Review Articles

Efficacy and safety of dabigatran etexilate: A narrative review

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Abstract

Dabigatran etexilate is a newly developed direct thrombin inhibitor. After oral administration, this novel anticoagulant drug has a predictable response, which allows fixed dose regimens without the need for routine laboratory monitoring. Dabigatran demonstrated to be at least as effective as the current standard of care in the primary and secondary prevention of several thromboembolic events, such as the prevention of venous thromboembolism after orthopaedic surgery, the acute and long-term treatment of deep vein thrombosis and pulmonary embolism, and the prevention of thromboembolic complications of atrial fibrillation. Dabigatran showed a favourable safety profile, causing less intracranial haemorrhages compared to warfarin. However, higher incidence of dyspepsia and gastrointestinal bleeding has been reported, probably due to the formulation of dabigatran containing a tartaric acid core. It is not clear whether the increased number of acute coronary syndrome, reported with the use of this thrombin inhibitor, might be due to an intrinsic property of dabigatran or to a protective effect of the comparator treatment with warfarin. In case of major bleeding events or urgent reversal, no specific antidote is available. Suggested measures include anticoagulant withdrawal, infusion of prothrombin complex concentrates, haemodialysis and administration of oral activated charcoal, in addition to haemostatic interventions and supportive care. Although laboratory monitoring is not necessary, the activated partial thromboplastin time and the thrombin clotting time may provide a qualitative measurement of dabigatran activity, while the dilute thrombin clotting time and the ecarin clotting time may provide a quantitative measurement. Dabigatran has been recently licensed by the European Medicine Agency for the prevention of venous thromboembolism in patients undergoing elective total hip or knee arthroplasty and for the treatment of patients with atrial fibrillation at moderate-high thromboembolic risk. This review will focus on the pharmacological properties of dabigatran and its efficacy and safety profile from the results of large randomized clinical trials.

Keywords: dabigatran; rivaroxaban; apixaban; atrial fibrillation; venous thromboembolism; bleeding.

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Introduction

For more than 60 years, the vitamin K antagonists (VKA) have been the only oral anticoagulant drugs available for primary and secondary prevention of thromboembolic events. However, the VKAs present several limitations, such as the delayed onset of action and the long half-life of about 36-42 h [1]. Because of the narrow therapeutic window, the intra- and inter-individual variability in dose response and several food and drug interactions, the VKAs necessitate regular laboratory monitoring and dose adjustment, usually performed in an anticoagulation clinic [2].

The last decade saw the development of novel oral anticoagulant drugs (NOAC), targeting central factors in the coagulation system: the activated factor X (e.g. rivaroxaban, apixaban, edoxaban) and the activated factor II or thrombin (e.g. ximelagatran, dabigatran) [3]. The NOACs have a rapid onset of action, a shorter half-life and a more predictable anticoagulant response, which allows fixed dose regimens without the need for routine monitoring [4]. Ximelagatran was the first oral thrombin inhibitor to be marketed, but it has already been withdrawn because of potential hepatic toxicity. Dabigatran is a new promising thrombin inhibitor which has obtained licence, in the European Union, for the prevention of venous thromboembolism (VTE) in orthopaedic surgery and for the management of atrial fibrillation (AF). It has several favourable properties in comparison to VKAs but some issues still need to be better assessed, such as the reversal of the anticoagulant effect or the safety for long-term administration. This review will focus on the pharmacological properties of dabigatran and its efficacy and safety profile from the results of large randomized clinical trials.

Pharmacology of dabigatran

Pharmacodynamics

Dabigatran is a competitive and reversible direct thrombin inhibitor. In the final common pathway of the coagulation cascade, thrombin converts fibrinogen into fibrin, leading to thrombus formation. Binding directly and exclusively to the active site of thrombin, dabigatran inactivates not only the enzymatically active free thrombin, but also the fibrin-bound thrombin, which is protected from the action of the indirect thrombin inhibitors, such as heparin, and which triggers continuous thrombus expansion [5]. Moreover, dabigatran has also been demonstrated to inhibit tissue factor-induced thrombin generation and to decrease endogenous thrombin generation [6].

Pharmacokinetics

Dabigatran is administered orally as a prodrug, dabigatran etexilate. The drug formulation consists in capsules containing multiple pellets of a tartaric acid core coated with dabigatran etexilate. The tartaric acid creates an acidic environment that favours drug dissolution and absorption, independently of gastric pH and co-administration of proton pump inhibitors [7].

Dabigatran etexilate is rapidly absorbed and completely hydrolysed to the active metabolite dabigatran by ubiquitous esterases. After oral administration, the absolute bioavailability of dabigatran, which is independent of dose or co-administration of food, is 6.5%[6].

In healthy volunteers, maximum plasma concentrations were reached within 2 h of initial administration, indicating a rapid onset of action, and steady state concentrations were achieved within 3 d after multiple-dose administration, with no evidence of significant accumulation [8].

About 20% of dabigatran is conjugated with glucuronic acid and excreted via the biliary system, while 80% is excreted unchanged via the kidneys [5]. Half-life of dabigatran is 12-17 h after multiple doses, and increases to more than 24 h in patients with severe renal failure. Given the relative low plasma protein binding (approximately 35%), in case of emergency reversal dabigatran may be dialyzable [2].

