

# Comparative efficacy and safety of the novel oral anticoagulants dabigatran, rivaroxaban and apixaban in preclinical and clinical development

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## Summary

Therapeutic oral anticoagulation is still commonly achieved by administration of warfarin or other vitamin K antagonists that are associated with an untoward pharmacokinetic / pharmacodynamic (PK/PD) profile leading to a high incidence of bleeding complications or therapeutic failure. Hence, there is an unmet medical need of novel easy-to-use oral anticoagulants with improved efficacy and safety. Recent developments include the identification of non-peptidic small-molecules that selectively inhibit certain serine proteases within the coagulation cascade. Of these, the thrombin inhibitor dabigatran and factor Xa inhibitor rivaroxaban have recently been licensed for thromboprophylaxis after orthopaedic surgery mainly in Europe. In addition, the factor Xa inhibitor apixaban is in late-stage clinical development. Each drug is prescribed at fixed doses without the need of anticoagulant monitor-

ing. Phase III trials in orthopaedic patients essentially resulted in non-inferior efficacy of dabigatran and superior efficacy of rivaroxaban over enoxaparin without any marked differences of drug safety, while apixaban data is still controversial. However, alterations of rivaroxaban and apixaban pharmacokinetics upon interactions with inhibitors and inducers of CYP3A4 or P-glycoprotein may complicate the use of these compounds in daily practice, whereas dabigatran elimination largely depends on renal function. Hence, this review reports PK/PD, efficacy and safety data of dabigatran, rivaroxaban and apixaban throughout preclinical and clinical development.

## Keywords

Clinical trials, oral anticoagulants, venous thrombosis, pharmacodynamics, pharmacokinetics, drug design

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## Introduction

Oral anticoagulants belong to the most frequently used drugs worldwide and along with global ageing their utilisation is still increasing (1). In most countries, warfarin is the anticoagulant of choice for long-term thromboprophylaxis in patients at risk (2). As a consequence of its narrow therapeutic range and interaction potential, the use of warfarin is still hampered by a high incidence of adverse drug reactions despite regular anticoagulant effect monitoring and an in-depth understanding of its pharmacokinetic/pharmacodynamic (PK/PD) properties (3, 4). Recent advances include the development genotype-based dosing algorithms that have prompted the US federal drug agency (FDA) to initiate a labelling change of warfarin that encourages pharmacogenetic testing of clinically relevant cytochrome P450 (CYP) 2C9 and vitamin K epoxide reductase polymorphisms in daily practice (5, 6). Moreover, self-monitoring of the anticoagulant effect and appropriate dosing adjustment has been reported to reduce the incidence of thromboembolic and major haemorrhagic events (7). Despite these promising efforts, there is still an unmet medical need of an anticoagulant drug with sufficient oral bioavailability and minor variability of its dose-response relation-

ship that may hence be orally administered without the need of regular anticoagulant monitoring (8).

Recent developments include the identification of non-peptidic small-molecules that are orally bioavailable and selectively inhibit certain serine proteases within the coagulation cascade (9). Among numerous oral anticoagulants currently under clinical development the thrombin inhibitor dabigatran and factor Xa inhibitor rivaroxaban have recently been licensed for prevention of venous thromboembolism (VTE) after total hip (THR) or total knee replacement (TKR) in Europe and other countries. The factor Xa inhibitor apixaban is another promising oral anticoagulant in late-stage clinical development. Hence, this review describes the PK/PD properties of dabigatran, rivaroxaban and apixaban and discusses their efficacy and safety throughout preclinical and clinical development.

## Dabigatran etexilate (Pradaxa®)

Dabigatran (BIBR 953) is a selective, reversible direct thrombin inhibitor that has recently been approved for thromboprophylaxis in

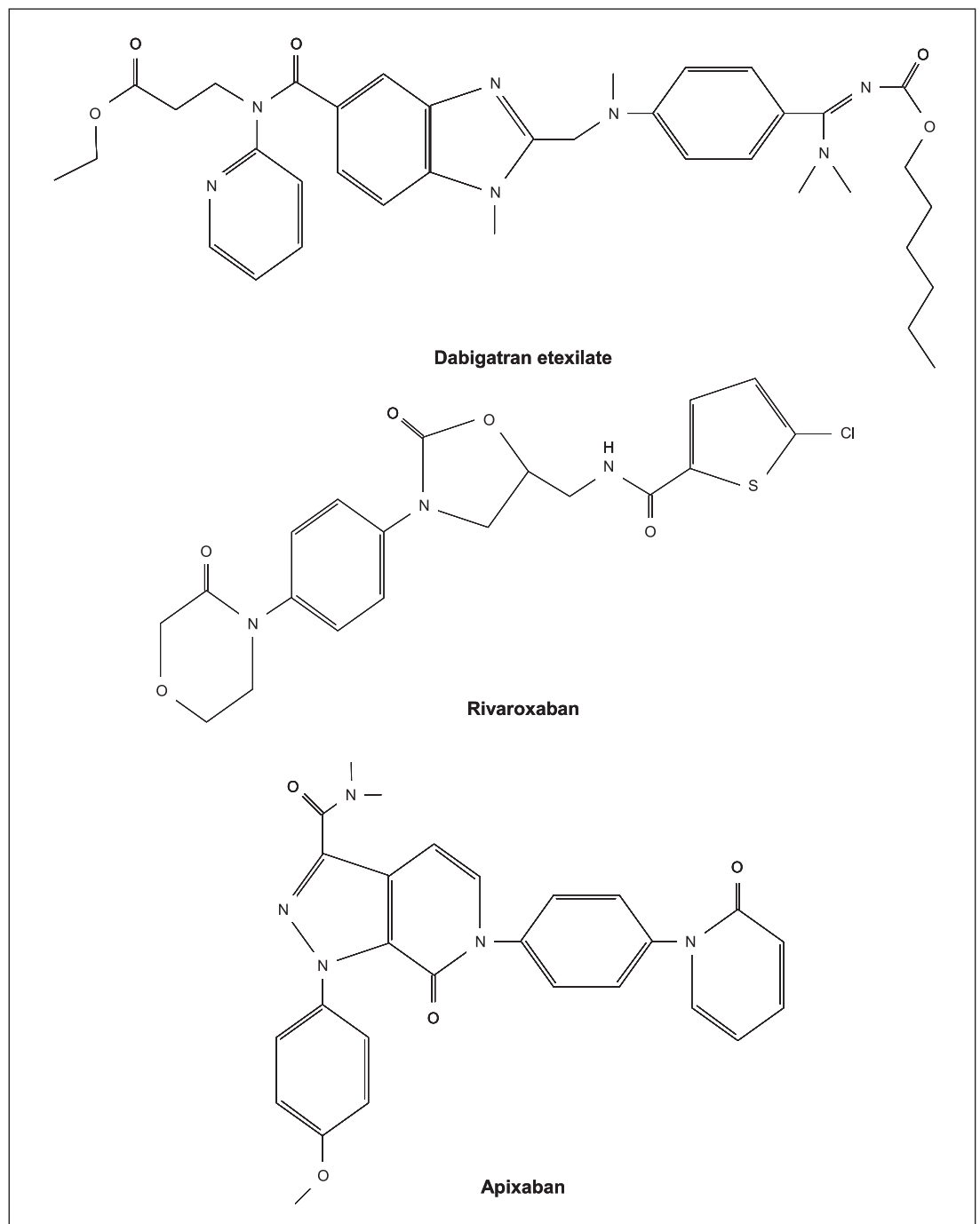
patients undergoing THR or TKR in Europe and many other countries world-wide except for the United States. It has been developed from the lead compound N- $\alpha$ -naphthylsulphonylglycyl-4-amidino-phenyl-alanine piperidine (N- $\alpha$ -NAPAP) and incorporates a benzimidazole structure that is crucial for its competitive, reversible binding affinity to the active site of thrombin. However, this basic functional group is protonated at physiological pH and hence responsible for the highly hydrophilic nature and lacking oral bioavailability of dabigatran. Hence, this basic moiety has been reversibly masked with an N-carboxyalkyl group leading to the develop-

ment of the prodrug dabigatran etexilate (BIBR 1048) with sufficient oral bioavailability (► Fig. 1) (10).

