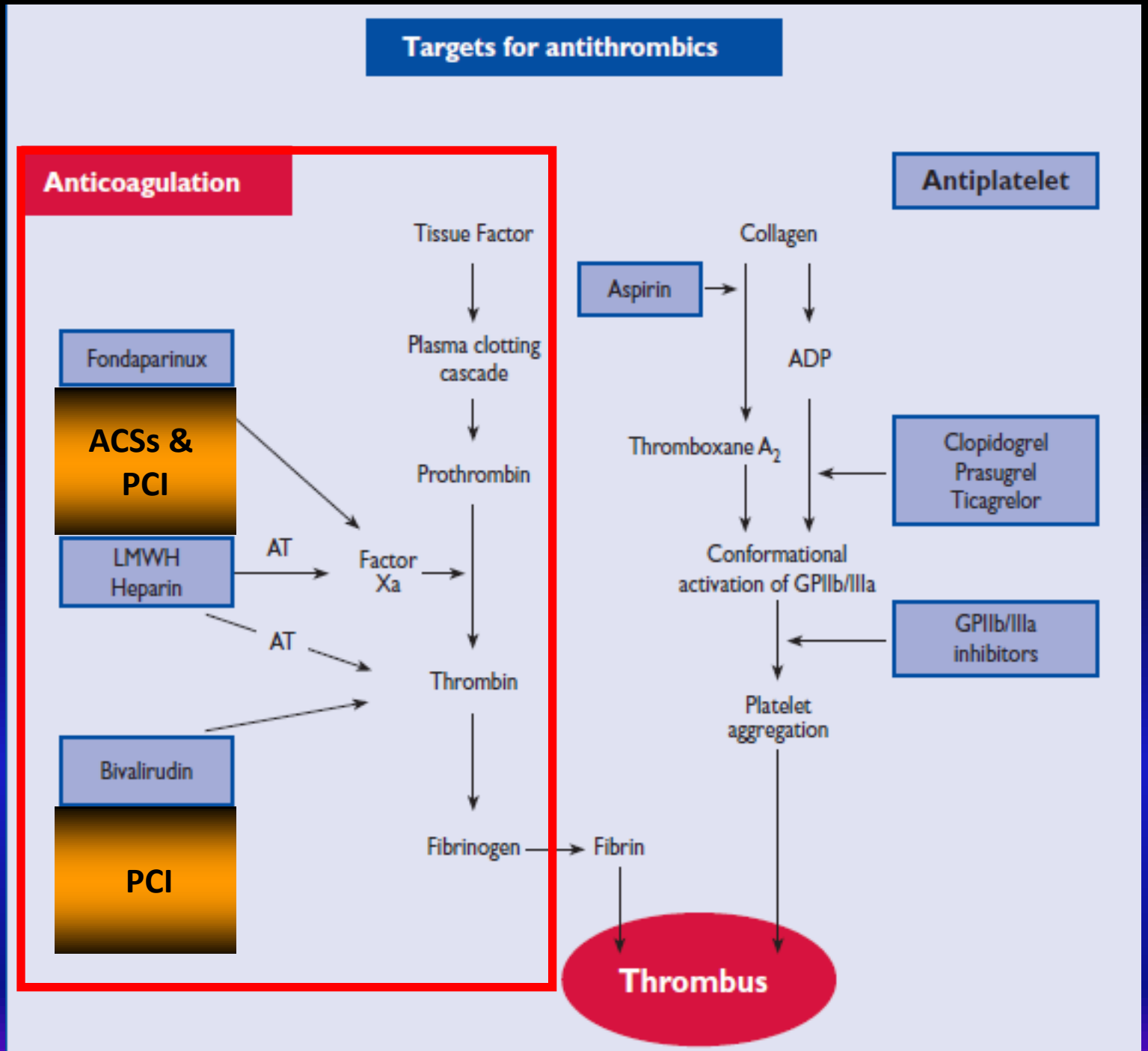
ALPIC 2012, Saturday January 28th, 2012
Round table: Anticoagulants: From the bench to the bedside

Intravenous Anticoagulants in ACS / PCI

George Hahalis
Associate Professor of Cardiology
University of Patras

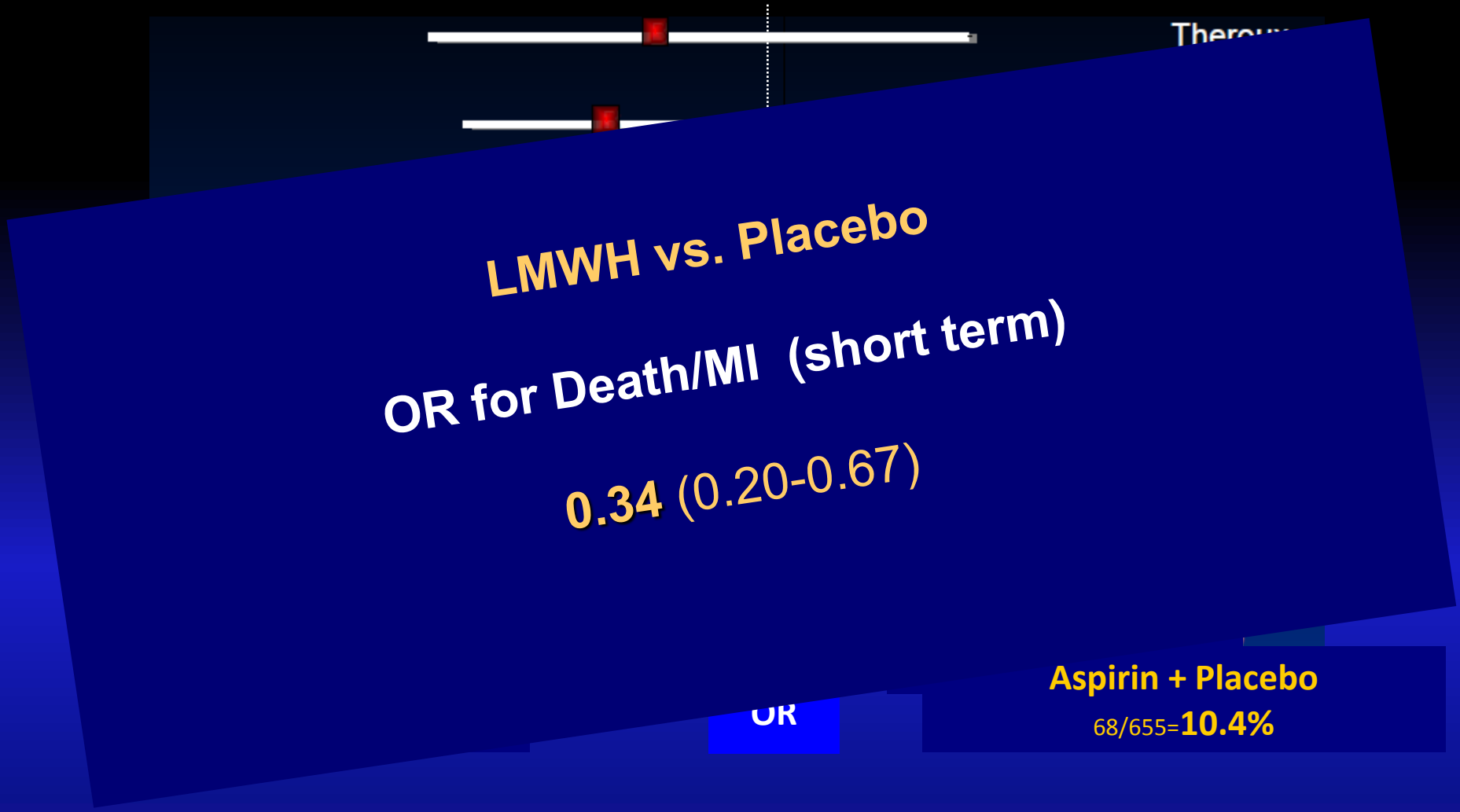

Targets for antithrombics
Anticoagulation
Antiplatelet
Tissue Factor
Plasma clotting cascade
Prothrombin
Thrombin
Fibrinogen
Fibrin
Fondaparinux
ACSs & PCI
LMWH Heparin
AT
AT
Factor Xa
Bivalirudin
PCI
Collagen
Aspirin
ADP
Thromboxane A2
Clopidogrel Prasugrel Ticagrelor
Conformational activation of GPIIb/IIIa
GPIIb/IIIa inhibitors
Platelet aggregation
Thrombus

	UFH	Enoxaparin	Fondaparinux	Bivalirudin
Factor Xa:IIa inhibition	1:1	3-4:1	100% anti-Xa	100% anti-IIa
Antithrombin required	Yes	Yes	Yes	No
Non-specific binding	Yes	Partial	No	No
Fibrin-bound thrombin inhibit	No	No	No	Yes
Platelet activation	Yes	Yes	Yes	No
Half-life	Variable with dose; ~ 60 min IV	300' min SC; 90-120' min IV	17 h SC	25 min IV
PF-4 complexing & risk of HIT	Yes	Reduced	Low	No

Stone GW and Ohman EM. *Lancet* 2011 Aug 20;378:643

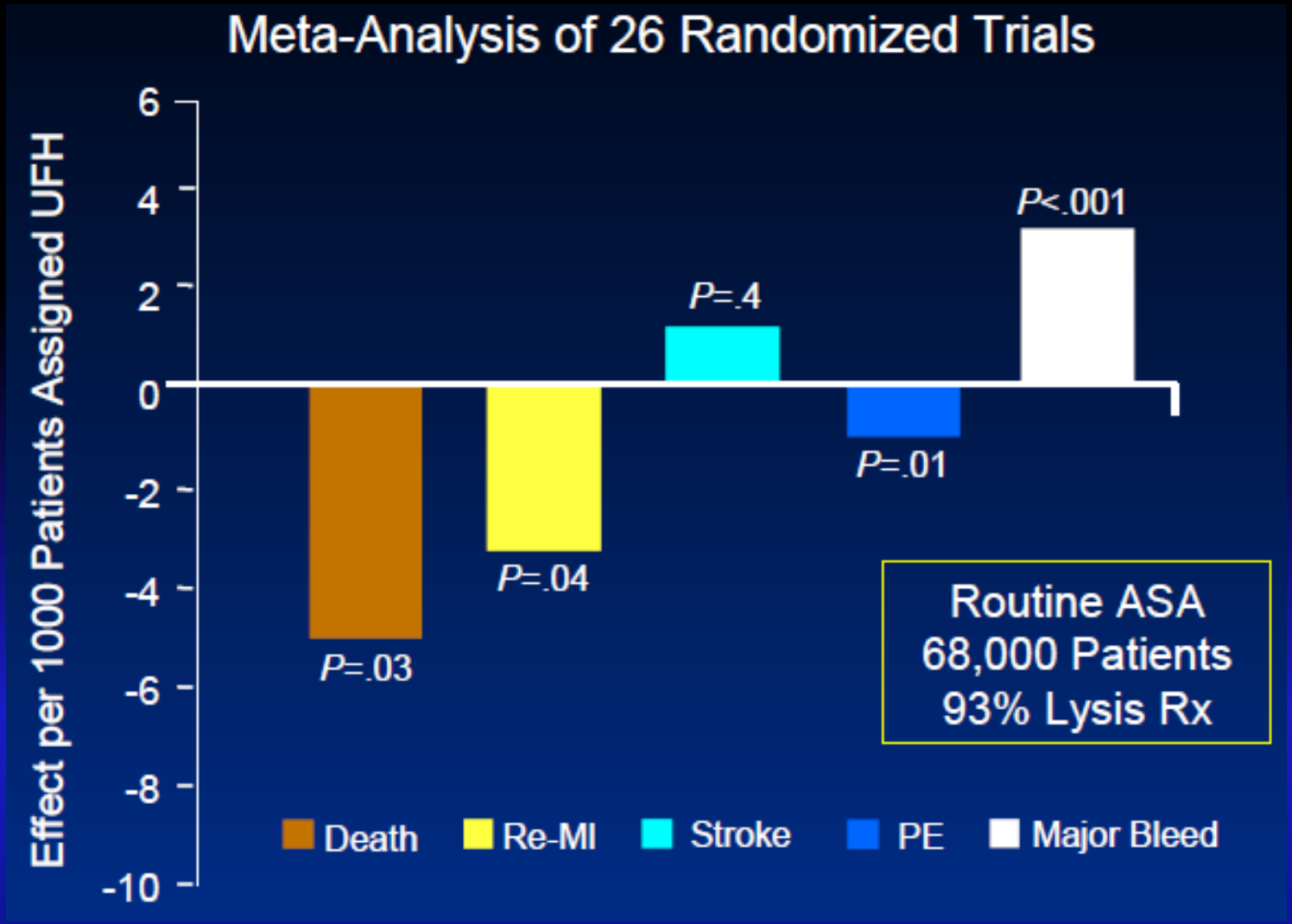
	UFH	Enoxaparin	Fondaparinux	Bivalirudin
Elective PCI		•STEEPLE		•REPLACE-2 •ISAR-REACT-3 •ACUITY (vs UFH + IIb/IIIa Inhibitors vs. Bivalirudin +IIb/IIIa Inhibitors)
NSTEMI-ACSs	•Meta-analysis	•ESSENCE •TIMI 11 •Metaanalyses •SYNERGY (vs. UFH in early PCI in high risk patients)	•OASIS 5 (vs. Enoxaparin) •FUTURA-OASIS 8 (PCI with low vs. high UFH dose in PCI)	•ISAR-REACT-4 (vs UFH + Abciximab in NSTEMI)
STEMI (thrombolysed, primary PCI, secondary PCI or no reperfusion)	•Meta-analysis	•ExTRACT--TIMI 25 (ve. UFH in thrombolysis) •ATOLL (primary PCI)	•OASIS 6 (thrombolysis, primary PCI or no reperfusion) (vs. UFH vs Placebo)	•HORIZON-AMI (primary PCI) (vs UFH + IIb/IIIa Inhibitors)

UFH or LMWH over Placebo
Reduces Mortality / MI in Patients with ACSs in Addition to Aspirin



