Chapter 3
Factor Xa Inhibitors

Factor Xa represents an attractive target for antithrombotic drugs as blockade of factor Xa permits inhibition of both the extrinsic and intrinsic coagulation pathways. Several factor Xa inhibitors, such as rivaroxaban, apixaban and edoxaban, have been approved for certain conditions, and are also in clinical development for other indications.

3.1 Rivaroxaban

Rivaroxaban (Fig. 3.1) is a novel factor Xa inhibitor that exhibits predictable pharmacokinetics, with high oral bioavailability, rapid onset of action (achieves maximum plasma concentration in 1.5–2.0 h), and no known food interactions [1] (see Table 2.1). The drug has a dual mode of elimination: two-thirds of it is metabolized by the liver (mostly via CYP3A4 and CYP2J2), with no major or active circulating metabolites identified, and one-third is excreted unchanged by the kidneys. Elimination of rivaroxaban from plasma occurs with a terminal half-life of 5–9 h in young individuals, and with a terminal half-life of 12–13 h in subjects aged >75 years [2]. Available data indicate that body weight, age, and gender do not have a clinically relevant effect on the

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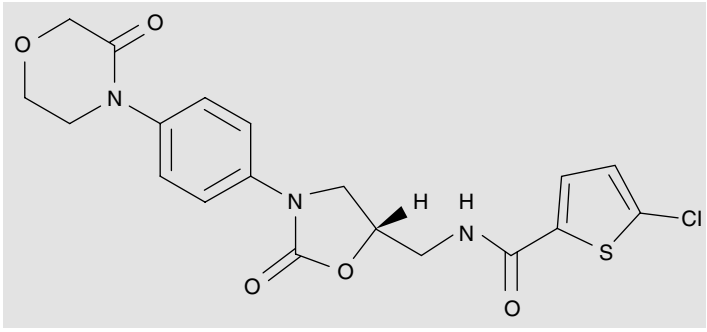

FIGURE 3.1 Rivaroxaban

pharmacokinetics and pharmacodynamics of rivaroxaban, and it thus can be administered in fixed doses without coagulation monitoring. Rivaroxaban has minimal drug interactions (eg, with naproxen, acetylsalicylic acid, clopidogrel, or digoxin) [1] and its predictable pharmacokinetics and pharmacodynamics allow use of rivaroxaban without regular laboratory monitoring. Although no specific antidote is known for rivaroxaban, preclinical data suggested that recombinant factor VIIa and activated prothrombin complex concentrate may reverse the effects of high-dose rivaroxaban [3–5]. The clinical development programs for rivaroxaban are outlined in Table 3.1 [6–23].

3.1.1 *Venous Thromboembolism Prevention following Joint Surgery*

Four completed phase II efficacy and safety studies of rivaroxaban for the prevention of VTE in patients undergoing elective THR and TKR ($n = 2907$ patients) have demonstrated comparable efficacy and safety of rivaroxaban and conventional management with subcutaneous enoxaparin [6–9, 24]. Efficacy was assessed as a composite of any DVT (proximal or distal), nonfatal objectively confirmed

Table 3.1 Clinical development program from rivaroxaban

Clinical condition	Trial	Comparator (n)
VTE prevention following joint surgery	*Phase II*	
	ODIXa-HIP [6]	Enoxaparin (722)
	ODIXa-KNEE [7]	Enoxaparin (621)
	ODIXa-OD-HIP [8]	Enoxaparin (873)
	Phase III	
	RECORD1 [9]	Enoxaparin (3153)
	RECORD2 [10]	Enoxaparin + placebo (2509)
	RECORD3 [11]	Enoxaparin (2556)
	RECORD4 [12]	Enoxaparin (3148)
VTE prevention	*Phase II*	
	ODIXa-DVT [13]	Enoxaparin/VKA (613)
	EINSTEIN DVT dose ranging [14]	LMWH/VKA (543)
	Phase III	
	EINSTEIN DVT [15]	Enoxaparin/VKA (3449)
	EINSTEIN PE [16]	Enoxaparin/VKA (4833)
	EINSTEIN-Ext [17]	Placebo (1197)
Stroke prevention in AF	*Phase III*	
	ROCKET-AF [18]	Warfarin (14,264)
	J-ROCKET [19]	Warfarin (1280)

(continued)

Table 3.1 (continued)

Clinical condition	Trial	Comparator (n)
Acute coronary syndrome	*Phase II*	
	ATLAS-ACS TIMI-46 [20]	Placebo (3500)
	Phase III	
	ATLAS-ACS 2 TIMI-51 [21]	Placebo (15,526)
VTE prevention in medically ill patients	*Phase III*	
	MAGELLAN [22, 23]	Enoxaparin (8101)

Data from [6–23]
AF atrial fibrillation, *LMWH* low-molecular-weight heparin, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

pulmonary embolism (PE) and all-cause mortality; safety was judged on the basis of major hemorrhage incidence. A pooled analysis of two of these studies confirmed non-inferiority of rivaroxaban in patients undergoing elective THR or TKR, with no significant dose-response relationship for efficacy but with a significant dose-related increase for the primary safety endpoint ($P < 0.001$), a total daily dose of 5–20 mg being the optimal dose range (Fig. 3.2) [9, 25].

Consequently, a fixed dose of rivaroxaban 10 mg qd was selected to be used in the phase III RECORD (REgulation of Coagulation in ORthopedic surgery to prevent DVT and PE) program (Table 3.2) [9–12]. The RECORD program included four large trials that recruited more than 12,500 patients undergoing elective THR or TKR. All RECORD trials have the composite primary efficacy endpoint of DVT, nonfatal PE, or all-cause mortality, and the main secondary efficacy endpoint was major VTE. The primary safety

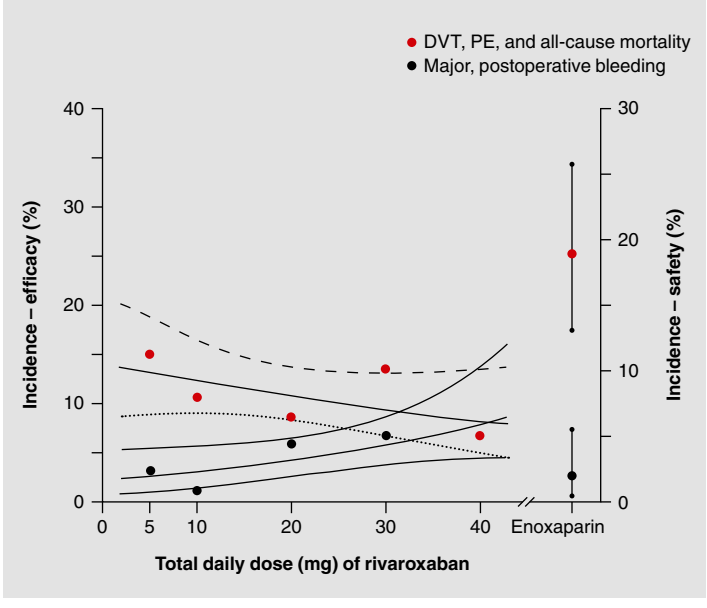

FIGURE 3.2 Dose-response relationships between rivaroxaban and primary efficacy and safety endpoint. Results for the prevention of venous thromboembolism after major orthopedic surgery. *DVT* deep vein thrombosis, *PE* pulmonary embolism (Reproduced with permission from Eriksson et al. [8])

endpoint was major hemorrhage. These studies had no upper age limit and allowed recruitment of patients with mild or moderate hepatic impairment.