Dabigatran etexilate is not metabolized by the cytochrome P450 isoenzymes, being therefore unaffected by mild to moderate hepatic impairment and ensuring a low risk for drug to drug interaction [5]. Dabigatran etexilate, but not dabigatran, is a substrate of the efflux permeability glycoprotein (P-gp) transporter, therefore any potential interaction is restricted to drug absorption into the gastrointestinal tract. In detail, dabigatran plasma concentrations may be reduced by potent P-gp inducers (such as rifampicin or some antiepileptic drugs) and may be increased by potent P-gp inhibitors (such as amiodarone, verapamil, quinidine, azole-antimycotics or some virus protease inhibitors) [5, 7].

The pharmacologic properties of dabigatran are summarized in **Table 1**.

Table 1. Pharmacologic properties of dabigatran.

Mechanism of action	Direct thrombin inhibition
Route of administration	Orally
Dose frequency	Once or twice daily
Absolute bioavailability	6.5%
Time to maximum plasma concentration	2 h
Half-life	12-17 h
Route of clearance	80% renal excretion 20% extrarenal excretion
Plasma protein binding	35%
Cytochrome P450 metabolism	No
P-glycoprotein transport	Yes

Peculiar Features of Dabigatran

The following pharmacological properties of the NOACs, including dabigatran, are potential advantages compared with the VKAs [2, 4]:

- Selective inhibition of specific factors in the final pathway of the coagulation cascade, which may reduce the risk of spontaneous bleeding events;
- Rapid onset of action and short half-life, which may prevent overdosage and may overcome the need for bridging therapy;
- Predictable anticoagulant effect, due to the low inter-individual variability in the anticoagulant response and the low potential for food and drug interactions, which allows fixed dose administration without the need for routine laboratory monitoring.

On the other hand, the following pharmacological properties of the NOACs, including dabigatran, are potential disadvantages, compared with the VKAs [2,4]:

- No specific antidote is currently available in the event of a major bleeding events;
- No standardized laboratory test is currently available to monitor the anticoagulation level of each single patient;
- The mainly renal clearance might provoke overdosing in elderly patients with impaired kidney function;
- Strict patients' compliance is required in order to maintain adequate anticoagulant plasma concentrations.

Efficacy of Dabigatran

Prevention of Venous Thrombo-Embolism

After being evaluated in four double-blind double-dummy phase III randomized controlled trials for VTE prevention in orthopaedic surgery (**Table 2**), dabigatran has become an alternative option to subcutaneous low molecular weight heparin (LMWH) after elective total hip arthroplasty (THA) or total knee arthroplasty (TKA) [9]. The NOACs have been suggested especially for patients who prefer to avoid the inconvenience of daily injections or who have history of heparin-induced thrombocytopenia [9].

In the setting of TKA, the RE-MODEL trial [10] randomized 2,101 patients to dabigatran 150 mg or 220mg once-daily (OD), starting with half-dose 1-4 h after surgery, or the standard European comparator, enoxaparin 40 mg OD starting the evening before surgery, for a total of 6-10 d. Dabigatran etexilate resulted as effective as enoxaparin in the primary efficacy outcome, the composite of asymptomatic and symptomatic deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE) and all-cause mortality (40.5% and 36.4% for the two dabigatran groups compared with 37.7% for

the enoxaparin group; absolute difference 2.8%, 95%CI -3.1 to 8.7, and -1.3%, 95%CI -7.3 to 4.6, for the two comparisons with enoxaparin). No difference emerged in the incidence of major bleeding complications. In the RE-MOBILIZE trial [11], dabigatran 150 mg or 220 mg OD, starting with half-dose 6-12 h after TKA surgery, has been compared with the North-American regimen of enoxaparin, 30 mg twice-daily (BID) starting 12-14 h after surgery, for a total of 12-15 d. Both dabigatran doses failed to show non-inferiority to enoxaparin, probably because of the latter's more intense and prolonged dose regimen. The primary outcome, total VTE and death, occurred in 33.7% and 31.1% for the two dabigatran dosages compared with 25.3% for enoxaparin (risk difference 8.4%, 95%CI 3.4-13.3, *P*=0.0009, and 5.8%, 95%CI 0.8-10.8, *P*=0.0234, respectively). Major bleeding complications were uncommon during treatment and did not significantly differ among the three groups.

In the setting of THA, two trials compared dabigatran, starting with half-dose 1-4 h after surgery, with enoxaparin 40 mg OD, starting the evening before surgery, for an extended prophylaxis of 28-35 d. The RE-NOVATE trial [12] investigated dabigatran 150 mg and 220 mg OD and both doses resulted non-inferior to enoxaparin in reducing the risk of total VTE and all-cause mortality (8.6% and 6.0% for the two dabigatran groups compared with 6.7% for the enoxaparin group; absolute difference 1.9%, 95%CI -0.6 to 4.4, and -0.7%, 95%CI -2.9 to 1.6, respectively). The RE-NOVATE II trial [13] assessed only the higher dosage of dabigatran, 220 mg OD, which resulted non-inferior to enoxaparin in the primary outcome (7.7% vs. 8.8%, risk difference -1.1%, 95%CI -3.8 to 1.6) and obtained a significant 46% relative risk reduction in the secondary outcome, major VTE (venographic or symptomatic proximal DVT and PE) and VTE-related mortality. In these two trials, the risk of bleeding and the safety profile of dabigatran and enoxaparin were similar.

Despite the heterogeneity in dosage and timing of the antithrombotic prophylaxis, a meta-analysis of RE-NOVATE, RE-MODEL and RE-MOBILIZE trials confirmed no significant differences in efficacy or safety endpoints between dabigatran 220 mg and enoxaparin [14]. A pooled analysis of the same three trials showed that both dabigatran doses were as effective as enoxaparin in reducing the risk of major VTE and VTE-related mortality and these results were apparently consistent according to age, gender, weight and renal function[15].