Eickelboom JW. *Lancet* 2000

UFH versus Placebo Reduces Mortality in Patients with **Thrombolysed STEMI**



Collins R, et al. *N Engl J Med. 1997;336:847-860*

Enoxaparin in non-emergent PCI

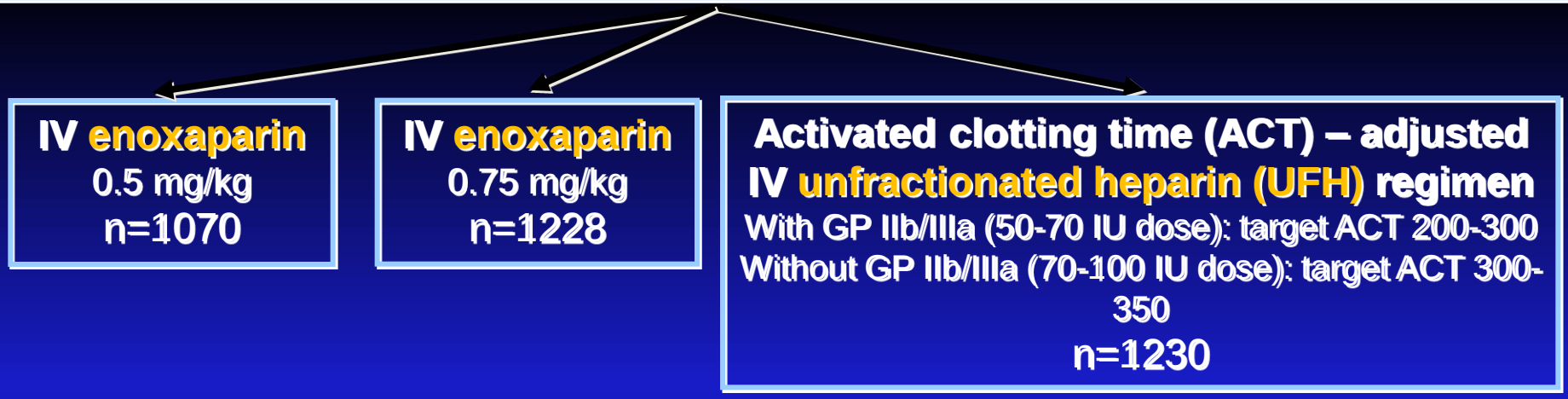
vs

UFH

STEEPLE

STEEPLE Trial

3528 patients. Non-emergent single or multi-vessel PCI
Randomized
25% female, mean age 64 years, mean follow-up 30 days
GP IIb/IIIa inhibitors were used in 41% of patients, and aspirin in 85%
DES were used in 57% of patients and multivessel PCI was performed in 16% of patients



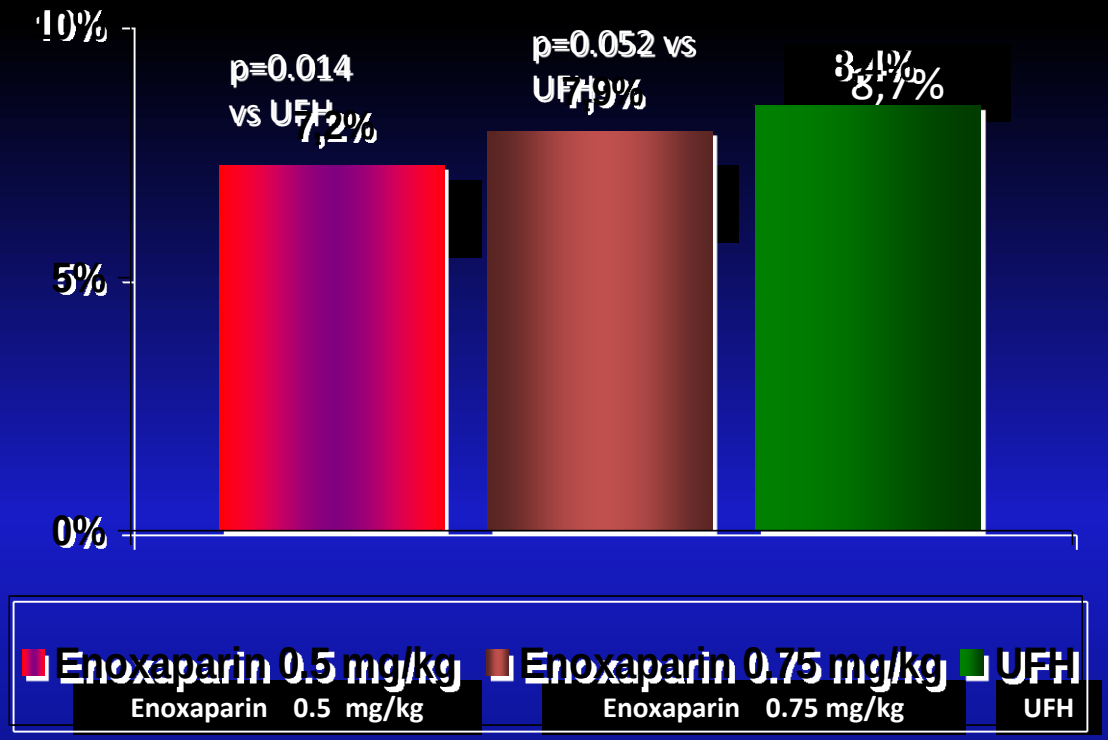
Primary Endpoint: Non-CABG major and minor bleeding 48h postPCI

- Secondary Endpoint: % of patients reaching target anticoagulation levels at the start and end of the procedure; composite of non-CABG major bleed @ 48 hrs; all-cause mortality; MI; urgent TVR @ 30 days

Montalescot G. Presented at ESC 2005

STEEPLE Trial: Primary Endpoint at 48 hours

Non-CABG major or minor bleeding (%):
Significant for major bleedings only



- Lower bleeding rate in the subgroup of patients treated with GP IIb/IIIa inh

Montalescot G. Presented at ESC 2005

ENOXAPARIN in STEMI

vs.

UFH

Thrombolysis and facilitated PCI:

- ASSENT-3
- ASSENT-3 PLUS
- ExTRACT-TIMI 25
- FINESSE

ASSENT-3 included 6095 STEMI patients <6 h Randomized to one of three regimens (open-label)

1) **Full-dose TNK + Enoxa** <7 d (enoxaparin group)
2) **Half-dose TNK** +**low-dose UFH** +**12-h Abciximab** (abciximab group)
3) **Full-dose TNK**+**UFH** for 48 h (UFH group)

- **Efficacy endpoint**: **C**omposite of 30-day Death, in-hospital re-MI, or in-hospital refractory ischemia:

Enoxaparin vs. UFH: 11.4% vs. 15.4%; **RR=0.74** [95% CI 0.63-0.87], p=0.0002
Abciximab vs. UFH: 11.1% vs. 15.4%; RR=0.72 [0.61-0.84], p<0.0001)

- **Efficacy plus safety endpoint:** The above endpoint + intracranial haemorrhage or major bleeding:

Enoxaparin vs. UFH: 13.7% vs. 17.0%; **RR=0.81** [95% CI 0.70-0.93], p=0.004
Abciximab vs. UFH: 14.2% vs. 17.0%; RR=0.84 [0.72-0.96], p=0.01)

- Similar clinical outcomes **after elective PCI**

*"**TNK +Enoxaparin** or +Abciximab regimens **reduced ischaemic STEMI** complications. TNK+enoxaparin is an attractive rerfusion regimen'*

Lancet 2001 Aug 25;358(9282): Dubois CL JACC 2003 Oct 1;42(7):1178

ASSENT-3 PLUS included 1639 STEMI patients **Pre-hospital thrombolysis**. Randomized to:

Full-dose TNK + enoxaparin <7 d (ENOX)
versus
Full-dose TNK + UFH for 48 h (UFH)

- Reductions in in-hospital reinfarction (3.5% vs. 5.8%, P=0.03) and refractory ischemia (4.4% vs. 6.5%, P=0.06)

- Increases in total stroke (2.9% versus 1.3%, P=0.03) and intracranial hemorrhage (2.20% versus 0.97%, P=0.04)

- The increase in intracranial hemorrhage was seen in patients >75 years of age

'Lower doses of ENOX need to be tested in elderly patients'

Walentin L Circulation. 2003 Jul 15;108(**2**):135

ExTRACT-TIMI 25

ExTRACT-TIMI 25: Study design

Patients with STEMI scheduled to undergo fibrinolysis (n=20506)
Randomized to receive enoxaparin throughout the index hospitalization or UFH for ≥48 hours

Age <75 years: 30 mg bolus IV; 15 min later:
SC Enoxaparin
1.0 mg/kg/12h
Age >75 years: NO bolus;
SC Enoxaparin
0.75 mg/kg/12h
First 2 SC injections < 100 mg
(≤75 mg for age ≥ 75 y)

aPTT– adjusted
IV unfractionated heparin (UFH)

60 IU kg bolus (≤4000)

12 IU kg/h infusion
(≤ 1000 IU U/h

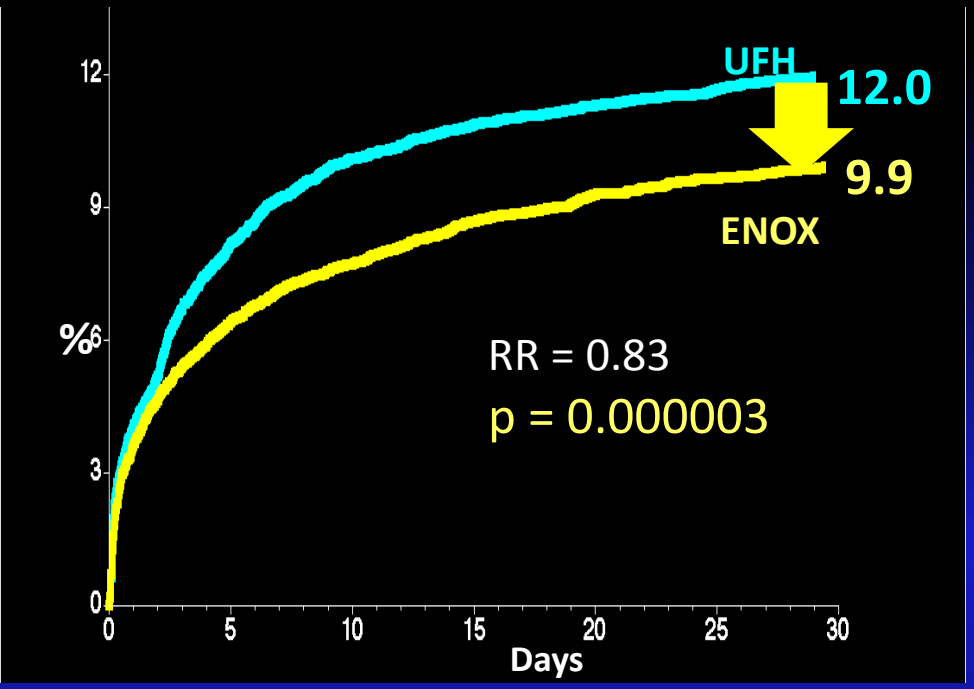
Primary Endpoint: Death or nonfatal recurrent MI through 30 days

Secondary Endpoint: 1) Composite of death from any cause, nonfatal reinfarction, or urgent TVR @ 30 d. 2) The composite of death from any cause, reMI or nonfatal disabling stroke or major bleeding or ICH

