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ORIGINAL ARTICLE

Antithrombotic and anticoagulant effects of the direct thrombin inhibitor dabigatran, and its oral prodrug, dabigatran etexilate, in a rabbit model of venous thrombosis

W. WIENEN,* J.-M. STASSEN,† H. PRIEPKE,* U. J. RIES* and N. HAUEL*
*Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany; and †Thromb-X NV, Leuven, Belgium

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Summary. *Background:* Oral anticoagulant therapies targeted at thrombin are being developed to overcome limitations associated with current standard therapies. *Objectives:* This study was undertaken to assess and compare the antithrombotic and anticoagulant effects of the novel, selective and reversible, direct thrombin inhibitor (DTI), dabigatran, and its oral prodrug dabigatran etexilate, to that of unfractionated heparin (UFH), hirudin and melagatran using a rabbit model of venous thrombosis. *Methods:* A rabbit model of venous thrombosis consisting of endothelial damage with blood flow reduction was used with minor modifications. *Results:* All compounds demonstrated a dose-dependent reduction in thrombus formation following i.v. administration with complete or almost complete inhibition at the highest doses. Dabigatran (in the dose range 0.03–0.5 mg kg^{-1}) had a 50% effective dose of 0.066 mg kg^{-1}. By comparison, UFH (5–50 U kg^{-1}), hirudin (0.01–0.05 mg kg^{-1}) and melagatran (0.01–0.3 mg kg^{-1}) had a 50% effective dose of 9.8 U kg^{-1}, 0.016 mg kg^{-1} and 0.058 mg kg^{-1}, respectively. Similarly, oral dabigatran etexilate (1–20 mg kg^{-1}) inhibited thrombus formation in a dose-dependent manner. Maximum inhibition was achieved within 1 h of administration, suggesting a rapid onset of action. For both routes of administration, inhibition of thrombus formation directly correlated with prolongation of the activated partial thromboplastin time. *Conclusions:* These findings demonstrate the potent anticoagulant and antithrombotic activity of dabigatran as a selective thrombin inhibitor in a rabbit model of venous thrombosis. Notably, dose-dependent and long-lasting antithrombotic efficacy was observed after application of its oral form dabigatran etexilate, which is currently undergoing phase III clinical development.

Keywords: anticoagulant, antithrombotic, dabigatran, dabigatran etexilate, thromboembolic disease, thrombosis.

Correspondence: Wolfgang Wienen, Department of Pulmonary Research, Boehringer Ingelheim Pharma GmbH & Co KG, Birkendorfer Strasse, D-88397 Biberach, Germany.
Tel.: + 49 7351 547264; fax: + 49 7351 837264; e-mail: wolfgang.wienen@bc.boehringer-ingelheim.com

The work was carried out at Boehringer Ingelheim Pharma GmbH & Co KG, Birkendorfer Strasse, D-88 397 Biberach, Germany. All authors are or were employees of Boehringer Ingelheim when these studies were performed. Part of this group of studies has been presented in abstract form at the International Society on Thrombosis and Hemostasis, in Paris, 2001: *Thromb Haemost* 2001; 86 (Suppl.): OC853.

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Introduction

Thrombin is a multifunctional trypsin-like serine protease that plays a central role in the coagulation cascade by converting fibrinogen to fibrin [1]. Given its significant involvement in the development of thromboembolic events, thrombin represents an important target for the treatment of numerous thromboembolic diseases [2].

Unfractionated heparin (UFH) and low-molecular-weight heparins are established therapies for the prophylaxis and treatment of deep vein thrombosis and act indirectly by enhancing the inhibitory function of antithrombin, the endogenous thrombin inhibitor [3]. However, these agents have to be administered parenterally and are therefore poorly suited for long-term use. Current oral anticoagulants include vitamin K antagonists, such as warfarin, which although effective and orally active, is associated with a number of well-recognized limitations [4,5].

Various low-molecular-weight compounds have been developed as potent direct thrombin inhibitors (DTIs) [6,7]. Moreover, unlike the antithrombin-dependent anticoagulants, DTIs inactivate both fibrin-bound and fluid-phase thrombin. Consequently, they may prevent thrombus formation more effectively [8–10]. In addition, they also exhibit a more predictable anticoagulant effect mostly as a result of the improved pharmacokinetic properties [11].

