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# Oral Anticoagulants in Development

## Focus on Thromboprophylaxis in Patients Undergoing Orthopaedic Surgery

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## Abstract

Current anticoagulant provision is dominated by parenteral heparin and oral warfarin, which act by inhibiting several steps of the coagulation pathway indirectly. Recent research efforts have focused on the identification of small molecule inhibitors of the coagulation enzymes as novel therapies for thrombotic disorders. There has been particular success in developing nonpeptidic, orally available, small molecules to directly inhibit the key proteases, factor IIa and factor Xa.

Of the new oral anticoagulants in development, the two agents in the most advanced stage are dabigatran etexilate (BIBR 1048) and rivaroxaban (BAY 59-7939), which inhibit factor IIa and factor Xa, respectively. Other agents in the early stages of development include several Xa inhibitors (LY-517717, YM150, DU-176b and apixaban [BMS-562247]), a factor IXa inhibitor (TTP889), and an orally active glycosaminoglycan enhancer (odiparcil [SB-424323]), which indirectly enhances thrombin inhibition via heparin cofactor II. Results have been reported from important, phase II dose-finding studies, and a number of registration-track phase III studies have been initiated, reflecting the drive towards potentially more effective, but primarily safer and more convenient therapies for the prevention and treatment of venous and arterial thrombosis. Indeed, two unmet needs for anticoagulation that can be easily identified are safety and ease of use. Safety relates primarily to the incidence of major bleeding and this remains the key concern of orthopaedic surgeons, over and above any efficacy advantage, and convenience of use, which centres on oral administration replacing the need for injections.

The clinical development of these new anticoagulants is following the well tested strategy of dose-ranging and registration studies in major orthopaedic surgery, prior to development in arterial indications. There are a number of subtle issues, including the timing of the first perioperative dose, duration of prophylactic treatment and definition/assessment of study endpoints that can influence study outcome and require careful consideration when evaluating study results with new agents and in the comparison with established agents, and which are considered in this review.

It is anticipated that over the next 3 years, at least one of these agents will be successfully licensed for the prevention of venous thromboembolism after major

orthopaedic surgery, which will act as a springboard for the gradual replacement of current anticoagulants.

## 1. Introduction

Research in the field of thrombosis prevention has advanced quickly in recent years, mainly because of advances in structure-function-based drug design, but also through an improved understanding of the molecular orchestration of coagulation. These advances have transformed drug discovery in the field of haemostasis and opened a new vista in anticoagulation research.

Anticoagulation, the controlled therapeutic inhibition of blood coagulation by means of appropriate anticoagulant drugs, has been dominated for many decades by parenteral heparin (unfractionated [UFH] and low-molecular-weight [LMWH] forms), and orally-delivered vitamin K antagonists, such as warfarin. Warfarin, although an oral anticoagulant, has well documented limitations, including a delayed onset of action and a poor pharmacokinetic profile, which requires intensive monitoring coupled with frequent dose adjustment.[1] Warfarin is frequently associated with adverse events leading to hospitalisation.[2]

More recently, subcutaneous fondaparinux sodium, a synthetic pentasaccharide based on the active pentasaccharide sequence of heparin, was licensed for the prevention and treatment of venous thromboembolism (VTE) after completing a large clinical development programme.[3-5] Hirudin-derived compounds, based on the naturally-occurring 65-amino acid polypeptide isolated from the medical leech *Hirudo medicinalis,* have also been licensed for the prevention of VTE after elective total hip replacement (THR) surgery, for the treatment of heparin-induced thrombocytopenia and for the treatment of arterial thrombotic indications.[6] However, because of the molecular characteristics of heparin and its derivatives (high molecular weight, highly anionic nature and poor lipid solubility),[7] and the peptidic nature of hirudin, drug delivery has not been possible through absorption in the gastrointestinal tract. Delivery must be parenteral, which represents an obstacle for both the short and long term management of thromboembolic diseases. It is clear that there is a low unmet need for novel parenteral anticoagulants and the focus of clinical development is oral delivery.

### 1.1 New Age of Oral Anticoagulants

The development of new anticoagulant agents is underpinned by our present understanding of the coagulation cascade, with drug development focused on the identification of orally active, synthetic compounds that act on distinct serine protease enzymes that drive clot propagation and fibrin deposition. The principal targets are factor IIa (FIIa) and factor Xa (FXa).

Two oral, synthetic compounds are in late-stage development: one FIIa inhibitor (dabigatran etexilate) and a direct FXa inhibitor (rivaroxaban), and perhaps have the best chance of emerging as new oral anticoagulants. Ximelagatran, a prodrug of melagatran, was the first orally available direct FIIa inhibitor and had undergone a large clinical evaluation for prevention and treatment of VTE,[8] stroke prevention with atrial fibrillation (SPAF) and recurrent coronary events after acute myocardial infarction.[9] Although oral ximelagatran and subcutaneous melagatran were licensed in Europe for VTE prevention in patients undergoing THR or total knee replacement (TKR), the license application was rejected by the US FDA in 2004, based on safety concerns, and ximelagatran was eventually withdrawn by AstraZeneca in February 2006.[10] Consequently, it is the development programmes of dabigatran etexilate and rivaroxaban that now come under scrutiny and form the focus of this article. A number of other recent review articles also offer other insights on this rapidly expanding field.[11-14]

### 1.2 The Orthopaedic Surgery Model

THR and TKR are successful orthopaedic procedures that relieve pain, improve function and en-

hance quality of life. Multiple studies have investigated anticoagulation to prevent VTE after major orthopaedic surgery[15] and this remains the preferred testing ground for anticoagulant drug development for a number of reasons.[16] First, the level and duration of the risk after THR/TKR are quite well characterised, and events occur at relatively high frequency. For example, historically it was shown that after THR, >50% of the patients develop deep-vein thrombosis (DVT) in the absence of thromboprophylaxis.[15] Secondly, pharmaceutical companies develop agents in this indication not because of a particular interest in this therapeutic setting, but because these patients undergoing THR/TKR are a large, well defined patient group at high risk of DVT after surgery and this can be shown either by validated screening techniques, such a venography, or by clinically apparent events. As a result, relatively small, dose-finding and registration-track studies proving anticoagulant efficacy and safety can be conducted. Thirdly, the elective nature of the surgery helps protocol adherence, with patients somewhat self-selecting in terms of their overall health status, that is, they tend to be medically optimised and survive these major elective procedures.

### 1.3 Search Strategy

Electronic databases (MEDLINE and EMBASE) from 1996 to July 2006 where searched for clinical trials of new anticoagulants. Bibliographies of journal articles were hand-searched to locate additional studies and abstracts from major international thrombosis meetings (American Society of Hematology [ASH]; American Heart Association [AHA]; European Society of Cardiology [ESC]; and International Society on Thrombosis & Haemostasis [ISTH]) that have taken place in the last 5 years were also reviewed. Relevance was assessed using a hierarchical approach based on title, abstract and the published manuscript. An electronic search of the US National Institute of Health Clinical trials database[17] and the internet search engine, Google was also performed.