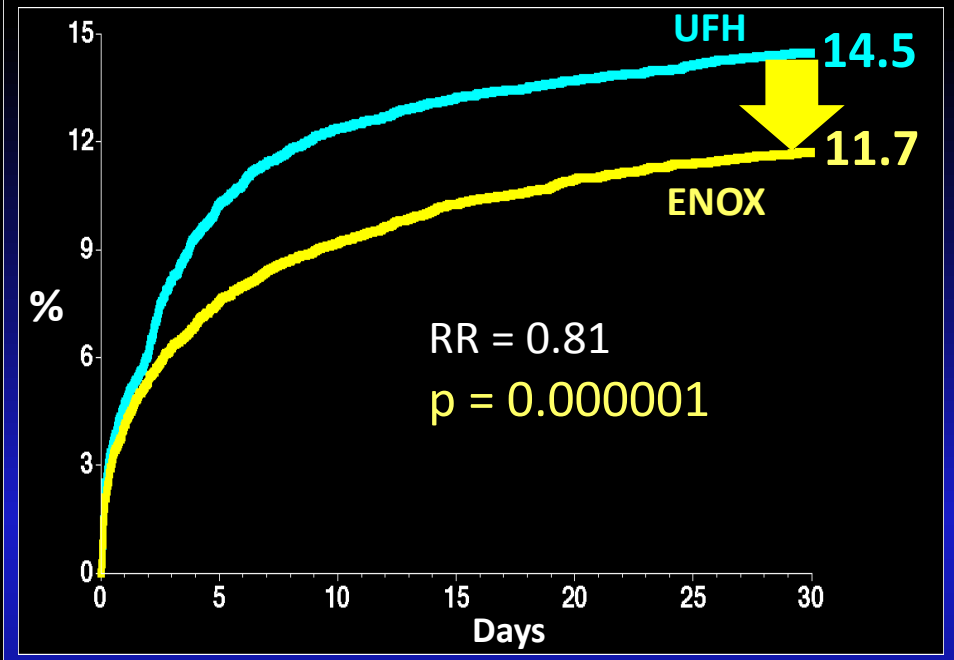
Main Results ExTRACT-TIMI 25

Streptokinase was given in 20.2%
Clopidogrel in 28.5% of the study patients

Death or non-fatal re-MI by 30 days



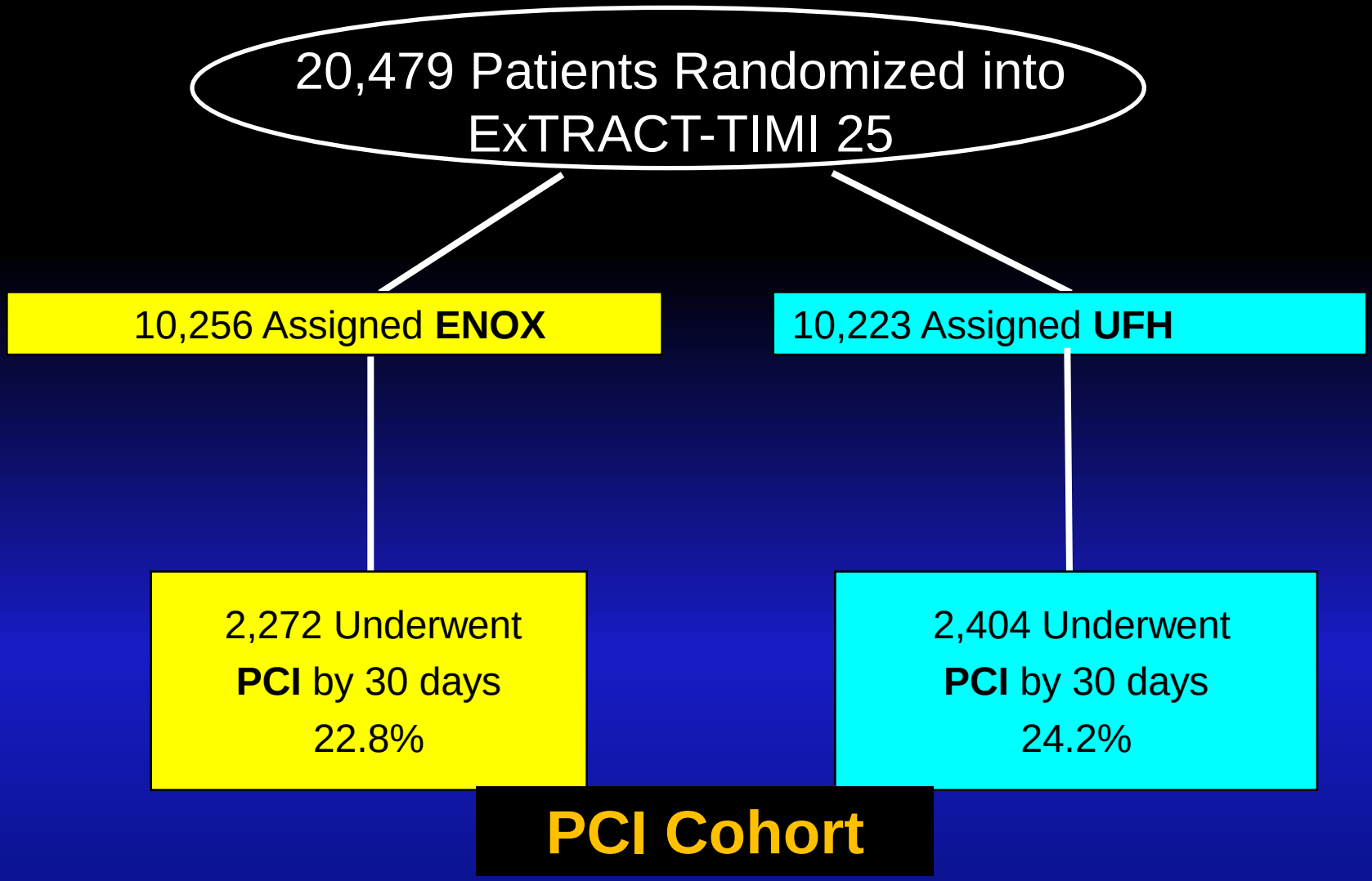
Main Secondary Endpoint: Death, non-fatal re-MI, urgent TVR by 30 d



As a result of 33% relative risk reduction of non fatal recurrent MI
Higher rates of major bleedings in the ENOX group (2.1% vs. 1.4%; p<0.0001)

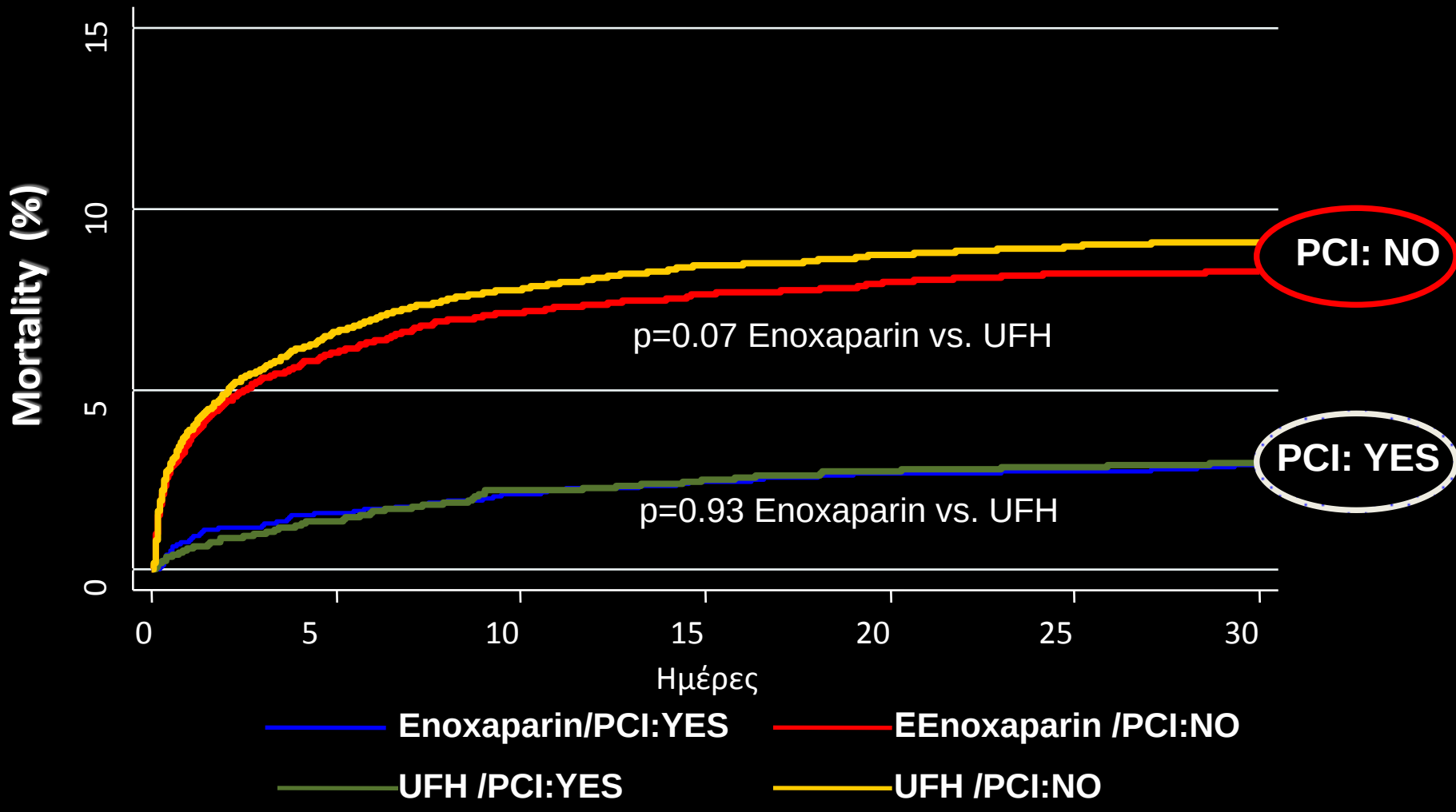
Anmtmann EM. N Engl J Med 2006;354:1477-88.

ExTRACT-TIMI 25 PCI Cohort
Study Profile



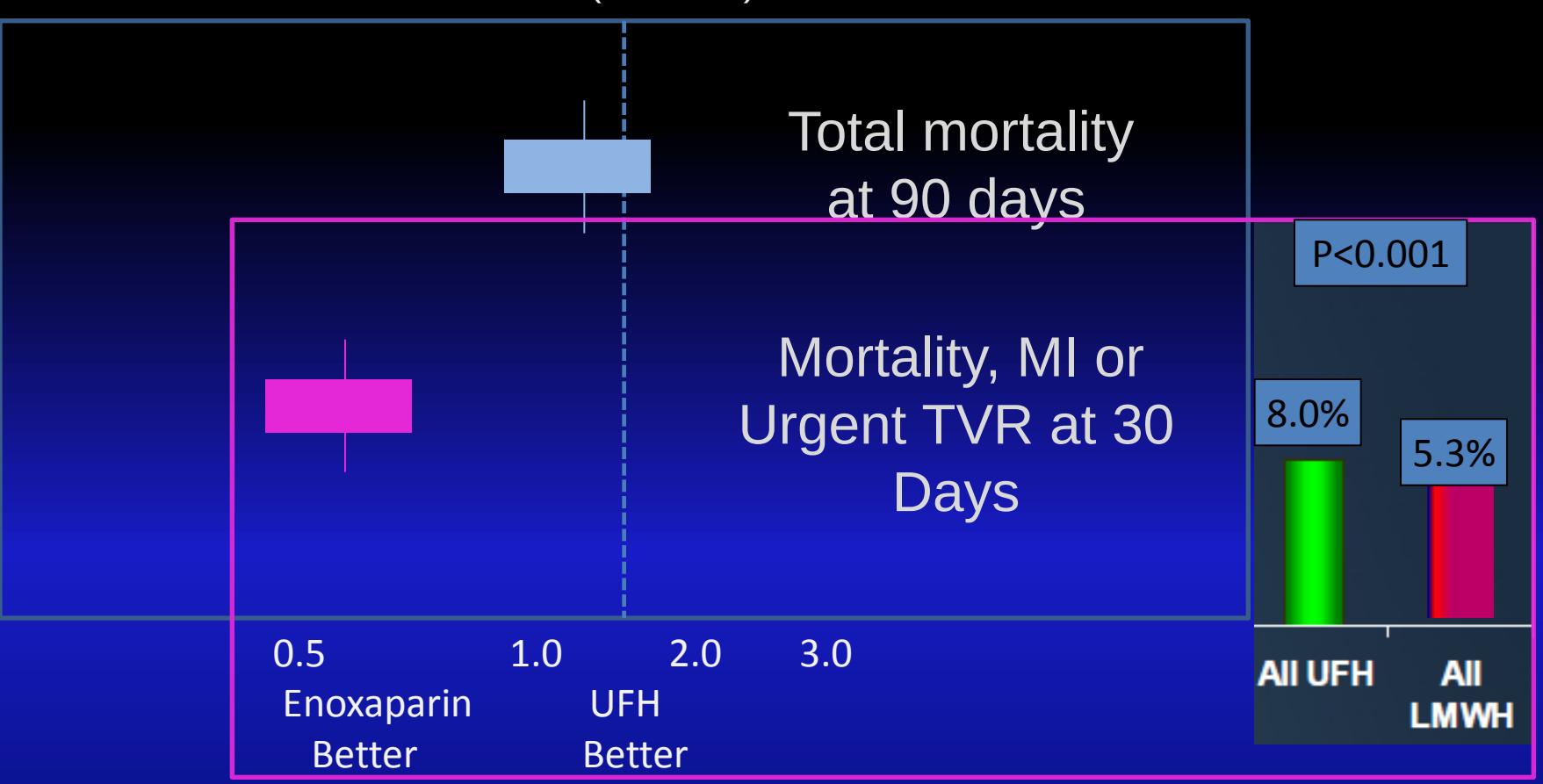
PCI/Ex-TRACT-TIMI 25:

Mortality at 30 days according to randomization and performance of PCI



UFH versus Enoxaparin in **facilitated PCI** in FINESSE Trial

Main Secondary (ischemic) end-point at 30 days: Total mortality, MI, Urgent TVR



Montalescot G et al. *J Am Coll Cardiol Intv* 2010;3:203–12

Enoxaparin in NSTEMI ACSs

Patients undergoing high risk early PCI in the era of contemporary treatment

SYNERGY

UFH versus Enoxaparin in high risk * ACSs and early PCI (n~10 000)

SYNERGY Trial

(n=10 027 patients, 30% diabetics, 34% women)

Randomization

Enoxaparin

(1 mg/kg/12h SC
(+0.3 mg/kg if last dose
> 8 ώρες

Heparin I.V.

(60 U/kg + 12 U/kg/h
(aPTT:50-70 s)

(ASA, β-blockers, α-MEA, clopidogrel (67%),
IIb/IIIa GP receptor inhibitors (57%)

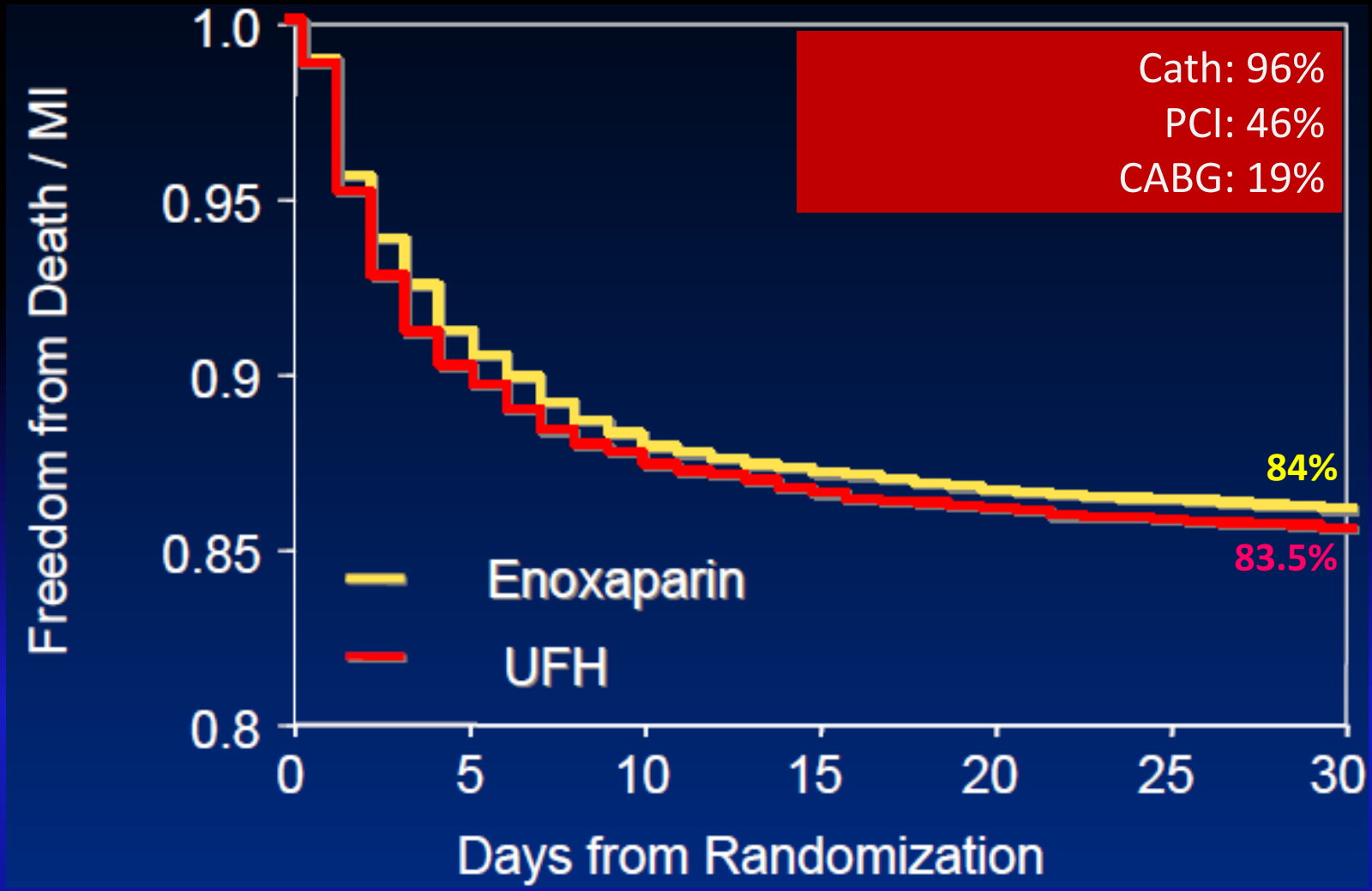
Primary end-point:
Death or MI at 30 days

