Factor Xa inhibitors
New anticoagulants for secondary haemostasis

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Keywords
Factor Xa inhibitors, anticoagulants, thrombosis

Summary
Oral factor Xa (FXa) inhibitors are a promising alternative to current anticoagulants. This paper reviews the latest developments of oral direct FXa inhibitors and focuses on those which have been approved for the prevention of venous thromboembolism (VTE) after total hip or knee replacement or are in advanced development and have passed phase II (proof of principle) testing.

The most advanced drugs are apixaban, betrixaban, edoxaban, rivaroxaban, LY517717, TAK-442, and YM150. Rivaroxaban (Xarelto®) is the first direct FXa inhibitor which has recently been approved for the prevention of VTE in adult patients after elective hip or knee replacement in several countries, including the European Union and Canada. Rivaroxaban has a flat dose-dependent anticoagulant response with a wide therapeutic window and low potential for drug-drug and drug-food interactions. Rivaroxaban can be given in fixed doses without coagulation monitoring.

This review describes the pharmacodynamic and pharmacokinetic profiles and the results of clinical trials with FXa inhibitors in the prevention and treatment of thromboembolic disorders.

Schlüsselwörter
Faktor-Xa-Hemmer, Antikoagulanzen, Thrombose

Zusammenfassung
Orale Faktor-Xa(FXa)-Hemmer sind viel versprechende Alternativen zu den gebräuchlichen Antikoagulanzen. In diesem Artikel werden Neuentwicklungen im Bereich der oralen direkten FXa-Hemmer vorgestellt mit Schwerpunkt auf solchen, die zur Prävention venöser Thromboembolien (VTE) nach Hüft- oder Kniegelenkersatz zugelassen sind oder sich in einem fortgeschrittenen Entwicklungsstadium befinden und die Phase-II-Studien zum Nachweis der Wirksamkeit (proof of principle) durchlaufen haben.


Diese Übersicht beschreibt das pharmakodynamische und pharmakokinetische Profil sowie die Ergebnisse klinischer Studien mit FXa-Hemmern zur Prävention und Behandlung von Thromboembolien.

Because of the key position of FXa in the coagulation pathway, the development of FXa inhibitors is an important approach in the search for novel antithrombotic therapies.

This paper focuses on oral direct FXa inhibitors in clinical development that have been shown to be effective in venous thromboembolism (VTE) prevention in patients after total hip (THR) or knee (TKR) replacement.

Indirect FXa inhibitors

The first selective FXa inhibitor was fondaparinux (Arixtra®) which was shown to be effective and safe in patients with acute coronary syndrome (ACS) and VTE. However, because it is an indirect FXa inhibitor, its effects depend on the level of antithrombin (AT) and fondaparinux cannot be administered orally. Other parenteral indirect FXa inhibitors, like idraparinux and idrabiotaparinux (biotiny-
lated idraparinux) are currently at different stages of clinical development.

**Oral direct FXa inhibitors**

Several oral direct FXa inhibitors are at different stages of clinical development for the short and long term prevention and treatment of thromboembolic diseases. These include:
- apixaban,
- betrixaban,
- edoxaban,
- eribaxaban,
- rivaroxaban,
- LY517717,
- TAK-442, and
- YM150.

Rivaroxaban has recently been approved for the prevention of VTE in adult patients after total hip or knee replacement (THR, TKR) in several countries, including the European Union and Canada.

These new, small molecule FXa inhibitors are AT-independent inhibitors and bind directly to the active FXa site, thereby blocking the interaction of FXa with its substrate thrombin. AT-independent inhibitors have the potential to inhibit:
- free FXa,
- prothrombinase and
- clot-bound FXa activity (10, 42).

Fondaparinux, an indirect AT-dependent FXa inhibitor, does not inhibit FXa in the prothrombinase complex at clinically relevant concentrations (36). The direct action of the new FXa inhibitors might mean that their action is more predictable and that they are more effective.

