# Fondaparinux – evolution or revolution in anticoagulant care?

**Mark Crowther, Wendy Lim**

Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Thrombosis, manifested clinically as myocardial infarction and ischemic stroke, remains a leading cause of death, hospitalization and long-term disability in Europe and North America. The costs associated with the prevention and treatment of thrombotic complications are enormous, consuming many billions of dollars each year. In addition to being highly prevalent in the developed world, these conditions are also of increasing importance in developing countries. Although primary prevention of such disorders is ideal, many patients with atherosclerotic vascular disease are recognized as having this disease at the time of an acute thrombotic event. As a result, increasing the safety and efficacy of anticoagulant therapy as an adjunct to the treatment of the acute thrombotic complications of atherosclerosis is of critical and increasing importance.

Anticoagulant management has advanced over the last 30 years as a result of improvements in our understanding of the mechanism of blood coagulation. Blood coagulation is a complex and tightly regulated process which produces physiologic hemostasis under normal circumstances and pathological thrombosis when inappropriately activated or improperly controlled. For many years, the two main anticoagulants in clinical practice were warfarin and heparin. Warfarin reduces the blood's coagulant potential through reduction in the levels of the vitamin K dependent clotting factors, while heparin catalyzes antithrombin-mediated inactivation of the same clotting factors.

Heparin was first used therapeutically more than 50 years ago and, despite this, remains the standard anticoagulant in many clinical situations. In the 1970s and early 1980s, efforts were made to improve the pharmacokinetic profile of unfractionated heparin (UFH) after it was recognized that the long heparin chains were subject to nonspecific protein binding which resulted in heparin's variable anticoagulant effect. This nonspecific binding is due to a charge effect, and blood researchers hypothesized that by reducing the charge on heparin chains, nonspecific protein binding would be reduced, which would result in a product with a more predictable anticoagulant effect for any given dose. This resulted in the development of the low molecular weight heparins (LMWHs), which are the products of chemical or enzymatic depolymerization of UFH. Although the LMWHs demonstrate more predictable pharmacokinetics than UFH, it was subsequently noted that the vast majority of LMWH chains did not have any anticoagulant potential. Only those low molecular weight fragments containing a specific five sugar sequence (known as pentasaccharide) were found to catalyze thrombin-mediated inactivation of coagulation factors.

LMWHs have a favorable pharmacokinetic profile. As a result of reduced nonspecific protein binding, a given dose of LMWH produces a much more predictable anticoagulant effect (as measured using anti-Xa heparin levels) compared to UFH. However, LMWHs do retain other characteristics of UFH which might make them less desirable, including the fact that they are animal-derived (rather than chemically synthesized), and they do retain some degree of nonspecific protein binding. Importantly, because LMWHs are manufactured using a heterogeneous group of chemicals, batch to batch variability is a real issue in the manufacturing of LMWHs. In part to deal with these issues, the pentasaccharide sequence which produces the true "anticoagulant effect" of both UFH and LMWH was chemically synthesized and has been produced as a pharmaceutical product. This drug, known as fondaparinux, has been evaluated in clinical trials compared to standard anticoagulant therapy for prophylaxis in orthopedic surgery [1] and medical patients [2], in the treatment of acute venous thromboembolism [3,4] and most recently in the treatment of patients with acute coronary syndromes [5,6].

Fondaparinux, due to its short chain length, is unable to inactivate any of the coagulation factors except factor Xa. As a result, it does not produce predictable effects in the commonly available coagulation monitoring tests. Fondaparinux can only be reliably measured using anti-Xa fondaparinux levels, which are neither widely available nor have target ranges been validated. As a result, the drug is administered without the capacity to monitor its effect. The inability to monitor the anticoagulant effect of fondaparinux may be an issue in patients with impaired renal function because fondaparinux is highly dependent on the kidneys for its clearance (a side effect of its lack of nonspecific protein binding since it is this binding which hastens the clearance of heparin through extra-renal mechanisms). Therefore, there is a risk of bioaccumulation when fondaparinux is used in patients with impaired renal function and its use in such patients should be undertaken

**Correspondence to:**
Mark Crowther, MD, MSC, FRCPC, Department of Medicine, McMaster University, St. Joseph's Hospital, room L208, 50 Charlton Ave. East, Hamilton, Ontario, Canada, L8N 4A6, phone: 001-905-521-6024, e-mail: crowthrm@mcmaster.ca
**Received:** April 30, 2007. **Accepted in final form:** May 9, 2007.
**Conflict of intereset: none declared.**
Pol Arch Med Wewn. 2007; 117 (3): 65-67

with the greatest of care. This latter concern is heightened by the lack of an antidote for its anticoagulant effect.

In evaluating fondaparinux it was found to be generally superior to the "standard comparative therapies" used in orthopedic prophylaxis, such as enoxaparin or warfarin [7], however considerable controversy continues over whether this effect was truly due to a better anticoagulant effect or was due to the earlier implementation of fondaparinux when compared to the "comparative therapies"[8].

In treating deep vein thrombosis and pulmonary embolism, fondaparinux at doses of 5 to 10 mg per day (based on the patients' weight category) followed by warfarin was shown to be equivalent to standard therapy with therapeutic dose LMWH followed by warfarin [3,4].

