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Efficacy and Safety of Fondaparinux Versus Enoxaparin in Patients With Acute Coronary Syndromes Treated With Glycoprotein IIb/IIIa Inhibitors or Thienopyridines

Results From the OASIS 5 (Fifth Organization to Assess Strategies in Ischemic Syndromes) Trial

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Objectives This study sought to evaluate the relative safety and efficacy of fondaparinux and enoxaparin in patients with acute coronary syndromes (ACS) treated with glycoprotein (GP) IIb/IIIa inhibitors or thienopyridines.

Background The OASIS 5 (Fifth Organization to Assess Strategies in Ischemic Syndromes) trial showed that fondaparinux reduced major bleeding by 50% compared with enoxaparin while preserving similar efficacy. Whether this benefit is consistent in the presence or absence of concurrent antiplatelet therapy with clopidogrel and GP IIb/IIIa inhibitors is unknown.

Methods Patients with ACS ($n = 20,078$) were randomized as a part of the OASIS 5 trial to receive either fondaparinux or enoxaparin. The use of GP IIb/IIIa inhibitors or thienopyridines was at the discretion of the treating physician. A Cox proportional hazard model was used to compare outcomes.

Results Of the 20,078 patients randomized, 3,630 patients received GP IIb/IIIa and 13,531 received thienopyridines. There was a 40% reduction in major bleeding with fondaparinux compared with enoxaparin in those treated with GP IIb/IIIa (5.2% vs. 8.3%, hazard ratio [HR]: 0.61, $p < 0.001$). A similar reduction was found in those treated with thienopyridines (3.4% vs. 5.4%, HR: 0.62, $p < 0.001$). Ischemic events were similar between the groups, resulting in a superior net clinical outcome (death, myocardial infarction, refractory ischemia, or major bleeding) favoring fondaparinux (GP IIb/IIIa subgroup 14.8% vs. 18.9%, HR: 0.77, $p = 0.001$ and thienopyridines subgroup 11.0% vs. 13.2%, HR: 0.82, $p < 0.001$).

Conclusions In patients receiving GP IIb/IIIa inhibitors or thienopyridines, fondaparinux reduces major bleeding and improves net clinical outcome compared with enoxaparin. (J Am Coll Cardiol 2009;54:468–76) © 2009 by the American College of Cardiology Foundation

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Antiplatelet therapy with either glycoprotein (GP) IIb/IIIa inhibitors or thienopyridines reduces ischemic events at the cost of an increase in bleeding in patients with acute coronary syndromes (1,2). The American College of Cardiology and American Heart Association as well as the European Society of Cardiology guidelines recommend early treatment with either clopidogrel or intravenous GP IIb/IIIa inhibitors (3,4). Major bleeding has been shown repeatedly in observational analyses to be associated with an increased risk of death (5–7). As a result, it is important to determine the risk of bleeding of novel antithrombotic agents when combined with these potent antiplatelet agents compared with standard therapies.

Fondaparinux is a synthetic factor Xa inhibitor (Arixtra, GlaxoSmithKline, Brentford, United Kingdom) that selectively binds antithrombin and potentiates neutralization of factor Xa. The OASIS 5 (Fifth Organization to Assess Strategies in Ischemic Syndromes) trial demonstrated that fondaparinux compared with enoxaparin reduced major bleeding by 50% and mortality by 17% in over 20,000 patients with non–ST-segment elevation (NSTE) (8).

The objective of this analysis was to determine the efficacy, safety, and net clinical outcome of fondaparinux versus enoxaparin in patients with NSTE-acute coronary syndrome (ACS) treated with: 1) a GP IIb/IIIa inhibitor; and 2) thienopyridines.

Abbreviations and Acronyms

ACS = acute coronary syndrome
CI = confidence interval
CK-MB = creatine kinase-myocardial band
GP = glycoprotein
HR = hazard ratio
MI = myocardial infarction
NSTE = non–ST-segment elevation
OR = odds ratio
PCI = percutaneous coronary intervention
RR = relative risk

Methods

Patients. The OASIS 5 trial briefly enrolled 20,078 patients with NSTE-ACS and randomized them to fondaparinux 2.5 mg subcutaneously once daily or enoxaparin 1 mg/kg of body weight subcutaneously twice daily in a double-blind fashion (8). Patients were eligible if they had had ischemic symptoms within 24 h and at least 2 of the 3 following criteria: an age of at least 60 years, an elevated level of troponin or creatine kinase-myocardial band (CK-MB) isoenzyme, or electrocardiographic changes indicative of ischemia. In the fondaparinux arm, patients were treated with fondaparinux for up to 8 days or until hospital discharge, whichever came first. In the enoxaparin arm, patients were treated with enoxaparin for 2 to 8 days until the patient was deemed clinically stable. The use of GP IIb/IIIa inhibitors or thienopyridines was left to the discretion of the treating physician.

