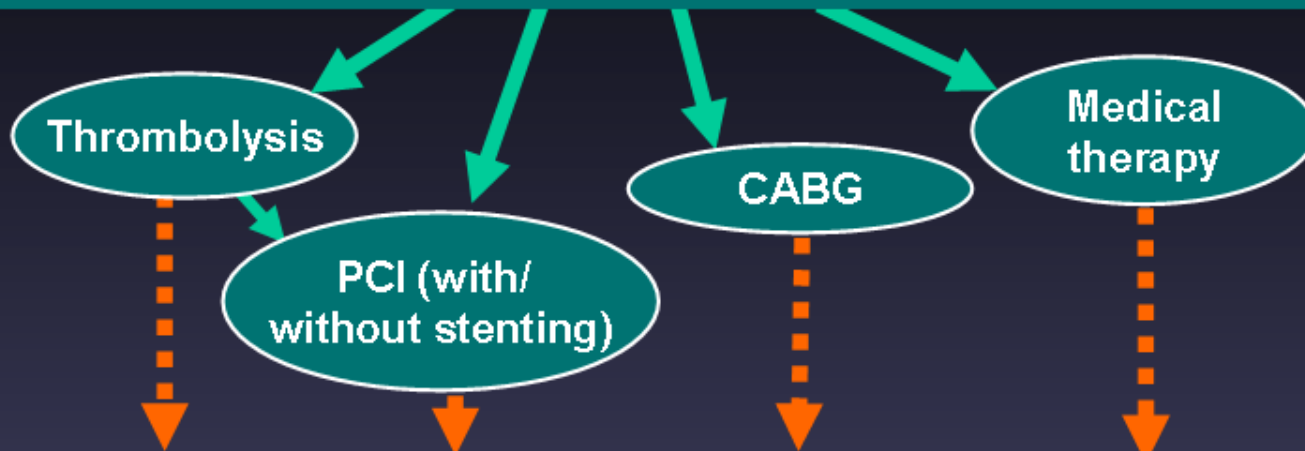


ACS Treatment Strategies

Reperfusion/Revascularization Choices



Antithrombotic Cotherapy Options

ASA

UFH

LMWH

Penta.

DTI

GP IIb/
IIIa

ADP
antagonist

Acute and Long-term Medical Therapy

Nitrates

BBs

ACEIs

ARBs

CCBs

Statins

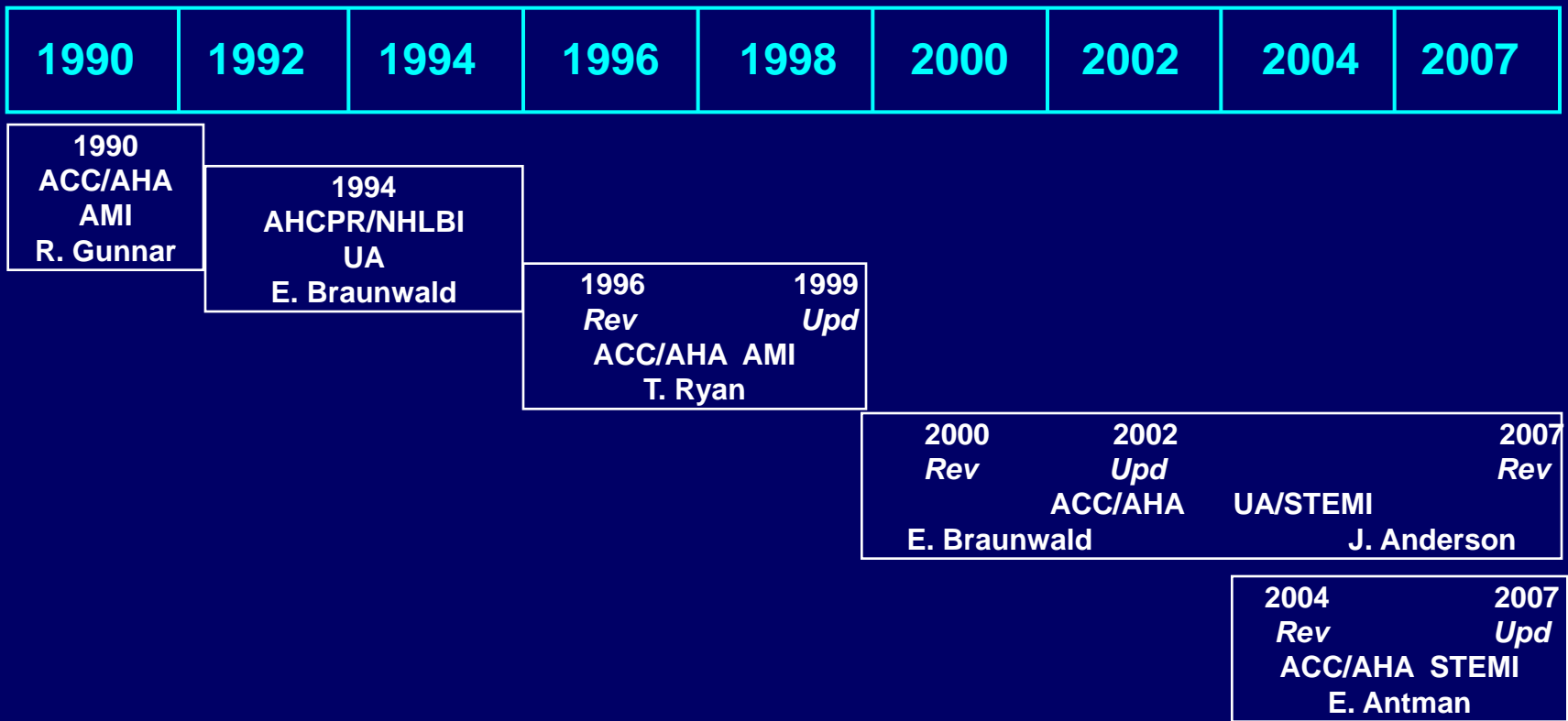
APT

PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; ASA = aspirin; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; Penta. = pentasaccharide; DTI = direct thrombin inhibitors; GP IIb/IIIa = glycoprotein IIb/IIIa inhibitors; ADP antagonist = adenosine diphosphate antagonist; BBs = β -blockers; ACEI = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; CCBs = calcium channel blockers; APT = antiplatelet therapy.





Evolution of Guidelines for Acute Coronary Syndromes (ACS)



ESC: UA/NSTEMI:

STEMI:

2000,

2003,

2007

2008

ΕΛΛΑΔΑ: ΟΣΣ

- 25 000 ΟΣΣ ετησίως
8 000 STEMI
- Άνδρες(75%) 65 ±13 γυναίκες 74 ±11 έτη
>75 ετών: 20%

Διαβήτης: 30%

Ιστορικό PCI/CABG: 20%

Θα υποβληθούν σε **ΣΦ** 75%, **PCI** 55%,
CABG 10%

30-day incidence of death/MI

7.2

TARGET

tirofiban
10 $\mu\text{g}/\text{kg}$ bolus
0.15 $\mu\text{g}/\text{kg}/\text{min}$
for 18–24 h

5.7

TARGET

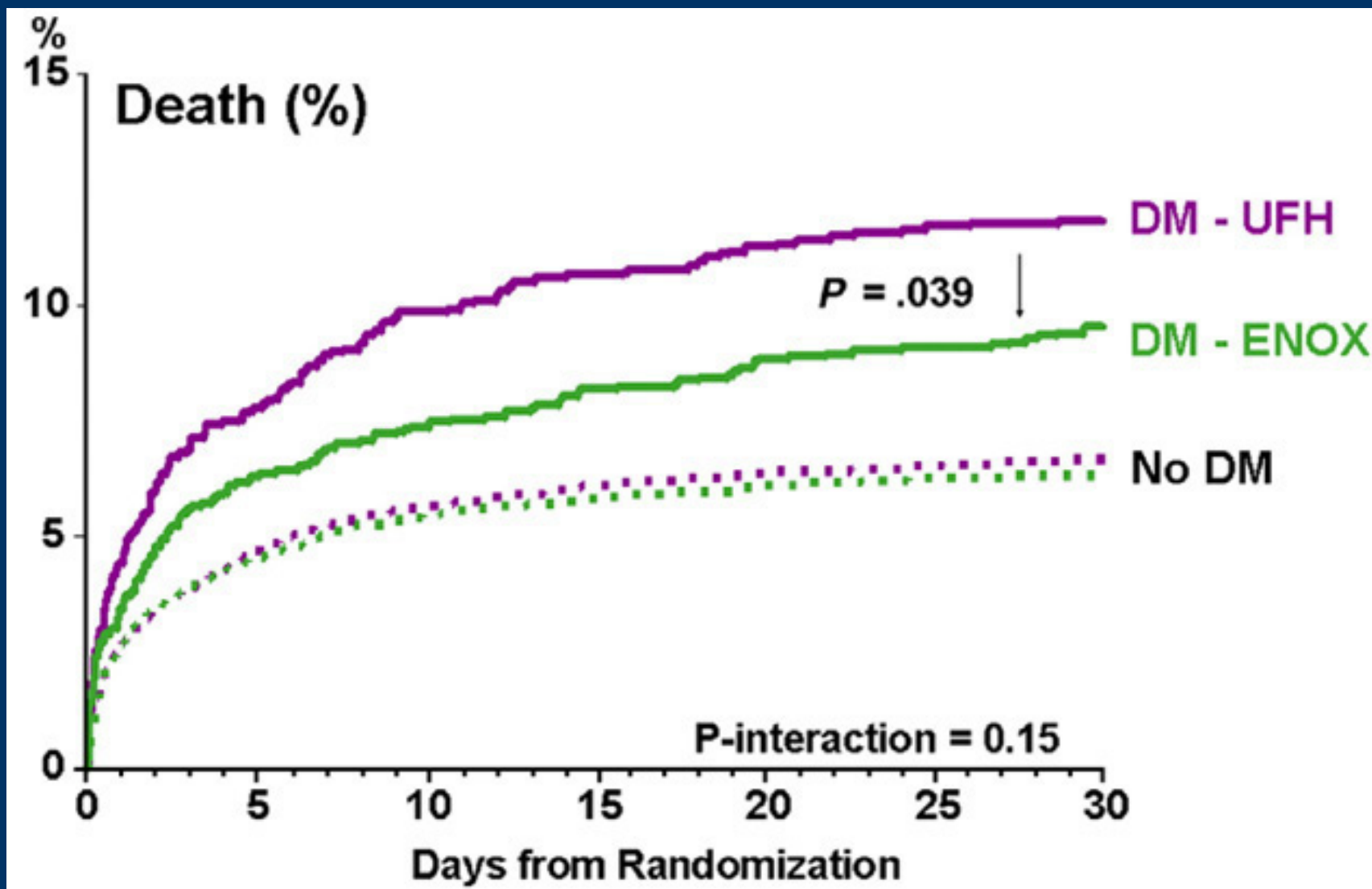
abciximab
0.25 mg/kg
0.125 $\mu\text{g}/\text{kg}/\text{min}$
for 12 h