**Rivaroxaban**

Rivaroxaban (Xarelto®, Bayer Schering Pharma AG) is a direct competitive FXa inhibitor (inhibitory constant \([K_i] = 0.4 \text{ nmol/l}\)) with >10000-fold greater selectivity for FXa than other serine proteases (41). It is a reversible \((k_{on} = 5 \times 10^7 \text{ M}^{-1} \text{s}^{-1})\) FXa inhibitor with a rapid onset of action \((k_{on} = 1.7 \times 10^7 \text{ M}^{-1} \text{s}^{-1})\) (44). It inhibits prothrombinase \((IC_{50} = 2.1 \text{ nmol/l})\) (41) and clot-bound \((IC_{50} = 92 \text{ nmol/l})\) (9) FXa activity in plasma. In human plasma, it inhibits thrombin generation by inhibiting FXa, generated via both the intrinsic and extrinsic coagulation pathways (17, 20). In addition, rivaroxaban concentration-dependently inhibits thrombin generation in the presence of thrombomodulin in human plasma, suggesting that it does not interfere with the thrombin-thrombomodulin-APC system, and therefore does not suppress the negative feedback reaction by activated protein C (40).

In vivo, rivaroxaban given prophylactically had potent and consistent antithrombotic effects in venous (5, 39, 41) and arterial (21, 39, 41) thrombosis models in mice, rats and rabbits. In a rabbit model, rivaroxaban reduced the deposition of radiolabeled fibrinogen into preformed clots in the jugular vein (5). Bleeding times in rats and rabbits were not significantly affected at antithrombotic doses (41).

Rivaroxaban has high oral bioavailability and a rapid onset of action, reaching maximum plasma concentrations 2.5–4 hours after administration (27, 28). It has a half-life of up to 9 hours in healthy young subjects (28) and 12–13 hours in healthy elderly subjects (26). Rivaroxaban is eliminated via two routes:
- one-third unchanged in the urine, and
- two-thirds after metabolic degradation, half of which is excreted via the kidney, half via the faecal route (48).

Rivaroxaban shows nearly linear pharmacokinetics up to 15 mg with no significant accumulation following repeat dosing. The plasma concentrations and pharmacodynamic effects of rivaroxaban (inhibition of FXa activity and prolongation of prothrombin time [PT]) correlate closely in healthy subjects and patients undergoing major orthopedic surgery (37, 38).

**RECORD program**

Rivaroxaban has recently been approved for the prevention of VTE after THR and TKR in several countries, based on the results of the phase III RECORD program, which comprised four large studies in more than 12 700 patients.

In all of the RECORD studies, the primary efficacy endpoint (total VTE) was the composite of deep venous thrombosis (DVT), nonfatal pulmonary embolism (PE) and all-cause mortality. A main secondary efficacy endpoint was major VTE: the composite of proximal DVT, nonfatal PE and VTE-related death. The primary safety endpoint was major bleeding, defined as bleeding event that was fatal, occurred in a critical organ (e.g. retroperitoneal, intracranial, intraocular, or intraspinal bleeding) or requiring reoperation, or extrasurgical-site bleeding that was associated with a fall in hemoglobin of 2 g/dl or more, or required an infusion of two or more units of blood (Tab. 1).

RECORD2 investigated the efficacy and safety of extended thromboprophylaxis with rivaroxaban (5 weeks) compared with short-term enoxaparin (10–14 days) in patients undergoing THR (24). The results of this
study demonstrated that extended prophylaxis with 10 mg rivaroxaban once daily (qd) given orally was superior to short-term prophylaxis with 40 mg enoxaparin qd given subcutaneously for the prevention of total, major and symptomatic VTE, after THR (►Tab. 1). Even though rivaroxaban was given for three weeks longer than enoxaparin, the incidence of major bleeding at five weeks was 0.1% in both groups. This study confirmed the benefits of extended prophylaxis over short-term prophylaxis and the safety of its use.

RECORD1 and RECORD 3 were designed to compare 10 mg rivaroxaban qd with 40 mg enoxaparin qd for 31–39 days (extended prophylaxis) after THR (RECORD1) (29) and 10–14 days (short-term prophylaxis) after TKR (RECORD3) (46). In both studies, rivaroxaban was significantly more effective than enoxaparin in the primary efficacy endpoint (total VTE), with no significant difference between the rates of major bleeding in the two groups (►Tab. 1).

ODIXa, EINSTEIN, MAGELLAN, ROCKET AF, ATLAS

The efficacy and safety of rivaroxaban in the treatment of VTE were assessed in two phase IIb studies:
- ODIXa-DVT (2) and
- EINSTEIN-DVT (7).

These studies demonstrated that rivaroxaban is effective and has a similar safety profile compared to standard therapy in the treatment of acute symptomatic DVT (►Tab. 2). An initial intensified regimen (15 mg rivaroxaban bid for three weeks) followed by long-term treatment with 20 mg qd was selected for investigation in three phase III studies on the efficacy and safety of rivaroxaban in VTE: EINSTEIN-DVT, -PE, -EXTENSION.

