (8.8)	277 (21.9)
	HR (95 % CI)		0.82 (0.45–1.48)	0.63 (0.47–0.84)**	0.71 (0.59–0.85)***
RE-COVER II (6 months) [33]	DAB 150 mg bid	1,280[a]	15 (1.2)	64 (5.0)	200 (15.6)
	WAR[b]	1,288[a]	22 (1.7)	102 (7.9)	285 (22.1)
	HR (95 % CI)		0.69 (0.36–1.32)	0.62 (0.45–0.84)[†]	0.67 (0.56–0.81)[†]
Pooled analysis [33][c]	DAB 150 mg bid	2,553	24 (1.0)	109 (4.4)	354 (14.4)
	WAR[b]	2,554	40 (1.6)	189 (7.7)	503 (20.4)
	HR (95 % CI)		0.60 (0.36–0.99)[†]	0.56 (0.45–0.71)[†]	0.67 (0.59–0.77)[†]
Extended treatment for prevention of VTE recurrence					
RE-MEDY (6–36 months) [34]	DAB 150 mg bid	1,430	13 (0.9)	80 (5.6)	277 (19.4)
	WAR[b]	1,426	25 (1.8)	145 (10.2)	373 (26.2)
	HR (95 % CI)		0.52 (0.27–1.02)	0.54 (0.41–0.71)***	0.71 (0.61–0.83)***
RE-SONATE (6 months) [34]	DAB 150 mg bid	681	2 (0.3)	36 (5.3)	72 (10.5)
	PL	662	0	12 (1.8)	39 (5.9)
	HR (95 % CI)			2.92 (1.52–5.60)***	1.82 (1.23–2.68)*

bid twice daily, *CI* confidence interval, *CRNM* clinically relevant nonmajor, *DAB* dabigatran etexilate, *HR* hazard ratio, *INR* international normalized ratio, *LMWH* low molecular weight heparin, *PL* placebo, *pts* patients, *VTE* venous thromboembolism (deep vein thrombosis + pulmonary embolism), *WAR* warfarin

* $p = 0.003$, ** $p = 0.002$, *** $p \leq 0.001$, [†] HR 95 % CI was exclusive of 1

[a] Analysis of bleeding events included the number of patients treated with DAB or WAR rather than the number assigned to treatment; in the RE-COVER trial one patient assigned to receive DAB mistakenly received WAR throughout the study, while in RE-COVER II one patient assigned to receive WAR was treated with DAB throughout the study

[b] Adjusted to achieve an INR of 2.0–3.0

[c] Analysis included bleeding events from the start of the oral drug only (double-dummy period only)

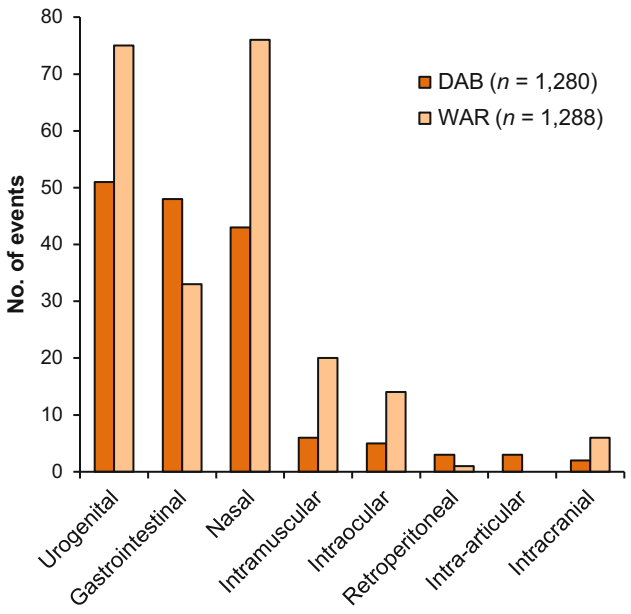

Fig. 2 Most common sites of any bleeding events during long-term treatment for acute venous thromboembolism in the RE-COVER II trial [33]. Patients may have had more than one type or site of bleeding event. *DAB* dabigatran etexilate, *WAR* warfarin

Pooled analysis from the RE-COVER and RE-COVER II trials showed the incidence of major or CRNM bleeding and of any bleeding was significantly lower in dabigatran etexilate than warfarin recipients [33]. The incidence of major bleeding events was also significantly lower with dabigatran etexilate treatment than warfarin during the double-dummy period only (i.e. after the start of the oral drug only) (Table 4). There was a similar incidence of major bleeding after the start of any study drug between the two treatment groups; however, this included major bleeding that occurred during the initial parenteral anticoagulation period [33].

