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Fondaparinux: a new anti-thrombotic treatment strategy in venous thromboembolism and acute coronary syndromes

Summary

Fondaparinux (Arixtra®) is a synthetic selective factor Xa inhibitor. On the grounds of its favorable benefit-risk ratio, fondaparinux is approved for the prevention and treatment of venous thromboembolism. Two large trials in about 32000 patients recently evaluated fondaparinux in the treatment of non-ST elevation acute coronary syndromes and ST elevation acute myocardial infarction. Fondaparinux was compared with enoxaparin or usual care, depending on the setting. A single once-daily 2.5 mg subcutaneous dose of fondaparinux was used in both studies. After a brief presentation of the drug, this review presents the results obtained in these trials with fondaparinux and compares them with those obtained with other anticoagulants. Overall, it appears that fondaparinux at the single once-daily dose of 2.5 mg represents a valuable new alternative for the treatment of patients with acute coronary syndromes. However, fondaparinux cannot be used as stand-alone anticoagulant in the setting of PCI, where an additional of unfractionated heparin is needed to eliminate the risk of catheter thrombus.

Key words: acute myocardial infarction; anticoagulant; arterial thrombosis; deep vein thrombosis; enoxaparin; fondaparinux; non-ST elevation acute coronary syndromes; percutaneous coronary intervention; pulmonary embolism; thrombolytic; thrombosis; unfractionated heparin; venous thromboembolism

Résumé

Fondaparinux (Arixtra®) est un inhibiteur synthétique sélectif du facteur X activé (facteur Xa). Il est approuvé dans la prévention et le traitement de maladie thromboembolique veineuse. Deux essais récents représentant au total 32000 patients ont évalué son efficacité dans le traitement des syndromes coronariens aigus (SCA) avec et sans surdécalage du seg-ment ST. Le fondaparinux a été comparé à l'énoxaparine ou au traitement conventionnel en fonction de la pathologie considérée. Une dose unique de 2,5 mg de fondaparinux injectée par voie sous-cutanée a été utilisée dans les deux études. Après une brève présentation du produit, cette revue présente les résultats obtenus dans ces deux essais et les compare avec ceux obtenus avec d'autres anticoagulants. Au total, le fondaparinux à une dose unique de 2,5 mg par jour représente une alternative intéressante au traitement anticoagulant classique par héparine non fractionnée ou énoxaparine dans les syndromes coronariens aigus. Toutefois, le fondaparinux ne peut être utilisé comme seul anticoagulant en salle de cathétérisme, où une dose additionnelle d'héparine non fractionnée est nécessaire du fait du risque de thrombose de cathéter.

Mot-clefs: infarctus aigu; anticoagulants; thrombose artérielle; thrombose veineuse profonde; enoxaparine; fondaparinux; syndromes coronariens aigus sans surdécalage du segment ST; intervention coronaire percutanée; embolie pulmonaire; thrombolytique; thrombose; héparine non fractionnée; maladie thrombo-embolique veineuse

Introduction

Fondaparinux is currently the only clinically available pure anti factor Xa agent. It was initially developed in the prevention and treatment of venous thromboembolism (VTE). It was subsequently tested in the setting of acute coronary syndromes (ACS) with and without ST segment elevation, and also in the setting of percutaneous coronary interventions (PCI).

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In ACS, fondaparinux showed a unique capacity to reduce the risk of ischaemic events (death, myocardial infarction [MI] and stroke), without increasing bleeding, and actually with a risk reduction for bleeding. This unique profile in the setting of ACS has led to a complete shift in the paradigm in management of ACS.

