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Low vs. Standard Dose Unfractionated Heparin for Percutaneous Coronary Intervention in Acute Coronary Syndromes Patients treated with Fondaparinux: the FUTURA/OASIS 8 Randomised Trial

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Population Health Research Institute
Health Through Knowledge
PHRI

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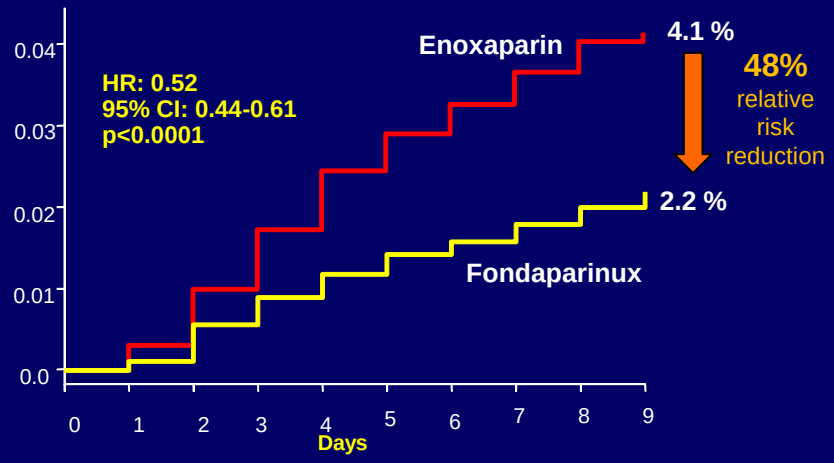
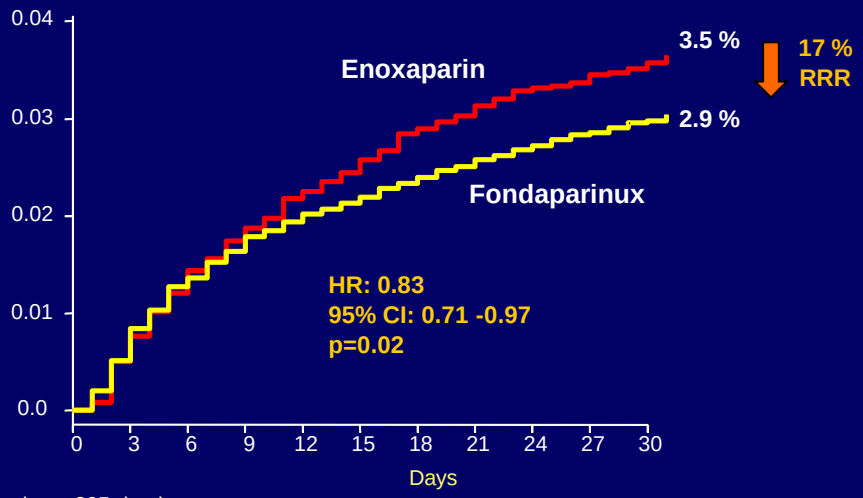
Background: OASIS 5

Randomized trial of Fondaparinux vs. Enoxaparin in NSTEACS (n=20,078) demonstrated non-inferiority for CV death, MI, Refractory Ischemia

Major Bleeding at 9 days



Mortality at 30 days



Fondaparinux: 295 deaths
Enoxaparin: 352 deaths

Fondaparinux vs. Enoxaparin reduced major bleeding by 48% and mortality by 17%

OASIS 5 Investigators. *N Engl J Med* 2006;354:1464-76

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Background: OASIS 5 Fondaparinux vs. Enoxaparin in ACS patients undergoing PCI (n=6177)

Outcome Day 9	Enox N = 3072	Fonda N = 3105	HR	P value
Death, MI or Stroke	6.2	6.3	1.03	0.79
Major Bleeding	5.1	2.4	0.46	<0.00001
Catheter Thrombosis	0.4	0.9	3.59	0.001

- Data from OASIS 5, that unfractionated heparin may prevent catheter thrombosis but optimal dose uncertain
- FUTURA trial was designed to determine the optimal regimen of heparin to prevent catheter thrombus and ischemic events in fondaparinux treated patients,without increasing bleeding.