## 2. New, Oral Anticoagulants Under Development in Major Orthopaedic Surgery

### 2.1 Agents in Late-Stage Development (Phase III)

#### *2.1.1 Dabigatran Etexilate*

Dabigatran etexilate (BIBR 1048), developed by Boehringer Ingelheim,[18] is an oral direct thrombin inhibitor and the prodrug of dabigatran (BIBR 953 ZW), a potent, nonpeptidic small molecule that specifically and reversibly inhibits both free and clot-bound thrombin. During oral absorption, dabigatran etexilate is converted by esterases to the active drug. The chemical structure of dabigatran etexilate[19] is shown in figure 1.

##### Completed Studies

BISTRO (Boehringer Ingelheim Study in ThROmbosis) I was an open-label, dose-escalating phase IIa study,[20] undertaken in 314 patients undergoing THR (table I). This was primarily a safety study, with dose escalation based on previous clinical and pharmacokinetic data. Patients received one of nine doses of dabigatran etexilate tablets post-operatively once or twice daily, beginning 4–8 hours after surgery, for 6–10 days. The primary safety endpoint was major bleeding; the primary efficacy endpoint included venographic DVT and symptomatic VTE during the treatment period (table II).

No major bleeding was observed, whereas a dose-response was demonstrated for minor bleeding. The DVT rates were relatively low, confirming the antithrombotic potential of the drug. No dose-response relationship was apparent but the study was not powered for such an analysis. Two patients receiving the highest dosage experienced bleeding from multiple sites, suggesting a wide therapeutic window between the lowest (12.5mg twice daily) and highest dosage (300mg twice daily).

BISTRO Ib, was a small, single-dose (150mg) phase IIa study evaluating a capsule formulation of dabigatran etexilate with improved pharmacokinetic properties compared with the tablet used in BISTRO

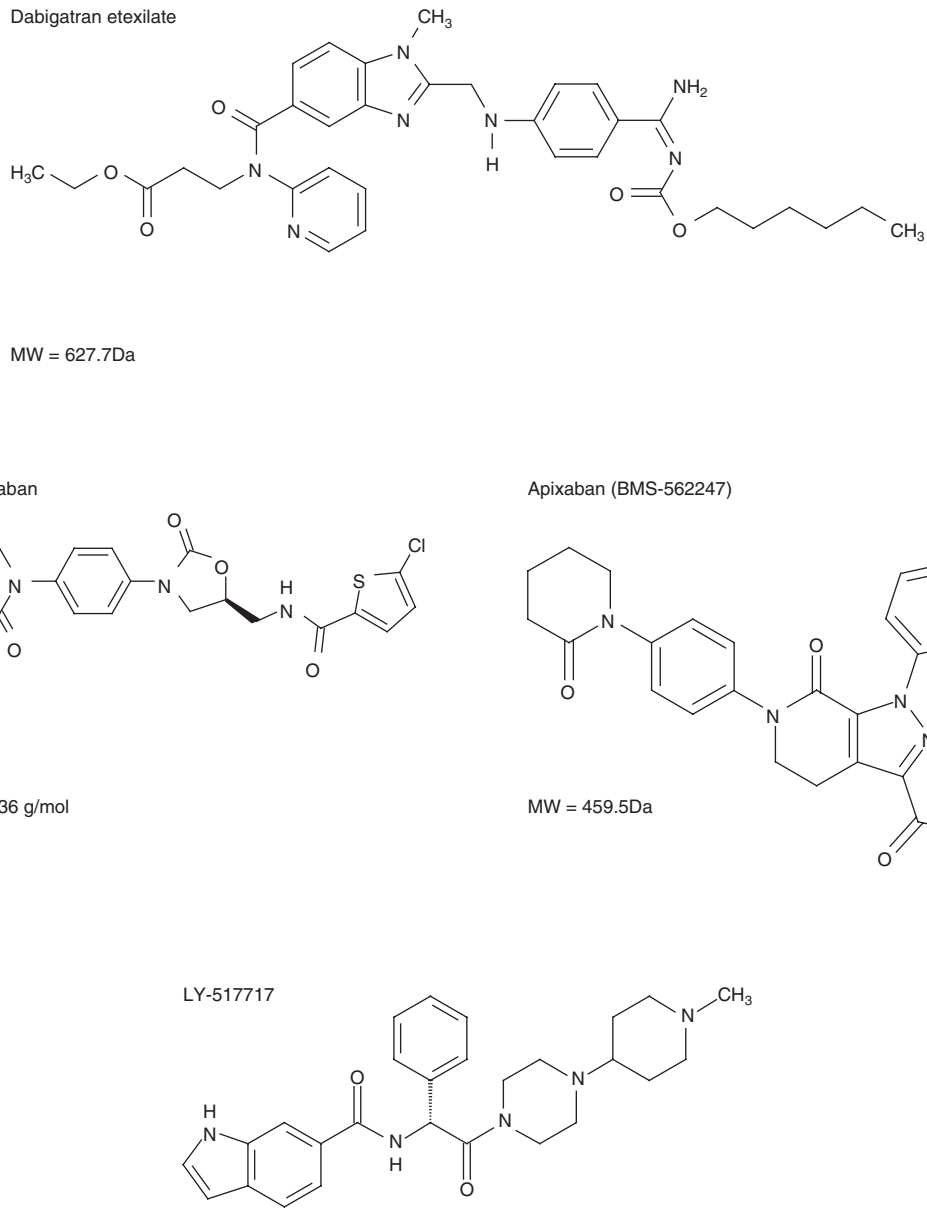


**Fig. 1.** Structures of new oral anticoagulants under development. **Da** = daltons; **MW** = molecular weight.

I.[21] The capsule was administered 1–3 hours after surgery and proved to be effective with prompt absorption and peak plasma concentrations of dabigatran occurring after 6 hours. Peak plasma concentrations and systemic exposure of dabigatran were approximately 75% of those seen at steady-state using the tablet formulation. These characteristics confirmed its suitability for use in future clinical trials.

BISTRO II was a large, double-blind, multicentre, parallel-group, phase IIb study,[22] which randomised 1973 patients undergoing either THR or

