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Scientific Update™

Optimal Use of Fondaparinux as Antithrombotic Therapy in Acute Coronary Syndromes – Integration of Two Major Trials – OASIS-5 and OASIS-6

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A Discussion and Analysis of Presentations at the 55th Annual Scientific Session of the American College of Cardiology

Atlanta, Georgia March 11-14, 2006

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Evidence-based therapy with thrombolytic therapy, primary percutaneous coronary intervention (PCI), antithrombotic therapy, and early cardiac catheterization significantly improves outcomes in patients with acute coronary syndromes (ACS). However, patients continue to have recurrent ischemic events and therapy is complicated by significant bleeding. Fondaparinux is a selective factor-Xa inhibitor, the first of a new class of antithrombotic drugs. Two large trials in ACS patients have demonstrated the efficacy of fondaparinux in reducing death and recurrent ischemic events with a reduction in bleeding complications; these were the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 and -6 trials:

- **OASIS-5 – examined fondaparinux in patients with non-ST-elevation ACS**
- **OASIS-6 – examined fondaparinux in patients with ST-elevation MI (STEMI).**

This issue of *Cardiology Scientific Update* presents the highlights of these trials.

Previously reported trials in patients with STEMI with unfractionated heparin (UFH), direct thrombin inhibitors, and enoxaparin have thus far failed to demonstrate mortality reductions in STEMI patients, and bleeding is substantially increased when these agents are used with aspirin and thrombolytic therapy. Therefore, there is a clear need for an effective, inexpensive, and safe antithrombotic agent for patients with STEMI. Fondaparinux is currently approved in many countries, including Canada, for the prevention of venous thrombosis in certain patient groups and for the treatment of deep vein thrombosis and pulmonary embolism. It is given as a once-daily, fixed-dose, subcutaneous injection. Factor Xa promotes the generation of thrombin (also known as factor IIa). The low-molecular-weight heparins (LMWHs), such as enoxaparin, are mixtures of factor-Xa and factor-IIa inhibitors. Inhibition of factor Xa may be a more efficient way of blocking thrombin than inhibition of factor IIa. Since one molecule of Xa can generate 50 molecules of IIa, a lower amount of drug is needed to inhibit the same amount of thrombin if the drug that is used targets factor Xa rather than IIa directly.

OASIS-5 – summary

In a previous issue of *Cardiology Scientific Update,* Dr. David Fitchett presented the findings of the OASIS-5 trial. This trial included 20,078 patients with non-ST-elevation myocardial infarction (NSTEMI) and demonstrated that fondaparinux, the anti-Xa inhibitor, was as effective as enoxaparin in reducing cardiovascular events in the short-term, while causing half the amount of bleeding. This benefit in bleeding also translated into significant reductions in morbidity and mortality: fondaparinux, at a dose of 2.5 mg once daily, was associated with a significantly reduced number of deaths at both 30 and 180 days and provided a net clinical benefit in both the conservative medical approach and the aggressive interventional approach. This trial was presented last year and was recently published in the *New England Journal of Medicine*.[1] Several additional sub-studies were presented at the recent ACC meeting.

There is an increasing volume of data demonstrating the relationship between bleeding and mortality in ACS. Thus, the 30-day benefit in bleeding in OASIS-5 translated into a significant reduction in mortality. The benefit of fondaparinux was observed in hospitals with and without angiographic capability.

Recently reported findings

Several abstracts that expand our understanding of the benefits of fondaparinux in NSTEMI patients were presented at the ACC meeting. In an analysis of the OASIS registry, OASIS-2,

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Table 1: OASIS-6: overall outcome of death or MI at 9 and 30 days, and at end of follow-up