The RECORD1 and the RECORD3 studies compared rivaroxaban 10 mg qd (starting 6–8 h after surgery) with enoxaparin 40 mg qd (starting the evening before surgery) both given for 31–39 days (extended prophylaxis) after THR (RECORD1) [9] or for 10–14 days (short-term prophylaxis) after TKR (RECORD3) [11]. In both studies treatment with rivaroxaban was significantly superior to enoxaparin for VTE prevention (Table 3.2). Recognizing that current guidelines recommend extended prophylaxis

TABLE 3.2 Incidence of venous thromboembolism and hemorrhage in the RECORD program

Trial	Regimen (qd)	Duration of treatment	Total VTE (%)	*P*	Major VTE (%)	*P*	Symptomatic VTE (%)	*P*	Major hemorrhage (%)	CRNM hemorrhage
RECORD1 (THR) *n* = 4541 [9]	Rivaroxaban 10 mg	5 weeks	1.1	<0.001	0.2	<0.001	0.3	0.22	0.3	2.9
	Enoxaparin 40 mg	5 weeks	3.7		2.0		0.5		0.1	2.4
RECORD2 (THR) *n* = 2509 [10]	Rivaroxaban 10 mg	10–14 days	2.0	<0.0001	0.6	<0.0001	0.2	0.004	<0.1	3.3
	Enoxaparin 40 mg	5 weeks	9.3		5.1		1.2		<0.1	2.7
RECORD3 (TKR) *n* = 2531 [11]	Rivaroxaban 10 mg	10–14 days	9.6	<0.001	1.0	0.01	0.7	0.005	0.6	2.7
	Enoxaparin 40 mg	10–14 days	18.9		2.6		2.0		0.5	2.3
RECORD4 (TKR) *n* = 3148 [12]	Rivaroxaban 10 mg	10–14 days	6.6	0.012	1.2	0.124	0.7	0.187	0.7	NA
	Enoxaparin 40 mg	10–14 days	10.1		2.0		1.2		0.3	NA

Data from [9–12]
CRNM clinically-relevant non-major, *NA* not available, *qd* once daily, *THR* total hip replacement, *TKR* total knee replacement, *VTE* venous thromboembolism

for patients undergoing THR, although this is not done in many countries, the RECORD2 trial investigated the efficacy and safety of extended thromboprophylaxis with rivaroxaban (5 weeks) compared with short-term enoxaparin 40 mg qd for 10–14 days [10]. The study demonstrated that prolonged prophylaxis with rivaroxaban was associated with reduced incidence of VTE, including symptomatic events, after THR. Of note, despite administration of rivaroxaban for 3 weeks longer than enoxaparin, the rate of major hemorrhage at 5 weeks was low and similar in both groups.

In the RECORD4 trial rivaroxaban 10 mg was significantly more effective than the North American regimen of enoxaparin 30 mg bid (10–14 days) for the prevention of VTE in patients undergoing TKR, with similar rates of major hemorrhage for both treatments and no serious liver toxicity with rivaroxaban [12]. Thus, the superiority of rivaroxaban over enoxaparin for VTE prevention was demonstrated in all four studies, with a good safety profile. As a result, in 2008 rivaroxaban received approval in the European Union (EU) and in Canada for the prevention of VTE in patients undergoing elective THR or TKR surgery. In July 2011, the FDA approved rivaroxaban for prophylaxis of DVT in adults undergoing hip and knee replacement surgery.

The utility of rivaroxaban (10 mg qd for up to 5 weeks) for VTE prevention in hospitalized medically ill patients was assessed in the phase III MAGELLAN study, with short-term enoxaparin (10 days followed by placebo) as the comparator [22]. At day 10, the primary efficacy outcome (composite asymptomatic proximal DVT, symptomatic DVT, symptomatic non-fatal PE and VTE-related death) occurred in 2.7 % of patients in both treatment groups, demonstrating the non-inferiority of rivaroxaban ($P=0.003$). At study end (day 35) fewer patients treated with rivaroxaban had the primary outcome (4.4 % vs 5.7 %; $P=0.02$ for superiority). However, there was an increase in the risk of clinically relevant bleeding in the rivaroxaban group (4.1 % vs 1.7 %; $P<0.0001$) [23].

3.1.2 Treatment of Venous Thromboembolism

The initial phase IIb ODIXa-DVT [13] and EINSTEIN-DVT [14] studies (Table 3.3) assessed the clinical efficacy and safety of rivaroxaban for the treatment of VTE in patients with acute, symptomatic, proximal DVT without symptomatic PE. The treatment was administered for 3 months, with open-label standard therapy (low-molecular-weight heparin/heparin following vitamin K antagonist [VKA]) as comparator.

In the ODIXa-DVT study, rivaroxaban doses 10, 20, or 30 mg bid, or 40 mg qd, were tested [13]. The primary efficacy endpoint of reduced thrombus burden on day 21 (assessed by quantitative compression ultrasonography) without recurrent VTE or VTE-related death was reported in 43.8–59.2 % of patients receiving rivaroxaban and in 45.9 % of patients receiving standard therapy. The incidence of the primary safety endpoint (major hemorrhage) was 1.7–3.3 % in the rivaroxaban groups; there were no events in the standard therapy group.

In the EINSTEIN-DVT study [14], therapy with rivaroxaban 20–40 mg qd was associated with an incidence of 5.4–6.6 % for the primary endpoint (the composite of symptomatic, recurrent VTE, and deterioration of thrombotic burden, as assessed by compression ultrasound and perfusion lung scan) compared with 9.9 % in the standard therapy group. The primary safety endpoint (any clinically relevant hemorrhage) developed in 2.9–7.5 % of patients receiving rivaroxaban and 8.8 % of those on the standard therapy, with no evidence of compromised liver function in those receiving rivaroxaban.

Of note, the phase II studies revealed that the twice-daily rivaroxaban regimen was more effective for thrombus regression at 3 weeks, whereas the once- and twice-daily regimens showed similar effectiveness at 3-month follow-up [13]. Accordingly, an initial intensified twice-daily regimen (rivaroxaban 15 mg bid for 3 weeks) followed by long-term 20 mg qd dosing was chosen for investigation in the phase III EINSTEIN studies: EINSTEIN-DVT, EINSTEIN-PE, and EINSTEIN- EXTENSION [15–17].

Table 3.3 Clinical efficacy and safety of rivaroxaban for the treatment of venous thromboembolism

EINSTEIN-DVT study		
	Rivaroxaban 20 mg qd (n = 1731)	*Standard therapy (n = 1718)*
Symptomatic recurrent VTE, n/N (%)	36/1731 (2.1)	51/1718 (3.0)
First major bleeding or clinically relevant non-major bleeding, n/N (%)	139/1718 (8.1)	138/1711 (8.1)
EINSTEIN-PE study		
	Rivaroxaban 20 mg qd (n = 2419)	*Standard therapy (n = 2413)*
Symptomatic recurrent VTE, n/N (%)	50/2419 (2.1)	44/2413 (1.8)
First major or clinically relevant non-major bleeding, n/N (%)	249/2412 (10.3)	274/2405 (11.4)
EINSTEIN-Ext study		
	Rivaroxaban 20 mg qd (n = 602)	*Placebo (n = 594)*
Recurrent VTE, (composite of DVT or non-fatal or fatal PE), n/N (%)	8/602 (1.3)	42/594 (7.1)
First major bleeding or clinically relevant non-major bleeding, n/N (%)	36/602 (6.0)	7/594 (1.2)

Data from [15–17]
DVT deep vein thrombosis, *LMWH* low-molecular-weight heparin, *PE* pulmonary embolism, *qd* once daily, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

EINSTEIN-DVT was an open-label, randomized, event-driven, non-inferiority study that compared oral rivaroxaban (15 mg bid for 3 weeks, followed by 20 mg qd) against subcutaneous enoxaparin followed by a VKA for 3, 6, or 12 months in patients with acute, symptomatic DVT [14]. In parallel, EINSTEIN-EXTENSION was a double-blind, randomized, event-driven superiority study that compared rivaroxaban alone (20 mg qd) with placebo for an additional 6 or 12 months in patients who had completed 6–12 months of treatment for VTE [15, 17]. The primary efficacy outcome for both studies was recurrent VTE. The principal safety outcome for EINSTEIN-DVT was major bleeding or clinically-relevant non-major (CRNM) bleeding in the initial-treatment study and major bleeding in the continued-treatment study. The study recruited 3449 patients: 1731 in the rivaroxaban arm and 1718 in the conventional management arm [15]. Rivaroxaban was non-inferior with respect to the primary efficacy outcome while the principal safety outcome occurred in 8.1 % of the patients in each group (Table 3.3). In the extended-treatment study, which included 602 patients in the rivaroxaban group and 594 in the placebo group, rivaroxaban had superior efficacy. Four patients in the rivaroxaban group had nonfatal major bleeding (0.7 %), versus none in the placebo group ($P=0.11$) (Table 3.3) [15].

In the randomized, open-label, event-driven, non-inferiority EINSTEIN-PE trial, 4832 subjects with acute symptomatic PE with or without DVT were assigned to either rivaroxaban (15 mg bid for 3 weeks, followed by 20 mg qd) or to standard therapy with enoxaparin followed by dose-adjusted VKA for 3, 6, or 12 months [16]. The trial demonstrated that rivaroxaban was non-inferior to standard therapy for the primary efficacy outcome symptomatic recurrent VTE (2.1 % versus 1.8 %, respectively, $P=0.003$ for non-inferiority margin) (Table 3.3). Also, 10.3 % of patients treated with rivaroxaban developed the principal safety outcome of major or CRNM bleeding versus 11.4 % in those on standard care ($P=0.23$), thus suggesting that fixed-dose rivaroxaban can be an effective and safe therapeutic option in PE.