Mehta SR., et al .*JACC*. 2007;50:1742-51
Mehta SR, et al. *Circulation*, 2008;118:2038-46

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FUTURA Trial Study Objectives

- **Primary Objective**: To determine whether Low fixed dose vs. Standard ACT guided unfractionated heparin during PCI reduces the composite of peri-PCI* major, minor bleeding and vascular access site complications in ACS patients treated with fondaparinux

- **Secondary Objective**: To determine if major bleeding rates in FUTURA (with unfractionated heparin added to fondaparinux) are higher than OASIS 5 PCI (with Fondaparinux used alone)

- *Peri-PCI defined within 48 hours following PCI

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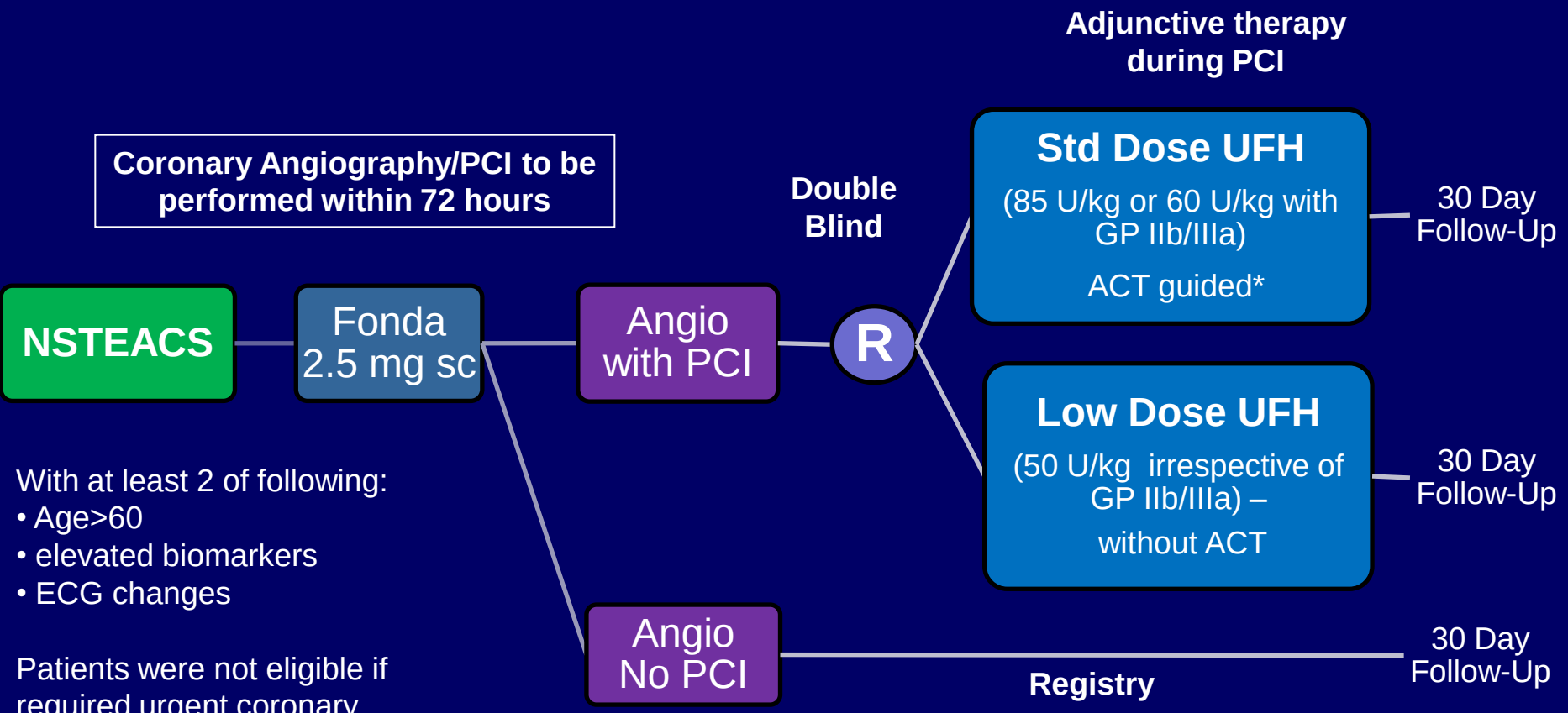
Study Design



