# Factor Xa Inhibitors in Acute Coronary Syndromes and Venous Thromboembolism

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**Abstract:** As an alternative to the inconvenient and labor intensive traditional anticoagulants, Factor Xa inhibitors may offer new options for the prevention and treatment of acute coronary syndromes (ACS) and venous thromboembolism (VTE). Fondaparinux, an indirect FXa inhibitor, has equivalent efficacy but decreased bleeding risk. It has been recommended by the American College of Cardiology (ACC)/American Heart Association (AHA) as the preferred anticoagulant in ACS patients with higher bleeding risk managed with a noninvasive strategy. Based on the composite results of several clinical trials, fondaparinux is also recommended for VTE prevention in the setting of major orthopedic surgery. Rivaroxaban, a direct FXa inhibitor, appears to have at least equal efficacy and safety to established anticoagulants in the prevention of VTE. With advantages such as oral administration and a wide therapeutic window, it may provide a useful alternative to current anticoagulants. Ongoing studies are exploring its use in treatment of VTE and ACS, as well as prevention of stroke among patients with atrial fibrillation. In this review, we examine the key recent studies on efficacy and safety of FXa inhibitors in ACS and VTE management.

## INTRODUCTION

For many years, routine clinical anticoagulant use has relied predominantly on vitamin K antagonists (e.g. warfarin), unfractionated heparin (UFH) and low molecular weight heparin (LMWH) for the prevention and treatment of venous thromboembolism (VTE) and acute coronary syndromes (ACS) (see Table **1**). However, these agents lack many of the characteristics of an ideal anticoagulant (see Table **2**). In the case of warfarin, the resource intensive monitoring required to maintain therapeutic levels and the unpredictable drug-drug and drug-food interactions equate to both clinical and financial disadvantages [1]. With regards to clinical safety, significant bleeding risks exist when levels are supra-therapeutic [2]. Regardless of proven efficacy at therapeutic levels, if patients find it difficult to reach those levels for practical reasons, then actual efficacy is diminished. Heparin is also resource intensive to administer, requiring intravenous (i.v.) or frequent subcutaneous (s.c.) delivery by healthcare staff, which is not cost-effective unless patients can be trained to self deliver their own medication [3].

Given these disadvantages, the advent of significant studies on Factor Xa (FXa) inhibitors, such as fondiparinux and more recently, rivaroxaban, have started to provide alternatives to our current approaches to VTE and ACS management (see Table **3**). FXa inhibitors function to decrease thrombin production by inhibiting the coagulation cascade upstream as shown in Fig. (**1**). Specifically, the clotting cascade begins at the site of a vascular wound, where tissue factor starts by serving as a cofactor for Factor VIIa, creating a complex that *via* activation of Factor IX, activates Factor X [4]. Factor Xa then forms a prothrombinase complex with cofactor Factor Va and anionic phospholipid from the activated cell surface. This complex subsequently activates prothrombin (Factor II) to thrombin (Factor IIa). Thus, through the inhibition of Xa, thrombin generation is inhibited, ultimately preventing clotting.

Two Factor Xa inhibitors will be reviewed here: the indirect FXa inhibitor, fondaparinux, and the first direct FXa inhibitor to reach phase III trials, rivaroxaban [5]. Other FXa inhibitors that are in earlier stages of investigation include apixiban, DX-9065a, Otamixaban, SR123781A, YM150, DU-176b, LY517717, PRT054021, YM-150, and GW-813893 [6, 7].

## INDIRECT FXA INHIBITOR: FONDAPARINUX

When fondaparinux was produced in 1988, it was the first in a new class of FXa inhibitor drugs [8]. It is a synthetic pentasaccharide that binds to antithrombin (AT), causing a conformational change in AT that significantly improves the ability of AT to selectively inhibit Factor Xa. This effectively inhibits thrombin generation, though the effect is indirect, as the structure of fondaparinux does not allow it to directly bind both AT and thrombin at the same time. It is thought that fondaparinux may offer a lower bleeding risk through the permission of trace thrombin activity [9].