*At least 2 of the following:

- Age > 60,
- ST deviation,
- Elevated cardiac markers

JAMA: 2004. 292:45-54

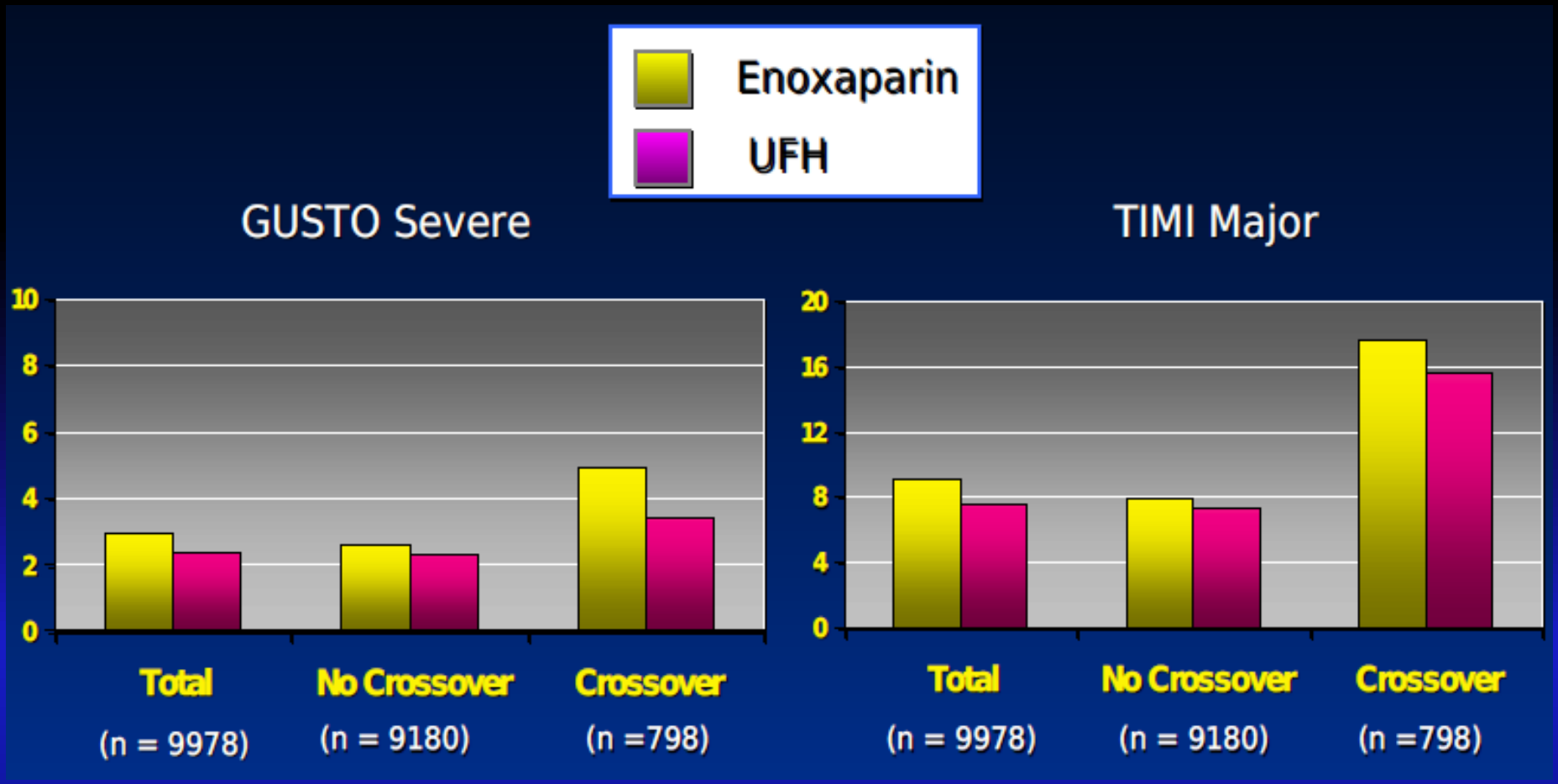
SYNERGY Trial: Mortality or MI at 30 days



JAMA: 2004. 292:45-54

SYNERGY: Hemorrhagic episodes

Cross-over in comparison with non-cross-over



JAMA: 2004. 292:45-54

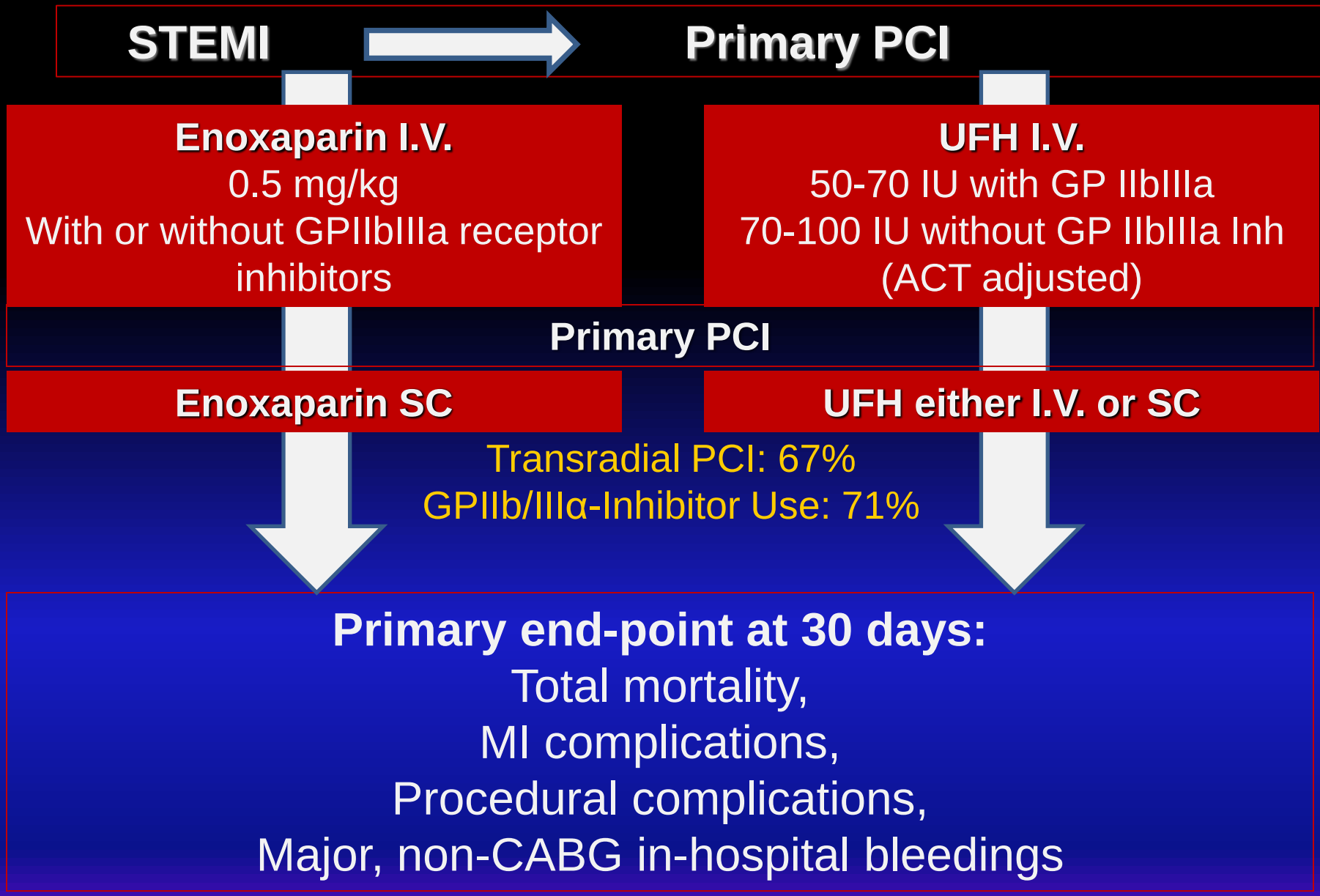
Enoxaparin in STEMI & primary PCI

vs

UFH

ATOLL

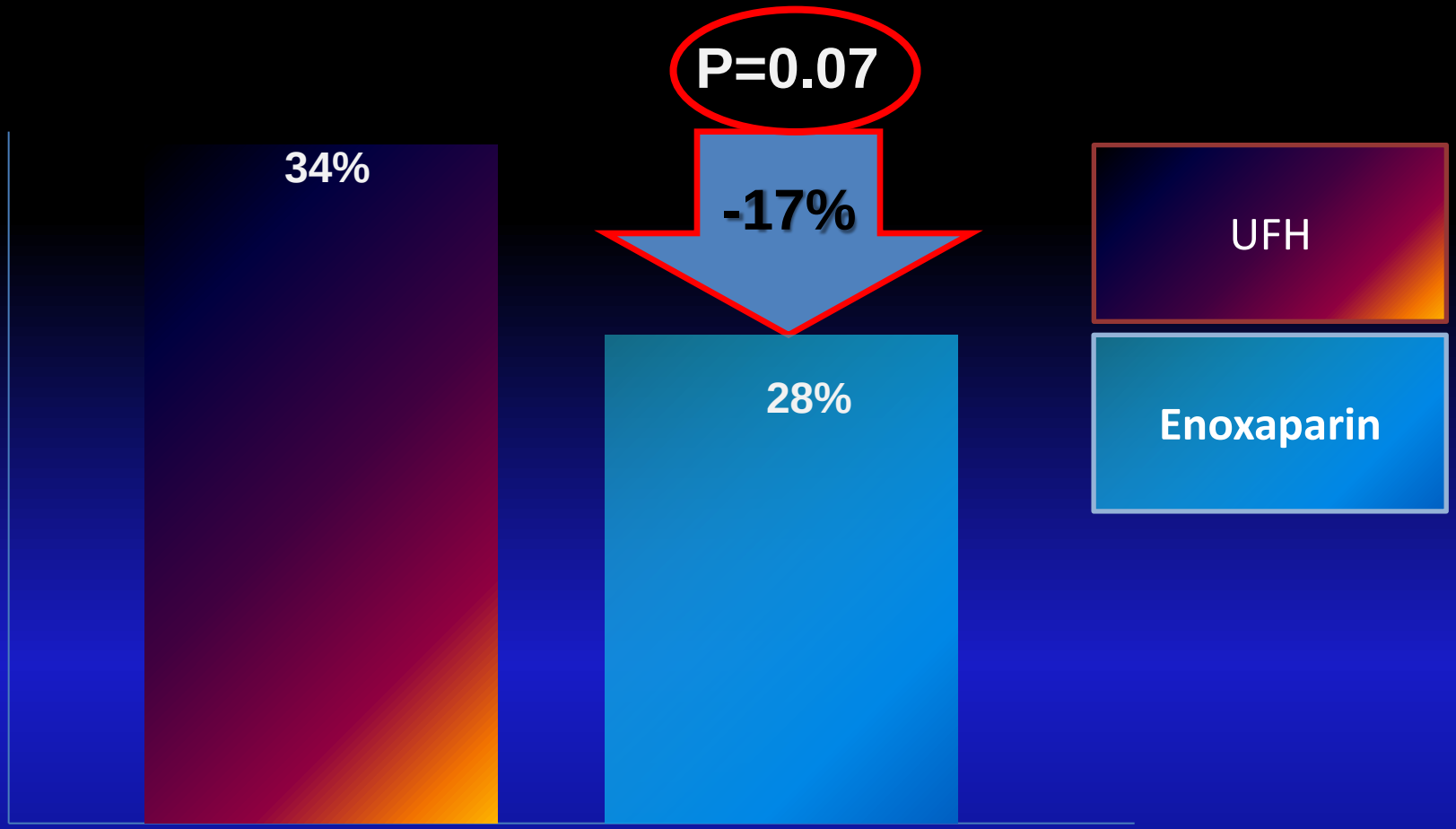
Enoxaparin versus UFH in primary PCI: **ATOLL**



ATOLL

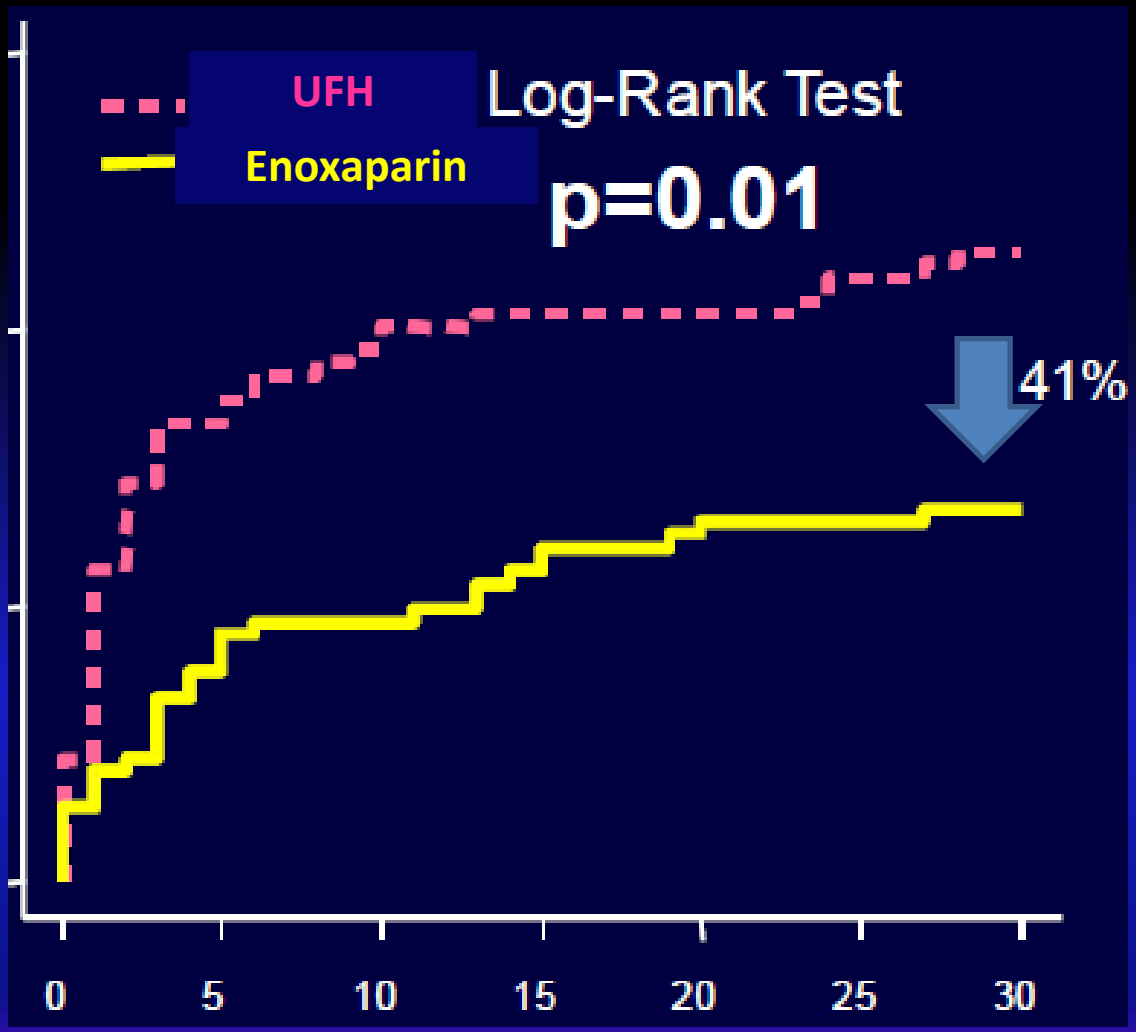
Primary end-point at 30 days:

Total mortality, MI complications, Procedural complications, Major, non-CABG in-hospital bleedings



Μελέτη **ATOLL**

Secondary, ischemic end-point at 30 days:
Total mortality, MI or Urgent TVR



ENOXAPARIN METAANALYSES

vs.