*ACT Targets consistent with current guidelines

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Statistical Considerations

- Primary Outcome: Peri-PCI (within 48 hours) major bleeding, minor bleeding or major vascular access site complications
- Key Secondary outcome: Peri-PCI major bleeding, death, MI, or TVR at 30 days
- Study power: Based on a 5% event rate in standard dose group, study had 81% power to detect a 50% RRR in the primary endpoint. (RRR derived from OASIS 5)
- 30 day Follow up complete in 99.9%

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Study Outcome Definitions

Major Bleeding (OASIS 5)	• Fatal • Symptomatic ICH • Retroperitoneal hemorrhage • Intraocular bleeding leading to significant vision loss • Requiring surgical intervention • Hb drop of ≥3 g/dL • Blood transfusion of ≥ two units RBCs
Minor Bleeding	Any other significant bleeding leading to transfusion of one unit of blood or discontinuation of antithrombotic therapy.
Major Vascular Access Site Complications	• Large hematoma (≥5 cm or requiring intervention) • Pseudoaneurysm requiring treatment • Arterio-venous fistula • Other vascular surgery related to the access site

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Baseline and Procedural Characteristics

	Standard Dose UFH N=1002	Low Dose UFH N=1024
Age (years)	65.5	65.3
Male (%)	68.5	67.3
Diabetes (%)	27.9	26.1
ECG changes (%)	74.6	75.3
Elevated Troponin I or T (%)	78.8	81.3
Aspirin (%)	96.1	95.4
Clopidogrel (%)	96.3	94.6
Procedural GP IIb/IIIa (%)	26.4	25.8
Femoral Access (%)	62.4	64.2
Any Stents placed (%)	94.0	93.7

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Median Times (IQR)

	Standard Dose UFH N=1002	Low Dose UFH N=1024
Symptom onset to PCI (h)	27 (16-42)	28 (17-43)
Last fondaparinux dose to PCI (h)	4:07 (2:43-14:20)	4:26 (2:45-14:44)
Duration of fondaparinux (days)	3 (2-5)	3 (2-5)
Duration of hospitalization (days)	4 (3-7)	4 (3-7)

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Primary Outcome at 48 h

	Standard Dose UFH (n=1002)	Low Dose UFH (n=1024)	OR	95% CI	P
Peri-PCI major, minor bleeds and vascular access complications	5.8%	4.7%	0.80	0.54-1.19	0.27

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Primary Outcome at 48 h

	Standard Dose UFH (n=1002)	Low Dose UFH (n=1024)	OR	95% CI	P
Peri-PCI major, minor bleeds and vascular access complications	5.8%	4.7%	0.80	0.54-1.19	0.27
Components :					
Major bleeds	1.2%	1.4%	1.14	0.53-2.49	0.73
Minor bleeds	1.7%	0.7%	0.40	0.16-0.97	0.04
Major vascular access site complications	4.3%	3.2%	0.74	0.47-1.18	0.21

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Secondary Outcomes at 30 days

	Standard Dose UFH (n=1002)	Low Dose UFH (n=1024)	OR	95% CI	P
Peri-PCI major bleeding, death, MI, TVR	3.9%	5.8%	1.51	1.00-2.28	0.05
Death, MI, TVR	2.9%	4.5%	1.58	0.98-2.53	0.06
Death	0.6%	0.8%	1.31	0.45-3.78	
MI	2.5%	3.0%	1.22	0.72-2.08	
TVR	0.3%	0.9%	2.95	0.80-10.9	
Stent thrombosis	0.5%	1.2%	2.36	0.83-6.73	0.11
Catheter thrombosis	0.1%	0.5%*	4.91	0.57-42.1	0.15