Mechanism of action and pharmacokinetics / pharmacodynamics

Fondaparinux is a synthetic pentasaccharide modelled after the antithrombin-binding sequence of UFH. It exerts a selective antithrom-
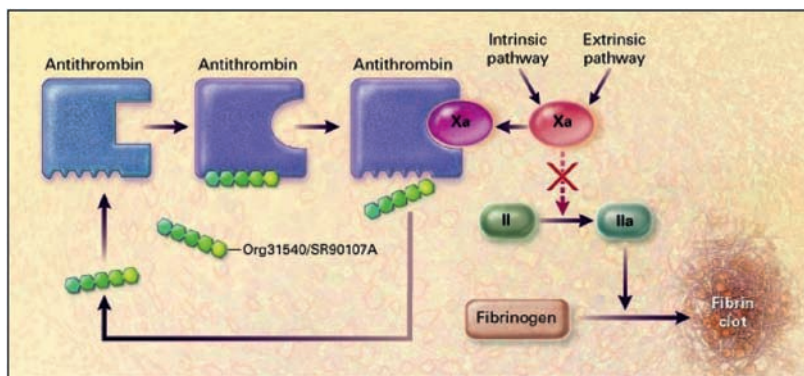

Figure 1

Mechanism of action of fondaparinux. The red X indicates that the inhibition of activated factor X leads to interruption of the coagulation cascade by preventing the activation of factor II (prothrombin) to factor IIa (thrombin). Fondaparinux binds with high affinity to the pentasaccharide binding site on antithrombin, producing an irreversible conformational change in antithrombin; an arginine residue is exposed, which binds to and inhibits activated factor X, a key factor in the activation of coagulation. Fondaparinux is then released and made available to bind to other antithrombin molecules. (from [3]: Turpie AG, Gallus AS, Hoek JA. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. N Engl J Med. 2001;344:619–25. Copyright © 2008, Massachusetts Medical Society. All rights reserved.)

Table 1

Pharmacokinetics of subcutaneous 2.5 mg fondaparinux in healthy volunteers (adapted from [1]).

Pharmacokinetic parameter	result
After a single 2.5 mg subcutaneous dose	
Bioavailability	100%
Time to peak plasma concentration (T_{max})	2 hours
Time to plasma concentration of $C_{max}/2$	25 minutes
Half-life	17 hours
Pharmacokinetic profile	linear, dose-independent
Distribution volume	7–11 liters
Elimination	unchanged in urine (up to 77% of a single dose within 72 hours)
After repeated administration	
Steady state	C_{max} reached after the 3rd or 4th dose
C_{max} on day 7/C_{max} on day 1	1.3
Inter- and intra-subject variability	narrow

bin-mediated inhibition of factor Xa, a dose-dependent inhibition of thrombin generation without inhibition of the thrombin molecule per se. A conformational change in the antithrombin molecule occurs when fondaparinux links to it, thereby making it possible for antithrombin to bind to factor Xa, thus inhibiting thrombin generation. Fondaparinux is then released and recirculated, and can start the same cycle of factor Xa inhibition all over again (fig. 1). It has a 100% bioavailability after subcutaneous injection with an elimination half-life of 17 h and can therefore be given once daily. It is contraindicated if creatinine clearance is lower than 20 ml/min. It is insensitive to inactivation by platelet-released heparin neutralisation proteins. Because it does not induce the formation of heparin-PF4 complexes, heparin-induced thrombocytopenia (HIT) is unlikely to occur with fondaparinux. No case of HIT has been reported with this drug, even after extensive use in the setting of prevention and treatment of VTE. Therefore, monitoring of platelet count is not necessary. After subcutaneous administration of 2.5 mg once daily, the absorption of fondaparinux is rapid and complete (table 1) [1]. Fondaparinux is almost completely excreted by the kidneys. The intra-subject and inter-subject variability is slight, eliminating the need for dose adjustments and routine coagulation monitoring in the majority of patients. However, in patients at high risk of thrombosis and/or bleeding, or whenever deemed necessary, monitoring of anti Xa activity is possible. Fondaparinux has no significant influence on the usual variables that monitor anticoagulant activity, such as aPTT, activated clotting time (ACT), prothrombin, and thrombin times. Furthermore, no interaction between fondaparinux and several other commonly used drugs, including acetylsalicylic acid, was observed [2].