**Table I.** Recently completed (C) or ongoing (O) studies with new oral anticoagulants in major orthopaedic surgery

| Drug class/ name | Company | Stage, status | Study name | Study population | No. of patients randomised | Dosage and administration schedule (mg) | Time of first dose | Treatment duration (d) | Comparator | References |
|---|---|---|---|---|---|---|---|---|---|---|
| **Direct FIIa inhibitors** | | | | | | | | | | |
| Dabigatran etexilate | Boehringer Ingelheim | IIa, C | BISTRO I | THR | 314 | 12.5, 25, 50, 100, 150, 200, 300 bid; 150, 300 od | 4–8h PO | 6–10 | Nil | 20 |
| | | IIa, C | BISTRO Ib | THR | 59 | 150 | 1–3h PO | Single dose | Nil | 21 |
| | | IIb, C | BISTRO II | THR/TKR | 1973 | 50, 150, 225 bid; 300 od | 1–4h PO | 6–10 | E 40mg od | 22 |
| | | III, O | RE-NOVATE | THR | 3330[a] | 150/220 od[b] | 1–4h PO | 28–35 | E 40mg od | 23 |
| | | III, O | RE-MODEL | TKR | 2010[a] | 150/220 od[b] | 1–4h PO | 6–10 | E 40mg od | 24 |
| | | III, O | RE-MOBILIZE | TKR | 2610[a] | 150/220 od[b] | 6–12h PO | 12–15 | E 30mg bid | 25 |
| | | IIb, O[c] | NK | TKR | 400[a] | 110/150/220 od[b] | 1–4h PO | 11–14 | Placebo | 26 |
| **Indirect FIIa inhibitors** | | | | | | | | | | |
| Odiparcil | GlaxoSmithKline | IIa, C | TEMPEST | THR | 225[a] | 125/500 bid | NK | 28 | Nil | 27,28 |
| | | IIb, O | TOPVENT | TKR | 915[a] | NK | NK | 8–12 | W | 29 |
| **FXa inhibitors** | | | | | | | | | | |
| Rivaroxaban | Bayer | IIb, C | ODIXa-KNEE | TKR | 621 | 2.5, 5, 10, 20, 30 bid | 6–8h PO | 5–9 | E 30mg bid | 30 |
| | | IIb, C | ODIXa-HIP | THR | 722 | 2.5, 5, 10, 20, 30 bid | 6–8h PO | 5–9 | E 40mg od | 31 |
| | | IIb, C | ODIXa-HIP | THR | 873 | 5, 10, 20, 30, 40 od | 6–8h PO | 6–10 | E 40mg od | 32 |
| LY-517717 | Eli Lilly | IIa, C | NK | THR/TKR | 511 | 25, 50, 75, 100, 125, 150 od[d] | 6–8h PO | 6–10 | E 40mg od | 33 |
| YM150 | Astellas | IIa, C | ONYX | THR | 178 | 3, 10, 30, 60 od | 6–10h PO | 7–10 | E 40mg od | 34 |
| DU-176b | Daiichi | IIa, O | NK | THR | 402[a] | NK | NK | NK | NK | 35 |
| Apixaban | Bristol-Myers Squibb | II, O | NK | TKR | 1202[a] | NK | NK | NK | E 30mg bid, W | 36 |
| GSK-813893[e] | GlaxoSmithKline | I, NK | NK | NK | NK | NK | NK | NK | NK | 37 |
| **FIXa inhibitors** | | | | | | | | | | |
| TTP889 | Transtech | IIa, O | FIXIT | HFS | 300[a] | 300 od | 5–9d PO | 21 | Placebo | 38 |

a Expected.

b 75 or 110mg on day of surgery.

c Conducted in Japan.

d 25, 50, 75mg doses stopped early because of lack of efficacy.

e Reported to be still in phase I for prevention of stroke in atrial fibrillation.[37]

**bid** = twice daily; **BISTRO** = Boehringer Ingelheim Study in ThROmbosis; **E** = enoxaparin sodium; **FIIa** = factor IIa; **FIXa** = factor IXa; **FIXIT** = Factor IX Inhibition in Thrombosis Prevention trial; **FXa** = factor Xa; **HFS** = Hip fracture surgery; **NK** = not known; **od** = once daily; **ODIXa-HIP** = Oral DIrect Factor Xa inhibitor-HIP; **ODIXa-KNEE** = Oral DIrect Factor Xa inhibitor-KNEE; **ONYX** = Oral direct iNhibition by YM150 of factor Xa; **PO** = post-operative; **TEMPEST** = ThromboEMbolism Prevention Efficacy and Safety Trial; **THR** = total hip replacement; **TKR** = Total knee replacement; **W** = warfarin.

**Table II.** Endpoints and adjudication in recent or ongoing studies with new oral anticoagulants in major orthopaedic surgery

| Drug name | Study name | Study hypothesis | Primary efficacy endpoint | Type of VTE assessment | Primary safety endpoint | Independent adjudication committee | Venogram adjudication committee | References |
|---|---|---|---|---|---|---|---|---|
| **Direct FIIa inhibitors** | | | | | | | | |
| Dabigatran etexilate | BISTRO I | Safety dose-response | VTE[a] | Venography, clinical | Major bleeding | Yes | Gothenburg | 20 |
| | BISTRO Ib | PK | PK characteristics | Venography, clinical | NA | NA | NA | 21 |
| | BISTRO II | Efficacy dose-response | VTE[a] | Venography, clinical | Major bleeding | Yes | Gothenburg | 22 |
| | RE-NOVATE | Non-inferiority | Composite of VTE[a] plus A-CM | Venography, clinical | Major bleeding | Yes | Amsterdam | 23 |
| | RE-MODEL | Non-inferiority | Composite of VTE[a] plus A-CM | Venography, clinical | Major bleeding | Yes | Gothenburg | 24 |
| | RE-MOBILIZE | Non-inferiority | Composite of VTE[a] plus A-CM | Venography, clinical | Major bleeding | Yes | Gothenburg | 25 |
| **Indirect FIIa inhibitors** | | | | | | | | |
| Odiparcil | TEMPEST | Efficacy dose-response | Composite of VTE[a] plus A-CM | Venography, clinical | Major bleeding | NK | NK | 26,27 |
| | TOPVENT | Efficacy dose-response | VTE[a] | Venography, clinical | Major bleeding | NK | NK | 28 |
| **FXa inhibitors** | | | | | | | | |
| Rivaroxaban | ODIXa-KNEE | Efficacy dose-response | Composite of VTE plus A-CM | Venography, ultrasound, clinical | Post-op major bleeding | Yes | Gothenburg | 30 |
| | ODIXa-HIP | Efficacy dose-response | Composite of VTE plus A-CM | Venography, ultrasound, clinical | Post-op major bleeding | Yes | Gothenburg | 31 |
| | ODIXa-HIP | Efficacy dose-response | Composite of VTE plus A-CM | Venography, ultrasound, clinical | Post-op major bleeding | Yes | Gothenburg | 32 |
| LY-517717 | NK | NK | All VTE[a] | Venography, clinical | Major bleeding | Yes | NK | 33 |
| YM150 | ONYX | Safety dose-response | All VTE[a] | Venography, clinical | Major bleeding and/or clinically relevant non-major bleeding | Yes | Gothenburg | 29 |
| DU-176b | NK | NK | NK | NK | NK | NK | NK | 35 |
| Apixaban | NK | NK | Composite of VTE plus A-CM | Venography, clinical | Major and minor bleeding | NK | NK | 34 |
| **FIXa inhibitors** | | | | | | | | |
| TTP889 | FIXIT | NK | NK | NK | NK | NK | NK | 38 |

a Includes venographic proximal and distal deep-vein thrombosis (DVT), symptomatic DVT and pulmonary embolism during treatment period.