Outcomes. Efficacy was assessed by evaluating rates of the composite of death, myocardial infarction (MI), and refractory ischemia at 30 days. Safety was assessed by evaluating rates of major bleeding, and net clinical outcome was assessed evaluating rates of the composite of death, MI, refractory ischemia, or major bleeding at 30 days.

MI was defined as the following: in those without previous infarction within 7 days, as prolonged ischemic symptoms with cardiac enzyme elevation (troponin or CK-MB) of >2× upper limit of normal, electrocardiographic changes indicative of ischemia or Q waves or pathologic evidence of acute MI (9). In those who presented with an MI at baseline, a new MI within 24 h was defined as >20 min of ischemic symptoms with either new ST-segment elevation or depression. In those who presented with an MI at baseline, a new MI within 24 h to 7 days was defined as ischemic symptoms >20 min with 1 of the following: 1) typical rise and fall of cardiac biomarker levels (including troponin, CK-MB) to at least 2× upper limit of normal (if markers are already elevated, then >50% increase in enzymes required); 2) new ST-segment elevation or depression; or 3) new Q waves in 2 contiguous leads. Within 48 h of percutaneous coronary intervention (PCI), a new MI was defined as CK-MB >3× the upper limit of normal (50% increase required if elevated) or new ST-segment elevation or development of new Q waves. Similarly, within 48 h of coronary artery bypass surgery, a new MI was defined as a CK-MB 5× upper limit of normal or new Q waves in 2 contiguous leads.

The definition of major bleeding was any clinically overt bleeding that was either fatal, intracranial bleeding, retroperitoneal, intraocular leading to significant visual loss, requiring ≥2 U of blood transfused, or associated with a decrease of hemoglobin >3 g/dl (with each unit of transfused blood counting for 1.0 g/dl).

Statistical analysis. Patients were stratified into subgroups that received GP IIb/IIIa inhibitors and the subgroup that did not. Patients were also stratified into subgroups that received thienopyridines in the hospital and those that did not. Baseline characteristics were compared using the chi-square test for proportions and Student *t* test for continuous variables.

A Cox proportional hazards model was used to compare efficacy (death, MI, or refractory ischemia) as well as major bleeding and net clinical outcome in the fondaparinux versus enoxaparin groups in: 1) those that received GP IIb/IIIa inhibitors; 2) those that received thienopyridines; and 3) those that received both agents. This analysis was repeated in the PCI subgroup in those that received GP IIb/IIIa inhibitors, those that received thienopyridines at least 6 h before PCI, and both. In the PCI subgroup, outcomes by type of GP IIb/IIIa inhibitor and loading dose of clopidogrel were compared between the fondaparinux and enoxaparin groups. Statistical significance was defined as a $p < 0.05$ and for interaction tests $p < 0.10$.

A propensity score was developed for the use of GP IIb/IIIa inhibitors and included variables that influenced the

use of GP IIb/IIIa inhibitors such as age, sex, diabetes, ST-segment deviation, and elevated cardiac enzymes and other baseline variables. The propensity score was used to adjust the Cox proportional hazards model to compare outcomes in the fondaparinux versus enoxaparin groups by use of GP IIb/IIIa. A second propensity score for the use of thienopyridines was developed similarly to adjust the Cox proportional hazard model comparing the fondaparinux versus enoxaparin groups by use of thienopyridines.

Results

In the OASIS 5 trial, of the 20,078 patients with acute coronary syndromes that were enrolled, 3,630 patients (18%) received a GP IIb/IIIa inhibitor, 13,532 patients (67%) received a thienopyridine, and 13,916 patients (69%) received either a thienopyridine or GP IIb/IIIa inhibitor in the hospital.

GP IIb/IIIa inhibitors. Baseline characteristics of patients who received a GP IIb/IIIa inhibitor are compared with those who did not receive one in Table 1. Patients treated with GP IIb/IIIa inhibitors were younger, were a higher proportion of male subjects, and had elevated cardiac enzymes. For geographic variation, the highest rate of GP IIb/IIIa use was in North America and Western Europe, and the lowest rates were in Asia and Eastern Europe (Table 1).

In those treated with GP IIb/IIIa inhibitors, fondaparinux had similar rates of death, MI, or refractory ischemia at 30 days as enoxaparin (11.8% vs. 13.2%, unadjusted hazard ratio [HR]: 0.89, 95% confidence interval [CI]: 0.74 to 1.07, p = 0.20, and adjusted HR: 0.87, 95% CI: 0.72 to 1.06, p = 0.16) (Table 2) (Fig. 1). In those not treated with GP IIb/IIIa inhibitors, there were similar rates of death, MI, or refractory ischemia between fondaparinux and enoxaparin, (7.1% and 7.7%, unadjusted HR: 0.93, 95% CI: 0.83 to 1.04, p = 0.23, and adjusted HR: 0.93, 95% CI: 0.82 to 1.04, p = 0.19, interaction p = 0.63).