In December 2011 rivaroxaban received approval by the European Commission for treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults. Additionally, in November 2012 rivaroxaban was approved by the FDA for DVT, PE and prevention of recurrent DVT and PE following initial treatment.

3.1.3 Stroke Prevention in Atrial Fibrillation

In terms of numbers of patients, stroke prevention in AF is potentially the largest indication that may benefit from the NOACs. The rising incidence of AF in a progressively aging population suggests that millions of people may eventually require life-long anticoagulant therapy to prevent severely disabling complications. The ROCKET AF study investigated the effectiveness and safety of rivaroxaban 20 mg qd (15 mg qd in those with moderate kidney impairment) versus warfarin for the prevention of stroke or systemic embolism in 14,264 patients with non-valvular AF (NVAF) who were at an increased risk for stroke [18]. Rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism (hazard ratio [HR] in the rivaroxaban group, 0.79; 95 % CI, 0.66–0.96; $P < 0.001$ for non-inferiority). Moreover, there was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group [18]. In the J-ROCKET AF study conducted in Japan, a lower dose of rivaroxaban (15 mg qd; 5 mg qd for patients with moderate renal impairment) was shown to be non-inferior to warfarin for the prevention of stroke or systemic embolism [19].

In November 2011, in view of the results of the ROCKET AF study, rivaroxaban was approved by the FDA for the prevention of stroke and systemic embolism in patients with NVAF, at a dose of 20 mg (or 15 mg if creatinine clearance 15–50 ml/min) qd. In December 2011, rivaroxaban was approved by the European Commission for prevention of

stroke and systemic embolism in adult patients with NVAF with one or more risk factors.

3.1.4 Acute Coronary Syndromes

In the phase IIb ATLAS ACS-TIMI 46 (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome) study, 3491 patients with recent acute coronary syndrome (ACS) were randomized to escalating total daily doses of rivaroxaban, ranging from 5 mg up to 20 mg (qd or bid), or placebo, in addition to the standard antiplatelet therapy of aspirin or aspirin plus a thienopyridine (eg, clopidogrel) for secondary prevention of cardiovascular events [20]. Patients on the rivaroxaban regimens had higher rates of hemorrhage than those on placebo, and the risk increased in a dose-dependent manner; however, no study arm was stopped due to increased hemorrhage. A strong trend towards reduction in cardiovascular events was observed with rivaroxaban, which reduced the main secondary efficacy endpoint of death, myocardial infarction, or stroke compared with placebo ($P = 0.0270$). Two doses of rivaroxaban were tested in the phase III ATLAS ACS 2 TIMI 51 study [21]. The study assigned 15,526 patients with a recent ACS to receive either 2.5 mg bid or 5 mg bid of rivaroxaban or placebo for a mean of 13 months and up to 31 months. The primary efficacy endpoint was a composite of death from cardiovascular causes, myocardial infarction, or stroke. The investigators concluded that in patients with a recent ACS, rivaroxaban reduced the risk of the composite endpoint (8.9 % versus 10.7 %, $P = 0.008$) but increased the risk of major bleeding (2.1 % versus 0.6 %, $P < 0.001$) and intracranial hemorrhage (0.6 % versus 0.2 %, $P = 0.009$) although not the risk of fatal bleeding [21].

Based on the results of the ATLAS ACS 2 TIMI-51 trial rivaroxaban 2.5 mg bid was approved by the European

Commission based on a positive from the EMA Committee for Medicinal Products for Human Use (CHMP) in March 2013 for secondary prevention of ACS.

3.2 Apixaban

Apixaban is another potent, highly selective, and reversible inhibitor of factor Xa and is active against both free enzyme and factor Xa bound within the prothrombinase complex (Fig. 3.3). The bioavailability of apixaban after oral absorption is over 50 % [26]. Peak plasma levels of apixaban are observed 3 h after administration and plasma concentrations reach the steady state by day 3. The half-life of apixaban is

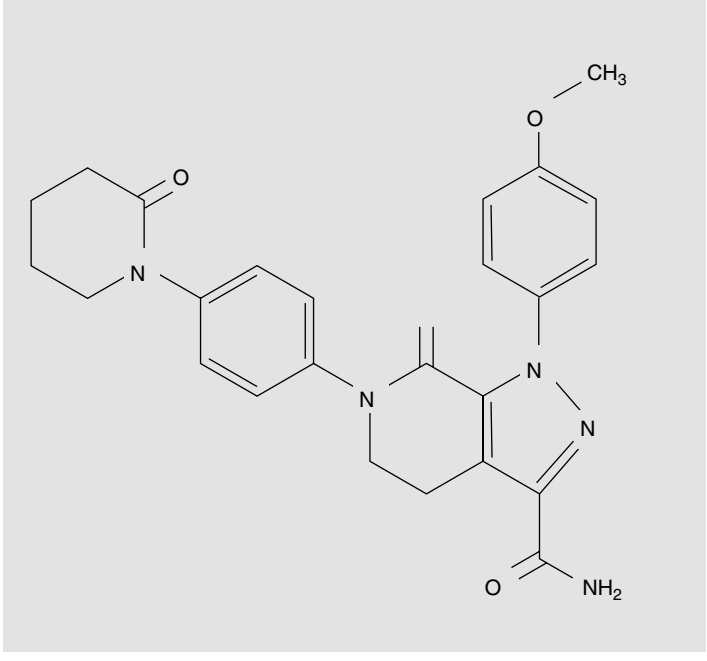

FIGURE 3.3 Apixaban

between 8 and 15 h, which allows twice-daily administration of the drug. The primary elimination route is fecal, with only about 25 % eliminated via the kidney. Apixaban has little effect on the prothrombin time at therapeutic concentrations, but plasma levels can be assessed using a factor Xa inhibition assay. The clinical development program of apixaban is summarized in Table 3.4 [27–39].

3.2.1 *Venous Thromboembolism Prevention in Major Orthopedic Surgery*

In a randomized phase II dose-response clinical trial in 1238 patients undergoing TKR, apixaban 5, 10, or 20 mg/day (administered qd or bid) was compared with enoxaparin (30 mg bid) and open-label warfarin [27]. Apixaban and enoxaparin were started 12–24 h after surgery; the warfarin dose was titrated from the evening of the day of surgery. After 10–14 days of the treatment, bilateral venography was performed and patients were further treated at the attending physician's discretion. The primary endpoint, a composite of VTE events plus all-cause mortality at 42-day follow-up, was significantly lower in the compound apixaban group (8.6 %) than in the enoxaparin (15.6 %, $P<0.02$) or warfarin (26.6 %, $P<0.001$) groups. The primary endpoint rates for apixaban 2.5 mg bid (9.9 %) and 5.0 mg qd (11.3 %) were lower than in the enoxaparin (15.6 %) and warfarin group (26.6 %). The incidence of major hemorrhage in apixaban-treated patients was low and ranged from 0 (2.5 mg bid) to 3.3 % (20 mg qd), with comparable results for once- and twice-daily administration. No major hemorrhage was observed in the enoxaparin and warfarin groups [27].

The clinical utility of apixaban for VTE prevention after major joint surgery was investigated in the phase III ADVANCE program (Table 3.4). In two multicenter, randomized, double-blind, active-controlled clinical trials (ADVANCE-1 and ADVANCE-2), the safety and efficacy of oral apixaban (2.5 mg bid) versus enoxaparin (30 mg bid in

Table 3.4 Clinical development of apixaban

Clinical condition	Trial	Comparator (n)
VTE prevention following joint surgery	*Phase II*	
	APROPOS [27]	Warfarin or Enoxaparin (1238)
	Phase III	
	ADVANCE-1 [28]	Enoxaparin (3195)
	ADVANCE-2 [29]	Enoxaparin (3057)
	ADVANCE-3 [30]	Enoxaparin (5407)
VTE prevention	*Phase II*	
	Botticelli trial [31]	Heparin/VKA (520)
	Phase III	
	AMPLIFY [32]	Enoxaparin + Warfarin (5400)
	AMPLIFY-Ext [33]	Placebo (2486)
Stroke prevention in atrial fibrillation	*Phase III*	
	AVERROES [34]	Aspirin (5599)
	ARISTOTLE [35]	Warfarin (18,201)
Acute coronary syndrome	*Phase II*	
	APPRAISE [36]	Placebo (1715)

(continued)

Table 3.4 (continued)

Clinical condition	Trial	Comparator (n)
Prevention of VTE in medically ill patients	*Phase III*	
	APPRAISE-2 [37]	Placebo (7392)
	ADOPT [38]	Enoxaparin (6528)
VTE prevention in cancer patients	*Phase II*	
	ADVOCATE [39]	Placebo (125)

Data from [27–39]
VTE venous thromboembolism

ADVANCE-1 and 40 mg qd in ADVANCE-2) for preventing DVT and PE after TKR was evaluated in 3195 patients in ADVANCE-1 and 3057 patients in ADVANCE-2 (Table 3.5) [28, 29]. The duration of treatment was 12 days and the primary outcome of both studies was defined as a combination of asymptomatic and symptomatic DVT, nonfatal PE and all-cause mortality. In ADVANCE-1, apixaban did not meet the pre-specified statistical criteria for non-inferiority versus enoxaparin, but its use was associated with lower rates of clinically relevant bleeding and it had a similar adverse-event profile [28]. In ADVANCE-2, apixaban 2.5 mg bid, starting the morning after TKR, offered a more effective orally administered alternative to 40 mg per day enoxaparin (relative risk 0.62; 95 % CI 0.51–0.74; $P < 0.0001$), without increased bleeding rates (Table 3.5) [29].

