Safety and Efficacy of Enoxaparin versus Unfractionated Heparin in Acute Coronary Syndrome

Seung-Woon Rha, MD, PhD
FACC, FAHA, FESC, FSCAI, FAPSIC

Cardiovascular Center,
Korea University Guro Hospital, Seoul, Korea

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- Global registry (FAST-MI, ACOS, KAMIR)

3. Summary & Conclusion

Need for new anti-coagulants ? Yes ! Because of limitations of UFH in PCI

1. **Current recommendations for ACT have become obsolete**

   Chew DP, et al. *Circulation*. 2001;103:961-966.

   Tolleson TR, et al. *J Am Coll Cardiol*. 2003;41:386-393.

   Brener, SJ, et al. *Circulation*. 2004;110:994-998.

2. **Anticoagulation with UFH is unpredictable**

   In STEEPLE, only 20% of patients were in the "official" target range

3. **Frequent medical errors with UFH**

   LaPointe NM, Jollis JG. *Arch Intern Med.* 2003;163:1461-1466.

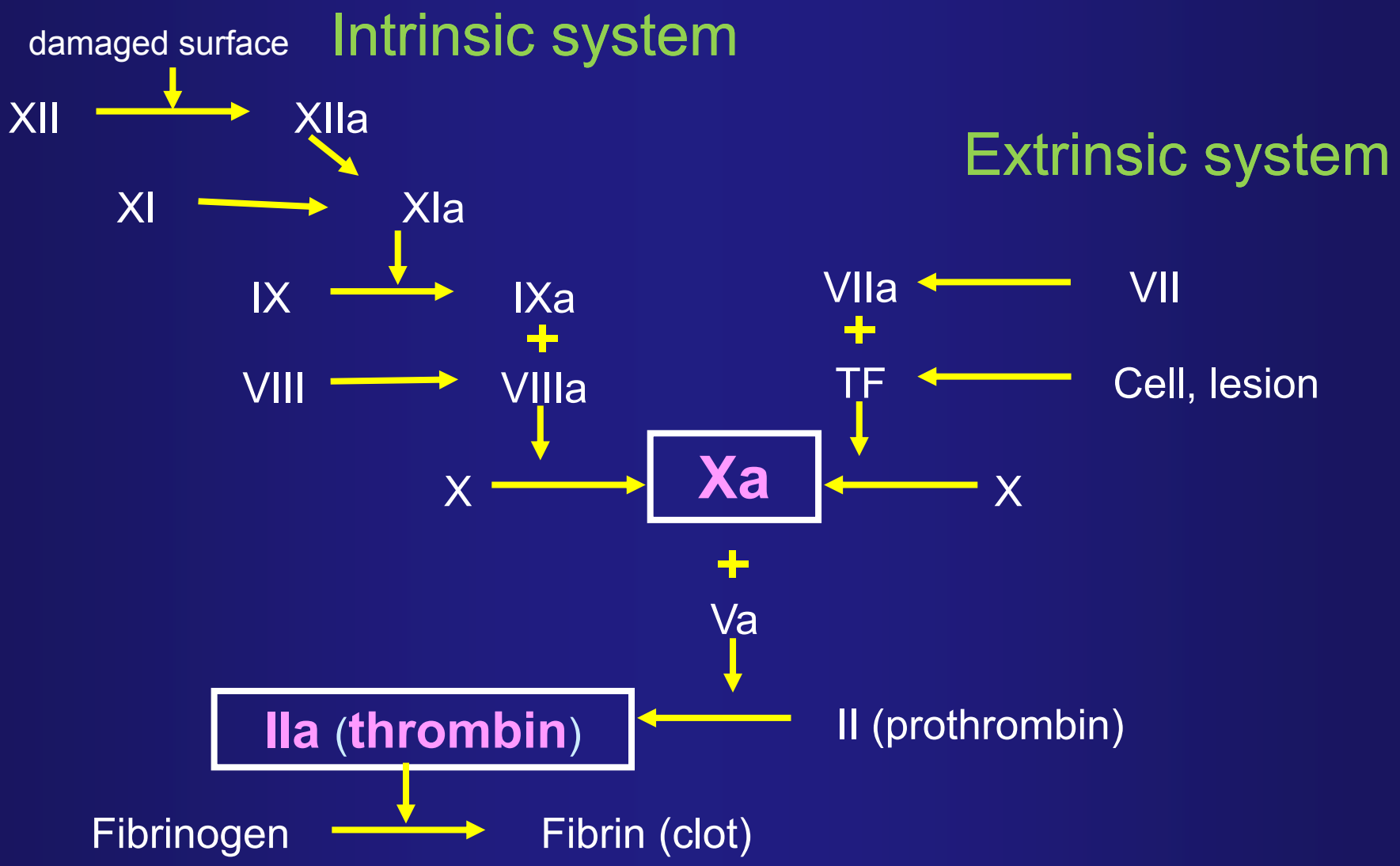
4. **Safety of UFH recently put into question d/t anaphylaxis**