	No. (%) of patients				
	Placebo or UFH (n = 6056)	Fondaparinux (n = 6036)	Absolute difference, %	HR (95% CI)	*P* value
Death or reinfarction					
Day 9	537 (8.9)	444 (7.4)	93 (-1.5)	0.83 (0.73-0.94)	.003
Day 30*	677 (11.2)	585 (9.7)	92 (-1.5)	0.86 (0.77-0.96)	.008
Study end (3-6 months)	857 (14.8)	756 (13.4)	101 (-1.5)	0.88 (0.79-0.97)	.008
Death					
Day 9	425 (7.0)	368 (6.1)	57 (-0.9)	0.87 (0.75-1.00)	.04
Day 30*	540 (8.9)	470 (7.8)	70 (-1.1)	0.87 (0.77-0.98)	.03
Study end (3-6 months)	674 (11.6)	598 (10.5)	75 (-1.0)	0.88 (0.79-0.99)	.03
Reinfarction					
Day 9	136 (2.3)	92 (1.6)	44 (-0.7)	0.67 (0.52-0.88)	.004
Day 30*	175 (3.0)	142 (2.5)	31 (-0.5)	0.81 (0.65-1.01)	.06
Study end (3-6 months)	245 (4.6)	200 (3.8)	45 (-0.8)	0.81 (0.67-0.97)	.03

and CURE data, Eikelboom demonstrated the adverse effects of bleeding in patients with NSTEMI.[2] There was a >4-fold increase in 30-day mortality in patients with bleeding. Budag performed a similar analysis of the OASIS-5 study and demonstrated that major bleeding resulted in a 5-fold increased risk of death at 30 days, with minor bleeding increasing the risk by >2-fold.[3] Fondaparinux was also associated with less bleeding and access site complications than enoxaparin in patients undergoing PCI for NSTEMI. However, death and MI were similar in both treatment groups (7.2% vs. 6.9%) that had PCI during hospitalization.[4]

There is evidence that renal dysfunction is an important marker of high risk in patients with ACS. In the OASIS-5 study, Fox demonstrated that there was a close relationship between a rising creatinine and death and bleeding.[5] In all quartiles of renal function, there was a higher event rate in patients treated with enoxaparin than in those treated with fondaparinux. At the highest creatinine level (>1.19), the mortality rate was 11.38% vs. 9.53%, p<0.023. The major bleeding rate in this highest quartile was greater in the enoxaparin group (8.2%) than in the fondaparinux group (5.5%).

As described in the publication of OASIS-5,[1] the net clinical benefit (endpoint of death/MI/refractory ischemia/major bleeding) at 9 days was similar for both enoxaparin and fondaparinux in patients aged <65 years in OASIS-5 (6.1% vs. 5.8%, respectively). However, in patients aged >65 years, the event rates were significantly higher with enoxaparin (12.3%) than with fondaparinux (9.3%). In the overall population at 30 days, the death/MI/revascularization/major bleeding rates were reduced by 19% with fondaparinux as compared to enoxaparin, p<0.00001.

OASIS-6 – summary

In the OASIS-6 trial in 12,092 patients presenting with STEMI, fondaparinux reduced mortality and reinfarction without increasing bleeding, compared to usual care (UFH or no antithrombotic therapy).[6] The drug was beneficial in all groups, apart from those patients undergoing primary PCI who had similar outcomes with both fondaparinux and UFH, but had a higher risk of catheter thrombosis with the Xa inhibitor.

According to the presenters, fondaparinux clearly demonstrates advantages over other antithrombotic drugs in STEMI since it saves lives and prevents recurrent infarction, without increasing bleeding. However, fondaparinux is not suitable for use in primary PCI and UFH is likely the preferred agent. Use of fondaparinux for up to 8 days after primary PCI was associated with a trend toward fewer ischemic events in OASIS-6.

Detailed description of OASIS-6

The OASIS-6 trial enrolled 12,092 patients with STEMI from 41 countries. All were randomized to fondaparinux (2.5 mg once daily given for up to 8 days) or usual care, depending on the presentation, and initial therapy according to the investigator's judgment. The first group of patients (designated Stratum 1) received either fondaparinux or placebo (since UFH was not indicated due to late presentation) or a nonfibrin-specific thrombolytic agent (n=5,658). The second group of patients (designated Stratum 2) received fibrin-specific thrombolytic therapy or primary PCI and were randomized to fondaparinux for up to 8 days or UFH for up to 48 hours, followed by placebo for up to 8 days (n=6,434). Patients with contraindications to anticoagulation or with a creatinine >265.2 mg/dL were excluded. UFH was administered as an intravenous bolus of 60 IU/kg (maximum, 4000 U), followed by an intravenous infusion at 12I U/kg/hr for 24-48 hours.