A further phase III study (MAGELLAN) is investigating the efficacy and safety of prophylaxis with 10 mg rivaroxaban qd for up to five weeks compared with short-term enoxaparin in hospitalized acute medically ill patients. 20 mg rivaroxaban qd is being compared with warfarin in the prevention of stroke in approximately 14000 patients with atrial fibrillation (AF) in a phase III study (ROCKET AF). Finally, a phase III study investigating secondary prevention in patients with ACS, ATLAS 2 TIMI 51, was started in late 2008. Two dosages of rivaroxaban, 2.5 and 5 mg bid, are being investigated, based on the results of a phase Iib study, the ATLAS ACS TIMI 46 study, which assessed safety and efficacy in about 3500 patients with recent ACS (18).

Apixaban

Apixaban (Bristol-Myers Squibb) is a small-molecule, oral, direct FXa inhibitor that selectively and reversibly inhibits free FXa ($K_i = 0.08$ nmol/l) (50). Apixaban rapidly reacts with FXa ($k_{on} = 2 \times 10^5$ M/s), binds with high affinity ($K_i = 0.3$ nmol/l at 37°C), and non-competitively inhibits prothrombin activation (32). The human plasma concentration required to double the prothrombin

Tab. 1 Incidence of venous thromboembolism and bleeding events across the four RECORD studies (11, 24, 29, 46)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RECORD1 (THR)*</th>
<th>RECORD2 (THR)*</th>
<th>RECORD3 (TKR)*</th>
<th>RECORD4 (TKR)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>enoxaparin</td>
<td>rivaroxaban</td>
<td>enoxaparin</td>
<td>rivaroxaban</td>
</tr>
<tr>
<td></td>
<td>5 weeks</td>
<td>10–14 days</td>
<td>5 weeks</td>
<td>10–14 days</td>
</tr>
<tr>
<td>total VTE (primary endpoint)</td>
<td>3.7 (58/1558) p&lt;0.001</td>
<td>1.1 (18/1595)</td>
<td>9.3 (81/869) p&lt;0.0001</td>
<td>2.0 (17/864)</td>
</tr>
<tr>
<td>major VTE</td>
<td>2.0 (33/1678) p&lt;0.001</td>
<td>0.2 (4/1668)</td>
<td>5.1 (49/962) p&lt;0.0001</td>
<td>0.6 (6/961)</td>
</tr>
<tr>
<td>symptomatic VTE</td>
<td>0.5 (11/2206) p=0.22</td>
<td>0.3 (6/2193)</td>
<td>1.2 (15/1207) p=0.004</td>
<td>0.2 (3/1212)</td>
</tr>
<tr>
<td>major bleeding (primary endpoint)</td>
<td>0.1 (2/2224)</td>
<td>0.3 (6/2209)</td>
<td>&lt;0.1 (1/1229)</td>
<td>&lt;0.1 (1/1228)</td>
</tr>
<tr>
<td>clinically relevant non-major bleeding</td>
<td>2.4 (54/2224)</td>
<td>2.9 (65/2209)</td>
<td>2.7 (33/1229)</td>
<td>3.3 (40/1228)</td>
</tr>
</tbody>
</table>

1 all p-values for efficacy calculated from absolute risk reduction; THR: total hip replacement; TKR: total knee replacement; VTE: venous thromboembolism; * dosage once daily: enoxaparin 40 mg; rivaroxaban 10 mg
time and the partial thromboplastin time is 3.6 and 7.4 μmol/l (50). Dose-dependent antithrombotic efficacy has been demonstrated in rabbit models of arteriovenous shunt thrombosis, venous thrombosis and electrically-mediated carotid arterial thrombosis (50).

Apixaban was shown to be effective in the prevention of experimental thrombosis at doses that preserve hemostasis in rabbits (50). Apixaban has high oral bioavailability in chimpanzees (51%) and dogs (88%), has a half-life of approximately 8–15 hours in humans, low metabolic clearance, and multiple pathways of elimination, including renal and intestinal excretion (22, 14).