5. **New alternatives are available, which are safer, more effective and easier to use**

Comparison of LMWH vs. UFH:

mode of action, advantages and disadvantages

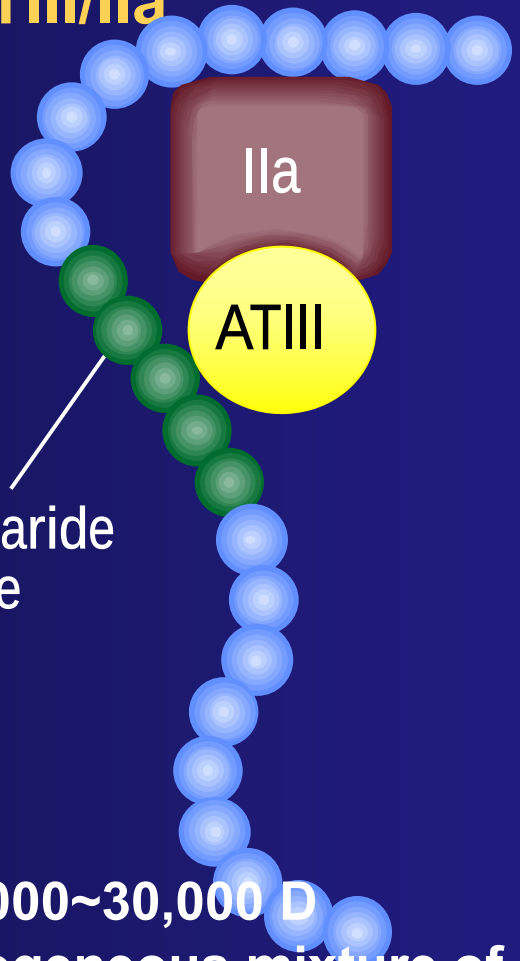
Coagulation Cascade

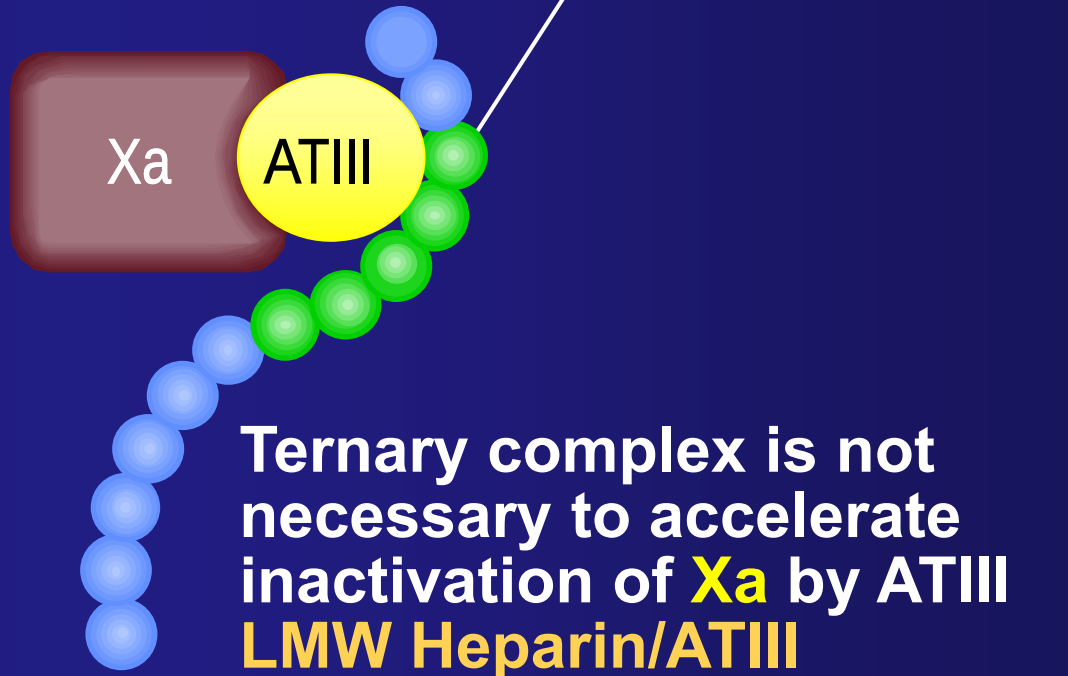


Mann KG, *Thromb. Haemost.* 1999, 82:165–174.

