Effects of Fondaparinux on Mortality and Reinfarction in Patients With Acute ST-Segment Elevation Myocardial Infarction

The OASIS-6 Randomized Trial

The OASIS-6 Trial Group*

Context Despite many therapeutic advances, mortality in patients with acute ST-segment elevation myocardial infarction (STEMI) remains high. The role of additional antithrombotic agents is unclear, especially among patients not receiving reperfusion therapy.

Objective To evaluate the effect of fondaparinux, a factor Xa inhibitor, when initiated early and given for up to 8 days vs usual care (placebo in those in whom unfractionated heparin [UFH] is not indicated [stratum 1] or unfractionated heparin for up to 48 hours followed by placebo for up to 8 days [stratum 2]) in patients with STEMI.

Design, Setting, and Participants Randomized double-blind comparison of fondaparinux 2.5 mg once daily or control for up to 8 days in 12 092 patients with STEMI from 447 hospitals in 41 countries (September 2003-January 2006). From day 3 through day 9, all patients received either fondaparinux or placebo according to the original randomized assignment.

Main Outcome Measures Composite of death or reinfarction at 30 days (primary) with secondary assessments at 9 days and at final follow-up (3 or 6 months).

Results Death or reinfarction at 30 days was significantly reduced from 677 (11.2%) of 6056 patients in the control group to 585 (9.7%) of 6036 patients in the fondaparinux group (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.77-0.96; *P*=.008); absolute risk reduction, 1.5%; 95% CI, 0.4%-2.6%). These benefits were observed at 9 days (537 [8.9%] placebo vs 444 [7.4%] fondaparinux; HR, 0.83; 95% CI, 0.73-0.94; *P*=.003, and at study end (857 [14.8%] placebo vs 756 [13.4%] fondaparinux; HR, 0.88; 95% CI, 0.79-0.97; *P*=.008). Mortality was significantly reduced throughout the study. There was no heterogeneity of the effects of fondaparinux in the 2 strata by planned heparin use. However, there was no benefit in those undergoing primary percutaneous coronary intervention. In other patients in stratum 2, fondaparinux was superior to unfractionated heparin in preventing death or reinfarction at 30 days (HR, 0.82; 95% CI, 0.66-1.02; *P*=.08) and at study end (HR, 0.77; 95% CI, 0.64-0.93; *P*=.008). Significant benefits were observed in those receiving thrombolytic therapy (HR, 0.79; *P*=.003) and those not receiving any reperfusion therapy (HR, 0.80; *P*=.03). There was a tendency to fewer severe bleeds (79 for placebo vs 61 for fondaparinux; *P*=.13), with significantly fewer cardiac tamponade (48 vs 28; *P*=.02) with fondaparinux at 9 days.

Conclusion In patients with STEMI, particularly those not undergoing primary percutaneous coronary intervention, fondaparinux significantly reduces mortality and reinfarction without increasing bleeding and strokes.

Trial Registration ClinicalTrials.gov Identifier NCT00064428

JAMA. 2006;295:1519-1530 www.jama.com

Of 55 million deaths globally every year, about 30% are from cardiovascular diseases.[1] Of these, 40% to 50% are likely to be due to acute myocardial infarction (AMI).[1] Antiplatelet therapy,[2,3] thrombolytic therapy[4] and angiotensin-converting enzyme inhibitors[5] improve prognosis in ST-segment elevation AMI (STEMI). Primary percutaneous coronary intervention (PCI) offers benefits over thrombolytic therapy, but access to this procedure is limited.[6] Advances in treatments are likely to have a greater public health and clinical impact if they are effective, safe, simple to administer, affordable, and applicable to a widely diverse spectrum of economic and health care settings.

Trials of unfractionated heparin (UFH),[7] direct thrombin inhibitors,[8] and enoxaparin[9] have thus far failed to demonstrate mortality reductions, and bleeding is substantially increased when these agents are used with aspirin and thrombolytic therapy. Reviparin (a low-molecular-weight heparin) has been recently shown to reduce mortality and reinfarction in the large CREATE (Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation) trial, but this drug is not widely available.[10] Furthermore, reviparin increases the risk of life-threatening bleeding; how-

For editorial comment see p 1579.

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ever, the net clinical benefit was favorable. Therefore, there is a clear need for an effective, inexpensive, and safe antithrombotic agent for patients with STEMI.

Fondaparinux, a synthetic pentasaccharide, is a factor Xa inhibitor that selectively binds antithrombin and rapidly inhibits factor Xa.[11] Fondaparinux has been shown to be superior to enoxaparin in several trials of venous thromboembolic prophylaxis,[12] and the OASIS-5[13] trial reported similar short-term efficacy of fondaparinux compared with enoxaparin in preventing ischemic events in patients without STEMI, with a large reduction in bleeding. This resulted in significant reductions in mortality, MI, and strokes at 3 to 6 months.

We conducted the OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes) trial to evaluate the impact of fondaparinux compared with standard approaches to antithrombotic therapy in a broad range of patients with STEMI in preventing the primary and composite outcome of death or reinfarction at 30 days. These outcomes were also assessed at 9 days and at study end (minimum of 3 and maximum of 6 months). The main safety outcome was severe bleeding and the balance of benefits and risks was assessed using the composite outcome of death, reinfarction, and severe bleeding at each of the above time points.

METHODS

OASIS-6 is a randomized, double-blind trial of fondaparinux vs usual care in 12 092 patients with STEMI involving 447 centers from 41 countries (September 2003-January 2006). The study was coordinated by the Canadian Cardiovascular Collaboration Project Office located at the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario. The study was approved by the respective ethics committees and regulatory bodies.

After obtaining written informed consent, patients presenting with STEMI within 24 hours of symptom onset were enrolled. This time window was shortened to less than 12 hours after approximately 4300 patients had been enrolled, based on the results of the CREATE trial,[10] and without knowledge of any interim results from OASIS-6. Patients with contraindications to anticoagulation, including those at high risk of bleeding, receiving oral anticoagulants, or with creatinine levels greater than 265.2 mg/dL (3.0 mmol/L), were excluded.

Randomization was stratified by indication for the use of UFH based on the investigator's judgment. Five thousand six hundred fifty-eight patients were enrolled in stratum 1 (no indication for UFH) and 6434 patients were enrolled in stratum 2 (indication for UFH, eg, intended use of fibrin-specific thrombolytic, patients not eligible for fibrinolytics but eligible for antithrombotics, or those scheduled for primary PCI). Patients in stratum 1 were assigned to receive blinded fondaparinux 2.5 mg initially subcutaneously once daily or matching placebo on subsequent days for up to 8 days or hospital discharge, if earlier. Patients in stratum 2 were assigned to receive either blinded fondaparinux (or matching placebo; initial dose intravenous and subsequent doses subcutaneously) for up to 8 days or hospital discharge. Those in the control group received UFH bolus injection of 60 IU/kg followed by an infusion of 12 IU/kg per hour for 24 to 48 hours. Equivalent placebo bolus and injections were used in the fondaparinux group. The maximum dose of the bolus was 4000 IU and maximum initial infusion rate of 1000 IU/h for patients weighing more than 70 kg and adjusted to maintain activated partial thromboplastin time within the therapeutic range of 1.5 to 2.0 times control. Higher doses could be used during PCI (TABLE 1).