Indications, studies

Apixaban is currently being evaluated in a number of indications, including the prevention and treatment of VTE (comprising DVT and PE), the prevention of stroke in patients with AF, and the prevention of cardiovascular events in ACS. The phase II APPROPO trial with apixaban (total daily dosage 5–20 mg qd or bid) vs. enoxaparin or warfarin for VTE prevention after TKR has demonstrated similar efficacy for apixaban, enoxaparin and warfarin in the reduction of the incidence of the primary efficacy endpoint (30). Based on these results, apixaban is currently being evaluated in phase III studies for the prevention of VTE after major orthopedic surgery (the ADVANCE program). ADVANCE-1 investigated the efficacy and safety of 2.5 mg apixaban orally bid compared with 30 mg enoxaparin s.c. bid for the prevention of VTE in patients undergoing TKR (Tab. 3). Apixaban did not meet the specified criteria for non-inferiority compared with enoxaparin with respect to the primary efficacy endpoint (a composite of symptomatic or asymptomatic DVT, PE and all-cause mortality) (31). The rate of the primary efficacy endpoint was 9.0% in the apixaban group and 8.9% in the enoxaparin group (p > 0.05). The rate of major bleeding with apixaban was 0.7% and with enoxaparin 1.4% (p = 0.054).

ADVANCE-2\(^2\) (2.5 mg apixaban bid versus 40 mg enoxaparin qd) is currently under way in patients undergoing TKR. A third study, ADVANCE-3\(^6\), is assessing extended prophylaxis (35 days) with 2.5 mg apixaban bid and 40 mg enoxaparin qd in patients undergoing THR.

The Botticelli-DVT phase II study for the treatment of acute symptomatic DVT examined the efficacy and safety of 5 and 10 mg apixaban bid and 20 mg qd compared with a low-molecular-weight heparin or fondaparinux and a vitamin K antagonist. All three doses of apixaban were considered similar to the comparators. The result of this study led to the phase III ARISTO study for the prevention of stroke or systemic embolism in patients with AF (6). The ARISTOTLE\(^7\) trial is investigating whether 5 mg apixaban bid is as effective as warfarin in preventing stroke and systemic embolism in subjects with AF and risk factors for stroke. The AVERROES\(^8\) trial is investigating whether 5 mg apixaban bid (2.5 bid in selected patients) are superior to 81–324 mg acetylsalicylic acid qd in preventing stroke or systemic embolism in patients with AF and at least one additional risk factor.

Apixaban is also currently under investigation in two phase III studies for the treatment of VTE. The AMPLIFY trial\(^9\) is evaluating the effects of 10 mg apixaban bid for 7 days followed by 5 mg bid for 6 months in preventing VTE recurrence or death in patients with DVT or PE compared to standard therapy (enoxaparin followed by warfarin). The AMPLIFY-EXT\(^10\) trial is evaluating the effects of 2.5 and 5.0 mg apixaban bid for 12 months in preventing VTE recurrence or death in patients who have completed their treatment for DVT or PE.

A phase III trial on the prevention of VTE in patients hospitalized for an acute medical illness (ADOPT\(^11\)) is comparing 2.5 mg apixaban bid for 30 days followed by 6–14 days placebo with 40 mg enoxaparin qd for 6–14 days followed by 30 days placebo. A phase II trial, ADVOCATE\(^12\), is investigating VTE prevention in cancer patients.

In a randomized, double-blind, phase II trial (APPRAISE-1), patients with ACS received ASA in combination with 2.5 mg apixaban bid or 10 mg qd for 26 weeks. Co-administration of clopidogrel was at the physician’s discretion. Apixaban 10 mg bid and apixaban 20 mg qd was discontinued early due to excess bleeding in patients receiving apixaban and dual antiplatelet therapy. Results showed non-significant relative risk reductions in cardiovascular events of 27% in the 2.5 mg group and 38% in the 10 mg group.
The incidence of major bleeding plus clinically relevant non-major bleeding was 5.7% in the 2.5 mg bid group, 7.9% for 10 mg qd, and 3% for placebo patients. A phase III study with 5 mg apixaban bid (APPRAISE-2) was started recently.

Betrixaban

Betrixaban (PRT 054021; Portola Pharmaceuticals) is a further, orally active, site-directed, competitive FXa inhibitor that selectively inhibits free FXa \( (K_i = 0.117 \text{ nmol/l}) \) (47). It has a bioavailability of 47%, and a half-life of about 20 h (47, 45). In vivo dose-dependent antithrombotic activity has been shown in arterial and venous thrombosis models in rats, rabbits and baboons (1). Clearance is primarily by biliary excretion with limited metabolism and minimal renal excretion (less than 5% of an administered dose) (47, 45). A phase II, randomized, open-label VTE prevention trial (EXPERT) in patients undergoing TKR provided proof of principle for 15 and 40 mg betrixaban bid and showed a good safety profile (45). The primary efficacy endpoint was the incidence of VTE (symptomatic DVT or PE, or asymptomatic DVT) on days 10–14. VTE occurred in 20% (15 mg) and 15.4% (40 mg) of patients receiving betrixaban, and in 10% of those receiving enoxaparin. Major bleeding events were not observed in either betrixaban group, but occurred in 2% of patients in the enoxaparin group.