Different mechanism in inactivation of IIa & Xa

Ternary complex accelerates inactivation of IIa by ATIII
Heparin/ATIII/IIa

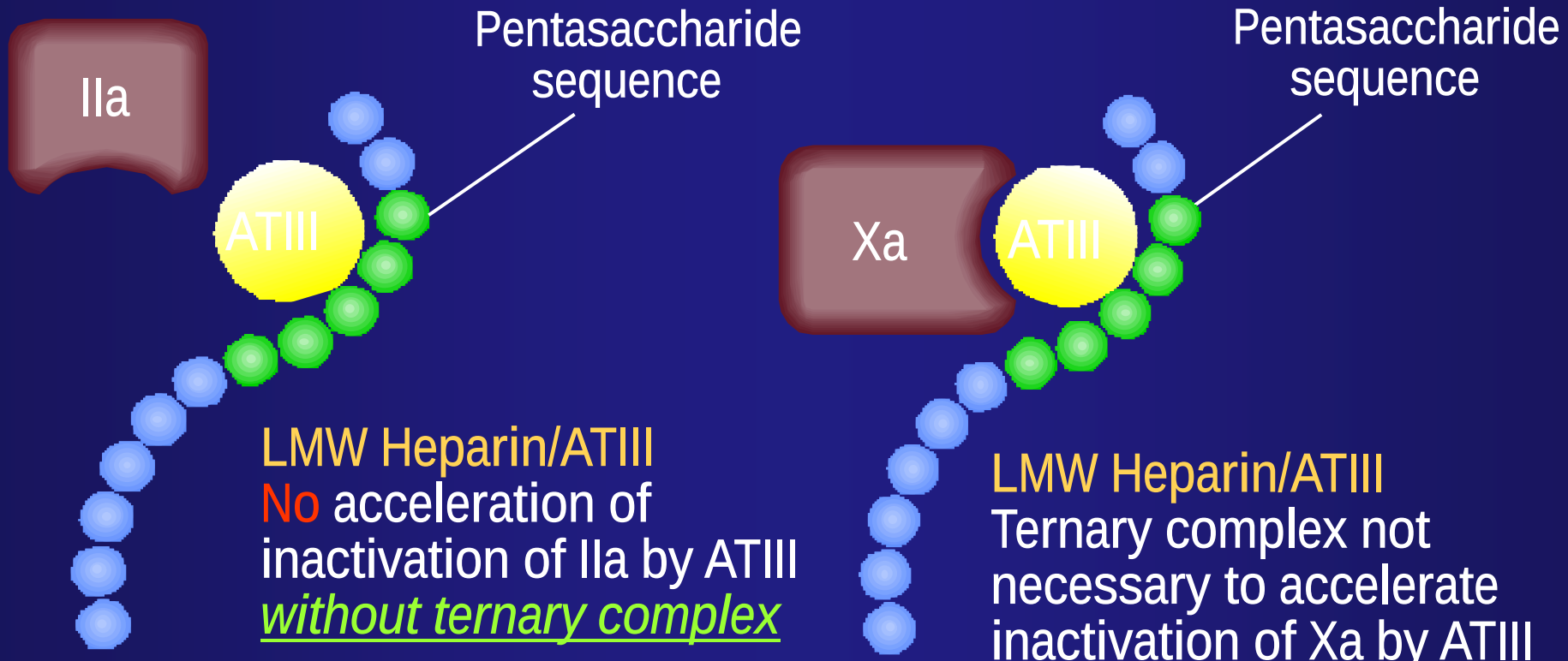




Ternary complex is not necessary to accelerate inactivation of Xa by ATIII