Ximelagatran was the first orally administered DTI to show clinical proof of principle in phase III trials [12]; however, its development has been stopped because of concerns about its long-term safety profile [13]. Dabigatran is a novel small

reversible DTI with both a high affinity and specificity for thrombin [14,15]. Dabigatran etexilate is a double prodrug that is rapidly converted into the active form upon absorption from the gastrointestinal tract [16]. The aim of the current study was to assess the antithrombotic and anticoagulant effects of dabigatran following either oral (p.o. as its prodrug) or i.v. administration in a rabbit model of venous thrombosis, and to compare it with UFH, hirudin and melagatran.

Methods

Test compounds

Animals in the control groups received an equal volume of saline. For i.v. administration of dabigatran (BIBR 953 ZW, Boehringer Ingelheim, Biberach, Germany), the compound was dissolved to a concentration of 10 mg mL^{-1} in a 1% dimethylsulfoxide in saline solution. Doses of dabigatran etexilate (BIBR 1048 MS, Boehringer Ingelheim, Biberach, Germany) for oral administration were prepared freshly as aqueous solutions containing 2% (v/v) dimethylsulfoxide and 50% (v/v) glycerol-formal-cremophore.

Hirudin (Refludan™; lyophilized recombinant lepirudin for injection; Hoechst Marion Roussell, Germany) was reconstituted in Tris buffer to a concentration of 10 mg mL^{-1} and further diluted in saline. Melagatran (synthesized in the Department of Medicinal Chemistry at Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany) was dissolved and diluted in saline. Heparin sodium (Ratiopharm, Ulm, Germany) was diluted with saline.

Induction of venous thrombosis in rabbits

All procedures were conducted in accordance with the German Animal Protection Act (Deutsches Tierschutzgesetz). A rabbit model of venous thrombosis consisting of endothelial damage with blood flow reduction [17] was used with minor modifications. Male rabbits (New Zealand White Chbb: NZW or Chinchilla Chbb: CH 2.8–3.2 kg) were anaesthetized with 2 mL i.m. xylazine chloride (BayerVital, Leverkusen, Germany; Rompun 2%) and 1 mL ketamine hydrochloride (Pharmacia & Upjohn, Erlangen, Germany; Ketavet 100 mg mL^{-1}). The left and right femoral veins were cannulated for i.v. injection of the study drugs and anaesthetics, and the left femoral artery was cannulated to collect blood samples. A 4 cm segment of each jugular vein was isolated to the main bifurcation of the external jugular vein and the facial vein. Small side branches were ligated and the facial vein was cannulated. A vein segment was isolated by clamping the vein proximally and distally and this was then emptied of blood via the facial vein cannula. Endothelial damage in the vein segment was induced by filling it with a solution of 0.5% polidocanol (Aethoxysklerol®, 5 mg mL^{-1}, Kreussler & Co., Wiesbaden, Germany) for 5 min. After polidocanol treatment, the vein segments were drained and rinsed with saline before removing the clamps. A ligature was then placed proximally to the segment in order to narrow the lumen diameter to 0.8 mm. After re-establishing blood flow for 25 min, the vein segments were isolated, opened and all thrombus material was removed, dried and weighed. The weight of the dry thrombus for each animal in each of the study drug or control treatment groups was determined as the mean weight of the thrombi from the left and right jugular veins. Control values for thrombus formation were pooled from time-matched control animals from the experimental groups.

Intravenous dosing

The study drugs, or saline (control), were administered as an i.v. bolus 2.5 min after induction of endothelial damage (but before blood flow was restored). The study drug doses and the numbers of animals per treatment group are presented in Tables 1 and 2, respectively. Blood samples for the measurement of activated partial thromboplastin time (APTT) were collected prior to, and at 2, 5, 15 and 30 min after i.v. administration of the study drug or control. Mean APTT values were determined for each drug treatment at each time point.

Oral dosing

Dabigatran etexilate, or the treatment vehicle, was administered at doses of 1, 3, 5, 10, or 20 mg kg^{-1} via oral gavage 120 min prior to anesthetizing the rabbits. The animals were then surgically prepared as described above. Approximately 150 min after oral treatment, the veins were damaged with polidocanol and the experiment was completed as described above. A blood sample for the APTT was taken just prior to injury (i.e. 150 min postdosing).