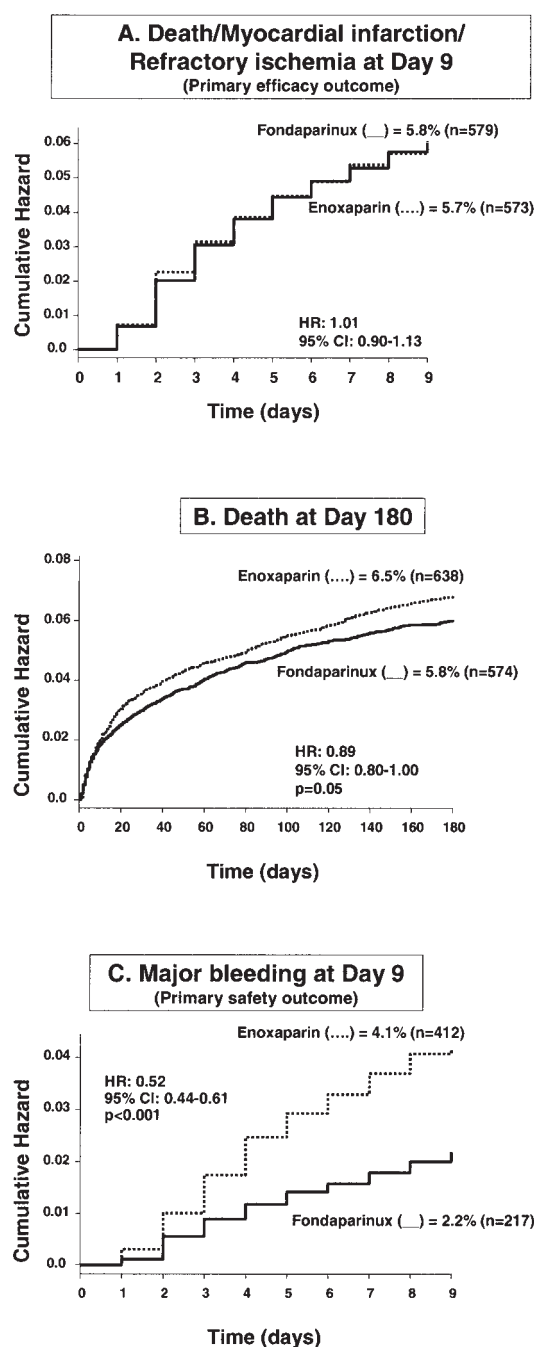## Fondaparinux in venous thromboembolism

Prophylaxis of venous thromboembolism

Fondaparinux, 2.5 mg once daily, administered subcutaneously, has been tested in a series of clinical trials in various clinical settings in the prevention of venous thromboembolism. The same 2.5mg dose, selected on the basis of a dose-ranging study in the setting of total hip replacement, was used regardless of patient, surgical or medical characteristics [3]. In patients undergoing major orthopedic surgery, fondaparinux reduced the incidence of docu-

mented deep vein thrombosis by more than 50% (p <0.001) as compared with enoxaparin [4–8]. Extended duration of fondaparinux administration in patients undergoing hip fracture surgery provided additional benefit [9]. In patients undergoing abdominal surgery, fondaparinux and intermittent pneumatic compression reduced the incidence of venous thromboembolism by 69.8% (p = 0.004) compared with intermittent pneumatic compression alone [10]. In high-risk abdominal surgery patients, fondaparinux was non-inferior to dalteparin, with a reduction in venous thromboembolism of 25.8% (p = 0.14), but superior to dalteparin in the subgroup undergoing cancer surgery [11]. In medical patients with restricted mobility, fondaparinux reduced the incidence of venous thromboembolism by 46.7% compared with placebo (p = 0.029), with a significant reduction in the occurrence of fatal pulmonary embolism [12]. In all these trials, the safety of fondaparinux in terms of bleeding risk, when used as recommended (first administration at least six hours after surgical closure), was generally comparable to that of the active comparators [2]. In acutely ill medical patients, the incidence of major bleeding in both the fondaparinux and placebo groups was very low (0.2% in both groups) [12].

Figure 2
Main results of the OASIS-5 trial (adapted from [19]).
HR = hazard ratio;
CI = confidence interval.