** One event occurred during coronary angiography after randomization*

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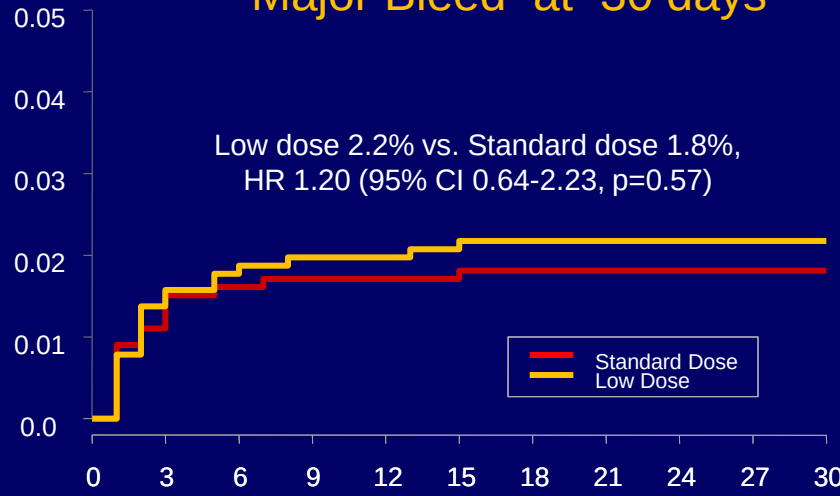
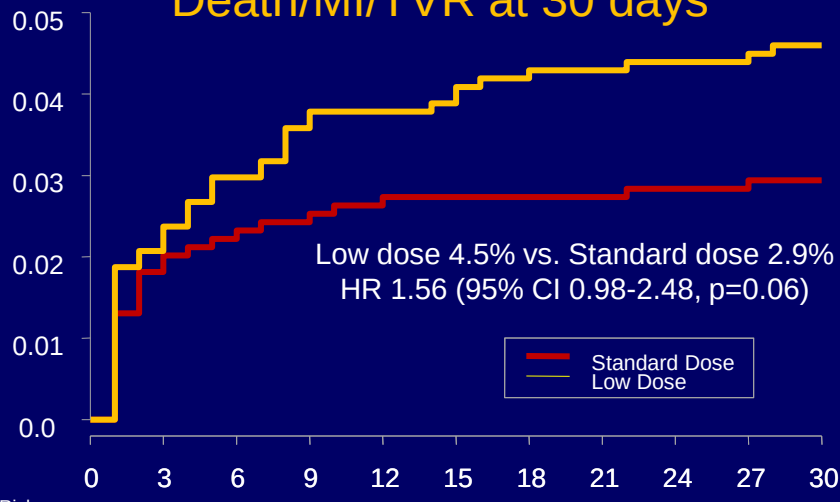
Outcomes to 30 days

Major Bleed at 30 days



No. at Risk						
Standard Dose	1002	986	981	980	980	978
Low Dose	1024	1002	1001	998	997	994

Death/MI/TVR at 30 days



No. at Risk						
Standard Dose	1002	980	975	975	974	971
Low Dose	1024	997	988	982	981	978

Consistent results by Age, Sex,
GP IIb/IIIa, BMI, CrCl, Arterial access site

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Comparison to OASIS 5 Major Bleeding (<48 h of PCI)

	Adjusted Major bleeding rate (95% CI)	OASIS 5 PCI Fondaparinux Major bleeding	OASIS 5 PCI Enoxaparin Major bleeding
FUTURA standard dose UFH	1.1% (0.6-2.1)	1.5%	3.6%
FUTURA low dose UFH	1.2% (0.6-2.2)		

Unfractionated heparin + fondaparinux does not increase peri-PCI major bleeding with rates apparently lower than when enoxaparin is used.

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Conclusions

- No significant difference in major/minor bleeding or vascular complications between Low fixed dose and Standard dose unfractionated heparin
- While low dose heparin reduced minor bleeding there was a trend towards reduced efficacy
- The use of unfractionated heparin for PCI on a background of fondaparinux did not increase major bleeding when compared to fondaparinux alone and lower than that previously observed with enoxaparin

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Implications

- ACS patients treated with fondaparinux can undergo PCI safely with unfractionated heparin
- No evidence to depart from guideline recommended standard dose regimen of unfractionated heparin during PCI
- Adding unfractionated heparin during PCI to fondaparinux preserves the benefits and safety of fondaparinux (ie. reduced bleeding) while minimizing catheter thrombus

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ORIGINAL CONTRIBUTION

Low-Dose vs Standard-Dose Unfractionated Heparin for Percutaneous Coronary Intervention in Acute Coronary Syndromes Treated With Fondaparinux

The FUTURA/OASIS-8 Randomized Trial

The FUTURA/OASIS-8 Trial Group*

Context The optimal unfractionated heparin regimen for percutaneous coronary intervention (PCI) in patients with non–ST-segment elevation acute coronary syndromes treated with fondaparinux is uncertain.