Similarly, in the ADVANCE-3 trial, the efficacy and safety of 5-week administration of apixaban (2.5 mg bid) in comparison with enoxaparin in the prevention of DVT and PE was assessed in 5407 patients after THR. Patients were randomized to receive apixaban plus placebo or enoxaparin plus placebo for 5 weeks. The primary outcome was again a combination of asymptomatic and symptomatic DVT, nonfa-

Table 3.5 Clinical efficacy and safety of apixaban for the treatment of venous thromboembolism following joint surgery

APROPOS trial								
	Apixaban							
	5 mg qd (n=97)	*2.5 mg bid (n=111)*	*10 mg qd (n=105)*	*5 mg bid (105)*	*20 mg qd (n=110)*	*10 mg bid (n=110)*	*Enoxaparin (n=109)*	*Warfarin (n=109)*
VTE events and death from any cause, n (%)	2 (2.1)	2 (1.8)	2 (1.9)	0 (0.0)	2 (1.8)	3 (2.7)	5 (4.6)	2 (1.8)
Major bleeding n (%)	4 (2.6)	0 (0.0)	1 (0.6)	4 (2.6)	5 (3.3)	4 (2.6)	0 (0.0)	0 (0.0)
ADVANCE-1								
	Apixaban 2.5 mg bid (n=1599)				*Enoxaparin 30 mg bid (n=1596)*			
Symptomatic and asymptomatic DVT, non-fatal PE, or death from any cause n/ (%)	104/1157 (9.0)				100/1130 (8.8)			
Adjudicated major or CRNM n/N (%)	46/1596 (2.9)				68/1588 (4.3)			

(continued)

Table 3.5 (continued)

ADVANCE-2		
	Apixaban 2.5 mg bid (*n=1528*)	*Enoxaparin 40 mg qd* (*n=1529*)
Symptomatic and asymptomatic DVT, non-fatal PE, or death from any cause n/N (%)	147/976 (15.1)	243/997 (24.4)
All bleeding n/N (%)	104/1501 (6.9)	126/1508 (8.4)

ADVANCE-3

	Apixaban 2.5 mg bid (*n* = *1949*)	*Enoxaparin 40 mg qd* (*n* = *1917*)
Symptomatic and asymptomatic DVT, non-fatal PE, or death from any cause n/N (%)	27/1949 (1.4)	74/1917 (3.9)
Major and CRNM bleeding n/N (%)	129/2673 (4.8)	134/2659 (5.0)

Data from [29–32]
Bid twice daily, *CRNM* clinically relevant non-major, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *qd* once daily, *VTE* venous thromboembolism

tal PE, and all-cause mortality. The ADVANCE-3 investigators concluded that, among patients undergoing hip replacement, apixaban was associated with lower rates of VTE without increased bleeding compared with subcutaneous enoxaparin (relative risk with apixaban, 0.36; 95 % CI, 0.22–0.54; $P<0.001$ for both non-inferiority and superiority) (Table 3.5) [30].

Apixaban received approval in the EU for the prevention of VTE in patients undergoing elective THR or TKR surgery in May 2011. In March 2014 apixaban was approved by the FDA for the prevention of VTE following hip or knee replacement surgery.

3.2.2 Stroke Prevention in Atrial Fibrillation

Two phase III clinical trials assessed apixaban for stroke prevention in patients with AF. In the first, the AVERROES study, the effectiveness of oral apixaban (5 mg bid; or 2.5 mg in selected patients) was compared with aspirin (81–324 mg qd) for 36 months in the prevention of stroke or systemic embolism in 5599 patients with permanent or persistent AF who had at least one additional risk factor for stroke but could not be treated with VKA (Table 3.6) [34]. The data and safety monitoring board recommended early termination of the study because of a clear benefit in favor of apixaban. Apixaban compared with aspirin, reduced the risk of stroke or systemic embolism (1.6 % versus 3.7 % per year, respectively, $P<0.001$) without significantly increasing the risk of major bleeding or intracranial hemorrhage [34].

The second phase III trial, the ARISTOTLE study, investigated whether apixaban (5 mg bid) was as effective as warfarin in preventing stroke and systemic embolism in 18,201 patients with AF who had at least one additional risk factor for stroke [35]. The primary efficacy endpoint was the composite outcome of stroke or systemic embolism. In ARISTOTLE, apixaban reduced the risk of stroke or systemic embolism by 21 % compared with warfarin. The reduction was significant

($P<0.01$) and supported the superiority of apixaban over warfarin for the primary outcome of preventing stroke or systemic embolism. Apixaban also reduced all-cause mortality by 11 % and major bleeding by 31 % (Table 3.6) [35]. Apixaban has become the first new oral anticoagulant superior to warfarin in reducing stroke or systemic embolism, all-cause mortality, and major bleeding in patients with AF. Apixaban received approval by the European Commission for the prevention of stroke and systemic embolism in patients with non-valvular AF in November 2012 and by the FDA in December 2012.

3.2.3 *Thromboprophylaxis in Other Clinical Settings*

Apixaban is being tested in several additional settings, which may expand the use of oral anticoagulation beyond currently established indications. The phase II randomized ADVOCATE study has been designed to determine the tolerability, effectiveness, and safety of apixaban in prevention of thrombolic events in patients with advanced or metastatic cancer on prescribed chemotherapy for more than 90 days [39]. In this randomized double-blind study 12-week administration of apixaban (5, 10, or 20 mg qd, $n=95$ overall) was compared with placebo ($n=30$). The primary outcome was either major bleeding or CRNM bleeding and secondary outcomes included VTE and grade III or higher adverse events related to the study drug. Although the study appeared to show a favorable safety profile for apixaban, it was underpowered to draw any reliable conclusions and further phase III evaluation of apixaban in this setting would be appropriate [39].

A further phase III randomized trial, ADOPT, compared the safety and efficacy of apixaban with enoxaparin in preventing DVT and PE in patients hospitalized with congestive heart failure, acute respiratory failure, infection (without septic shock), acute rheumatic disorder, or inflammatory bowel disease [38]. A total of 6528 subjects underwent randomization, 4495 of whom could be evaluated for the primary efficacy outcome: 2211 in the

TABLE 3.6 Clinical efficacy and safety of apixaban for stroke prevention in atrial fibrillation

AVERROES trial		
	Apixaban 5 mg bid (n=2808)	*Aspirin 81–324 mg qd (n=2791)*
Occurrence of stroke (ischemic or hemorrhagic) or systemic embolism, n/N (%/y)	51/2808 (1.6)	113/2791 (3.7)
Major Bleeding, n/N (%/y)	44/2808 (1.4)	39/2791 (1.2)
ARISTOTLE trial		
	Apixaban 5 mg bid (n=9120)	*Warfarin (n=9081)*
Occurrence of stroke or systemic embolism, n/N (%/y)	212/9120 (1.3)	265/9081 (1.6)
Major bleeding, n/N (%/y)	327/9088 (2.1)	462/9052 (3.1)

Data from [34, 35]
bid twice daily, *qd* once daily

apixaban group and 2284 in the enoxaparin group. The primary outcome was the composite of VTE or VTE-related death, whereas secondary outcome measures included all-cause mortality, major hemorrhage, and CRNM hemorrhage. Among the patients who could be evaluated, 2.71 % in the apixaban group and 3.06 % in the enoxaparin group met the criteria for the primary efficacy outcome (relative risk with apixaban, 0.87; 95 % CI, 0.62–1.23; $P=0.44$). Major bleeding occurred in 0.47 % of the patients in the apixaban group and in 0.19 % of the patients in the enoxaparin group. The investigators therefore concluded that in medically ill patients, an extended course of thromboprophylaxis with apixaban was not superior to a shorter course with enoxaparin and was associated with significantly more major bleeding events than was enoxaparin [38].

