**CLINICAL RESEARCH**                                                    **Clinical Trial**

# Efficacy and Safety of Fondaparinux Versus Enoxaparin in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention

## Results From the OASIS-5 Trial

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| **Objectives** | This study reports a prospectively planned analysis of patients with acute coronary syndrome who underwent early percutaneous coronary intervention (PCI) in the OASIS-5 (Fifth Organization to Assess Strategies in Ischemic Syndromes) trial. |
| **Background** | In the OASIS-5 trial, fondaparinux was similar to enoxaparin for short-term efficacy, but reduced major bleeding by one-half and 30-day mortality by 17%. |
| **Methods** | The OASIS-5 trial was a double-blind, randomized comparison of fondaparinux and enoxaparin in 20,078 patients with acute coronary syndrome. A total of 12,715 patients underwent heart catheterization during the initial hospitalization, and 6,238 patients underwent PCI. In the fondaparinux group, intravenous fondaparinux was given for PCI. In the enoxaparin group, no additional anticoagulant was given if PCI was <6 h from last subcutaneous dose, and additional intravenous unfractionated heparin (UFH) was given if PCI was >6 h. |
| **Results** | Fondaparinux compared with enoxaparin reduced major bleeding by more than one-half (2.4% vs. 5.1%, hazard ratio [HR] 0.46, p < 0.00001) at day 9, with similar rates of ischemic events, resulting in superior net clinical benefit (death, myocardial infarction, stroke, major bleeding: 8.2% vs. 10.4%, HR 0.78, p = 0.004). Fondaparinux reduced major bleeding 48 h after PCI irrespective of whether PCI was performed <6 h of the last enoxaparin dose (1.6% vs. 3.8%, HR 0.42, p < 0.0001) or >6 h when UFH was given (1.3% vs. 3.4%, HR 0.39, p < 0.0001). Catheter thrombus was more common in patients receiving fondaparinux (0.9%) than enoxaparin alone (0.4%), but was largely prevented by using UFH at the time of PCI, without any increase in bleeding. |
| **Conclusions** | Upstream therapy with fondaparinux compared with upstream enoxaparin substantially reduces major bleeding while maintaining efficacy, resulting in superior net clinical benefit. The use of standard UFH in place of fondaparinux at the time of PCI seems to prevent angiographic complications, including catheter thrombus, without compromising the benefits of upstream fondaparinux.    (J Am Coll Cardiol 2007;50:1742–51) © 2007 by the American College of Cardiology Foundation |

Despite advances in antithrombotic therapies and percutaneous coronary intervention (PCI) for the management of patients with acute coronary syndrome (ACS), major cardiovascular events and bleeding complications remain important concerns. Evidence for the effectiveness of an early invasive management strategy in higher-risk ACS patients has led to the increasing use of PCI worldwide (1–4). In the U.S., contemporary registry data suggest that approximately 30% of all individuals presenting with ACS presently undergo a PCI procedure during the initial hospitalization (5). Efforts to further improve antithrombotic therapy in patients presenting with ACS have focused on preserving or enhancing efficacy while reducing major bleeding complications. Major bleeding has been associated with increased rates of ischemic events and mortality in rigorously performed observational analyses (6–8).

The OASIS-5 (Fifth Organization to Assess Strategies in Ischemic Syndromes) trial showed that the synthetic factor Xa inhibitor fondaparinux reduced major bleeding by 50% and 30-day mortality by 17% compared with enoxaparin in more than 20,000 patients with unstable angina or non–ST-segment elevation myocardial infarction (MI) (9). More than 14,000 patients in the OASIS-5 trial were randomized from centers with on-site catheterization laboratories, and more than 12,000 patients underwent heart catheterization during the initial hospitalization (10). Here we report the results of a prospectively planned analysis of the efficacy and safety of fondaparinux compared with enoxaparin in patients enrolled in the OASIS-5 trial who underwent PCI (including early PCI) during the study treatment period.

## Methods

**Patients.** The OASIS-5 trial design and rationale and the primary results have been previously published (9,10). Briefly, patients with unstable angina or non–ST-segment elevation MI were randomized, in a double-blind, double-dummy fashion, to receive either subcutaneous fondaparinux 2.5 mg once daily or subcutaneous enoxaparin 1 mg/kg twice daily (dose reduced to 1 mg/kg once daily in patients with creatinine clearance <30 ml/min). Patients were eligible for inclusion in the OASIS-5 trial if they met at least 2 of the following criteria: age ≥60 years, positive cardiac biomarkers, or electrocardiographic changes compatible with ischemia. Key exclusion criteria were any contraindication to low-molecular-weight heparin, hemorrhagic stroke within the last 12 months, an indication for anticoagulation other than ACS, revascularization procedure already performed for the qualifying event, and severe renal insufficiency (i.e., serum creatinine ≥3 mg/dl or 265 μmol/l). Patients could be treated with study drug for a maximum of 8 days after randomization. However, the median duration of therapy in patients undergoing PCI was only 2.5 days. Study drug was stopped because of either clinical stabilization, a revascularization procedure, or discharge home from hospital.

**Protocol for study drug administration in PCI patients.** The administration of study drugs during PCI maintained the double-dummy, double-blind design (Fig. 1) (10). The dose of study drug administered at PCI was determined by the time that had elapsed since administration of the last subcutaneous injection of study drug, and by whether concurrent glycoprotein (GP) IIb/IIIa inhibitors were to be used (Fig. 1). Monitoring of the activated clotting time (ACT) during PCI was not recommended because standard doses of unfractionated heparin (UFH) were used, but the ACT could be measured at the discretion of the investigator, particularly if a clinical need arose. Centers had the option of continuing study drug after a revascularization procedure, but this was not mandated by the study protocol. Sheaths could be removed immediately after PCI if a vascular closure device was used or a radial artery procedure was performed or >6 h after the last injection of fondaparinux or enoxaparin.