## 2.1. Preclinical *in vitro* and *in vivo* data

### Pharmacokinetics

In human liver microsomes, the radiolabelled prodrug dabigatran etexilate was cleaved via esterases to the major intermediate meta-



**Figure 1:** Chemical structures of rivaroxaban, dabigatran etexilate and apixaban.

**Table 1: Pharmacokinetic properties of dabigatran, rivaroxaban and apixaban in humans.** Data is reported for single or multiple doses of  $\leq 400$  mg dabigatran,  $\leq 10$  mg rivaroxaban and  $\leq 50$  mg apixaban. F: absolute oral bioavailability;  $t_{max}$ : time of maximum plasma concentration;  $t_{1/2}$ : terminal

elimination half-life; Cl/F: apparent total clearance;  $V_z/F$ : apparent volume of distribution;  $f_u$ : unbound fraction in plasma; CYP: cytochrome P450; \*including 1.2% active glucuronides; #re-calculated based on a body weight of 75kg; #obtained in different animal species (e.g. monkeys, dogs and rats).

	Dabigatran	Reference	Rivaroxaban	Reference	Apixaban	Reference
F	~7.2%*	(11)	~90%	(42)	~66%	(82)
$t_{max}$ (h)	1.25–1.5	(17)	0.5–3	(41, 44)	0.5–2	(81)
$t_{1/2}$ (h)	7.1–17	(17)	3.2–9.1	(41, 44)	8.0–15	(81, 83)
Cl/F (L/min)	1.5–2.4	(11, 17)	0.15–0.4	(44)	0.08	(81)
$V_z/F$ (L/kg)	~20–30 <sup>+</sup>	(17)	~0.6–1.5	(44)	=0.3 <sup>#</sup>	(73)
$f_u$	~65–70%	(11, 18)	~5–10%	(43)	13%	(73)
Elimination pathway	~100% unchanged drug and active metabolites	(11, 17)	~50% unchanged drug ~50% inactive metabolites	(42)	~70% unchanged drug ~30% inactive metabolites	(72)
Route of elimination	Urine: ~90–95% Faeces: ~5–10%	(11, 17)	Urine: ~70% Faeces: ~30%	(42)	Urine: ~30% Faeces: ~70%	(81)
Substrate of CYP enzymes	No	(11)	Yes (CYP3A4, CYP2J2)	(35)	Yes (CYP3A4)	(73)
Substrate of drug transporters	Yes	(12)	Yes	(37)	Yes	(71)

Data is reported for single or multiple doses of  $\leq 400$ mg dabigatran,  $\leq 10$ mg rivaroxaban and  $\leq 50$ mg apixaban. F: absolute oral bioavailability;  $t_{max}$ : time of maximum plasma concentration;  $t_{1/2}$ : terminal elimination half-life; Cl/F: apparent total clearance;  $V_z/F$ : apparent volume of distribution;  $f_u$ : unbound fraction in plasma; CYP: cytochrome P450. \*including 1.2% active glucuronides. #re-calculated based on a body weight of 75 kg. #obtained in different animal species (e.g. monkeys, dogs and rats).

bolite BIBR 1087 that is subsequently hydrolysed by microsomal carboxylesterases to ultimately form active dabigatran (11). None of the most relevant human recombinant CYP enzymes resulted in a significant metabolite formation from dabigatran etexilate. Conversely, dabigatran or its intermediate metabolites BIBR 1087 and BIBR 951 did not exhibit any significant CYP inhibition. Exclusively, dabigatran etexilate inhibited CYP2E1 and CYP3A4 activity by about 50% at supratherapeutic concentrations (11). Notably, dabigatran etexilate also showed moderate affinity to the major human efflux transporter P-glycoprotein (P-gp) that may lead to increased bioavailability upon co-administration of P-gp inhibitors or reduced bioavailability upon intake of P-gp inducers (► Table 1) (12).

## Pharmacodynamics

Three main pharmacodynamic properties of dabigatran have been described *in vitro*. Firstly, dabigatran competitively and concentration-dependently inhibits activated thrombin with a  $K_i$  value of 4.5 nM, whereas other serine proteases are inhibited only at  $K_i$  values of  $\geq 3,500$  nM indicating dabigatran as a highly potent and selective thrombin inhibitor (13). Secondly, dabigatran concentration-dependently inhibited thrombin-induced platelet aggregation with an  $IC_{50}$  of 10 nM without any inhibitory effect on other platelet-stimulating agents such as arachidonic acid, collagen or ADP. Thirdly, tissue-factor induced thrombin generation was concentration-dependently inhibited by dabigatran in human platelet-poor plasma with an  $IC_{50}$  of 0.56  $\mu$ M (13).

In a rabbit model, venous thrombus formation induced by endothelial damage and blood flow reduction was dose-dependently

inhibited by dabigatran with an intravenous  $ED_{50}$  of 0.066 mg/kg and oral  $ED_{50}$  of 4.7 mg/kg (14). Maximum inhibition of thrombus formation was obtained 1 hour (h) after oral drug intake and maintained with a biological effect half-life of 7 h (14). In a rat model, venous thrombosis was dose-dependently inhibited after single, intravenous doses of dabigatran with an  $ED_{50}$  of 0.033 mg/kg that was about 15-fold lower than the  $ED_{50}$  determined for rat tail bleeding time suggesting a wide therapeutic window (15). However, dabigatran has most recently been shown to induce longer bleeding times than apixaban or rivaroxaban at equivalent antithrombotic doses in rabbits (16).

## 2.2. Phase-I trials

### Pharmacokinetics

After oral intake of single and multiple doses of dabigatran etexilate by healthy volunteers, maximum plasma concentrations of dabigatran were obtained within 75–90 minutes (min) (17). The absolute oral bioavailability of total dabigatran calculated as  $AUC_{0-ral}/AUC_{iv}$  ratio of the radiolabelled compound amounted to 7.2% consisting of dabigatran (6.0%) and its active glucuronides (1.2%). Importantly, dabigatran etexilate and its intermediate metabolites were almost undetectable in plasma indicating nearly complete pre-systemic conversion to active dabigatran (11). As expected, only about 30–35% of the hydrophilic dabigatran was bound to plasma proteins over a wide concentration range (Table 1) (11, 18). Dose-proportional increases of  $C_{max}$  and AUC data

were reported both for single and multiple doses (17). The high apparent volume of distribution  $V_z/F$  was essentially independent of dose and ranged from 1400–2400 L suggesting extravascular deposition (17).

After intravenous administration of radiolabelled dabigatran, about 85% of radioactivity was primarily recovered as unchanged dabigatran in urine indicating renal excretion as primary route of elimination (11). The terminal elimination half-life ( $t_{1/2}$ ) ranged from 7–9 h after single-dosing and was dose-dependently prolonged after multiple-dosing ranging from 7–17 h (17). However, there was no evidence for any accumulation of dabigatran after multiple dosing and steady-state conditions were obtained within three days (Table 1) (17).

After a single, oral dose of 150 mg dabigatran etexilate, its pharmacokinetic properties were essentially unaffected by moderate hepatic dysfunction (Child-Pugh B) except for a slightly prolonged

bioactivation (18). In healthy elderly volunteers aged  $\geq 65$  years, AUC and  $C_{max}$  data was about 20–30% higher in female than male subjects (19). Importantly, AUC data was about two-fold greater in these elderly than in young subjects after twice-daily dosing, presumably due to the 20–30% lower creatinine clearance (19). As dabigatran is primarily eliminated via renal excretion, a reduction of the daily dose from 220 mg to 150 mg is recommended in patients with moderate renal impairment ( $Cl_{CR}$  30–50 ml/min) and its use is contraindicated in patients with severe renal insufficiency ( $Cl_{CR} < 30$  ml/min) (12).