3.2.4 Treatment of Venous Thrombosis

Investigation of the utility of apixaban for the treatment of patients with VTE started with the phase II Botticelli DVT dose-ranging clinical trial [31]. In this study 520 patients with symptomatic DVT were randomized to receive apixaban (5 mg or 10 mg bid or 20 mg qd) or traditional treatment with LMWH or fondaparinux followed by VKA. After management for 84–91 days, no significant difference was reported between the treatments in the rate of occurrence of the primary outcome, a composite of symptomatic recurrent VTE and asymptomatic deterioration of bilateral compression ultrasound or perfusion lung scan (4.7 % for apixaban and 4.2 % in control patients) [31]. The primary outcome rates for the tested apixaban doses were 6.0 % for 5 mg bid, 5.6 % for 10 mg bid, and 2.6 % for 20 mg qd. The principal safety outcome (a composite of major and CRNM hemorrhage) developed at a similar rate in the apixaban-treated patients (7.3 %) and the control group (7.9 %). The principal safety outcome rates for the tested apixaban doses were 8.6 % for 5 mg bid, 4.5 % for 10 mg bid, and 7.3 % for 20 mg qd.

In the Phase III randomized, multicenter AMPLIFY study [32] apixaban was compared with the conventional treatment (enoxaparin/warfarin) in 5395 patients with VTE. Patients randomized to apixaban received 10 mg bid for 7 days followed by 5 mg bid for 6 months. The primary outcome was the rate of symptomatic, recurrent VTE and related deaths; the principal safety outcomes were major bleeding alone and major bleeding plus CRNM bleeding. The results from the AMPLIFY study found apixaban to be non-inferior to conventional therapy, with symptomatic recurrent VTE occurring in 2.3 % of patients in the apixaban group and 2.7 % of patients who received conventional therapy (relative risk, 0.84; $P<0.001$) (Table 3.7). Rates of VTE or cardiovascular (CV)-related death and VTE or all-cause death were lower in patients who received apixaban compared with those who received standard therapy. Moreover, apixaban resulted in significantly less major bleeding (0.6 % vs 1.8 %; $P<0.001$ for superiority).

TABLE 3.7 Clinical efficacy and safety of apixaban in the prevention of recurrent VTE

Botticelli trial

	Apixaban			*LMWH/VKA* (*n* = *128*)
	5 mg bid (*n* = *130*)	*10 mg bid* (*n* = *134*)	*20 mg qd* (*n* = *128*)	
Symptomatic recurrent VTE and symptomatic deterioration in the thrombotic burden, n (%)	7 (6.0)	7 (5.6)	3 (2.6)	5 (4.2)
Major and clinically relevant non-major bleeding	11 (8.6)	6 (4.5)	11 (8.9)	10 (7.9)

AMPLIFY study

	Apixaban (*n* = *2691*)	*Enoxaparin/VKA* (*n* = *2635*)
First recurrent VTE or VTE-related death, n (%)	59 (2.3)	71 (2.7)
Major bleeding, n (%)	15 (0.6)	49 (1.8)
Clinically relevant non-major bleeding n, (%)	103 (3.8)	215 (8.0)

(continued)

Table 3.7 (continued)

AMPLIFY-Ext study

	Apixaban 2.5 mg bid (n = 840)	*Apixaban 5 mg bid (n = 813)*	*Placebo (n = 829)*
Symptomatic recurrent VTE or death from any cause, n (%)	32 (3.8)	34 (4.2)	96 (11.6)
Major bleeding, n (%)	2 (0.2)	1 (0.1)	4 (0.5)

Data from [31–33]
bid twice daily, *LMWH* low-molecular weight heparin, *qd* once daily, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

Additionally, the AMPLIFY-EXT trial assessed the efficacy and safety of apixaban in preventing VTE recurrence or death in 2486 patients with clinical diagnosis of DVT or PE who had completed 6–12 months of standard treatment for DVT or PE or had completed treatment with apixaban or enoxaparin and warfarin as participants in the AMPLIFY trial [33]. Patients received apixaban (2.5 or 5 mg bid) or placebo for 12 months. The study found that VTE or related death occurred in 8.8 % of patients who received placebo, as compared with 1.7 % who received apixaban 2.5 mg (95 % CI 5.0–9.3) and 1.7 % apixaban 5 mg (95 % CI 4.9–9.1; $P < 0.001$ for both). There were fewer significant events of primary outcome with the both apixaban 2.5 mg (relative risk 0.33 [95 % CI 0.22–0.48]) and 5 mg (relative risk 0.36 [95 % CI 0.25–0.53]) compared with placebo (Table 3.7). Bleeding results from the AMPLIFY-Extension study showed that both apixaban 2.5 mg and 5 mg doses were associated with low bleeding levels that were similar to placebo [33].

Based on the results of the AMPLIFY and AMPLIFY-Ext studies in June 2014 apixaban was approved in the EU for the treatment and prevention of DVT and PE. Following this

approval in August 2014, apixaban 2.5 mg and 5 mg was approved by the FDA for the treatment of recurrent DVT and PE following initial therapy.

3.2.5 Acute Coronary Syndrome

The phase II APPRAISE-1 clinical trial evaluated the safety of apixaban in 1715 patients with recent ACS. Patients were randomized to receive apixaban (2.5 mg bid or 10.0 mg qd) or placebo for 26 weeks. The primary outcome was the incidence of major or CRNM hemorrhage; the secondary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, severe recurrent ischemia, or ischemic stroke. The investigators reported a dose-related increase in bleeding compared with placebo (apixaban 2.5 mg bid: HR, 1.78; 95 % CI 0.91–3.48; $P = 0.09$; 10 mg qd: HR, 2.45; 95 % CI, 1.31–4.61; $P = 0.005$) and a trend toward a reduction in ischemic events with the addition of apixaban to antiplatelet therapy in patients with recent ACS [36]. Whether apixaban could improve outcomes in patients after an ACS was further investigated in the phase III trial APPRAISE-2. This trial was a randomized, double-blind, placebo-controlled clinical trial comparing apixaban, at a dose of 5 mg bid, with placebo, in addition to standard antiplatelet therapy, in patients with a recent ACS and at least two additional risk factors for recurrent ischemic events. The trial was terminated prematurely due to an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events [37].

3.3 Edoxaban

Edoxaban (Fig. 3.4) is a potent, highly selective factor Xa inhibitor with a high affinity for free factor Xa (K_i 0.56 nM) and for factor Xa bound to the prothrombinase complex (K_i 2.98 nM) [40]. It has predictable and consistent

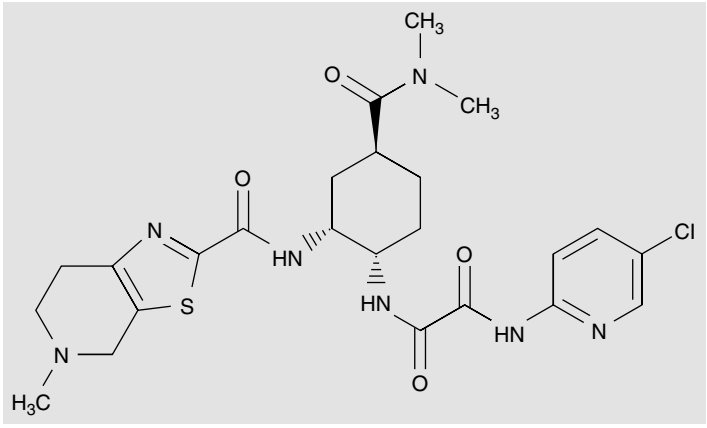

FIGURE 3.4 Edoxaban

pharmacokinetics with dose proportional increases in plasma concentrations, and a half-life of approximately 10–14 h [10, 41, 42]. Additionally, edoxaban has a rapid onset of action and high oral bioavailability (61.8 %), reaching maximum plasma concentrations 1–2 h after administration, and inhibition of thrombin formation over ~24 h, supporting once-daily dosing [10, 12, 43]. Moreover, edoxaban is mainly metabolized via hydrolysis, whereas CYP450 enzymes play an insignificant role.