4.7

TACTICS

invasive arm
tirofiban
for 4–48 h
(mean 24 h)
before PCI
0.4 $\mu\text{g}/\text{kg}/\text{min}$
for 30 min then
0.1 $\mu\text{g}/\text{kg}/\text{min}$

EXTRACT TIMI15



Θνητότητα στις 30 ημέρες : 10.7% διαβητικοί, 6.5% μη διαβητικοί

Am Heart J 2007;154:1078-84

Two-year risk-adjusted outcomes, by MI type

End point, group	DES (%)	Bare-metal stent (%)	p
Mortality, all AMI	10.7	12.8	0.02
Mortality, STEMI	8.5	11.6	0.008
Mortality, non-STEMI	12.8	15.6	0.04
Recurrent MI, all AMI	8.8	10.2	0.09
Recurrent MI, STEMI	7.0	8.0	0.34
Recurrent MI, non-STEMI	10.3	13.3	0.02

ΑΝΤΙΘΡΟΜΒΩΤΙΚΑ

Αντιαιμοπεταλιακά

Ασπιρίνη

Κλοπιδογρέλη

Prasugrel

Triflusal (AFLEN)

Αναστολείς GP IIb/IIIa

Αντιπηκτικά

Ανταγωνιστές Βιτ Κ

Αναστολείς θρομβίνης

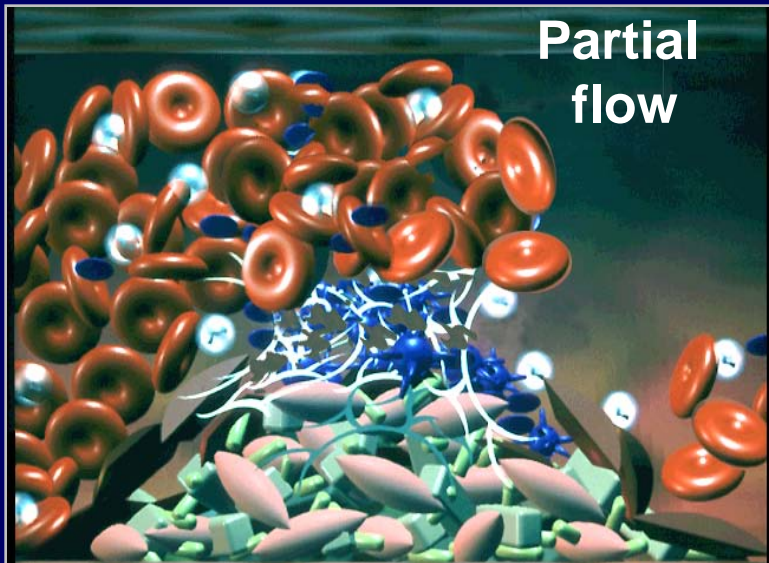
έμμεσοι: ήπαρίνη, ΧΜΒΗ

άμεσοι: Μπιβαλιρουδίνη



Acute coronary syndrome

No ST elevation



UA/NSTEMI

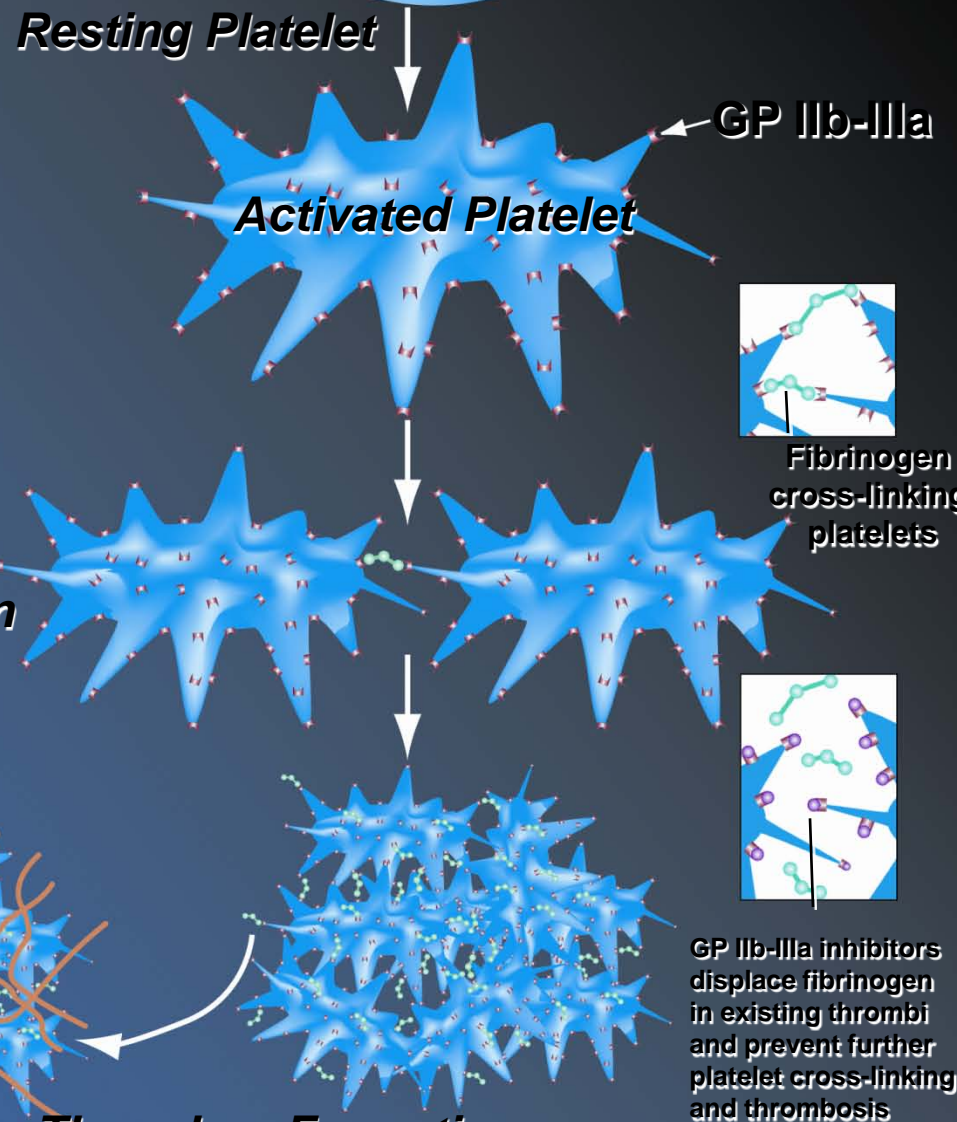
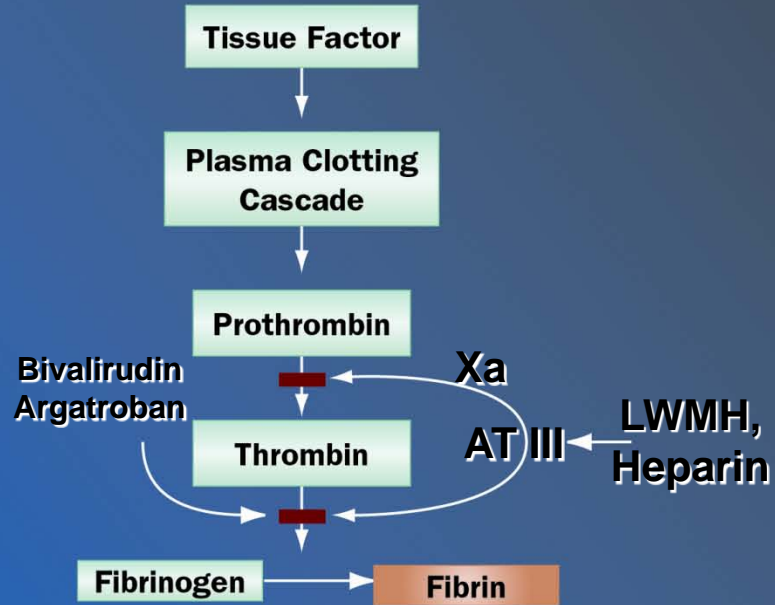
ST elevation