In addition, the time course of antithrombotic efficacy of dabigatran etexilate was investigated by administering a single dose (10 mg kg^{-1}) at varying times before inducing thrombosis. The pretreatment period was defined as the time between the administration of compound and the induction of anesthesia; pretreatment periods of 1, 2, 3, 5, 7, and 24 h were used. An additional 30 min was required for the surgical preparation and vessel wall damage; this was constant among all treatment groups. In preliminary experiments, it was shown that there was no effect of the pretreatment period on thrombus size, or the APTT in vehicle-treated animals. Thus,

Table 1 Dose ranges and antithrombotic effects (ED_{50}) of dabigatran and other thrombin inhibitors after i.v. administration. 95% CI denotes 95% confidence interval

Compound	Dose range	ED_{50}	95% CI
Dabigatran (mg kg^{-1})	0.03-0.1-0.3–0.5	0.066	0.042–0.103
Hirudin (mg kg^{-1})	0.01–0.03-0.05	0.016	0.013–0.02
Melagatran (mg kg^{-1})	0.01–0.03-0.1-0.3	0.058	0.038–0.079
Unfractionated heparin (U kg^{-1})	5–10-30-50	9.84	7.16–13.52

Table 2 Effects on activated partial thromboplastin time (APTT) of i.v. administered dabigatran and other tested thrombin inhibitors measured at peak levels (2 min post-administration). The doses administered are those given in Table 1. Data expressed as the mean ± SEM; number of animals given in parentheses

APTT (s)	Dabigatran	Hirudin	Melagatran	Heparin
Control	22.5 ± 5.4 (10)	23.3 ± 0.3 (6)	20.5 ± 2.0 (6)	22.3 ± 6.9 (6)
Dose 1	33.8 ± 7.5 (4)	24.8 ± 3.0 (6)	24.2 ± 3.7 (4)	26.2 ± 2.7(4)
Dose 2	40.0 ± 10.6 (4)	27.8 ± 3.3 (6)	27.9 ± 2.7 (5)	31.4 ± 6.3 (6)
Dose 3	50.5 ± 4.4 (4)	38.1 ± 6.8 (4)	38.3 ± 3.0 (4)	45.8 ± 9.0 (4)
Dose 4	60.6 ± 4.4 (4)	ND	59.0 ± 11.6 (4)	75.6 ± 15.0 (4)

a time point of 2 h was used as a control for both sets of experiments (data not shown).

Analytical methods

Activated partial thromboplastin time The whole blood APTT was measured in a coagulometer (Biomatic B10, Sarstedt, Germany) using PTT reagent (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions. Blood samples (2 mL) were anticoagulated with sodium citrate (final concentration of 0.313%). A 100 μL aliquot of each blood sample was placed into a test tube prewarmed to 37 °C. To this, 100 μL PTT reagent was added and the solution was mixed and incubated for 3 min. Thereafter, 100 μL calcium chloride solution (37 °C) was then added to activate coagulation, and the APTT was determined as the time elapsed (in s) between the addition of calcium chloride and the onset of clotting. Control values for APTT were pooled from the vehicle-treated groups.

Statistics

Assignment of the animals to one of the respective treatment groups was performed in a randomized fashion. All data are expressed as mean ± SEM. For experiments investigating the i.v. administration of DTIs and dabigatran etexilate (p.o.), calculation of the 50% effective dose (ED_{50}) for clot inhibition with corresponding 95% confidence interval was determined by regression analysis from the dose–response curve for each compound using validated methods from the Department of Biostatistics (Boehringer-Ingelheim Pharma GmbH). Statistical comparisons of APTT values and clot weights were performed using Dunnett's test for multiple comparisons. A P-value of < 0.05 was considered statistically significant for all tests.

Results

Antithrombotic and anticoagulant effects of i.v. dabigatran

The average dry clot weight in the saline-treated group was 32.5 ± 2.4 mg. Intravenous administration of increasing doses of dabigatran (0.03–0.5 mg kg^{-1}) resulted in a dose-dependent decrease in clot weight with an ED_{50} of 0.07 mg kg^{-1} (Fig. 1). Complete inhibition of thrombus formation was achieved with the highest dose of 0.5 mg kg^{-1}. Similarly, UFH (5–50 U kg^{-1}) inhibited clot formation with an ED_{50} of 9.8 U kg^{-1}. Hirudin (0.01–0.05 mg kg^{-1}) and melagatran (0.01–0.3 mg kg^{-1}) inhibited clot formation with ED_{50} values of 0.016 and 0.058 mg kg^{-1}, respectively (Table 1). In all cases, complete, or near complete, inhibition of clot formation was obtained with the highest dose of inhibitor used.