**Randomized to Fondaparinux Group**

|  | Last sc fonda dose <6 hours | Last sc fonda dose >6 hours |
|---|---|---|
| **GP IIb/IIIa Inhibitor YES** | No additional study drug given (patients were considered fully anticoagulated on fondaparinux). | IV fondaparinux 2.5mg was used for the procedure. |
| **GP IIb/IIIa Inhibitor NO** | IV fondaparinux 2.5mg was used for the procedure. | IV fondaparinux 5.0mg was used for the procedure. |

**Randomized to Enoxaparin Group**

|  | Last sc enox dose <6 hours | Last sc enox dose >6 hours |
|---|---|---|
| **GP IIb/IIIa Inhibitor YES** | No additional study drug given (patients were considered fully anticoagulated on enoxaparin). | Study UFH was used for the procedure. As a guideline to the investigator, the dose of UFH was 65 IU/kg. |
| **GP IIb/IIIa Inhibitor NO** | No additional study drug given (patients were considered fully anticoagulated on enoxaparin). | Study UFH was used for the procedure. As a guideline to the investigator, the dose of UFH was 100 IU/kg. |

**Figure 1    Dosing of Study Drug in Patients Undergoing PCI**

The dosing regimen for percutaneous coronary intervention (PCI) procedures in the fondaparinux (fonda) and enoxaparin (enox) groups according to time after last subcutaneous (sc) dose of study drug and use of glycoprotein (GP) IIb/IIIa antagonists. All study drugs were given in a double-blind, double-dummy fashion. IV = intravenous; UFH = unfractionated heparin.

After isolated reports of catheter thrombosis in a small number of patients (whose treatment allocation remained blinded), a protocol amendment was instituted on June 24, 2004, that detailed the correct method of administration of intravenous study drug and emphasized the importance of flushing all catheters and the intravenous line to ensure that the entire bolus of study drug (0.5-ml fondaparinux) reached the patient. In addition, centers were reminded that, at the investigator's discretion, it was permissible to give open-label UFH before PCI in addition to the protocol-mandated study drug (10). Importantly, the case report forms were amended to capture all cases of catheter thrombus and to capture whether open-label UFH was given in the catheterization laboratory before PCI.

**Outcomes.** The PCI analysis was a prespecified subgroup analysis of the OASIS-5 trial. Safety was assessed by evaluating rates of major bleeding and efficacy by evaluating the composite of death, MI, or stroke at days 9, 30, and 180. Definitions of these outcomes have been previously reported (9,10). Major bleeding was defined as clinically overt bleeding that was either fatal, intracranial, retroperitoneal, intraocular, a decrease in hemoglobin of ≥3.0 g/dl (with each blood transfusion unit counting for 1.0 g/dl of hemoglobin), or requiring transfusion of ≥2 U of red blood cells. An analysis of efficacy and safety results in patients undergoing very early PCI (within 24 h) was also prespecified. Creatine kinase and creatine kinase-MB were measured routinely at 6 to 8 h and 12 to 14 h after PCI. Within 48 h after PCI, a new MI was defined by creatine kinase-MB >3× the upper limit of normal (or increased by 50% from the preprocedural valley level) or new ST-segment elevation or new Q waves (10). Threatened abrupt closure was defined as the composite of new angiographic thrombus, major dissection, or no-reflow phenomenon. Guiding catheter-related thrombus was reported as an adverse event in the first 4,480 PCIs performed and was routinely collected in the final 1,758 patients undergoing PCI after implementation of the modification to the case report forms.

To evaluate the potential impact of additional UFH, the rates of catheter thrombus and major bleeding were examined separately using 2 approaches. In patients randomized to enoxaparin, the use of protocol-mandated UFH during PCI was assessed according to whether the PCI was performed <6 h of the last enoxaparin dose (where no UFH was given by protocol) or >6 h after the last enoxaparin dose (where UFH was recommended). The use of additional open-label UFH immediately before PCI was evaluated in both treatment groups.

**Statistical analysis.** An intention-to-treat approach was used for all analyses. All patients undergoing PCI during the study treatment period were included. All events occurring from randomization up to 9, 30, and 180 days were included in the analysis. Event rates within each group were calculated using the Kaplan-Meier estimator. For death, MI, stroke, and bleeding, the hazard ratio (HR) and 2-sided 95% confidence interval (CI) were calculated with use of the Cox proportional hazards model, with treatment effect as the only covariate. For all other comparisons, means and proportions were compared using the unpaired *t* test and chi-square test, respectively. A chi-square test was also used to compare the groups for major bleeding according to day after randomization. Separate analyses were performed comparing the treatment groups according to whether PCI was performed within 6 h of the last study drug administration (where fondaparinux was compared with enoxaparin) or more than 6 h from the last study drug administration (where fondaparinux was compared with the combination of enoxaparin and protocol-mandated UFH), and according to whether open-label UFH was used. All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

## Results

The disposition of patients undergoing PCI in the trial in relation to randomized treatment and use of open-label UFH is summarized in Figure 2. A total of 14,206 patients enrolled in the OASIS-5 trial underwent heart catheterization, 12,715 during the study drug administration period. A total of 8,100 patients underwent revascularization, including 6,238 PCIs and 1,862 coronary artery bypass grafts. Overall, 1,414 and 1,420 patients in the fondaparinux and enoxaparin groups, respectively, had early PCI within 24 h of randomization; an additional 1,976 and 1,972 within 48 h and 1,158 and 1,162 between 48 h and 8 days. Subcutaneous fondaparinux/placebo was given for a mean of 2.4 (standard deviation ±1.8) days before PCI and enoxaparin/placebo was given for a mean of 2.6 (standard deviation ±1.8) days before PCI.

**Baseline characteristics.** The baseline characteristics are well matched between the 2 randomized treatment groups (Table 1). Overall, 98.9% of patients in the fondaparinux group and 98.6% in the enoxaparin group received aspirin, 91.1% and 92.3% received a thienopyridine, and 38.8% and 40.4%, respectively, received an intravenous GP IIb/IIIa inhibitor (Table 1). Of the 8,754 lesions that were intervened on, 84.4% in the fondaparinux group and 85.3% in the enoxaparin group were treated with an intracoronary stent, of which 23.2% versus 22.9%, respectively, were drug-eluting stents (Table 1).

