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REVIEW

Treatment Options in Acute Coronary Syndromes: Focus on Fondaparinux Sodium

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Abstract: Anticoagulants are the mainstay for treating thromboembolism and acute coronary syndromes (ACS). In comparison to heparin newer agents such as bivalirudin and fondaparinux have improved the outcome of ACS in patients managed by using an invasive or conservative strategy, respectively. Using antithrombotic therapy, however, we need to strike a careful balance between reducing ischemic events and running an increased risk of bleeding complications. Fondaparinux is the first selective inhibitor of the coagulation factor Xa that is commercially available for clinical use. This new drug was accepted for priority review by the Food and Drug Administration based on the positive results of two pivotal, phase III trials (OASIS 5 and 6) that evaluated its role in the treatment of patients with acute coronary syndromes. Fondaparinux was associated with a significantly lower rate of bleeding than enoxaparin in the first 9 days, and at 3 and 6 months, respectively, resulting in a lower long-term mortality and morbidity in comparison to enoxaparin. A small, but definite increase in the risk of catheter-related thrombosis has been found among patients undergoing percutaneous coronary interventions, which is ameliorated by administering unfractionated heparin during the procedure.

Keywords: acute coronary syndrome, fondaparinux, treatment options

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**Introduction**

Cardiovascular diseases are currently the leading cause of death in industrialized countries and it seems this will also hold true worldwide in the future. The term acute coronary syndrome (ACS) summarizes the instantaneous life-threatening manifestations of coronary artery disease, specifically, unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI), which are all associated with high mortality and morbidity. The common underlying pathophysiological cause of this progression is disruption or erosion of an atherosclerotic plaque and subsequent formation of an occluding thrombus, resulting in myocardial underperfusion. Percutaneous coronary intervention (PCI) plays a very important role in the treatment of ischemic heart disease. Since Andreas Gruntzig first described coronary angioplasty in a human, the technique, equipment, and associated pharmacotherapy have evolved substantially, and have significantly reduced the rate of periprocedural complications.

Anticoagulants are used to inhibit thrombus generation and/or activity, thereby reducing thrombus-related events. Ideally, an antithrombotic agent should reduce ischemic complications without increasing bleeding complications.

Unfractionated heparin (UFH) has been the standard of care for anticoagulation in patients with ACS in the recent past. However, limitations such as frequent monitoring, a narrow therapeutic window, heparin-associated thrombocytopenia, and, in particular, bleeding complications prompted an intensive search for new treatment options. The list of anticoagulants recommended as alternatives in the current guidelines has expanded, including superior anticoagulants such as the low-molecular-weight heparin enoxaparin, the direct thrombin inhibitor bivalirudin, and finally fondaparinux, an indirect selective Xa inhibitor. The purpose of this review is to consider the pharmacokinetic profile, recent clinical data, and the place fondaparinux has in treating patients with ACS.

**Mechanism of Action, Metabolism, and Pharmacokinetic Profile**

Fondaparinux sodium is the first representative of a new class of anticoagulant agents that target a single coagulation factor. It consists of a synthetic methoxy derivative of the natural pentasaccharide sequence with a molecular mass of 1,728 dalton. The quintessence—so to speak—of UFH is that it binds specifically and with high affinity to antithrombin, thereby inducing a conformation change which promotes an approx. 300-fold faster and selective inhibition of coagulation factor Xa. Whereas UFH contains a large fraction of anionic chains without AT binding capacity and which interact nonspecifically with a large number of plasma proteins, this is not the case for fondaparinux.

Positioned at the start of the common pathway of intrinsic and extrinsic coagulation, factor Xa is a very attractive target for inhibiting a single coagulation factor. It has been hypothesized that the selective inhibition of a coagulation factor above thrombin might represent a very attractive antithrombotic strategy as the amount of serine protease is amplified at each step of the cascade. The interaction of fondaparinux with Xa is reversible whereas the inhibition of factor Xa by antithrombin is irreversible. Fondaparinux can inhibit several molecules of Xa consecutively; however, when antithrombin is saturated with fondaparinux, no more interactions take place.