The oral administration in surgical patients, however, can arise some problems. The optimal timing for initiation of dabigatran is 1-4 h after surgery, but a delay in dosing may occur for logistical or clinical reason, such as post-operative nausea or vomiting. Although 13.3% of patients from the RE-MODEL and RE-NOVATE trials experienced dosing delay more than 4 h after surgery, a post-hoc analysis excluded loss of efficacy of dabigatran 220 mg in these subjects [16].

Another problem arising from oral administration is compliance. Antithrombotic prophylaxis in orthopaedic surgery is a preventive treatment in which patients are not stimulated to comply by symptoms, and particularly an extended prophylaxis up to 35 d is suggested after major interventions [9]. In contrast to LMWH, injected directly by health care professionals in some countries, the oral administration is entirely responsibility of patients after hospital discharge. In a recently published cohort of 56 patients undergoing THA, overall compliance was very good, with 98.1% of capsules correctly taken, but there was a tendency towards reduction over time, even if it never fell below 97.1% [17]. Therefore, at the time of prescription, patients should be appropriately informed about risks and benefits of the oral anticoagulant therapy, in order to improve their compliance.

Treatment of Venous Thromboembolism

Dabigatran has been assessed in two phase III randomized controlled trials regarding the treatment of acute VTE (**Table 2**). Patients with acute symptomatic DVT or PE firstly received an approved parenteral anticoagulant, unfractionated heparin or LMWH, for at least 5 d, and were therefore randomized to dabigatran 150 mg BID or warfarin titrated to a range INR 2.0-3.0. Each treatment was given for 6 months in a double-blind double-dummy manner. The decision to treat the dabigatran group with initial parenteral anticoagulation was taken with the purpose to reduce the risk of early recurrences, which were commonly observed when the precursor ximelagatran has been administered as a stand-alone treatment from the beginning [18].

Table 2. Results of the phase III randomized controlled trials evaluating dabigatran in different indications.

	Setting	*Patients,n*	*Intervention*	*Duration of treatment*	*Primary outcome, n/N (% or %/y)*	*Major bleeding, n/N (% or %/y)*
Prevention of VTE					**Total VTE and death**	
RE-MODEL [10]	TKR	2101	Dabigatran 150 mg OD	6–10 days	213/526 (40.5%)	9/703 (1.3%)
			Dabigatran 220 mg OD		183/503 (36.4%)	10/679 (1.5%)
			Enoxaparin 40 mg OD		193/512 (37.7%)	9/694 (1.3%)
RE-MOBILIZE [11]	TKR	2615	Dabigatran 150 mg OD	12–15 days	219/649 (33.7%)	5/871 (0.6%)
			Dabigatran 220 mg OD		188/604 (31.1%)	5/857 (0.6%)
			Enoxaparin 30 mg BID		163/643 (25.3%)	12/868 (1.4%)
RE-NOVATE [12]	THR	3494	Dabigatran 150 mg OD	28–35 days	75/874 (8.6%)	15/1163 (1.3%)
			Dabigatran 220 mg OD		53/880 (6.0%)	23/1146 (2.0%)
			Enoxaparin 40 mg OD		60/897 (6.7%)	18/1154 (1.6%)
RE-NOVATE II [13]	THR	2055	Dabigatran 220 mg OD	28–35 days	61/792 (7.7%)	14/1010 (1.4%)
			Enoxaparin 40 mg OD		69/785 (8.8%)	9/1003 (0.9%)
Treatment of VTE					**Recurrent VTE and related death**	
RE-COVER [19]	Acute VTE	2564	Dabigatran 150 mg BID	6 months	30/1274 (2.4%)	20/1273 (1.6%)
			Warfarin (range INR 2.0-3.0)		27/1265 (2.1%)	24/1266 (1.9%)
RE-MEDY [21]	Extended treatment of VTE	2866	Dabigatran 150 mg BID	6-36 months	26/1430 (1.8%)	13/1430 (0.9%)
			Warfarin (range INR 2.0-3.0)		18/1426 (1.3%)	25/1426 (1.8%)
RE-SONATE [21]	Extended treatment of VTE	1353	Dabigatran 150 mg BID	6 months	3/681 (0.4%)	2/681 (0.3%)
			Placebo		37/662 (5.6%)*	0/662 (0%)
Prevention of thromboembolic complications in AF					**Stroke or systemic embolism**	
RE-LY [26]	Non-valvular AF**	18113	Dabigatran 110 mg BID	2.0 years (median)	183/6015 (1.54%/y)	342/6015 (2.87%/y)
			Dabigatran 150 mg BID		134/6076 (1.11%/y)	399/6076 (3.32%/y)
			Warfarin (range INR 2.0-3.0)		202/6022 (1.71%/y)	421/6022 (3.57%/y)

* In the RE-SONATE study, the primary efficacy outcome included also unexplained deaths;
** In the RE-LY trial, patients included had at least one additional risk factor (previous stroke or transient ischemic attack, symptomatic heart failure or left ventricular ejection fraction <40%, age ≥75 years or age 65-74 years associated with diabetes mellitus, hypertension or coronary artery disease);
Abbreviation: AF = atrial fibrillation, BID = twice daily, INR = international normalised ratio, OD = once daily, THA = total hip arthroplasy, TKA = total knee arthroplasy, VTE = venous thromboembolism.