Treatment of established venous thromboembolism

The clinical benefit of fondaparinux in the treatment of venous thromboembolism was demonstrated in the two randomised, non-inferiority MATISSE trials [13, 14]. The dose of fondaparinux was selected by a dose-ranging study and set at 7.5 mg subcutaneously once daily (adjusted to 5 mg for patients with a body weight <50 kg and 10 mg for those with a body weight >100 kg). Fondaparinux was shown to be non-inferior to enoxaparin in the setting of DVT, and non-inferior to UFH setting of pulmonary embolism.

Overall safety

The overall safety of fondaparinux was good [2]. No immuno-allergic thrombocytopenia was reported, although Warkentin et al. recently reported a case of suspected HIT after bilateral knee replacement in a fondaparinux-treated woman [15]. However, the relation to the drug remains uncertain. Since it was first marketed in 2001, more than 1 million patients have been treated with fondaparinux and no proven causal association between fondaparinux and HIT has ever been established. Moreover, a growing number of clinical reports suggest that fondaparinux may be a safe antithrombotic drug in patients with a history or acute episode of HIT caused by UFH or LMWH [16]. Finally, no liver toxicity was observed [2].

Fondaparinux in non-ST elevation acute coronary syndromes (NSTE-ACS)

In ACS, with or without ST segment elevation, fondaparinux has been used at a unique dose of 2.5 mg, selected on the basis of the PENTUA

trial [17], and injected by subcutaneous injection once daily (first dose IV in STEMI).

The OASIS-5 study was a phase III, multicenter, randomised, double-blind study comparing fondaparinux 2.5 mg once daily administered subcutaneously with enoxaparin in 20078 patients with UA or NSTEMI [18, 19]. Enoxaparin was given subcutaneously (1 mg/kg twice daily). In patients with severe renal impairment (creatinine clearance below 30 ml/min), the dose of enoxaparin was 1 mg/kg once daily. Both treatments were given an average of 5.3 days. Follow-up was continued for a minimum of 90 days to a maximum of 180 days.

Fondaparinux was shown to be non-inferior at 9 days for the primary efficacy outcome (a composite of death, MI or refractory ischaemia) versus enoxaparin (fig. 2). Efficacy was consistent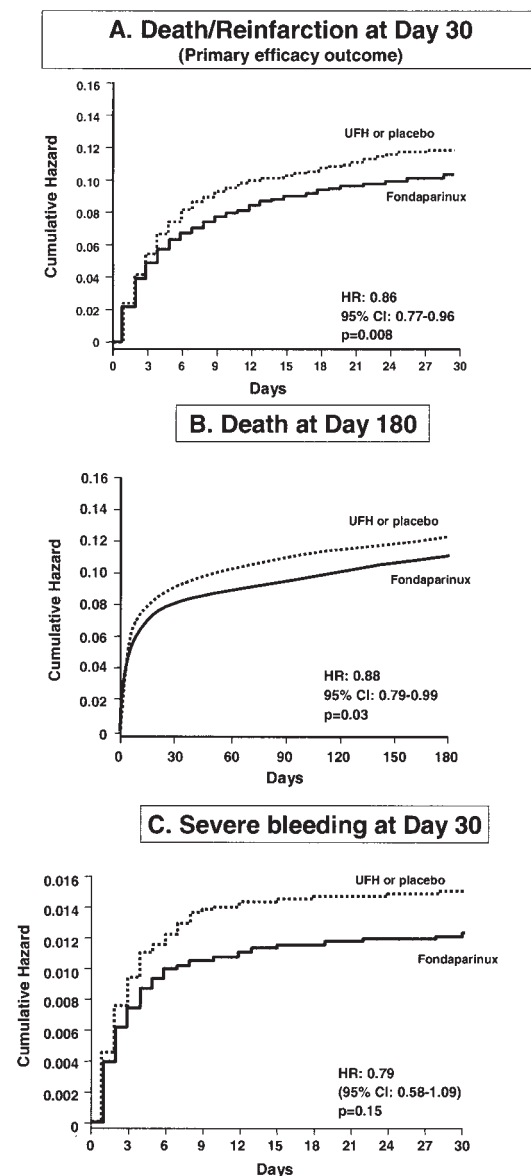 in all key subgroups of patients (according to age, sex, serum creatinine level, use of heparin at randomisation, revascularisation procedure within 9 days). There was a trend towards a reduction in the occurrence of the composite endpoint, in favor of fondaparinux at day 30 (p = 0.13) and at six months (p = 0.06). A significant 17% risk reduction for death was observed with fondaparinux as compared to enoxaparin at 30 days (p = 0.02) with a risk reduction of 11% at six months (p = 0.05). Moreover, the risk of stroke at six months was significantly lower in the fondaparinux (1.3%) than in the enoxaparin (1.7%) group (p = 0.04).