Fondaparinux inhibits thrombus formation and growth, but has no known effect on platelet function. Furthermore, by not inhibiting thrombin activity directly this agent might allow traces of thrombin to escape neutralization, thereby facilitating hemostasis and leading to a favorable safety profile with respect to bleeding. Fondaparinux’s mode of action is entirely mediated through antithrombin, which is responsible for the linear pharmacokinetic profile; thus, the resulting dose scheme is very simple. After subcutaneous administration, fondaparinux takes effect fast; it is totally resorbed, not metabolized, and then about 70% is eliminated unchanged via the kidneys. Its bioavailability is 100% and steady-state is reached after the third or fourth once-daily dose. Distribution of fondaparinux is probably limited to the vascular compartment only, with a volume of distribution of 7–11 liters. In young patients the elimination half-life is dose independent and lasts about 17 hours. In elderly patients it increases up to 21 hours, whereby impaired renal function can prolong the elimination half-life. Thus, once-daily administration, 2.5 mg s.c. qd for prophylactic, 7.5 mg s.c. qd for therapeutic anticoagulation, is effective without laboratory monitoring being required.
However, in patients with impaired renal function and a glomerular infiltration rate under 50 ml/min, a reduced dosage of 1.5 mg fondaparinux is recommended for thromboprophylaxis. In patients receiving an ACS dosage of 2.5 mg, fondaparinux can also be used also if the GFR >20 ml/min. Fondaparinux is not approved, however, in patients in whom the GFR is under 20 ml/min. Furthermore, for treatment of patients with venous thrombosis or lung embolism, dosage depends on body weight (and renal function). For patients who weigh under 50 kg, 5 mg s.c. qd is recommended and for patients who weigh above 100 kg, 10 mg s.c. qd is recommended. In this setting, fondaparinux is not approved for patients in whom the GFR is below 30 ml/min; if the GFR is between 30 and 50 ml/min, reducing the dose to 7.5 mg s.c. qd after an initial dose of 10 mg qd can be considered.4,7 The main reasons for using fondaparinux with caution are the increased bleeding risk associated with concomitant renal dysfunction and a body weight under 50 kilogram.

The role of fondaparinux in the management of heparin induced thrombocytopenia (HIT) is controversially discussed in literature and under experts today. There was an open-label, prospective pilot study of 7 patients with acute HIT supports fondaparinux as an alternative anticoagulant. Additionally, a total of 12 patients with HIT from a larger case study and retrospective cohort were successfully treated with fondaparinux. In the recently passed cases, fondaparinux might have caused a HIT. Most of the data exists in the form of case reports with differences in clinical scenarios and dosages of fondaparinux, which make the interpretation of these reports very difficult. The updated American College of Chest Physicians consensus guidelines now recognize fondaparinux as an option in the management of HIT; however, the level of evidence supporting this is of low quality. It requires further studies before it can be recommended or not.8

It has not been clearly established yet whether fondaparinux is safe in pregnancy or children. In 2004 Dempfle and colleagues treated five pregnant women with fondaparinux (2.5 mg s.c. qd) who required anticoagulant therapy and had developed severe cutaneous allergic reactions in response to low-molecular-weight heparin. No allergic reactions at injection sites, thromboembolic events, or abnormal bleeding were observed. Furthermore, no adverse effects in the newborns were reported. However, the current results of that case series indicate that fondaparinux may pass the placental barrier in vivo, resulting in measurable anti–factor Xa activity in umbilical-cord blood. Although the concentration of fondaparinux in umbilical-cord blood was well below the concentration required for effective anticoagulation, a potentially hazardous effect cannot be ruled out. Therefore, the use of fondaparinux in pregnant women should be limited to those for whom there are no obvious therapeutic alternatives, such as patients with heparin-induced thrombocytopenia type 2 or severe allergic reactions to heparin.9

Clinical Studies
UFH was and remains the most frequently used anticoagulant in the setting of ACS. A pooled analysis of six trials testing short-term UFH vs. placebo or untreated controls showed a significant risk reduction of 33% for death and MI (P = 0.045).10

Apart from being inexpensive, its antithrombotic effect can be fully neutralized with protamine sulfate. However, the therapeutic window is narrow and the pharmacokinetics are neither stable nor predictable, requiring frequent monitoring of the activated partial thromboplastin time (aPTT), with an optimal target level of 50–75 s, and possible dose adjustment. The elimination half-life depends on dosage (the higher the dosage, the higher the half-life), patient age, and renal function. At higher aPTT values, the risk of bleeding complications is increased, without showing further antithrombotic benefits.