Drug interaction studies of dabigatran etexilate in combination with atorvastatin (CYP3A4 and P-gp substrate) (20), diclofenac (CYP2C9 substrate) (21) and digoxin (P-gp substrate) (22) did not result in any significant pharmacokinetic changes of dabigatran or co-administered drugs. However, co-administration of amiodarone (P-gp inhibitor) increased dabigatran bioavailability by about

**Table 2: Phase II trials of rivaroxaban, dabigatran and apixaban in patients undergoing total hip or knee replacement.** q.d.: once-daily; b.i.d.: twice-daily; THR: total hip replacement; TKR: total knee replacement; VTE: venous thromboembolism (including symptomatic/venographic deep-vein thrombosis and/or pulmonary embolism); \*an additional comparator group received warfarin (INR of 1.8–3.0).

	Eriksson et al. (24) BISTRO I	Eriksson et al. (28) BISTRO II	Turpie et al. (53)	Eriksson et al. (54)	Eriksson et al. (56)	Eriksson et al. (57)	Lassen et al. (86) APROPOS
Study drug	Dabigatran		Rivaroxaban				Apixaban
Dosing regimen	12.5–300 mg b.i.d. or 150–300 mg q.d.	50–225 mg b.i.d. or 300 mg q.d.	2.5–30 mg b.i.d.	2.5–30 mg b.i.d.	2.5–30 mg b.i.d. or 30 mg q.d.	5–40 mg q.d.	2.5–10 mg b.i.d. or 5–20 mg q.d.
Time of 1st dose	After surgery	After surgery	After surgery	After surgery	After surgery	After surgery	After surgery
Comparator	None	Enoxaparin (40 mg q.d.)	Enoxaparin (30 mg b.i.d.)	Enoxaparin (40 mg q.d.)	Enoxaparin (40 mg q.d.)	Enoxaparin (40 mg q.d.)	Enoxaparin* (30 mg b.i.d.)
Time of 1st dose	-	Prior to surgery	After surgery	Prior to surgery	Prior to surgery	Prior to surgery	After surgery
Treatment duration	6–10 d	6–10 d	5–9 d	5–9 d	5–9 d	5–9 d	10–14 d
Study arms	9	5	6	6	7	6	8
Mean age (years)	67	66	66	65	65	65	67
Female gender (%)	53	61	62	60	58	59	63
No. of randomised patients	289	1973	621	722	641	873	1238
Patients included in safety/efficacy analysis (%)	100/77.9	98.8/74.2	98.7/65.1	97.5/75.9	97.5/72.7	96.8/70.8	98.3/66.3
Follow-up duration	28–42 d (after surgery)	28–42 d (after surgery)	30–60 d (after last dose)	30–60 d (after last dose)	30–60 d (after last dose)	30–60 d (after last dose)	30 d (after last dose)
Indication	THR	THR/TKR	TKR	THR	THR	THR	TKR
Primary efficacy outcome	VTE	VTE	VTE, death	VTE, death	VTE, death	VTE, death	VTE, death
Incidence of efficacy outcome (Study drug vs. comparator group)	6.1–20.8%	13.1–28.5% vs. 24.0%	23.3–40.4% vs. 44.3%	6.9–18.2% vs. 17.0%	10.2–23.8% vs. 16.8%	6.4–14.9% vs. 25.2%	6.8–10.6% vs. 15.6% vs. 26.6%*
Primary safety outcome	Major bleeding	Major bleeding	Major bleeding	Major bleeding	Major bleeding	Major bleeding	Major bleeding
Incidence of safety outcome (Study drug vs. comparator group)	Not observed	0.3–4.7% vs. 2.0%	0.0–7.5% vs. 1.9%	0.8–5.4% vs. 1.5%	0.0–10.8% vs. 0.0%	0.7–5.1% vs. 1.9%	0.0–3.3% vs. 0.0%

d: day; q.d.: once-daily; b.i.d.: twice-daily; THR: total hip replacement; TKR: total knee replacement; VTE: venous thromboembolism (including symptomatic/venographic deep-vein thrombosis and/or pulmonary embolism) . \*an additional comparator group received warfarin (INR of 1.8–3.0).

50–60% and an appropriate dose reduction is recommended in this context (12). In contrast, dabigatran bioavailability was about 20–30% lower when pantoprazole was co-administered indicating its decreased oral bioavailability at elevated gastric pH (19, 23). However, dietary factors appear to have only a minor impact on the dabigatran pharmacokinetics, as a high-fat breakfast moderately prolonged its absorption without altering its ultimate bioavailability in healthy volunteers (23).

### Pharmacodynamics

Pharmacodynamics of dabigatran showed little interindividual variability with maximum effects being obtained within 2 h and a biological effect half-life of about 12 h (17). After intake of single and multiple doses of dabigatran by healthy volunteers, activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT) and ecarin clotting time (ECT) were dose-proportionally prolonged and closely correlated with dabigatran plasma concentrations (17–19).

### 2.3. Phase-II trials

In the BISTRO Ib trial, 59 patients undergoing THR received a single, oral dose of 150 mg dabigatran etexilate (23). In these patients, the pharmacokinetic properties of dabigatran previously determined in healthy volunteers have essentially been confirmed. However, dabigatran absorption was prolonged and associated with high interindividual variability. Based on predefined criteria, almost every fourth patient showed a low absorber status that was associated with the covariates male gender and increased renal clearance in a logistic regression model (23).

In the BISTRO I dose-finding study, 289 patients received once- or twice-daily doses of 25–600 mg/day dabigatran etexilate for 6–10 days after THR (► Table 2) (24). The incidence of total VTE including deep-vein thrombosis (DVT) and pulmonary embolism as primary efficacy outcome was not dose-dependent and ranged from 6.1–20.8%. The predefined primary safety outcome of major bleeding was not observed in any dose group. However, a strong dose dependency for minor bleeding events was determined. Two patients of the highest dose group developed bleeding from multiple sites associated with a substantial prolongation of clotting times and extraordinary high plasma concentrations of dabigatran presumably due to low creatinine clearance ( $\approx 45$  ml/min) (24). Pharmacokinetics of dabigatran was best described by a two-compartment model with first-order absorption and elimination (25). As noted earlier, dabigatran bioavailability was associated with high interindividual variability that has been attributed to postsurgical alterations of gastric pH and motility (25). Importantly, plasma concentrations of dabigatran and clotting times were closely correlated (26, 27).

In the BISTRO II dose-finding trial, 1,973 patients were randomised to once- or twice-daily doses of 100–450 mg/d dabigatran etexilate or once-daily enoxaparin for 6–10 days after THR or TKR

(Table 2) (28). In patients treated with dabigatran, the incidence of the primary efficacy outcome of total VTE dose-dependently decreased from 13.1–28.5% and was significantly lower than 24.0% in the active comparator at daily doses of  $\geq 300$  mg. However, the incidence of major bleeding was nominally higher in these dabigatran dose groups ranging from 3.8–4.7% compared with 2.0% in the enoxaparin group even though it was significantly lower at a daily dose of 100 mg dabigatran (0.3%) (28).

In the 12-week PETRO trial, the safety of dabigatran was compared with warfarin in 502 patients with atrial fibrillation under long-term thromboprophylaxis (27). Patients were randomised to twice-daily doses of 100–600 mg/day dabigatran etexilate alone or in combination with salicylic acid (81 or 325 mg) and warfarin as active comparator. The primary safety outcome of major bleeding was exclusively noted in four patients treated with the highest dabigatran dose in combination with salicylic acid. However, none of the patients receiving dabigatran alone experienced major bleeding suggesting salicylic acid to substantially potentiate the bleeding risk. The incidence of total bleeding was significantly higher in patients treated with dabigatran at daily doses of  $\geq 300$  mg/day (17.8–23.1%) than 100 mg/day (6.5%) irrespective of salicylic acid treatment. Thromboembolic events were noted in only two patients receiving the lowest dabigatran dose (27).