Fondaparinux is also unique in that it has no action on any other coagulation factors except AT, unlike UFH and LMWH that act on a number of factors in the coagulation cascade. One of the major areas this becomes clinically relevant is with regards to platelet activity. With the use of UFH,

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**Table 1.    Comparison of Anticoagulants**

| Drug | Type | Delivery | Therapeutic Window | Half Life | Excretion | Dosing | Reversible |
|------|------|----------|--------------------|-----------|-----------|--------|------------|
| Warfarin | VKA | Oral | Narrow | 20-60 hrs | urinary | 1x daily | Yes |
| UFH | Heparin | IV or SQ | Wide | 1-1.5 hrs | urinary, RE | 2-3x daily | Yes |
| LMWH | Heparin | SQ | Wide | 4-6 hrs | urinary | 1-2x daily | Yes |
| Fondaparinux | Indirect FXa inhibitor | SQ | Wide | 17 hrs | urinary | 1x daily | No |
| Rivaroxaban | Direct FXa inhibitor | Oral | Wide | 5-9 hrs | urinary, fecal/biliary | 1x daily | Yes |

**Table 2.    Characteristics of an Ideal Anticoagulant**

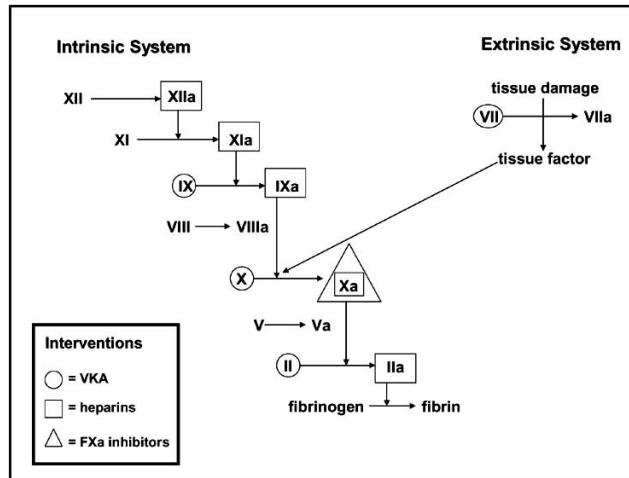| |
|---|
| Oral administration |
| Wide therapeutic window |
| Infrequent dosing requirements |
| Reversible |
| Minimal drug-drug interactions |
| Reasonable cost |
| Minimal side effects |
| Rapid onset of action |



**Fig. (1).** Pharmaceutical intervention targets in the coagulation cascade.

there is a risk of developing heparin-induced thrombocytopenia (HIT). HIT is caused by platelet-activating antibodies against platelet factor 4 (PF4)-heparin complexes, resulting in hypercoagulability requiring alternative anticoagulation [8]. The risk of HIT can be reduced by tenfold with the use of LMWH in place of UFH [8]. However, since fondaparinux has no interactions with platelets or platelet factor 4 at therapeutic doses, it is thought to not be associated with HIT [10]. Preliminary evidence suggests that the risk may not completely eliminated, especially at supratherapeutic

doses, when fondaparinux may interfere with PF4 binding to platelets, HIT antibody binding to PF4-heparin complexes, and/or activation of platelets by HIT antibodies [8, 11]. At the present time, large *in vivo* trials are still necessary to determine if fondaparinux can provide an appropriate treatment in the case of HIT; it is not yet approved by the FDA for HIT treatment [12]. Note that fondaparinux can also be used in patients with heterozygous AT deficiency (unlike heparins) because in prophylactic doses, it remains completely bound to AT despite its concentration which is ten times less than the physiologic concentration of AT [9]. Unlike heparin, it does not need to consume AT in order to inhibit both FXa and thrombin.