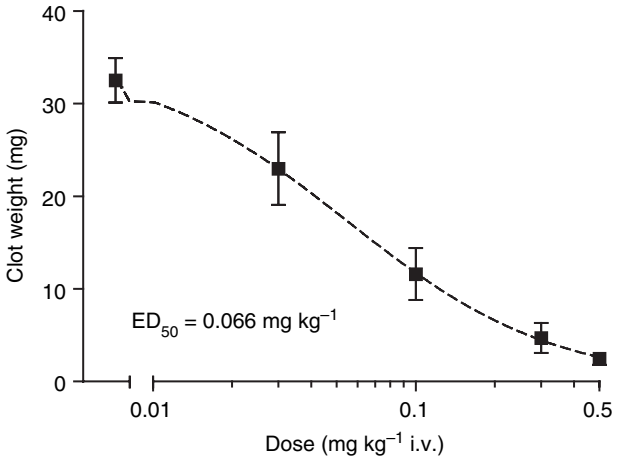

Fig. 1. Antithrombotic efficacy of dabigatran measured as inhibition of clot formation in a rabbit venous thrombosis model. Dabigatran dose 0.03–0.5 mg kg^{-1} i.v. Average dry clot weight in the vehicle-treated group was 32.5 ± 2.4 mg. Values are presented as mean ± SEM, n = 4–10 animals per group.

The pooled control APTT value prior to drug administration in rabbit whole blood was 21.3 ± 0.6 s (mean ± SEM, n = 28). The i.v. administration of dabigatran resulted in a dose-dependent increase in APTT, which peaked at 2 min (Fig. 2). This response was similar to the other compared thrombin inhibitors tested, which also caused dose-dependent increases in the APTT with a maximum at 2 min (Table 2). To investigate the relationship between the antithrombotic and the anticoagulant effects of each compound, dry clot weight was plotted against peak APTT levels for each dose. Data showed an inverse correlation between the anticoagulant effect (i.e. increase in APTT) of dabigatran and the reduction in dry clot weight (Fig. 3). Similar trends were observed with the other tested thrombin inhibitors (results not shown).

Antithrombotic and anticoagulant effects of oral dabigatran etexilate

To determine the effect of increasing oral doses of dabigatran etexilate (1–20 mg kg^{-1}), rabbits were given an oral dose 2 h

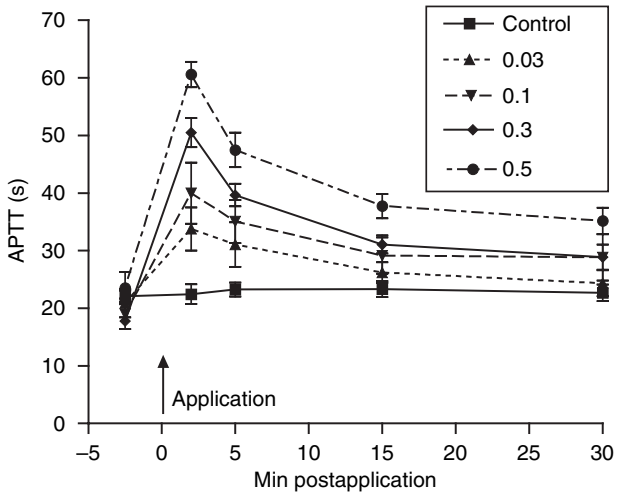

Fig. 2. Anticoagulant efficacy of dabigatran measured as prolongation of activated partial thromboplastin time compared with control treatment. Dabigatran treatment 0.03–0.5 mg kg^{-1} i.v., $n = 4$ each; control $n = 10$. Data are presented as mean ± SEM; $P < 0.05$ vs. control for all doses at the 2 min postapplication time point.