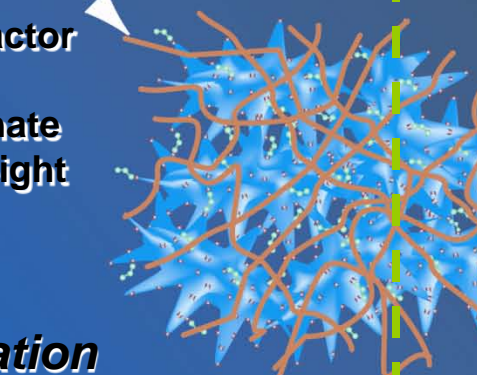
STEMI



Antithrombin Pathway



Platelet Aggregation



Thrombus Formation

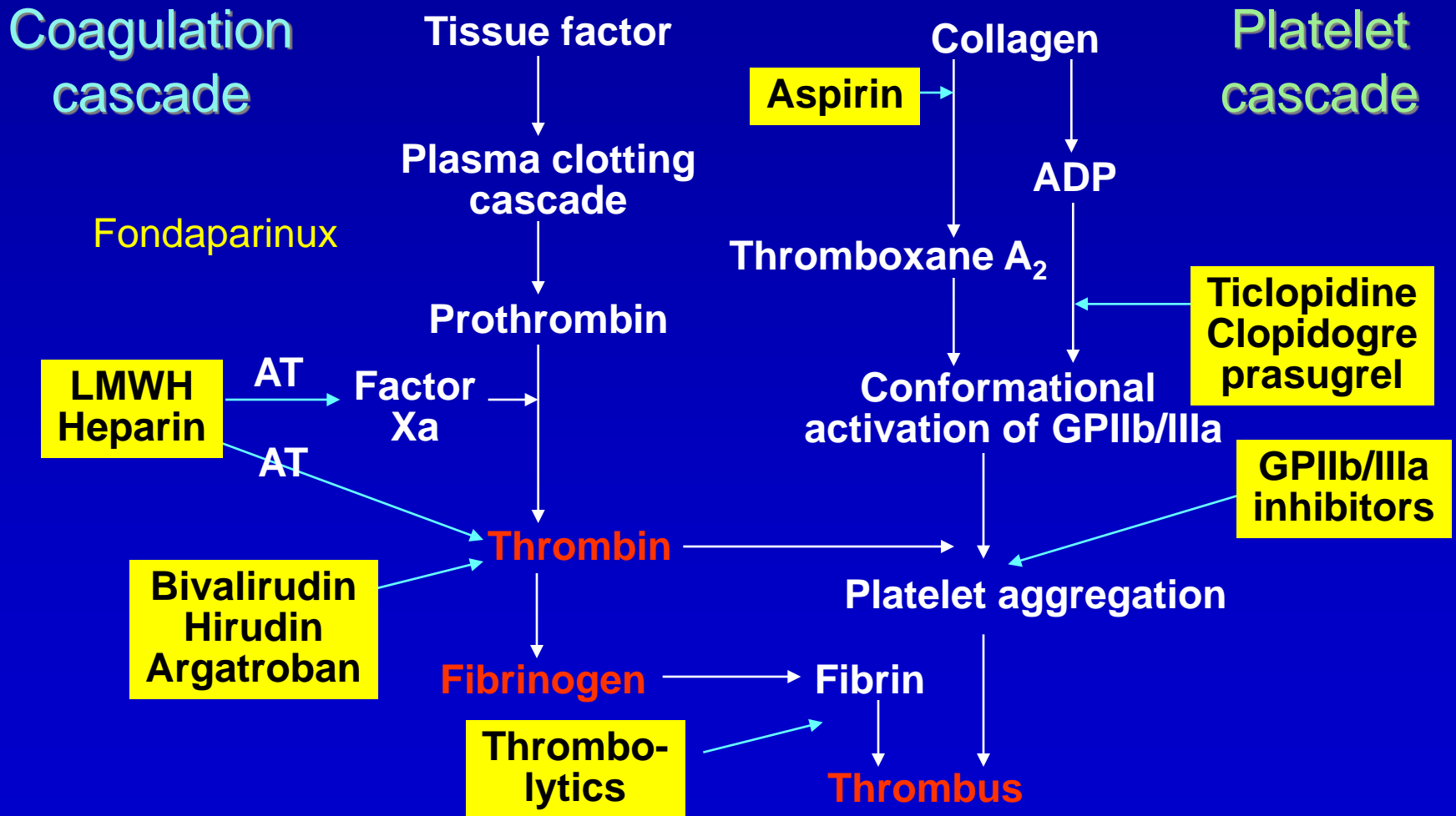
GP IIb-IIIa inhibitors displace fibrinogen in existing thrombi and prevent further platelet cross-linking and thrombosis

AT III = Antithrombin III
 Xa = Factor Xa
 PAF = Platelet Activating Factor
 TxA₂ = Thromboxane A₂
 ADP = Adenosine Diphosphate
 LMWH = Low-molecular-weight Heparin

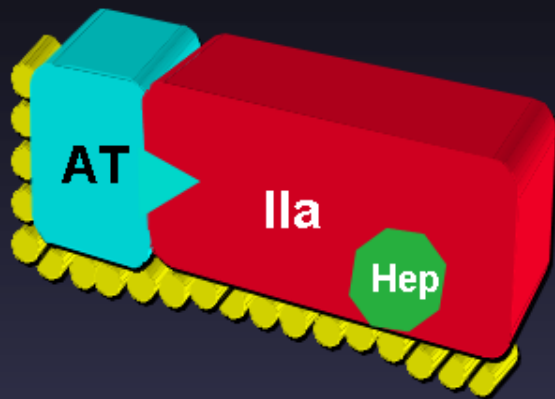
Occlusive Clot Formation



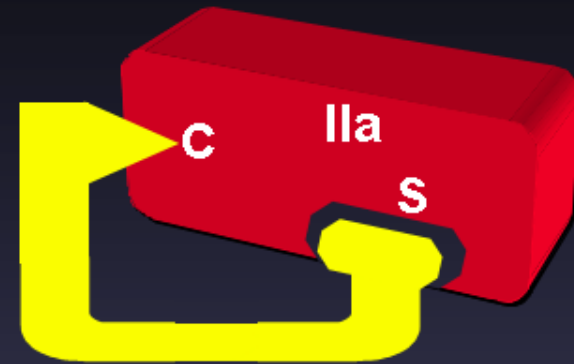
Θέσεις δράσης των αντιθρομβωτικών φαρμάκων



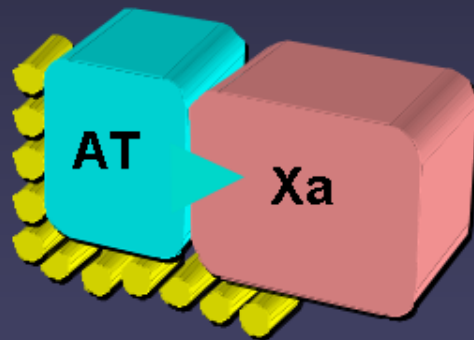
Four Anticoagulant Choices



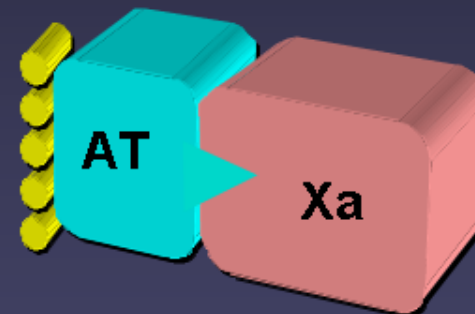
UFH



Direct antithrombin



LMWH



Pentasaccharide

Konkle BA, Schafer AI. In: Zipes DP, Libby P, Bonow RO, Braunwald E, eds. *Braunwald's Heart Disease*. Vol 2. 7th ed. Philadelphia: Elsevier Saunders; 2005:2067-2092.

 = saccharide unit.