**Clinical outcomes.** In the fondaparinux group, 6.3% of patients experienced a death, MI, or stroke by day 9, compared with 6.2% of patients in the enoxaparin group (HR 1.03, 95% CI 0.84 to 1.25, p = 0.79) (Table 2). Each outcome taken individually and at 30 days and 6 months was also similar between the groups (Table 2). After PCI, the proportion of patients requiring urgent intervention within 24 h of recurrent ischemia did not differ between the 2 groups: 0.2% versus 0.2% at 48 h after the PCI and 0.7% versus 0.7% at 6 months.

Major bleeding at day 9 was significantly reduced with fondaparinux compared with enoxaparin (2.4% vs. 5.1%,
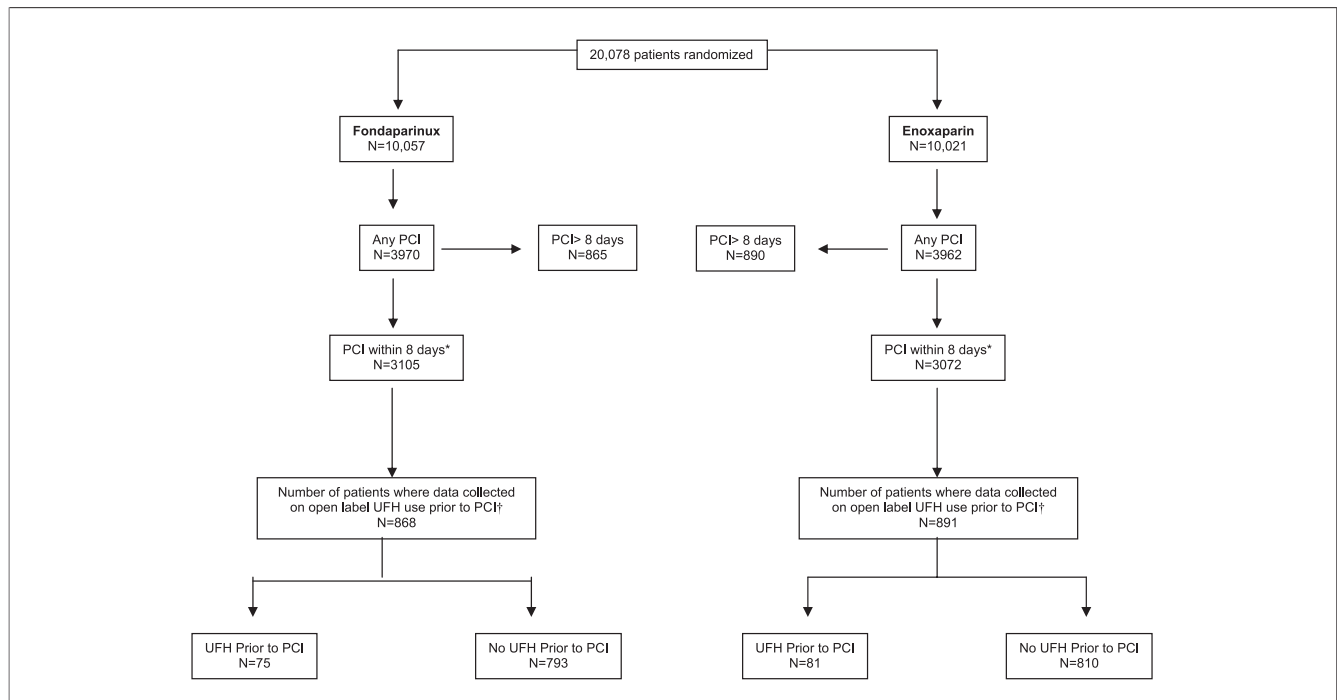
**Figure 2**    **Flow Diagram of Patients Undergoing PCI**

The disposition of patients undergoing percutaneous coronary intervention (PCI) in the OASIS-5 trial in relation to randomized treatment and use of open-label unfractionated heparin (UFH). *8 days was the maximum duration of study drug administration. Mean duration of treatment was 2.5 days. †Following protocol amendment.

HR 0.46, p < 0.00001) (Table 2). Similarly, there were large reductions in minor and total bleeding with fondaparinux (Table 2). Major bleeding was reduced with fondaparinux as early as the same day of randomization (i.e., within hours after administration of the first dose of study drug) (Table 3). Similarly, major bleeding was lower with fondaparinux on the first day and subsequent days after randomization (Table 3).

In addition, fondaparinux was superior to enoxaparin in reducing major bleeding at day 9 irrespective of whether the study drug was restarted after PCI (1.9% vs. 4.4%, HR 0.42, p < 0.00001) or was not restarted after the procedure (3.7% vs. 6.6%, HR 0.55, p < 0.00001). The study drug was restarted after PCI in 67.4% of patients for a median of 1 day after PCI. Overall, restarting of the study drug after PCI did not seem to increase major bleeding (3.1% study drug restarted vs. 5.1% study drug not restarted, relative risk [RR] 0.61, p < 0.0001).

The bleeding reduction with fondaparinux compared with enoxaparin was consistent irrespective of age or renal function. Major bleeding at 30 days in those ≥65 years old (4.1% vs. 8.0%, HR 0.49, 95% CI 0.37 to 0.66, p < 0.00001) and those <65 years old (1.5% vs. 2.5%, HR 0.58, 95% CI 0.34 to 0.99, p = 0.047) was significantly lower with fondaparinux. Similarly, major bleeding at 30 days in patients with a glomerular filtration rate below the median of 71 ml/min (3.9% vs. 8.0%, HR 0.47, 95% CI 0.34 to 0.66, p < 0.00001) and greater than or equal to the median

(2.0% vs. 3.5%, HR 0.58, 95% CI 0.39 to 0.88, p = 0.01) was also consistently reduced with fondaparinux.