By day 9, the rate of major bleeding was reduced by 48% in the group of patients treated with fondaparinux (2.2% *vs* 4.1% with enoxaparin; p <0.001). The reduction was also evident irrespective of adjunctive therapy (clopidogrel and/or GP IIb/IIIa inhibitors), as well as in all subgroups of patients – high or low risk, elderly, women, diabetics, and in pts at high risk of bleeding, notably in 535 patients with creatinine clearance below 30 ml/min (2.4% *vs* 9.9%, p = 0.001) [19]. Indeed, in patients with renal failure, a risk reduction for bleeding was observed with fondaparinux as compared to enoxaparin at any level of renal function [20].

The reduction applied to every category of bleed, namely major bleeding (except intracranial haemorrhage, which occurred with similar frequency in both groups), and minor bleeding. Furthermore, major bleeding was associated with an increased risk of death, MI or stroke at day 30 or 180 [21]. Overall, the net clinical benefit at 9 days, 30 days and 6 months was in favor of fondaparinux, with a 7.3% rate of death, MI, refractory ischaemia or major bleeding at 9 days with fondaparinux compared to 9.0% with enoxaparin (p <0.001).

Fondaparinux in ST elevation acute myocardial infarction (STEMI)

Fondaparinux was initially tested in a dose-ranging study in 333 patients submitted to thrombolytic treatment with alteplase versus UFH as comparator [22]. In this study, no significant difference in reperfusion at 90 minutes was observed, but there was a strong trend in favor of a risk reduction for re-occlusion at 7 days. No excess of bleeding was observed with fondaparinux *vs* UFH.

The OASIS-6 study was a phase III, multicenter, randomised, double-blind study of fon-

Figure 3

Main results of the OASIS-6 trial (adapted from [23]). HR = hazard ratio; UFH = unfractionated heparin; CI = confidence interval.

A. Death/Reinfarction at Day 30
(Primary efficacy outcome)

HR: 0.86
95% CI: 0.77-0.96
p=0.008

B. Death at Day 180

HR: 0.88
95% CI: 0.79-0.99
p=0.03

C. Severe bleeding at Day 30

HR: 0.79
(95% CI: 0.58-1.09)
p=0.15

daparinux versus standard therapy (placebo or UFH) in 12092 patients with confirmed STE-MI [23]. Patients were eligible, regardless of their therapeutic management, i.e., thrombolysis, primary PCI, or no reperfusion therapy. As in OASIS-5, fondaparinux was administered at a dose of 2.5 mg subcutaneously once daily, with the first dose given intravenously. Randomisation was stratified by the patient's indication for the use of UFH, based on the investigator's judgment. Patients with no indication for UFH were enrolled in stratum 1; they were assigned to receive either fondaparinux

or matching placebo for up to 8 days or hospital discharge if earlier. Patients with an indication for UFH (i.e., patients in whom use of a fibrin-specific thrombolytic drug was envisaged, patients not eligible for thrombolysis but eligible for anticoagulants, and patients scheduled for primary PCI) were enrolled in stratum 2. In this stratum, fondaparinux was administered for an average of 5.4 days, or UFH at standard dose for up to 48 hours according to existing guidelines. The dose regimen of UFH and fondaparinux depended on whether or not glycoprotein IIb/IIIa inhibitors were used. Follow-up was for a minimum of 90 days up to a maximum of 180 days.