Some advantages of low-molecular-weight heparins (LMWH), such as enoxaparin, have been identified as compared with UFH. Beside a higher bioavailability and longer half-life after subcutaneous administration, the risk of heparin-induced thrombocytopenia is considerably lower. Enoxaparin has been shown to be superior to UFH for noninvasive management strategies or in patients with ST-elevation myocardial infarction (STEMI) treated by thrombolytic therapy.11,12 Moreover recent review on efficacy and safety of enoxaparin in the setting of non-ST- elevation ACS (NSTEMI) showed that although bleeding was increased with enoxaparin, this increase was offset by a reduction in death or MI. The net clinical benefit in favour of enoxaparin
was evident among the STEMI population and was neutral among patients with NSTEACS.13

Bivalirudin, a direct thrombin inhibitor, represents another attractive alternative. Two large randomized trials have compared bivalirudin to a combination of UFH and anti GP IIb/IIIa inhibitors. Both studies showed that bivalirudin is as safe and effective as UFH, with fewer bleeding events under bivalirudin therapy in the setting of NSTEMI14 and lower mortality in the setting of STEMI treated by primary angioplasty.15

Fondaparinux was the first selective factor Xa inhibitor to receive Food and Drug Administration (FDA) approval for the prevention and treatment of venous thromboembolism. Extensive preclinical and clinical studies were conducted to evaluate this unique new drug. The thromboprophylactic efficacy and safety of fondaparinux were studied in more than 7,000 patients in four multicenter, prospective, randomized, double-blind, comparative studies (PENTHATLON, PENTAMAKS, EPHECUS, PENTHIRFA).16–19

Furthermore, in modelled cost-utility analyses conducted from a healthcare payer perspective in Spain, France and the US with a lifetime horizon, fondaparinux once daily was predicted to be cost effective compared to enoxaparin twice daily with regard to the incremental cost per QALY gained. In Spain and the US, fondaparinux dominated enoxaparin (ie, was less costly and more effective) and, in the French analysis, the incremental cost per QALY gained with fondaparinux versus enoxaparin was well within recommended thresholds. Results of short-term (6-month) cost analyses in the US and France also favoured fondaparinux over enoxaparin. In conclusion, in patients with NSTEACS receiving antiplatelet therapy, fondaparinux was cost effective relative to enoxaparin in cost-utility analyses in Europe and the US.20

According to earlier studies of patients with ACS or patients undergoing a PCI we can assume that fondaparinux is at least as effective as enoxaparin and maybe even safer than unfractionated heparin in the treatment of acute coronary syndromes.21

PENTUA, an earlier dose-finding study, compared four different regimens of fondaparinux (2.5 mg, 4 mg, 8 mg, and 12 mg, qd) with enoxaparin (1 mg/kg body weight, bid) in patients with ACS. No relevant dose-dependent differences in antiischemic or bleeding complications were observed. Surprisingly, the lowest rate of the combined endpoint of death, myocardial infarction, and refractory ischemia was found in the group receiving the lowest dosage of 2.5 mg fondaparinux (30%), representing a significant reduction of these adverse events compared to enoxaparin (40.2%). Considering those findings 2.5 mg fondaparinux were used in patients with ACS in subsequent studies.22

The OASIS (Organization to Assess Strategies in Acute Ischemic Syndromes) trials, two multicenter, doubleblind, randomized studies, contributed the most evidence for using fondaparinux in treating ACS. The OASIS-5 trial compared fondaparinux 2.5 mg qd and enoxaparin 1 mg/kg bid (qd for those with creatinine clearance <30 mL/min) in patients with ACS without ST-segment elevation. The strategy regarding other treatment options (invasive vs. non-invasive) was at the discretion of the treating physician. Primary endpoints were death, MI, or refractory ischemia at day 9. The secondary outcomes included individual components of the primary efficacy outcome at 30 days and 6 months. The primary safety outcome was major bleeding. Results showed that fondaparinux was not only not inferior to enoxaparin in terms of death, MI, or refractory ischemia at day 9, but it substantially reduced major bleeding and improved long term mortality and morbidity.

In OASIS-6 fondaparinux was shown to be superior to the comparator (UFH vs. placebo). A total of 12,092 patients were randomized to two strata, depending on whether heparin was indicated or not (in stratum 1 the comparator was placebo, in stratum 2 UFH). The results showed a reduction in mortality and re-infarction. In parallel there was a trend towards fewer major bleedings in the fondaparinux group.23,24

Unfractionated heparin or low–molecular-weight heparin reduces nonfatal outcomes in patients with ACS, but at the cost of an increase in major bleeding complications and no reduction in mortality.25–27

An ideal antithrombotic agent is one which minimizes death and myocardial ischemia while producing no bleeding complications. As long as such a substance does not exist, fondaparinux at least fulfills a few of these criteria.