In the RE-COVER trial [19], the fixed dose of dabigatran resulted as effective as warfarin in the primary efficacy outcome of recurrent symptomatic VTE and VTE-related deaths, occurring in 2.4% and 2.1% for the two treatment groups, respectively (hazard ratio (HR) 1.10, 95%CI 0.65-1.84). Major bleeding episodes did not differ between the two groups (1.6% vs. 1.9%, respectively, HR 0.82, 95%CI 0.45-1.48), while the composite outcome of major and clinically relevant non-major bleeding was significantly lower in the dabigatran arm compared with warfarin (5.6% vs. 8.8%, HR 0.71, 95%CI 0.59-0.85, *P*=0.002). Dyspepsia emerged as the only adverse event related with the use of dabigatran (2.9% vs. 0.6%, *P*<0.001).

Similar findings of efficacy and safety were reported from a replica study, the RE-COVER II trial [20], whose results are currently available only as conference abstract.

Dabigatran has subsequently been evaluated in two double-blind phase III randomized controlled trials regarding the long-term secondary prevention of VTE, in patients who had completed at least 3 initial months of treatment with an approved anticoagulant or with experimental dabigatran (**Table 2**).

In the RE-MEDY trial [21], 2,866 patients were randomized to dabigatran 150 mg BID or warfarin for an additional 6-36 months. Dabigatran was non inferior to warfarin with regard to the prevention of recurrent or fatal VTE (1.8% vs. 1.3% respectively, HR 1.44, 95%CI 0.78-2.64). In the dabigatran group, there was a trend towards less major bleeding events (0.9% vs. 1.8%, HR 0.52, 95%CI 0.27-1.02), while the composite outcome of major and clinically relevant non-major

bleeding was significantly lower (5.6% vs. 10.2% respectively, HR 0.54, 95%CI 0.41-0.71, $P < 0.001$). However, higher incidence of acute coronary events has been reported with the use of dabigatran (0.9% vs. 0.2%, $P = 0.02$).

In the RE-SONATE trial [21], after 6-18 months of anticoagulant treatment, 1,353 patients were randomized to dabigatran 150 mg BID or placebo, for an additional 6 months. This trial confirmed the efficacy of the extended treatment with dabigatran, since this novel drug obtained a 92% relative risk reduction of recurrent VTE (0.4% vs. 5.6%, HR 0.08, 95%CI 0.02-0.25, $P<0.001$). Nonetheless, the prolonged anticoagulant treatment was burden with a significantly higher risk of major and clinically relevant non-major bleeding events (5.3% vs. 1.8%, HR 2.92, 95%CI 1.52-5.60, $P=0.001$).

A recently published meta-analysis found no difference between any of the NOACs and the VKAs, in the risk of recurrent VTE and all-cause mortality [22]. However, given the only recent evidences on the efficacy of dabigatran and factor Xa inhibitors in this setting, no recommendation is currently available regarding the use of the NOACs for the treatment of VTE[23].

Prevention of Thromboembolic Complications in Atrial Fibrillation

After the positive results of the RE-LY trial (**Table 2**), dabigatran has been recently suggested as first option therapy, rather than VKAs, in patients with non-valvular AF who require oral anticoagulation [24-25].

In the RE-LY trial [26], 18,113 patients with non-valvular AF and at least one additional risk factor (previous stroke, transient ischemic attack or systemic embolism; symptomatic heart failure or left ventricular ejection fraction <40%; age ≥75 years or age 65-74 years associated with diabetes mellitus, hypertension or coronary artery disease) were randomized to two blinded doses of dabigatran, 110 or 150 mg BID, or open-label warfarin titrated to target INR 2.0-3.0.

Dabigatran 110 mg BID resulted non-inferior to warfarin in the primary efficacy outcome of stroke and systemic embolism (1.54% vs. 1.71% per year, relative risk (RR) 0.90, 95%CI 0.74-1.10) and showed lower rates of major bleeding (2.87% vs. 3.57% per year, RR 0.80, 95%CI 0.70-0.93, $P=0.003$). Dabigatran 150 mg BID resulted, instead, superior to warfarin in the primary efficacy outcome (1.11% vs. 1.71% per year, RR 0.65, 95%CI 0.52-0.81, $P<0.001$) and showed similar rate of major bleeding (3.32% vs. 3.57% per year, RR 0.93, 95%CI 0.81-1.07).

The efficacy and safety of dabigatran was proven also in secondary prevention [27], and irrespective of the type of AF [28] and previous VKA exposure [29]. Moreover, dabigatran resulted particularly advantageous, in the endpoints vascular events, non-haemorrhagic events, and mortality, at sites with poor INR control [30].

Dyspepsia was more frequently reported with the use of dabigatran (11.8% and 11.3% with the two dabigatran dosages vs. 5.8% with warfarin, $P<0.001$ for both comparisons); while numerically, but not statistically significant, higher incidence of acute coronary events has been reported in the dabigatran groups compared to warfarin (0.82% and 0.81% per year vs. 0.64% per year, $P=0.09$ and $P=0.12$, respectively) [26].

With regards to interventional strategies for rhythm control, dabigatran may be a reasonable alternative to warfarin in patients requiring cardioversion [31], and in patients undergoing catheter ablation [32-33].

An extension trial, the RELY-ABLE [34], investigated the long-term safety of the two dosages of dabigatran etexilate in patients with AF who completed the RE-LY trial. This trial has been recently concluded and the results are expected by the end of the year.

Furthermore, dabigatran has been indirectly compared with antiplatelet drugs in a network meta-analysis [35]. The higher dosage (150 mg BID) was estimated to reduce the risk of all stroke by approximately 60%, compared to both monotherapy and double antiplatelet therapy, without increasing the risk of intracranial or extracranial bleeding. The lower dosage (110 mg BID) was estimated to reduce the risk of all stroke by approximately 50%, compared to aspirin and aspirin plus clopidogrel, although the latter was borderline statistically significant, with a trend towards a reduction of bleeding complications.