Milestones in ACS Management

Anti-Thrombin Rx

Heparin

LMWH

Bivalirudin [Fondaparinux]

Anti-Platelet Rx

Aspirin

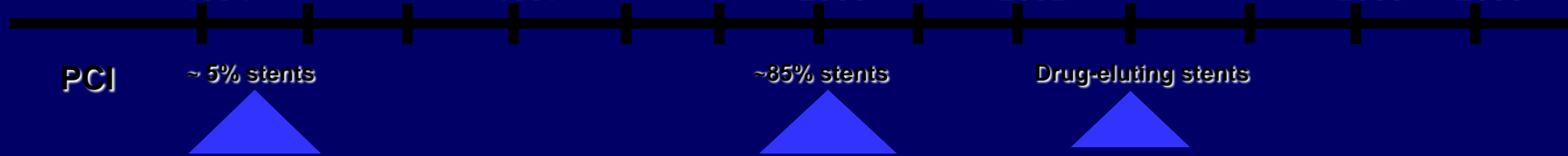
GP IIb/IIIa
blockers

Clopidogrel

Treatment Strategy

Conservative

Early invasive

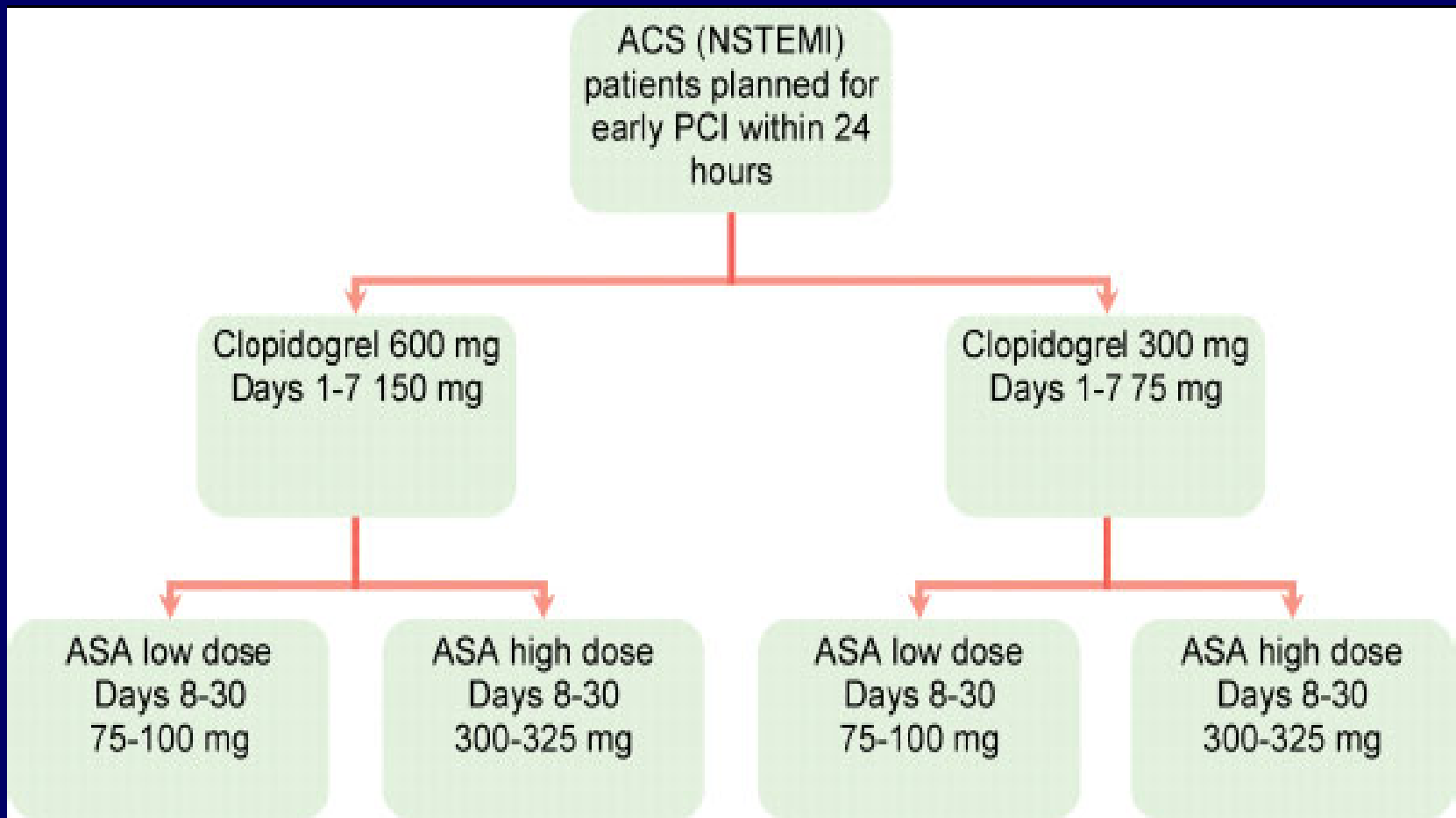


Ischemic risk

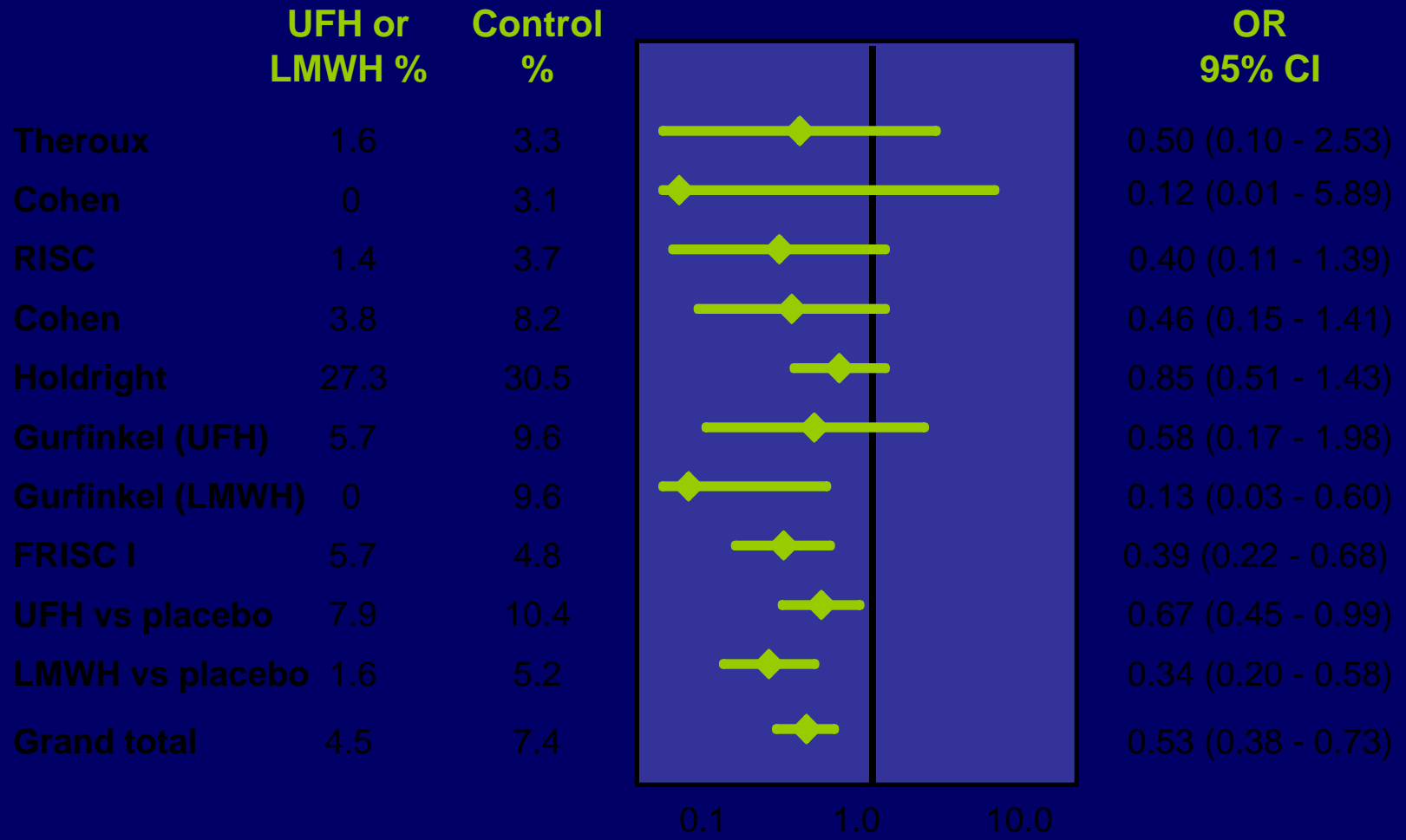
Bleeding risk

Adapted from and with the courtesy of Steven Manoukian, MD.