Further analysis of pooled data from the RE-COVER trials during the double-dummy period ($n = 4,918$) indicated that although the frequency of any GI bleeding event was numerically higher in the dabigatran etexilate group than the warfarin group, the frequency of major GI bleeds was numerically lower with dabigatran etexilate (reported in an abstract) [38]. Also in this analysis, there were numerically fewer major intracranial bleeding events and major urogenital bleeding events in the dabigatran etexilate group than in the warfarin group [38]. Based on the

Thrombolysis in Myocardial Infarction (TIMI) major bleeding event definition (i.e. events resulting in a decrease in haemoglobin of >50 g/L or haematocrit of >15 %, or intracranial bleeding), there were 9 (0.4 %) versus 11 (0.4 %) events in the dabigatran etexilate and warfarin groups, respectively [38].

When age was analysed as a continuous variable in the pooled analysis, the reduction in the risk of clinically relevant bleeding with dabigatran etexilate compared with warfarin showed variation according to age ($p = 0.01$ for interaction), with a greater risk reduction with dabigatran etexilate than warfarin up to ≈85 years, at which point, the risk reduction tended to become higher with warfarin [33].

The risk of major bleeding or any bleeding with dabigatran etexilate compared with warfarin was not influenced by: a history of bleeding, sex, BMI, geographical region, ethnicity, CL_{CR}, history of previous VTE and concomitant medications [33]. Similarly, in predefined subgroup analyses of the RE-COVER [32] and RE-MEDY [34] trials, there was no significant difference in the risk of bleeding according to study treatment.

In a subsequent, prespecified pooled analysis of data from the RE-COVER and RE-COVER II trials, patients without active cancer had a significantly lower risk of major or CRNM bleeding with dabigatran etexilate than warfarin ($p = 0.0189$), and experienced significantly fewer bleeding events overall than patients with active cancer ($p < 0.0001$) (reported in an abstract) [36].

Patients in the dabigatran etexilate treatment group had a higher risk of bleeding than patients in the placebo group in the RE-SONATE trial [34]. Two patients in the dabigatran etexilate treatment group experienced major bleeding events compared with no major bleeding events in the placebo group (Table 4); both patients developed GI bleeding requiring a transfusion of ≥2 units of blood. The incidence of major or CRNM bleeding events and the cumulative risk of any bleeding was significantly greater in patients receiving dabigatran etexilate than placebo (Table 4) [34].

6 Dosage and Administration

In the USA [8] and the EU [9], oral dabigatran etexilate is indicated for the treatment of DVT and PE and to reduce the risk of recurrence of DVT and PE. For the long-term treatment of acute VTE and extended treatment for prevention of recurrent VTE, the recommended dabigatran etexilate dosage for patients with an estimated CL_{CR} >30 mL/min (i.e. those with normal renal function or mild to moderate renal impairment) is 150 mg twice daily to be commenced after an initial period of parenteral anticoagulation, with the recommended period of parenteral anticoagulation being ≥5 days in the EU [9] and 5–10 days in the USA [8].

In the EU, the recommended dabigatran etexilate dosage is 110 mg twice daily in patients aged ≥80 years and in patients who receive concomitant verapamil [9]. A reduced dosage (110 mg twice daily) can also be selected based on individual assessment of thromboembolic risk versus the risk of bleeding in patients aged 75–80 years, in patients with moderate renal impairment (CL_{CR} 30–50 mL/min), gastritis, esophagitis or gastroesophageal reflux, and other patients at increased risk of bleeding [9].

In the EU, dabigatran etexilate therapy duration should be individualized after careful assessment of the treatment benefit against the bleeding risk [9]. Short treatment duration (at least 3 months) should be based on transient risk factors (e.g. immobilization, recent surgery or trauma), while longer treatment durations should be based on permanent risk factors or idiopathic DVT or PE [9].