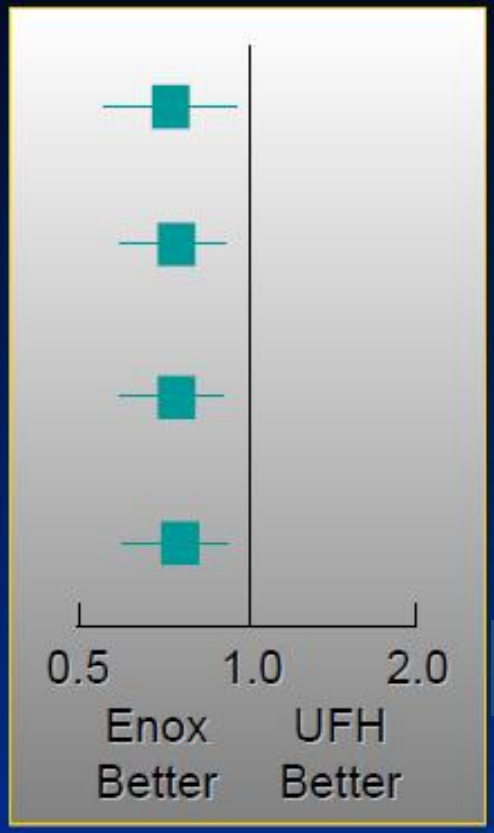
UFH

Enoxaparin vs. UFH Metaanalysis in ACSs

(Essence & TIMI 11)

Mortality, MI, Urgent TVR (n=7081)

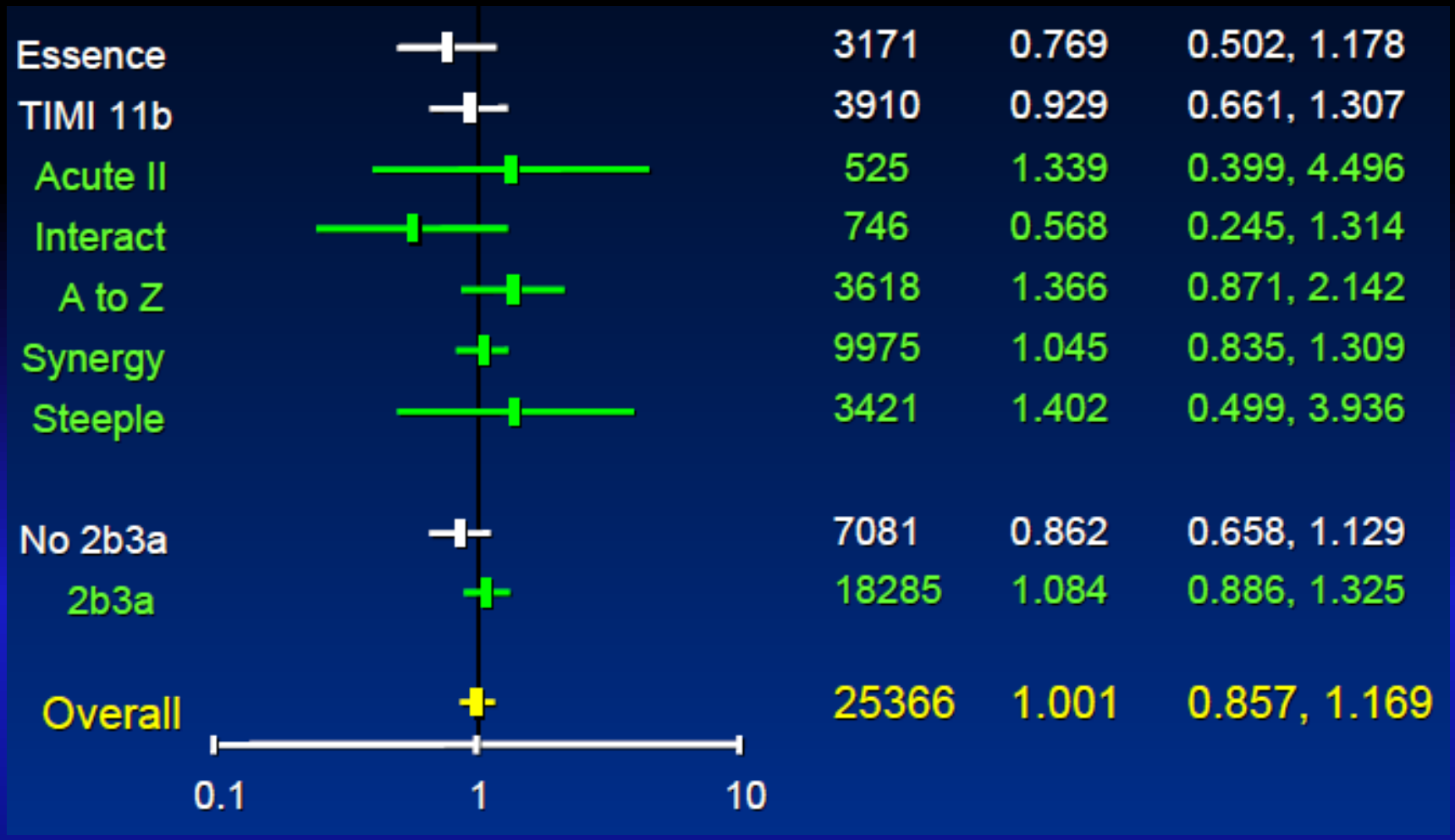
Day	UFH	Enox	OR [95% CI]	P
2	6.3%	4.9%	0.77 [0.63, 0.94]	0.02
8	13.5%	11.0%	0.79 [0.69, 0.91]	0.001
14	15.7%	12.8%	0.79 [0.69, 0.90]	0.0005
43	18.8%	15.6%	0.80 [0.71, 0.91]	0.0005



~20% RRR over UFH

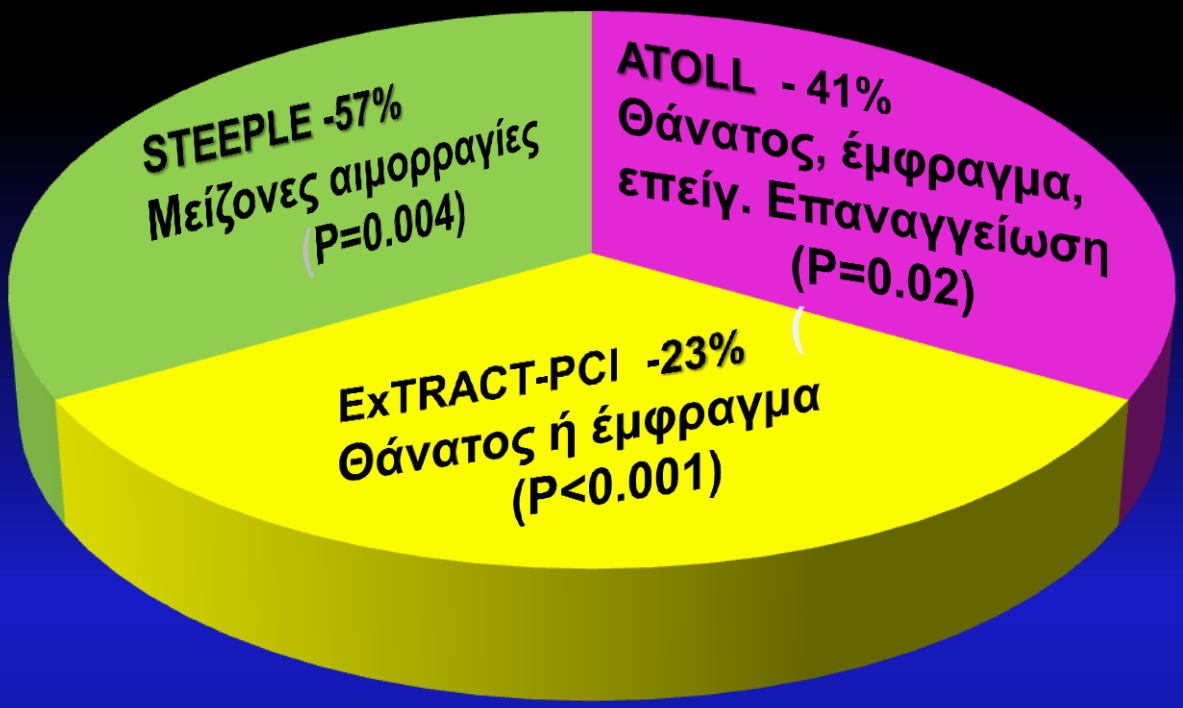
Circulation 1999;100:1602-1608

UFH versus Enoxaparin Meta-analysis: No Mortality Difference



JAMA 2004;292:89-96; ESC 2005

Enoxaparin I.V. versus UFH in **PCI**



- Πρωτογενής αγγειοπλαστική σε STEMI (ATOLL)
- Εκλεκτική αγγειοπλαστική (STEEPLE)
- Δευτερογενής αγγειοπλαστική (ExTRACT-PCI)

Fondaparinux in NSTEMI-ACSs

vs.

Enoxaparin

OASIS 5

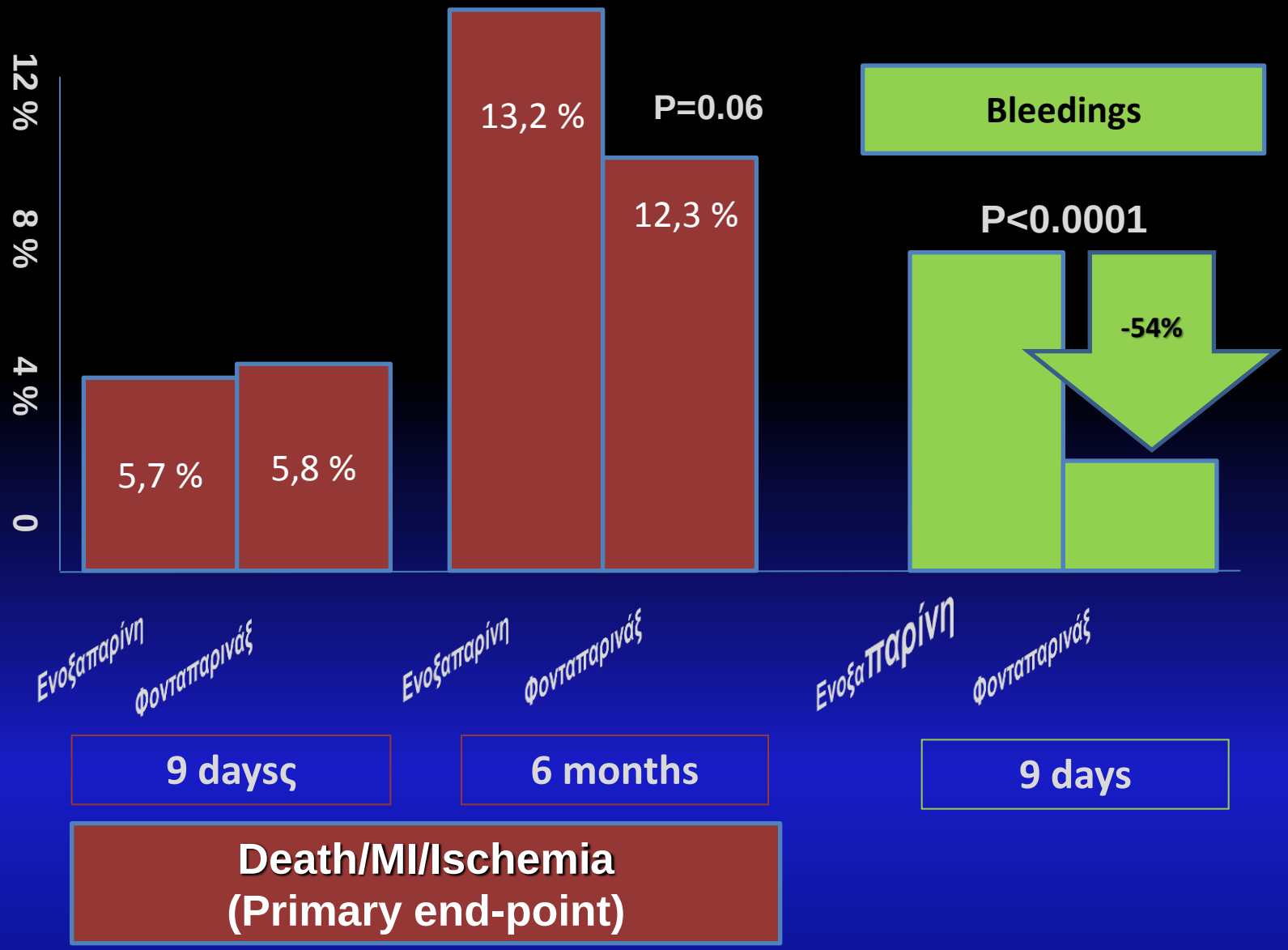
OASIS 5: Fondaparinux vs. Enoxaparin in NSTEMI-ACSs