Around 35 % of the given dose is eliminated via the kidneys [44], indicating the importance of the kidneys in the excretion of edoxaban. Consequently, studies have evaluated edoxaban in patients with renal impairment and suggest that in patients with chronic kidney disease, edoxaban exposure is increased and a lower dose is appropriate [45].

The pharmacokinetics of edoxaban are not influenced by gender, age, ethnicity, or food intake, although small but clinically insignificant changes in pharmacokinetics after a high fat meal or in the elderly is observed [10, 46]. Edoxaban has minimal drug interactions, however like all factor Xa inhibitors, edoxaban is a substrate of P-glycoprotein (P-gp) and there-

fore has potential for interaction with strong P-gp inhibitors. As such, a 50 % dose reduction to edoxaban 30 mg is recommended when concomitantly used with the P-gp inhibitors, ciclosporin, dronedarone, erythromycin, or ketoconazole. In contrast no dose adjustment is necessary with amiodarone, quinidine or verapamil [47]. The predicable pharmacokinetic and pharmacodynamics profiles of edoxaban allows for its use without regular laboratory monitoring [10].

Similar to other factor Xa inhibitors, currently there is no antidote for edoxaban. However a recently completed phase I study evaluated the effects of PER977 on bleeding following administration of edoxaban to healthy subjects (clinicaltrials.gov identifier NCT01826266) [48]. PER977 was found to be effective in restoring baseline hemostasis 10–30 min after administration of 100–300 mg PER977, this effect was sustained for 24 h [49]. An additional phase II study is underway investigating the re-anticoagulation effect of edoxaban following reversal by PER977 (clinicaltrials.gov identifier NCT02207257) [50]. This trial also aims to identify a dose regimen of PER977 that is able to reverse the effects of edoxaban for 21 h.

Edoxaban was approved in Japan for prevention of VTE following lower-limb orthopedic surgery and in the US for the prevention of stroke and systemic embolic events (SEE) in NVAF and for the treatment of PE and DVT and prevention of recurrent VTE [51]. Edoxaban received European approval in June 2015 following a positive opinion from the CHMP for the use of edoxaban for the prevention of AF related stroke and treatment of PE and DVT and prevention of recurrent VTE [52]. The clinical development of edoxaban can be seen in Table 3.8.

3.3.1 Venous Thromboembolism Prevention in Major Orthopedic Surgery

Two phase II dose-finding studies, 011 [54] and J04 [53], investigated the use of edoxaban for the prevention of VTE after joint replacement. Study J04 was a placebo controlled

Table 3.8 Clinical development program for edoxaban

Clinical condition	Trial	Comparator (n)
VTE prophylaxis following joint surgery	*Phase II*	
	Study J04 [53]	Placebo (523)
	Study 011 [54]	Dalteparin (774)
	Phase III	
	STARS E-III [55]	Enoxaparin (716)
	STARS J-IV [56]	Enoxaparin (92)
	STARS J-V [57]	Enoxaparin (610)
Stroke prevention in atrial fibrillation	*Phase II*	
	Study 018 [58]	Warfarin (1146)
	Phase III	
	ENGAGE AF-TIMI 48 [59, 60]	Warfarin (21,105)
Prevention of VTE	*Phase III*	
	Hokusai-VTE [61, 62]	Warfarin (8292)

Data from [53–62]
VTE venous thromboembolism

study that evaluated edoxaban 5, 15, 30, or 60 mg qd for prevention of VTE following TKR in Japanese patients [53]. Patients were treated for 11–14 days following surgery. There was a significant, dose-dependent reduction in the incidence of VTE with edoxaban compared with placebo, with a comparable risk of bleeding across all treatment groups with no significant differences among edoxaban doses or between edoxaban and placebo.

In the double-blind, active-controlled, multicenter 011 study, 903 patients were randomized to receive oral edoxaban (15, 30, 60, or 90 mg od) or subcutaneous dalteparin qd

(initial dose 2500 IU, subsequent doses 5000 IU) [54]. Both medications were started 6–8 h after surgery and administered for 7–10 days. Data from 776 participants were included into the primary efficacy analysis. The primary efficacy endpoint of total VTE was significantly lower in subjects treated with edoxaban (28.2 %, 21.2 %, 15.2 %, and 10.6 % for edoxaban 15, 30, 60, and 90 mg, respectively) than in those receiving dalteparin (43.8 %, $P<0.005$) (Table 3.9).

The open-label STARS J-IV [56] trial investigated the safety and efficacy of edoxaban in preventing VTE after major joint surgery in 92 Japanese patients undergoing hip fracture surgery. Patients were randomized to either edoxaban 30 mg qd (6–24 h post-surgery) or enoxaparin 2000 IU bid (24–36 h after surgery). The primary endpoints were bleeding events and secondary events included thromboembolic events and adverse events. STARS J-IV found that treatment with edoxaban was as safe and efficacious as enoxaparin treatment, and major or CRNM bleeding occurred less often in the edoxaban group compared with the enoxaparin group (3.4 % and 6.9 % respectively). However, thromboembolic events occurred more often in the edoxaban group (6.5 % vs 3.7 %) (Table 3.9).

Two pivotal, randomized, double-blind, multicenter, phase III trials compared edoxaban 30 mg qd to enoxaparin in knee surgery, STARS E-III [55], and hip surgery, STARS J-V [57]. In both STARS E-III and STARS J-V edoxaban 30 mg qd was superior to enoxaparin in the preventions of VTE, with comparable rates of bleeding [55, 57]. Supported by the data from these phase III studies edoxaban was approved in Japan in April 2011 for the prevention of VTE following lower-limb orthopedic surgery.

A post-marketing vigilance report [63] recorded all spontaneously reported adverse drug reactions (ADR) that occurred following the launch of edoxaban in Japan, from July 2011 to January 2012. During this time approximately 20,000 patients had been treated with edoxaban. A total of 67 ADR were reported in 57 patients, the majority of ADR were bleeding events, 15 of which were serious. Most ADR occurred in the first week of treatment and none were fatal.

Table 3.9 Clinical efficacy and safety of edoxaban in prevention of VTE following major joint surgery

Study J04

	Edoxaban				*Placebo* (*n* = *102*)
	5 mg qd (*n* = *103*)	*15 mg qd* (*n* = *106*)	*30 mg qd* (*n* = *103*)	*60 mg qd* (*n* = *106*)	
Incidence of VTE, n (%)	26 (29.5)	24 (26.1)	11 (12.5)	8 (9.1)	43 (48.3)
Major and CRNM bleeding, n (%)	2 (1.9)	4 (3.8)	4 (3.9)	5 (4.7)	4 (3.9)

Study 011

	Edoxaban				*Dalteparin* (*n* = *172*)
	15 mg qd (*n* = *192*)	*30 mg qd* (*n* = *170*)	*60 mg qd* (*n* = *185*)	*90 mg qd* (*n* = *177*)	
Incidence of total VTE, n/N (%)	48/170 (28.2)	32/151 (21.2)	24/158 (15.2)	16/151 (10.6)	63/144 (43.8)
Major and CRNM bleeding, n (%)	3/192 (1.6)	3/170 (1.8)	4/185 (2.2)	4/177 (2.3)	0/172 (0.0)

STARS E-III

	Edoxaban 30 mg qd (*n* = *354*)	*Enoxaparin 20 mg bid* (*n* = *349*)
Symptomatic PE, and symptomatic and asymptomatic DVT, n/N (%)	22/299 (7.4)	41/295 (13.9)
Major and CRNM bleeding, n/N (%)	22/354 (6.2)	13/349 (3.7)

(continued)

Table 3.9 (continued)

STARS J-IV		
	Edoxaban 30 mg qd (n = 59)	*Enoxaparin 2000 IU (n = 29)*
Major and CRNM Bleeding, n (%)	2/59 (3.4)	2/29 (6.9)
Thromboembolic events, n/N (%)	3/46 (6.5)	1/27 (3.7)
STARS J-V		
	Edoxaban 30 mg qd (n = 303)	*Enoxaparin 20 mg bid (n = 301)*
Composite of symptomatic and asymptomatic DVT, and PE, n/N (%)	6/255 (2.4)	17/248 (6.9)
Major and CRNM bleeding, n/N (%)	8/303 (2.6)	11/301 (3.7)

Data from [53–57]
bid twice daily, *CRNM* clinically relevant non-major, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *qd* once daily, *VTE* venous thromboembolism

The post-marketing analysis found that in the real-life setting the safety profile of edoxaban was consistent with that found in clinical trials and no unforeseen safety signals were observed.