### 2.4. Phase-III trials

In the RE-NOVATE non-inferiority trial, 3,494 patients undergoing THR were randomised to once-daily doses of 150 or 220 mg dabigatran etexilate or once-daily enoxaparin as active comparator over 28–35 days (► Table 3) (29). The incidence of total VTE and all-cause mortality as primary efficacy outcome was compared applying a non-inferiority margin of 7.7% for absolute differences in event rates. The primary efficacy endpoint occurred in 8.6% (150 mg) or 6.0% (220 mg) of patients dabigatran-treated as opposed to 6.7% in the enoxaparin group demonstrating non-inferiority for both doses of dabigatran (► Fig. 2). The incidence of major bleeding in subjects treated with 150 mg (1.3%) or 220 mg (2.0%) dabigatran was not different from enoxaparin (1.6%). Six patients died during dabigatran treatment as opposed to none in the enoxaparin group. However, none of these fatal events were judged to be drug-related. Importantly, the incidence of liver enzyme elevations and acute coronary events was not different between study groups (29).

In the RE-MODEL non-inferiority trial, 2,101 patients undergoing TKR were randomised to once-daily doses of 150 mg or 220 mg dabigatran or once-daily enoxaparin over 6–10 days (Table 3) (30). As expected in the context of TKR surgery, the overall incidence of total VTE and all-cause mortality was higher than in the RE-NOVATE trial. This primary efficacy outcome occurred with a similar incidence in patients treated with 150 mg (36.4%) or 220 mg dabigatran (40.5%) as in enoxaparin-treated subjects (37.7%) (Fig. 2). The incidence of major bleeding as primary safety outcome was also not different between the three study groups ranging from 1.3–1.5%.

**Table 3: Phase III trials of rivaroxaban, dabigatran and apixaban in patients undergoing total hip or knee replacement.** Data is reported for the same primary efficacy (deep-vein thrombosis, pulmonary embolism and all-cause mortality) and safety (major bleeding) outcomes. q.d.: once-daily; b.i.d.: twice-daily; THR: total hip replacement; TKR: total knee replacement.

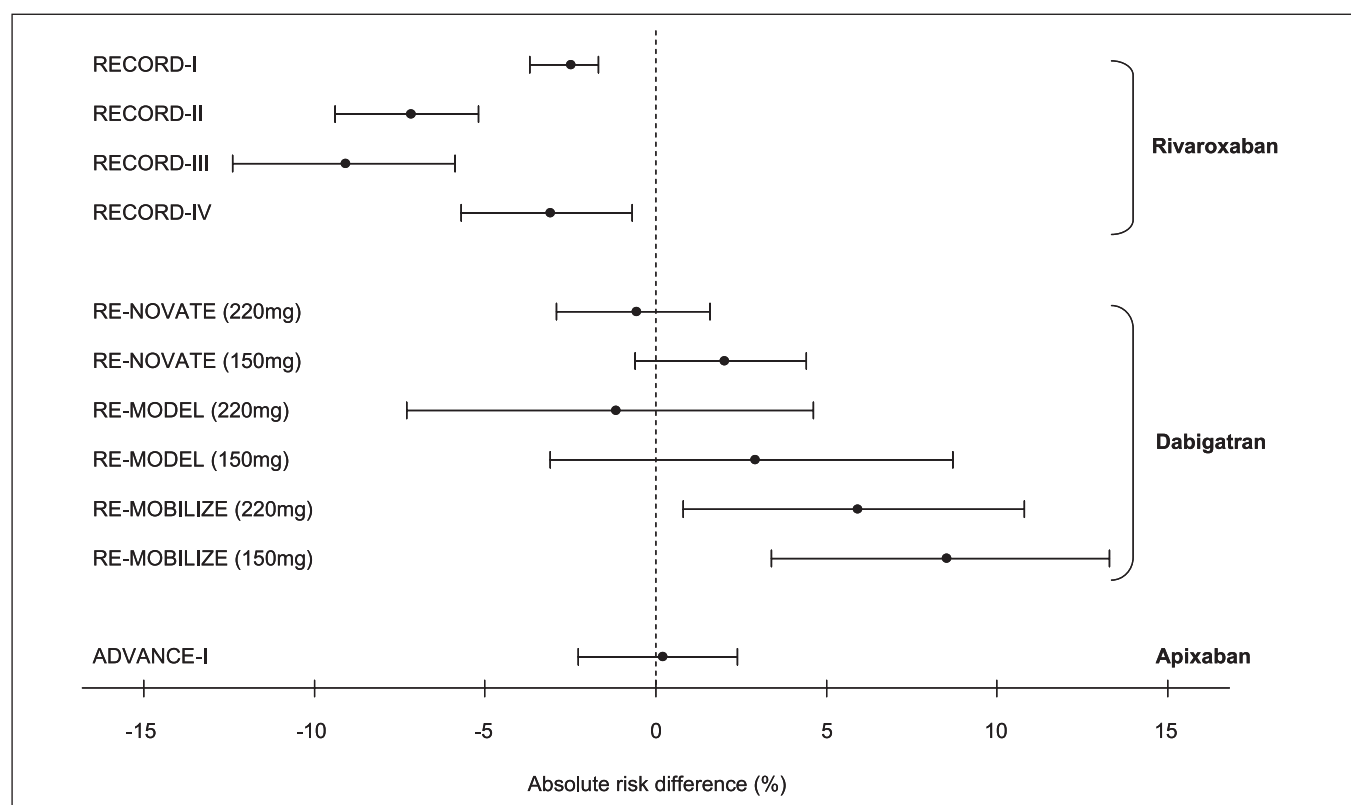
Study name	RECORD-I	RECORD-II	RECORD-III	RECORD-IV	RE-NOVATE	RE-MODEL	RE-MOBILIZE	ADVANCE-I
Study drug	Rivaroxaban (10 mg q.d.)				Dabigatran (150 mg or 220 mg q.d.)			Apixaban (2.5 mg b.i.d.)
Time of 1st dose	After surgery				After surgery			After surgery
Treatment duration	31–39 d	31–39 d	10–14 d	10–14 d	28–35 d	6–10 d	12–15d	10–14 d
Active comparator	Enoxaparin (40 mg q.d.)	Enoxaparin (30 mg b.i.d.)	Enoxaparin (40 mg q.d.)	Enoxaparin (30 mg b.i.d.)	Enoxaparin (30 mg b.i.d.)			
Time of 1st dose	Prior to surgery			After surgery	Prior to surgery		After surgery	After surgery
Treatment duration	31–39 d	10–14 d	10–14 d	10–14 d	28–35 d	6–10 d	12–15 d	10–14 d
Study design	Non-inferiority →superiority	Superiority	Non-inferiority →superiority	Non-inferiority →superiority	Non-inferiority	Non-inferiority	Non-inferiority	Non-inferiority
Study arms	Two				Three			Two
Mean age (years)	63	62	68	65	64	68	66	66
Female gender (%)	56	54	68	65	56	66	58	62
No. of randomised patients	4541	2509	2531	3148	3494	2101	2615	3195
Patients included in safety/efficacy analysis (%)	97.6/66.7	97.9/69.1	97.2/67.2	96.4/61.1	99.1/75.9	98.8/73.3	99.3/72.5	99.6/71.6
Sensitivity analysis	No change				No change	Not reported	Not reported	No change
Follow-up duration	30–35 d				90 d			60 d
Indication	THR		TKR		THR	TKR		TKR
Incidence of efficacy outcome (Study drug vs. comparator group)	1.1% vs. 3.7%	2.0% vs. 9.3%	9.6% vs. 18.9%	6.9% vs. 10.1%	6.0% (220 mg) vs. 8.6% (150 mg) vs. 6.7%	36.4% (220 mg) vs. 40.5% (150 mg) vs. 37.7%	31.1% (220 mg) vs. 33.7% (150 mg) vs. 25.3%	9.0% vs. 8.8%
Incidence of safety outcome (Study drug vs. comparator group)	0.3% vs. 0.1%	<0.1% vs. <0.1%	0.6% vs. 0.5%	0.7% vs. 0.3%	2.0% (220 mg) vs. 1.3% (150 mg) vs. 1.6%	1.5% (220 mg) vs. 1.3% (150 mg) vs. 1.3%	0.6% (220mg) vs. 0.6% (150mg) vs. 1.4%	0.7% vs. 1.4%
Data is reported for the same primary efficacy (deep-vein thrombosis, pulmonary embolism and all-cause mortality) and safety (major bleeding) outcomes. q.d.: once-daily; b.i.d.: twice-daily; THR: total hip replacement; TKR: total knee replacement.								