LMW Heparin/ATIII

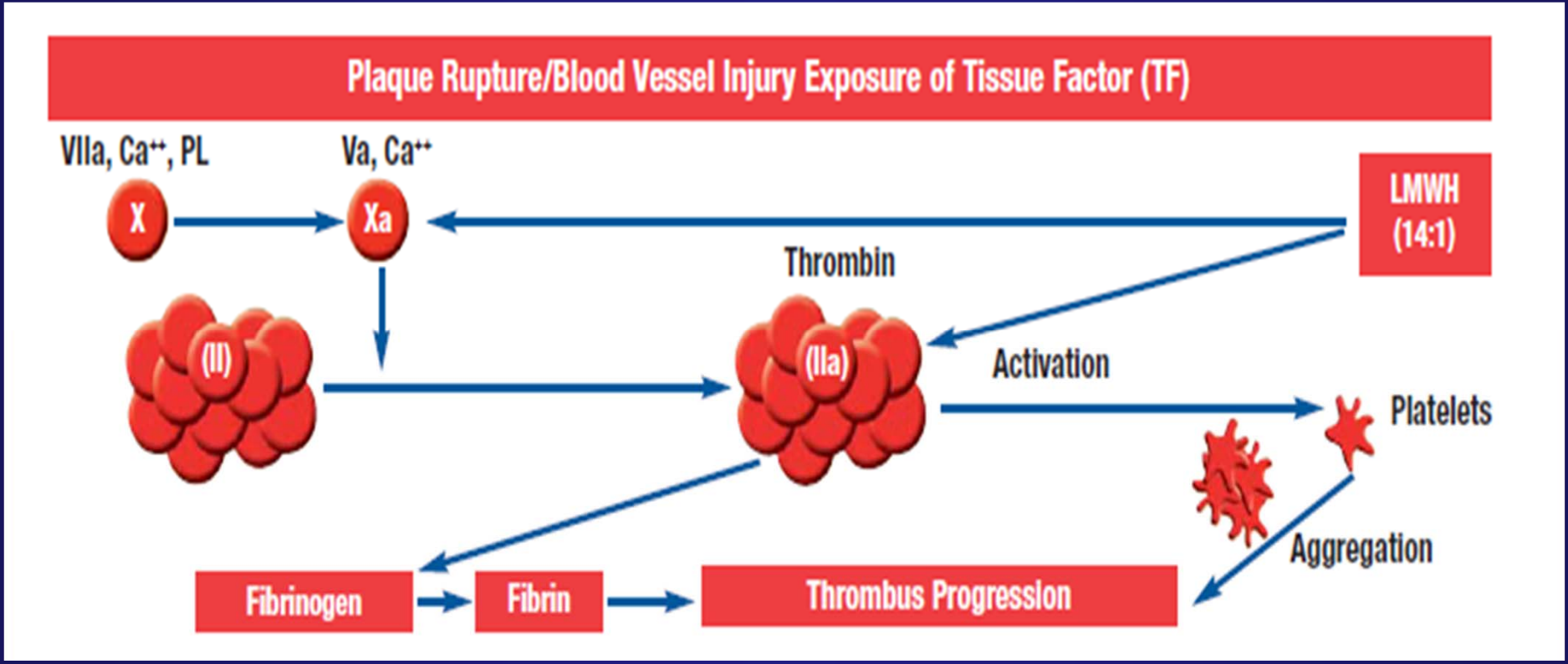
- MW 3000~30,000 D
- Heterogeneous mixture of polysaccharide chains
- Anticoagulation activity by catalyzing antithrombin