Ασπιρίνη στα ΟΣΣ



UFH or LMWH in UA/NSTEMI



Favors Heparin OR and 95% CI Favors Control

LMWH versus UFH in UA/NSTEMI: Effect on Death, MI, Recurrent Ischemia

Trial:

FRIC

(dalteparin; n=1482)

FRAXIS

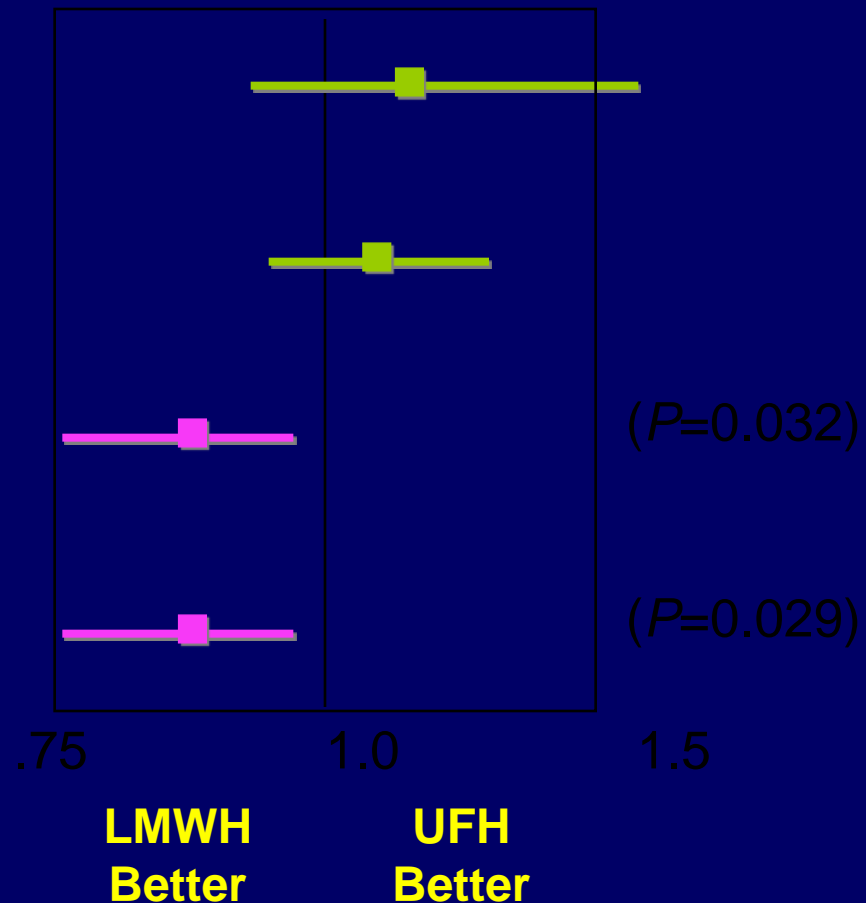
(nadroparin; n=2357)

ESSENCE

(enoxaparin; n=3171)

TIMI IIB

(enoxaparin; n=3910)

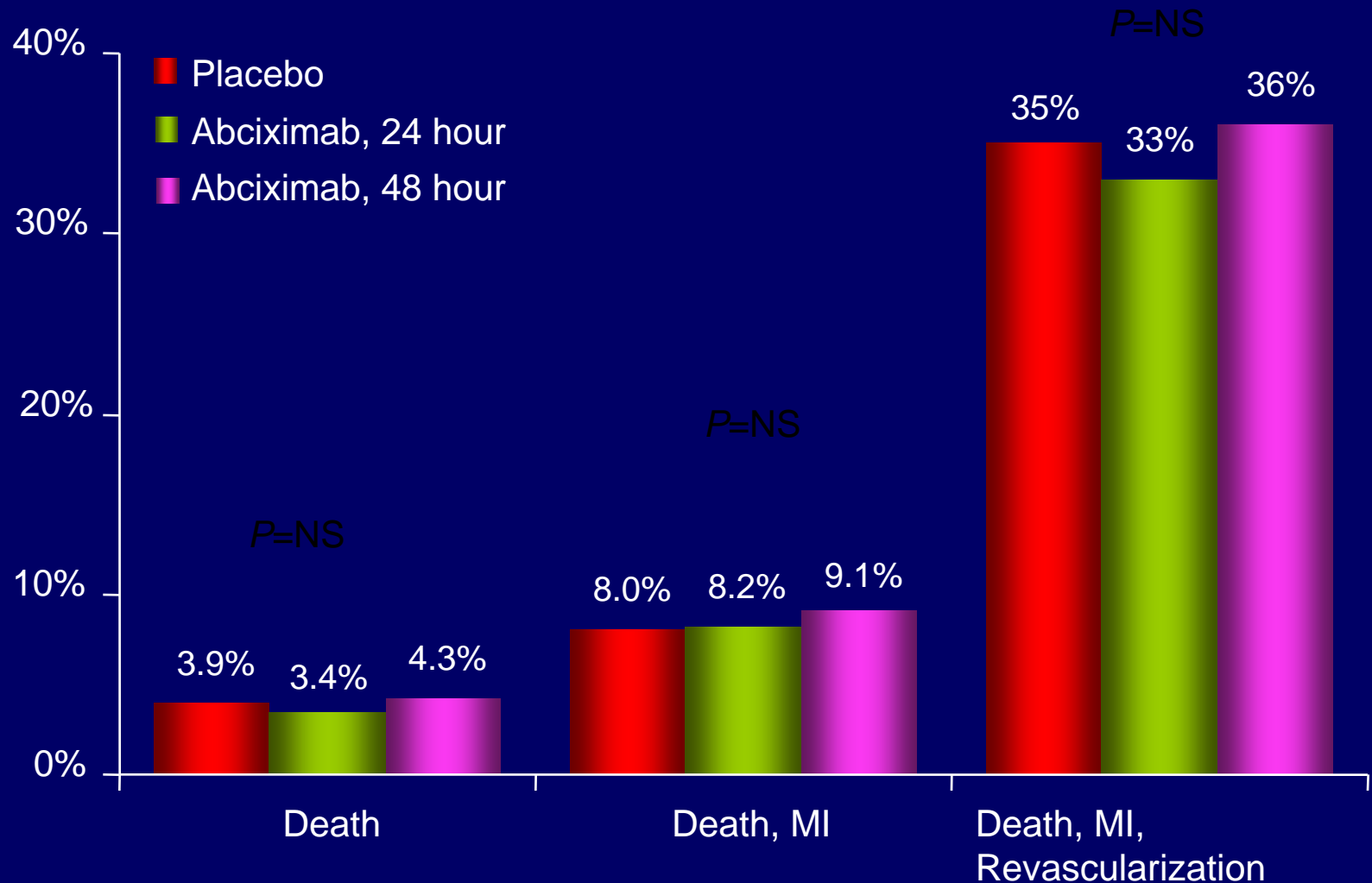


SYNERGY: Major Clinical Endpoints at 30 Days

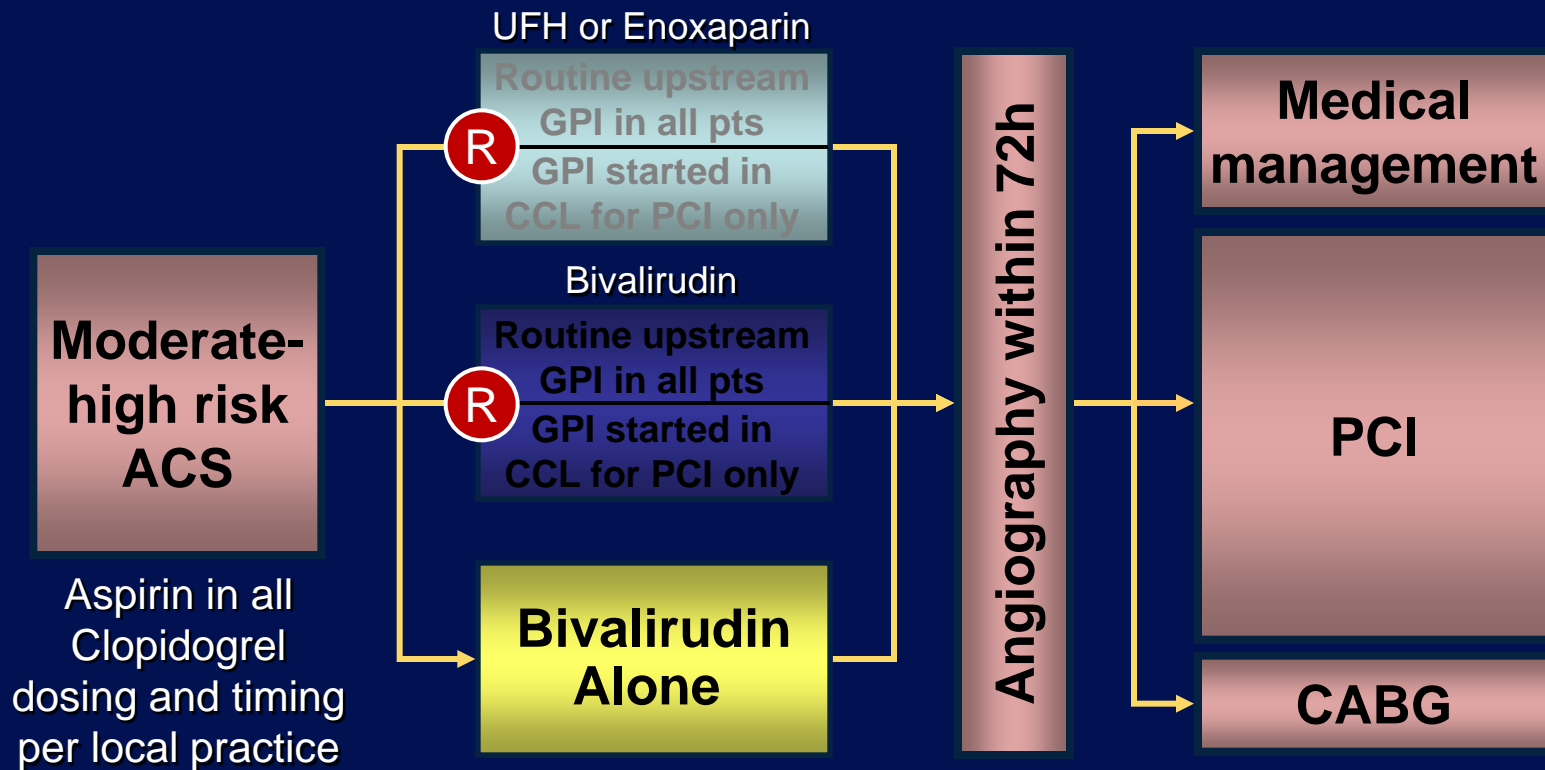
Endpoint	Enoxaparin	UFH	Significant
Death/MI (primary endpoint) (%)	14	14.5	No
Death (%)	3.2	3.1	No
MI (%)	11.7	12.7	No
Stroke	1.0	0.9	No
Hemorrhagic stroke (%)	<0.1	<0.1	No