In those treated with GP IIb/IIIa inhibitors, there was a 40% reduction in major bleeding with fondaparinux versus enoxaparin at 30 days (5.2% vs. 8.3% respectively, unadjusted HR: 0.61, 95% CI: 0.47 to 0.79, p < 0.001, and adjusted HR: 0.60, 95% CI: 0.46 to 0.78, p < 0.001) (Fig. 2). In those not treated with GP IIb/IIIa inhibitors, there was

Table 1 Baseline Characteristics for Patients Treated With and Without GP IIb/IIIa Inhibitors

Characteristic	GP IIb/IIIa Use (n = 3,630)	No GP IIb/IIIa Use (n = 16,448)	p Value
Geographic region			
North America	853 (39)	1,309 (61)	<0.001*
Latin America	189 (10)	1,738 (90)	
Western Europe	2,058 (29)	4,952 (71)	
Eastern Europe	306 (5)	6,477 (95)	
Australia	139 (27)	384 (73)	
South Africa	15 (8)	181 (92)	
Asia	70 (5)	1,407 (95)	
Age (mean)	65	67	<0.001
Age ≥75 yrs	737 (20)	4,297 (26)	<0.001
Male sex	2,591 (71)	9,788 (60)	<0.001
Prior MI	787 (22)	4,377 (27)	<0.001
Diabetic	913 (25)	4,165 (25)	0.83
Prior coronary bypass surgery	376 (10)	1,267 (8)	<0.001
Prior PCI	546 (15)	1,786 (11)	<0.001
Troponin/CK-MB >ULN	3,097 (85)	11,041 (67)	<0.001
ST-segment depression ≥1 mm	1,554 (43)	8,688 (53)	<0.001
Transient ST-segment elevation >2 mm	333 (9)	820 (5)	<0.001
T-wave inversion (≥2 mm)	754 (21)	4,235 (26)	<0.001
Medications after randomization			
Aspirin	3,576 (99)	16,000 (97)	<0.001
Clopidogrel	3,159 (87)	9,351 (57)	<0.001
Beta-blocker	3,210 (88)	14,348 (87)	0.049
ACE inhibitor	2,427 (67)	11,636 (71)	<0.001
Statin	3,121 (86)	12,541 (76)	<0.001
Intravenous heparin	833 (23)	1,988 (12)	<0.001
Revascularization during initial hospitalization			
PCI	2,592 (71)	4,297 (26)	<0.001
Coronary bypass surgery	367 (10)	1,495 (9)	0.06

*Data are presented as n (%). The p value refers to difference in use of GP IIb/IIIa inhibitor between the different geographic regions.

ACE = angiotensin-converting enzyme; CK-MB = creatine kinase myocardial band; GP = glycoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention; ULN = upper limit of normal.

Table 2 Death, MI, Refractory Ischemia, Major Bleeding, and Net Clinical Outcome at 30 Days in Those Treated With a GP IIb/IIIa Inhibitor

Outcome	GP IIb/IIIa Use (n)	Fondaparinux (%)	Enoxaparin (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Interaction p Value*
Death, MI, refractory ischemia	Yes (3,630)	220 (11.8)	232 (13.2)	0.89 (0.74–1.07)	0.87 (0.72–1.06)	0.63
	No (16,448)	585 (7.1)	632 (7.7)	0.93 (0.83–1.04)	0.93 (0.82–1.04)	
Death	Yes (3,630)	58 (3.1)	64 (3.6)	0.85 (0.60–1.22)	0.85 (0.59–1.23)	0.89
	No (16,448)	237 (2.9)	288 (3.5)	0.83 (0.70–0.98)	0.79 (0.66–0.95)	
MI	Yes (3,630)	118 (6.4)	129 (7.4)	0.86 (0.67–1.10)	0.83 (0.64–1.07)	0.46
	No (16,448)	269 (3.3)	282 (3.5)	0.96 (0.81–1.14)	0.99 (0.83–1.17)	
Major bleeding	Yes (3,630)	96 (5.2)	146 (8.3)	0.61 (0.47–0.79)	0.60 (0.46–0.78)	0.86
	No (16,448)	218 (2.7)	349 (4.3)	0.62 (0.53–0.74)	0.62 (0.52–0.73)	
Net clinical outcome†	Yes (3,630)	278 (14.9)	333 (18.9)	0.77 (0.66–0.90)	0.76 (0.65–0.90)	0.42
	No (16,448)	748 (9.1)	906 (11.0)	0.83 (0.75–0.91)	0.81 (0.74–0.90)	