Fondiparinux is delivered subcutaneously and eliminated renally (thus contraindicated in patients with a creatinine clearance <30 ml/min). With a half-life of 17 h (as compared to the 1-2 h half-life of UFH and 3-5 h half-life of LMWH), it can be administered once daily. With a wide therapeutic window, close monitoring of levels is not usually required. If desired, an anti-factor Xa assay specifically designed for fondaparinux can be used for monitoring, but otherwise, fondaparinux only partially prolongs PTT at therapeutic doses [13]. It does not affect PT, bleeding time, platelet function or fibrinolysis [13]. It is not inactivated by protamine and has no known effective antidote [14]. Thus, while it does not solve the shortcomings of mainstream anticoagulants in terms of ease of delivery and it also lacks reversibility, it does minimize dose monitoring and frequency of delivery significantly.

**FONDAPARINUX IN ACS**

Fondiparinux currently has indications both in ACS and VTE. According to the 2007 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for management for unstable angina (UA)/non-ST elevation myocardial infarction (NSTEMI) [2], fondaparinux is recommended as the preferred anticoagulant in patients with higher bleeding risk managed with a noninvasive strategy. Its indications for noninvasive strategy use are based on data from the Organization to Assess Strategies for Ischemic Syndromes (OASIS) trials indicating a possible higher catheter thrombosis risk when percutaneous coronary intervention (PCI) is undertaken for ACS patients. The OASIS-5 trial was a randomized controlled trial comparing fondaparinux with

**Table 3.    Summary of Published Factor Xa Inhibitor Studies**

| Fondaparinux | | | |
|---|---|---|---|
| **Trial** | **Indication** | **Comparator** | **Superior Outcome** |
| OASIS-5 | ACS | Enoxaparin | Fondaparinux |
| OASIS-6 | ACS | Enoxaparin | Fondaparinux (except catheter thrombosis) |
| ASPIRE | ACS with PCI | UFH | Fondaparinux |
| PENTAMAKS | VTE prevention | Enoxaparin | Fondaparinux |
| PENTATHLON | VTE prevention | Enoxaparin | Fondaparinux |
| EPHESUS | VTE prevention | Enoxaparin | Fondaparinux |
| PENTHIFRA | VTE prevention | Enoxaparin | Fondaparinux |
| PEGASUS | VTE prevention | Dalteparin | Comparable |
| MATISSE | VTE treatment | Enoxaparin | Fondaparinux |
| **Rivaroxaban** | | | |
| **Trial** | **Indication** | **Comparator** | **Superior Outcome** |
| RECORD1 | VTE prevention | Enoxaparin | Rivaroxaban |
| RECORD2 | VTE prevention | Enoxaparin | Rivaroxaban |
| RECORD3 | VTE prevention | Enoxaparin | Rivaroxaban |
| RECORD4 | VTE prevention | Enoxaparin | Rivaroxaban |
| ODIXa-DVT | VTE treatment | VKA w/Enoxaparin bridge | Equivalent |
| EINSTEIN-DVT | VTE treatment | VKA w/Enoxaparin bridge | Rivaroxaban |

enoxaparin among 20,078 ACS patients with the composite outcome of death, MI or refractory ischemia at 9 days [15]. Rates of bleeding at 9 days were significantly lower with fondaparinux (2.4% compared with 5.1%, P<0.00001). The results indicated non-inferiority of fondaparinux in terms of ischemia, with a greater net clinical benefit (death, MI, stroke, major bleeding: 8.2% fondaparinux *vs.* 10.4% enoxaparin, p<0.004). Primary composite events were also lower among fondaparinux patients followed at 6 months (12.7% fondaparinux *vs.* 14.8% enoxaparin, p=0.013). OASIS-6 compared fondaparinux to either UFH or placebo in patients with ST-elevation myocardial infarction (STEMI) [16]. Fondaparinux treated patients had a 15% relative risk reduction in the incidence of death or recurrent MI at day 30 (9.7% *vs.* 11.2%, p=0.0008), with similar incidence of bleeding in both arms. It was noted however, that patients who underwent PCI did have a higher incidence of catheter thrombosis, thus influencing current guidelines for fondaparinux use in patients managed by a noninvasive strategy, and the continuation of UFH during angiography/PCI. However, the data on risks during invasive strategies was not supported by the smaller ASPIRE trial of 350 patients undergoing urgent or elective PCI, almost all receiving stents. This trial found no significant difference in efficacy or safety between fondaparinux and UFH [17]. Further studies will be needed to clar-

ify the risks of fondaparinux use in the invasive setting. Limited data support the cost-effectiveness of fondaparinux as well, but this requires further investigation [18].