Clopidogrel : 66%
 GP IIb/IIIa : 57%

GUSTO-IV: 30-day Outcomes



Moderate-high risk unstable angina or NSTEMI undergoing an invasive strategy (n = 13,800)

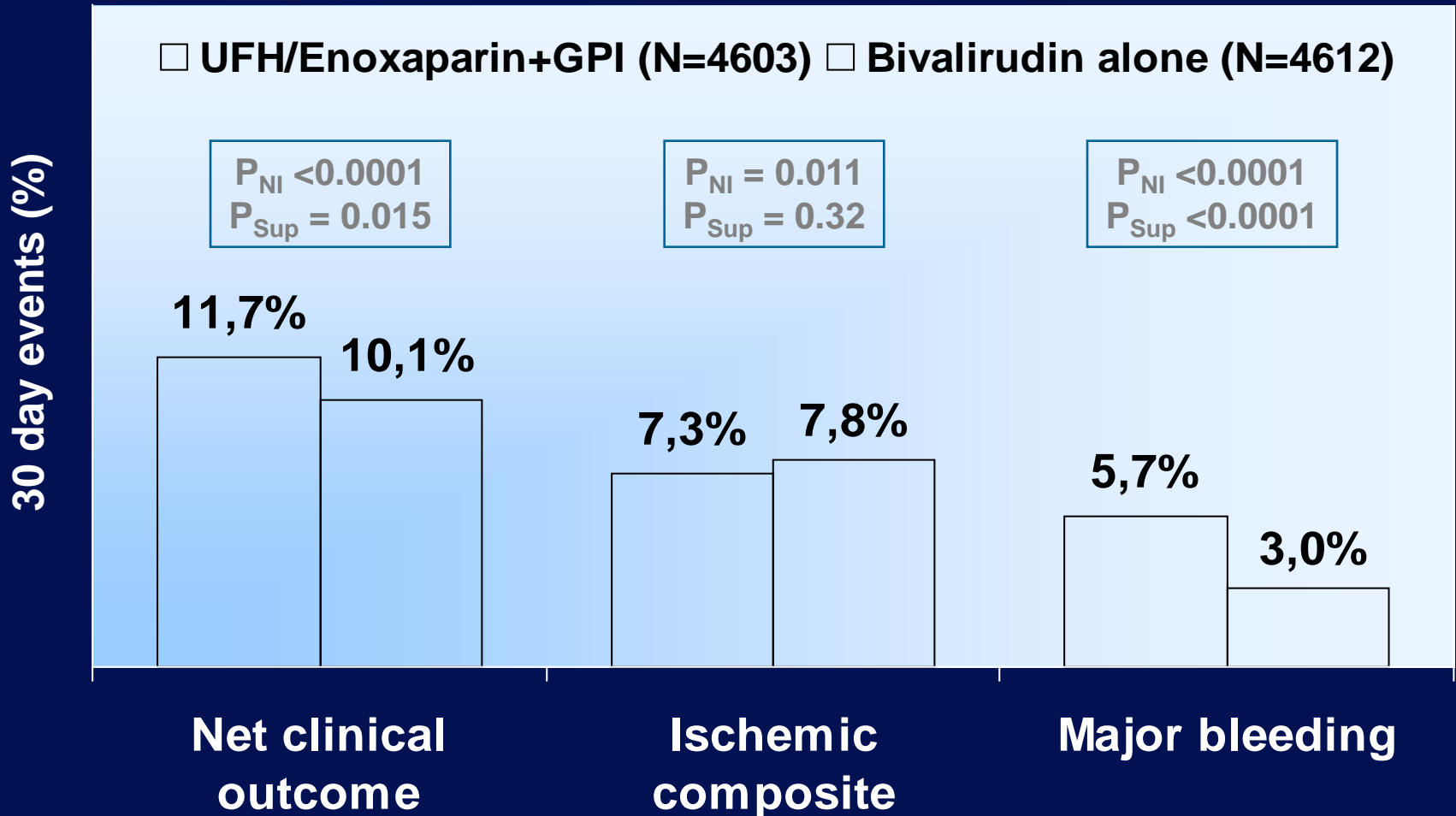


ACUITY NEJM 2006

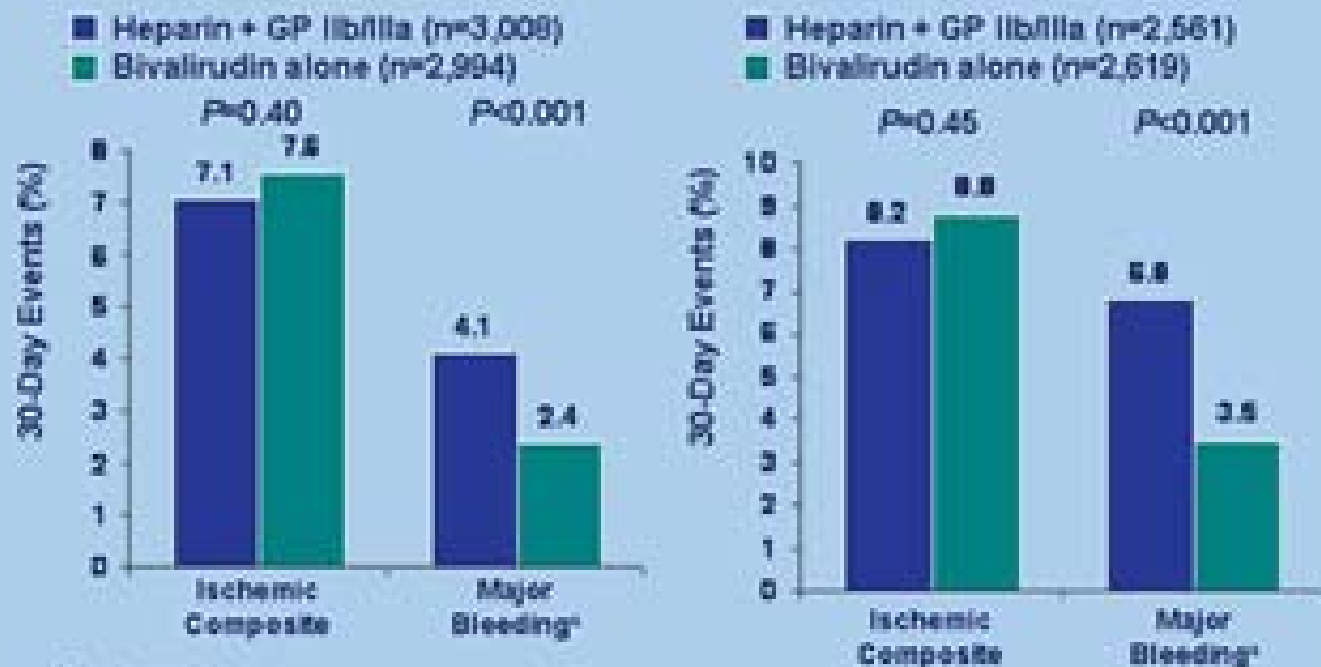
Clopidogrel before angio 64%

Primary Endpoint Measures

UFH/Enoxaparin + GPI vs. Bivalirudin Alone



REPLACE 2 (PCI) and ACUITY (PCI Patients Only)



GP=glycoprotein
 MI=myocardial infarction
 *REPLACE-2 definition

Stone GW, et al. *N Engl J Med* 2008;356:2203-2216.
 Leira AM, et al. *JAMA* 2004;292:696-703.

plateletNEWS.org

NSTEMI: αντιπηκτικά

• Αντιμετώπιση	Συντηρητική		Επεμβατική	
	ACC/AHA	ESC	ACC/AHA	ESC
• Ηπαρίνη	IA	IC	IA	IC
• Ενοξαπαρίνη	IA	IIa B	IA	IIa B
• Fondaparinux	IB	IA	IB	-
• Μπιβαλιρουδίνη	-	-	IB	IB