**A-CM** = all-cause mortality; **BISTRO** = Boehringer Ingelheim Study in ThROmbosis; **FIIa** = factor IIa; **FIXa** = factor IXa; **FIXIT** = Factor IX Inhibition in Thrombosis Prevention trial; **FXa** = factor Xa; **NA** = not applicable; **NK** = not known; **ODIXa-HIP** = Oral DIrect Factor Xa inhibitor-HIP; **ODIXa-KNEE** = Oral DIrect Factor Xa inhibitor-KNEE; **ONYX** = Oral direct iNhibition by YM150 of factor Xa; **PK** = pharmacokinetic; **post-op** = post-operative; **TEMPEST** = ThromboEMbolism Prevention Efficacy and Safety Trial; **VTE** = venous thromboembolism.

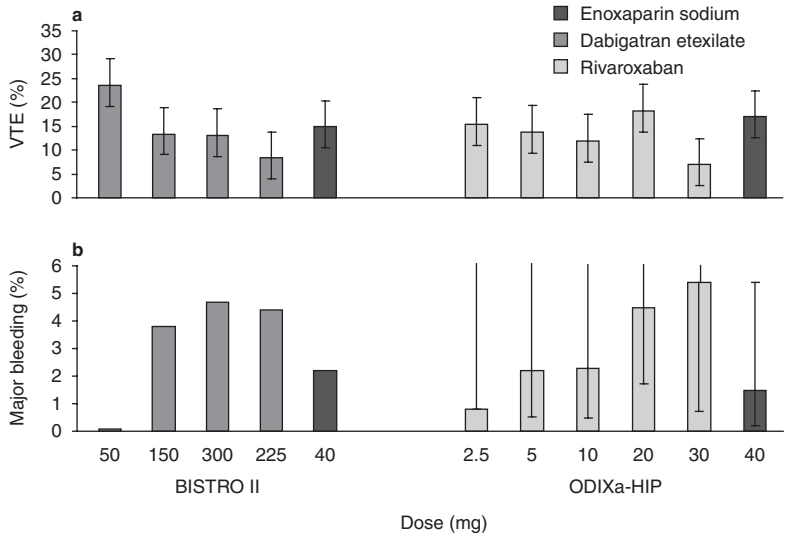


**Fig. 2.** Efficacy (**a**) and safety (**b**) dose-response curves (point estimates and 95% CIs) in phase II total hip replacement studies with dabigatran etexilate and rivaroxaban. All doses were administered twice daily, except dabigatran etexilate 300mg, which was administered once daily. **BISTRO I** = Boehringer Ingelheim Study in ThROmbosis I; **ODIXa-HIP** = Oral DIrect Factor Xa inhibitor-HIP; **VTE** = venous thromboembolism.

TKR (table I). Patients received one of four dabigatran etexilate dosages (50 or 150mg twice daily, 300mg once daily, 225mg twice daily), starting 1–4 hours after surgery, or enoxaparin sodium (40mg once daily) initiated 12 hours prior to surgery, for 6–10 days. The primary efficacy endpoint, DVT detected by venography or symptomatic VTE during treatment (table II), showed a significant dose-dependent decrease (from 28.5% to 13.1%) with increasing dosage of dabigatran etexilate (figure 2a) and compared favourably with enoxaparin sodium (24%). Major bleeding was significantly lower with the lowest (50mg twice daily) dosage of dabigatran etexilate (0.3% vs 2.0%; p = 0.047) compared with enoxaparin sodium, with a dose-dependent increase at higher dosages (figure 2b).

### Ongoing Studies

Three phase III, comparative primary prevention trials involving nearly 8000 patients undergoing THR (RE-NOVATE)[23] or TKR (RE-MODEL[24] and RE-MOBILIZE[25]) were initiated in November 2004 and are expected to report in late 2006/early 2007. The studies are all randomised and double-blind, and patients receive one of two dosage regimens of dabigatran etexilate capsules (150 or 220mg once daily, starting with a half dose [75 or 110mg] on the day of surgery), or enoxaparin sodium with US (30mg twice daily) or EU (40mg once daily) dosage regimens (table I). The RE-NOVATE study is comparing dabigatran etexilate with enoxaparin sodium (40mg once daily) for an extended period (28–35 days). The primary endpoint is the composite of total VTE (the composite of proximal and distal venographic DVT and symptomatic DVT/pulmonary embolism [PE]) and all-cause mortality during the treatment period (table II).

#### *2.1.2 Rivaroxaban*

Rivaroxaban (BAY 59-7939) is a potent and selective oral FXa inhibitor, developed by Bayer HealthCare AG.[39] Rivaroxaban belongs to a new class of oxazolidinone-based, active-site directed, FXa inhibitors. The chemical structure is shown in figure 1.[39] A unique feature of the molecule is the lack of a highly basic group in its active-site binding region, which is an important contributing factor to the oral absorption profile. A high relative bioavailability has been confirmed for rivaroxaban in healthy volunteers.[40]

#### Completed Studies

ODIXa-KNEE (Oral DIrect Factor Xa inhibitor-KNEE) was a double-blind, multicentre, parallel-group, phase IIb study that randomised 621 patients undergoing elective TKR to one of five dosages of rivaroxaban (2.5, 5, 10, 20, or 30mg twice daily), starting 6–8 hours postsurgery, or enoxaparin sodium (30mg twice daily) starting the day after surgery, for 5–9 days (table I).[30] The primary efficacy endpoint was the composite of all DVT, confirmed nonfatal PE and all-cause mortality during treatment (table II). There was no significant dose-response for the primary endpoint with increasing dosages of rivaroxaban (23–40%). The rate with enoxaparin sodium was 44%. The rate of major, postoperative bleeding increased with increasing dose of rivaroxaban (1.0–7.5%). In comparison, the rate of major, postoperative bleeding with enoxaparin sodium was 1.9%.

ODIXa-HIP, an almost identical dose-ranging study to ODIXa-KNEE, randomised 722 patients undergoing elective THR.[31] Rivaroxaban administration was identical to the KNEE study but enoxaparin sodium (40mg once daily) was started on the evening before surgery. Again, there was no significant dose-dependent decrease in the incidence of the primary endpoint (rates of the primary efficacy endpoint ranged from 7% to 18% compared with 17% for enoxaparin sodium) [figure 2a], and the primary safety endpoint of major postoperative bleeding showed a significant increase in frequency with increasing dose of rivaroxaban (0.8–5.4%). In comparison, the rate of major postoperative bleeding with enoxaparin sodium was 1.5% (figure 2b).

An additional phase IIb study assessed a once daily administration regimen of rivaroxaban after THR (table I).[32] The double-blind study randomised 873 patients to rivaroxaban (5, 10, 20, 30 or 40mg once daily), starting 6–8 hours after surgery, or enoxaparin sodium (40mg once daily), initiated the evening before surgery, for 6–10 days. Again, there was no significant dose-response for the primary endpoint with increasing doses of rivaroxaban (8.5–15%), while the rate for enoxaparin sodium was 25%. An assessment of major VTE (proximal DVT, PE, VTE-related death) did, however, show a significant dose trend ($p = 0.0072$). Major bleeding rates significantly increased in frequency with increasing dose of rivaroxaban (0.7–5.1%). In comparison, the rate of major postoperative bleeding with enoxaparin sodium was 1.9%.