## FONDAPARINUX IN PREVENTION AND TREATMENT OF VTE

Fondaparinux is currently approved by the Food and Drug Administration for VTE prevention following hip fracture surgery, total hip replacement, total knee replacement, and major abdominal surgery [1]. Guidelines from the American College of Chest Physicians (ACCP) recommend VTE prophylaxis for hip or knee arthroplasty patients with either LMWH, fondaparinux or warfarin. For patients undergoing hip fracture repair, fondaparinux is the preferred agent. Extended duration (4-5 week) prophylaxis is recommended for patients undergoing hip arthroplasty or hip fracture repair, however, knee arthroscopy does not require routine pharmacologic VTE prophylaxis [19].

These recommendations were predominantly based on the results of a meta-analysis of 4 multicenter, randomized, double-blind phase III trials, all of which examined prevention of VTE after major orthopedic surgery [20]. Among them, PENTAMAKS [21] studied elective major knee surgery patients, EPHESUS [22] and PENTATHLON [23, 24]

studied elective hip replacement surgery patients, and PENTHIFRA [25] studied patients undergoing hip fracture repair. In all cases, fondaparinux was administered at a dose of 2.5 mg/day, with therapy beginning 4 to 8 h after surgery. PENTATHLON and PENTAMAKS compared it to twice-daily 30 mg enoxaparin, while the others compared it with once-daily 40 mg enoxaparin. The meta-analysis of the 7344 total patients studied concluded that use of fondaparinux, as compared with enoxaparin, was associated with reduced risk of VTE by day 11 (6.8 *vs.* 13.7%, odds reduction of 55.2%, 95% CI 45.8-63.1%). There was no significant difference in pulmonary embolism among the groups. There was no significant difference in outcomes of major bleeding or death in the EPHESUS, PENTATHLON, or PENTHIFRA trials, however, the PENTAMAKS trial did show 11 major bleeding episodes among the fondaparinux group compared with 1 episode among the enoxaparin group (n=1049, p=0.0006). However, there was no significant difference in incidence of bleeding leading to death, re-operation, or bleeding into a critical organ. In summary, fondaparinux has been shown to be as effective as other first line agents for VTE prophylaxis among orthopedic surgery patients, and specifically in hip fracture patients, is the preferred agent.

Other studies of note include PEGASUS, that compared fondaparinux with dalteparin for VTE prevention in high risk abdominal surgery patients [26]. Overall, both groups showed similar efficacy and safety, and in a subset of patients with malignancy, fondaparinux patients had an improved VTE prevention profile. More studies will need to explore the reasons for improved efficacy among the subset of patients with malignancy.

In terms of therapy for both DVT and PE, the MATISSE trials showed similar efficacy of once-daily fondaparinux to twice-daily LMWH [27]. Of the 1098 patients treated with fondaparinux, 3.9% had recurrent thrombotic events over 3 months compared with 4.1% of 1107 patients treated with enoxaparin (absolute difference -0.15 percentage points, [95% CI -1.8 to 1.5 percentage points]). Major bleeding was comparable, 1.1% for fondaparinux patients *vs.* 1.2% for enoxaparin patients (-0.1, [-1.0 to 0.8]). Mortality rates were 3.8% and 3.0% respectively (0.8, [-0.8-2.3]).

Further investigation is now underway on an analogue of fondaparinux called idraparinux [28-31]. This novel agent has a half-life of approximately 80 h, making it possible to be dosed as a once weekly oral drug. The first phase III Amadeus trial for stroke prevention among patients with atrial fibrillation was prematurely stopped after the idraparinux patients showed significantly higher rates of bleeding than VKA patients. The investigators believe it may still provide a safe profile at lower doses, thus requiring further studies to evaluate this possibility [32].