Other Applications

Dabigatran has been assessed also in patients with acute coronary syndromes (ACS). In a phase II double-blind dose-escalation trial, the RE-DEEM [36], 1,861 patients with a recent ST-elevation or non-ST-elevation myocardial infarction, were randomized to dabigatran

50 mg, 75 mg, 110 mg or 150 mg BID or placebo, for 6 months. At randomization, 99.2% of patients were on antiplatelet treatment with both aspirin and clopidogrel, the standard of care for ACS, while at the end of the study the proportion was 83.8%. Dabigatran significantly reduced D-dimer levels and showed a trend towards a reduction of cardiovascular ischemic events, for the two higher dosages. On the other hand, it was associated with a two to four times dose-dependent increased risk of major and clinically relevant minor bleeding, although the absolute incidence of major bleeding events was low.

Another phase II randomized controlled trial, the RE-ALIGN, has been planned in patients with a mechanical bileaflet heart valve [37]. In an open-label blinded endpoint manner, the current standard of care warfarin has been compared with dabigatran, at dose ranges between 150 mg BID and 300 mg BID, according to creatinine clearance and dabigatran plasma level at steady state. However, this trial was terminated early because of an excess of thromboembolic complications and major bleeding events in the dagibatran arm and the US Food and Drug Administration recently released an alert against the use of dabigatran in patients with mechanical prosthetic heart valves [38].

Safety of Dabigatran

Haemorrhagic Complications

Bleeding events are the most common and feared complication of antithrombotic drugs [39]. In orthopaedic surgery, dabigatran and enoxaparin showed a similar haemorrhagic profile. The pooled rate of major bleeding was 1.1% and 1.4% for dabigatran 150 mg and dabigatran 220 mg OD vs. 1.4% for enoxaparin, while the pooled rate of major and clinically relevant non-major bleeding was 5.6% in both dabigatran groups and 5.0% in the enoxaparin group [15]. Moderate renal impairment (defined as creatinine clearance 30-50 ml/min) and age above 75 years were associated with higher rates of major bleeding events in all groups [15]. A post-hoc analysis showed no increased risk of major bleeding events when dabigatran etexilate was administered with non-steroidal anti-inflammatory drugs (with half-life of ≤ 12 h) or acetylsalicylic acid (at dosage ≤ 160 mg/d), compared to dabigatran alone [40].

In the acute and long-term treatment of VTE, dabigatran showed similar rate of major bleeding events compared to warfarin, but significantly fewer episodes of the composite safety outcome, including major and clinically relevant non-major bleeding (5.6% vs. 8.8%, HR 0.63, 95%CI 0.47-0.84, P=0.002 in the RE-COVER trial [19]; 5.6% vs. 10.2%, HR 0.54, 95%CI 0.41-0.71, P<0.001 in the RE-MEDY trial [21]).

In patients with AF, the rates of major bleeding events were similar between dabigatran 150 mg BID and warfarin (3.32% vs. 3.57%, RR 0.93, 95%CI 0.81-1.07, P=0.32), and significantly lower with dabigatran 110 mg BID compared to warfarin (2.87% vs. 3.57%, RR 0.80, 95%CI 0.70-0.93, P=0.003) [26].

The RE-LY trial represents the largest cohort of dabigatran-treated patients, with a consistent number of events in all tested groups, providing also information on different sites of bleeding. Intracranial haemorrhages were significantly lower in both dabigatran groups compared to warfarin (0.23% and 0.32% with dabigatran vs 0.76% with warfarin, P<0.001 for both comparisons) [26]. Interestingly, this property is common also to direct factor Xa inhibitors, since in a recently published meta-analysis the NOACs were associated with a significant reduction in the risk of intracranial bleeding events compared to warfarin (RR 0.46, 95% CI 0.39-0.56) [41]. This finding, which is certainly an advance compared to VKAs, might be partly due to the selective inhibition of specific coagulation factors and to the maintenance of other haemostatic mechanisms.

Higher rates of major gastrointestinal bleeding have been reported with dabigatran 150 mg compared to warfarin and to the lower dosage of dabigatran (1.15% and 1.56% with the two dabigatran groups vs. 1.07% with warfarin, P<0.05 for the two above-mentioned comparisons) [26]. In particular, elderly patients (≥ 75 years) appeared to be at higher risk of gastrointestinal bleeding with the use of both dabigatran dosages compared to warfarin [42]. The formulation of dabigatran, indeed, contains a tartaric acid core, coated with dabigatran, in order to lower the gastric pH and to enhance the absorption of the drug. This acidity may explain not only the greater incidence of gastrointestinal bleeding, but also the increased occurrence of dyspepsia, reported in 11% of patients in the RE-LY trial [26] and 3% of patients in the RECOVER trial [19]. Since in the RE-LY trial, proton pump inhibitors (PPI) showed only a little decrease in bioavailability of dabigatran

[43], without any reduction in its efficacy [26], co-administration of a PPI might be a reasonable option for patients who experience dyspeptic symptoms. In addition, careful monitoring of patients and faecal occult blood testing within the first month of treatment have been suggested as reasonable option to detect early signs of gastrointestinal bleeding [44].