The occurrence of the primary efficacy outcome (composite of death or recurrent MI up to day 30) was significantly reduced by 14% (p = 0.008) at 9 days in the fondaparinux group (fig. 3). This benefit persisted up to six months after the event. It was consistent according to gender, age, time from symptom onset to randomisation, use of pre-randomisation UFH, or type of thrombolytic agent used. Moreover, there was a significant 13% reduction in mortality at 9 (p = 0.04) and 30 days (p = 0.03), and 12% at the study-end (p = 0.03) in the fondaparinux group versus UFH/placebo. A trend (p = 0.13) towards fewer severe bleeds was evident in the fondaparinux group (1.0%) compared with the control group (1.3%). Throughout the study period, the net clinical benefit, defined by the composite of death, recurrent MI, or severe bleeding, was in favor of fondaparinux.

The effect of fondaparinux on the composite outcome of death or recurrent MI was not statistically different between the two strata, but was more marked in stratum 1 than in stratum 2. Patients who did not undergo primary PCI had a significant risk reduction for death (21% risk reduction, p = 0.03) and death/recurrent MI (23% risk reduction, p = 0.008) at six months. Those patients who were not submitted to reperfusion derived a large benefit from fondaparinux, (fig. 4A), with a trend towards less frequent severe bleeding (1.6% *vs* 1.8%, p = 0.06). Patients who underwent thrombolysis also derived benefit from fondaparinux as compared to the comparator (fig. 4B). Furthermore, within this subgroup, there was no heterogeneity in the response for patients submitted to non-fibrin specific versus fibrin-specific thrombolytic agents. Lastly, patients submitted to primary PCI did not derive any benefit, with a significant interaction across the groups by type of reperfusion (fig. 4C).
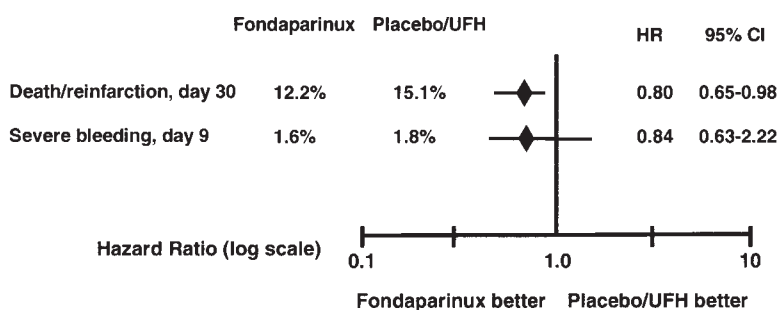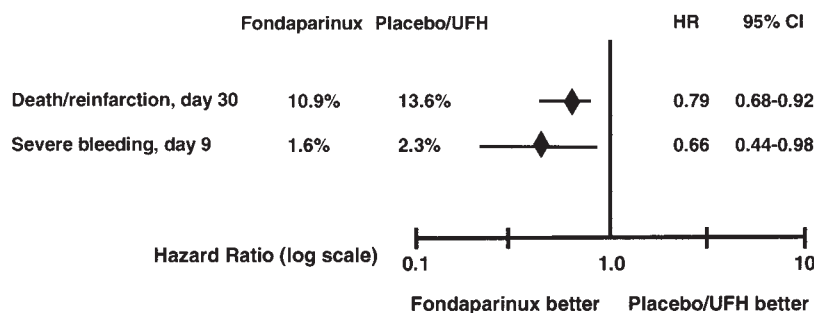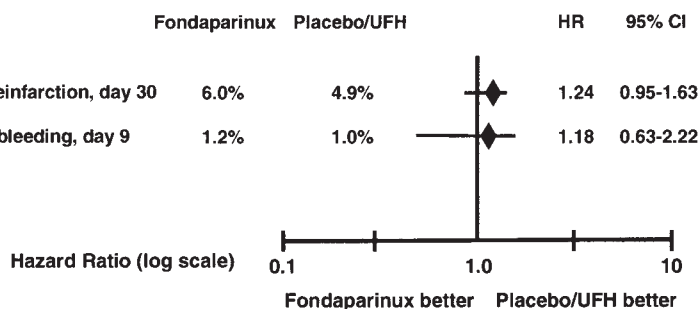

Figure 4
Results according to the type of reperfusion therapy in OASIS-6 (Adapted from [23]).
HR = hazard ratio; NA = not available; UFH = unfractionated heparin; CI = confidence interval.