## DIRECT XA INHIBITOR: RIVAROXABAN

The success of fondaparinux as a prophylactic and therapeutic agent in ACS and VTE paved the way for further development of selective Xa inhibitors. In particular, direct Xa inhibitors have recently become high profile because of their oral administration, absence of monitoring required for dosing, and phase III studies of efficacy in prevention of VTE. Direct Xa inhibitors range from natural inhibitors, such as

antistasin from leeches and NAP59 from the nematode Ancylostoma caninum [8], to synthetic inhibitors, most notably rivaroxiban.

The efficacy of rivaroxiban is the most studied among the many synthetic direct FXa inhibitors currently being developed. Rivaroxiban is an orally active, highly selective, direct inhibitor of factor Xa. Oral bioavailability of rivaroxaban is approximately 80%, and its half-life is 5-9 h [33].

In contrast to the indirect FXa inhibitors, direct FXa inhibitors such as rivaroxaban inactivate not only free FXa, but also FXa bound to platelets within the prothrombinase complex. Note that this complex is protected from inhibition by AT bound inhibitors, such as indirect FXa inhibitors [1]. Small molecule inhibitors such as rivaroxaban may also have an advantage regarding inhibitory activity because they can diffuse more easily into the FXa active site within the prothrombinase complex. A recent *in vitro* study comparing rivaroxaban with other anticoagulants showed that rivaroxaban (like fondaparinux) did not cause platelet activation or aggregation in the presence of HIT antibodies, unlike enoxaparin and UFH [34]. It also did not release PF4 or interact with PF4. While more extensive studies are still necessary, this preliminary data suggests that FXa inhibitors may also be a viable option for patients with HIT [34].

Pharmacokinetic and pharmacodynamic studies on daily *vs.* twice daily dosing of rivaroxaban were studied through the collection of blood samples from patients in 2 phase IIb trials investigating thromboprophylaxis after total hip replacement [35]. As expected, age and renal function affected clearance and body surface area affected volume of distribution. The 90% intervals for maximum and minimum plasma concentrations for the once *vs.* twice daily overlapped, despite higher maximum and lower minimum plasma concentrations for the once daily dosing. PT correlated linearly with plasma concentration of rivaroxaban in both studies. These findings concluded that once daily dosing should be used for all phase III trials. These findings were supported by another pharmacokinetic and pharmacodynamic study of 1009 patients in 2 phase II double-blind randomized studies of total hip and knee replacement patients which also supported the predictability of fixed dosing of rivaroxaban [36]. A third dose-ranging study of hip replacement patients showed that a 10-mg dose of rivaroxaban once daily was suitable for investigation for phase 3 trials [37]. More specifically, rivaroxaban pharmacokinetics and pharmacodynamics were also studied in a small dose escalation study of healthy elderly patients [38]. A single-blind, placebo-controlled study of 48 patients aged 60-76 compared 30, 40, and 50 mg daily dosing. Peak plasma concentrations were reached 4 h after administration. Bioavailability was greater among the 40 mg compared to 30 mg group, but did not increase further at 50 mg. Pharmacodynamic effects (such as FXa inhibitor activity and elevation of PT time) followed a parallel pattern of FXa inhibitor activity greater among 40 mg compared with 30 mg group, but not higher among 50 mg patients. For example, FXa inhibitor activity increased from 68% at 30 mg to 75% at 40 mg, without further increase at 50 mg. Adverse events were mild with a rate only similar to placebo even at 50 mg. No gender differences were found. However, given the small size of this study, only trends can be observed.