*Interaction p value for unadjusted analysis. †Net clinical outcome is defined as composite of death, MI, refractory ischemia, or major bleeding.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

also a 40% reduction in major bleeding with fondaparinux compared with enoxaparin (2.7% vs. 4.3%, respectively, unadjusted HR: 0.62, 95% CI: 0.53 to 0.74, $p < 0.001$, and adjusted HR: 0.62, 95% CI: 0.52 to 0.73, $p < 0.001$, interaction $p = 0.86$). In terms of net clinical outcome (composite of death, MI, refractory ischemia, or major bleeding) at 30 days, there was a consistent benefit for fondaparinux for those treated with GP IIb/IIIa inhibitors (14.9% vs. 18.9%, unadjusted HR: 0.77, 95% CI: 0.66 to 0.90, $p < 0.001$, and adjusted HR: 0.76, 95% CI: 0.65 to 0.90, $p = 0.001$) as well those not treated with GP IIb/IIIa (9.1% vs. 11.0%, unadjusted HR: 0.83, 95% CI: 0.75 to 0.91, $p < 0.001$, and adjusted HR: 0.81, 95% CI: 0.65 to 0.90, $p < 0.001$, interaction $p = 0.42$).

For the PCI subgroup, there were similar rates of death, MI, and refractory ischemia in both the fondaparinux and

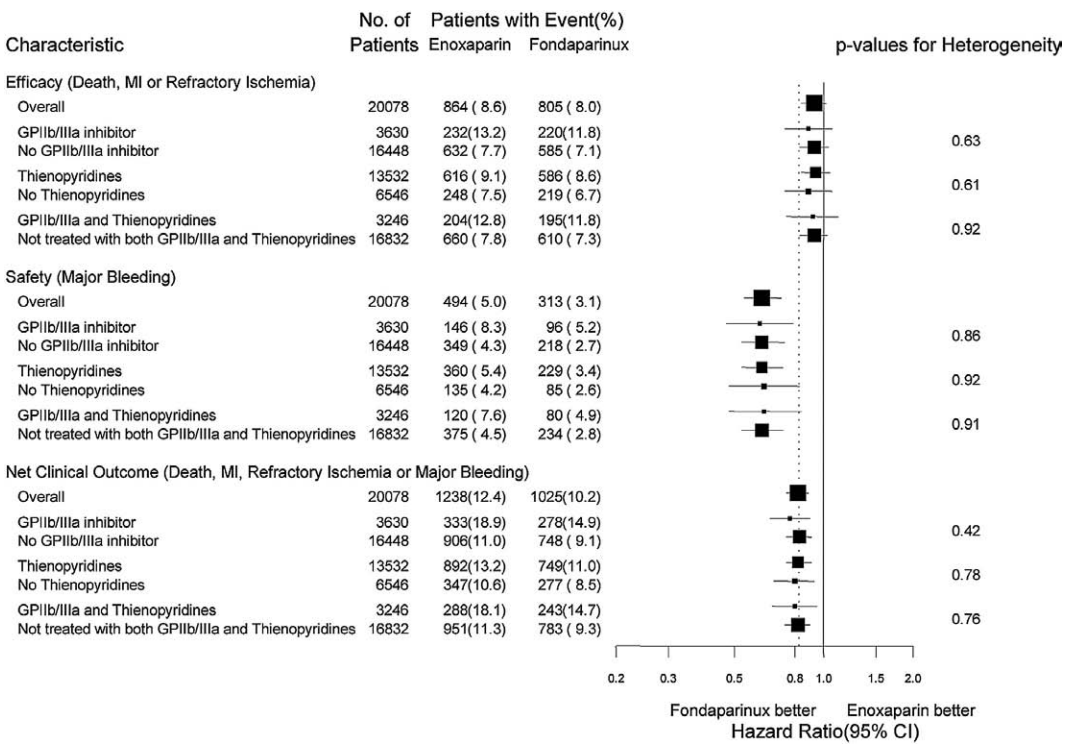

Figure 1 Safety and Efficacy of Fondaparinux Versus Enoxaparin in GP IIb/IIIa and Thienopyridine Subgroups

Fondaparinux reduced major bleeding and improved net clinical outcome compared with enoxaparin irrespective of glycoprotein (GP) IIb/IIIa or thienopyridine use. CI = confidence interval; MI = myocardial infarction.