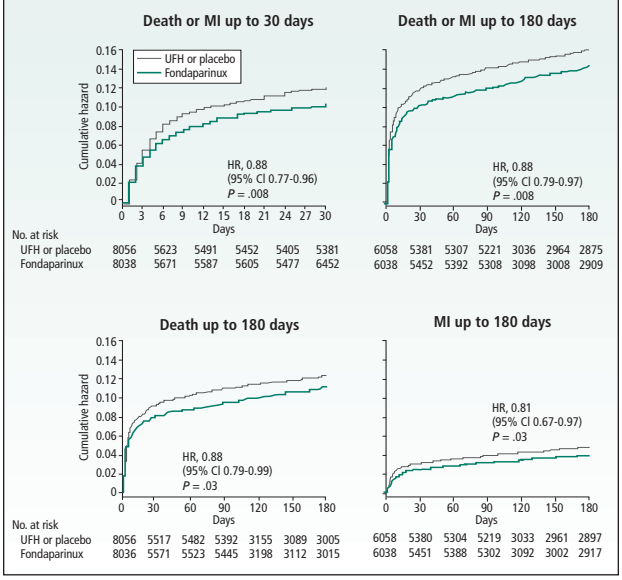
The primary endpoint was a composite of death or reinfarction (recurrent symptoms with ST elevation and/or significant enzyme rise depending upon timing of the event) at 30 days, with secondary assessment at 9 days and 3 months in all, and at 6 months in 6,976 patients. Major bleeds were identified up to day 9 and were centrally adjudicated with standard criteria, including fatal hemorrhage, intracranial hemorrhage, cardiac tamponade, or a fall in hemoglobin of >5 g/dL (TIMI criteria). Follow-up was concluded in January 2006 and over 99% complete.

Patients were equally randomized within each stratum, the median age was 62 years, 72% were male, 44% underwent cardiac catheterization, 29% with primary PCI, and 45% with thrombolytic therapy. No reperfusion therapy was given to 24% of the total population.

Overall study population results

Table 1 summarizes the overall outcome of death or MI at 9 days, 30 days (primary), and at the end of follow-up. At 30 days,

Figure 1: Comparison of the rates of death and myocardial infarction (MI)



the hazard ratio (HR) of 0.86 was highly significant, demonstrating the efficacy of fondaparinux in the whole population for reducing death and MI.[6] The absolute difference was 1.5% at 30 days. The significant reduction in mortality was due to a reduction in cardiac mortality, from 9.5% to 8.2%, and these events included death as a result of reinfarction, congestive heart failure, cardiogenic shock, and asystole.

The survival curves in the total patient population at various time periods and according to the type of event are shown in Figure 1. When comparing the two strategies, similar results were demonstrated if the events considered were death, MI, and severe bleeding. Thus, at 30 days, the study demonstrated a significant overall relative risk reduction of 14% in the primary endpoint of mortality and reinfarction.

With respect to bleeding at 30 days, there was a nonsignificant reduction in bleeding in the fondaparinux group as compared to both the placebo and UFH groups, with an HR of 0.79, but an absolute difference of only 0.3%. There was a significant reduction in myocardial rupture, a nonsignificant reduction in fatal bleeding, no differences in intracranial hemorrhage, retroperitoneal bleeding, and hemoglobin drop of >5 g/dL.

In the overall population, there was a significant reduction in total events, including death, MI, stroke, and major bleeding. The HR of 0.88 was highly significant (p<.009), indicating the overall efficacy of fondaparinux in STEMI.