## RIVAROXABAN IN PREVENTION OF VTE

The most significant data on the use of rivaroxaban is for VTE prevention in postoperative orthopedic patients. Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism 1 (RECORD1) [39], was a phase III, randomized, multinational, double-blind trial conducted to assess the efficacy and safety of a postoperative 10 mg oral dose of rivaroxaban given once daily (starting after surgery) as compared with a 40 mg s.c. once-daily dose of enoxaparin (starting the evening before surgery) for extended (5 week) thromboprophylaxis after total hip arthroplasty. The primary efficacy outcome was DVT, nonfatal PE or death at 36 days, which occurred in 1.1% (18/1595 patients) of the rivaroxaban group compared to 3.7% (58/1558 patients) of the enoxaparin group (2.6% absolute risk reduction, p<0.001). The secondary efficacy outcome was major VTE, which occurred in 0.2% of the rivaroxaban group compared to 2% of the enoxaparin group (absolute risk reduction 1.7%, p<0.001). The primary safety outcome was major bleeding, which occurred in 0.3% of the rivaroxaban group compared to 0.1% of the enoxaparin group (p=0.18). This showed that rivaroxaban had an improved efficacy profile to enoxaparin for thromboprophylaxis with an equivalent bleeding profile. The data from this study was confirmed in RECORD2, a similar double-blind, randomized controlled trial comparing extended use of rivaroxaban to short term enoxaparin for prevention of VTE after total hip arthroplasty. The key distinguishing factor of RECORD2 compared to RECORD1 is that the enoxaparin dose was given for only 10-14 days followed by placebo in RECORD2, as opposed to being continued for the entire 5 weeks during which rivaroxaban was continued. The primary efficacy outcome was the composite of DVT, nonfatal PE and all-cause mortality up to postoperative day 30-42, which was found in 2% of rivaroxaban patients (17/864 patients) compared with 9.3% (81/869 patients) in the enoxaparin group (absolute risk reduction 7.3%, p<0.0001). The bleeding profiles were comparable (rivaroxaban 6.6% *vs.* enoxaparin 5.5%, p=0.25) [40].

RECORD3 study group compared rivaroxaban *vs.* enoxaparin for thromboprophylaxis after total knee arthroplasty [41]. This study showed that the primary efficacy outcome of DVT, nonfatal PE or death within 13-17 days post surgery occurred in 9.6% (79/824) of rivaroxaban patients and 18.9% (166/878) of enoxaparin patients (absolute risk reduction of 9.2%, p<0.001). Major VTE occurred in 1% of rivaroxaban patients compared to 2.6% of enoxaparin patients (absolute risk reduction 1.6%, p=0.01). Major bleeding occurred in 0.6% of rivaroxaban patients *vs.* 0.5% of enoxaparin patients. The incidence of drug-related adverse events (mostly gastrointestinal) was 12% in the rivaroxaban group compared with 13% in the enoxaparin group.

RECORD4 trial of 3148 patients compared rivaroxaban with enoxaparin for 10-14 days of prophylaxis after total knee replacement. Patients were followed for 40 days, at which time venograms of all extremities were performed. Total VTE events (DVT, nonfatal PE, and all-cause mortality) was significantly reduced in the rivaroxaban group (6.9% *vs.* 10.1%, p=0.012). Major bleeding was not significantly different between the 2 groups [42].

In terms of treatment of DVT, there is also evidence that rivaroxaban may be equivalent to enoxaparin bridge to a VKA. In the ODIXa-DVT study (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients with Acute Symptomatic DVT), patients with symptomatic DVT were randomised to either rivaroxaban (doses ranging from 10mg BID to 30 mg BID) or VKA with enoxaparin bridge until therapeutic INR was achieved. The primary efficacy endpoint was improvement in thrombotic burden at day 21 as assessed by ultrasound. It was found that this endpoint was achieved in 43.8% to 59.2% of rivaroxaban patients (variable depending on dose) compared with 45.9% of enoxaparin/VKA patients. No significant dose response relationship was found among rivaroxaban patients (p=0.67). Major bleeding events occurred in 1.7-3.3% of rivaroxaban patients compared to no major bleeding events among enoxaparin/VKA patients [43].