Following the large number of postmarketing reports regarding dabigatran-induced bleeding events, the FDA assessed the actual rates of bleeding in new users of dabigatran and warfarin, using an insurance claim database. For gastrointestinal haemorrhages the incidence rate was 1.6 vs. 3.1 per 100,000 days at risk with dabigatran and warfarin respectively; while for intracranial haemorrhages, the respective rates were 0.9 vs. 1.9 per 100,000 days at risk [45]. Early experiences with the use of dabigatran in real life clinical practice suggested also that patients admitted with dabigatran-induced bleeding complications might have a more benign clinical course with a shorter length of stay [46].

Laboratory Monitoring

The NOACs have predictable pharmacokinetic and pharmacodynamic response that allows fixed dose regimens without the need for routine anticoagulation monitoring. However, the quantitative measurement of the anticoagulant effect might be required in some clinical circumstances, such as in case of bleeding, thrombotic events, emergency surgery, concomitant interfering medications, deteriorating renal function, suspicion of overdose, and so on [47].

Based on a population pharmacokinetic model, dabigatran plasma concentrations after 150 mg BID are expected to be approximately 180 ng/ml at peak and 90 ng/ml at trough, while after 220 mg OD are expected to be approximately 180 ng/ml at peak and 40 ng/ml at trough [48].

The activated partial thromboplastin time (aPTT), which targets the intrinsic pathway of the coagulation cascade, is sensitive to dabigatran and shows a curvilinear concentration-response relationship, with a steep increase at low concentrations and linearity at higher concentrations (≥ 200 ng/ml). In patients receiving dabigatran 150 mg BID, the median peak aPTT is approximately 2-times that in controls and the median trough is approximately 1.5-times, being therefore insensitive within the range of therapeutic plasma concentrations [48]. Higher aPTT levels may indicate supratherapeutic concentrations but need to be interpreted with caution as they vary according to coagulometers and reagents [49]. The aPTT may provide a readily available qualitative indication of the anticoagulant activity of dabigatran, but should not be used to determine the drug plasma levels [47].

The prothrombin time (PT) and the international normalized ratio (INR), which target the extrinsic pathway of the coagulation cascade, are relatively insensitive to dabigatran, showing only modest elevation at clinically relevant plasma concentrations [48].

The thrombin clotting time (TT), which directly assesses the activity of thrombin, provides a direct measure of the activity of dabigatran, with a linear dose-response relationship over therapeutic concentrations [48]. A normal TT indicates very low or undetectable dabigatran concentrations [47]. However, at concentrations >600 ng/mL the maximum measurement is often exceeded, suggesting that the TT may be too sensitive for emergency monitoring [48]. The dilute TT in combination with dabigatran calibrant plasma is very sensitive and can be used to determine the drug concentrations at levels <300 ng/mL [47].

The ecarin clotting time (ECT), which is a specific assay for thrombin generation, is sensitive and shows a linear relationship with dabigatran concentrations, but it is rarely available [48].

Additionally, measurement of fibrinogen can be significantly affected by dabigatran, producing an underestimation of the actual fibrinogen concentration [47]. In patients taking dabigatran, laboratory tests may therefore simulate a disseminated intravascular coagulation, with prolonged aPTT and low fibrinogen levels, but dabigatran does not cause thrombocytopenia and D-dimer levels are usually lowered by the anticoagulant treatment [47].

Reversal of Action

A problem arising with the use of the NOACs is the lack of a specific antidote in case of a major bleeding event or emergency reversal [50]. A monoclonal antibody targeting dabigatran is currently under development and demonstrated to inhibit the anticoagulant activity of dabigatran in human plasma in vitro and in rats *ex vivo* [51].

Table 3. Approved indications and dosages of dabigatran etexilate (up to May 2013).

Indications	*Recommended dosages*	*Drug interactions and precautions*
EMA		
Prevention of VTE after THA or TKA	220 mg OD, starting with half-dose within 1-4 h of completed surgery, for a total of 28-35 d (THA) or 10 d (TKA) Reduction to 150 mg OD if: moderate renal impairment (creatinine clearance 30-50 ml/min) or age ≥ 75 years Contraindicated if: creatinine clearance < 30 ml/min	Reduction to 150 mg OD if: strong P-gp inhibitors (e.g. amiodarone, quinidine, verapamil) Reduction to 75 mg OD if: P-gp inhibitor (verapamil) in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) Avoid: P-gp inhibitors (systemic ketoconazole, posaconazolo, itraconazole, cyclosporine, tacrolimus, dronedarone); P-gp inducers (e.g. rifampicin, St. John's wort, carbamazepine, phenytoin); protease inhibitors (ritonavir and its combinations with other protease inhibitors)
Prevention of stroke and systemic embolism in AF	150 mg BID Reduction to 110 mg BID if: age ≥80 years, or low thromboembolic risk associated with high bleeding risk (e.g. age 75-80 years, moderate renal impairment, gastritis, esophagitis or gastroesophageal reflux) Contraindicated if: creatinine clearance <30 ml/min	Reduction to 110 mg BID if: P-gp inhibitor (verapamil) Avoid: P-gp inhibitors (systemic ketoconazole, posaconazolo, itraconazole, cyclosporine, tacrolimus, dronedarone); P-gp inducers (e.g. rifampicin, St. John's wort, carbamazepine, phenytoin); protease inhibitors (ritonavir and its combinations with other protease inhibitors) No dose adjustment: amiodarone or quinidine
FDA		
Prevention of stroke and systemic embolism in AF	150 mg BID Reduction to 75 mg BID if: severe renal impairment (creatinine clearance 15-30 ml/min) Contraindicated if: creatinine clearance <15 ml/min	Reduction to 75 mg BID if: P-gp inhibitors (dronedarone or systemic ketoconazole) in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) Avoid: P-gp inducers (e.g. rifampin); P-gp inhibitors in patients with severe renal impairment (15-30 ml/min) No dose adjustment: P-gp inhibitors (verapamil, amiodarone, quinidine, clarithromycin)

Abbreviation: AF = Atrial fibrillation, BID = twice daily, EMA = European Medicine Agency, FDA = Food and Drug Administration, OD = once daily, P-gp = P-glycoprotein, THA = total hip arthroplasy, TKA = total knee arthroplasy, VTE = venous thromboembolism.