Bleeding in the setting of ACS is associated with adverse prognosis independent of other risk factors and is associated with a fivefold higher incidence
of death during the first 30 days. One of the main reasons for the increased rates of bleeding associated with heparins is the unreliable pharmacokinetics and the nonspecific inhibition of several different factors in the coagulation cascade in an unpredictable manner.\textsuperscript{28,29}

The efficacy and safety of fondaparinux has been studied in a pooled analysis of the OASIS-5 and 6 data. Overall 26,512 patients were included in these analyses. The results were stratified according to either an early invasive, a delayed invasive, or an initially conservative management strategy. Fondaparinux was shown to be superior to heparin in reducing the composite endpoint of death, myocardial infarction, or stroke (8.0\% versus 7.2\%; hazard ratio, 0.91; $P = 0.03$) and death alone (4.3\% versus 3.8\%; HR, 0.89; $P = 0.05$). Furthermore, fondaparinux reduced major bleeding by 41\% (3.4\% versus 2.1\%; HR, 0.59; $P < 0.001$) and was associated with a more favorable net clinical outcome than heparin (11.1\% versus 9.3\%; HR, 0.83; $P < 0.001$). In 19,085 patients treated by using an invasive strategy, fondaparinux suppressed ischemic events to an extent similar as heparin and reduced major bleeding by more than one-half, resulting in a superior net clinical outcome (10.8\% versus 9.4\%; HR, 0.87; $P = 0.008$). A similar benefit was also observed in those patients treated by using a conservative strategy (HR, 0.74; 95\% confidence interval, 0.64 to 0.85; $P = 0.001$). To summarize, compared with a heparin-based strategy, fondaparinux reduced mortality, ischemic events, and major bleeding across the full spectrum of acute coronary syndromes and was associated with a more favorable net clinical outcome in patients undergoing either an invasive or a conservative management strategy.\textsuperscript{30}

The reason for the decreased bleeding rates under fondaparinux compared to enoxaparin treatment may be explained by the fact that thrombin activity is not directly inhibited and that traces of thrombin can escape neutralization. Another possible explanation is that different regimes of anticoagulation were used in the OASIS studies (fondaparinux in prophylactic vs. enoxaparin in therapeutic). Anderson et al compared the anti-Xa concentration (reflecting drug levels), Xa clot time (reflecting anticoagulant effect) and endogenous thrombin potential (a global test of hemostatic function) in plasma samples collected in 48 patients randomly assigned fondaparinux 2.5 mg oncedaily and 42 patients assigned enoxaparin 1 mg/kg twice daily in the OASIS-5 trial. It was shown that Fondaparinux compared with enoxaparin produces less variable anticoagulant effect and lower mean anticoagulant intensity.\textsuperscript{31}

Although fewer bleeding complications were observed using fondaparinux than with UFH or enoxaparin, the fact that no antidote is available is still a source of concern, especially because of its long half-life. Using recombinant factor VIIa may be an option, but this needs to be further investigated.\textsuperscript{32}

Even though it was not one of the predefined endpoints, the OASIS-5 trial showed a significant increase in the incidence of catheter thrombus in patients undergoing PCI under fondaparinux (0.9\%) in comparison to enoxaparin (0.4\%), although other PCI-related complications developed less frequently ($P < 0.001$). This was confirmed in OASIS-6 versus UFH in the setting of primary angioplasty ($n = 0$ vs. $n = 22$, $P < 0.001$).\textsuperscript{23,24}

The mechanism underlying the higher incidence of catheter thrombosis is still not completely understood. A possible explanation might be found in an alternative, factor Xa-independent activation of the coagulation cascade. In vitro studies have shown that kallikrein can be activated by factor XIIa, which undergoes autoactivation after contact with a foreign surface, for example, a heart catheter.\textsuperscript{33,34} Kallikrein then catalyzes the change from prothrombin to thrombin. It seems that in the setting of ACS with an invasive intervention, it is not sufficient just to inhibit factor Xa.