To maintain the double-blind criteria, patients receiving UFH or placebo infusion (for more than 3 hours) have regular activated partial thromboplastin time monitoring using a hemachron device. A central computerized system produced either real or sham activated partial thromboplastin time values, which were used to adjust the rate of infusion. In the stratum 2 group, no heparin was used in 101 control patients and 108 fondaparinux patients, an intravenous bolus and infusion was used in 1132 and 1131 patients, intravenous bolus was used only in 1986 and 1966, and an infusion alone was used in 2 and 8 patients, respectively.

Stratum 2 patients scheduled for primary PCI received single-bolus injections (either fondaparinux or UFH) immediately before the procedure and were dosed according to use of prerandomization UFH and glycoprotein IIb/IIIa inhibitor use (Table 1).

Patients were also randomly assigned to receive an infusion of glucose-insulin-potassium (GIK) or no infusion in a partial factorial design to evaluate its effects in preventing death or nonfatal cardiac arrest. This part of the study was discontinued in November 2004 after the results of the CREATE-ECLA (Estudios Cardiologicas Latin America) GIK study indicated that GIK was not beneficial.[14] At that time, 2747 patients had been randomly assigned to receive GIK or usual care. The results of this comparison will be reported separately, but adjustment for the GIK randomization did not alter the main comparison of fondaparinux reported herein.

Follow-up, Outcome Ascertainment, and Classification

Patients were scheduled to be followed up at hospital discharge, at 30 days, and at 3 months. In addition, the first 6976 patients were followed up to 6 months. Vital status was ascertained in 12 085 patients (99.9%) at hospital discharge, 12 072 (99.8%) at 30 days, and 12 052 (99.7%) at the final visit.

The primary efficacy outcome was death or reinfarction at 30 days, with the same outcomes assessed at 9 days and at study end, ie, 3 or 6 months (secondary outcomes). All deaths, reinfarction, strokes, and severe or

major bleeds were centrally adjudicated using standardized definitions. Deaths were classified further as cardiovascular, cardiac, other vascular, and non-cardiovascular.

Reinfarction was defined as follows: (1) within 24 hours of randomization—recurrent ischemic symptoms with new persistent ST elevation greater than 1 mm in at least 2 contiguous leads or new persistent ST depression greater than 1 mm in at least 2 contiguous leads not due to changes from evolution of the index MI; (2) between 24 hours and 7 days of randomization—ischemic symptoms greater than 20 minutes and either creatine kinase-CK (CK-MB; or total CK if CK-MB not available) greater than twice the upper limit of normal or further elevations more than 50% above previous lowest level in patients with already elevated enzymes or new or recurrent STEMI or depression of more than 1 mm or new significant Q waves in at least 2 contiguous leads, which was separate from the baseline MI; (3) after 7 days of randomization—either typical rise and fall of biochemical markers of myocardial necrosis to greater than twice the upper limit of normal or if markers were already elevated, further elevation of a marker to greater than 50% of the lowest recovery level from the index MI with either ischemic symptoms, development of new pathological Q waves, or other ischemic changes on the electrocardiogram or coronary artery intervention. After PCI, a new MI was defined by CK-MB greater than 3 times the upper limit of normal (and this elevation was greater than 50% of the lowest recovery level).

Two approaches to classifying bleeding were used. For comparison with the Thrombolysis in Myocardial Infarction (TIMI) trials,[15] we subdivided all bleeding episodes into severe (fatal hemorrhage, intracranial hemorrhage, cardiac tamponade, or a clinically significant hemorrhage with a decrease in hemoglobin [Hb] of >5 g/dL, with each blood transfusion unit counting for 1.0 g/dL of Hb), minor (clinically overt hemorrhage with decrease in Hb >3.0 to ≤5.0 g/dL that did not meet criteria for severe hemorrhage, with each blood transfusion unit counting as the equivalent of a 1 g/dL of Hb), and other. For comparison with the OASIS-5 trial of fondaparinux in acute coronary syndrome, we classified bleeding events as major (≥2 units of blood transfused, decrease of hemoglobin of >3 g/dL, intracranial, fatal, retroperitoneal, intraocular, or needing surgical intervention) bleeds and other minor bleeds. The balance of benefit and risk was assessed using the composite outcome of death, MI, or severe (or major) bleeds at 9 and 30 days and at study end.

Sample Size Calculations, Interim Monitoring, and Statistical Analysis

A sample size of 10 000 patients and an expected event rate of 8% at 9 days allowed for a 90% power to detect a relative risk reduction of 20% (2-sided $\alpha = .05$). When about 8000 patients had been randomized, the overall event rates were observed to be lower than expected, so the study sample size was increased to 12 000 patients with the primary efficacy outcome being ascertained at 30 days (for consistency with previous trials) and the secondary outcome (original primary at 9 days) was to be ascertained at 9 days and at study end.

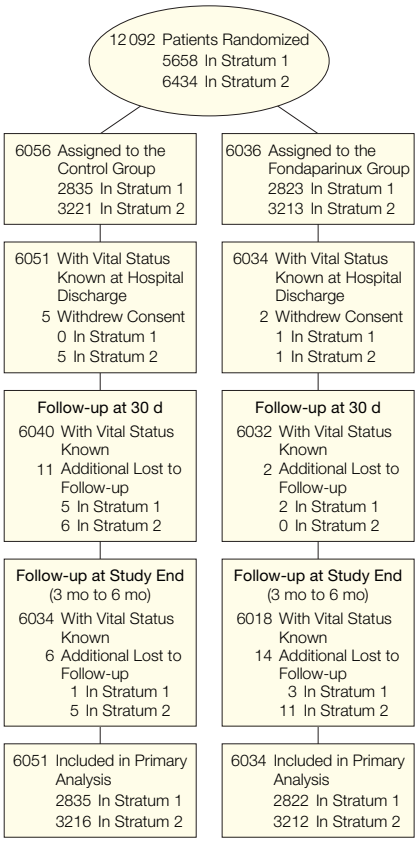
An independent data and safety monitoring board periodically reviewed the data. Two formal interim analyses were planned: when one half and three fourths of the expected events at day 30 had been observed. Extreme monitoring boundaries were used as guidelines to consider stopping the trial early. The trial could be stopped if the rates

Table 1. OASIS-6: Study Drug Regimen and Dosing*

Patients Not Receiving Primary PCI		
Indication for UFH	**Fondaparinux Regimen**	**Control Regimen**
No (stratum 1)	2.5 mg subcutaneously once daily (first dose given intravenously)	Matching placebo subcutaneously once daily
Yes (stratum 2)	2.5 mg subcutaneously once daily (first dose given intravenously)†	UFH at 60 IU/kg (maximum, 4000 U) followed by intravenous infusion at 12 IU/kg/h†
Patients Scheduled for Primary PCI (Stratum 2)		
Prerandomization	**Fondaparinux Regimen**	**UFH Control Regimen**
Received UFH plus Gp IIb/IIIa antagonist	2.5-mg intravenous bolus followed by 2.5 mg subcutaneously daily for up to 8 days	Measure ACT preprocedure; UFH as per local practice (maximum, 65 IU/kg)‡
Received UFH without Gp IIb/IIIa antagonist	5.0-mg intravenous bolus followed by 2.5 mg subcutaneously for up to 8 days	Measure ACT preprocedure; UFH as per local practice (maximum, 100 IU/kg)‡
Did not receive UFH and received Gp IIb/IIIa antagonist	2.5-mg intravenous bolus followed by 2.5 mg subcutaneously daily for up to 8 days	UFH at 65 IU/kg in intravenous bolus
Did not receive either UFH or Gp IIb/IIIa antagonist	5.0-mg intravenous bolus followed by 2.5 mg subcutaneously daily for up to 8 days	UFH at 100 IU/kg in intravenous bolus

Abbreviations: ACT, activated clotting time; Gp, glycoprotein; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.
*A double-blind, double-dummy technique was used for administration of all study drugs.
†If prerandomization UFH was given, study drugs were started 2 to 3 hours after the initial open-label UFH bolus or 2 to 3 hours after termination of the initial UFH infusion.
‡In patients who received UFH prior to randomization, it was recommended that an ACT be checked prior to PCI. Heparin was administered according to level of ACT, as per local practice. In those centers that did not have ACT measurement capability, it was recommended that fondaparinux, 5.0 mg intravenously, or UFH, 100 IU/kg, be given if prerandomization UFH dose was less than 4000 U and fondaparinux, 2.5 mg intravenously, or UFH, 65 IU/kg, be given if prerandomization UFH dose was 4000 to 5000 U. Patients who received more than 5000 U of prerandomization UFH were excluded from the trial.