Dabigatran etexilate capsules can be taken with or without food, and should be swallowed whole with a glass of water; chewing, breaking or emptying the capsule contents can result in increased dabigatran etexilate exposure [8, 9].

Dabigatran etexilate is contraindicated in patients with severe renal impairment (CL_{CR} <30 mL/min) in the EU [9], whereas the US prescribing information states that dosage recommendations cannot be provided for these patients [8]. As the $t_{½\beta}$ and anticoagulant effect of dabigatran etexilate are increased in patients with renal impairment (Sect. 3.1), renal function should be assessed before starting treatment and periodically thereafter as clinically indicated [8, 9]. In particular, patients aged ≥75 years receiving dabigatran etexilate should undergo renal function assessment at least once a year, or more frequently during clinical circumstances where renal function could potentially be reduced (e.g. dehydration, hypovolaemia or concomitant use of certain medications) [9].

The risk of bleeding is increased with dabigatran etexilate, and any signs or symptoms of blood loss should be promptly evaluated [8]. Factors that are associated with increased dabigatran etexilate exposure may result in an increased risk of bleeding, and include age (≥75 years), renal impairment and concomitant medications (Sects. 2, 3). Additionally, comorbidities such as thrombocytopenia and bacterial endocarditis are associated with increased haemorrhagic risk [9]. Therefore, patients with an increased risk of bleeding require close clinical surveillance for signs of anaemia or blood loss, and treatment should be interrupted when clinically relevant bleeding occurs [9].

The US prescribing information includes a black-box warning regarding the increased risk of thrombotic events

with premature discontinuation of dabigatran etexilate without adequate alternative anticoagulation therapy [8]. Epidural or spinal haematomas may also occur in patients receiving dabigatran etexilate who are undergoing spinal puncture or neuraxial anaesthesia. Long-term or permanent paralysis may result as a consequence of these haematomas. Placement or removal of a lumbar puncture or epidural catheter should be performed when the anticoagulant effect is low; however, the optimal timing for each patient between stopping dabigatran etexilate administration and the neuraxial procedure is not known [8].

Local prescribing information should be consulted for detailed information, including dosage adjustments for special patient populations, contraindications, warnings and precautions, potential drug interactions and recommended assays for monitoring in cases of increased bleeding risk.

7 Place of Dabigatran Etexilate in the Treatment of Acute Venous Thromboembolism and Preventing Recurrence of Venous Thromboembolism

Novel oral anticoagulants have been developed in recent years as a result of the limitations of VKA therapy, including the numerous drug and food interactions and the need for ongoing, frequent monitoring. Dabigatran etexilate is an oral direct thrombin inhibitor that binds to the active site of thrombin and inhibits thrombus formation by preventing the conversion of fibrinogen to fibrin (Sect. 2). Other novel oral anticoagulants include the direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban, which bind competitively to the active site of factor Xa and have high oral bioavailability [10]. Of these novel oral anticoagulants, dabigatran etexilate, rivaroxaban and apixaban have been approved for the treatment of acute VTE and prevention of VTE recurrence [8, 9, 39, 40].

The approval of dabigatran etexilate for the long-term treatment of acute VTE and extended treatment for prevention of recurrent VTE in the USA and the EU was based on data from over 9,300 patients in four randomized, double-blind clinical trials (Sect. 4). Results from the RE-COVER and RE-COVER II trials showed oral dabigatran etexilate 150 mg twice daily for 6 months had noninferior therapeutic efficacy to that with warfarin in the long-term treatment of acute VTE (Sect. 4.1). The RE-MEDY trial also demonstrated the noninferior efficacy of dabigatran etexilate 150 mg twice daily to warfarin as extended treatment over 6–36 months, while the RE-SONATE trial showed that dabigatran etexilate at the same dosage was more effective in the prevention of recurrent VTE than placebo (Sect. 4.2). Dabigatran etexilate is approved for treatment of acute VTE after an initial parenteral anticoagulation period of 5–10 days in the USA and ≥5 days in the EU (Sect. 6). Therefore, outpatients require training in the correct subcutaneous administration technique of LMWH or fondaparinux sodium before they can start dabigatran etexilate treatment.