Objective To compare the safety of 2 unfractionated heparin regimens during PCI in high-risk patients with non–ST-segment elevation acute coronary syndromes initially treated with fondaparinux.

Design, Setting, and Participants Double-blind randomized parallel-group trial in 179 hospitals in 18 countries involving 2026 patients undergoing PCI within 72 hours, nested within a cohort of 3235 high-risk patients with non–ST-segment elevation acute coronary syndromes initially treated with fondaparinux enrolled from February 2009 to March 2010.

Interventions Patients received intravenously either low-dose unfractionated heparin, 50 U/kg , regardless of use of glycoprotein IIb/IIIa (GpIIb-IIIa) inhibitors or standard-dose unfractionated heparin, 85 U/kg (60 U/kg with GpIIb-IIIa inhibitors), adjusted by blinded activated clotting time (ACT).

Main Outcome Measures Composite of major bleeding, minor bleeding, or major vascular access-site complications up to 48 hours after PCI. Key secondary outcomes include composite of major bleeding at 48 hours with death, myocardial infarction, or target vessel revascularization within day 30.

Results The primary outcome occurred in 4.7% of those in the low-dose group vs 5.8% in the standard-dose group (odds ratio [OR], 0.80; 95% confidence interval [CI], 0.54-1.19; $P=.27$). The rates of major bleeding were not different but the rates of minor bleeding were lower with 0.7% in the low-dose group vs 1.7% in the standard-dose group (OR, 0.40; 95% CI, 0.16-0.97; $P=.04$). For the key secondary outcome, the rates for low-dose group were 5.8% vs 3.9% in the standard-dose group (OR, 1.51; 95% CI, 1.00-2.28; $P=.05$) and for death, myocardial infarction, or target vessel revascularization it was 4.5% for the low-dose group vs 2.9% for the standard-dose group (OR, 1.58; 95% CI, 0.98-2.53; $P=.06$). Catheter thrombus rates were very low (0.5% in the low-dose group and 0.1% in the standard-dose group, $P=.15$).

Conclusion Low-dose compared with standard-dose unfractionated heparin did not reduce major peri-PCI bleeding and vascular access-site complications.

Trial Registration clinicaltrials.gov Identifier: NCT00790907

JAMA. 2010;304(12):(doi:10.1001/jama.2010.1320) www.jama.com

IN RECENT YEARS, IMPORTANT ADvances have been made in the management of non–ST-segment elevation acute coronary syndromes, with new antithrombotic agents, increasing use of percutaneous coronary intervention (PCI) for high-risk cases, and improved secondary prevention. Among newer antithrombotics, fondaparinux, a synthetic factor Xa inhibitor, has recently emerged as an attractive option. Fondaparinux was compared with subcutaneous enoxaparin in the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial, a large international randomized trial.[1] ST elevation acute coronary syndrome was evaluated in the OASIS-6 trial.[2] In OASIS-5, fondaparinux was noninferior to enoxaparin for the primary efficacy outcome of death, myocardial infarction (MI), and refractory ischemia but halved major bleeding leading to a significant mortality reduction with fondaparinux compared with enoxaparin. However, in OASIS-5, there was a small but significant increase in catheter-related thromboses with fondaparinux in patients who underwent cardiac catheterization or PCI. This result prompted the OASIS investigators and guideline committees to recommend the use of unfractionated heparin as adjunctive therapy at the time of PCI for patients with non-ST-segment elevation acute coronary syndromes who were treated with fondaparinux and undergoing PCI[3-5]; although the range of dosing recommended differs between the European Society of Cardiology guidelines (50-100 U/kg) and American College of

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