Fondaparinux in percutaneous coronary interventions

The use of fondaparinux in the setting of PCI, planned interventions or in ACS with or without ST elevation, demonstrated the limits of a pure anti Xa agent used as stand-alone anticoagulant in PCI. In the ASPIRE study, where 2 doses of fondaparinux (2.5 mg or 5.0 mg) were compared to UFH in 350 patients submitted to planned PCI with or without use of glycoprotein IIb/IIIa inhibitors, no significant difference in primary outcome was observed [24]. There was no significant difference in the rate of bleeding between the fondaparinux and UFH groups.

The incidence of the efficacy outcome (composite outcome of all-cause death, myocardial (re)infarction, urgent revascularisation, and need for bail-out glycoprotein IIb/IIIa inhibitors) was 6.0% in the combined fondaparinux group and 6.0% in the UFH group. The incidence of total (major and minor) bleeding occurring within 48 h after randomisation was 6.4% in the combined fondaparinux group and 7.7% in the UFH group (p = 0.61). However, total bleeding was less common in the 2.5 mg fondaparinux group than in the 5.0 mg fondaparinux group (3.4% *vs* 9.6%, p = 0.06). Thrombus formation on the angioplasty material (catheter thrombus) and in coronary arteries were observed in the ASPIRE study [24].

In OASIS-5, consistent with clinical practice in UA/NSTEMI, patients could undergo PCI at any time after initiation of the study drug. Per protocol, patients received either a single pre-procedural intravenous dose of fondaparinux (fondaparinux subjects) or UFH (enoxaparin subjects), using a double-dummy technique to maintain study blind, if PCI was carried out more than 6 hours following the last injection of study drug. The dose of additional drug given at the time of PCI was also modulated according to the use of GP IIb/IIIa inhibitors. Study medication was resumed after the procedure at the investigator's discretion. It was recommended that all patients be treated with clopidogrel and acetylsalicylic acid at least six hours before PCI, if possible.

A total of 6239 patients (31.1%) enrolled in OASIS-5 underwent PCI during the first 8 days after randomisation [19]. Consistent with the data obtained in the overall population, efficacy was similar between the two treatment groups. Furthermore, the bleeding advantage of fondaparinux over enoxaparin in the overall population was confirmed, with a significant 55% lower incidence of major

bleeds at day 9 between treatment groups. The rate of major bleeding was lower in the fondaparinux group, irrespective of the timing of PCI (<6 or >6 hours after the last subcutaneous dose of study treatment) and irrespective of the administration of additional UFH (or placebo) [25]. Vascular access site complications were less frequent (p <0.001) in fondaparinux-treated patients. In contrast, catheter thrombosis was more frequent (p = 0.001) with fondaparinux (0.9%) than with enoxaparin (0.4%). Catheter thrombus was eliminated after an amendment to protocol was introduced authorising the use of additional UFH at the time of PCI. Overall, the net clinical benefit was significantly in favor of fondaparinux.

Contrary to the results observed in the SYNERGY trial [26], there was no excess of bleeding when UFH was added per protocol to enoxaparin in patients submitted to PCI. Similarly, no excess of bleeding was observed in patients who received UFH in addition to fondaparinux.

In OASIS-6, patients scheduled for primary PCI received single-bolus injections (either fondaparinux or UFH) immediately before the procedure. The dose depended on the pre-randomisation use of UFH and glycoprotein IIb/IIIa inhibitors. After the initial phase, patients requiring non-primary PCI received open-label UFH at the time of PCI.

A total of 3788 patients (31.3%) underwent primary PCI during hospitalisation [23]. Efficacy and safety data were similar between the two groups (fig. 4). However, there was a higher rate of catheter thromboses (0 *vs* 22, p <0.001) and more frequent coronary complications (225 *vs* 270, p = 0.04) in fondaparinux-treated patients. When open-label UFH was administered prior to primary PCI, no catheter thrombus and no excess of bleeding was observed. A total of 231 fondaparinux patients and 226 control patients underwent non-primary PCI in hospital with UFH at the time of the procedure. There were no differences in the rates of death or recurrent MI at day 30, coronary complications, and severe bleeds. No cases of catheter thrombus were reported [25].