3.3.2 Stroke Prevention in Atrial Fibrillation

In a parallel-group, active controlled phase II study the safety of four fixed-dose regimens of edoxaban were compared with warfarin in 1146 patients with NVAF. Patients were random-

ized to edoxaban 30 mg od, 60 mg od, 30 mg bid, 60 mg bid, or warfarin (INR 2.0–3.0) [58]. A significantly higher incidence of major and/or CRNM bleeding was seen in the twice-daily edoxaban regimen (60 mg bid, 10.6 %, $P=0.002$; 30 mg bid, 7.8 %, $P=0.029$) than warfarin (3.2 %), however there were no significant differences between the warfarin and once-daily regimens. For the same total daily dose of edoxaban, 60 mg, the 30 mg bid dose was associated with a trend towards an increase in major bleeding plus CRNM bleeding compared with 60 mg qd ($P=0.08$). This study concluded that treatment with edoxaban 30 or 60 mg qd was safe and well tolerated.

A pooled pharmacokinetic analysis [64] was performed on data from 15 phase I and II studies which aimed to characterize edoxaban population pharmacokinetics. Using an exposure-response analysis (in which C_{min} was the best predictor of bleed probability), a 50 % dose reduction in selected patients was recommended, especially in patients with renal impairment, concomitant use of P-gp inhibitors, and body weight ≤60 kg. Consequently, two doses of edoxaban (30 mg and 60 mg od) were selected for investigation in the phase III ENGAGE AF-TIMI 48 trial.

The ENGAGE AF-TIMI 48 study [59] investigated the safety and efficacy of two doses of edoxaban compared with warfarin. A total 21,105 patients with a history of AF were enrolled into the study making this the largest study of a NOAC in patients with AF to date. Patients were randomized to edoxaban 60 mg qd ($n=7012$), edoxaban 30 mg qd ($n=7002$) or warfarin ($n=7012$; median time in therapeutic range, 68.4 %). In the edoxaban group, patients with moderate renal impairment (creatinine clearance [CrCl] 30–50 mL/min), weight ≤60 kg or who were receiving select P-gp inhibitors had a 50 % dose reduction. Median follow-up duration was 2.8 years. The primary efficacy objective was the non-inferiority of edoxaban compared with warfarin in the prevention of stroke and SEE, key secondary outcomes included a composite of stroke, SEE or death from CV causes, major adverse cardiac events (MACE), and stroke, SEE or death [59].

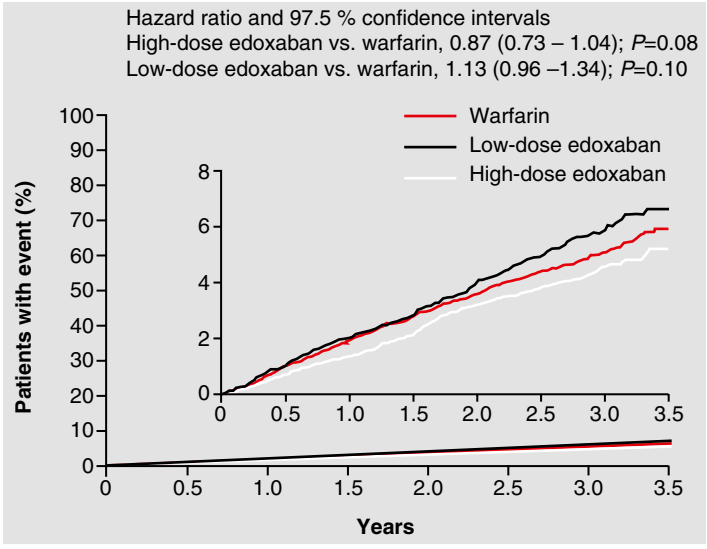

FIGURE 3.5 Kaplan-Meier curve for stroke of systemic embolic events in ENGAGE AF-TIMI 48 (Reproduced with permission from Giugliano et al. [60])

The primary safety outcome was major bleeding during treatment. The primary efficacy endpoint occurred in 232 patients treated with warfarin (1.50 %/y), 182 patients treated with edoxaban 60 mg qd (1.18 %/y; HR vs warfarin 0.79, 95 % CI 0.63–0.99; $P<0.001$ for non-inferiority), and 253 patients treated with edoxaban 30 mg qd (1.61 %/y; HR vs warfarin 1.07. 95 % CI 0.87–1.31; $P=0.005$ for non-inferiority). Additionally, ENGAGE AF-TIMI 48 met the pre-specified criteria for non-inferiority and both doses were compared with warfarin in a test for superiority. For patients treated with warfarin the annualized rate of the primary endpoint was 1.80 % compared with 1.57 % in the edoxaban 60 mg qd group (HR 0.87, CI 0.73–1.08; $P=0.08$), and 2.04 % in the edoxaban 30 mg qd group (HR 1.13, CI 0.96–1.34; $P=0.10$) (Fig. 3.5) [60].

The primary safety endpoint of major bleeding occurred in 524 patients in the warfarin group (3.43 %/y), compared with

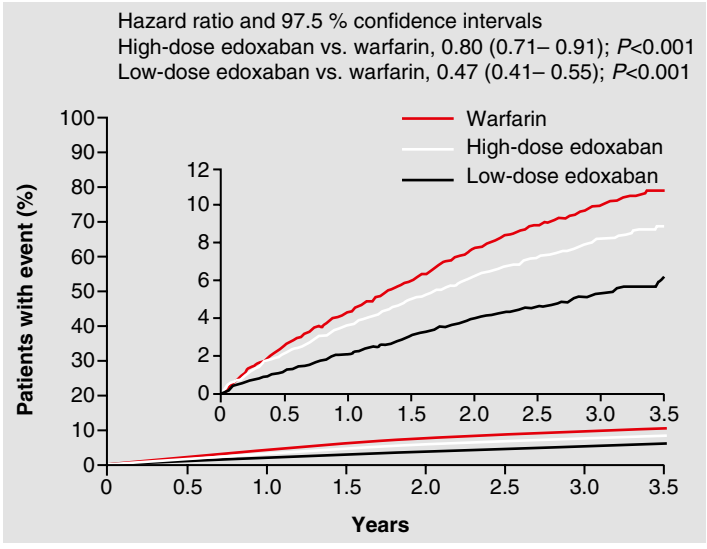

FIGURE 3.6 Kaplan-Meier curve for major bleeding events in ENGAGE AF-TIMI 48 (Reproduced with permission from Giugliano et al. [60])

418 patients in the edoxaban 60 mg qd group (2.75 %/y; HR 0.80; 95 % CI, 0.71–0.91; $P<0.001$), and 254 patients in the edoxaban 30 mg qd group (1.61 %/y; HR, 0.47; 95 % CI, 0.41–0.55; $P<0.001$) (Fig. 3.6) [60]. The rates of all three prespecified secondary outcomes were significantly lower with edoxaban 60 mg than with warfarin.

Based on the findings from ENGAGE AF-TIMI 48, edoxaban 60 mg was approved by the FDA in January 2015 for the prevention of stroke and SEE in NVAF. According to the label given by the FDA edoxaban 60 mg dose should be reduced to 30 mg in patients with a CrCl 15–30 mL/min and should not be used in patients with CrCl >95 mL/min due to increased risk of ischemic stroke compared with warfarin. In ENGAGE AF-TIMI 48, 77 % of patients had a CrCl <95 mL/min [52]. Additionally, edoxaban received European approval following a positive opinion from the CHMP for the use of

edoxaban in Europe in patients with NVAF, which did not include a limitation according to renal function [52]. Edoxaban has also been approved in Japan and Switzerland for prevention of ischemic stroke and systemic embolism in patients with AF.

3.3.3 Treatment of Venous Thromboembolism

The phase III, event-driven, randomized, double-blind, double-dummy, parallel-group, multinational study Hokusai-VTE [61, 62] investigated the safety and efficacy of edoxaban in prevention of VTE. The design of Hokusai-VTE aimed to broaden the applicability of edoxaban use in VTE treatment to real world practice, and encourage enrolment of a broad type of patients, including those with extensive disease [61]. Hokusai-VTE allowed for variable treatment duration from 3 to 12 months, regardless of treatment duration all patients were observed for 12 months [61].