Figure 1. Study Flow Diagram



of death or MI favored fondaparinux by 4 SDs in the first half, or by 3 SDs in the second half of the trial on 2 consecutive examinations of data about 3 months apart. The study could also be stopped for safety if the rates of the primary event were higher in the fondaparinux group (excess of 3 standard deviations in the first half, and 2 and a half standard deviations in the second half).

All randomized patients are included in the analysis in their originally allocated treatments groups (intent to treat). All events unrefuted by the adjudication committee are included. The Cox proportional hazards model stratified by the indication for UFH was used, and estimates of the hazard ratios (HRs) and 2-sided 95% confidence intervals (CIs) were calculated.

The primary efficacy and safety outcomes were also summarized by constructing Kaplan-Meier curves. The prespecified 2-sided α level to test for interactions between subgroups was .01 for efficacy outcomes and .05 for safety outcomes. In addition to the 2 strata by indication for use of UFH, other prespecified subgroups included age (above and below the median), sex, initial reperfusion strategy (thrombolytic, primary PCI, or neither), time to reperfusion therapy from symptoms, GRACE (Global Registry of Acute Coronary Events) risk score[16] (above or below the median), and prerandomization heparin use.

The statistical analyses were performed by 2 statisticians at the Population Health Research Institute (R.A., J.P., who are members of the writing committee). SAS version 9.1 was used for analysis (SAS Institute Inc, Cary, NC), and SPlus version 6.2 (Insightful Corp, Seattle, Wash) was used for graphics.

RESULTS

A total of 12 092 patients were randomly assigned to receive either fondaparinux or placebo between September 2003 and September 2005. The flow of patients through the trial is summarized in FIGURE 1.

TABLE 2 summarizes the key baseline characteristics. The median time from symptom onset to randomization was 4.8 hours, with a slightly longer delay in stratum 1 (5.3 hours) compared with stratum 2 (4.3 hours). A higher proportion of patients in stratum 1 had heart failure at entry (18.3% vs 10.1%), fewer had prior revascularization (2.2% vs 5.9%) or were taking aspirin (52.8% vs 69.6%) or a thienopyridine (8.3% vs 23.7%) prior to randomization. There were no major differences between the 2 strata in other clinical characteristics or the use of drugs prior to randomization.

Overall the use of oral antiplatelet agents, blockers of the renin-angiotensin system, and lipid-lowering drugs were high (Table 2). Thrombolytic therapy was used in 45.0% of the patients (78.0% in stratum 1; 15.9% in stratum 2), and primary PCI in 28.9% (0.2% in stratum 1 and 53.2% in stratum 2). Streptokinase was the most commonly used thrombolytic agent (about 73%). Two thousand eight hundred sixty-seven (23.7%) did not receive any reperfusion therapy. The final diagnosis of MI was not confirmed in 110 (1.8%) of placebo patients compared with 142 (2.4%) of those allocated to receive fondaparinux ($P=.04$), with similar directional results in stratum 1 (43 vs 47) and stratum 2 (67 vs 95).

Adherence

The median duration of blinded therapy was 8 days in stratum 1 and 7 days in stratum 2. The median duration of use of UFH in stratum 2 was 45 hours (interquartile range, 25-48). The median bolus dose of UFH was 4875 IU, and the rate of infusion was 12 units/kg per hour in those actually receiving the above treatments. Three thousand eight hundred eighty-six patients (69%) in stratum 1 received study medication for 7 days compared with 3369 (52%) in stratum 2. Prerandomization UFH was used in 880 (14.5%) of patients in the placebo group compared with 907 (15.0%) in the fondaparinux group (342 [6.0%] in stratum 1 and 1445 [22.5%] in stratum 2). Postrandomization nonstudy UFH was used in 681 (11.2%) patients in the placebo group compared with 651 (10.8%) in the fondaparinux group (stratum 1, 8.5% vs 7.5%; stratum 2, 13.7% vs 13.6%). Glycoprotein IIb/IIIa inhibitors were used in 15.5% of patients in the placebo group and 15.8% of patients in the fondaparinux group (stratum 1, 62 [2.2%] vs 52 [1.8%]; stratum 2, 879 [27.3%] vs 899 [28.0%]).

Open label low-molecular-weight heparin was used in significantly fewer patients receiving fondaparinux (384 [6.3%] placebo vs 322 [5.3%] fondaparinux, $P=.02$), with similar patterns in stratum 1 (132 [4.7%] vs 101 [3.6%]) and stratum 2 (252 [7.8%] vs 221 [6.9%]). Activated partial thromboplastin time values were collected using the Hemochron device on 1134

(97%) stratum 2 patients who had an infusion of more than 3 hours and randomized to UFH (median activated partial thromboplastin time, 54) and sham activated partial thromboplastin time values were collected in 1117 (97%) stratum 2 patients randomized to fondaparinux (median activated partial thromboplastin time, 65).

Efficacy Outcomes

The composite of death or MI was significantly reduced at 9 days, 30 days (primary outcome), and at the end of the study (TABLE 3). The relative risk reduction was 17% at 9 days, 14% at day 30, and 12% at study end. The absolute difference between the 2 treatment groups at 9 days was about 1.5% (95% CI, 0.4%-2.6%) lower with fondaparinux compared with control. This difference persisted throughout the study indicating that the benefits of treatment accrue early and are maintained long term (FIGURE 2). Consistent reductions in both death and reinfarction were observed at each of the 3 time points, with the reduction in deaths being statistically significant throughout (eg, at day 30, 540 [8.9%] deaths among controls vs 470 [7.8%] among those receiving fondaparinux; $P=.03$).

There were no significant differences in refractory ischemia (26 vs 27), cardiac arrests (239 vs 229), or strokes (55 vs 43) at 9 days among the controls vs those receiving fondaparinux. There was, however, a trend toward fewer patients developing heart failure or cardiogenic shock (599 controls vs 563 fondaparinux) so that the composite outcome of death, reinfarction, cardiogenic shock, or heart failure was significantly reduced at 9 days (920 [15.2%] vs 828 [13.7%]; $P=.02$) and at 30 days (1082 [17.9%] vs 991 [16.4%]; $P=.04$).