Results in predefined groups

To clarify the application of these results in patients presenting with STEMI, it is important to analyze the OASIS-6 data according to clinically-relevant subgroups and, importantly, to the subgroups receiving different reperfusion strategies. In this study, the 2 study groups were predefined and could be evaluated independently and the second Stratum was also divided into patients receiving thrombolytic therapy and those treated with primary PCI. In addition, patients were evaluated according to the Global Registry of Acute Coronary Events (GRACE) risk score and categorized as being "above" or "below" the mean score of 112.

In the group of patients randomized to placebo or fondaparinux (Stratum 1 – nonfibrin-specific thrombolytic or no reperfusion), there was a significant reduction in death or MI at 30 days (from 14.0% to 11.2 %; HR 0.79). In the patients randomized to UFH versus fondaparinux, there was no significant reduction in death or MI (8.7% and 8.3%, respectively). At study end, the findings were statistically unchanged in both Strata, but the effect sizes were similar (HR 0.87 in Stratum 1, HR 0.88 in Stratum 2).

In Stratum 2, 3768 patients underwent primary PCI and 2,666 had thrombolytic therapy. The 30-day rate of death and reinfarction was reduced nonsignificantly from 13.8% to 11.5% with fondaparinux versus UFH in the thrombolytic-treated patients. At study end, there was a significant reduction in death and MI (from 19.0% to 14.9%) with fondaparinux (HR 0.77, p<0.008). However, in the patients treated with primary PCI, the death and reinfarction rate was statistically nonsignificantly increased from 5.1% to 6.1% with fondaparinux as compared to UFH. In addition, in the group given fondaparinux, there were 22 patients with thrombus in the guiding catheter, but none were identified in patients receiving UFH. Similarly, there was a more frequent incidence of acute coronary complications in the fondaparinux group. Patients undergoing nonprimary PCI were given UFH by protocol and there were no differences in complications between the patients randomized to either fondaparinux or UFH.

In the 5,958 patients with a low GRACE risk score (<112), no statistically-evident treatment benefit was observed for fondaparinux versus either placebo or UFH in terms of death and MI (4.6% versus 4.3%, respectively). However, in the 6,134 higher risk patients (GRACE score >112), there was a significant benefit with fondaparinux, with a reduction in death and MI from 18.0% to 14.5% (HR 0.79). If 1,000 patients were treated with fondaparinux in this high-risk group, 34 events would be prevented.

A similar benefit with fondaparinux was observed in men and women, patients above or below the age of 62 years, patients presenting early or late, and those receiving or not receiving pre-randomization UFH. The presenters concluded that if 1,000 patients with STEMI who were not receiving reperfusion therapy received fondaparinux, there would be a reduction of 39 events (including 26 deaths, 17 MIs, 8 strokes, and 2 severe bleeds). In 1,000 patients with STEMI who were receiving thrombolytic therapy and fondaparinux, there would be a reduction of 21 events (including 15 deaths, 9 MIs, and 1 stroke at the expense of 7 severe bleeds).

Summary

This large study in STEMI patients demonstrates:

- the significant benefit of fondaparinux in patients receiving thrombolytic therapy (HR 0.79; p=0.003)
- the significant benefit of fondaparinux in patients not receiving any reperfusion therapy (HR 0.80; p=0.03)
- no benefit of fondaparinux in patients undergoing primary PCI for STEMI
- that the benefit in preventing MI and death with fondaparinux does not occur at a cost of increased bleeding
- the addition of UFH with fondaparinux during PCI largely avoids the presence of guiding catheter thrombosis and procedural coronary complications.

Discussion

The OASIS-5 and -6 trials in patients presenting with ACS and a creatinine <265 µmol/L demonstrate that fondaparinux is a safe and efficacious antithrombotic agent. Fondaparinux affords a simple regimen that can be used as a single fixed dose, with no requirement for monitoring. Improved outcomes are associated with reduced bleeding complications and low cost. However, it is important to clearly define the patient population that benefits from this therapy. There is a question about whether the OASIS-6 data are relevant in centres where primary PCI has been established as the preferred treatment for STEMI. Fondaparinux may be more preferable in settings in which the use of angiographic-based reperfusion is not routine. In patients requiring rescue PCI or other PCI after admission, initial management with fondaparinux followed by standard UFH during PCI, is adequate to prevent adverse events.