Patients undergoing PCI who experienced a major bleeding event during the initial hospitalization had substantially higher rates of death (1.7% vs. 10.1%, HR 6.00, 95% CI 3.82 to 9.42, p < 0.00001), MI (5.3% vs. 14.3%, HR 2.77, p < 0.00001), and stroke (0.5% vs. 3.1%, HR 5.99, p < 0.00001) at 30 days and at 6 months (death: HR 4.31, p < 0.00001; MI: HR 2.47, p < 0.00001; stroke: HR 5.55, p < 0.00001).

The net clinical composite of death, MI, stroke, or major bleeding was significantly lower with fondaparinux compared with enoxaparin at day 9 (8.2% vs. 10.4%, HR 0.78, p = 0.004). This net clinical benefit of fondaparinux was preserved at longer-term follow-up at day 30 and at 6 months (Table 2).

**Outcomes in patients undergoing early PCI.** In patients undergoing PCI within the first 24 h, death, MI, or stroke occurred in 5.3% in the fondaparinux group and 5.4% in the enoxaparin group (HR 0.98, 95% CI 0.71 to 1.34) (Table 3). However, there was a marked reduction in major bleeding with fondaparinux (2.3% vs. 4.9%, HR 0.48, p = 0.0005) (Table 4). The net clinical outcome of death, MI, stroke, or major bleeding favored fondaparinux in those undergoing early PCI (7.3% vs. 9.5%, HR 0.76, p = 0.035) (Table 4).

**Angiographic outcomes and vascular access site complications.** Abrupt closure (1.5% vs. 1.1%) and threatened abrupt closure (5.3% vs. 4.7%) did not differ significantly between the fondaparinux and enoxaparin groups, respec-

| Table 1 | Baseline Characteristics, Concurrent Medications, and Procedural Details | |
|---|---|---|
| Outcome | Fondaparinux (%) (n = 3,134) | Enoxaparin (%) (n = 3,104) |
| Age, yrs (mean) | 64.6 | 64.5 |
| Female | 28.3 | 30.9 |
| Troponin/creatine kinase-MB > upper limit of normal | 79.0 | 80.3 |
| ST-segment depression ≥1 mm | 42.3 | 39.2 |
| Transient ST-segment elevation >2 mm | 3.5 | 3.8 |
| Transient ST-segment elevation ≤1 mm | 3.5 | 4.3 |
| T-wave inversion (≥2 mm) | 21.3 | 22.0 |
| Prior heart failure | 7.2 | 7.4 |
| Prior MI | 22.6 | 20.0 |
| Diabetic | 23.5 | 23.1 |
| Prior CABG | 9.0 | 8.4 |
| Prior PCI | 16.9 | 16.1 |
| Medications after randomization | | |
| ASA | 98.6 | 98.9 |
| Clopidogrel | 91.1 | 92.3 |
| Clopidogrel 6 h before | 29.1 | 29.7 |
| Beta-blocker | 88.1 | 89.5 |
| ACE/ARB | 73.7 | 73.8 |
| Statin | 83.7 | 83.6 |
| Glycoprotein IIb/IIIa inhibitor | 40.4 | 38.8 |
| Procedural details | | |
| Number of lesions | 4,417 | 4,337 |
| Complete success | 91.8 | 91.9 |
| Partial success | 3.1 | 2.8 |
| Intracoronary stent | 84.4 | 85.3 |
| Drug-eluting stent | 23.2 | 22.9 |
| Thrombus before PCI | 15.2 | 14.1 |
| Access site | | |
| Femoral | 87.5 | 88.4 |
| Radial | 12.0 | 11.0 |
| Brachial | 0.6 | 0.5 |
| PCI location | | |
| Left main | 1.0 | 1.5 |
| Left anterior descending | 41.5 | 42.0 |
| Circumflex artery | 26.4 | 25.9 |
| Right coronary artery | 27.7 | 27.1 |
| Saphenous vein graft | 3.3 | 3.4 |

p values for all comparisons >0.05.

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PCI = percutaneous coronary intervention.

tively. Overall vascular access site complications 48 h after PCI were substantially lower with fondaparinux than enoxaparin (3.2% vs. 8.1%, HR 0.40, p < 0.0001), including large hematomas (1.5% vs. 4.5%, HR 0.34, p < 0.0001) and pseudoaneurysms (1.0% vs. 1.6%, HR 0.63, p = 0.038). Catheter thrombus occurred in <1% of patients and was observed in both the fondaparinux and the enoxaparin groups. Overall, it was more common in the fondaparinux group (0.9%) compared with those undergoing PCI with enoxaparin alone (0.4%) and with those undergoing PCI with UFH added to enoxaparin 6 h after the last subcutaneous dose (0.2%). Irrespective of randomized treatment group, patients who experienced catheter-related thrombus

had significantly higher rates of MI (27% catheter thrombus vs. 4.2% no catheter thrombus, RR 6.51, 95% CI 3.78 to 11.20) and stroke (5.4% vs. 0.6%, RR 9.48, 95% CI 2.37 to 38.0) at 30 days. Mortality was 2.7% in those patients who had a catheter thrombus and 2.1% in those who did not (RR 1.31, 95% CI 0.19 to 9.17).

**Catheter thrombus and concomitant use of UFH.** EFFECT OF PROTOCOL-RECOMMENDED UFH. When PCI was performed <6 h of the last enoxaparin subcutaneous dose, the rates of abrupt closure and threatened abrupt closure did not differ between the enoxaparin and fondaparinux groups (5.9% fondaparinux alone vs. 6.2% enoxaparin alone, HR 0.96, 95% CI 0.73 to 1.26, p = 0.78); however, there was a large reduction in vascular access site complications in favor of fondaparinux (3.5% vs. 8.8%, HR 0.40, p < 0.0001) and major bleeding 48 h after the PCI (1.6% vs. 3.8%, HR 0.42, p < 0.0001) (Fig. 3). When PCI was performed after 6 h from the last subcutaneous enoxaparin dose and UFH was added in the enoxaparin group (but not the fondaparinux group), abrupt/threatened abrupt closure was reduced (6.6% fondaparinux alone vs. 4.3% UFH added to enoxaparin, RR 1.40, p = 0.048) (Fig. 3). The addition of UFH to the enoxaparin group 6 h after the last subcutaneous enoxaparin injection lowered the rate of abrupt/threatened abrupt closure compared with those undergoing PCI with enoxaparin alone (4.3% UFH added to enoxaparin vs. 6.2% enoxaparin alone, HR 0.70, p = 0.026) (Fig. 3). Importantly, the use of UFH at least 6 h after the last enoxaparin subcutaneous injection did not increase the risk of major bleeding in the enoxaparin group (3.8% enoxaparin alone vs. 3.4% UFH added to enoxaparin at least 6 h after the last subcutaneous dose) (Fig. 3).