Bleeding

There was a nonsignificant trend toward fewer severe hemorrhages (using a modified TIMI–major bleeding definition) with fondaparinux compared with the placebo group at 9 days (79 [1.3%] control vs 61 [1.0%]

Table 2. OASIS-6 Patient Characteristics and Ancillary Treatments

Variable	Placebo or Unfractionated Heparin (n = 6056)	Fondaparinux (n = 6036)
Age, mean (SD), y	61.5 (12.2)	61.6 (12.3)
Men, No. (%)	4353 (71.9)	4393 (72.8)
Time from onset of pain to randomization, median (IQR), h	4.8 (3.0-8.5)	4.8 (2.9-8.6)
Heart rate, mean (SD), beats/min	76.0 (14.4)	76.3 (14.5)
Systolic blood pressure, mean (SD), mm Hg	134.3 (23.5)	134.0 (23.2)
Medical history, No. (%)		
Current or former smoker	3467 (57.2)	3552 (58.8)
Hypertension	3307 (54.6)	3274 (54.3)
Diabetes	1064 (17.6)	1088 (18.0)
Heart failure	840 (13.9)	844 (14.0)
Myocardial infarction	746 (12.3)	772 (12.8)
Stroke	385 (6.4)	416 (6.9)
CABG surgery or PCI	237 (3.9)	235 (3.9)
Baseline electrocardiogram, No. (%)		
ST-segment elevation >2 mm	3728 (61.6)	3610 (59.8)
ST-segment elevation >1 mm	2183 (36.0)	2282 (37.8)
New left bundle-branch block	60 (1.0)	58 (1.0)
Indicative of true posterior MI	74 (1.2)	80 (1.3)
Medications within 7 days of randomization, No. (%)		
Aspirin	3741 (61.8)	3728 (61.8)
β-Blockers	1593 (26.3)	1597 (26.5)
ACE inhibitor or ARB	1560 (25.8)	1516 (25.1)
Clopidogrel or ticlopidine	1006 (16.6)	957 (15.9)
Unfractionated heparin	880 (14.5)	907 (15.0)
Lipid-lowering agents	689 (11.4)	671 (11.1)
Calcium channel blockers	598 (9.9)	648 (10.7)
LMW heparin	107 (1.8)	114 (1.9)
Gp IIb/IIIa receptor antagonist	117 (1.9)	113 (1.9)
Bivalirudin or hirudin	2 (<0.1)	2 (<0.1)
Medications in hospital after randomization, No. (%)		
Aspirin	5839 (96.4)	5841 (96.8)
β-Blockers	5074 (83.8)	5092 (84.4)
ACE inhibitor or ARB	4847 (80.0)	4795 (79.4)
Clopidogrel or ticlopidine	3540 (58.5)	3481 (57.7)
Unfractionated heparin	681 (11.2)	651 (10.8)
Lipid-lowering agents	4529 (74.8)	4494 (74.5)
Calcium channel blockers	624 (10.3)	639 (10.6)
LMW heparin	384 (6.3)	322 (5.3)
Gp IIb/IIIa receptor antagonist	941 (15.5)	951 (15.8)
Bivalirudin or hirudin	7 (0.1)	5 (0.1)
Procedures in hospital, No. (%)		
Coronary angiography	2625 (43.3)	2656 (44.0)
PCI	2231 (36.8)	2228 (36.9)
Primary (for current event)*	1903 (31.4)	1886 (31.2)
Other	328 (5.4)	342 (5.7)
Thrombolytic therapy for index MI	2744 (45.3)	2692 (44.6)
CABG surgery	80 (1.3)	69 (1.1)
Procedures after discharge, No.(%)		
Coronary angiography	413 (6.8)	396 (6.6)
PCI	201 (3.3)	213 (3.5)
CABG surgery	144 (2.4)	170 (2.8)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; Gp, glycoprotein; IQR, interquartile range; LMW, low-molecular-weight; MI, myocardial infarction; PCI, percutaneous coronary intervention.
*There were additional primary PCIs for reinfarctions.

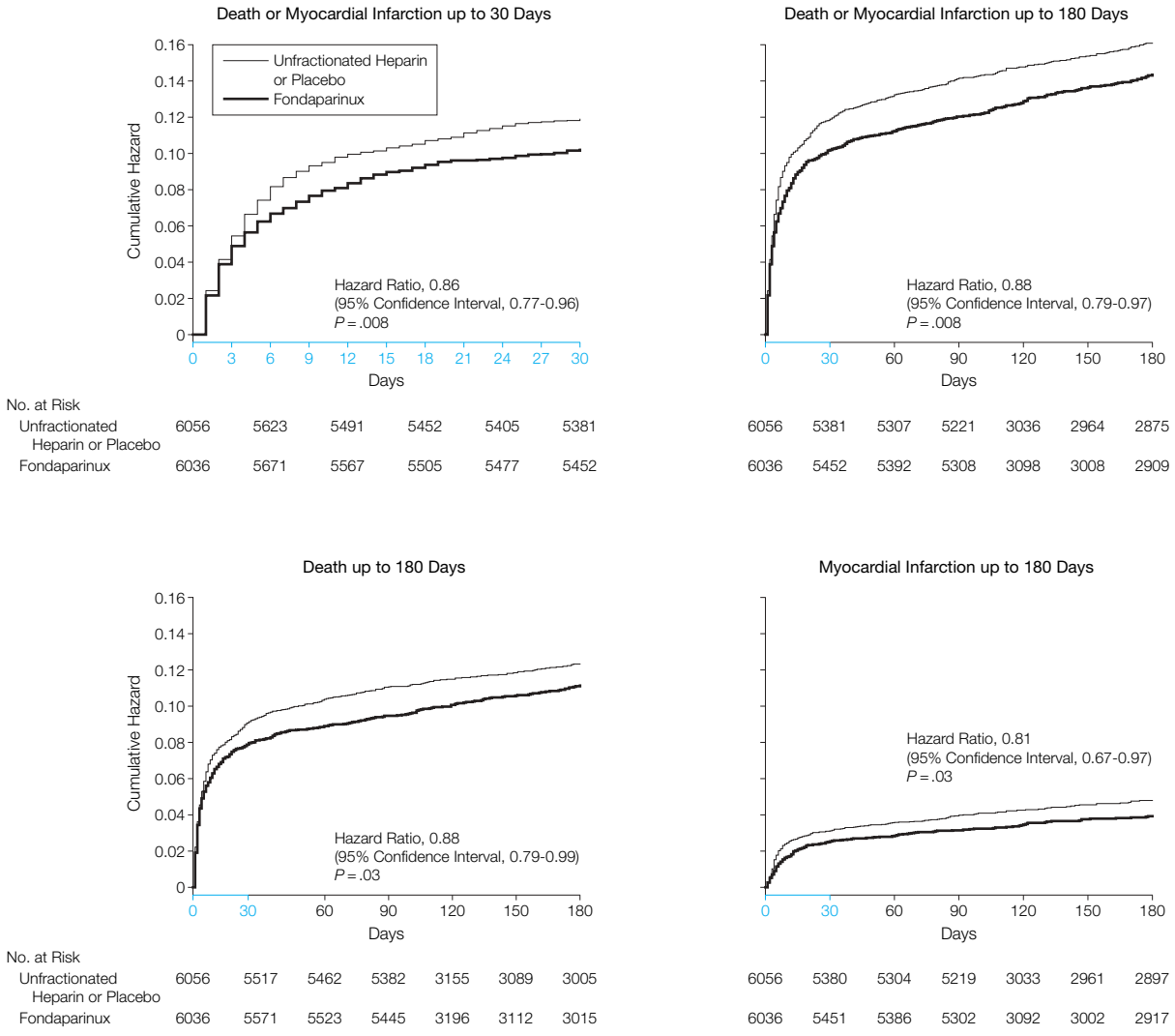
Table 3. Efficacy of Fondaparinux at Days 9 and 30 and Study End on Death or Reinfarction