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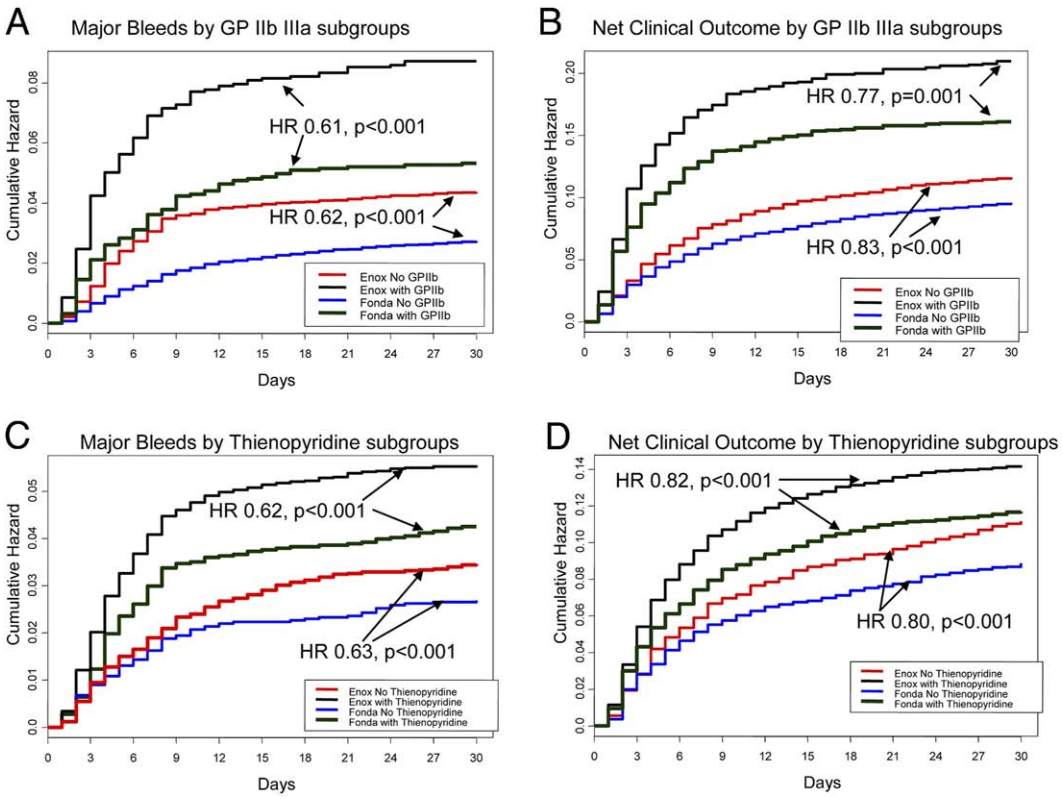

Figure 2 **Kaplan-Meier Event Curves for Major Bleeding and Net Clinical Outcome for GP IIb/IIIa and Thienopyridine Subgroups**

Net clinical outcome (death, myocardial infarction, refractory ischemia, or major bleeding). GP = glycoprotein; HR = hazard ratio.

the enoxaparin groups, regardless of GP IIb/IIIa use (Fig. 3). There were consistent benefits in terms of major bleeding of fondaparinux compared with enoxaparin in the PCI population in both those treated and not treated with GP IIb/IIIa inhibitors (Fig. 3). In terms of net clinical outcome, there was trend for a reduction in events in the PCI populations in those treated with GP IIb/IIIa with fondaparinux versus enoxaparin ($p = 0.05$) (Fig. 3). The outcomes by type of GP IIb/IIIa inhibitor during PCI are shown in Table 3.

Up-front GP IIb/IIIa inhibitors for patients undergoing PCI (excludes bailout treatment after PCI started) did not seem to be protective against catheter thrombus in both the fondaparinux (0.7% [15 of 2,028] not receiving up-front GP IIb/IIIa vs. 1.3% [14 of 1,077] receiving up-front GP IIb/IIIa, $p = 0.12$) and enoxaparin groups (0.3% [5 of 1,987] not receiving up-front GP IIb/IIIa vs. 0.3% [3 of 1,085] receiving up-front GP IIb/IIIa, $p = 0.90$).

Thienopyridines. As shown in Table 4, 13,532 patients (67%) received thienopyridines versus 6,546 (33%) patients not treated with thienopyridines in the hospital. Patients treated with thienopyridines were slightly younger and more likely to be male and to have elevated cardiac enzyme levels. Patients treated with thienopyridines were more likely to have been treated with statins, unfractionated heparin, and PCI in the hospital (Table 4). The highest rate of thienopyridine use was in Asia and North America, and the lowest rate was in Eastern Europe (Table 4).

For the composite of death, MI, or refractory ischemia, fondaparinux had similar efficacy compared with enoxaparin in both those treated with thienopyridines (8.6% vs. 9.1%, respectively, unadjusted HR: 0.94, 95% CI: 0.84 to 1.05, $p = 0.20$, and adjusted HR: 0.94, 95% CI: 0.84 to 1.06, $p = 0.29$) and those not (6.7% vs. 7.5%, respectively, unadjusted HR: 0.89, 95% CI: 0.74 to 1.07, $p = 0.21$, and adjusted HR: 0.87, 95% CI: 0.72 to 1.05, interaction $p = 0.61$) (Table 5) (Fig. 1).

In terms of safety, fondaparinux was associated with a 40% reduction in major bleeding at 30 days in both the subgroup treated with thienopyridines (3.4% vs. 5.4%, respectively, unadjusted HR: 0.62, 95% CI: 0.53 to 0.73, $p < 0.001$, and adjusted HR: 0.62, 95% CI: 0.52 to 0.73, $p < 0.001$) and the subgroup not treated with thienopyridines (2.6% vs. 4.2%, unadjusted HR: 0.63, 95% CI: 0.48 to 0.83, $p < 0.001$, and adjusted HR: 0.62, 95% CI: 0.47 to 0.83, $p = 0.001$, interaction $p = 0.92$) (Fig. 2) (Table 5).