Again, there were no significant differences of liver function tests or in the frequency of acute coronary events (30).

In contrast to the established non-inferiority of dabigatran efficacy in the RE-NOVATE and RE-MODEL trials, the same doses of dabigatran were inferior to enoxaparin in the RE-MOBILIZE trial involving 2,615 patients undergoing TKR (Table 3) (31). The incidence of total VTE and all-cause mortality as primary efficacy outcome was significantly higher in patients treated with dabigatran relative to the enoxaparin group. Both in the 150 mg and 220 mg group, absolute risk differences of 8.4% (3.4–13.3%) and 5.8% (95% confidence interval [CI] 0.8–10.8 %) exceeded the predefined non-inferiority margin of 9.2% for the upper limit of the 95% CI. In contrast to the European RE-MODEL trial, the RE-MOBILIZE study was conducted in North-America and hence active comparator treatment was commenced after surgery and

twice-daily at a 50% higher total daily dose of 60 mg enoxaparin. These differences may explain the lower incidence of the same primary efficacy outcome in the RE-MOBILIZE than in the RE-MODEL trial (25.3% vs. 37.7%). Hence, the inferior efficacy of dabigatran in the RE-MOBILIZE trial appears to primarily stem from the more efficacious enoxaparin treatment. Moreover, differential findings may also have been influenced by the later starting time of anticoagulant treatment in the RE-MOBILIZE trial (dabigatran: 6–12 h after surgery; enoxaparin: 12–24 h after surgery) than in the RE-MODEL and RE-NOVATE trial (dabigatran: 1–4 h after surgery; enoxaparin: evening before surgery). The incidence of major bleeding, alterations of liver function or serious cardiac adverse events was similar in each study group (31).

In the large RE-LY non-inferiority trial, the efficacy and safety of dabigatran has been investigated in 18,113 patients with atrial



**Figure 2: Primary efficacy data of rivaroxaban, dabigatran and apixaban in phase-III trials.** Absolute risk differences including 95% confidence intervals are shown in relation to the active comparator enoxaparin for the composite primary efficacy outcome of deep-vein thrombosis, pulmonary embolism and all-cause mortality.

fibrillation (32, 33). In this three-arm study, twice-daily doses of 110 mg or 150 mg dabigatran were compared with warfarin (international normalised ratio [INR] 2–3) over two years. The incidence of the primary efficacy outcome of stroke or systemic embolism was higher in the warfarin group (1.69%) than in patients treated with dabigatran at a daily dose of 220 mg (1.53%) or 300 mg (1.11%). Hence, both dabigatran doses were non-inferior to warfarin and the relative risk of stroke or systemic embolism was even significantly reduced at the higher dose of dabigatran indicating superiority over warfarin (relative risk [RR] 0.66 [0.53–0.82];  $p < 0.001$ ). Importantly, the incidence of haemorrhagic stroke was significantly lower in both dabigatran groups compared with warfarin (0.10% and 0.12% vs. 0.38%;  $p < 0.001$ ). Myocardial infarction was the only efficacy parameter that occurred at a higher frequency in dabigatran-treated subjects relative to warfarin (0.72% and 0.74% vs. 0.53%). The primary safety outcome of major bleeding was more common in the warfarin group (3.36%) than in patients treated with dabigatran at twice-daily doses of 110 mg (2.71%;  $p = 0.003$ ) or 150 mg (3.11%;  $p = 0.31$ ) resulting in a significant risk reduction for the lower dose group. Except for dyspepsia, none of the other adverse events or safety measures occurred at a higher frequency in the dabigatran group. In comparison with warfarin, the RE-LY trial strongly suggests superior efficacy and non-inferior safety of dabigatran for thromboprophylaxis in patients with atrial fibrillation at the twice-daily dose of 150 mg and

non-inferior efficacy and superior safety at the 110 mg dose (32, 33).

## Rivaroxaban (Xarelto®)

Rivaroxaban (BAY 59–7939) is a selective, reversible direct factor Xa inhibitor that has also recently been approved for thromboprophylaxis in patients undergoing THR or TKR in Europe and many other countries world-wide except for the United States. It has been developed as lead compound of oxazolidinone derivatives representing a novel class of active-site directed factor Xa inhibitors. As S-enantiomer rivaroxaban competitively binds to factor Xa with high affinity despite the absence of any basic or positively charged functional group resulting in sufficient oral bioavailability along with a highly potent factor Xa inhibition (Fig. 1) (34).

### 3.1. Preclinical *in vitro* and *in vivo* data

#### Pharmacokinetics

In liver microsomes and hepatocytes of rats, dogs and humans, 18 different, pharmacologically inactive metabolites of rivaroxaban

were identified (35). CYP-catalysed oxidative and CYP-independent hydrolytic pathways accounted for about 80–90% and 10–20% of total *in-vitro* metabolism, respectively (35). The major oxidative pathways of rivaroxaban were hydroxylation at its morpholinone and oxazolidinone moiety primarily catalysed by CYP3A4 and CYP2J2 (35). However, rivaroxaban has been shown not to inhibit or induce any clinically relevant CYP enzyme (36). Yet, it has been reported as P-gp substrate and its bioavailability may hence be altered upon co-administration of potent P-gp inhibitors or inducers (37).

### Pharmacodynamics

Three main pharmacodynamic features of rivaroxaban have been confirmed *in vitro*. Firstly, rivaroxaban concentration-dependently inhibited factor Xa with high potency and selectivity indicated by a  $K_i$  value of 0.4 nM that is more than 10,000-fold lower than corresponding  $K_i$  values of other serine proteases (38). Secondly, the generation of thrombin from prothrombin was concentration-dependently inhibited by rivaroxaban with an  $IC_{50}$  of 2.1 nM (38). Thirdly, rivaroxaban dose-dependently inhibited tissue-factor induced thrombin generation in human plasma with an  $IC_{50}$  of 25 nM leading to an almost complete inhibition at concentrations three-fold greater than the determined  $IC_{50}$  (39).

In a rat thrombosis model mimicking the extrinsic activation of the coagulation cascade, rivaroxaban inhibited factor Xa activity, dose-dependently prolonged the prothrombin time and reduced venous thrombus formation with an oral  $ED_{50}$  of 0.1 mg/kg (38). Arterial thrombus formation was also dose-dependently inhibited by rivaroxaban in rats ( $ED_{50}$  5.0 mg/kg) and rabbits ( $ED_{50}$  0.6 mg/kg) applying an arterio-venous shunt model of the intrinsic coagulation cascade (38). In rabbits, rivaroxaban plasma concentrations and prothrombin times were closely correlated ( $r=0.98$ ) (38). In rabbits, orally administered rivaroxaban was effective both in the prevention ( $ED_{50}$  1.3 mg/kg) and treatment ( $ED_{50}$  3.0 mg/kg) of venous thrombus formation (40). Importantly, antithrombotic effective doses of rivaroxaban did not markedly prolong bleeding times both in rats or rabbits (38).

## 3.2. Phase-I trials

### Pharmacokinetics

After oral intake of rivaroxaban by healthy volunteers, maximum plasma concentrations were obtained after 30–180 min (single-dosing) and 120–180 min (multiple-dosing) (41). About 90% of radiolabelled rivaroxaban was recovered unchanged in human plasma suggesting an equivalent absolute oral bioavailability and mainly bound to plasma proteins with an unbound fraction of about 5–10% (Table 1) (42, 43).