- 20,078 ACS patients
- Fondaparinux 2.5 mg/d or Enoxaparin 1 mg/kg X2 for 6 days

- Primary end-points:
  - Death/MI/Refractory ischemia at 9 days
  - Incidence of major bleedings
  - Composite of ischemic episodes + major bleedings

N Engl J Med 2006;354:1464

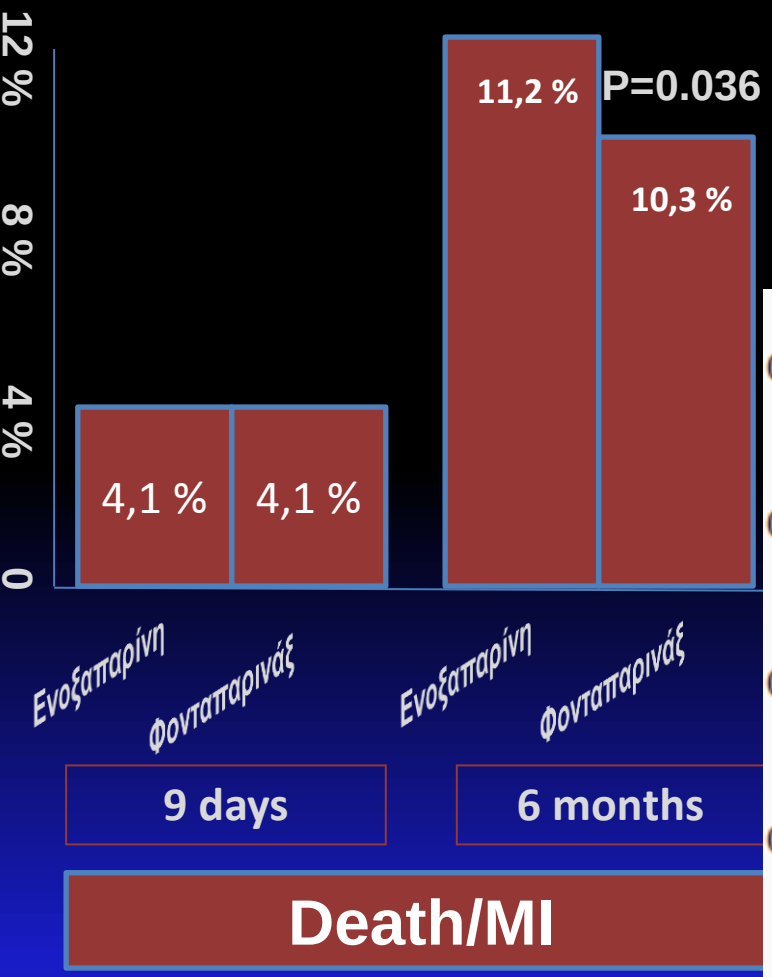
OASIS 5



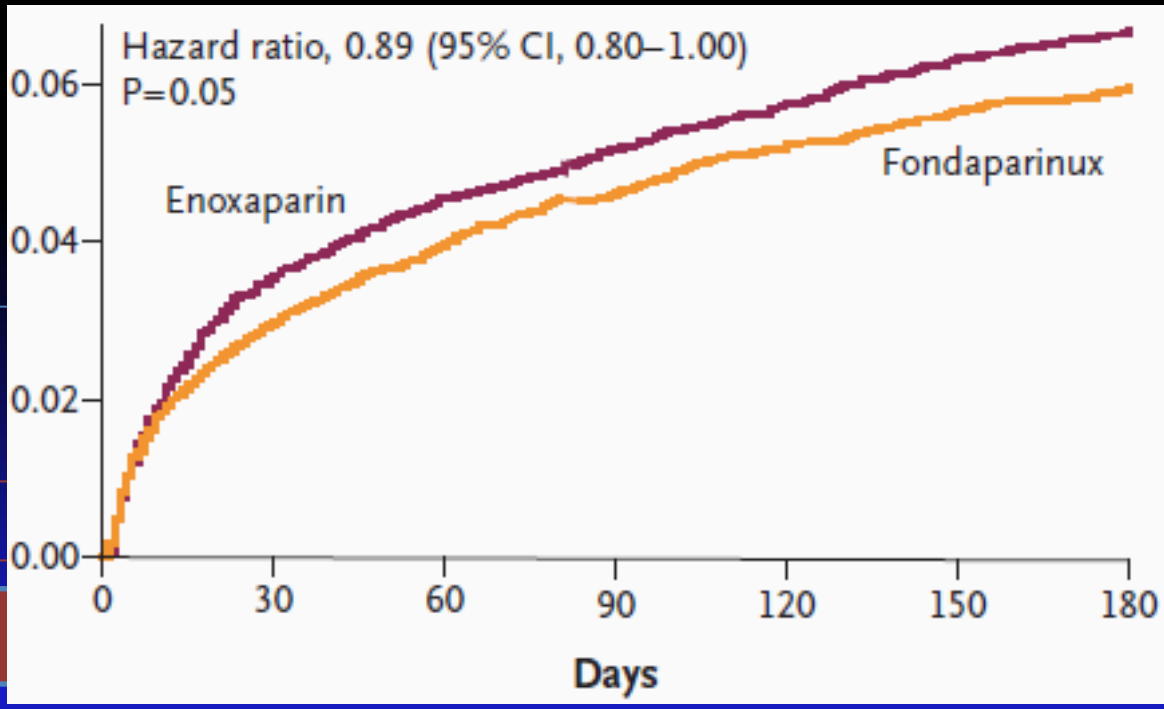
Similar Fondaparinux benefit in those receiving IIb/IIIa Inh & Clopidogrel over those patients not receiving these drugs

Jolly S. JACC 2009;54:468 N Engl J Med 2006;354:1464

OASIS 5



OASIS 5: Survival curves over 6 months



Conclusion: "Fondaparinux is similar to enoxaparin in reducing the risk of ischemic events at nine days, but it substantially reduces major bleeding and improves long term mortality and morbidity"

N Engl J Med 2006;354:14

Fondaparinux in STEMI

vs.

UFH

vs

Placebo

OASIS 6

OASIS-6: Fondaparinux vs. UFH vs Placebo in **STEMI**

12,092 PATIENTS: Randomized to

- **Fondaparinux** 2.5 mg in comparison with:
- **Placebo** (8 days; stratum 1)
- **UFH** (2 days + 6 days placebo; stratum 2)

Patients underwent thrombolysis (44%, more often streptokinase) , primary PCI (37%) or no reperfusion

Yusuf S et al. *JAMA 2006;295(13):1519*

OASIS-6: Death/MI at 30 days according to reperfusion strategy

	Placebo /UFH	Fonda -parinux	HR	*P*
		%		
No reperfusion (n = 4,233)	15.1	12.2	0.80	0.002
Thrombolysis (n = 4,421)	13.6	10.9	0.79	0.045
Primary PCI (n = 3,438)	4.9	6.0	1.24	NS

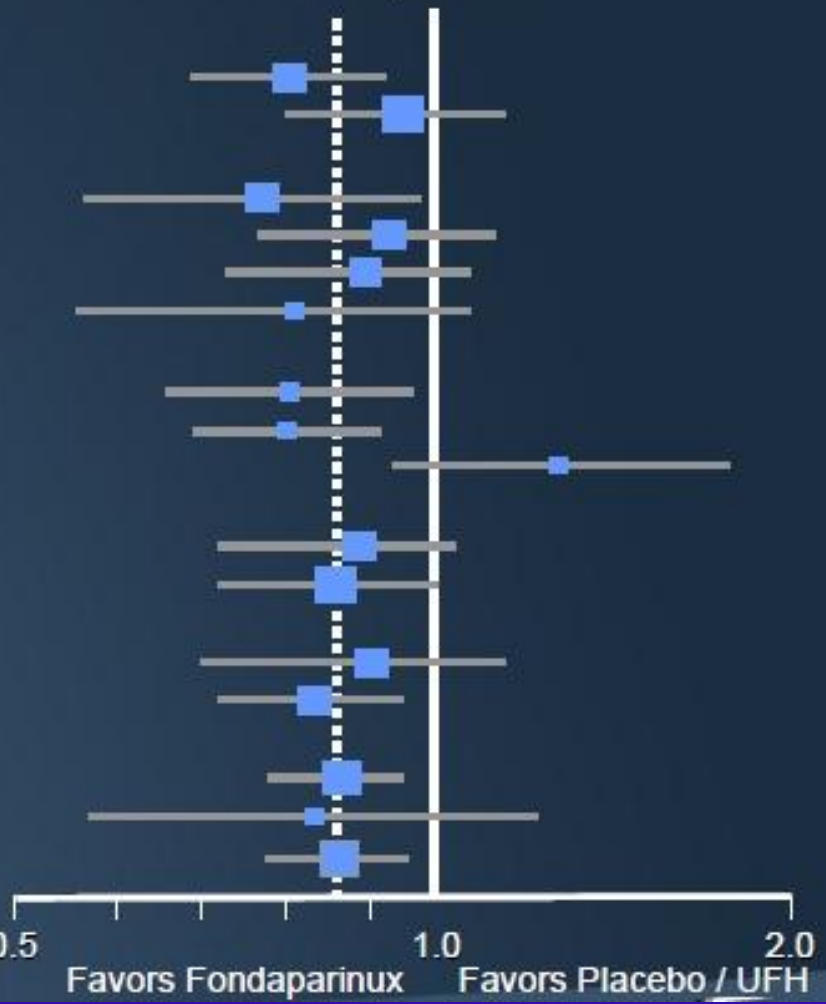
Yusuf S et al. *JAMA 2006;295(13):1519*

OASIS-6: Fondaparinux vs. UFH vs Placebo in STEMI

Predefined subgroup analysis

Death/MI at 30 days

Characteristics	No of patients	Placebo / UFH (%)	Fondaparinux (%)
Stratum			
UFH not indicated	5,658	14.0	11.2
UFH indicated	6,434	6.7	6.3
Time from onset to randomization (h)			
< 3	3,008	9.5	7.2
3 – < 6	4,300	10.3	9.6
6 – < 12	3,290	13.3	11.9
≥ 12	1,460	12.5	10.1
Initial reperfusion therapy			
None	2,867	16.9	15.0
Thrombolytic	5,346	9.0	7.7
Primary PCI	3,879	4.9	6.0
Sex			
Female	3,345	16.9	15.0
Male	8,746	9.0	7.7
Age (y)			
< 62	5,980	5.6	5.1
≥ 62	6,106	16.8	14.1
Prerandomization UFH			
No	10,304	11.8	10.3
Yes	1,787	7.7	6.4
Overall	12,092	11.2	9.7



Yusuf S et al. *JAMA 2006;295(13):1519*

OASIS-6: Complications of primary PCI

	Placebo (n=1898)	Fondaparinux (n=1878)	*P*
PCI complications (n)	97	124	0.057
Catheter thrombus (n)	0	21	<0.001
Death/MI (n)	98	115	NS

Administration of:	No upstream UFH		Upstream UFH	
N	UFH (n = 1,652)	Fonda (n = 1,641)	UFH (n = 251)	Fonda (n = 245)
Catheter thrombus	0	19	**0**	**2**

Yusuf S et al. *JAMA 2006;295(13):1519*

OASIS-6 : Conclusions

•**Benefit** of Fondaparinux over Placebo or UFH in thrombolysed STEMIs

- -21% death/MI (-23% over UFH), with
- -34% hemorrhages

New gold standard in thrombolysis

•**Benefit** of Fondaparinux over Placebo or UFH in non-thrombolysed STEMIs

•**No benefit** of Fondaparinux over placebo or UFH in primary PCI

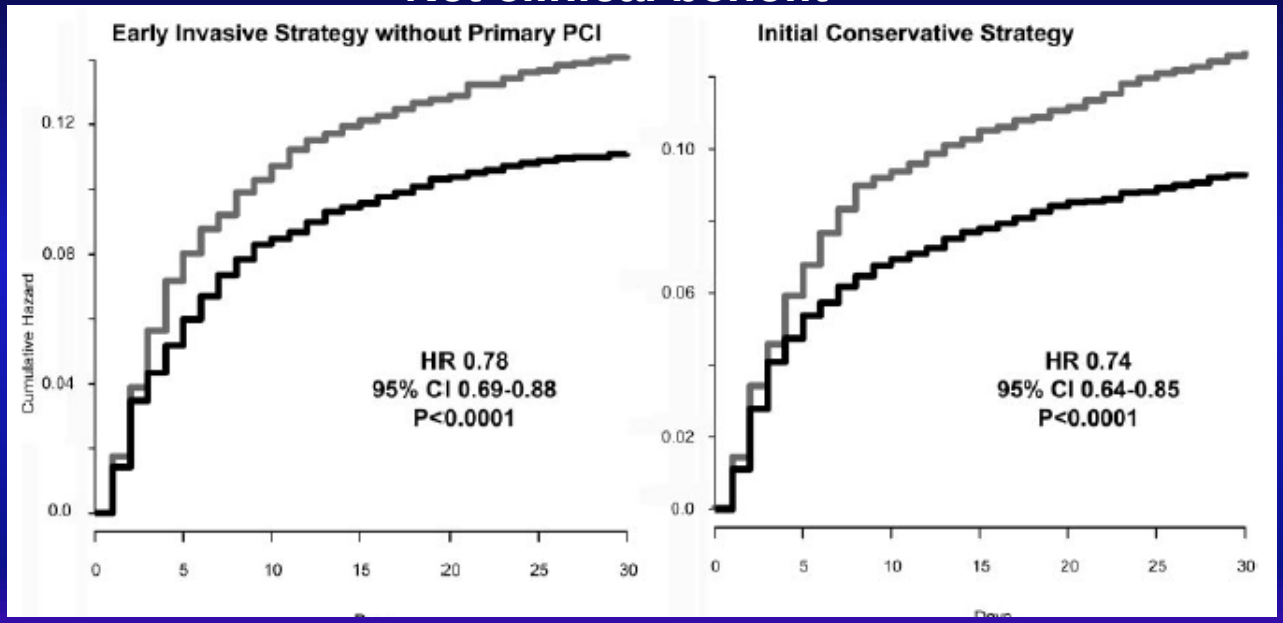
From day 2nd -9th : Fondaparinux superior tp Placebo