	No. (%) of Patients				
	Placebo or Unfractionated Heparin (n = 6056)	Fondaparinux (n = 6036)	Absolute Difference, %	Hazard Ratio (95% Confidence Interval)	*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 mo)	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 mo)	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 mo)	245 (4.6)	200 (3.8)	45 (–0.8)	0.81 (0.67-0.97)	.03

*Primary efficacy outcome.

fondaparinux; FIGURE 3), with differences observed chiefly in fatal bleeds (49 vs 35) and in cardiac tamponade (48 vs 28; *P* = .02; TABLE 4). Fewer bleeds in the fondaparinux group were also observed using the OASIS-5 definition of major bleeds (130 vs 107). Surprisingly, lower rates were observed for severe hemorrhage (44 vs 28; *P* = .06) and for major bleeds (57 vs 39; *P* = .07) with fondaparinux compared with placebo in stratum 1. In stratum 2, the rates of severe and major bleeds were similar in the 2 groups. In patients not undergoing primary PCI, there were 29 patients with severe bleeds in the UFH group compared with

Figure 2. Comparison of the Rates of Death and Myocardial Infarction



20 in the fondaparinux group. The rates of intracranial hemorrhage were similar in the 2 groups (10 [0.2%] vs 11 [0.2%]).

Subgroup Analyses

The effect of fondaparinux on the composite outcome of death or reinfarction was not statistically heterogenous between the 2 strata at day 9 and day 30, although the apparent effect size was larger in those in stratum 1. However, by study end, the effect sizes were almost identical (HRs of 0.87 in stratum 1 and 0.88 in stratum 2; TABLE 5). Similar results were observed for the composite outcome that included death, MI, or severe bleeds.

When patients in stratum 2 were subdivided into those undergoing or not undergoing primary PCI for the index event, there was little apparent benefit of receiving fondaparinux in the former group, whereas in the latter subgroup fondaparinux appeared to be superior to UFH at 30 days (189 vs 154; HR, 0.80; 95% CI, 0.65-0.99; $P=.04$) and study end (251 vs 193; HR, 0.75; 95% CI, 0.62-0.90; $P=.002$; TABLE 6). The results on death or MI were not significantly heterogenous in men and women, in those older or younger than the median age, in subgroups defined by the time from symptom onset to randomization (FIGURE 4), with use of various concomitant therapies or various types of thrombolytic agents (data available on request).

There was, however, significant heterogeneity in the effect of fondaparinux at 30 days in subgroups based on the type of reperfusion strategy (Figure 4). At 30 days, significant benefits were observed in those who received no reperfusion therapy (15.1% control vs 12.2% fondaparinux; HR, 0.80; 95% CI, 0.65-0.98; $P=.003$), a thrombolytic agent (13.6% vs 10.9%; HR, 0.79; 95% CI, 0.68-0.92; $P=.003$), but not in those undergoing primary PCI (4.9% vs 6.0%; HR, 1.24; 95% CI, 0.95-1.63; $P=.12$; P for heterogeneity = .04; Figure 4). Patients undergoing primary PCI were at lower predicted risk (mean entry GRACE score, 101), compared with those receiving thrombolytic therapy (entry GRACE score, 114) or no reperfusion therapy (entry GRACE score, 124). The number of days of use of study antithrombotic therapy was shorter in those undergoing primary PCI (5.4 days) compared with those receiving thrombolytic therapy (6.3 days) or no reperfusion therapy (6.6 days). There was no heterogeneity of results by the type of thrombolytic therapy used.

When patients were subdivided by the GRACE score, there was a highly significant reduction in death or MI at day 30 in patients predicted to be at high risk (GRACE score ≥112; 18.0% vs 14.5%, HR, 0.79; 95% CI, 0.70-0.90; $P<.001$) with no apparent benefit in low-risk patients (4.3% vs 4.6%; HR, 1.07; 95% CI, 0.84-1.36; $P=.57$; P for heterogeneity = .03). Similar patterns were observed separately for both death and MI.

Figure 3. Comparison of Rates of Severe Bleeding at 30 Days (Modified TIMI Criterion)

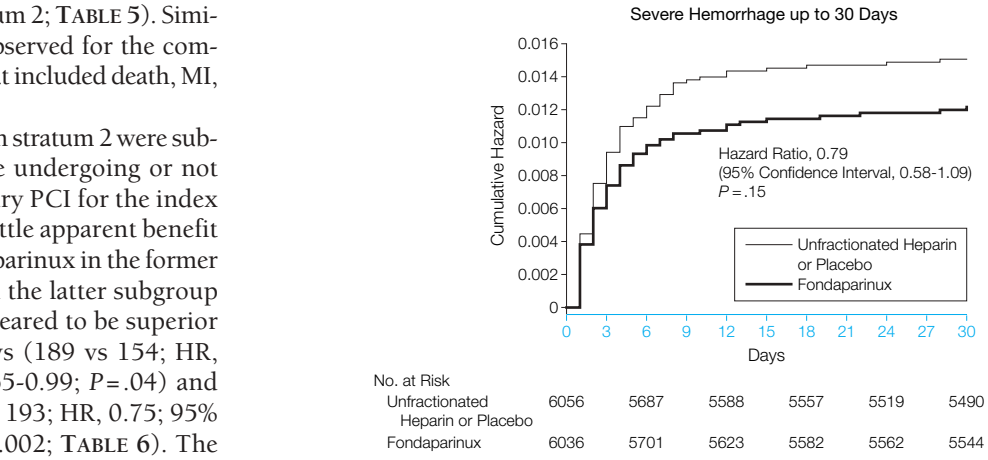


Table 4. Bleeding at 9 Days

	No. (%) of Patients		Hazard Ratio (95% Confidence Interval)	*P* Value
	Placebo or UFH (n = 6056)	Fondaparinux (n = 6036)		
Severe hemorrhage*				
All cases	79 (1.3)	61 (1.0)	0.77 (0.55-1.08)	.13
Fatal	49 (0.8)	35 (0.6)	0.72 (0.47-1.10)	.13
Intracranial	10 (0.2)	11 (0.2)	1.10 (0.47-2.60)	.82
Retroperitoneal	2 (0.0)	0 (0.0)		
Cardiac tamponade†	48 (0.8)	28 (0.5)	0.59 (0.37-0.93)	.02
Decrease in hemoglobin by ≥5 g/dL	17 (0.3)	19 (0.3)	1.12 (0.58-2.15)	.74
Stratum 1 (vs placebo)	44 (1.6)	28 (1.0)	0.63 (0.40-1.02)	.06
Stratum 2 (vs UFH)	35 (1.1)	33 (1.1)	0.95 (0.59-1.52)	.82
No PCI	29 (2.2)	20 (1.5)	0.69 (0.39-1.22)	.20
PCI	6 (0.3)	13 (0.7)	2.18 (0.83-5.74)	.11
Major bleeds‡				
All cases	130 (2.1)	107 (1.8)	0.83 (0.64-1.06)	.14
Stratum 1	57 (2.0)	39 (1.4)	0.68 (0.45-1.02)	.07
Stratum 2	73 (2.3)	68 (2.1)	0.93 (0.67-1.30)	.69
No PCI	42 (3.2)	28 (2.2)	0.66 (0.41-1.07)	.09
PCI	31 (1.7)	40 (2.2)	1.30 (0.81-2.08)	.27

Abbreviations: PCI, percutaneous coronary intervention; UFH, unfractionated heparin.
*Modified TIMI is defined in the "Methods" section.
†Some of these were identified during autopsy.
‡Major bleeds for comparison with OASIS-5.