In healthy volunteers,  $C_{max}$  and AUC data increased less than dose-proportional at single doses greater than 10 mg (44). Consequently, the apparent volume of distribution  $V_z/F$  increased from about 0.6–1.5 L/kg in subjects receiving  $\leq 10$  mg rivaroxaban to 7.7

L/kg in the 80 mg group. It has been suggested that these data result from a limited solubility of rivaroxaban at higher doses leading to reduced bioavailability (44). Accordingly, a ceiling effect of rivaroxaban absorption has been reported for single doses of  $\geq 50$  mg in elderly aged  $\geq 60$  years (45).

Rivaroxaban is mainly eliminated in urine and to a minor extent in faeces (42). About equal amounts of radiolabelled rivaroxaban are eliminated as unchanged drug and metabolites. About 2/3 of these metabolites are formed via CYP-dependent oxidative and about 1/3 via CYP-independent hydrolytic pathways (42). The total apparent clearance  $Cl/F$  ranging from 0.15–0.4 L/min classifies rivaroxaban as low-clearance drug. Its terminal  $t_{1/2}$  dose-dependently increased from about 3–4 h after single doses of  $\leq 10$  mg to 17 h in the 80 mg group (44). However, after multiple-dosing,  $t_{1/2}$  at steady-state was not influenced by dose and ranged from 5.7–9.2 h without any evidence for drug accumulation (41). Pharmacokinetics of rivaroxaban was best described by a two-compartment model with first-order absorption and elimination (46).

Interaction studies reported the lack of any clinically relevant interaction of rivaroxaban with salicylic acid (47), aluminium-magnesium hydroxide (48), ranitidine (48) or naproxen (49). However, rivaroxaban bioavailability was increased by about 2.5-fold upon co-administration of CYP3A4/P-gp inhibitors such as ketoconazole or ritonavir and decreased by about 50% after administration of the CYP3A4 inducer rifampicin (37). In healthy subjects, rivaroxaban pharmacokinetics was unaffected by gender and weight (50). In addition, PK/PD of rivaroxaban has been shown not to differ between young (41, 44) and elderly volunteers aged  $\geq 60$  years (45). Concomitant food intake only marginally increased rivaroxaban bioavailability in healthy subjects (48). Pharmacokinetic properties of rivaroxaban have essentially been confirmed in healthy Chinese volunteers after once-daily and twice-daily dosing (51).

### Pharmacodynamics

Rivaroxaban dose-dependently inhibited factor Xa activity by about 20–60% after single- and multiple-dosing with a maximum about 1–4 h after drug intake and a biological effect half-life of 6–7 h (41, 44). Plasma concentrations of rivaroxaban were closely correlated with factor Xa activity and prothrombin time suggesting suitability of the latter coagulation test for anticoagulant monitoring throughout clinical development (46, 52).

## 3.3. Phase-II trials

In the initial phase-II dose-ranging study, 621 patients were randomised to twice-daily doses of 5–60 mg/d rivaroxaban or twice-daily enoxaparin as active comparator for 5–9 days after TKR (Table 2) (53). In rivaroxaban-treated patients, the incidence of the primary efficacy endpoint of total VTE and all-cause mortality dose-independently ranged from 23.3–40.4%. At daily doses of

20 mg (23.3%) and 60 mg (25.4%), it was significantly lower than in the enoxaparin group (44.3%). However, the incidence of major bleeding in rivaroxaban-treated subjects dose-dependently increased ranging from 0–7.5% and was nominally higher than in the enoxaparin group (1.9%) at doses of  $\geq 40$  mg/day (53).

In another dose-ranging study, 722 patients undergoing THR were randomised to twice-daily doses of 5–60 mg/day rivaroxaban or once-daily enoxaparin and compared with respect to the same primary efficacy and safety endpoints (Table 2) (54). The primary efficacy endpoint dose-independently occurred in 6.9–18.2% of rivaroxaban-treated patients as opposed to 17.0% in the enoxaparin group. The incidence of major bleeding dose-dependently increased from 0.8–5.4% and nominally exceeded the corresponding frequency of 1.5% in the enoxaparin group at twice-daily doses of  $\geq 10$  mg/day rivaroxaban (54).

Based on a pooled analysis of these two studies (53, 54), daily doses of 5–20 mg rivaroxaban were recommended for VTE prevention after major orthopaedic surgery (55).

The results from the first THR study (54) were confirmed in a similarly designed trial investigating 625 patients after THR (Table 2) (56). The primary efficacy endpoint occurred in 10.2–23.8% of rivaroxaban-treated subjects and was not different from the corresponding incidence of 16.8% in patients treated with once-daily enoxaparin. The frequency of major bleeding dose-dependently increased from 0.0–10.8% in rivaroxaban-treated patients, whereas none of the patients in the enoxaparin group developed major bleeding (Table 2) (56).

A further phase-II trial compared the efficacy and safety of once-daily dosing regimens of 5–40 mg rivaroxaban with once-daily enoxaparin in 873 patients undergoing THR over 5–9 days (Table 2) (57). The incidence of the primary efficacy endpoint of total VTE and all-cause mortality was lower in each rivaroxaban dose group (6.4–14.9%) than in enoxaparin-treated subjects (25.2%). The frequency of major bleeding again dose-dependently increased from 0.7–5.1% as opposed to 1.9% in the enoxaparin group (57).

In patients undergoing THR or TKR, pharmacokinetics of rivaroxaban were best described by an oral one-compartment model and PK-PD modeling revealed a close correlation of rivaroxaban plasma concentrations with prothrombin times and factor Xa activity (52). Pooled analysis of two dose-finding studies (54, 57) confirmed once-daily and twice-daily dosing of rivaroxaban to be equally effective and safe suggesting a fixed once-daily dose of 10 mg as most suitable for phase-III trials (58).

Additional rivaroxaban phase-II studies have been conducted involving patients with DVT or acute coronary syndrome. In 613 patients with proximal DVT, the efficacy and safety of 40 mg once-daily or 10–30 mg twice-daily rivaroxaban has been compared with enoxaparin followed by warfarin (INR 2–3) over 12 weeks (59). The incidence of the primary efficacy outcome defined as improvement in thrombotic burden and lack of recurrent thrombosis was not significantly different between patients treated with rivaroxaban (43.8–59.2%) or enoxaparin (45.9%). The primary safety outcome of major bleeding was exclusively observed in the rivaroxaban group at an incidence of 1.7–3.3% (59).

In a similar 12-week trial, 543 patients with acute DVT were randomised to twice-daily doses of 20–40 mg rivaroxaban or heparin treatment followed by vitamin K antagonists as active comparator (60). The primary efficacy outcome of symptomatic VTE or asymptomatic deterioration in thrombotic burden occurred at a nominally lower frequency in rivaroxaban-treated subjects (5.4–6.6%) than in the comparator group (9.9%). Moreover, the incidence of major and clinically-relevant non-major bleeding was moderately lower in the rivaroxaban (2.2–6.0%) than in the comparator group (8.8%) (60).

Finally, the therapeutic potential of 5–20 mg/day rivaroxaban after acute coronary syndrome has been studied in the placebo-controlled ATLAS trial involving 3,491 patients over six months (61). The incidence of death, myocardial infarction, stroke or severe recurrent ischaemia as primary efficacy outcome was not significantly different between subjects treated with rivaroxaban or placebo (5.6% vs. 7.0%; HR: 0.79 [0.60–1.05];  $p=0.10$ ). However, the incidence of the secondary outcome of death, myocardial infarction or stroke was significantly reduced in the rivaroxaban group (3.9% vs. 5.5%; HR: 0.69 [0.50–0.96];  $p=0.027$ ). Contrariwise, rivaroxaban dose-dependently increased the risk of clinically significant bleeding by about two- to five-fold over placebo (61).