### Tab. 3 Other direct factor Xa inhibitors in clinical development

<table>
<thead>
<tr>
<th></th>
<th>VTE prevention after major orthopaedic surgery (phase III)</th>
<th>VTE prevention in TKR patients (phase II)</th>
<th>VTE prevention in TKR patients (phase II)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADVANCE-1 TKR ( n = 3202 ) (31)</td>
<td>EXPERT ( n = 215 ) (45)</td>
<td>STARTS THR phase IIb ( n = 950 ) (43)</td>
</tr>
<tr>
<td></td>
<td>apixaban enoxaparin p value</td>
<td>betrixaban enoxaparin</td>
<td>edoxaban placebo</td>
</tr>
<tr>
<td></td>
<td>primary efficacy outcome composite of symptomatic or asymptomatic DVT, PE and all-cause mortality</td>
<td>5 mg 15 mg 30 mg 60 mg</td>
<td>15 mg 30 mg 60 mg 90 mg</td>
</tr>
<tr>
<td></td>
<td>primary safety outcome major bleeding</td>
<td>primary efficacy outcome VTE incidence</td>
<td>primary efficacy outcome VTE incidence</td>
</tr>
<tr>
<td></td>
<td>9.0% 8.9% NS</td>
<td>29.5% (p&lt;0.01) 26.1% (p&lt;0.001)</td>
<td>28.2% 21.2% 15.2% 10.6% 43.8%</td>
</tr>
<tr>
<td></td>
<td>primary safety outcome major bleeding</td>
<td>12.5% (p&lt;0.001) 9.1% (p&lt;0.001)</td>
<td>15.2% 10.6% 2.2% 2.3% 0%</td>
</tr>
<tr>
<td></td>
<td>clinically relevant bleeding</td>
<td>2.9% (p=0.445) 4.7% (p=1.00)</td>
<td>1.6% 1.8% 2.2% 2.3% 0%</td>
</tr>
<tr>
<td></td>
<td>0.7% 1.4% NS</td>
<td>3.9% (p=1.00) 4.7% (p=1.00)</td>
<td>3.9% 0% 2.3% 0%</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; THR: total hip replacement; TKR: total knee replacement; NS: non-significant; CRNM: clinically relevant non-major; AF: atrial fibrillation; qd: once daily; bid: twice daily

ADVANCE-1: apixaban 2.5 mg bid; or enoxaparin 30 mg bid for 10 days; EXPERT: betrixaban 15 or 40 mg bid; or enoxaparin 30 mg bid for 10–14 days; edoxaban phase II: edoxaban 5, 15, 30 or 60 mg qd; or placebo for 11–14 days; STARTS: edoxaban 15, 30, 60 or 90 mg qd; or dalteparin for 7–10 days; phase II stroke prevention in patients with AF: edoxaban 30 or 60 mg qd and bid; or warfarin (INR 2–3) for 3 months.

### References

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A phase II study (EXPLORE-Xa\textsuperscript{14}) to investigate the safety, tolerability and efficacy of 40, 60, and 80 mg betrixaban qd (double-blind) compared to warfarin (open-label, dose-adjusted) for 3 months in patients with atrial fibrillation that has started recruitment.

**Edoxaban**

Edoxaban (DU-176b; Daiichi Sankyo) is an oral, direct and competitive FXa inhibitor. FXa is inhibited with Ki values of 0.56 nmol/l for free FXa and 2.98 nmol/l for prothrombinase with a >10000-fold selectivity for FXa (16). In human plasma, edoxaban doubles the prothrombin time and activated partial thromboplastin time at concentrations of 0.256 and 0.508 µmol/l.

In vivo, edoxaban dose-dependently inhibited thrombus formation in rat and rabbit thrombosis models, and the bleeding time in rats was not significantly prolonged at an antithrombotic dose (16). It is rapidly absorbed (median $t_{\text{max}}$, 1.0–1.5 h), with a plasma half-life of 9–11 h and a bioavailability of about 45% (51). In healthy volunteers, a single 60 mg dose of edoxaban reduced ex vivo thrombus formation in a flow chamber under venous and arterial flow conditions for up to 5 h (51).