Details of Outcomes in Patients Undergoing PCI

During the initial hospitalization, 1898 patients allocated to receive UFH or placebo and 1890 patients allocated to receive fondaparinux underwent any primary PCI in the hospital. All patients in the control group received UFH during the procedure (by protocol) compared with 20.8% in the fondaparinux group. The rate of death and MI did not differ significantly between the 2 groups at 30 days (93 UFH vs 114 fondaparinux, respectively). The rates of severe bleeds were also similar (9 vs 16). However, there was a higher rate of guiding catheter thrombosis (0 vs 22; $P<.001$) and more coronary complications (abrupt coronary artery closure, new angiographic thrombus, catheter thrombus, no reflow, dissection, or perforation; 225 vs 270; $P=.04$) with fondaparinux.

Among the 496 patients who received UFH prior to primary PCI, these differences were no longer noted, because the rates of death or reinfarction at 30 days (9 controls vs 8 fondaparinux), coronary complications (24 vs 24), catheter thrombus (0 vs 2), and severe bleeding (1 vs 4) were similar. In the 226 control patients and 231 fondaparinux patients who underwent a PCI (other than primary) in hospital (where UFH was recommended prior to the procedure), the rates of death or reinfarction at 30 days (33 vs 31), coronary complications (15 vs 21), catheter thrombus (0 vs 0), and severe bleeds at 30 days (6 vs 6) were similar. These data suggest that the use of UFH with fondaparinux during PCI largely avoids complications and is safe.

Table 5. Efficacy of Fondaparinux on Death or Reinfarction in the 2 Strata

	No. (%) of Events			
	Placebo or Unfractionated Heparin	Fondaparinux	Hazard Ratio (95% Confidence Interval)	*P* Value for Interaction*
At 9 days				
Stratum 1†	314 (11.1)	239 (8.5)	0.76 (0.64-0.89)	.13
Stratum 2‡	223 (6.9)	205 (6.4)	0.92 (0.76-1.11)	
At 30 days				
Stratum 1	396 (14.0)	317 (11.2)	0.79 (0.68-0.92)	.10
Stratum 2	281 (8.7)	268 (8.3)	0.96 (0.81-1.13)	
Study end				
Stratum 1	469 (17.3)	413 (15.9)	0.87 (0.76-0.99)	.88
Stratum 2	388 (12.7)	343 (11.2)	0.88 (0.76-1.02)	

*Given the several sets of subgroup analyses identified in the protocol, $P \leq .01$ was prespecified for an interaction to be considered statistically significant.
†The median number of days for fondaparinux treatment was 8 days.
‡The median number of days for fondaparinux treatment was 7 days.

Table 6. Results in Stratum 2 Based on Whether Patients Underwent Primary PCI (n = 3768) or Not (n = 2666)*

	No. (%) of Patients				
	Unfractionated Heparin	Fondaparinux	Hazard Ratio (95% Confidence Interval)	*P* Value	*P* Value for Interaction
9 Days					
Death or reinfarction					
No primary PCI	145 (10.9)	127 (9.5)	0.87 (0.69-1.10)	.25	.46
Primary PCI	78 (4.1)	78 (4.2)	1.01 (0.74-1.38)	.96	
Death					
No primary PCI	113 (8.5)	106 (7.9)	0.94 (0.72-1.22)	.62	.74
Primary PCI	60 (3.2)	60 (3.2)	1.01 (0.70-1.44)	.97	
Reinfarction					
No primary PCI	43 (3.4)	24 (1.9)	0.55 (0.34-0.91)	.02	.17
Primary PCI	21 (1.1)	20 (1.1)	0.96 (0.52-1.77)	.90	
30 Days					
Death or reinfarction					
No primary PCI	184 (13.8)	153 (11.5)	0.82 (0.66-1.02)	.08	.03
Primary PCI	97 (5.1)	115 (6.1)	1.20 (0.91-1.57)	.19	
Death					
No primary PCI	145 (10.9)	128 (9.6)	0.88 (0.69-1.12)	.29	.17
Primary PCI	74 (3.9)	85 (4.5)	1.16 (0.85-1.58)	.36	
Reinfarction					
No primary PCI	54 (4.3)	33 (2.6)	0.60 (0.39-0.93)	.02	.03
Primary PCI	29 (1.6)	36 (2.0)	1.25 (0.77-2.05)	.36	
Study end (90-180 days)					
Death or reinfarction					
No primary PCI	245 (19.0)	193 (14.9)	0.77 (0.64-0.93)	.008	.04
Primary PCI	143 (8.2)	150 (8.5)	1.06 (0.84-1.33)	.61	
Death					
No primary PCI	195 (15.1)	155 (11.9)	0.79 (0.64-0.97)	.03	.11
Primary PCI	104 (5.9)	107 (6.1)	1.04 (0.79-1.36)	.79	
Reinfarction					
No primary PCI	75 (6.5)	47 (4.0)	0.61 (0.43-0.88)	.009	.06
Primary PCI	53 (3.2)	53 (3.2)	1.01 (0.69-1.48)	.95	

Abbreviation: PCI, percutaneous coronary intervention.
*Includes all primary PCIs in hospital not only for index myocardial infarction.

Analysis of Strata by Duration of Treatment

To explore the independent impact of whether differences emerge during therapy with UFH vs fondaparinux, in patients undergoing or not undergoing PCI, as well as the impact of prolonged treatment with fondaparinux vs no antithrombotic therapy, TABLE 7 presents data in the 2 strata (and subgroups of stratum 2 by primary PCI) from randomization (day 1) to day 3 and from day 3 to day 9.

In the overall group, in stratum 1 and in patients in stratum 2 not undergoing primary PCI (and receiving UFH), there were fewer events in the fondaparinux group. In patients in stratum 2 undergoing primary PCI, there was a trend toward more events in the fondaparinux group. By contrast, be-

tween 3 and 9 days, there was a consistent lower rate of events overall, in both strata including those in stratum 2 who had undergone primary PCI. These data suggest that the benefits observed with fondaparinux may be partly due to enhanced efficacy compared with UFH and partly due to the more prolonged duration of antithrombotic therapy.