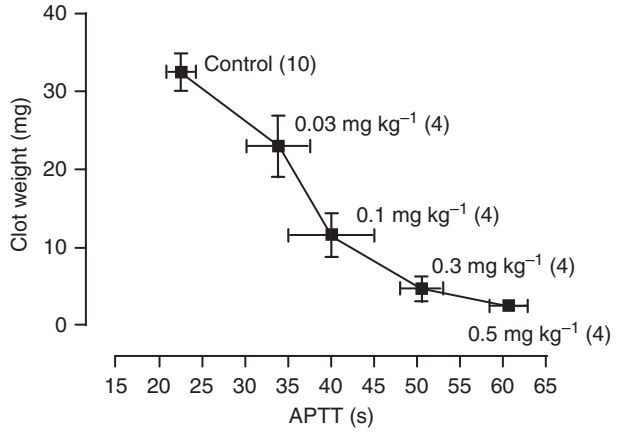

Fig. 3. Relationship between the antithrombotic and anticoagulant effects of dabigatran plotted as clot weight vs. activated partial thromboplastin time at peak anticoagulant levels, compared with control treatment. Values are presented as mean ± SEM; numbers of animals in each group are given in parentheses.

prior to anesthesia. There was a dose-dependent inhibition of clot formation (Fig. 4A), measured approximately 2.5 h after dosing (including the ~30 min for surgical intervention and induction of venous thrombosis). This effect was significant for doses ≥ 3 mg kg^{-1}, with an ED_{50} of 4.7 mg kg^{-1} p.o. A dose-dependent prolongation of the APTT, expressed as fold increase over control, was also observed after oral administration of dabigatran etexilate (Fig. 4B).

To determine the duration of this antithrombotic effect, a dose (10 mg kg^{-1}) of dabigatran etexilate resulting in almost maximal thrombus inhibition was selected. This dose was administered orally to rabbits at different time points prior to anesthesia (1–24 h; Fig. 5). Maximum inhibition of clot formation was achieved with the 1 h pretreatment period,

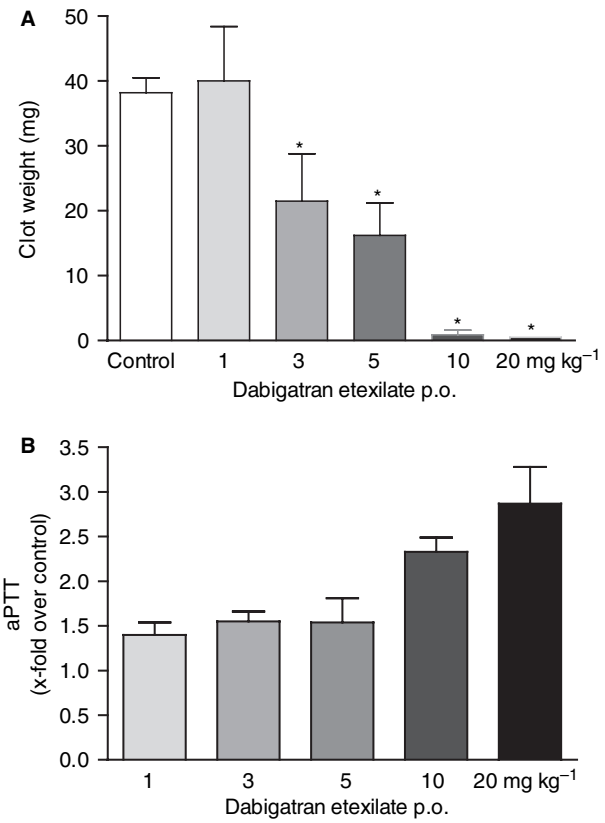

Fig. 4. Antithrombotic and anticoagulant efficacy of orally administered dabigatran etexilate, on the inhibition of clot formation (A) and prolongation of activated partial thromboplastin time (B), compared with control treatment. Dabigatran etexilate dose 1–20 mg kg^{-1} p.o. Average dry clot weight in the vehicle-treated group was 38.2 ± 2.3 mg ($n = 9$). Values are presented as mean ± SEM, $n = 4$–6 animals per group; * $P < 0.05$ vs. vehicle.