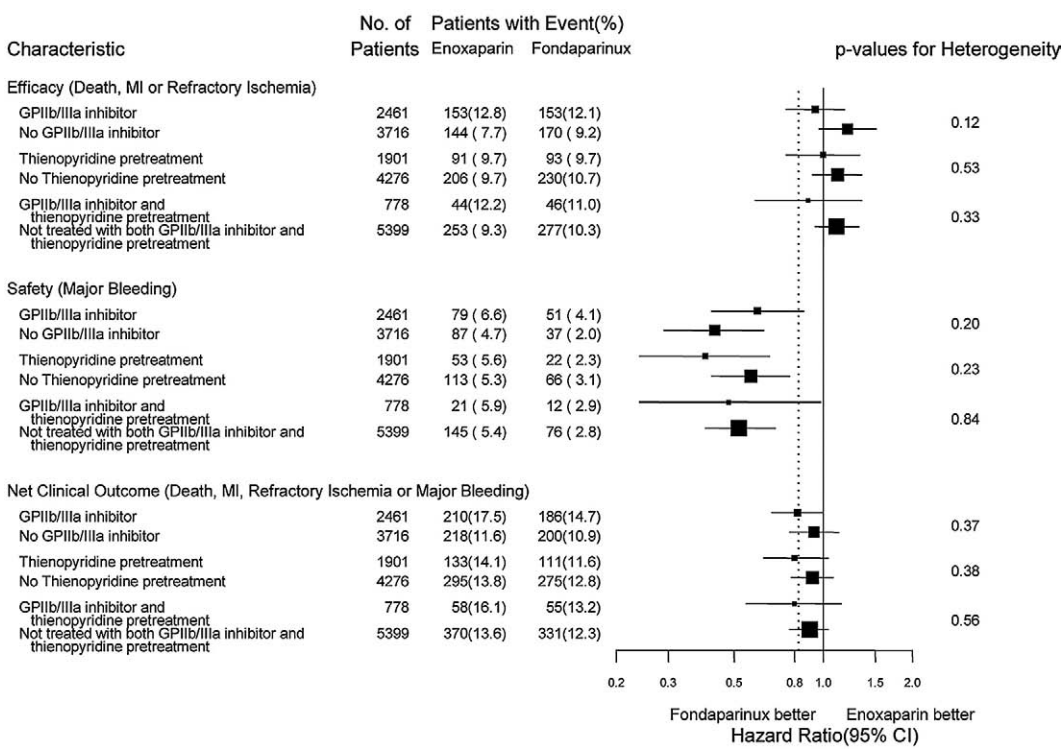

Figure 3 **In Those Undergoing PCI, the Efficacy and Safety of Fondaparinux Versus Enoxaparin in Those Treated With GP IIb/IIIa Inhibitors or Pre-Treated (≥6 h) With Thienopyridines or Both**

In the PCI population, fondaparinux reduced major bleeding compared with enoxaparin regardless of GP IIb/IIIa or thienopyridine pre-treatment. PCI = percutaneous coronary intervention; other abbreviations as in Figure 1.

With regard to net clinical outcome at 30 days (death, MI, refractory ischemia, or major bleeding), fondaparinux was associated with a 20% reduction in both the subgroup treated with thienopyridines (11.0% vs. 13.2%, unadjusted HR: 0.82, 95% CI: 0.75 to 0.91, $p < 0.001$, and adjusted HR: 0.82, 95% CI: 0.74 to 0.90, $p < 0.001$) and those not treated with thienopyridines (8.5% vs. 10.6%, unadjusted HR: 0.80, 95% CI: 0.68 to 0.93, $p < 0.001$, and adjusted HR: 0.78, 95% CI: 0.66 to 0.92, $p = 0.003$, interaction $p = 0.78$) (Table 5).

For those patients undergoing PCI during the initial hospitalization, there were similar rates of death, MI, and refractory ischemia in both the fondaparinux and enoxaparin groups at 30 days, regardless of whether thienopyridines

Table 3 **Death, MI, or Refractory Ischemia or Major Bleeding in Patients Undergoing PCI by Loading Dose of Clopidogrel or Type of GP IIb/IIIa Inhibitor**