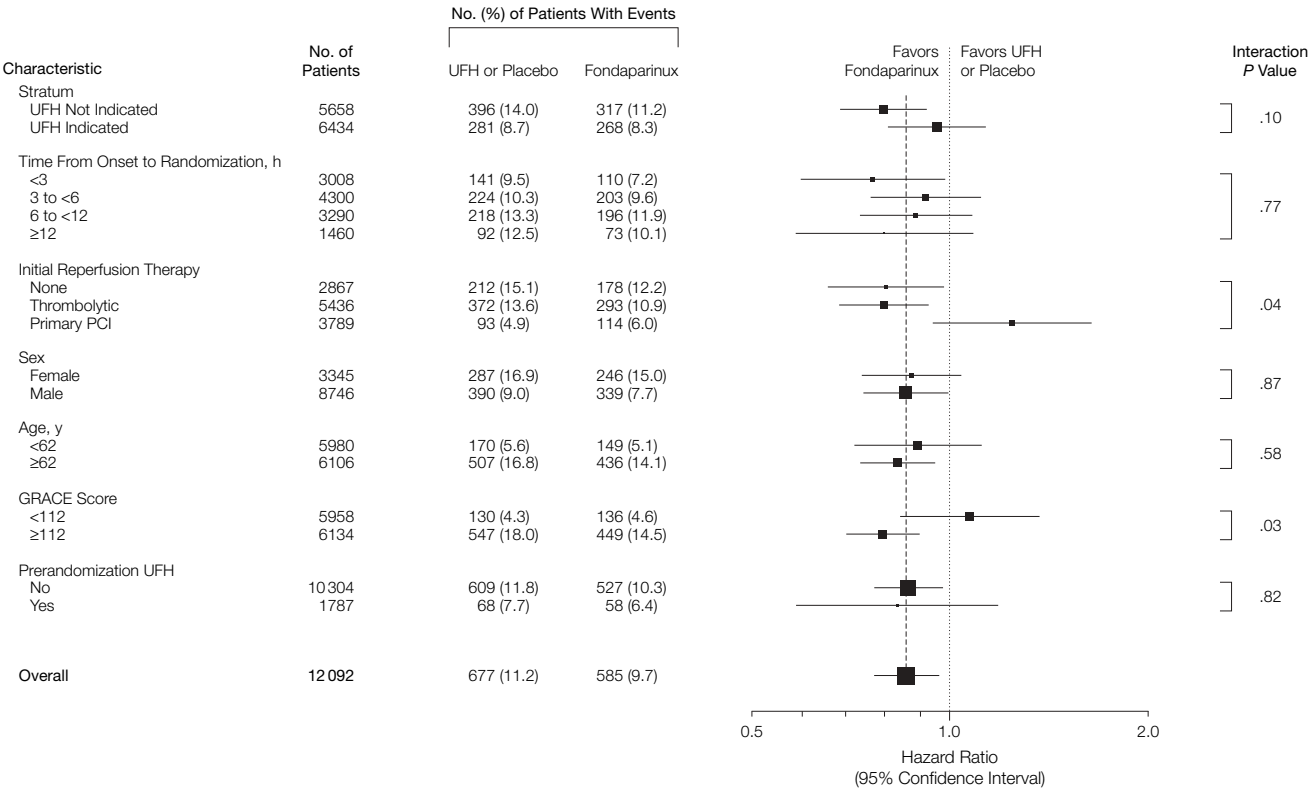
Causes of Death

The reduction in total mortality (674 vs 598) by study end with fondaparinux was entirely due to a reduction in cardiac deaths (573 [9.5%] vs 492 [8.2%], HR, 0.86; 95% CI, 0.77-0.97). There were lower rates of death from new infarction (35 vs 28), heart failure or cardiogenic shock (197 vs 164), and asystole (119 vs 88). There was no difference in noncardiac deaths. Fifty of 51 patients in the control group and 27 of 33 in the fondaparinux group who experienced cardiac tamponade died.

Benefit-Risk Balance

The rates of death, MI, and severe bleeding were significantly lower at

Figure 4. Rates of Death and Myocardial Infarction in Prespecified Subgroups at 30 Days



Comparison of fondaparinux vs unfractionated heparin or placebo in subgroups. The dashed vertical line represents the overall effect. The sizes of the boxes are proportional to the numbers of patients. GRACE indicates Global Registry of Acute Coronary Events; PCI, percutaneous intervention; and UFH, unfractionated heparin. Data in this figure are based on the modality of initial reperfusion therapy. In some patients information used to characterize patients into subgroups is missing.

Table 7. Post-hoc Analysis of Death or Reinfarction at 3 Days and >3 to 9 Days Overall and by Stratum*

	No. (%) of Events From Randomization to 3 Days			No. (%) of Events >3 to 9 Days		
	Placebo or UFH	Fondaparinux	Hazard Ratio (95% Confidence Interval)	Placebo or UFH	Fondaparinux	Hazard Ratio (95% Confidence Interval)
Overall	320 (5.3)	288 (4.8)	0.90 (0.77-1.06)	217 (3.8)	156 (2.7)	0.71 (0.58-0.88)
Stratum 1	197 (6.9)	158 (5.6)	0.80 (0.65-0.99)	117 (4.4)	81 (3.0)	0.68 (0.51-0.90)
Stratum 2	123 (3.8)	130 (4.0)	1.06 (0.83-1.36)	100 (3.2)	75 (2.4)	0.75 (0.56-1.01)
No primary PCI	82 (6.2)	77 (5.8)	0.94 (0.69-1.28)	63 (5.0)	50 (4.0)	0.78 (0.54-1.14)
Primary PCI	41 (2.2)	53 (2.8)	1.30 (0.87-1.96)	37 (2.0)	25 (1.4)	0.68 (0.41-1.13)

Abbreviations: PCI, percutaneous coronary intervention; UFH, unfractionated heparin.
*No *P* values for any comparison provided because of the post-hoc nature of these analyses, the low statistical power, and because individuals with events prior to day 3 are no longer at risk in the period >3 days to 9 days. Day 1 (the day of randomization) is on average about 12 hours. Therefore, to include all events that may have occurred during any infusion of heparin (or soon afterward), a cutoff of midnight on day 3 (about 60 hours) was used.

day 9 with fondaparinux (559 vs 464; HR, 0.83; 95% CI, 0.73-0.94; *P*=.003), day 30 (701 vs 603; HR, 0.86; 95% CI, 0.77-0.95; *P*=.005), and at study end (888 vs 779; HR, 0.87; 95% CI, 0.79-0.96; *P*=.005). The composite outcome of death, MI, or stroke was also reduced at day 9 (575 vs 475; HR, 0.82; 95% CI, 0.73-0.93; *P*=.002), at 30 days (718 vs 617; HR, 0.85; 95% CI, 0.77-0.95; *P*=.004) and at study end (904 vs 803; HR, 0.88; 95% CI, 0.80-0.97; *P*=.009).

COMMENT

The OASIS-6 trial demonstrates a moderate reduction in mortality and reinfarction with the use of fondaparinux compared with usual care. Unlike other antithrombotic agents, such as low-molecular-weight heparin,[9] direct thrombin inhibitors,[10] or intravenous antiplatelet agents,[17] fondaparinux reduced death and reinfarction without increasing bleeding or hemorrhagic stroke. In fact, there was a significant reduction in cardiac tamponade, likely related to less intrapericardial bleed or a smaller infarct size leading to fewer cases of myocardial rupture.

A 17% relative risk reduction in death and reinfarction was observed in the first 9 days after randomization, and this early benefit persisted during follow up. The reduction in mortality can be entirely attributed to significant reductions in cardiac deaths, with little impact on noncardiac deaths. This pattern of reduction in mortality and reinfarction, without an increase in bleeds, is unique among antithrombotic agents. The reduction in death or MI was most marked in those not undergoing PCI and those who were at higher risk. Therefore, the absolute benefits in this high-risk subgroup are substantial (34 deaths or reinfarctions prevented by treating 1000 individuals).