With regard to catheter thrombus, there were a total of 8 cases reported with enoxaparin, 6 (0.4%) of which occurred when PCI was performed using enoxaparin alone and 2 (0.16%) of which occurred when protocol-mandated UFH was used (in 1 of these patients, PCI was performed with UFH before any study drug was given).

EFFECT OF OPEN-LABEL UFH. After the OASIS-5 protocol amendment, open-label UFH was permitted at the discretion of the investigator and information regarding its use was collected routinely in the final 1,758 patients undergoing PCI. Additional open-label UFH before PCI was given in 75 patients randomized to fondaparinux and 80 patients randomized to enoxaparin. The mean dose of UFH used in the fondaparinux group was 47 IU/kg. Catheter thrombus occurred in 10 fondaparinux-treated patients after the protocol amendment; 9 events occurred when no UFH was given before PCI (Table 5) and the remaining 1 case occurred in a patient who received a very low dose of open-label UFH (570 IU or 5 IU/kg). Importantly, major bleeding was not increased with use of open-label UFH in the fondaparinux group (1.3% with open-label UFH vs. 3.3% with no open-label UFH) (Table 5).

**Table 2    Short-Term and Long-Term Major Adverse Clinical Events in PCI Patients**

| Outcome | Fondaparinux (n = 3,105) | Enoxaparin (n = 3,072) | Hazard Ratio (95% CI) | p Value |
|---|---|---|---|---|
| **At 9 days** | | | | |
| Death, MI, or stroke | 197 (6.3) | 190 (6.2) | 1.03 (0.84–1.25) | 0.79 |
| Death | 37 (1.2) | 38 (1.2) | 0.96 (0.61–1.52) | 0.87 |
| MI | 160 (5.2) | 154 (5.0) | 1.03 (0.82–1.28) | 0.80 |
| Stroke | 12 (0.4) | 13 (0.4) | 0.91 (0.42–2.00) | 0.82 |
| Major bleeding | 73 (2.4) | 155 (5.1) | 0.46 (0.35–0.61) | <0.00001 |
| TIMI major bleeding | 19 (0.6) | 44 (1.4) | 0.43 (0.25–0.73) | 0.0019 |
| Minor bleeding | 51 (1.6) | 138 (4.5) | 0.36 (0.26–0.50) | <0.00001 |
| Total bleeding | 121 (3.9) | 289 (9.4) | 0.40 (0.33–0.50) | <0.00001 |
| Death, MI, stroke, major bleeding | 255 (8.2) | 318 (10.4) | 0.78 (0.67–0.93) | 0.004 |
| **At 30 days** | | | | |
| Death, MI, or stroke | 229 (7.4) | 227 (7.4) | 1.00 (0.83–1.20) | 0.99 |
| Death | 62 (2.0) | 65 (2.1) | 0.94 (0.67–1.34) | 0.74 |
| MI | 177 (5.7) | 168 (5.5) | 1.04 (0.84–1.29) | 0.69 |
| Stroke | 17 (0.6) | 22 (0.7) | 0.76 (0.41–1.44) | 0.40 |
| Major bleeding | 88 (2.9) | 166 (5.4) | 0.52 (0.40–0.67) | <0.00001 |
| TIMI major bleeding | 25 (0.8) | 46 (1.5) | 0.54 (0.33–0.87) | 0.012 |
| Minor bleeding | 53 (1.7) | 139 (4.5) | 0.37 (0.27–0.51) | <0.00001 |
| Total bleeding | 136 (4.4) | 301 (9.8) | 0.44 (0.36–0.53) | <0.00001 |
| Death, MI, stroke, major bleeding | 296 (9.5) | 361 (11.8) | 0.80 (0.69–0.93) | |
| **At 6 months** | | | | |
| Death, MI, or stroke | 312 (10.1) | 311 (10.2) | 0.99 (0.85–1.16) | 0.95 |
| Death | 99 (3.2) | 107 (3.5) | 0.92 (0.70–1.20) | 0.53 |
| MI | 230 (7.5) | 210 (6.9) | 1.09 (0.90–1.31) | 0.38 |
| Stroke | 25 (0.8) | 35 (1.2) | 0.71 (0.42–1.18) | 0.18 |
| Major bleeding | 104 (3.4) | 190 (6.3) | 0.53 (0.42–0.68) | <0.00001 |
| TIMI major bleeding | 28 (0.9) | 53 (1.7) | 0.52 (0.33–0.82) | 0.0052 |
| Minor bleeding | 56 (1.8) | 142 (4.6) | 0.39 (0.28–0.53) | <0.00001 |
| Total bleeding | 155 (5.0) | 326 (10.7) | 0.46 (0.38–0.55) | <0.00001 |
| Death, MI, stroke, major bleeding | 390 (12.7) | 452 (14.8) | 0.84 (0.74–0.96) | 0.013 |

CI = confidence interval; MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

**Bleeding in relation to use of GP IIb/IIIa inhibitors and pretreatment with clopidogrel.** Figure 4 shows bleeding rates at day 30 in the enoxaparin and the fondaparinux groups according to the concomitant use of GP IIb/IIIa inhibitors and pretreatment with clopidogrel at least 6 h before PCI. There was a significant reduction in bleeding

with fondaparinux irrespective of whether GP IIb/IIIa inhibitors or clopidogrel was used. The distribution of catheter thrombus in patients pretreated with clopidogrel, a GP IIb/IIIa inhibitor, or neither was similar in both treatment groups, suggesting that antiplatelet therapy does not guard against this phenomenon.