Prothrombin complex concentrates (PCC) may potentially reverse the effect of direct thrombin inhibitors, since they contain high concentration of the coagulation factors II, VII, IX, X and they enhances thrombin generation. Nonetheless, in 12 healthy volunteers taking dabigatran 150 mg BID for 2.5 d, the administration of 4-factors PCC (50 U/kg) did not restore the increased aPTT, ECT and TT [52]. Since in animal bleeding models PCC reversed the prolonged bleeding time and reduced the amount of blood loss or the intracranial haematoma expansion [53-54], the results of the study in healthy volunteers raised the question whether coagulation assays are inadequate surrogate markers for bleeding tendency or whether animal models are not representative of haemorrhagic events in human [52]. Activated PCC (aPCC) (80 U/kg) have been shown to correct thrombin generation parameters in vitro in plasma from healthy volunteers receiving single doses or chronic dabigatran treatment [55-56]. However, there are no studies evaluating the effect of PCC or aPCC on human subjects with active bleeding during treatment with NOACs.

Fresh frozen plasma (FFP) and recombinant activated factor VII (rVIIa) have been evaluated only in murine model of intracranial haemorrhage associated with dabigatran [54]. FFP reduced the volume of intracerebral haemorrhage, while rVIIa did not reduce hematoma size significantly, and neither FFP nor rVIIA had an impact on mortality. There are currently no data regarding the use of FFP or rVIIa in human subjects.

Protamine sulfate and vitamin K, used for the reversal of unfractionated heparin and vitamin K antagonists respectively, are not expected to affect the anticoagulant activity of dabigatran.

Given the high percentage of renal excretion, dabigatran may accumulate and the half-life may double in subjects with severe renal impairment [57]. However, since the plasma protein binding is low, haemodialysis may be a suitable option in emergency situations. In human subjects with end-stage renal disease, up to 68% of active dabigatran was removed with haemodialysis [57].

Because dabigatran etexilate is a lipophilic molecule, the use of activated charcoal *in vitro* successfully absorbed >99.9% of the drug. Despite this finding has not been confirmed in vivo or in human patients, activated charcoal may be a reasonable option in case of an overdose of dabigatran and within 1–2 h from the ingestion[48].

Several algorithms have been proposed for patients experiencing major bleeding events during dabigatran treatment [48, 58-60]. The suggested procedures can be summarized as follow:

- Patients evaluation (monitor vital parameters, assess full blood count and renal function, consider coagulation screen with aPTT or TT, which provide qualitative measures, and diluted TT or ECT, which provide quantitative measures of dabigatran activity);
- Discontinuation of the drug;
- Supportive care (fluid resuscitation or red blood cell transfusion, maintenance of renal function and adequate urinary output, identification of bleeding source and application of local haemostatic measure as needed);
- Activated charcoal (if dabigatran ingestion within two hours);
- Haemodialysis and haemoperfusion (if patients with impaired renal function);
- PCC (if life-threatening bleeding).

Moreover, patients should be managed differently according to the severity of bleeding and the thromboembolic risk [48, 58]:

- Minor bleeding events (e.g. epistaxis, ecchymosis, menorrhagia): local haemostatic measures, delay next dose or consider short anticoagulant withdrawal;
- Moderate bleeding: anticoagulant withdrawal, haemostatic interventions, supportive measures, hemodynamic status monitoring;
- Life-threatening bleeding: anticoagulant withdrawal, life-supporting therapies in intensive care units, supportive measures, consider oral charcoal and haemodialysis, consider PCC (aPCC 80 U/kg may be better than 4-factors PCC 50 IU/kg).

In patients undergoing elective surgery, dabigatran should be discontinued at least 24 h before, depending on the degree of renal impairment and the anticipated risk of bleeding. In patients with normal renal function (creatinine clearance ≥80 ml/min), the pre-operative suspension should be increased to 2 d if major surgery or high risk of bleeding. In patients with moderate renal

impairment (creatinine clearance 30-50 ml/min), more than 48 h are required for standard risk surgery and 4 d for major surgery or high risk of bleeding [48]. In case of emergency surgery, the intervention should be delayed, if possible, until coagulation screening is normal (using either aPTT or TT) or until at least 12 h after the last dose [44]. This peri-procedural algorithm for dabigatran patients, introduced during the course of the RE-LY trial, resulted in similar rate of perioperative bleeding and thrombotic complications, compared to warfarin, with the advantage of a shorter interruption of the oral anticoagulation [61].