### 3.4. Phase-III trials

The efficacy and safety of rivaroxaban for thromboprophylaxis after THR or TKR has been investigated by means of the RECORD 1–4 phase III trials (62–65). In each of these two-arm trials, a once-daily dose of 10 mg rivaroxaban was compared with once-daily (RECORD 1–3) or twice-daily enoxaparin (RECORD 4). The composite of DVT, non-fatal pulmonary embolism or all-cause mortality was defined as primary efficacy outcome and major bleeding served as primary safety outcome.

In the RECORD 1 non-inferiority/superiority trial, 4,591 patients undergoing THR were enrolled and rivaroxaban was compared with enoxaparin over 31–39 days of treatment (64). The primary efficacy outcome occurred significantly less often in patients treated with rivaroxaban (1.1%) than with enoxaparin (3.7%) ( $p<0.001$ ). Major VTE was also less commonly observed in the rivaroxaban (0.2%) than enoxaparin group (2.0%) ( $p<0.001$ ). The incidence of major bleeding was not significantly different between subjects treated with rivaroxaban (0.3%) or enoxaparin (0.1%) (64).

The RECORD 2 superiority trial comprised 2,551 patients also undergoing total hip arthroplasty (62). In contrast to RECORD 1, 31–39 days of rivaroxaban treatment was compared with 10–14 days of enoxaparin treatment. The primary efficacy outcome occurred in 2.0% of patients treated with rivaroxaban as opposed to 9.3% in the enoxaparin group ( $p<0.0001$ ). In each group, only a single patient suffered from major bleeding as primary safety outcome. Notably, the longer duration of rivaroxaban treatment is likely to have biased efficacy data in favor of rivaroxaban (62).

In the RECORD 3 non-inferiority/superiority trial, 2,531 patients undergoing TKR were randomised to rivaroxaban or enox-

aparin (65). The short treatment duration of 10–14 days was applied to both study groups. Again, the primary efficacy outcome occurred significantly less often in patients treated with rivaroxaban (9.6%) than in enoxaparin-treated subjects (18.9%) ( $p < 0.001$ ). Major VTE was determined in 1.0% of patients receiving rivaroxaban as opposed to 2.6% of enoxaparin-treated patients ( $p = 0.01$ ). However, the incidence of major bleeding was not significantly different between rivaroxaban (0.6%) and enoxaparin (0.5%) (65).

In the RECORD 4 non-inferiority/superiority trial, 3,148 patients undergoing total knee arthroplasty were randomised to rivaroxaban or enoxaparin (63). In contrast to RECORD 3, the active comparator enoxaparin was administered at a twice-daily dose of 30 mg. The primary efficacy outcome occurred in 6.9% of patients treated with rivaroxaban as opposed to 10.1% in the enoxaparin group ( $p = 0.012$ ). Hence, the results of the otherwise almost equally designed RECORD 3 trial were essentially confirmed. Again, the incidence of major bleeding was not significantly different between the rivaroxaban (0.7%) and enoxaparin (0.3%) group.

Phase-III trials investigating rivaroxaban in the context of stroke prevention in patients with atrial fibrillation (66) and secondary thromboprophylaxis in patients with recurrent VTE (67), pulmonary embolism (68) or acute coronary syndrome (69) are currently ongoing.

## Apixaban

Apixaban (BMS-562247) is a selective, reversible direct factor Xa inhibitor that is currently in late-stage clinical development for prophylaxis of thromboembolic events. It represents a follow-on compound to the initially developed lead substance razaxaban (BMS-561389) (70). Both compounds consist of a pyrazole linked to a phenyl piperidinone moiety via a peptide bond. The pyrazole-carboxamido moiety is also crucial for active-site directed binding of apixaban and razaxaban to factor Xa. In this context, concerns have been raised due to the possible formation of putatively mutagenic anilines from razaxaban in the course of amide hydrolysis. Hence, the carboxamido linker has been further stabilised by cyclisation thereby prohibiting aniline formation and resulting in the discovery of apixaban that also shows an improved pharmacokinetic profile relative to razaxaban (Fig. 1) (71).

### 4.1. Preclinical *in vitro* and *in vivo* data

#### Pharmacokinetics

In hepatocytes of rats, mice, rabbits, dogs, monkeys or humans, fourteen different inactive metabolites of apixaban were identified (72). *O*-Demethyl-apixaban was the most abundant metabolite that is primarily formed via CYP3A4 (73) and undergoes subsequent sulphation to *O*-Demethyl-apixaban sulphate catalysed by SUL1A1/2 (74). Apixaban did not inhibit or induce clinically rel-

evant CYP enzymes *in vitro*, suggesting a minor interaction potential (73). However, the low apparent permeability quotient obtained with Caco-2 cell monolayers suggests apixaban to be a substrate of drug transporters (71, 75).

#### Pharmacodynamics

Apixaban potently, selectively and concentration-dependently inhibited human factor Xa with a  $K_i$  value of 0.08 nM, whereas  $K_i$  values  $\geq 3 \mu\text{M}$  were determined for other serine proteases (76, 77). Moreover, apixaban showed moderate selectivity for clot-bound over free factor Xa ( $\text{IC}_{50}$  1.3 vs. 7.6 nM) (78). Secondly, apixaban inhibits thrombin generation rate with an  $\text{IC}_{50}$  of 35 nM (79). However, platelet aggregation was not significantly inhibited by apixaban *in vitro* up to a concentration of 10  $\mu\text{M}$  (76).

In rabbits, apixaban administered as constant intravenous infusion dose-dependently inhibited venous, arterio-venous and arterial thrombosis with an  $\text{ED}_{50}$  of 0.11, 0.27 and 0.07 mg/kg•h, respectively (78). In another rabbit model, intravenous apixaban also dose-dependently inhibited carotid artery thrombosis with an  $\text{ED}_{50}$  of 0.3 mg/kg•h (80). Importantly, additional administration of salicylic acid further reduced thrombus weight and did not result in a significant prolongation of cuticle bleeding time (80).

### 4.2. Phase-I trials

#### Pharmacokinetics

After oral intake of a single dose of 20 mg radiolabelled apixaban by healthy volunteers, maximum plasma concentrations were obtained within 30–120 min (81). About 2/3 of the dose is absorbed in humans (82) and mainly bound to plasma proteins (Table 1) (73). After multiple-dosing, plasma concentrations of apixaban dose-proportionally increased (83). The small volume of distribution  $V_d$  of  $\leq 0.3 \text{ L/kg}$  obtained in animals along with moderate plasma protein binding suggests the lack of extravascular deposition of apixaban (73).

A single dose of radiolabelled apixaban was recovered mainly in faeces (50–55%) and also in urine (25–30%) of healthy volunteers within 12 days after oral intake (81). The recovery loss of 15–25% was suggested to stem from logistic problems, even though tissue accumulation of apixaban can not be excluded (81). Of the recovered dose, unchanged apixaban constituted about 85–90% in urine and 60–75% in faeces (81). The remainder was eliminated after biotransformation primarily as inactive *O*-Demethyl-apixaban and *O*-Demethyl-apixaban sulphate with minor contribution of hydroxylated metabolites (81). Apixaban is a particularly low-clearance drug with a total apparent clearance of 0.08 L/min (Table 1) (81). In humans, it showed a biphasic elimination pattern with a  $t_{1/2}$  of  $12.7 \pm 8.6 \text{ h}$  (81). After multiple-dosing, steady-state concentrations were achieved within three days (83).

Apixaban did not significantly alter the pharmacokinetics of the co-administered P-gp model substrate digoxin (84). Data of other interaction studies has not yet been reported.

## Pharmacodynamics

In healthy volunteers, aPTT and modified PT were dose-dependently prolonged and correlated with the determined plasma concentrations of apixaban (83, 85).