On this background the OASIS V study was performed [5]. This highly innovative trial compared prophylactic doses of fondaparinux (less than one half of the standard dose used in the treatment of most patients with acute venous thromboembolism) with the usual therapeutic dose of enoxaparin in patients with acute coronary syndromes without ST elevation. Overall, the two interventions were equivalently effective however as would be expected when comparing prophylactic with therapeutic dose anticoagulants, the risk of major bleeding was dramatically reduced with fondaparinux. Thus the number of patients with primary-outcome events (death, myocardial infarction or refractory ischemia at 9 days) was similar in the two groups (579 with fondaparinux [5.8%] vs. 573 with enoxaparin [5.7%]; hazard ratio (HR) 1.01, 95% confidence interval (CI), 0.90 to 1.13). Major bleeding at 9 days occurred less frequently with fondaparinux than enoxaparin (217 events [2.2%] vs. 412 events [4.1%]; HR 0.52; $P < 0.001$). This reduction in bleeding translated into a reduced risk of death at 30 days (295 vs. 352, $P = 0.02$). There was an increase in the risk of catheter-associated thrombosis with fondaparinux, which was likely due to the fact that, unlike heparin derivatives, fondaparinux is unable to block contact activation of the coagulation cascade as would be seen when flowing blood interacts with catheter surfaces.

Simultaneously, the results of the OASIS VI study were presented [6]. This study enrolled approximately 12 000 patients with ST segment elevation acute myocardial infarction from more than 400 hospitals in 41 countries. In this study, fondaparinux administered at a dose of 2.5 mg per day was initiated very early in the hospital course and given for up to eight days. It was compared with "usual care" which consisted of placebo for those patients in whom UFH was felt to not be indicated or UFH for two days followed by placebo in those patients in whom UFH was felt to be indicated. The main outcome measure was the composite of death or recurrent myocardial infarction at 30 days. The study found that death or recurrent myocardial infarction was more frequent in patients who received placebo (677 [11.2%] of 6056 patients compared with 585 [9.7%] of 6036 patients [HR 0.86, 95% CI 0.77 to 0.96; $P = 0.008$]). No benefit to fondaparinux was observed in patients undergoing percutaneous coronary interventions, although fondaparinux was found to be superior in patients receiving thrombolytic therapy or those receiving no reperfusion therapy. Consistent with the results of OASIS V, a trend towards reduced bleeding was seen in the patients allocated to fondaparinux.

These studies have potentially major impact on the way that anticoagulant therapy is delivered to patients with acute coronary syndromes. Firstly, in both studies, fondaparinux was at least as effective as its comparator in studies sufficiently large to conclude that the results are robust. Secondly, both studies address the toxicity of therapy insofar as hemorrhage and its complications are a frequently under-recognized effect of our current highly aggressive anticoagulant approach in patients with acute coronary syndromes. Bleeding, particularly anticoagulant-associated bleeding occurring in otherwise well medical patients, is associated with an increased risk of adverse outcomes including death and is associated with increased duration of hospitalization and the increased costs associated with hospital care [9]. Bleeding is potentially an avoidable complication as excessive anticoagulation is commonly seen in hospitalized patients [9].

In our own practice, fondaparinux is used in all patients undergoing surgical repair of a fractured hip. We administer fondaparinux for 10 days irrespective of the duration of hospitalization and follow with an alternate prophylactic anticoagulant if the patient remains significantly immobile after 10 days. This practice is based on a randomized controlled trial which demonstrated efficacy of fondaparinux for the prevention of deep vein thrombosis in patients undergoing hip fracture repair surgery [10]. We continue to use LMWH for other forms of orthopedic prophylaxis, but acknowledge that fondaparinux may be superior to our current strategies in many such patients. Given our extensive experience using LMWH transitioned to long-term warfarin for the treatment of acute venous thromboembolism and the lack of approval of therapeutic doses of fondaparinux in Canada, we continue to treat patients with acute venous thromboembolism with LMWH in preference to fondaparinux. Regionally, our cardiology program has recently changed from LMWH to fondaparinux for the management of patients with acute coronary syndromes. Patients undergoing percutaneous coronary interventions may receive UFH around the time of the procedure to address the observation that fondaparinux may be associated with catheter-associated thrombosis.

Should fondaparinux be used as first-line therapy in patients with acute coronary syndromes? The OASIS V study suggests that fondaparinux would be preferable to therapeutic dose enoxaparin, and many hospital centers have adopted this practice. However, the enthusiasm for its widespread adoption should be tempered by the following observations: 1) OASIS V was a single study with surprising results that ideally should be confirmed; 2) fondaparinux is not licensed or approved for the treatment of acute coronary syndromes in many jurisdictions and off-label use of such a medication may be problematic; 3) very wide variations in the cost of fondaparinux are

found between different countries and as a result, widespread implementation of fondaparinux may be cost-saving in some jurisdictions while in others, it could be significantly more expensive; 4) in centers with interventional cardiology and the ability to perform (primary) percutaneous coronary intervention, the potential for catheter-associated thrombosis may somewhat reduce the enthusiasm for the use of fondaparinux. However, this latter concern would probably be ameliorated by the use of UFH around the time of such procedures.

In summary, the authors of the OASIS V and OASIS VI study are to be congratulated on their bold decision to compare prophylactic dose fondaparinux with therapeutic dose enoxaparin. This study not only has the potential to change the way that many patients with acute coronary syndromes are treated, it also, by questioning standard therapeutic dogma, may lead to other innovative studies using "standard therapies" in different ways in the management of cardiovascular disease.

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