Outcome	Fondaparinux (%)	Enoxaparin (%)	Unadjusted HR (95% CI)*
Death, MI, or refractory ischemia			
Tirofiban (n = 1,102)	62 (11.2)	70 (12.8)	0.87 (0.62–1.22)
Eptifibatide (n = 773)	35 (9.1)	31 (7.9)	1.15 (0.71–1.87)
Abciximab (n = 686)	60 (16.6)	42 (12.9)	1.32 (0.89–1.96)
Clopidogrel loading dose 300 mg (n = 2,977)	155 (10.4)	143 (9.6)	1.09 (0.87–1.37)
Clopidogrel loading dose 600 mg (n = 145)	6 (8.8)	5 (6.5)	1.40 (0.43–4.58)
Major bleeding			
Tirofiban (n = 1,102)	21 (3.8)	25 (4.6)	0.83 (0.46–1.48)
Eptifibatide (n = 773)	9 (2.4)	28 (7.2)	0.32 (0.15–0.68)
Abciximab (n = 686)	16 (4.5)	23 (7.1)	0.62 (0.33–1.17)
Clopidogrel loading dose 300 mg (n = 2,977)	47 (3.2)	77 (5.2)	0.61 (0.42–0.87)
Clopidogrel loading dose 600 mg (n = 145)	1 (1.5)	2 (2.6)	0.57 (0.05–6.32)

*Interaction p values are nonsignificant for these subgroups ($p > 0.05$).
Abbreviations as in Table 2.

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Table 4 Baseline Characteristics for Patients Treated With and Without Thienopyridines

Characteristic	Thienopyridine Use (n = 13,532)	No Thienopyridine Use (n = 6,545)	p Value
Geographic region			
North America	1,783 (82)	379 (18)	<0.001*
Latin America	1,434 (74)	493 (26)	
Western Europe	5,591 (80)	1,419 (20)	
Eastern Europe	3,058 (45)	3,725 (55)	
Australia	332 (63)	191 (37)	
South Africa	38 (19)	158 (81)	
Asia	1,296 (88)	181 (12)	
Age (mean)	66	68	<0.001
Age ≥75 yrs	3,187 (24)	1,847 (28)	<0.001
Male sex	8,792 (65)	3,587 (55)	<0.001
Prior MI	3,382 (25)	1,782 (27)	<0.001
Diabetic	3,423 (25)	1,655 (25)	0.98
Prior coronary bypass surgery	1,264 (9)	379 (6)	<0.001
Prior PCI	1,910 (14)	422 (6)	<0.001
Troponin/CK-MB >ULN	10,035 (74)	4,103 (63)	<0.001
ST-segment depression ≥1 mm	6,655 (49)	3,587 (55)	<0.001
Transient ST-segment elevation >2 mm	874 (7)	279 (4)	<0.001
T-wave inversion (≥2 mm)	3,283 (24)	1,706 (26)	0.006
Medications after randomization			
Aspirin	13,193 (98)	6,383 (98)	0.95
Beta-blocker	11,960 (88)	5,598 (86)	<0.001
ACE inhibitor	9,311 (69)	4,752 (73)	<0.001
Statin	11,266 (83)	4,396 (67)	<0.001
Intravenous heparin	2,138 (16)	683 (10)	<0.001
GP IIb/IIIa inhibitors	3,246 (24)	384 (6)	<0.001
Revascularization during initial hospitalization			
PCI	6,650 (49)	239 (4)	<0.001
Coronary bypass surgery	1,111 (8)	751 (11)	<0.001

Data are presented as n (%). *The p value refers to difference in use of thienopyridines between the different geographic regions. Abbreviations as in Table 1.

were given at least 6 h before PCI (Fig. 3). There were consistent benefits in terms of major bleeding of fondaparinux compared with enoxaparin in the PCI population in both those pre-treated (minimum 6 h) and not pre-treated with thienopyridines (Fig. 3). The outcomes by loading dose of clopidogrel in PCI population are shown in Table 3, which shows that the vast majority of patients received a 300-mg loading dose of clopidogrel.

GP IIb/IIIa inhibitors and thienopyridine use. For patients treated with both GP IIb/IIIa inhibitors and

Table 5 Death, MI, Refractory Ischemia, Major Bleeding, and Net Clinical Outcome at 30 Days in Those Treated With Thienopyridines

Outcome	Thienopyridine Use (n)	Fondaparinux n (%)	Enoxaparin n (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Interaction p Value*
Death, MI, or refractory ischemia	Yes (13,532)	586 (8.6)	616 (9.1)	0.94 (0.84–1.05)	0.94 (0.84–1.06)	0.61
	No (6,545)	219 (6.7)	248 (7.5)	0.89 (0.74–1.07)	0.87 (0.72–1.05)	
Death	Yes (13,532)	178 (2.6)	218 (3.2)	0.81 (0.66–0.98)	0.79 (0.64–0.96)	0.59
	No (6,545)	117 (3.6)	134 (4.1)	0.88 (0.69–1.13)	0.84 (0.65–1.10)	
MI	Yes (13,532)	291 (4.3)	305 (4.6)	0.94 (0.80–1.11)	0.95 (0.81–1.12)	0.85
	No (6,545)	96 (3.0)	106 (3.3)	0.91 (0.69–1.20)	0.92 (0.69–1.21)	
Major bleeding	Yes (13,532)	229 (3.4)	360 (5.4)	0.62 (0.53–0.73)	0.62 (0.52–0.73)	0.92
	No (6,545)	85 (2.6)	135 (4.2)	0.63 (0.48–0.83)	0.62 (0.47–0.83)	
Net clinical outcome†	Yes (13,532)	749 (11.0)	892 (13.2)	0.82 (0.75–0.91)	0.82 (0.74–0.90)	0.78
	No (6,545)	277 (8.5)	347 (10.6)	0.80 (0.68–0.93)	0.78 (0.66–0.92)	