The non-inferiority of rivaroxaban in the ODIXa-DVT study was supported by the EINSTEIN-DVT phase II dose ranging study that compared 4 rivaroxaban doses and LMWH followed by VKA to assess the optimal dose of rivaroxaban for the treatment of DVT [44]. A total of 543 patients with acute DVT received rivaroxaban 20, 30 or 40 mg once-daily or comparator for 84 days. The primary efficacy outcome of decreased thrombotic burden and symptomatic VTE complications occurred in 6.1% (CI 2.5-12.1%), 5.4% (CI 2-11.3%) and 6.6% (CI 2.9-12.6%) of the rivaroxaban 20, 30, and 40 mg treatment groups, respectively, and in 9.9% (CI 4.9-17.5%) receiving standard therapy. The main safety outcome of major and clinically relevant bleeding occurred in 5.9% (CI 2.6-11.3%), 6.0% (2.6-11.4%), and 2.2% (0.5-6.3%) of the rivaroxaban 20, 30, and 40 mg treatment groups, respectively, and in 8.8% (4.6-14.8%) during standard therapy. This study concluded that DVT treatment may be best served by 20 mg daily dosing, given the similar clot resolution and safety profile of the various doses studied.

Currently, there are trials in phase III for prevention of stroke in high risk atrial fibrillation patients (ROCKET AF) [45, 46], as well as phase II trials of patients post-ACS (ATLAS ACS TIMI 46 study) [47].

## APIXABAN

The next most promising direct FXa inhibitor after rivaroxaban is apixaban. The Botticelli DVT dose ranging study [48] of 520 patients randomized to 3 different doses of apixaban compared with LMWH/VKA showed comparable outcomes (in terms of recurrent symptomatic DVT and asymptomatic detectable ultrasound or VQ scan changes). No dose response to apixaban was found. Presented at the European Society of Cardiology Conference 2008 (not yet published[1]), the subsequent APPRAISE-1 dose guiding trial studied 4 doses of apixaban given over 26 weeks (either as a 10 mg daily or 2.5 mg BID dose) compared with placebo among 547 patients with ACS within 7 days who were already receiving either aspirin or dual-antiplatelet therapy. Apixaban patients showed a trend towards a reduction in clinically important ischemic events, but with a dose-

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[1] Alexander J, *et al*. Safety of the Factor Xa Inhibitor, apixaban, in combination with antiplatelet therapy after acute coronary syndromes: Results of the APPRAISE-1 dose guiding trial. Presentation at European Society of Cardiology Conference, 2008 Sep.

dependent increased bleeding risk. These initial promising results will require more studies to further evaluate apixaban's potential to safely reduce recurrent events in patients with ACS.

## SUMMARY

Growing evidence for the efficacy and safety of both indirect and direct FXa inhibitors is supporting them as viable alternatives to the traditional anticoagulants. For today's clinician, fondaparinux is already recommended as first-line for VTE prevention among hip fracture patients, and approved by the FDA for hip and knee arthroplasty and abdominal surgery. It is also recommended for ACS in the absence of invasive management. However, for patients treated with fondaparinux undergoing PCI, continuation of UFH is still recommended given the increased risks of catheter thrombosis with fondaparinux alone. On October 19th, 2008, there were 17 clinical trials on fondaparinux in progress registered with clinicaltrials.gov. Future directions for fondaparinux studies include further investigation of catheter-associated thrombosis risk among ACS patients as well as efficacy among subsets of patient populations such as those with malignancy.

While showing promise in phase III clinical trials, rivaroxaban has yet to become standard of care in VTE or ACS management. Current data suggests that rivaroxaban may actually be more efficacious than enoxaparin for VTE prevention in major orthopedic surgery with an equivalent bleeding profile. In terms of DVT treatment, rivaroxaban offers at least equivalent outcomes compared with enoxaparin bridge to VKA, with incongruent evidence from different studies on increased bleeding risk. On October 19th, 2008, there were 6 clinical trials on rivaroxaban in progress registered with clinicaltrials.gov. Future directions for studies on rivaroxaban include its role in preventing stroke among atrial fibrillation patients and efficacy for ACS treatment.

The perfect agent for ACS and VTE management prevents coagulation without excess risk of bleeding, can be taken orally, does not require frequent monitoring because of a wide therapeutic range and good safety profile, and is not influenced by drug-drug interactions. The agents reviewed here, fondaparinux and rivaroxaban, achieve many but not all of these goals. Further studies that may support their role in both prevention and treatment of VTE and ACS are eagerly awaited.

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