#### Ongoing Studies

Bayer has announced that the major, phase III clinical study programme known as the RECORD (REgulation of Coagulation in major Orthopaedic surgery reducing the Risk of DVT and PE) studies will investigate one dose of rivaroxaban, 10mg once daily,[41] and enroll >9000 patients. The studies will compare rivaroxaban with enoxaparin sodium and at least one of the studies will be for an extended duration of up to 5 weeks of treatment.

### 2.2 Agents in Early Stage Development (Phase II)

#### *2.2.1 LY-517717*

LY-517717, an Eli Lilly compound, is another oral FXa inhibitor. The first phase II findings were reported at the ASH Meeting in 2005.[33] This was a double-blind, dose-escalation study that enrolled 511 patients undergoing TKR or THR. Patients received one of six oral doses of LY-517717 once daily, starting 6–8 hours after surgery, or enoxaparin sodium (40mg once daily), starting the night before surgery, for 6–10 days (table I). Efficacy was assessed by all VTE events during the treatment period (table II). The three lower doses were not completed because of a high rate of VTE. For the three highest doses, the VTE prevalence ranged from 24% to 17.1% with increasing LY-517717 dose, comparable with enoxaparin sodium (22.2%) and with few bleeding events. These findings suggest the drug may have a relatively narrow therapeutic window compared with other oral agents in development.

#### *2.2.2 YM150*

YM150, developed by Astellas, is another oral FXa inhibitor. Provisional findings were reported at the ASH Meeting in 2005[34] from an open-label, dose-escalation safety study that randomised 178 patients undergoing THR (table I) who received one of four doses of YM150 once daily, starting 6–10

hours after surgery, or enoxaparin sodium (40mg once daily), starting the night before surgery, for 7–10 days. Safety was defined as major and/or clinically relevant nonmajor bleeding, and efficacy as venographic or symptomatic VTE events during treatment (table II). No major bleeding events occurred, with no dose trend for clinically relevant nonmajor bleeding events. The proportion of patients with minor bleeding events in the enoxaparin sodium group was similar to that in the group receiving the highest dosage of YM150. The primary efficacy endpoint occurred in 19–52% of patients, compared with 39% for enoxaparin sodium, with a statistically significant dose-related trend ($p = 0.006$) among the YM150 groups.

#### 2.2.3 Apixaban (BMS-562247)

Apixaban (BMS-562247), developed by Bristol-Myers Squibb, is an orally active, FXa inhibitor (figure 1). It is a variant of the orally active agent razaxaban (an aminobenzisoxazole that binds to the active site of FXa with high affinity) with superior pharmacological properties.[12] The antithrombotic potential of razaxaban was investigated in a phase II trial in patients undergoing TKR in which participants received various dosages of razaxaban or enoxaparin sodium for 10 days.[42] The primary endpoint, a composite of venographic DVT and symptomatic VTE, occurred in 8.6% of patients receiving the lowest dosage of razaxaban and in 15.9% with enoxaparin sodium. Major bleeding occurred in 0.7% of patients given this dosage of razaxaban and in none of those treated with enoxaparin sodium. The three higher dosages of razaxaban were stopped prematurely because of major bleeding. Further development of razaxaban was halted.[12] A Phase IIb dose-ranging study of apixaban in 1200 patients undergoing elective TKR is ongoing (table I and table II).[36]

#### 2.2.4 Odiparcil (SB-424323)

Odiparcil (SB-424323), undergoing development by GlaxoSmithKline and Solvay, is an orally-active glycosaminoglycan enhancer which indirectly inhibits thrombin via heparin cofactor II (HCII).[43] HCII is one of the body's natural anticoagulants and a strong inhibitor of thrombin. Odiparcil increases the activation of HCII. A phase IIa, randomised, placebo-controlled study, known as TEMPEST (ThromboEMbolism Prevention Efficacy and Safety Trial), investigated the use of odiparcil for up to 28 days in patients ($n = 225$) undergoing THR.[27] Among patients with evaluable venograms, the total VTE rate was reduced from 15.5% in patients receiving placebo to 6.5% in those receiving 125mg twice daily and 3.9% for the highest dosage of 500mg twice daily.[28] There were no drug-related major bleeding events reported and no liver enzyme abnormalities observed. A phase IIb, dose-ranging study, comparing odiparcil with warfarin in 915 patients undergoing TKR is ongoing (table I and table II).[29]

#### 2.2.5 TTP889

TTP889, manufactured by TransTech Pharma, is an orally active, factor IXa (FIXa) inhibitor. TTP889 inhibits the ability of FIXa to form a fully functional tenase complex with FVIIIa. A 300-patient, phase IIa proof-of-concept clinical trial involving administration of TTP889 for up to 28 days in patients undergoing hip fracture surgery is ongoing in several European countries (table I and table II).[38]

#### 2.2.6 DU-176b

DU-176b, developed by Daiichi, is an oral FXa inhibitor.[44-46] A phase IIa, open-label, dose-ranging study, with DU-176b administered once or twice daily in 400 patients undergoing THR, is ongoing (table I and table II).[35]

## 3. Critical Issues in the Development of New Oral Anticoagulants in Orthopaedic Surgery

A vast literature exists describing the efficacy and safety of heparins and warfarin in the prevention of thrombosis in patients undergoing major orthopaedic surgery, which provides an important evidence base to inform the development steps for new oral agents.[15] Determining the optimal efficacy/safety balance for each new anticoagulant agent is the central issue in the development process, with any reduction in the risk of VTE balanced against

**Table III.** Issues to consider in the development of oral anticoagulants

| Duration of treatment | Primary indications | Issues |
|---|---|---|
| Short-term use | Prevention of VTE after major orthopaedic surgery | Efficacy/safety balance<br>Preoperative vs postoperative administration<br>Once daily vs twice daily administration<br>Pharmacokinetic profile<br>Food/drug interactions |
| Long-term use | Prevention of thromboembolic complications associated with atrial fibrillation<br>Secondary prevention of recurrent VTE | Convenience of administration<br>Adverse-effect profile<br>Liver function |

**VTE** = venous thromboembolism.

the risk of bleeding, and this balance exerts a strong influence on the potential marketability of a new agent. Optimising the design of clinical trials remains a challenging proposition. A number of subtle issues, including choice of study endpoints, method of endpoint assessment, sample size, timing of first perioperative dose and definition/assessment of study endpoints all influence study outcome and, therefore, require careful consideration when evaluating study results with new agents and in the comparison with established agents (table III).

## 3.1 Sample Size, Dose Administration, Timing and Duration of Drug Delivery

### *3.1.1 Sample Size*

Sample size calculation for a phase IIa trial is usually based on comparisons with VTE rates from historical data. This is a perilous exercise because of the considerable variations in VTE rates seen in different studies. This relates to the different approaches to defining VTE (see section 3.2.1) and the variations in event rates determined by the use of venography. In some dose-escalation studies formal sample size calculations are not performed, with about 30–50 patients generally enrolled in each dosage group in order to obtain a sufficient number of evaluable venograms for assessment of the efficacy of each dosage.