*Interaction p value for unadjusted analysis. †Net clinical outcome is defined as composite of death, MI, refractory ischemia, or major bleeding. Abbreviations as in Table 2.

thienopyridines, there were similar rates of death, MI, and refractory ischemia in both the fondaparinux and the enoxaparin groups (Fig. 1). There was a significant reduction in the rates of major bleeding and net clinical outcome with fondaparinux compared with enoxaparin in those treated with both agents during initial hospitalization (Fig. 1). In those undergoing PCI during the initial hospitalization, there was a significant reduction in major bleeding with fondaparinux regardless of whether patients received combined therapy with both GP IIb/IIIa inhibitors and thienopyridine pre-treatment (at least 6 h pre-PCI) (Fig. 3).

Discussion

Our analysis shows that fondaparinux is associated with a 40% reduction in major bleeding compared with enoxaparin when used on top of background therapy with GP IIb/IIIa inhibitors or thienopyridines. Ischemic outcomes were similar between the 2 groups, but fondaparinux was associated with superior net clinical outcomes. These data provide support for the efficacy and safety of fondaparinux use in patients treated concurrently with GP IIb/IIIa inhibitors and thienopyridines.

Thienopyridines have been shown to reduce the composite of death, MI, or stroke in patients with acute coronary syndromes in the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial by 20% (relative risk [RR]: 0.80, 95% CI: 0.72 to 0.90) but at the expense of an increased risk of bleeding (RR: 1.38, 95% CI: 1.13 to 1.67) (1). Similarly, GP IIb/IIIa inhibitors have been shown to have a modest benefit with regard to death or MI in all patients with acute coronary syndromes from a meta-analysis (odds ratio [OR]: 0.91, 95% CI: 0.85 to 0.99) but at the expense of a 60% increase in the odds of bleeding (OR: 1.62, 95% CI: 1.36 to 1.94) (2).

Both thienopyridines and GP IIb/IIIa inhibitors were tested on top of either enoxaparin or unfractionated heparin in this analysis of the OASIS 5 study. Our study suggests that fondaparinux instead of enoxaparin can potentially offset the increased bleeding risk associated with thienopyridines and GP IIb/IIIa inhibitors, both agents recommended as options in the current European and American guidelines (3,4). In the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, bivalirudin alone reduced major bleeding compared with unfractionated heparin plus GP IIb/IIIa inhibitors (10). However, in this trial, bivalirudin plus GP IIb/IIIa had similar rates of major bleeding compared with heparin plus GP IIb/IIIa. These results suggested that the increased risk of bleeding with GP IIb/IIIa inhibitors was so significant that it seemed to overwhelm the effect of different antithrombins in terms of bleeding. On the other hand, our analysis shows that in the setting of GP IIb/IIIa use, the choice of antithrombin agent is important and fondaparinux can reduce bleeding events compared with enoxaparin in this setting.

A number of studies (5–7) have shown a marked increased risk in death associated with major bleeding. In an analysis of over 34,000 patients with acute coronary syndromes, major bleeding was associated with not only a 5-fold increase in mortality but also a 4-fold increase in MI after adjusting for covariates (5). With increased use of thienopyridines and GP IIb/IIIa inhibitors, the bleeding risk associated with combining these agents with different antithrombotic medications is an important issue in the therapy of NSTE-ACS.

The safety and efficacy of enoxaparin compared with unfractionated heparin with frequent use of GP IIb/IIIa inhibitors use was assessed in the SYNERGY (Superior Yield of the New strategy of Enoxaparin, Revascularization, and GlYcoprotein inhibitors) trial (11). In over 10,000 patients with NSTE-ACS, enoxaparin was associated with a 20% increase in risk of major bleeding compared with unfractionated heparin (11). The finding of an increased risk of bleeding with enoxaparin in the setting of potent antiplatelet therapy is consistent with our findings.

Study limitations. The main limitation of this study is that it is based on a post-randomization subgroup and the results may have been influenced by potential confounding variables. To partially offset this, we extensively adjusted both the efficacy and the safety results with a propensity analysis. In addition, these subgroup results are consistent with the results of the overall trial.

Conclusions

Fondaparinux had a superior net efficacy to safety balance compared with enoxaparin in those treated with either GP IIb/IIIa inhibitors or thienopyridines. In the setting of GP IIb/IIIa inhibitors, fondaparinux is the only agent compared with enoxaparin that has been shown to have a superior net efficacy to safety balance.

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