## Discussion

The results of the current analysis provide clear evidence that upstream therapy with fondaparinux in ACS patients targeted for early PCI was superior to enoxaparin in reducing major bleeding by one-half while maintaining similar efficacy, which resulted in superior net clinical benefit. The reduction in bleeding in ACS patients undergoing PCI who were treated with fondaparinux was similar to the reduction in bleeding observed with fondaparinux in patients not undergoing PCI in the main OASIS-5 trial (9). The reduction in bleeding complications was evident irrespective of the use of concomitant GP IIb/IIIa antagonists

**Table 3    Major Bleeding in PCI Patients According to the Day After Randomization**

| Days After Randomization | Fondaparinux (n = 3,105) | Enoxaparin (n = 3,072) | Relative Risk | p Value |
|---|---|---|---|---|
| Same day | 0.2 | 0.5 | 0.35 | 0.037 |
| 1 | 0.7 | 1.7 | 0.40 | <0.001 |
| 2 | 1.1 | 2.8 | 0.40 | <0.001 |
| 3 | 1.4 | 3.6 | 0.40 | <0.001 |
| 4 | 1.7 | 4.0 | 0.42 | <0.001 |
| 5 | 1.8 | 4.3 | 0.42 | <0.001 |
| 6 | 2.0 | 4.7 | 0.42 | <0.001 |
| 7 | 2.2 | 5.0 | 0.43 | <0.001 |
| 8 | 2.4 | 5.0 | 0.45 | <0.001 |

| Table 4 | Clinical Outcomes at Day 9 in Patients Undergoing Early PCI (Within 24 h of Randomization) | | | |
|---|---|---|---|---|
| Outcome | Fondaparinux (n = 1,414) | Enoxaparin (n = 1,420) | Hazard Ratio (95% CI) | p Value |
| Death, MI, or stroke | 75 (5.3) | 77 (5.4) | 0.98 (0.71–1.34) | 0.89 |
| Death | 19 (1.3) | 19 (1.3) | 1.01 (0.53–1.90) | 0.98 |
| MI | 53 (3.8) | 55 (3.9) | 0.97 (0.66–1.41) | 0.86 |
| Stroke | 6 (0.4) | 8 (0.6) | 0.76 (0.23–2.18) | 0.60 |
| Major bleeding | 33 (2.3) | 69 (4.9) | 0.48 (0.31–0.72) | 0.0005 |
| Minor bleeding | 30 (2.1) | 78 (5.5) | 0.38 (0.25–0.58) | <0.00001 |
| Total bleeding | 62 (4.4) | 144 (10.2) | 0.42 (0.31–0.57) | <0.00001 |
| Death, MI, stroke, major bleeding | 103 (7.3) | 135 (9.5) | 0.76 (0.59–0.98) | 0.035 |

Abbreviations as in Table 2.

or pretreatment with a thienopyridine. Major bleeding was significantly reduced by 65% with fondaparinux as early as the end of the day of randomization and by 60% by the end of the first day after randomization. These data show that, in the context of an aggressive early invasive strategy in which relatively short durations of antithrombotic treatment are administered, fondaparinux has substantial safety advantages over enoxaparin. Thus, the net efficacy–safety balance favors the use of upstream fondaparinux over enoxaparin in patients with ACS undergoing PCI, including those patients undergoing early PCI.

Patients in the OASIS-5 study who underwent PCI more than 6 h after the last study drug administration received additional intravenous fondaparinux if they were



**Figure 3** **Major Bleeding and Angiographic Complications**

Major bleeding 48 h after PCI and angiographic complications, according to use of protocol-specified UFH in the enoxaparin group. If PCI was performed within 6 h of the last subcutaneous enoxaparin dose, no additional UFH was given. If PCI was performed after 6 h from the last subcutaneous enoxaparin dose, supplemental UFH was administered for the PCI. Major bleeding was reduced with fondaparinux irrespective of whether UFH was used in the enoxaparin group. Angiographic complications were reduced when UFH was used for the PCI procedure compared with either fondaparinux alone or with enoxaparin alone. CI = confidence interval; RR = relative risk; other abbreviations as in Figure 1.

randomized to fondaparinux, but received UFH if they were randomized to enoxaparin. The UFH rather than intravenous enoxaparin was used in the latter case for 3 reasons. First, enoxaparin is not approved for use by regulatory agencies in patients undergoing PCI. Second, the American College of Cardiology/American Heart Association guidelines (11) and the European Society of Cardiology guidelines (12) recommend UFH as the anticoagulant of choice in patients undergoing PCI. Third, there were limited randomized data to support the use of enoxaparin during PCI.

In the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein Inhibitors) trial (13), crossover from enoxaparin to UFH was associated with higher bleeding complications. An adverse effect of crossover was not observed in the OASIS-5 trial among patients receiving protocol-mandated heparin at the time of PCI. Because the SYNERGY study was an open-label trial, the decision to cross over treatment from low-molecular-weight heparin to UFH may have been prompted by the development of a complication that resulted in a higher incidence of bleeding. The OASIS-5 study was a double-blind trial and, unlike the SYNERGY study, the use of UFH in the enoxaparin group was defined according to a set protocol. The addition of UFH to enoxaparin in over 2,750 patients undergoing PCI in the OASIS-5 trial caused no increase in bleeding complications, but had the advantage of preventing angiographic complications and catheter thrombus in those patients randomized to the enoxaparin group. The lack of increased bleeding with UFH was likely mitigated by the minimum 6-h time delay between the last subcutaneous injection of enoxaparin and the administration of UFH for the PCI procedure.