Dabigatran etexilate was generally well tolerated in patients receiving long-term treatment for acute VTE or extended treatment for prevention of recurrent VTE (Sect. 5). The risk of bleeding complications is an important consideration with any anticoagulation therapy [37]. In the RE-COVER, RE-COVER II and RE-MEDY trials, the incidence of major bleeding in patients receiving dabigatran etexilate was not significantly different to those receiving warfarin, while the incidences of the combined endpoint of major or CRNM bleeding and of any bleeding were significantly lower with dabigatran etexilate than warfarin (Sect. 5.1). Pooled analysis from the RE-COVER and RE-COVER II trials also demonstrated fewer major bleeding events and fewer bleeding events overall with dabigatran etexilate than warfarin, as well as a lower risk of major or CRNM bleeding with dabigatran etexilate than warfarin in patients younger than ≈85 years of age; in patients older than 85 years, warfarin had a lower risk.

The RE-COVER, RE-COVER II and RE-MEDY trials were included in a meta-analysis of five randomized controlled trials on the risk of bleeding comparing dabigatran etexilate with VKAs (warfarin was used in all studies) [41]. The meta-analysis also included data from the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) [42] and PETRO (Prevention of Embolic and Thrombotic Events in Patients with Persistent Atrial Fibrillation) trials [43], which are the focus of a previous review of the use of dabigatran etexilate in the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation [13]. The meta-analysis found that the risk of any bleeding with dabigatran etexilate was lower than with warfarin across all five randomized trials, with a pooled relative risk of 0.77 (95 % CI, 0.64–0.93) [41]. Based on pooled data from the RE-LY and RE-COVER trials, there was a lower risk of major intracranial bleeding with dabigatran etexilate than warfarin [relative risk of 0.40 (95 % CI, 0.27–0.59)], and a higher relative risk of major GI bleeding with dabigatran etexilate than warfarin [relative risk of 1.51 (95 % CI, 1.23–1.84)] [41].

Another analysis of pooled data from the RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE trials, together with results from the RE-LY trial, showed that patients with major bleeding during dabigatran etexilate therapy had a significantly lower mean CL_{CR} (53 mL/min) and were older (mean age 75.3 years) than patients with major bleeding during warfarin therapy (62 mL/min and 71.8 years, respectively; $p < 0.0001$ for both parameters) [44]. This study also demonstrated that among patients

with major bleeding, a greater proportion receiving dabigatran etexilate than warfarin had received concomitant aspirin ($p = 0.026$) or a NSAID ($p = 0.023$) [44]. Using lower dosages of dabigatran etexilate and avoiding aspirin and NSAIDs may help to avoid major bleeding events in patients with increased risk factors [44]. In the USA and the EU, assessment of renal function is recommended prior to starting dabigatran etexilate therapy, and warnings are in place for the increased risk of bleeding in special patient populations, including elderly patients and those receiving concomitant agents that also increase the risk of bleeding (Sect. 6).

In the months following the approval of dabigatran etexilate for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, there were many reports of serious bleeding events during treatment, with a higher incidence reported with dabigatran etexilate than warfarin over the same period [45]. Subsequent independent postmarketing studies conducted by the FDA [46] and the EMA [47] found no evidence of an excess risk of bleeding with dabigatran etexilate. According to these safety updates, the increased incidence of postmarketing bleeding reports with dabigatran etexilate was attributed to an under-reporting of events with warfarin [45–47]. Case review studies have identified prescriber error, comedication with P-gp inhibitors or antiplatelet drugs, impaired renal function, old age and low body weight (<60 kg) as risk factors for haemorrhagic complications with dabigatran etexilate, emphasizing the need for careful patient selection [48, 49]. According to the FDA, dabigatran etexilate continues to have a favourable benefit-to-risk profile, and no changes have been made to the current dabigatran etexilate label or recommendations for use [50]. Both the FDA and the EMA are continuing to closely monitor the ongoing safety concerns regarding the risk of bleeding with dabigatran etexilate [46, 47].