LMWH : Inactivation of Xa >> IIa



- **MW 4,500~6,000 D**
- **Isolated antithrombotic effect from unfractionated heparin**
- **Anti Xa activity greater than antithrombin activity**

LMWH offers greater Xa activity for greater antithrombotic effect



1. LMWH acts on 2 sites of the coagulation cascade, factors Xa and IIa (thrombin), reducing thrombin generation and inhibiting fibrin clot formation
2. The earlier the inhibition, the greater the anticoagulation effect
3. One factor Xa molecule generates ~100 molecules of thrombin in 1 second. Thus, by limiting factor Xa, Enoxaparin inhibits the subsequent step—the explosive generation of thrombin

Büller HR. Factor Xa is a superior target to factor IIa for antithrombotic therapies. *Semin Thromb Hemost.* 2003;29(suppl 1):37.

Unfractionated Heparin

Advantages

- Long history of clinical use
- Multiple sites of action in coagulation cascade
- Immediate anticoagulation

Disadvantages

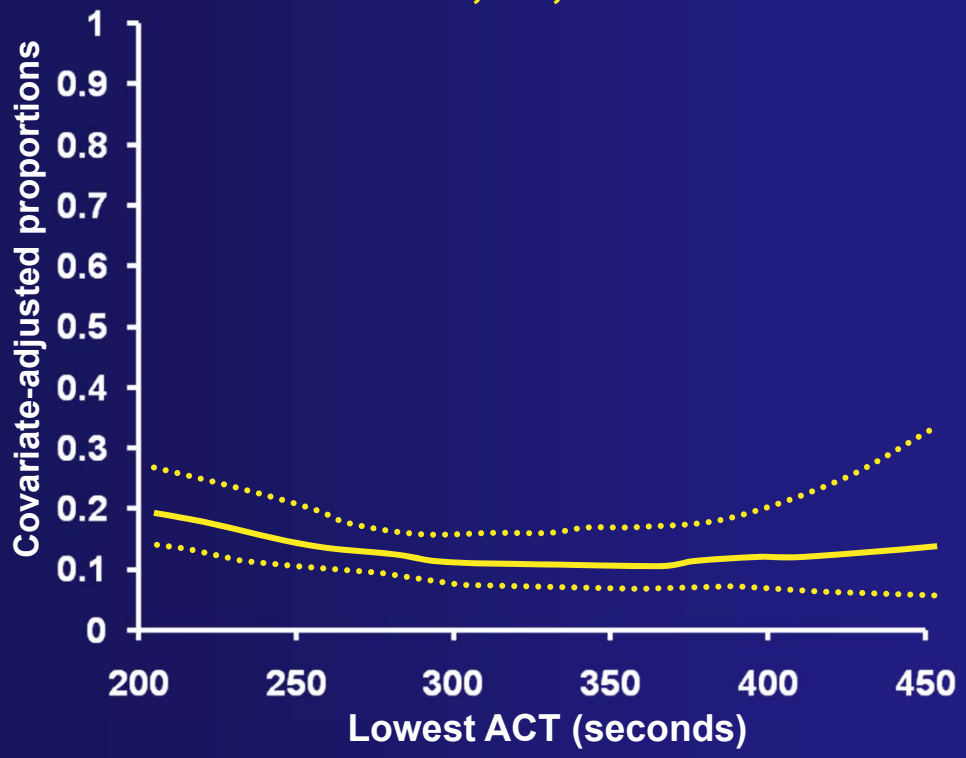
- Nonspecific binding to:
  - Serine proteases
  - Endothelial cells