### *3.1.2 Choice of Dosage*

Choice of dosage forms an integral part of an anticoagulant drug development process but making the choice may be difficult, especially if there is no obvious correlation between pharmacokinetic and pharmacodynamic data obtained from preclinical and phase I studies. Phase IIa studies are often undertaken in a small number of experienced trial centres, and the drug is tested on a limited number of patients with the primary aims of assessing tolerance and safety and to obtain proof-of-principle of efficacy. Most phase IIb studies are conducted with a range of dosages using a double-blind, parallel group design to establish the best dosage for efficacy and safety in comparison with an active comparator, usually a LMWH. The aim in phase IIb dose-finding studies is to show a statistically significant dose trend with respect to efficacy and safety, which allows the identification of the lowest, minimally effective dosage.

The phase IIb programmes of dabigatran etexilate and rivaroxaban are useful models to consider in the choice of dosage for subsequent phase III studies. Both drugs showed efficacy over a relatively wide dosage range (4.5–12 times lowest dosage), suggesting these agents may have a wider therapeutic window than previous anticoagulants such as warfarin.

BISTRO I and II[20,22] showed that once daily administration of dabigatran etexilate 300mg was almost identical in terms of efficacy and bleeding rates as twice-daily administration of 150mg, with the findings correlating with an almost identical drug exposure at steady state. A logistic regression model correlating the pharmacokinetic parameters for once and twice daily administration with the clinical efficacy and safety helped inform decisions regarding the dosages to be investigated in the phase III studies,[23-25] namely 150 or 220mg once daily; a 50% starting dose (75 or 110mg) was chosen to potentially reduce the bleeding risk in the immediate

postoperative state and hence improve the benefit-risk ratio.

In the ODIXa studies with rivaroxaban, no efficacy dose response was found in any of the three studies over a wide range of once and twice daily doses,[30-32] but a significant dose response with regard to major bleeding events confirmed the pharmacodynamic action of the drug. A logistic regression analysis, as reported at the ASH 2005 meeting,[47] on the combined findings from the ODIXa twice daily studies again found no dose response apparent for the primary efficacy outcome in this larger, combined data pool. The lack of efficacy dose response may be related to the dosage range being set too high, with the lowest dosage set above the threshold for efficacy. The findings from the once daily administration study of rivaroxaban,[32] showing a significant dose trend for major VTE and major bleeding, helped inform the choice of the dosage for the phase III studies, namely 10mg once daily, which offered the best efficacy-safety balance.

#### 3.1.3 Timing of First Dose

Because of the difference in clinical practice between North America and Europe, the clinical development of the LMWH, enoxaparin sodium, in the early 1980s for the prevention of VTE after major joint arthroplasty proceeded along different lines with different regimens investigated. In Europe, the first dose of enoxaparin sodium (40mg) was traditionally administered preoperatively, the evening before surgery, and continued postoperatively once daily. In North America, the regimen evaluated and used was 60 mg/day as two 30mg doses, with the first dose administered 12–24 hours after operation, largely driven by the perception that this minimises bleeding potential. However, most new anticoagulants are being developed using a postoperative initiation.

Detailed investigation of the impact of the exact timing of prophylaxis on drug efficacy and safety has shown that substantial differences in VTE risk reduction can be achieved through optimising the dose administration schedule. Not only does the postoperative approach close the transatlantic divergence seen with LMWH prescribing, it offers significant practical advantages. These include allowing drug administration on the day of surgery, with no requirement for hospitalisation the evening before surgery, and a simpler protocol when patients are undergoing neuraxial anaesthesia.

A number of studies, *post hoc* analyses and meta-analyses have been conducted to better define the effects of anticoagulant timing on efficacy and safety parameters, and the findings from these studies are now being reflected in the study design of new anticoagulants. To summarise, considering LMWH, preoperative administration does not seem to offer a significant advantage over LMWH initiated early postoperatively, with preoperative LMWH administration potentially associated with increased bleeding.[48,49]

Findings from studies with fondaparinux sodium show that initiation 6 hours post-surgery is associated with superior efficacy and similar safety as LMWH, given either the evening before surgery or 12–24 hours after surgery.[50] Earlier delivery of fondaparinux sodium (<6 hours) was associated with increased bleeding and with no efficacy advantage.[51]

With ximelagatran, the clinical studies investigated a combination of subcutaneous melagatran initiated either pre- or postoperatively, followed by oral ximelagatran for the remainder of the prophylaxis period. The administration of ximelagatran alone or combined with subcutaneous melagatran postoperatively was less effective than LMWH but more effective than warfarin, with a similar bleeding profile.[52,53] Preoperative prophylaxis and the use of a combination of melagatran and ximelagatran were more effective than LMWH, but with more bleeding episodes apparent.[54] These studies suggested that early administration in the postoperative period was the optimal delivery window and this was reflected in the approved label in the EU for melagatran before its withdrawal, with an early postoperative start of treatment and the initial subcutaneous dose of melagatran administered 4–8 hours after surgery.

Development of a new antithrombotic therapy to be given orally in close proximity to surgery repre-

sents a challenging proposition compared with existing parenteral therapies. The effect of the postoperative state on drug absorption can create difficulties in achieving an optimal formulation that offers prompt absorption and significant anticoagulant effect in the majority of patients without compromising safety. This is borne out in the BISTRO II study.[22] Dabigatran etexilate was administered orally 1–4 hours after surgery, with plasma concentration peak at 3.7–4.5 hours. At days 4–5, the peak plasma concentration was higher and occurred earlier (2.3–2.9 hours) compared with administration on the day of surgery. The delay in peak drug concentrations on the day of surgery may offer additional safety advantages. While the impact of the postoperative state on the absorption of rivaroxaban has not been reported, the first dose is not administered until 4–8 hours after surgery, suggesting a more prompt absorption profile.

#### 3.1.4 Frequency and Complexity of Dose Administration

The ideal dose administration regimen of a new anticoagulant for optimal convenience is straightforward to define: oral provision, once daily and it is on this basis that the phase III studies have been designed for dabigatran etexilate and rivaroxaban, following investigation in phase II studies of both once and twice daily regimens. The relatively long half-life of both dabigatran etexilate (14–17 hours)[22] and rivaroxaban (9 hours)[55] permit once daily administration. It is worth contrasting this simple, oral, once daily administration with the rather complex administration schedules that were investigated several years ago in the development programme of, for example, melagatran/ximelagatran. This approach reflects the increasing use of postoperative initiation of VTE prophylaxis in clinical practice across Europe, like that in North America, enabling oral treatment to be easily continued following discharge from hospital.

#### 3.1.5 Parallel and Dose-Escalation Studies

Phase II studies, conducted to determine the minimum effective and maximum tolerated dosage by using an escalating dose of drug, employ gradual increases of dose under continuous monitoring and communication with the study Steering Committee (dose escalation) or by parallel assessment of a range of dosages. While the majority of phase II studies use a double-blind, parallel dose design, two recent phase IIa studies[20,34] have used a dose-escalation design, using predefined dose-escalation steps and rules for continuation or termination of the study, based on the safety and tolerability of the previous doses. This type of study enables closer assessment of adverse events, especially bleeding, and therefore may allow early discontinuation of dosages at the extremes of the therapeutic range. A disadvantage of these studies is that they are open-label, which may introduce some bias into the reporting of bleeding events when the investigator knows the patient has received an experimental anticoagulant, in addition to the fact that dose-escalation studies may take longer to complete. Choosing the study design is challenging, with the decisions driven by the findings from preclinical and healthy volunteer studies, and made on an individual drug basis.