Yusuf S et al. *JAMA 2006;295(13):1519*

OASIS-5 & OASIS-6 at 30 days

	LMWH/UFH,% (N=13 242)	Fondaparinux, % (N=13 270)	HR 95% CI	*P*
Net clinical benefit	11.1	9.3	**0.83** (0.77–0.89)	<0.0001
Death, MI, Stroke	8.0	7.2	**0.91** (0.83–0.99)	0.03
Death	4.3	3.8	**0.89** (0.79–1.00)	0.05
MI	3.8	3.5	**0.92** (0.81–1.04)	0.19
Stroke	1.0	0.8	**0.82** (0.64–1.07)	0.14
Major bleeding	4.4	3.0	**0.67** (0.59–0.76)	<0.000

Net clinical benefit



Mehta S et al. *Circulation 2008;118:2038*

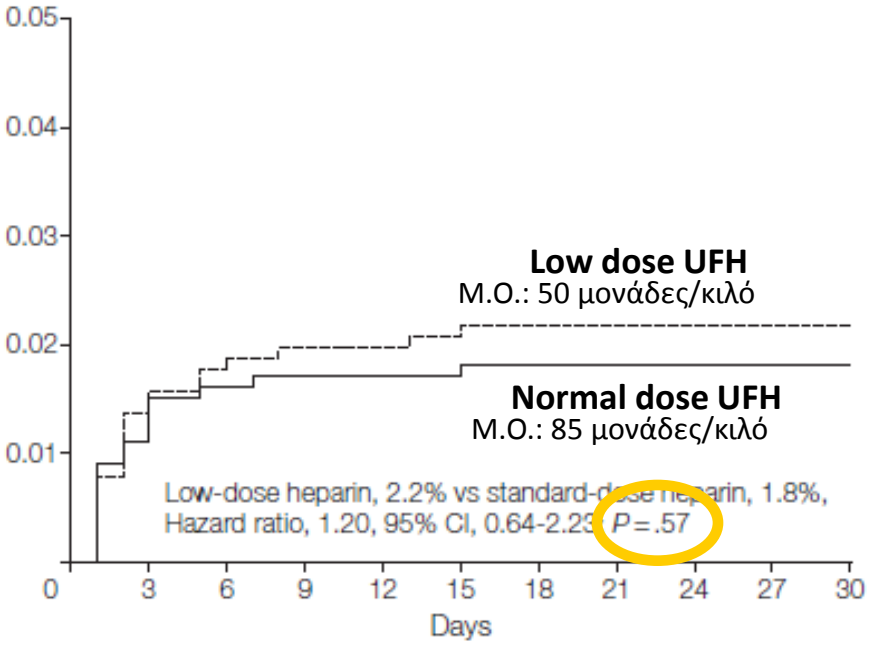
FUTURA/OASIS 8

A randomized trial of I.V UFH during PCI in patients with NSTE-ACCs initially treated with fondaparinux

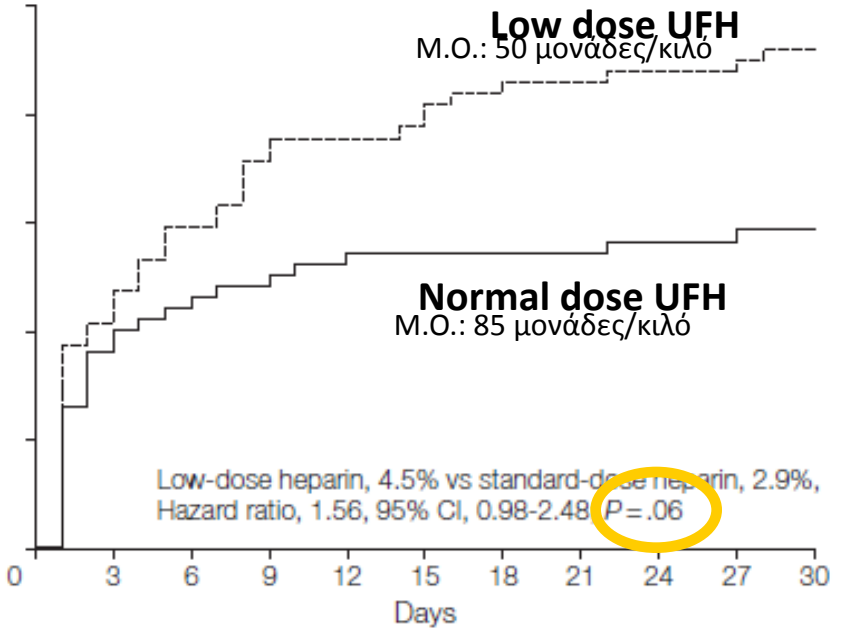
High Risk NSTEMI-ACS patients on Fondaparinux (~ 3 days)
Randomization & PCI (n=2026)

UFH, normal dose: No GP IIb/IIIa Inh.: 85 IU/kg; target-ACT: 300”-350” (Hemochrom) or 250”-300”(Hemotec) **With GP IIb/IIIa Inh;** Target-ACT **>**200
compared with **UFH low-dose:** 50 IU/kg

Major bleeding



Death, MI, Urgent TVR



Θρόμβος καθετήρα: 0.1% (κανονική δόση) έναντι 0.5% (χαμηλή δόση), P= ΜΣ

JAMA. 2010;304(12):1339

BIVALIRUDIN

- Replace 2
- Isar-React 3
- Acuity
- Horizons-AMI
- Isar-React 4
- Metaanalysis of all trials + Premier Registry

Summary of Bivalirudin Trials -1 (primary EPs outcome)

REPLACE-2 6010 pts **Urgent or elective PCI** Lincoff.JAMA 2003	Bivalirudin (+provis.Gp IIb/IIIa inh) vs. UFH+Gp IIb/IIIa Inh (abciximab or eptifibatide) (on top of Aspirin & Ticlo/Clopi)	Death, MI, urgent TVR, or in-hospital major bleeding @ 30d: 9.2% (Biv) vs 10% (UFH+ IIb/IIIa) (OR, 0.92; 95% CIs, 0.77-1.09; *P*=.32) Bivalirudin:Non-inferior
ISAR-REACT 3 4570 **biomarker negative** pts undergoing PCI 2 h post-LD with600 mg clopidogrel	Bivalirudin vs. UFH (140 U/kg)	Death, MI, or TVR at 1 year: 17.5% vs 17.1% (p=ns) *Bivalirudin & UFH during PCI: comparable outcomes but*
Stone NEJM 2006	Heparin in the ER in ~2/3 of the pts	of enoxaparin+Gp IIb/IIIa Inh) NACE: RRR=14%; P<0.001

ACUITY-conclusions:

In patients with moderate- or high-risk ACSs undergoing invasive treatment with glycoprotein IIb/IIIa inhibitors, bivalirudin was associated with rates of ischemia and bleeding that were similar to those with heparin

Bivalirudin alone was associated with similar rates of ischemia and significantly lower rates of bleeding

Summary of Bivalirudin Trials -2 (primary EPs outcome)

HORIZONS-AMI — UFH (60 U/kg) +Gp IIb/IIIa

3602 STEMI

All-cause deaths: 2.1% vs. 3.1%; **RR: 0.66** (0.44 to 1.00) P = 0.047

Stent thrombosis within the first 24 hours: 1.3% vs. 0.3%, P<0.001)

between 24 h and 30 d: 1.2% vs. 1.7%, P = 0.28)

HORIZONS-AMI-Conclusions:

In STEMI pts undergoing primary PCI, anticoagulation with bivalirudin alone, as compared with heparin plus glycoprotein IIb/IIIa inhibitors, results in significantly reduced 30-day rates of major bleeding and net adverse clinical events

(P<0.001; **RRR=40%**) Bivalirudin vs UFH+Gp IIb/IIIa Inh

ISAR-REACT 4

1721 **NSTEMI** pts

Bivalirudin (+provis.Gp IIb/IIIa inh) NACE: Death. MI

vs.

ISAR-REACT 4-Conclusions

Abciximab and unfractionated heparin, as compared with bivalirudin, failed to reduce the rate of the primary end point and increased the risk of bleeding among patients with NSTEMI who were undergoing PCI

Meta-Analysis of Bivalirudin Monotherapy vs. Heparin + GP IIb/IIIa Inhibitors

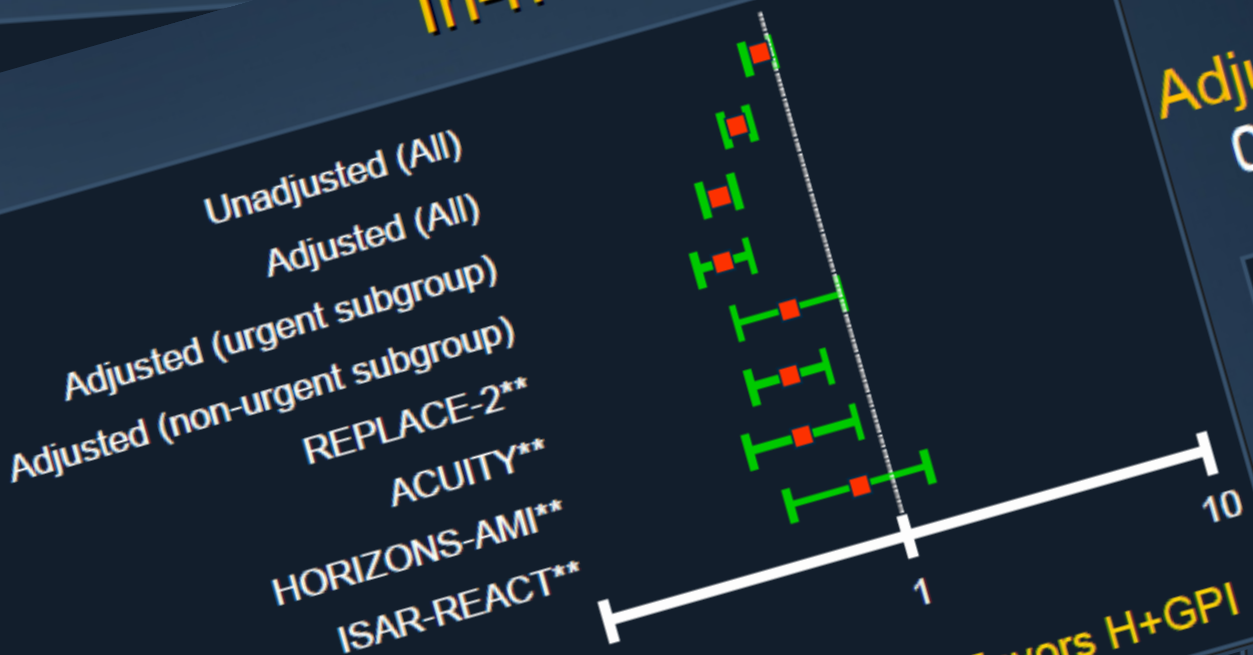
1 year mortality in all pati

N = 127,185 pts undergoing PCI 2003-200

(Premier Perspective Database, ~1/6th of

In-h

In-hospital transfusion



Bivalirudin	H+GPI
3.0%	4.6%

Adjusted HR [95%CI]*

0.67 [0.61 - 0.73]

33% ⇩ Transfusion

Death

Favors Bival Favors H+GPI

**30

**30 days

Jassen RA et al *EHJ* 2010;31:561

* Fixed effects model

NSTEMI-ACS Guidelines AHA 2011

•Αρνητική δοκιμασία κοπώσεως, ασθενής χαμηλού κινδύνου
•Ή ασθενής χωρίς καμία δοκιμασία κοπώσεως ή στεφ/φία

•**Ηπαρίνη για 48 ώρες**

•**Φονταπαρινάξ** (προτιμητέα σε υψηλό αιμορραγικό κίνδυνο)

•**Ενοξαπαρίνη**

•Μετά τη στεφανιογραφία, προγραμματίζεται εγχείρηση Α.Σ.Π.

Ηπαρίνη: Συνεχίζεται

Φονταπαρινάξ: Διακοπή 24 ώρες προηγουμένως

Ενοξαπαρίνη: Διακοπή 12-24 ώρες προηγουμένως

I

(LoE: A or B)

Thrombolysed STEMI with Streptokinase

Fondaparinux, or

Enoxaparin, or

UFH

} I.V. bolus

IIa

(LoE: B or C)

2011 **NSTEMI-ACS &** 2008 **STEMI** Guidelines ESC

In Chronic Kidney diease:

CrCl< 20 ml/min Fondaparinux: Contraindicated
CrCl 30-60 ml/min Fondaparinux: Anticoagulant of choice

CrCl< 30 ml/min Enoxaparin: 1mg/kg/24h

CrCl< 30 ml/min Bivalirudin:1mg/kg/min (instead of 1.75)

Hemodialysis Bivalirudin: 0.25 mg/kg/min

OASIS-6

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

	No. (%) of Patients		Hazard Ratio (95% Confidence Interval)	*P* Value	*P* Value for Interaction
	Unfractionated Heparin	Fondaparinux			
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.