STEMI: στρατηγικές αντιμετώπισης

- Άμεση αγγειοπλαστική: 9%
- Θρομβόλυση: >70%
- Όχι επαναιμάτωση: 25%

ΣΤΑΘΜΟΙ ΣΤΗΝ ΑΝΤΙΜΕΤΩΠΙΣΗ ΤΩΝ STEMI

Αντιπηκτικά
Ηπαρίνη

Ηπαρίνη/LMWH Fondaparinux

Μπιβαλιρουδίνη

Αντιαιμοπεταλιακά

Ασπιρίνη

GPIIb/IIIa

Κλοπιδογρέλη

Πρασουγρέλη

Στρατηγική

Θρομβόλυση

Αγγειοπλαστική

Διευκολυνόμενη

GISSI

1986

ISIS-2

1988

GUSTO I-V

1998

STENT

PRAGUE DANAMI

2000

CLARITY
COMIT

2003

EXTRACT
TIMI

OASIS-6

2006

TRITON

2007

HORIZON

FINESE

2008

OASIS-6 Trial: Study Design

12,092 patients presenting with STEMI within 24 hours of symptom onset
(shortened to 12 hours of symptom onset midway through trial)

Randomized, Blinded, Factorial

28% female; mean age, 62 years; mean follow-up, 3-6 months

Stratum 1 (No UFH)
n=5658

Stratum 2 (UFH)
n=6434

Fondaparinux
n=2823

2.5 mg/day for up to 8 days
or hospital discharge

Placebo
n=2835

Fondaparinux
n=3213

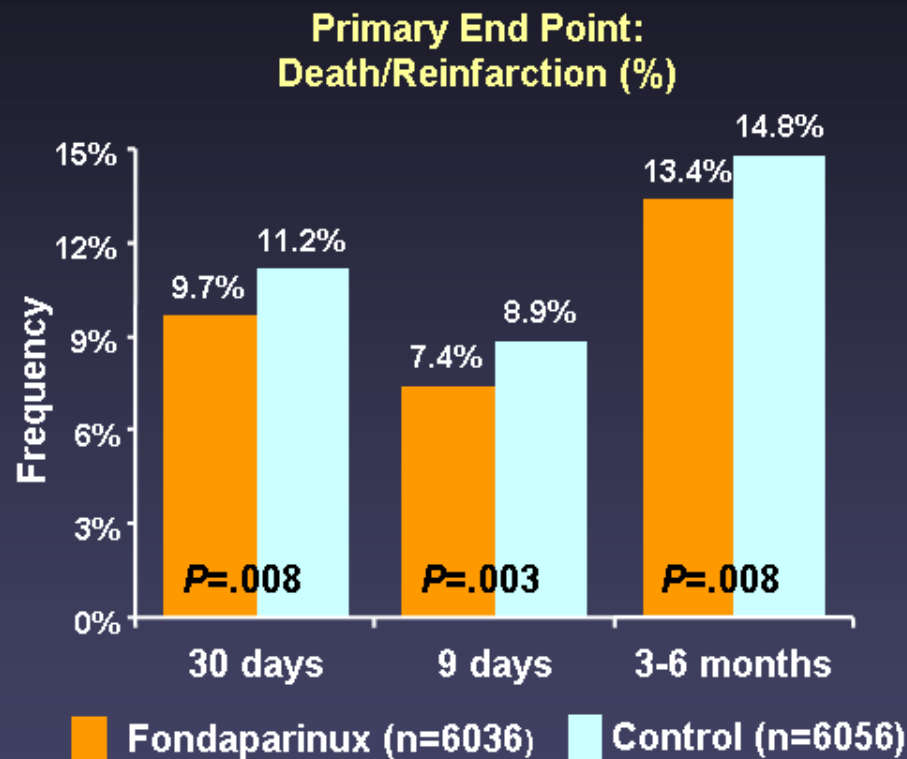
2.5 mg/day for up to 8 days
or hospital discharge

UFH
n=3221

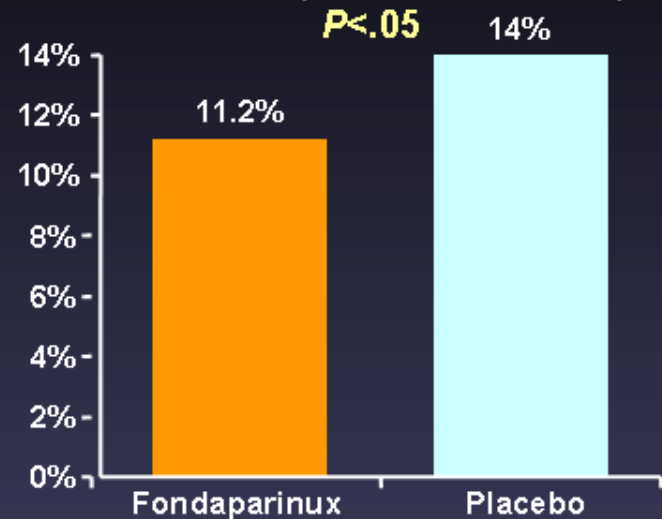
- Primary end point: Composite of death or reinfarction at 30 days
- Secondary end point: Composite of death or reinfarction at 9 days and at final follow-up



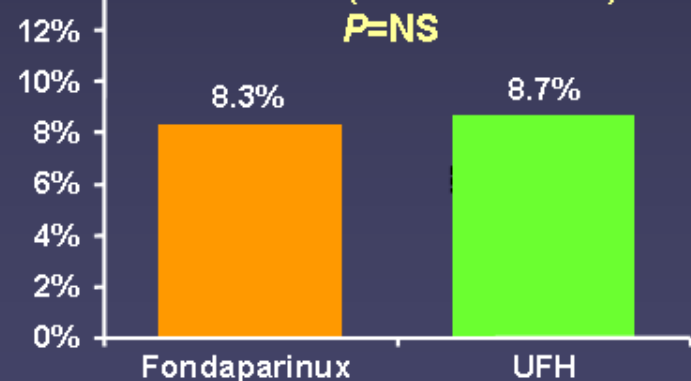
OASIS-6: Results



**Reduction in Death/MI at 30 days:
Stratum 1 (No UFH indicated)**



**Reduction in Death/MI at 30 days:
Stratum 2 (UFH indicated)**

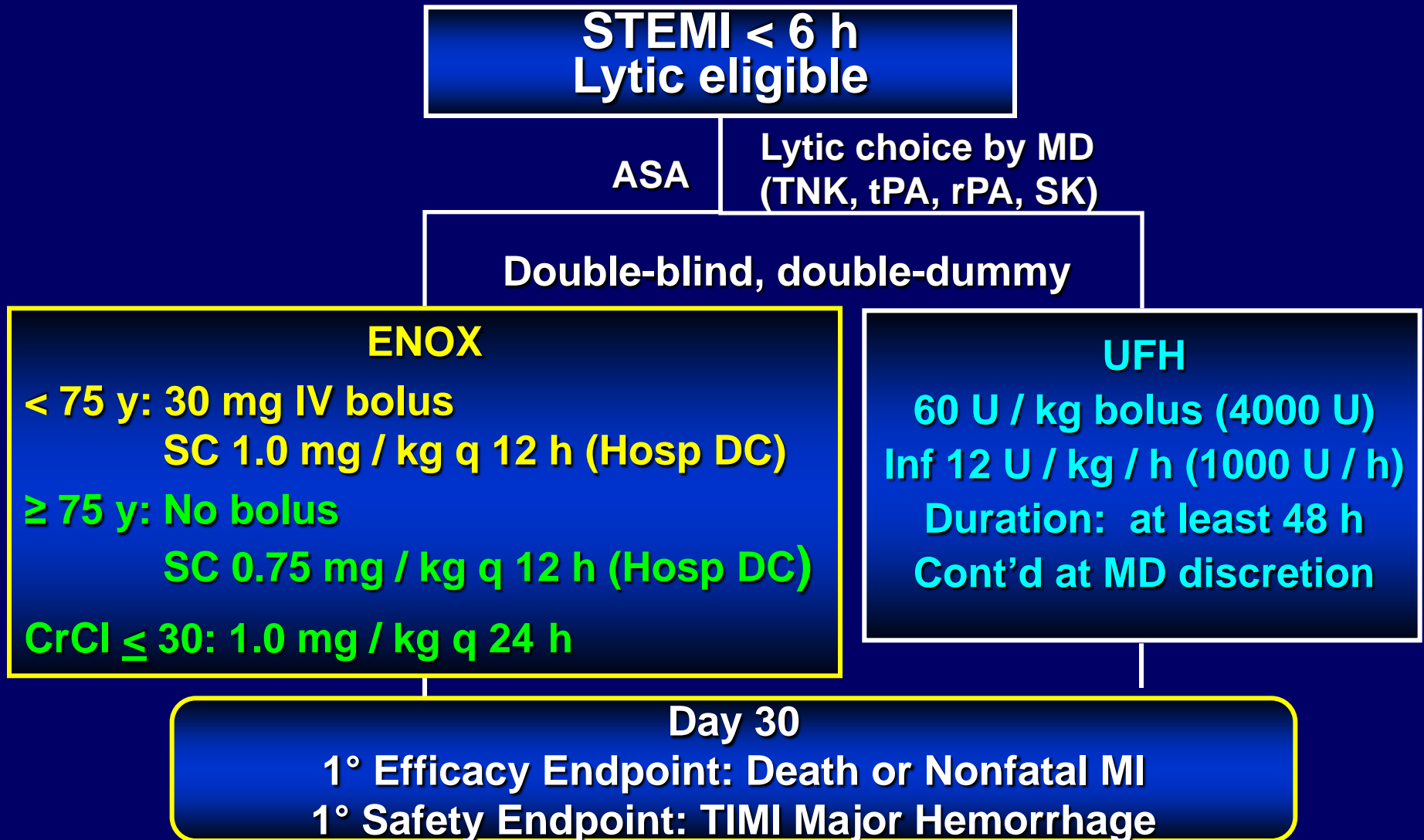


Yusuf S, et al. *JAMA*. 2006;295:1519-1530.
Adapted with permission from www.clinicaltrialresults.org.