#### 3.1.6 Drug and Food Interactions

The pharmacokinetic profile of an oral drug in the perioperative period maybe influenced by factors such as gastric pH and motility changes (intestinal paresis and vomiting), and co-medications such as opioids, the effect of anaesthesia and food. Defining interactions is important for the development of a new oral anticoagulant as any effect can change bioavailability, and hence efficacy and safety parameters. Such interactions are especially relevant when the drug is to be given on the day of surgery. In studies of dabigatran etexilate, there is no evidence in the studies reported to date to indicate any interaction with drugs influencing intestinal pH or any food effect.[21] For rivaroxaban, a mild increase in absorption is observed with the administration of food, and no interaction is observed with drugs influencing intestinal pH when administered to healthy volunteers.[56]

Another potentially important interaction is that between anticoagulants and antiplatelet drugs (e.g. aspirin and clopidogrel) or NSAIDs, all of which are commonly employed in patients with osteoarthritis

who undergo major joint replacement. An analysis of the METHRO (MElagatran for THRombin inhibition in Orthopaedic surgery) III study,[52] investigated the effect of the concomitant administration of aspirin and NSAIDs with the direct thrombin inhibitor melagatran/ximelagatran or the LMWH enoxaparin sodium on bleeding in patients undergoing major joint surgery.[57] When given in conjunction with melagatran/ximelagatran or enoxaparin sodium, aspirin and NSAIDs showed no increase in bleeding, irrespective of the timing of the initial postoperative dose of melagatran/ximelagatran (4–8 hours, compared with 4–12 hours) or with preoperative administration of enoxaparin sodium.

#### 3.1.7 Duration of Treatment

Anticoagulant prophylaxis is generally continued at least until patients are no longer confined to bed. Studies investigating dabigatran etexilate and rivaroxaban have so far administered the treatment for 5–9 days after surgery, reflecting current guideline recommendations for thromboprophylaxis in these patient groups.[15] Given that early discharge after major joint replacement surgery is now common with in-hospital length of stay frequently reduced to as little as 3 days, these oral agents are particularly suited to maintain 5–9 days of treatment through patient self-administration outside of the hospital.

The optimal duration of thromboprophylaxis following THR and TKR is still a controversial subject, despite a number of studies and meta-analyses suggesting that both venographic and symptomatic DVT are significantly reduced by extending prophylaxis to 4–6 weeks.[58-60] There is a perceived risk of increased bleeding episodes and wound complications in patients who are treated with prolonged oral or subcutaneous anticoagulant therapy. Although the initial stimulus for DVT occurs during the perioperative period, clinically manifest DVT frequently develops later in the postoperative course, and the clinical course of clot formation differs between TKR and THR. In a large population-based study, the median time to diagnosis of symptomatic DVT post THR was 17 days, with three-quarters of symptomatic events after hospital discharge.[61] For TKR, the time course was different, with symptomatic DVT occurring frequently at 7 days postsurgery and approximately 40% of the events diagnosed postdischarge.

Because these findings suggest differences in the time frame of clot formation after THR and TKR, phase III studies have been initiated with dabigatran etexilate and rivaroxaban to determine the efficacy and safety of these agents in THR for up to 5 weeks.[23,41] Certainly, an oral agent in this extended prophylaxis setting would offer substantial convenience benefits over existing parenteral agents such as LMWH or fondaparinux sodium.

#### 3.1.8 Duration of Follow-Up

The lessons from the adverse events of liver dysfunction and cardiac events observed in the ximelagatran studies[10,62] have resulted in the regulators placing greater emphasis on longer follow-up of patients enrolled in major orthopaedic surgery studies. This will involve follow-up periods of up to 6 months in many of the ongoing phase III studies. This was not undertaken in studies of previous agents such as LMWH, and much closer scrutiny of liver function and cardiac events is being performed in current studies of new agents. In some cases, this has also influenced the timing of laboratory measurements associated with the study, in particular, liver function tests, which are performed after surgery but before drug administration of anticoagulant in order to better define the postsurgical baseline liver function.[30]

### 3.2 Clinical Trial Endpoints

#### 3.2.1 Definition of Efficacy Endpoints

The efficacy measure of an anticoagulant is the ability to decrease the number of VTE events within the period of treatment. Mandatory, bilateral, centrally adjudicated venography is currently the standard required to assess the incidence of DVT in confirmatory trials of new antithrombotic agents. Studies employ definitions of the efficacy endpoint that are a composite of venographic DVT, clinical events and VTE-related mortality, but overwhelmingly it is the number of asymptomatic DVT that

drive the efficacy outcomes. The primary importance of asymptomatic DVT, in particular distal DVT, has been a source of criticism of thromboprophylaxis trials in general. In particular, a review by the European Medicines Agency (EMEA) of their guidelines on "Clinical investigation of Medicinal Product for Prophylaxis of Intra- and Postoperative Venous Thromboembolic Risk" will hope to clarify the value of detecting asymptomatic distal DVT in clinical studies.[63] Relevant data come from the development programme of the FXa inhibitor, fondaparinux sodium; to counteract these criticisms, a *post hoc* analysis was conducted of the principle phase III findings in major orthopaedic surgery to determine the effect of fondaparinux sodium on an alternative composite efficacy outcome that had been defined previously by the American College of Chest Physician guidelines[15] as clinically relevant. When the composite outcome of any proximal DVT, symptomatic proven DVT or PE was calculated, the level of risk reduction was almost identical to that seen for the primary study outcome that incorporated asymptomatic distal DVT.[64]

#### Central versus Local Venogram Adjudication

Although venography is routinely undertaken at the clinical trial centre, it is common in thromboprophylaxis studies that the interpretation of the venogram for the purposes of the trial findings is undertaken by the lead investigators or by an independent venogram adjudication committee at a remote site. This is because venograms are challenging to interpret and this is highly dependent on the experience of the radiologist. The criteria used across studies differ and this can significantly impact on the efficacy assessment.[65,66]

The clinical studies of dabigatran etexilate and rivaroxaban used an identical central venogram adjudication committee (Gothenburg adjudication centre) [table II] with the same rigorous and specific venogram adjudication techniques that had been previously employed in studies with ximelagatran.[52,54] Results from this adjudication centre show remarkable consistency in the VTE rates in these studies for the comparator drug, enoxaparin sodium, ranging from 44% to 46% in patients undergoing TKR.[52,54] These event rates differed from those reported in two North American TKR trials,[67,68] which reported VTE rates of 23–28% in patients receiving enoxaparin sodium. The most likely explanation for the difference in event rates is the more detailed, bilateral assessment for DVT that required visualisation of muscular calf and anterior tibial veins.