Traditionally, UFH (which is predominantly a factor IIa inhibitor with some factor Xa inhibitory capacity) has been the anticoagulant used during PCI. The true rates of catheter thrombus with UFH are unknown, but are likely to be very low. More recently, low-molecular-weight heparins, including enoxaparin and dalteparin, have been evaluated in randomized trials of PCI. The rates of catheter thrombus reported with both of these agents are substantially higher than those observed with UFH
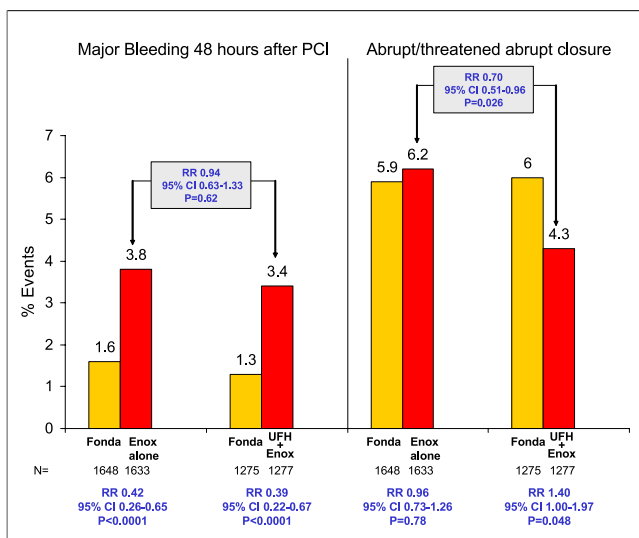
| Table 5 | PCI-Related Angiographic and Clinical Outcomes According to Use of Open-Label UFH Given in the Catheterization Laboratory Before PCI | | | | | |
|---|---|---|---|---|---|---|
| | **No UFH Before PCI** | | | **UFH Before PCI** | | |
| | Fonda (%) | Enox (%) | Hazard Ratio (95% CI) | Fonda (%) | Enox (%) | Hazard Ratio (95% CI) |
| Number randomized | 793 | 810 | — | 75 | 80 | — |
| Mean dose of open-label UFH (IU/kg) | — | — | — | 47 | 37 | — |
| Median dose of open-label UFH (IU/kg) | — | — | — | 33 | 30 | — |
| **At 30 days** | | | | | | |
| Death/MI/stroke/major bleed | 80 (10.1) | 90 (11.1) | 0.90 (0.67–1.22) | 4 (5.3) | 9 (11.2) | 0.45 (0.14–1.47) |
| Death/MI/stroke | 57 (7.2) | 60 (7.4) | 0.97 (0.68–1.40) | 3 (4.0) | 5 (6.3) | 0.62 (0.15–2.61) |
| Major bleed | 26 (3.3) | 35 (4.3) | 0.75 (0.45–1.25) | 1 (1.3) | 5 (6.2) | 0.21 (0.02–1.79) |
| **At study end** | | | | | | |
| Death/MI/stroke/major bleed | 101 (13.2) | 109 (13.6) | 0.94 (0.72–1.24) | 5 (6.7) | 13 (18.6) | 0.38 (0.14–1.07) |
| Death/MI/stroke | 77 (10.1) | 78 (9.8) | 1.02 (0.74–1.39) | 3 (4.0) | 6 (8.1) | 0.52 (0.13–2.06) |
| Major bleed | 28 (3.6) | 41 (5.1) | 0.69 (0.24–0.79) | 2 (2.7) | 9 (13.5) | 0.22 (0.05–1.03) |
| **Angiographic variables** | | | | | | |
| Abrupt closure | 15 (1.9) | 13 (1.6) | 1.18 (0.56–2.5) | 1 (1.3) | 0 | — |
| Threatened abrupt closure | 31 (3.9) | 38 (4.7) | 0.83 (0.52–1.32) | 4 (5.3) | 2 (2.5) | 2.13 (0.40–11.3) |
| Catheter thrombus | 9 (1.1) | 4 (0.5) | 2.30 (0.71–7.4) | 1 (1.3)* | 0 | — |
| Vascular access site complication | 22 (2.8) | 56 (6.9) | 0.40 (0.25–0.65) | 1 (1.3) | 5 (6.3) | 0.21 (0.03–1.8) |
| Pseudoaneurysm | 6 (0.8) | 8 (1.0) | 0.77 (0.27–2.2) | 0 | 0 | — |
| Large hematoma | 7 (0.9) | 29 (3.6) | 0.25 (0.11–0.56) | 0 | 4 (5.0) | — |

*This 1 patient received a suboptimal dose of UFH (only 570 IU or 5 IU/kg) before PCI, compared with the mean UFH dose of 3,561 IU or 47 IU/kg in the fondaparinux group.

Enox = enoxaparin; Fonda = fondaparinux; UFH = unfractionated heparin; other abbreviations as in Tables 1 and 2.

(14–16). In a recent trial evaluating enoxaparin in ST-segment elevation MI patients targeted for primary PCI, there were 3 cases of catheter thrombus of only 36 patients treated (12%), prompting a protocol amendment (14). In the OASIS-5 trial, catheter thrombus occurred



HR 0.56
95% CI 0.39–0.81
P=0.002

HR 0.43
95% CI 0.30–0.63
P<0.0001

HR 0.45
95% CI 0.28–0.72
P=0.001

HR 0.52
95% CI 0.39–0.71
P<0.0001

| Figure 4 | Major Bleeding With Concurrent Use of GP IIb/IIIa Antagonists and Pretreatment With Clopidogrel |
|---|---|

Major bleeding in relation to concurrent use of glycoprotein (GP) IIb/IIIa antagonists and clopidogrel pretreatment at least 6 h before percutaneous coronary intervention (PCI). Major bleeding was significantly reduced with fondaparinux **(yellow)** compared with enoxaparin **(red)** with or without concurrent use of these antiplatelet agents. GP IIb/IIIa (+) = GP IIb/IIIa inhibitor used before/during PCI; GP IIb/IIIa (−) = GP IIb/IIIa inhibitor not used before/during PCI; clopidogrel (+) = clopidogrel given at least 6 h before PCI; clopidogrel (−) = clopidogrel not given at least 6 h before PCI. CI = confidence interval; HR = hazard ratio.