Novel oral anticoagulants have been designed to be administered without routine coagulation monitoring; however, assessment of the anticoagulant effect of dabigatran etexilate may be required in certain clinical circumstances, such as bleeding into critical organs, emergency surgery or potential overdose [22]. In these instances, an accurate assessment of anticoagulant activity using the dTT assay is possible (Sect. 2) and may provide additional assistance with emergency patient care. Recent media reports have claimed that the safety of dabigatran etexilate could be further enhanced by regular drug level monitoring [51]. However, simulations based on dabigatran etexilate plasma concentration data from the RE-LY trial in patients with atrial fibrillation could not provide reliable predictions of actual patient outcomes [52]. Furthermore, because of the wide therapeutic variation in dabigatran etexilate plasma concentrations, no single plasma concentration range has been recommended to provide optimal benefit–risk for all patients [11]. Taken together, these data reinforce the need for careful patient selection and individualization of anticoagulation therapy [37, 52] (Sect. 6).

While the incidence of acute coronary syndrome was very rare, it occurred in more patients receiving dabigatran etexilate than warfarin in the RE-MEDY trial, although the difference between treatment groups did not reach significance in the RE-COVER and RE-COVER II trials (Sect. 5). A pooled analysis of cardiovascular outcomes using individual patient data from 14 comparative clinical trials of dabigatran etexilate, including the four studies discussed in Sects. 4 and 5, showed an increased incidence of MI with dabigatran etexilate 150 mg twice daily compared with well controlled warfarin [53]. However, the rates of MI were not significantly different between dabigatran etexilate patients and those receiving enoxaparin sodium or placebo. Based on these findings, it was concluded that dabigatran etexilate is not associated with MI, but rather is less effective than well controlled warfarin in preventing MI [53]. Data from meta-analysis of 11 randomized controlled trials comparing warfarin to direct thrombin inhibitors, including dabigatran etexilate, ximelagatran and AZD0837, indicated that the comparatively increased risk of acute coronary syndrome appeared to be a class effect of these agents rather than specific effect of dabigatran etexilate [54].

Dabigatran etexilate was associated with a higher incidence of dyspepsia than warfarin in the RE-COVER and RE-COVER II trials (Sect. 5). Tartaric acid, which is added to dabigatran etexilate capsule formulations to increase drug absorption, is thought to play a role in the development of dyspeptic symptoms [55]. While dyspepsia was the only nonhaemorrhagic adverse event that was specifically attributed to dabigatran etexilate, this can lead to treatment discontinuation in some patients [56]. In the RELY-ABLE (Long-term Multicentre Extension of Dabigatran Treatment in Patients with Atrial Fibrillation) trial, 20.7 % of patients from the RE-LY trial who continued to receive dabigatran etexilate 150 mg twice daily reported dyspepsia-like symptoms (reported in an abstract plus poster) [57]. However, ≈90 % of the patients who used specific measures to alleviate symptoms reported improvement in dyspepsia symptoms. These measures included using proton pump inhibitors, nonprescription antacids, histamine H2 receptor antagonists or taking dabigatran etexilate with food [57]. While concomitant use of pantoprazole with dabigatran etexilate reduces the bioavailability of dabigatran etexilate, this does not appear to reduce dabigatran etexilate efficacy in clinical trials (Sect. 3.2). Given that proton pump inhibitor use was the most common method for alleviating dyspepsia-like

symptoms in dabigatran etexilate recipients in the RELY-ABLE trial [57], real-world data on how their use affects dabigatran etexilate efficacy in clinical practice would be of interest.

Two factor Xa inhibitors, rivaroxaban and apixaban, have also been approved for use in the treatment of acute VTE and prevention of VTE recurrence [39, 40]. Unlike dabigatran etexilate, both of these agents have been approved for the treatment of acute VTE from diagnosis [39, 40]. The $t_{½\beta}$ and time to peak effect of rivaroxaban and apixaban are similar to that observed with dabigatran etexilate, with all three drugs having dose-proportional pharmacodynamics and pharmacokinetics that allow for twice-daily fixed-dose administration in most patients [37]. In contrast to dabigatran etexilate, rivaroxaban is metabolized by the liver enzyme CYP3A4, and therefore can potentially interact with CYP3A4 inducers and inhibitors [10]. As yet there are no head-to-head trials comparing dabigatran etexilate with rivaroxaban or apixaban; however, indirect comparisons of phase III trial data evaluating the efficacy and safety of novel oral anticoagulants for the treatment of acute VTE have been performed [58, 59]. These meta-analyses included results from the RE-COVER and RE-COVER II trials, together with data from trials comparing apixaban, rivaroxaban and edoxaban to conventional therapy. With all comparisons, there was no significant difference in efficacy outcomes. The risk of major bleeding with dabigatran etexilate and rivaroxaban was similar, whereas apixaban was associated with fewer major bleeding events than dabigatran etexilate [58, 59]. In the absence of direct comparative evidence, no recommendations have been made in favour of one of these novel oral anticoagulants [37]. Clinical practice guidelines in the USA include dabigatran etexilate and rivaroxaban among the suggested agents for long-term and extended treatment of VTE; however, until more extensive evidence outside the clinical trial setting is available, a preference for VKAs and LMWHs over these novel oral anticoagulants is expressed [5]. However, these guidelines, which were prepared in October 2011, also note the need for more clinical trial data and state that dabigatran etexilate and rivaroxaban may prove to be associated with better clinical outcomes than VKA and LMWH therapy [5].