#### Use of Ultrasound

Compression ultrasound (CUS) has been suggested as a noninvasive and less cumbersome alternative to venography in major orthopaedic studies and a current review of trial design guidelines by the EMEA[63] has suggested that the role of CUS and venography in new drug development should be clearly delineated. A recent substudy of the two phase IIb trials of rivaroxaban compared the findings of mandatory bilateral venography,[69] performed 5–9 days after surgery with CUS performed on the same day, by sonographers blinded to the venography result. In all, 870 matching pairs of evaluable venograms and CUS videos were obtained. The observed prevalence of any DVT was 19% with venography and 13% with CUS, but the sensitivity of CUS was poor, with a low number of true positives detected. This suggests that CUS is not a viable technique to replace venography for the screening of DVT early after major orthopaedic surgery in confirmatory trials of novel antithrombotic agents.

### *3.2.2 Definition of Safety Endpoints*

The greatest hurdle for any developmental oral anticoagulant to overcome is to meet the demand for less anticoagulant-related bleeding, but it will be a hurdle worth passing as this safety aspect is of paramount importance to surgeons and physicians. The design of recent clinical trials evaluating new anticoagulant compounds reflects the view that, although there remains an unmet need for improved efficacy, in particular with regards to VTE mortality, its importance has decreased, as physicians concentrate on the bleeding profile of new compounds. Not only does bleeding take precedence over efficacy in terms of unmet needs, efficacy is actually not rated as an unmet need. The launch of fondaparinux

sodium serves as an example to illustrate the lesser relevance of improved efficacy as an unmet need. The initial trial strategy to show superior efficacy of the parenteral anticoagulant fondaparinux sodium over LMWH in its launch indication of VTE prophylaxis following major orthopaedic surgery was not successful from a marketing point of view, with limited uptake of the new compound, despite convincing superiority in terms of efficacy because of the question of greater major bleeding events. There is a perception that there was a focus on the efficacy of fondaparinux sodium and not on the bleeding. Thus, it seems that a strategy of equivalent efficacy, increased convenience and less bleeding is the ideal requirement for a new anticoagulant.

A clear definition of how bleeding endpoints in anticoagulation studies should be defined is lacking, making the comparison of aspects of bleeding reported in different studies difficult. While major bleeding is often a well recognised term to measure perioperative bleeding, other terms such as overt bleeding, serious bleeding, nonmajor, clinically relevant bleeding, excessive bleeding, bleeding index and minor bleeding are often used on their own or combined with major bleeding into composite bleeding endpoints. This has created some confusion among surgeons not familiar with the details of thromboprophylaxis studies on how to interpret and apply these findings.

In the dabigatran etexilate and rivaroxaban studies, major bleeding was defined as (i) clinically overt bleeding associated with a ≥20 g/L fall in haemoglobin; (ii) clinically overt leading to transfusion of ≥2 units packed cells or whole blood; (iii) fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding; or (iv) bleeding warranting treatment cessation or leading to reoperation. Clinically significant bleeding events (termed clinically relevant, nonmajor bleeding in the rivaroxaban studies) were defined as: (i) spontaneous skin haematoma >25 $cm^2$; (ii) wound haematoma >100 $cm^2$; (iii) epistaxis >5 minutes; (iv) spontaneous macroscopic haematuria; (v) bleeding lasting >24 hours if associated with an intervention; (vi) spontaneous rectal bleeding; (vi) gingival bleeding >5 minutes; and (vii) any other bleeding event judged as clinically significant by the investigator. Minor bleeding events were defined as those not fulfilling the criteria of major or clinically significant bleeding. All studies used a centralised, independent committee to classify all bleeding events (table II).

All the new agents described in this review are predominantly renally excreted. This has implications in elderly patients who may have impaired renal function and then may require either dose adjustment or increased dose administration intervals. As has been reported in the ximelagatran studies, effects on liver function are being closely observed and reported in all ongoing studies. Similarly, drug interactions will require close observation in ongoing studies.

## 4. Clinical Indications Beyond Orthopaedic Surgery

The primary aim in the development of new, oral anticoagulants is for a replacement for warfarin (table III). Warfarin is widely used as an oral anticoagulant, but its well documented limitations and frequent association with adverse events leading to hospitalisations, undermine its use, especially in the largest market for warfarin, namely in SPAF. The development of new, oral anticoagulants without a monitoring requirement will substantially improve the quality of life of patients receiving long-term anticoagulation and several agents are now being investigated for the SPAF indication, in addition to acute VTE treatment and secondary prevention of VTE.

Progression from the orthopaedic prophylaxis studies described in sections 2 and 3, to the SPAF and VTE treatment indications requires careful evaluation to define the correct therapeutic range in these patient populations. In this regard, new anticoagulants usually undergo the same phase II dose-ranging assessment as previously described. Dose-ranging studies are often performed either in patients with symptomatic VTE, which enables some indication of efficacy response based on recurrence rates, or in patients with atrial fibrillation (AF) who are at low risk for stroke, which enables long-term

safety data of the new anticoagulant. More detailed discussion of the issues surrounding these studies is beyond the scope of this article. Nonetheless, several completed or ongoing studies are briefly mentioned here.

The safety and antithrombotic efficacy of three doses of dabigatran etexilate (50, 150 or 300mg twice daily) was investigated in 502 patients with AF.[70] Patients were randomised to 12 weeks treatment with dabigatran etexilate. The 150mg dose achieved a similar level of coagulation activity as higher doses and as warfarin, with minimal elevation of liver enzymes. The phase II results formed the basis for a large phase III trial (RE-LY) which is now investigating two dosages of dabigatran etexilate (200–300mg daily) versus warfarin in 15 000 patients.[71] Similarly, phase II SPAF studies with rivaroxaban[41] and odiparcil[72] are ongoing. The odiparcil study will evaluate the pharmacodynamic and pharmacokinetic response and safety and tolerability of three doses (250, 375 and 500mg) in addition to aspirin in >600 patients.

Several VTE treatment studies are also ongoing. Apixaban is undergoing investigation for the treatment of DVT in a phase II study involving 500 patients compared with LMWH and fondaparinux sodium,[73] while a phase III study is comparing dabigatran etexilate (150mg twice daily) with warfarin (following initial treatment for 5–10 days with a parenteral anticoagulant) for the short and long term treatment of symptomatic VTE in >2500 patients.[74]

## 5. Conclusion

The orthopaedic surgery model is the testing ground of choice for new anticoagulant agents. Two new orally available compounds, dabigatran etexilate and rivaroxaban, have entered late stage clinical development using this model as the first step in a wider development programme. Many factors, especially the timing of first dose and the approaches taken to measure efficacy and safety, influence the trial findings and an intimate knowledge of these issues is important to understand fully the relevance of the trial results. Phase II findings have been reported with other compounds and some of these are expected to proceed to late-stage development. The findings from the ongoing phase III programmes of dabigatran etexilate and rivaroxaban will be critical in determining whether these agents will provide an oral anticoagulant that is efficacious and can be safely used without monitoring. If yes, the door opens to a much wider range of therapeutic indications, in particular SPAF, and this will signal the opening of a new vista in anticoagulant care

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