in <1% of patients overall. Regardless of treatment, patients undergoing PCI who had catheter-related thrombus experienced significantly higher rates of ischemic events, including death, MI, or stroke, whereas patients who experienced major bleeding had a lower rate of these same events. Despite there being a higher proportion of catheter thrombus in the fondaparinux group, the rates of death, MI, or stroke in the fondaparinux and the enoxaparin groups were not different. It is possible that any excess ischemic events caused by catheter thrombus were balanced by a lower rate of these events secondary to reduced bleeding. This suggests that if catheter thrombus could be prevented (for example by using UFH at the time of PCI), a benefit of fondaparinux on late ischemic events and mortality might be apparent, as it was in the overall OASIS-5 trial (9). Certainly, the 8% lower mortality at 6 months observed in the fondaparinux group undergoing PCI is consistent with the 17% reduction observed in the overall trial, albeit with wide confidence intervals, because it a subgroup involving about one-third of the total OASIS-5 trial sample size.

The higher rate of catheter thrombosis among patients treated with fondaparinux compared with enoxaparin might be explained, in part, by the additional use of UFH in about half of the enoxaparin patients, which may have protected this group against catheter thrombus. Other potential explanations are the differences in intensity of anticoagulation and increased contact pathway activation of the coagulation system in patients treated with a selective factor Xa inhibitor. When either protocol-mandated UFH (in the enoxaparin group) or open-label UFH (in the fondaparinux group) were used, catheter thrombosis was almost com-
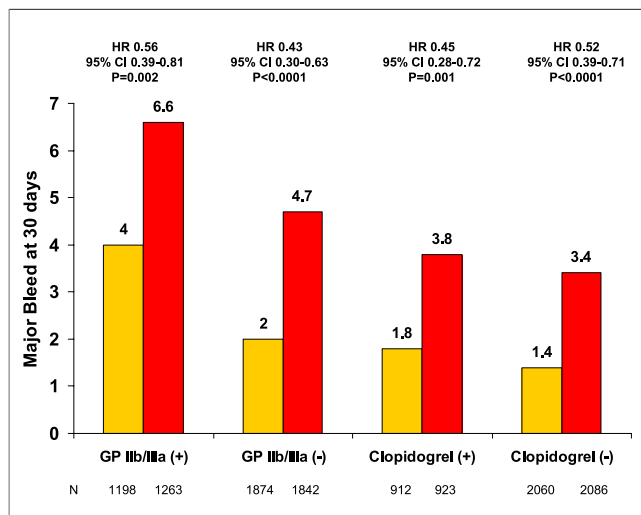
pletely eliminated, as might be expected. Therefore, although upstream fondaparinux is superior to enoxaparin in terms of net clinical benefit, we recommend that in fondaparinux-treated patients, UFH rather than intravenous fondaparinux be used as adjunctive therapy at the time of PCI. The use of UFH for PCI is familiar to interventional cardiologists, can be monitored using the ACT, and to our knowledge, no other antithrombin evaluated to date has proven to be superior in terms of efficacy to UFH for PCI.

Importantly, the protection provided against catheter thrombus and angiographic complications by adding conventional doses of UFH to fondaparinux or enoxaparin (6 h after the subcutaneous dose of the latter) did not increase the risk of major bleeding in either randomized treatment group, thus ensuring that the substantial benefit of upstream fondaparinux in reducing bleeding was maintained. The CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) registry showed that about 30% of ACS patients in the U.S. will undergo early PCI (5). Fondaparinux might be used upstream in these patients, with UFH added at PCI, whereas those patients not undergoing PCI can be treated with fondaparinux alone.

Bivalirudin was not used in the OASIS-5 trial, but previous randomized studies in patients undergoing elective PCI (17) or urgent PCI (18) have shown lower rates of bleeding with bivalirudin compared with UFH and a GP IIb/IIIa inhibitor. It follows logically that the use of bivalirudin during PCI in patients treated upstream with fondaparinux might be a very attractive option for the management of ACS patients. Such a strategy should be tested in future randomized controlled trials.

A limitation of our analysis is that the randomized treatments themselves may have influenced which patients underwent PCI. However, the types of patients undergoing PCI and the number and timing of PCI procedures was similar in the 2 randomized treatment groups. Secondly, the number of patients who received open-label UFH before PCI in the OASIS-5 trial was modest. However, UFH is standard therapy for PCI (11,12) and is associated with a low rate of catheter thrombus. Thus, the key issue is not whether UFH can prevent catheter thrombus in patients treated with upstream fondaparinux, but rather whether the addition of UFH to fondaparinux is safe. The OASIS-5 trial data suggest that the substantial reduction in bleeding with fondaparinux compared with enoxaparin is maintained even when open-label UFH is used on top of upstream fondaparinux (19).

In the OASIS-6 trial, fondaparinux did not increase bleeding compared with placebo in stratum 1, but nevertheless reduced mortality and recurrent MI (20). There were no cases of catheter thrombus and no increase in bleeding in OASIS-6 among the 231 patients undergoing nonprimary PCI who received protocol-mandated UFH on top of upstream fondaparinux (including those undergoing rescue,

facilitated, or early routine PCI) (20). This is consistent with the results of the OASIS-5 study and supports the conclusion that the use of UFH for the PCI procedure in patients treated upstream with fondaparinux is both safe and effective.

## Conclusions

For upstream management of ACS patients undergoing PCI, fondaparinux is superior to enoxaparin in preventing major bleeding while maintaining similar efficacy, thereby resulting in superior net clinical benefit. Catheter-related thrombosis occurs rarely when either fondaparinux or enoxaparin is used as the only anticoagulant during PCI. Adding UFH during PCI reduces the risk of catheter thrombus, without increasing bleeding. Thus, a tailored approach of using fondaparinux in a broad range of patients with ACS as initial upstream therapy, followed by targeted therapy with UFH in those who require a PCI procedure, is an attractive strategy for the management of ACS.

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