A total of 8292 patients were randomized to receive open-label heparin (for ≥5 days) followed by either edoxaban 60 mg qd (started after discontinuation of heparin) or warfarin (started concurrently with heparin and until INR 2.0–3.0). A 50 % dose adjustment occurred in the edoxaban group at randomization and any point during the study in patients with moderate renal impairment (CrCl 30–50 mL/min), weight ≤60 kg or who were receiving select P-gp inhibitors. Hokusai-VTE was unique in that dose adjustment not only occurred at randomization but could occur at any point during the study as necessary. Additionally, the flexible treatment duration is unique to Hokusai-VTE, which is unusual in clinical trials but is more in line with clinical practice. The primary efficacy endpoint was symptomatic recurrent VTE during the 12 month study period and the objective of the study was to determine the non-inferiority of heparin follow by edoxaban compared with heparin followed by warfarin. The secondary endpoints included a composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE and all-cause mortality, and a

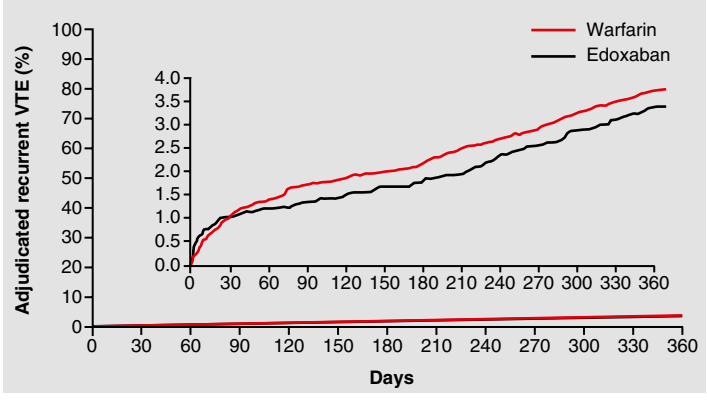

FIGURE 3.7 Kaplan-Meier cumulative event rates for the symptomatic recurrent VTE in Hokusai-VTE (Reproduced with permission from The Hokusai-VTE Investigators [62])

composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and CV mortality. The primary safety endpoint was major or CRNM bleeding, secondary endpoints included all deaths, major adverse cardiovascular events, liver enzyme and bilirubin abnormalities. Over the 12 month study period edoxaban was found to be non-inferior to warfarin for the primary outcomes; symptomatic recurrent VTE occurred in 3.2 % of patients in the edoxaban group and 3.5 % of patients in the warfarin group (HR 0.89; 95 % CI, 0.70–1.13; $P<0.001$ for non-inferiority) (Fig. 3.7).

Additionally, Hokusai-VTE analyzed events that occurred on-treatment. Symptomatic recurrent VTE occurred in 1.6 % of the edoxaban group and 1.9 % of the warfarin group (HR, 0.82; 95 % CI, 0.60–1.14; $P<0.001$ for non-inferiority). In a pre-specified analysis of patients that required dose adjustment edoxaban was also found to be non-inferior to warfarin, with events occurring in 3.0 % and 4.2 %, respectively (HR, 0.73; 05 % CI, 0.42–1.26). In the subgroup of patients with PE and evidence of right ventricular dysfunction (N-terminal-prohormone of brain natriuretic peptide level of ≥500 pg/mL),

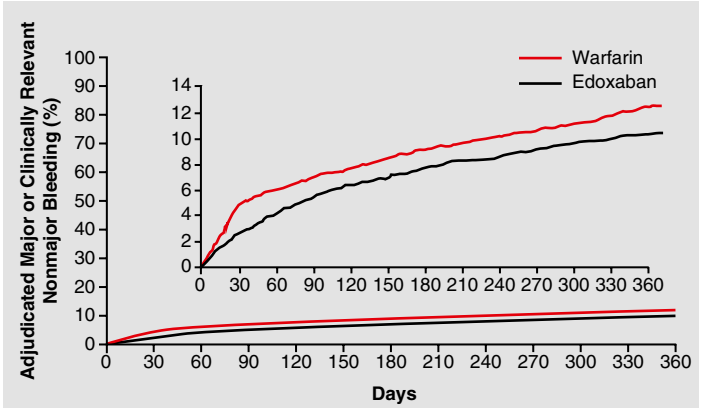

FIGURE 3.8 Kaplan-Meier curve of major of clinically relevant nonmajor bleeding events in Hokusai-VTE (Reproduced with permission from The Hokusai-VTE investigators [62])

recurrent VTE occurred in 3.3 % of patients (15/454) in the edoxaban group and in 6.2 % of patients (30/484) in the warfarin group (HR, 0.52; 95 % CI, 0.28–0.98). Similar results were observed among patients with right ventricular dysfunction as assessed by means of computed tomography (HR, 0.42; 95 % CI, 0.15–1.20). During the 12 month study period the primary safety outcome occurred in 8.5 % of the edoxaban group and 10.3 % of the warfarin group (HR, 0.81; 95 % CI, 0.71–0.94; $P = 0.004$ for superiority) demonstrating that edoxaban caused significantly less bleeding than warfarin (Fig. 3.8).

In the pre-specified analyses of the dose adjusted edoxaban patients first major or CRNM bleeding occurred in 7.9 % of edoxaban patients and 12.8 % of warfarin patents (HR, 0.62; 95 % CI, 0.44–0.86).

In January 2015, based on the results from Hokusai-VTE, edoxaban 60 mg was approved in the US for the treatment of DVT and PE following 5–10 days parenteral heparin. In patients with CrCl 30–50 mL/min, body weight ≤60 kg and patients receiving concomitant P-gp inhibitors edoxaban 60 mg should be reduced to 30 mg [52]. Additionally, based

on data from Hokusai-VTE edoxaban was recommended by the CHMP for the treatment of DVT and PE and prevention of recurrent PE and DVT in adults [52]. Edoxaban has also been approved in Japan and Switzerland for VTE treatment and secondary prevention.

3.4 Emerging Factor Xa Inhibitors

Currently, the factor Xa inhibitor betrixaban (PRT-054021) is in phase III clinical development for the prevention of thromboembolism and the partial factor IXa inhibitor TTP889 is in phase II development for the prevention of VTE reflecting interest in the high clinical potential of this pharmaceutical group (Table 3.10) [65–67]. Enrollment has begun for a phase I study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of the direct factor Xa inhibitor GCC-4401C compared with placebo and rivaroxaban (clinicaltrials.gov identifier NCT01954238) [68].

3.4.1 Betrixaban

Betrixaban (PRT-054021) specifically and reversibly inhibits factor Xa with a K_i of 0.117 nmol/L. It has a bioavailability of 47 %, a half-life of 19 h, and is excreted almost unchanged in bile. Betrixaban has demonstrated antithrombotic activity in animal models and in human blood. It is well tolerated in healthy individuals across a wide range of doses. Betrixaban has been investigated in phase II trials for VTE prevention in patients after major joint surgery (EXPERT) [65] and for stroke prevention in patients with AF (EXPLORE-Xa) [66]. Currently a phase III double-blind trial of betrixaban is recruiting patients, with the aim of enrolling ~6850 patients, to evaluate the extended treatment (35–42 days) of oral betrixaban in hospitalized patients compared with standard treatment of enoxaparin (clinicaltrials.gov identifier NCT01583218) [69]. Primary efficacy endpoint is a composite

Table 3.10 Clinical development of emerging factor Xa inhibitors

Clinical condition	Phase	Trial title	Comparator (n)
Betrixaban (*PRT054021*)			
Extended VTE prevention	III	Acute medically ill VTE prevention with extended duration Betrixaban Study (The APEX Study)	Enoxaparin (6850)
VTE prevention in major joint surgery	II	Factor Xa inhibitor, PRT054021, against Enoxaparin for the Prevention of Venous Thromboembolic Events (EXPERT) [65]	Enoxaparin (200)
Stroke prevention in atrial fibrillation	II	Study of the safety, tolerability and pilot efficacy of oral factor Xa inhibitor betrixaban compared with warfarin (EXPLORE-Xa) [66]	Warfarin (500)
TTP889			
VTE prevention		Partial factor IXa inhibition with TTP889 for prevention of venous thromboembolism: an exploratory study [67]	Placebo (260)

Data from [65–67]
VTE venous thromboembolism

of asymmetrical proximal DVT, symptomatic DVT, non-fatal PE, or VTE-related death through day 35, primary safety outcome is major bleeding [70].

3.4.2 TTP889

TTP889 is a small-molecule, orally available selective factor IXa antagonist with a dose-dependent inhibition of factor IXa≈90 % [67] and a half-life between 21 and 25 h [71]. In an

exploratory study of the antithrombotic potential of TTP889, 260 patients, who had hip fracture repair and who and had received LMWH or unfractionated heparin for thromboprophylaxis 5–9 days after surgery, were randomized to receive TTP889 300 mg or placebo. No significant differences in the number of total VTE events were observed, and no major bleeding occurred [67] Further studies are warranted [67, 71].

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