Previously there have been concerns regarding the lack of specific antidotes to reverse the anticoagulant effects of novel oral anticoagulants [10]. In patients receiving these agents with mild bleeding complications (e.g. mild GI bleeding with stable cardiovascular parameters), drug discontinuation with clinical observation is considered to be sufficient [60]. In the event of severe haemorrhagic complications or emergency interventional surgery in patients receiving dabigatran etexilate, potential reversal strategies that may be employed in addition to standard supportive measures include the use of activated charcoal (within first 2 h of last drug intake) and haemodialysis [61]. Administration of prothrombin complex concentrate may also be considered; however, there is insufficient data to support this approach as a standard of care [62].

The FDA has recently granted a Breakthrough Therapy Designation for an antidote for dabigatran etexilate (idarucizumab) [63]. The purpose of the FDA's Breakthrough Therapy Designation is to help accelerate the development of drugs for serious or life-threatening conditions where preliminary clinical evidence has shown a substantial improvement over existing therapies [63]. Idarucizumab, a fully humanized antibody fragment with specific affinity for dabigatran, conferred complete and sustained reversal of dabigatran-induced anticoagulation and was well tolerated in a phase I study of 145 healthy male volunteers (reported in an abstract) [64]; a global phase III trial (RE-VERSE AD™) is currently in progress [65]. The availability of a specific reversal agent for dabigatran etexilate may assist in the management of emergency patients. A specific antidote for factor Xa inhibitors (andexanet alpha) is also being developed [63].

As with other novel anticoagulant therapies, dabigatran etexilate has a higher drug cost than VKAs. However, other cost factors need to be considered when selecting treatment, including the cost of frequent patient monitoring associated with warfarin therapy and the potential cost of bleeding events [10]. While there are very little pharmacoeconomic data available regarding the use of dabigatran etexilate in the long-term treatment of acute VTE or extended treatment for prevention of VTE recurrence, results of a recent modelled analysis based on data from the RE-SONATE trial that evaluated outcomes over a lifetime horizon suggested that 6 months' treatment with dabigatran etexilate 150 mg twice daily (following 6–18 months of initial anticoagulant therapy) dominates placebo for the secondary prevention of recurrent VTE in the UK (reported in an abstract) [66]. Further studies are needed to help clarify the cost effectiveness of dabigatran etexilate in patients with VTE.

In conclusion, dabigatran etexilate had noninferior efficacy compared with warfarin in the long-term treatment of acute VTE and in the extended treatment for prevention of recurrent VTE in randomized controlled trials. In these trials, dabigatran etexilate was generally well tolerated, with a lower risk of the combined endpoint of major or CRNM bleeding and of any bleeding than warfarin. Dabigatran etexilate provides a convenient alternative to VKA therapy, as it can be administered as a fixed dose without the need for routine monitoring; however, careful

patient selection is advised. Thus, dabigatran etexilate is a valuable option for the long-term treatment of acute VTE and extended treatment for prevention of recurrent VTE.

Data selection sources: Relevant medical literature (including published and unpublished data) on dabigatran etexilate was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 22 September 2014], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Dabigatran etexilate, dabigatran, deep vein thrombosis, venous thrombosis, venous thromboembolism, DVT, pulmonary embolism, lung embolism
Study selection: Studies in patients with deep vein thrombosis or pulmonary embolism who received dabigatran etexilate. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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