Protocol Design

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



HORIZONS AMI: Impact of Clopidogrel Loading Dose on Efficacy of Bivalirudin

	Clopidogrel 300 mg (n=1,248)			Clopidogrel 600 mg (n=2,349)		
	BY	UFH + GPI	RR (95% CI)	BY	UFH + GPI	RR (95% CI)
Major Bleeding	6.5%	9.6%	0.68 (0.46-0.99)	4.1%	7.6%	0.54 (0.38-0.76)
MACE	7.0%	6.8%	1.04 (0.69-1.57)	4.5%	4.8%	0.95 (0.66-1.37)
NACE	12.0%	14.5%	0.83 (0.62-1.10)	7.7%	10.8%	0.71 (0.55-0.920)

Bivalirudin

GPI=glycoprotein IIb/IIIa inhibitor

MACE=major adverse cardiac events: death, reinfarction, ischemic TIA, or stroke

NACE=net adverse clinical events: MACE or major bleeding

UFH=unfractionated heparin

Dangas G, et al. *J Am Coll Cardiol*. 2009;51(10)(suppl B):B1. Abstract 2801-5.

plateletNEWS.org

STEMI: αντιθρομβωτικά

- **Ασπιρίνη:** 150-250mg IB
- **Κλοπιδογέλη:** 300 -600mg IC
αν όχι pr PCI 300 mg <75 ετών
75mg >75
- **Ηπαρίνη** 100 u/kg(60 αν και GPI)
- **GP IIb/IIIa** IIB
- **Ενοξαπαρίνη**
- **Φονταπαρινη** αν όχι επαναιμάτωση

Άμεση αγγειοπλαστική (συμπληρωματική αντιθρομβωτική θεραπεία)

Ασπιρίνη	I A
Κλοπιδογρέλη	I A
Ηπαρίνη	I C
Μπιβαλιρουδίνη	IIa B

Θρομβόλυση.

Συμπληρωματική αντιθρομβωτική θεραπεία

- **Ασπιρίνη IA**
- **Κλοπιδογρέλη IC**
- **Ενοξοπαρίνη IIa B** (αν χαμηλού κινδύνου για αιμορραγία)
- **Φονταπαρίνη IIa B** (αν ψηλού κινδύνου για αιμορραγία)
- **Κλασσική ηπαρίνη IIa C** (για 48 ώρες)

Καμμία μορφή επαναιμάτωσης

- Ασπιρίνη I A
- Ενοξαπαρίνη ή
φονταπαρίνη IIα B

ACS: Bleeding Complications

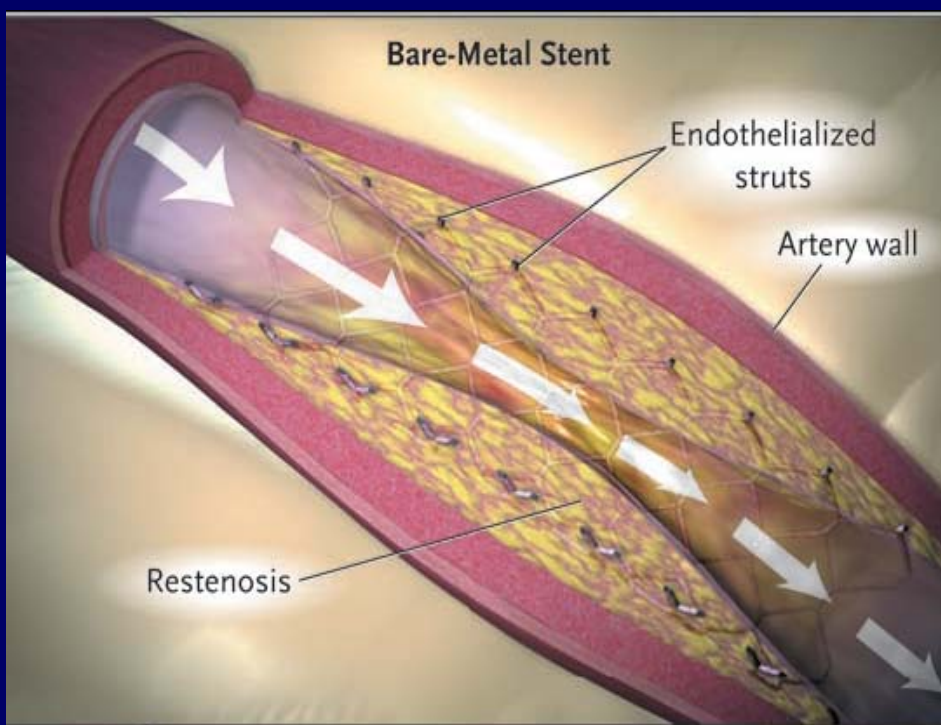
STEMI: with fibrinolytics: 5-6%, ICH: 1-2%
men vs women 14.4 vs 25.2 0.4% vs 1.2 (GUSTO V 30 d)

with PrPCI: 2-3%
7%: major bleeding, ICH 0.05

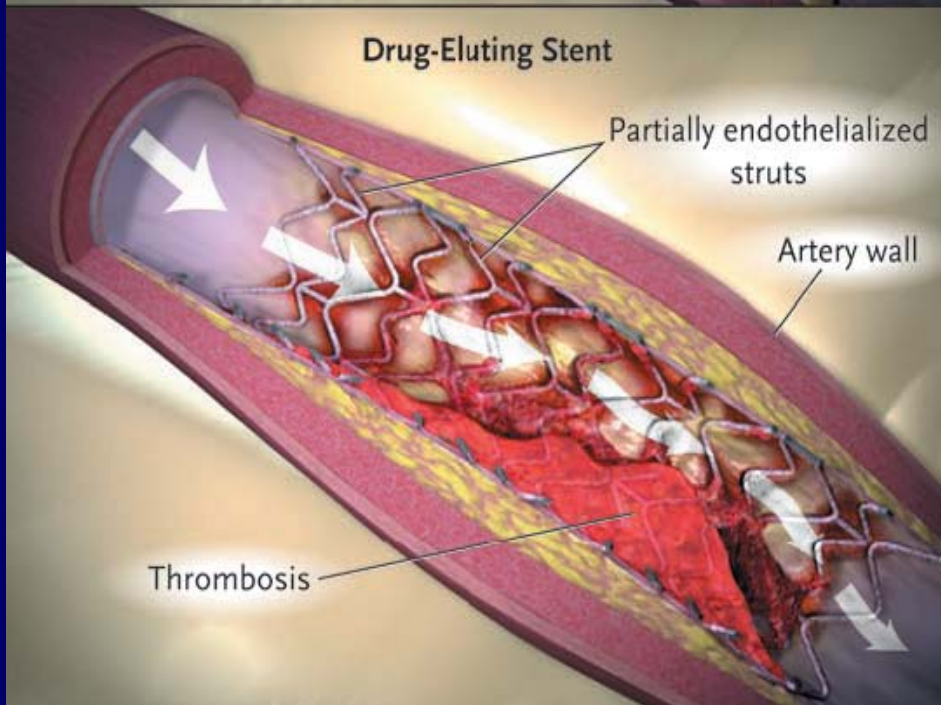
pr PCI UFH+GPI 30 day : 8.5% (HORIZONS AMI)
Biv 5.1%

NSTEMI; 3%

plus PCI: 5.4% (similar to ref ischemia, MI, death)



Achilles' heel



Damocles sword

Κλινικές Μελέτες

- Τι είδους
 - ασθενής;** χαμηλού –ψηλού κινδύνου
 - θεραπεία;** συνδιασμός, δόση, διάρκεια
- Υποομάδες πληθυσμού
 - ηλικιωμένοι, διαβητικοί

Clinical Trials and Clinical Judgment



The experience and wisdom of a thoughtful physician can make an important contribution to the application of the evidence base that is available

ACS: The Tip of the Atherothrombotic “Iceberg”

Acute Plaque Rupture
(UA/NSTEMI/STEMI)



Clinical

Subclinical

Presence of Multiple
Coronary Plaques

**Persistent Hyperreactive
Platelets**

Vascular
Inflammation

ACS=acute coronary syndrome.

UA=unstable angina.

Bhatt DL. *J Invasive Cardiol.* 2003;15:3B-9B.

NSTEMI=non-ST-segment elevation myocardial infarction.

STEMI=ST-segment elevation myocardial infarction.