However, an additional bolus of UFH at the time of angioplasty seems to prevent catheter thrombi from developing. This strategy was applied in the OASIS-5 trial. These findings were confirmed in an in vitro model published by or group.\textsuperscript{35} The recently published OASIS-8 trial determined the optimal dose of UFH in combination with fondaparinux in PCI for ACS. The primary outcome of major bleeding at 48 h with death/MI or target vessel revascularization at day 30 occurred in 4.7\% of the low and 5.8\% of the standard dose group ($P = 0.27$). The rates of major bleeding were not different, but the rates of minor bleeding were lower with low vs. standard dose regimen (0.7\% vs. 1.7\%, $P = 0.04$). Rates of catheter thrombus were very low (0.5 and 1.0\% in the low and standard dose groups, respectively, $P = 0.15$).\textsuperscript{36}
Patient Preference
Since fondaparinux is comparable to LMWH in terms of safety and efficacy of treatment, once-daily administration is sufficient both for prophylactic and therapeutic anticoagulation, as compared to the necessity of twice-daily LMWH administration. Another advantage is that dose adjustment is not necessary, which makes fondaparinux very easy to use. Of course, patients with severe renal dysfunction need to be excluded from this treatment strategy.

Place in Therapy
Since the results of the OASIS-5 and OASIS-6 studies were published, the guidelines issued by the ESC, ACC/AHA and ACCP for the management of STEMI and NSTE-ACS have all been updated. The European and American guidelines do not give exactly the same levels of recommendation, although both updates are based on equal scientific evidence. In the ACC/AHA guidelines, fondaparinux has a grade IA recommendation in case of a conservative strategy, but grade IB for an invasive strategy, with no distinction for urgent angioplasty. In the setting of STEMI, fondaparinux is recommended over no anticoagulation for patients not undergoing reperfusion but who require thrombolytic therapy, but not if primary angioplasty is needed. The ESC and ACCP guidelines recommend fondaparinux in the setting of NSTE-ACS with a grade IA, except in case of urgent angioplasty. In case of primary angioplasty both recommend against using fondaparinux. If patients are already pretreated with fondaparinux, an additional bolus between 50 to 100 IU/kg of unfractionated heparin is recommended.\(^{37-40}\)

In spite of the strong recommendations given in the European and American guidelines and the convincing findings of the OASIS trials, fondaparinux has not been used as much as expected in the setting of ACS. The Euro Heart Survey ACS III registry shows that fondaparinux is used in only 3% of patients, compared with 43% of UFH and 53% of enoxaparin.

Recently, Schiele et al published the results of a multicenter registry of more than 2,800 patients analyzing the routine use of fondaparinux in acute coronary syndromes. The primary aim of this study was to describe the changes in anticoagulant use for a 2-year period. The secondary aim was to compare the 30-day mortality and the rate of a combined endpoint (30-day death or major bleeding) according to the initial and final anticoagulant use. Fondaparinux was only chosen in 15% as the first anticoagulant, whereas UFH was used in 26% and enoxaparin in 59%. The acceptance of fondaparinux in routine practice depends heavily on local factors. In this setting, the choice of one anticoagulant over another is multifactorial. Patient characteristics, renal function or bleeding risk, the use of an invasive or conservative strategy, as well as regional consensus play important roles in such a decision. Further reasons may be still existing doubts about the efficacy of fondaparinux in the setting of angioplasty, the problem of catheter thrombosis, and the lack of antidote in case of bleeding complications.\(^{41}\)

Other Possible Indications
There are several other settings in which the administration of fondaparinux may be of high interest. As yet, studies of fondaparinux in patients suffering from atrial fibrillation or with mechanical heart valves are lacking. Our study group showed previously that fondaparinux seemed to be at least as effective as UFH and LMWH in two in vitro models of mechanical heart valves.\(^{42,43}\) Corbett et al also reported that fondaparinux was successfully used in a patient who had received a mechanical heart valve replacement and who had a history of heparin-induced thrombocytopenia.\(^{44}\)

However, data about the use of this new anticoagulant in patients with atrial fibrillation and/or after heart valve replacement are still lacking and treatment of those patients with fondaparinux is therefore currently not recommended.

Conclusion
Fondaparinux is the first selective inhibitor of the coagulation factor Xa that is commercially available for clinical use. Data from two pivotal studies, OASIS-5 and OASIS-6, have convincingly demonstrated that fondaparinux is at least as effective and safe as heparins in the setting of ACS. It reduces major bleeding by up to 50% as compared to heparin and reduces the rate of death or MI. An exception must be made in patients receiving primary PCI. A small, but significant amount of catheter-related thrombosis has been reported in patients undergoing PCI, which seems to be attenuated by adjuvant UFH. To date, there

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is no routine experience of the use of fondaparinux in ACS and acceptance of fondaparinux as the first-line anticoagulant probably requires more time. Bearing in mind that European and US American guidelines recommend fondaparinux as the anticoagulant of choice and which has an undeniable clinical benefit, this unique new drug may become one of the most frequently used anticoagulants in the setting of ACS.

Disclosure
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