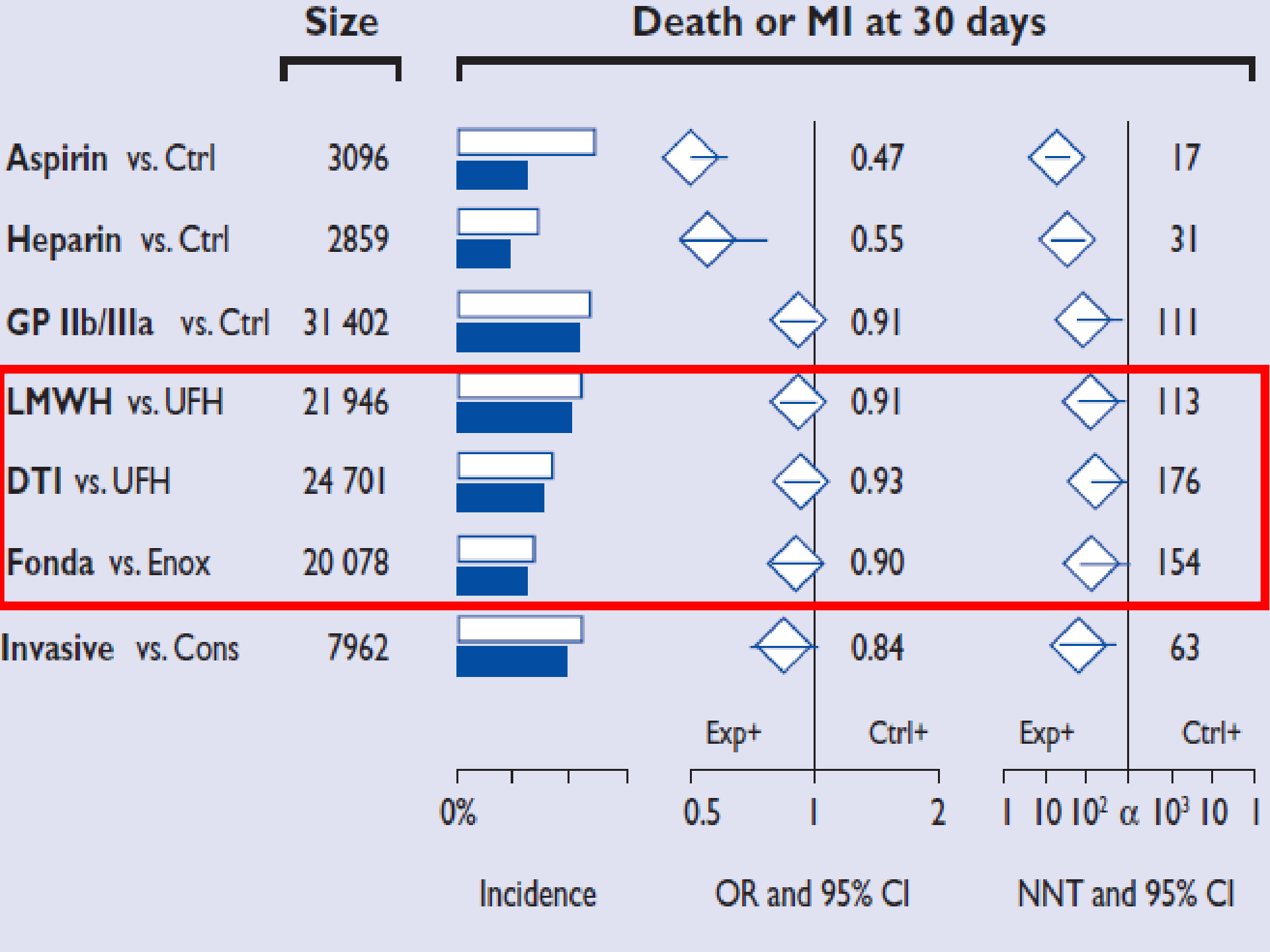
OASIS-6

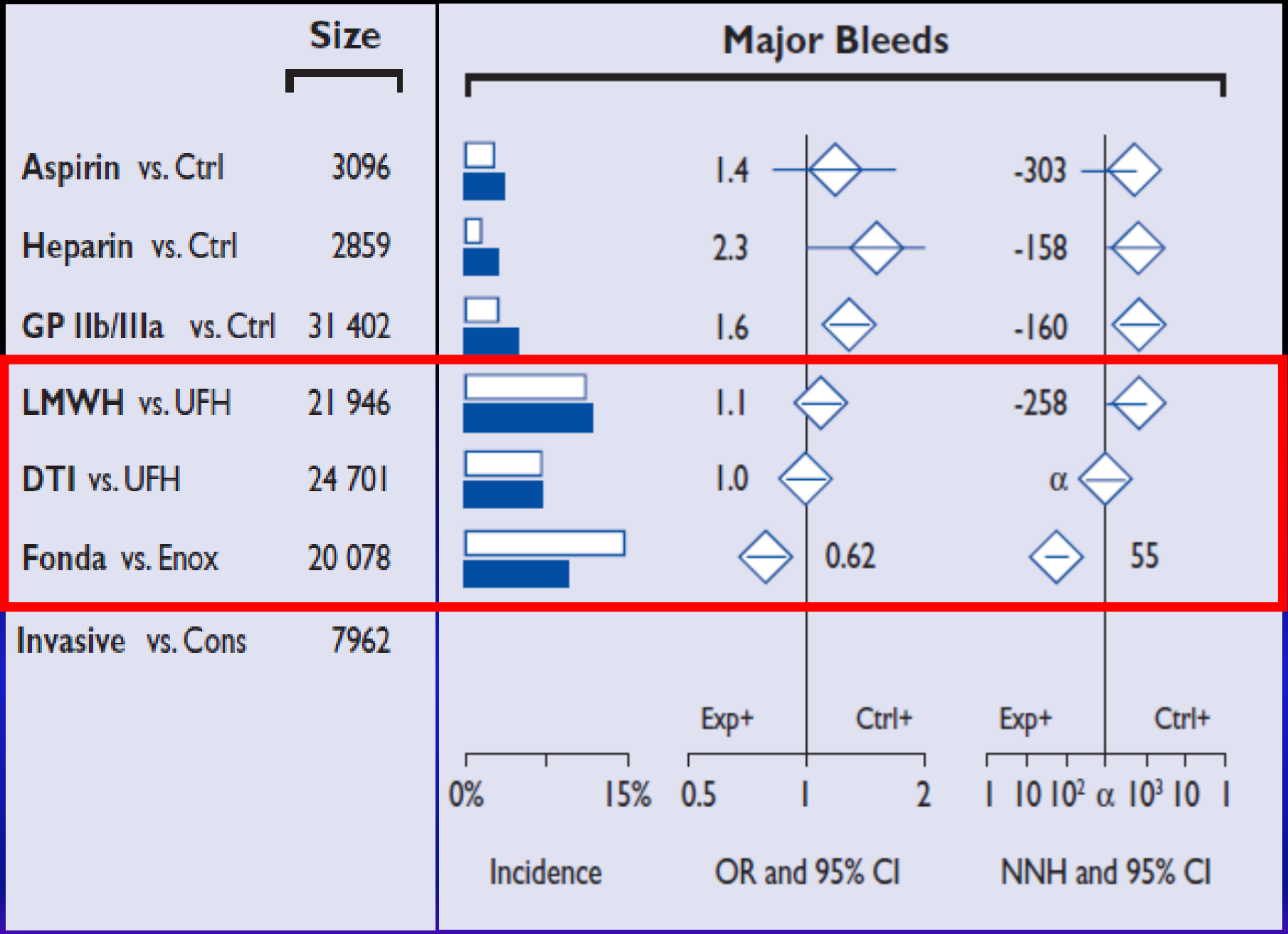
Table 7. Post-hoc Analysis of Death or Reinfarction at 3 Days and >3 to 9 Days Overall and by Stratum*

	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 Interva
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 n 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 ar infusion of heparin (or soon afterward), a cutoff of midnight on day 3 (about 60 hours) was used.


Size
Death or MI at 30 days
Aspirin vs. Ctrl
3096
0.47
17
Heparin vs. Ctrl
2859
0.55
31
GP IIb/IIIa vs. Ctrl
31 402
0.91
111
LMWH vs. UFH
21 946
0.91
113
DTI vs. UFH
24 701
0.93
176
Fonda vs. Enox
20 078
0.90
154
Invasive vs. Cons
7962
0.84
63
Exp+
Ctrl+
Exp+
Ctrl+
0%
0.5
1
2
1
10
10²
α
10³
10
1
Incidence
OR and 95% CI
NNT and 95% CI

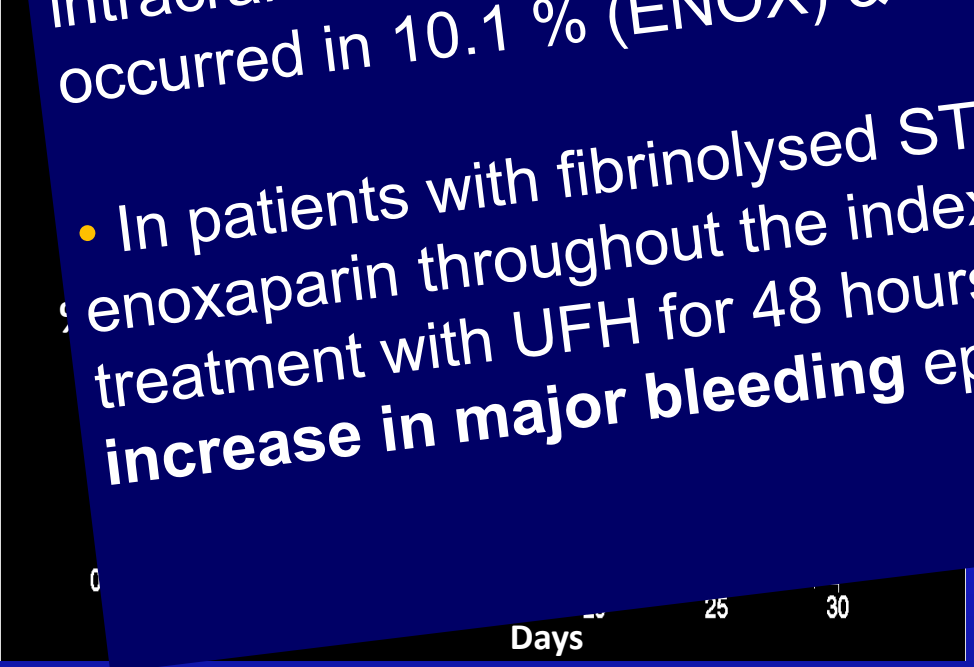

Size
Major Bleeds
Aspirin vs. Ctrl
3096
1.4
-303
Heparin vs. Ctrl
2859
2.3
-158
GP IIb/IIIa vs. Ctrl
31 402
1.6
-160
LMWH vs. UFH
21 946
1.1
-258
DTI vs. UFH
24 701
1.0
α
Fonda vs. Enox
20 078
0.62
55
Invasive vs. Cons
7962
Exp+
Ctrl+
Exp+
Ctrl+
0%
15%
0.5
1
2
1
10
10²
α
10³
10
1
Incidence
OR and 95% CI
NNH and 95% CI

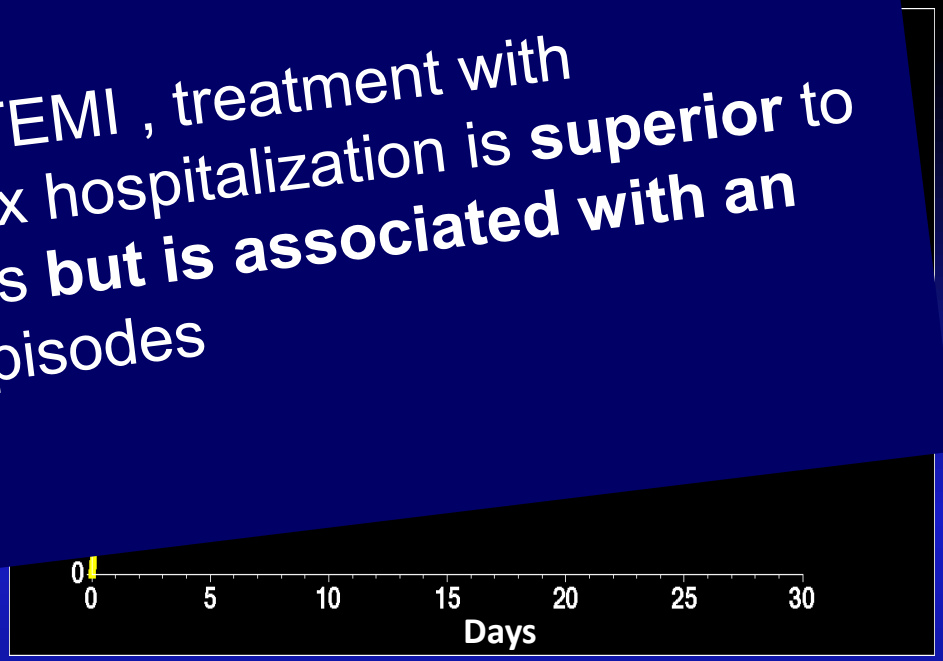
Main Results ExTRACT-TIMI 25

Streptokinase was ...

- **The composite of** death, nonfatal reinfarction, or nonfatal intracranial hemorrhage (a measure of net clinical benefit) occurred in 10.1 % (ENOX) & 12.2 % (UFH) (P<0.001)

- In patients with fibrinolysed STEMI , treatment with enoxaparin throughout the index hospitalization is **superior** to treatment with UFH for 48 hours **but is associated with an increase in major bleeding** episodes

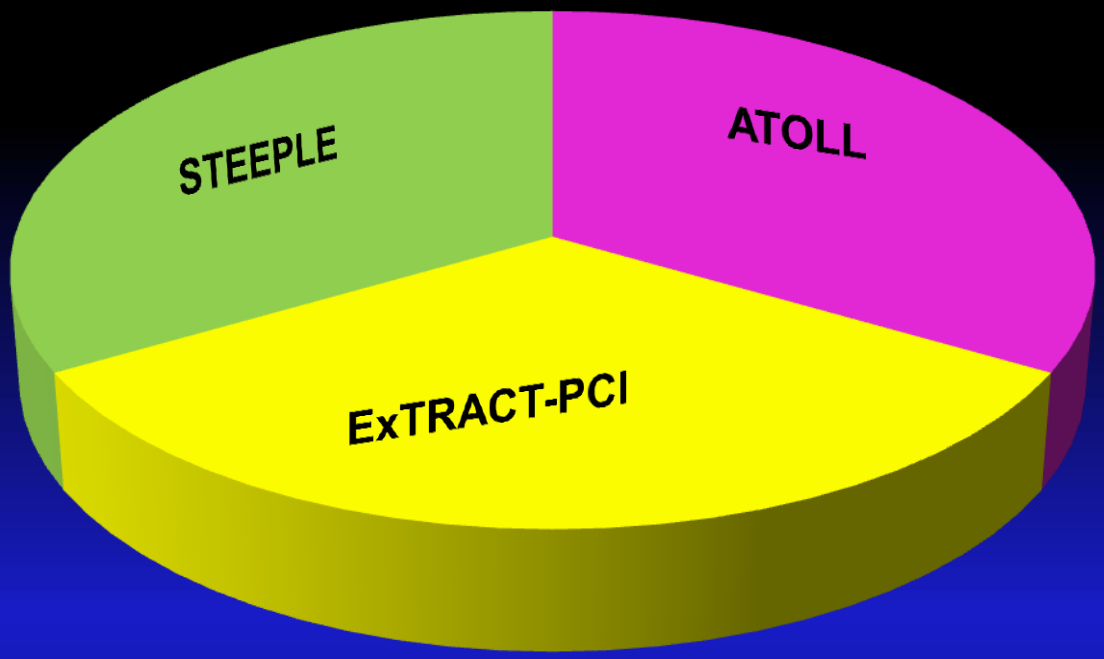




As a result of 33% relative risk reduction of non fatal recurrent MI
Higher rates of major bleedings in the ENOX group (2.1% vs. 1.4%; p<0.0001)

Anmtmann EM. N Engl J Med 2006;354:1477-88.

Enoxaparin I.V. versus UFH in **PCI**



- Πρωτογενής αγγειοπλαστική σε STEMI (ATOLL)
- Εκλεκτική αγγειοπλαστική (STEEPLE)
- Δευτερογενής αγγειοπλαστική (ExTRACT-PCI)