Acute Coronary Syndromes

Higher rates of acute coronary syndromes (ACS) have been recently reported with the use of dabigatran, raising the issue of a possible side effect of this drug. In patients with AF, the RE-LY trial described a trend towards higher rates of myocardial infarction (MI) (0.82% and 0.81% per year with dabigatran 110 mg and 150 mg BID vs. 0.64% per year with warfarin, *P*=0.09 and *P*=0.12, respectively) [26], although a post-hoc analysis failed to show a significant excess in the composite outcome of MI, unstable angina, cardiac arrest and cardiac death (3.16% and 3.33% per year with the two dabigatran dosages vs. 3.41% with warfarin, *P*=0.28 and *P*=0.77, respectively) [62]. Similarly, in the long-term secondary prevention of VTE, the REMEDY trial described a higher incidence of ACS with dabigatran compared to warfarin (0.9% vs. 0.2%, *P*=0.02) [21]. On the other hand, in major orthopaedic surgery, where the comparator treatment has been enoxaparin, dabigatran did not elevate the risk of definite or likely ACS during treatment (0.95% and 0.60% with dabigatran 150 mg and 220 mg OD vs. 0.74% with enoxaparin, *P*=0.46 and *P*=0.62, respectively) and did not induce a clinically important rebound effect in the post-treatment period (0.08% and 0.08% with the two dabigatran dosages vs. 0.27% with enoxaparin, *P*=0.11 and *P*=0.18, respectively) [63].

Several meta-analyses have been recently published with contrasting results, ranging from an about 30% relative risk increase for ACS with the use of dabigatran in primary and secondary prevention of cardiovascular diseases [64-65], to a not statistically significant difference in the subgroup analysis of dabigatran versus warfarin in AF patients [41]. At present, it is not clear whether the increased number of ACS might be due to an intrinsic property of dabigatran or rather to a protective effect of the comparator warfarin [66].

Approval of Dabigatran

The European Medicine Agency (EMA) [67] licensed dabigatran in 2008 for the prevention of VTE after THA and TKA. The recommended dosage is 220 mg OD, which should be reduced to 150 mg OD if age 75 or above, moderate renal impairment or concomitant administration of certain P-gp inhibitors (**Table 3**). In 2011 the authorisation has been extended to the prevention of stroke and systemic embolism in patients with non-valvular AF with at least one additional risk factor from the RE-LY trial [26]. The recommended dosage is 150 mg BID, which should be reduced to and 110 mg BID if age 80 or above, concomitant treatment with verapamil or in patients with low thromboembolic risk and high bleeding risk [67].

The US Food and Drug Administration (FDA) [68] has not licenced dabigatran for VTE prevention in orthopaedic surgery. In patients with AF, the approved dosage is 150 mg BID, which should be reduced to 75mg BID if severe renal impairment (creatinine clearance 15-30 ml/min) or concomitant administration of certain P-gp inhibitors (**Table 3**), even if the latter dosage has not been tested in the setting of AF.

Given the only recently published evidences of efficacy and safety in the treatment of VTE, dabigatran has not been licenced yet for the treatment of VTE.

Conclusion

Dabigatran etexilate is a recently developed NOAC, with favourable pharmacological properties. This novel drug is a selective and direct thrombin inhibitor, has rapid onset of action, short half-life and a predictable anticoagulant response, which allow fixed dose regimen without the need for routine laboratory monitoring. In several large clinical trials, dabigatran demonstrated to be at least as effective as the current standard of care in the primary and secondary prevention of several thromboembolic events, such as VTE prevention after orthopaedic surgery, the acute and long-term treatment of DVT and PE, and the prevention of thromboembolic complications of AF. In the treatment of acute coronary syndromes further evidences are needed, while in pa-

tients with mechanical prosthetic heart valves dabigatran obtained disappointing results.

Bleeding events are the most common and feared complication of the oral anticoagulant treatment, especially the NOACs, since a specific antidote is lacking. Given the short half-life of dabigatran, withholding the anticoagulant treatment and supportive measures are likely to be sufficient for patients with mild or moderate bleeding events. In case of a major bleeding event or emergency reversal, suggested measures include haemostatic interventions, haemodialysis in patients with impaired renal function and administration of oral activated charcoal, if recent ingestion of dabigatran. Despite the paucity of evidence on the effect of prothrombin complex concentrates, they are a reasonable option in case of a life-threatening bleeding.

Nevertheless, dabigatran showed a favourable safety profile, causing equal or less major bleeding events compared to warfarin and significantly lower intracranial haemorrhages. On the other hand, higher incidence of dyspepsia and gastrointestinal bleeding has been reported, probably due to the formulation of dabigatran containing a tartaric acid core, and an increase risk of ACS.

Although laboratory tests and dose adjustment are not necessary, particular situations might require monitoring the anticoagulation level of a single patient, such as in case of bleeding or thrombotic events, emergency surgery, concomitant interfering medications, deteriorating renal function or suspicion of overdose. At present, there is no standardized laboratory test, but the activated partial thromboplastin time and the thrombin clotting time may provide a qualitative measurement of dabigatran activity, while the dilute thrombin clotting time and the ecarin clotting time may provide a quantitative measurement.

Finally, the NOACs open the issue that strict patients' compliance is required in order to maintain adequate anticoagulant plasma concentrations. In the absence of a routine laboratory monitoring, the oral administration is entirely responsibility of patients. Moreover, antithrombotic prophylaxis in orthopaedic surgery or in atrial fibrillation is a preventive treatment, in which patients are not stimulated to comply by symptoms. Therefore, at the time of prescription, patients should be appropriately informed about risks and benefits of the oral anticoagulant therapy, in order to improve their compliance.

In conclusion, dabigatran is a promising direct thrombin inhibitor, which has been recently licensed by the European Medicine Agency for the prevention of venous thromboembolism in patients undergoing elective total hip or knee arthroplasty and for the treatment of patients with atrial fibrillation at moderate-high thromboembolic risk. Some issues regarding the reversal of the anticoagulant effect, the lack of standardized laboratory test and the safety for long-term administration still need to be further investigated assessed.

Disclosure

There are no conflicts of interest.

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