The results were consistent in the 2 strata in the trial, especially during long-term follow up. Furthermore, the results on both efficacy and safety were consistent in those who received or did not receive UFH prior to randomization. This suggests that fondaparinux can be used safely in patients who received previous UFH (as long as the dose was less than 5000 units). Three thousand seven hundred eighty-nine patients underwent primary PCI and little benefit was apparent in these patients. Given the very limited time for antithrombotic therapy prior to the procedure and the need for UFH during the procedure, there is probably little advantage in using fondaparinux as the initial treatment in patients in whom primary PCI is intended. However, in all other patients (including those who may need a rescue PCI or other PCI after admission), initial management with fondaparinux followed by standard UFH during PCI is an attractive choice.

In patients undergoing primary PCI (during which intravenous heparin was used in all patients in the control group and in only 21% in the fondaparinux group), there were higher rates of coronary complications with fondaparinux chiefly due to guiding catheter thrombus. However, the number of individuals who died or had an MI during primary PCI was not significantly different with fondaparinux compared with the control group. Thus the increase in procedural complications did not negate the overall clinical benefits. Among the 496 individuals who received UFH in hospital just before primary PCI, the rates of PCI and clinical complications were similar, with very low rates of catheter thrombosis. Similar results were observed in those undergoing later PCI in hospital (among whom pretreatment with UFH was frequent) without an excess of bleeds, confirming that UFH can be safely used during PCI in patients with acute coronary syndrome already treated with fondaparinux as the initial strategy.

Although the total experience with combined use of UFH and fondaparinux is relatively modest in this trial, it is consistent with similar data from OASIS-5[13] and the collective data from both trials strongly suggest that using UFH with fondaparinux during PCI substantially reduces the risk of catheter thrombosis and related complications without an increase in clinical complications or major bleeds.

Exploratory analyses of the number of events between days 3 and 9 suggests a tendency toward fewer deaths or reinfarctions in this period, even in those who had undergone primary PCI. These data along with similar trends observed in the CREATE trial[10] with reviparin compared with placebo for 7 days, suggests that prolonged antithrombotic therapy in patients undergoing primary PCI is likely to further reduce ischemic complications, even if they are receiving aspirin and clopidogrel. If this hypothesis is confirmed, then the optimal antithrombotic strategy in patients undergoing primary PCI may be initial therapy with UFH during the procedure followed by fondaparinux (or a similar drug) for several days.

In OASIS-6, fondaparinux reduced death and reinfarction in those receiving thrombolytic therapy by 21% and death by 19% at 30 days and those not receiving reperfusion therapy. The most common thrombolytic agent used was streptokinase, but there was no evidence of heterogeneity in results by the type of thrombolytic therapy and there is no pharmacological reason why the benefits of fondaparinux should differ with different thrombolytic agents. Furthermore, given that fondaparinux reduces severe bleeding compared with enoxaparin in OASIS-5 and there is a trend for fewer bleeds in OASIS-6, addition of fondaparinux to thrombolytic therapy (including fibrin-specific agents that increase the risk of bleeding and strokes), probably represents an attractive, effective, and safe option as an initial adjunctive antithrombotic agent in AMI in patients not undergoing primary PCI. A substantial proportion of patients with STEMI do not receive any form of reperfusion therapy. Such patients are at higher risk of death and reinfarction. In this subgroup, fondaparinux produced substantial benefits without an excess of bleeding.

OASIS-6 also provides evidence of the superiority of fondaparinux when compared with UFH in patients not

undergoing PCI. These results are consistent with the results of OASIS-5, in which fondaparinux appeared to be superior to enoxaparin in reducing death, reinfarction, and strokes in patients with non-STEMI. Collectively the data from both trials indicate that fondaparinux is an attractive antithrombotic agent in terms of efficacy and safety in patients with varying presentations of acute coronary syndrome and treated with different pharmacologic modalities (other than primary PCI). It might also be useful as adjunctive therapy given for about a week in patients after they have undergone PCI (with UFH being used during the procedure). However, this strategy requires prospective evaluation.

In OASIS-6 there was no increase in major bleeding or intracranial hemorrhage with the use of fondaparinux, unlike the experiences with other antithrombotic agents in acute myocardial infarction such as UFH,[7] low-molecular-weight heparin,[9] direct thrombin inhibitors,[8] or intravenous glycoprotein IIb/IIIa inhibitors.[17] In fact, there was a significant reduction in cardiac tamponade (which is part of the TIMI criterion for severe bleeds; but this may be due to fewer cases of myocardial rupture) and a trend toward fewer fatal bleeds with fondaparinux. The trend toward lower rates of fatal and life-threatening bleeding seen in OASIS-6 is consistent with the markedly lower rates of bleeding with fondaparinux compared with enoxaparin in OASIS-5, suggesting that fondaparinux may actually reduce or at very least not increase the risk of major bleeds at the doses used. The lower rates of bleeding with fondaparinux vs placebo in patients in stratum 1 is puzzling. It may be due to the play of chance, or suggests some novel mechanism by which fondaparinux may counteract bleeding caused by degradation products of fibrin or fibrinogen induced by thrombolytic therapy.

The significant reduction in death and MI is observed in both OASIS-6 and OASIS-5 with fondaparinux (vs placebo, vs UFH [in those without primary PCI], or vs enoxaparin), and reinforces the efficacy and safety of fondaparinux in a broad spectrum of patients with varying presentations and management of acute coronary syndrome. We used a single fixed dose (2.5 mg once daily) of fondaparinux without any monitoring or dose adjustments for weight across a broad range of creatinine levels. The simplicity of this regimen, lack of monitoring, its safety and efficacy in the full spectrum of acute coronary syndrome facilitates the use of fondaparinux in a range of settings. It may even be applicable in the prehospital or posthospital settings in appropriate patients.

In summary, fondaparinux reduces mortality and reinfarction early, and this benefit persists long term. There is a higher rate of guiding catheter thrombosis if PCI is performed without UFH, but this is largely avoided if UFH is used before the procedure. There is a trend toward fewer severe bleeds with a significant reduction in cardiac tamponade with fondaparinux. The consistent results from OASIS-5 and OASIS-6 confirm the value and safety of fondaparinux as a simple and widely applicable antithrombotic therapy in a broad group of patients with acute coronary syndrome.

Published Online: March 14, 2006 (doi:10.1001/jama.295.13.joc60038).

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Financial Disclosures: Dr Yusuf has received honoraria for lectures, has served as a consultant for, and has received research grants from Sanofi-Aventis and GlaxoSmithKline. Dr Mehta has served as a consultant for and on the speaker's bureau of Saofi Aventis and GlaxoSmithKline. Dr Budaj has served on the advisory board for GlaxoSmithKline and on the speaker's bureau of Sanofi-Aventis. Except for Drs Afzal, Pogue, and Chrolavicius, the rest of the authors have received honoraria and research support from GlaxoSmithKline and Sanofi-Aventis
Funding/Support: This study was conducted independently by the Steering Committee and the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario. No direct compensation was received by these individuals. The study was jointly funded by Sanofi-Aventis, Organon, and GlaxoSmithKline.
Role of the Sponsors: The sponsors had nonvoting membership of the steering committee. Although they provided comments on the manuscript, the writing committee made final decisions on the interpretation of study results and contents of the manuscript.

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Acknowledgment: We are grateful to the patients for agreeing to participate in the trial, to Kelly TenBrinke and Judy Lindeman, BA, for secretarial assistance, to Ton Lensing, MD, and Inge Bobbink, PhD, of Organon; Roger Cariou, MD, and Angele Moryusef of Sanofi-Aventis; Steve Okada, MD, Nevine Zariffa, MMath, Shiona Laing, PhD, and Lawson Macartney, DVM, of GlaxoSmithKline for their support and assistance.

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