Duration of therapy

During active treatment with UFH (48 hours) or fondaparinux, analysis of the event curves reveals minimal evidence that fondaparinux is superior. The event reduction at 9 and 30 days may have been related to the continuation of anticoagulation therapy with fondaparinux for 6-7 days. Prolonged therapy with fondaparinux was not associated with increased bleeding and may have further prevented recurrent ischemic events. Since UFH is not administered for >48 hours in most patients with STEMI, this study suggests that the strategy of prolonged therapy with fondaparinux up to the time of hospital discharge, results in an improvement in outcome in STEMI patients.

A significant issue with fondaparinux is its relationship with catheter thrombus in patients undergoing PCI. In both OASIS-5 and OASIS-6, there was an increase in thrombotic complications with fondaparinux, resulting in the need for UFH if, and when, PCI is performed. Catheter thrombus was also observed when enoxaparin was used alone in OASIS-5, but at one-third the frequency with fondaparinux. These data strongly support the use of UFH as the antithrombotic therapy of choice in primary PCI for STEMI patients.

ExTRACT-TIMI 25 results

The study was also reported at the recent ACC and should be taken into consideration when making decisions for the appropriate therapy of patients presenting with an STEMI.[7] The study patients were similar to the Stratum 2 patients treated with thrombolysis in the OASIS-6 trial. ExTRACT-TIMI 25 randomized 20,506 patients receiving thrombolysis for STEMI and compared treatment with a new dosing regimen of the LMWH, enoxaparin, for up to 8 days versus UFH for at least 48 hours. The new regimen of enoxaparin involved lower doses in elderly patients and in those with renal dysfunction. The dose of enoxaparin was reduced to three-quarters of the standard dose, with no bolus in patients aged ≥75 years and to once-daily in those who had clinically significant impairment in renal function.

Although enoxaparin did not reduce mortality alone as compared to UFH in ExTRACT-TIMI 25 (6.9% vs. 7.5%), it did reduce the primary endpoint of death or nonfatal recurrent MI (by one-third) (9.9% vs. 12.0%), urgent revascularization (2.1% vs. 2.8%) at 30 days and was associated with a net clinical benefit when the efficacy and bleeding results were combined (11.0% vs. 12.8%, $p<0.001$). However, major bleeding was significantly increased by 53% with enoxaparin and fatal bleeding was increased by 80% ($p<0.001$). The improved efficacy likely was related to the superior antithrombotic effect of enoxaparin, the longer duration of therapy, and the previously documented rebound thrombosis that may occur with discontinuation of UFH. The investigators concluded that for every 1,000 patients treated with the enoxaparin strategy, there would be 15 fewer nonfatal reinfarctions, 7 fewer episodes of urgent revascularization, and 6 fewer deaths, at the cost of 4 additional episodes of nonfatal major bleeding.

Conclusions

These important trials presented at the ACC meeting and subsequently published demonstrate that antithrombotic therapy in ACS patients with either NSTEMI or STEMI reduces the composite endpoints of death, recurrent MI, and recurrent ischemia. When compared with placebo in Stratum 1 of OASIS-6, fondaparinux did not increase bleeding and reduced mortality and MI. Fondaparinux is a safe drug and as effective as enoxaparin in NSTEMI patients, but with significantly reduced bleeding, particularly in the elderly and in those with an elevated creatinine. Fondaparinux and enoxaparin are more effective than UFH in patients with STEMI receiving thrombolytic therapy in reducing death, MI, and recurrent ischemic events. Fondaparinux is the only anticoagulant shown to reduce mortality in ACS and STEMI. In addition, fondaparinux appears to have no adverse effect on bleeding as compared to enoxaparin and likely improves 30-day survival. In patients undergoing PCI or rescue PCI, UFH appears to be superior to fondaparinux.

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SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from GlaxoSmithKline Inc. to support the distribution of this issue of *Cardiology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Division of Cardiology and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party.