### 4.3. Phase-II trials

In the initial phase-II dose-ranging study, 1,238 patients undergoing TKR and post-operative thromboprophylaxis were randomised to once- or twice-daily apixaban (5–20mg/d) or active comparator treatment represented by twice-daily enoxaparin or warfarin (Table 2) (86). The incidence of total VTE or all-cause mortality as primary efficacy endpoint was lower in apixaban-treated subjects (6.8–10.6%) than in the enoxaparin (15.6%) or warfarin (26.6%) group, even though these differences were not statistically significant. Total VTE rates were consistently lower under twice-daily than once-daily dosing of apixaban. The incidence of major bleeding as primary safety outcome ranged from 0.0–3.3% in apixaban-treated subjects, whereas none in the active comparator groups experienced major bleeding. Notably, three patients died throughout the study due to pulmonary embolism, myocardial infarction or heart failure each of those receiving apixaban (86).

In the Botticelli DVT phase-II study, the efficacy and safety of apixaban for secondary prophylaxis of DVT has been investigated (87). In this four-arm study, 520 patients with DVT were randomised to three once- or twice-daily doses of apixaban (10–20 mg/day) or heparin treatment followed by vitamin K antagonist over three months. The primary efficacy outcome of symptomatic VTE or deterioration of thrombotic burden dose-independently occurred at a similar frequency of 4.7% in apixaban-treated subjects as opposed to 4.2% in the comparator group (87). The incidence of the primary safety outcome of major and clinically-relevant non-major bleeding was also essentially not different between apixaban-treated subjects (7.3%) and controls (7.9%). Importantly, no alterations of liver transaminase or bilirubin plasma concentrations were observed (87).

In the APPRAISE phase-II trial, primarily the safety of apixaban has been investigated in the context of myocardial ischaemia (88). In this five-arm study, 1,715 patients with a recent myocardial infarction or ST-elevation were randomised to four once- or twice-daily doses of apixaban (5–20 mg/day) or placebo over six months. Interim analysis revealed a dose-dependent increase in bleeding risk leading to the discontinuation of two study arms with the highest daily dose of 20 mg apixaban. At the time of discontinuation, the incidence of major and clinically-relevant non-major bleeding as primary safety outcome ranged from 5.0–7.8% as opposed to 0.8% in the placebo group. After termination of the study, the incidence of 5.7% and 7.9% in subjects treated with 5–10 mg/day apixaban still exceeded the bleeding frequency of 3.0% in the placebo group. The dose-dependent increase of bleeding risk was much more pronounced in patients with concomitant clopidogrel treatment. Other safety measures including alterations of liver

function tests were not significantly different between study groups. The incidence of ischaemia or cardiovascular death was lower in apixaban-treated subjects (6.0–7.6%) than in the placebo group (8.7%) without reaching statistical significance (88).

### 4.4. Phase-III trials

In the ADVANCE-I non-inferiority trial, 3,195 patients undergoing TKR were randomised to twice-daily apixaban (5 mg/day) or twice-daily enoxaparin as active comparator over 10–14 days (Table 3) (89). Total VTE and all-cause mortality as primary efficacy outcome occurred at a similar frequency in 9.0% and 8.8% of patients treated with apixaban or enoxaparin, respectively. However, the predefined criteria for non-inferiority were not reached, which has been explained by the almost two-fold lower than expected overall incidence of the efficacy outcome. The incidence of any bleeding as primary safety outcome was lower in patients treated with apixaban (5.3%) than enoxaparin (6.6%). This difference was even statistically significant for the composite of major or clinically-relevant non-major bleeding (2.9% vs. 4.3%;  $p=0.03$ ). The incidence of other adverse safety measures including alterations of liver enzyme or bilirubin concentrations was similar in both study groups (89).

In the ADVANCE-II non-inferiority trial, 3,057 patients undergoing TKR were also randomised to twice-daily apixaban (5 mg/day) or enoxaparin (90). In contrast to ADVANCE-I, the European regimen of once-daily enoxaparin was chosen as active comparator arm. The primary efficacy outcome was again total VTE and all-cause mortality that occurred at a significantly lower frequency in patients treated with apixaban (15.1%) than in the active comparator group (24.4%) ( $p=0.001$ ). Major VTE occurred in 1.1% vs. 2.2% of patients treated with apixaban or enoxaparin, respectively. Moreover, major or clinically-relevant non-major bleeding occurred at a nominally lower frequency in the apixaban group (3.5% vs. 4.8%;  $p=0.09$ ) (90).

A number of additional phase-III studies are planned as part of the extensive clinical trial programme of apixaban involving about 45,000 patients world-wide. The therapeutic potential of apixaban is currently being investigated in the context of VTE prevention in hospitalised patients at thromboembolic risk (ADOPT) (91), in patients with atrial fibrillation (ARISTOTLE, AVERROES) (92, 93) and as prophylaxis of recurrent pulmonary embolism and DVT (AMPLIFY) (94).

## Discussion

The PK/PD profile of dabigatran etexilate is characterised by rather large interindividual variability of drug absorption with almost every fourth patient being identified as low-absorber (23). Moreover, dabigatran elimination is highly dependent on renal function and its use is hence contraindicated in patients with se-

vere renal insufficiency. In none of the orthopaedic trials, superior efficacy of dabigatran over enoxaparin has been demonstrated and its inferiority was even determined in the RE-MOBILIZE trial most likely due to the more efficacious twice-daily dosing regimen of enoxaparin. However, a meta-analysis of all three trials supported the non-inferiority of dabigatran compared with enoxaparin (95). Moreover, the risk of major bleeding appeared not to be increased relative to enoxaparin including bleeding at the surgical site that is crucial for therapeutic outcome of THR or TKR surgery. In contrast to ximelagatran, there was no evidence for hepatotoxicity throughout clinical development of dabigatran.

Rivaroxaban shows an excellent oral bioavailability and minor interindividual PK/PD variability in drug-free healthy subjects, even though its bioavailability was markedly influenced upon co-administration of CYP3A4/P-gp inhibitors or inducers. Despite convincing efficacy data of the RECORD trials, statistical power of any single RECORD trial was insufficient for meaningful evaluation of major bleeding risk as primary safety outcome. Pooled analysis of all four RECORD trials even revealed a significantly higher incidence of major and clinically relevant non-major bleeding in patients treated with rivaroxaban compared with enoxaparin (96, 97). Moreover, surgical site bleeding was excluded from the primary safety analysis in each RECORD trial.

Apixaban is eliminated via multiple elimination pathways suggesting minor predisposition for drug interactions, though it is partially metabolised by CYP3A4 and data from interaction studies have not yet been published. Even though apixaban failed to achieve non-inferior efficacy relative to twice-daily enoxaparin in the initial ADVANCE-I trial (89), its superior efficacy has most recently been reported when compared with once-daily enoxaparin in the ADVANCE-II trial (90). In the ADVANCE-I trial, the risk of major bleeding was nominally reduced compared with twice-daily enoxaparin.

In summary of the phase-III trial data, drug efficacy in VTE prevention after major orthopaedic surgery appears superior for rivaroxaban and essentially non-inferior for dabigatran compared with enoxaparin, while corresponding apixaban data is still controversial (Fig. 2). In this context, greatest cost-effectiveness has most recently been claimed for rivaroxaban followed by dabigatran and enoxaparin in the orthopaedic trials (98). Nevertheless, one should still avoid claiming any definite superiority of rivaroxaban over dabigatran or apixaban, as dabigatran data may have been influenced by a markedly higher incidence of the primary efficacy outcome in these trials and most apixaban trials are still ongoing. In addition, dabigatran appears very promising for thromboprophylaxis in patients with atrial fibrillation, indicated by essentially superior efficacy and safety data relative to warfarin in the large RE-LY trial.

About 60 years after the discovery of warfarin, the era of vitamin K antagonists is again expected to come to an end soon (99, 100). However, withdrawal of ximelagatran due to hepatotoxicity clearly emphasises the difficulties in developing an anticoagulant drug that is sufficiently effective, safe and orally bioavailable. Considerable research efforts are currently being made by various drug companies in order to develop such novel oral anticoagulant drugs. Thus far, marketing authorisation has been granted for da-

bigatran and rivaroxaban that are both very promising compounds and will hopefully contribute to a substantial improvement of the efficacy and safety of oral anticoagulation in the best interest of any given patient.

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