Comments

Fondaparinux has been shown to be clearly superior to any comparator in the prophylaxis of deep vein thrombosis, without an increased risk of bleeding, provided it is given 6 hours following intervention in major orthopedic surgery. In established venous thromboembolism,

it has been shown to have at least similar activity *vs* any comparator (enoxaparin or UFH). The major advantage of fondaparinux is that it is administered in a unique, daily dose, without need for dose adaptation, except in established VTE, low body mass index or high body weight. There is no need for monitoring of treatment, and there is no risk of heparin induced thrombocytopenia.

In ACS, fondaparinux was shown to have the unique capacity of reducing ischaemic events without increasing the risk of bleeding, and even with a risk reduction for bleeding. Pooled analysis of the Oasis-5 and Oasis-6 studies, representing more than 32 000 patients, confirmed that whatever the comparator, there was a significant risk reduction for bleeding, and a significantly improved net clinical benefit in favor of fondaparinux (death + MI + stroke + major bleeding). In addition, for the first time ever in patients with STEMI not submitted to reperfusion therapy, fondaparinux showed a significant risk reduction for death without an increased risk of bleeding. The capacity of an anticoagulant to reduce death in this population was previously shown in the CREATE trial with reviparin, but at the cost of an excess of bleeding, especially intracranial bleeding.

The Oasis-5 study included moderate- to high-risk patients with a high rate of biomarker release, treated according to the guidelines with a high rate of use of antiplatelet agents, aspirin, ADP receptor antagonists, beta blockers. The Oasis-6 study represented the full spectrum of ST elevation MI encountered in real practice, with about 24% of patients not submitted to any reperfusion, 45% submitted to thrombolytic treatment, and 31% submitted to primary PCI.

A new concept is therefore born: as bleeding carries a high risk of ischemic events in terms of death, MI and stroke at 30 days and 6 months [19, 27], prevention of bleeding has become equally as important as the prevention of ischaemic events. Therefore, in the management of ACS, the selection of drugs or strategies with a known risk reduction for bleeding should be favored over other treatments. In this regard, fondaparinux is the treatment of choice in all settings in ACS [28].

The only drawback with fondaparinux is the risk of catheter thrombus formation during PCI, which requires an additional dose of UFH at the time of PCI. The addition of UFH was shown to abolish the risk of catheter thrombus in both Oasis-5 and Oasis-6, without increasing the risk of bleeding as observed in

SYNERGY [26]. The reasons why thrombi form on the angioplasty material during PCI remain unclear. It should be pointed out that this phenomenon is observed not just with fondaparinux, but with many different anticoagulants, including enoxaparin in Oasis-5, and others currently under development (personal communication). It is possible that UFH exerts the unique effect of inhibiting the intrinsic coagulation pathway, particularly factor XII, which is responsible for contact coagulation. This ability to inhibit the intrinsic pathway is nil with fondaparinux, and weak with enoxaparin, while for other anticoagulants, this capacity is as yet unknown (personal communication).

In severe renal failure, fondaparinux has been shown to be safer than enoxaparin at any level of creatinine clearance [20]. In addition, according to the official local labeling, fondaparinux can be used for creatinine clearance as low as 20 ml/min. For lower levels, UFH should be preferred.

Finally, the recently published recommendations for the use of fondaparinux in the setting of non-ST segment elevation ACS and ST elevation MI have [28–30] stipulate that:

– In the setting of non-ST elevation ACS, fondaparinux can be used in all situations (unstable angina or non-STEMI).
– Fondaparinux cannot be used as standalone anticoagulant in case of PCI, where an additional dose of UFH is required.
– Fondaparinux is recommended in STEMI patients who are not eligible for reperfusion, as well as in patients submitted to thrombolytic treatment.
– Fondaparinux is not recommended in the setting of primary PCI.

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