A placebo-controlled, phase II study in patients undergoing TKR showed that edoxaban dose-dependently reduced VTE without increases in major or clinically relevant bleeding (\textsuperscript{15}). The incidence in placebo patients was 48.3%, and was reduced by edoxaban to 29.5% (5 mg qd), 26.1% (15 mg qd), 12.5% (30 mg qd), and 9.1% (60 mg qd). The results of a randomized, double-blind, phase IIb study (STARTS II) comparing edoxaban with dalteparin in patients undergoing THR were reported recently (43). The incidence of VTE on dalteparin was 43.8% and was dose-dependently lower on edoxaban: 31.7% to 13.3%, and decreased significantly to days 7–10 of prophylaxis) ranged from 3.1% to 3.3%.

In a phase IIa study for the prevention of VTE after orthopedic surgery have recently been completed. In a phase IIa study for the prevention of VTE after THR, 10–60 mg YM150 qd was shown to be safe, well tolerated and effective (12). A phase Ib study, ONYX-2, to determine the optimal dose of YM150 (5–120 mg qd) for the prevention of VTE after THR, has recently been completed (13). The incidence of the primary efficacy endpoint (composite of DVT, symptomatic VTE, PE and death up to days 7–10 of prophylaxis) ranged from 31.7% to 3.3%, and decreased significantly with increasing doses of YM150. Further phase II studies have been started to evaluate the efficacy and safety of 11.1% (10.0) compared with 18.1% for 30 mg enoxaparin s.c. bid. A dose-related increase in the incidence of total bleeding, driven mainly by minor bleeding, was not statistically significant. No further studies have been reported.

LY517717

LY517717 difumarate (Eli Lilly) is an oral, direct FXa inhibitor with a Ki for FXa of 4.6–6.6 nmol/l and an elimination half-life of about 25 h in healthy subjects; it is eliminated mainly in faeces (47). In a randomized, double-blind, dose-escalation study in patients undergoing TKR or THR, total VTE rates were 19% for 100 mg LY517717, 19% for 125 mg, and 16% for 150 mg compared with 21% for 40 mg enoxaparin qd (3). The incidence of bleeding events was similar for LY517717 and enoxaparin. No information on future studies is available.

**Eribaxaban**

Eribaxaban (PD0348292; Pfizer) has a high affinity for human FXa (Ki = 0.32 nmol/l) (25). In vivo antithrombotic activity has been demonstrated in an AV shunt model in rabbits (25). Clinical data from a dose-ranging study with eribaxaban in the prevention of VTE in TKR patients have recently been presented (8). All doses were well tolerated. VTE frequency was as follows (eribaxaban dose in mg): 37.1% (0.1), 37.1% (0.3), 28.8% (0.5), 19.2% (1.0), 14.3% (2.5), 1.4% (4.0), and 11.1% (10.0) compared with 18.1% for 30 mg enoxaparin s.c. bid. A dose-related increase in the incidence of total bleeding, driven mainly by minor bleeding, was not statistically significant. No further studies have been reported.

**TAK-442**

TAK-442 (Takeda Pharmaceutical) is a further orally active, direct FXa inhibitor. A phase II dose-ranging study\textsuperscript{29} to evaluate the efficacy and safety of TAK-442 (10, 40, 80 mg qd and bid) in subjects undergoing TKR has been recently completed, and a further phase...
Il study in subjects with ACS is ongoing. No pharmacodynamic or pharmacokinetic data are available.

Conclusion

The efficacy and safety of new oral, direct FXa inhibitors in recent clinical studies potentially heralds a new era for anticoagulation. The positive results showed for the prevention of VTE in patients undergoing THR and TKR surgery have led to the approval of the direct factor Xa inhibitor rivaroxaban for these indications. Several FXa inhibitors are currently being investigated in chronic use in indications such as the prevention of stroke in patients with AF, the secondary prevention of ACS and treatment of VTE.

In future, anticoagulant treatment will favour oral agents with a
- wide therapeutic window and
- predictable anticoagulant response that do not need routine monitoring.

Emerging data suggest that direct FXa inhibitors are effective antithrombotic agents for short-term usage and promising agents for long-term usage. Since they have shown a predictable pharmacological profile, are given orally, and do not require routine coagulation monitoring, these new agents are likely to improve anticoagulation treatment in thromboembolic disorders and reduce the burden associated with long-term treatment.

References