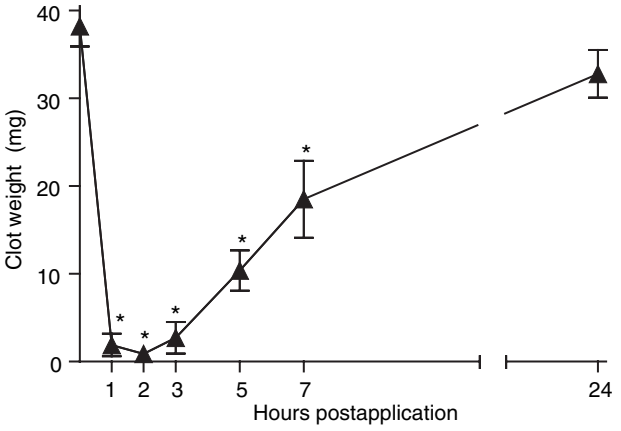

Fig. 5. Antithrombotic effects of dabigatran etexilate over time measured as clot weight at varying intervals post-treatment. Dabigatran etexilate dose 10 mg kg^{-1} p.o. Values are presented as mean ± SEM; * $P < 0.05$ vs. vehicle; $n = 4$–9.

suggesting a rapid onset of action following oral administration. Significant inhibition of clot weight was still observed after 7 h (~52% reduction), the antithrombotic effect was no longer apparent after 24 h (Fig. 5).

Discussion

This study investigated the antithrombotic and anticoagulant effects of dabigatran and compared these with other thrombin inhibitors – UFH (indirect inhibitor), and hirudin and melagatran (direct inhibitors) – in the prevention of venous thrombosis in the rabbit jugular vein. To minimize experimental variability in anticoagulation resulting from different pharmacokinetic behavior of the respective anticoagulants, we administered all compounds i.v. during the surgical procedure for endothelial damage, but before declamping the injured vessel.

Dabigatran was shown to effectively reduce thrombus formation in a dose-dependent manner, with an ED_{50} of 0.07 mg kg^{-1} obtained after i.v. administration. The reference thrombin inhibitors also revealed dose-dependent antithrombotic effects with comparable ED_{50} values to dabigatran in this animal model. The results are consistent with those previously obtained in various models of thrombosis [18–21]. Therefore, in this animal model, dabigatran is as effective at inhibiting venous thrombosis as melagatran and the other clinically available anticoagulants.

Similar antithrombotic and anticoagulant properties were observed with oral administration of the prodrug, dabigatran etexilate, prior to induction of vessel injury. It should be noted that antithrombotic therapy in our experimental model is more reflective of prophylactic (e.g. prevention of thrombus formation in patients with atrial fibrillation), rather than curative treatment of an established thrombosis.

There was a dose-dependent inhibition of thrombus formation, with an ED_{50} of 4.65 mg kg^{-1}, demonstrating effective antithrombotic activity. In addition, thrombus formation was almost maximally reduced with 10 mg kg^{-1} of dabigatran etexilate within 1 h after pretreatment, indicating a fast onset of action. This dose still resulted in a significant 50% antithrombotic activity 7 h after administration, consistent with its pharmacokinetic profile. Dabigatran etexilate is differentiated from vitamin K antagonists through the rapid onset of action and the clear dose-dependent, reversible antithrombotic efficacy. Vitamin K antagonists only reach therapeutically effective levels of anticoagulation after repeated administration for several days in preclinical models [19,21] and in the clinical setting [3,4]. Our experimental data are also in line with current data from human studies. Dabigatran has a half-life of 8 h after single administration, with peak plasma levels measured 2 h after oral administration [16].

An inverse correlation between the dose-dependent decrease in thrombus weight and peak APTT values was also demonstrated. This direct relationship between the antithrombotic and anticoagulant effects of dabigatran illustrates the feasibility of monitoring the drug in case of an overdose, for example. The need for routine drug level monitoring of dabigatran etexilate in the clinic may not be required because of its more consistent pharmacokinetic profile in comparison to indirect thrombin inhibitors or warfarin [16].

In conclusion, these data show that in a rabbit model of venous thrombosis, dabigatran administered i.v. in its active form or orally as the prodrug demonstrates a potent and dose-dependent antithrombotic effect. After oral administration, these effects have a rapid onset and long duration of action. The potency of dabigatran is similar to the effects of known potent inhibitors of thrombin. The present findings suggest that dabigatran may provide a potentially effective alternative antithrombotic therapy in both the prevention and treatment of thromboembolic disorders. The antithrombotic efficacy of dabigatran etexilate in patients undergoing orthopedic surgery and in patients with established deep vein thrombosis, as well as prevention of stroke in patients with atrial fibrillation is currently being evaluated in phase III clinical trials [22].

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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