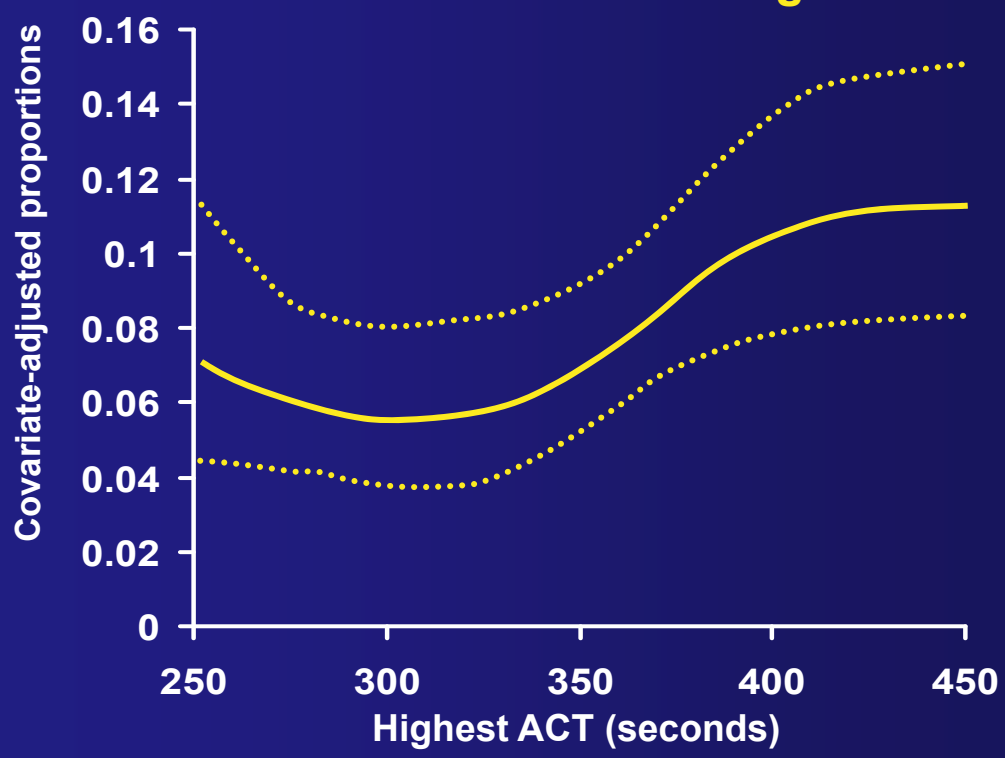
  (can lead to variability in level of anticoagulation)
- Not consistent half life (30min ~ 2.5h)
- Nonlinear pharmacokinetics
- Reduced effect in ACS
  - Inhibited by PF-4
- Causes platelet aggregation
- Risk of HIT

Hirsh J, et al. *Circulation*. 2001;103:2994-3018. aPTT = activated partial thromboplastin time; ACT = activated coagulation time; PF-4 = platelet factor 4; HIT = heparin-induced thrombocytopenia.

UFH: Relationship between ACT levels and outcomes

N = 1,230





ACT > 325 seconds ➔ independent predictor of bleeding
(OR 1.6, 95% CI 1.1–2.2 per 100 units; p = 0.049)

CI = confidence interval; MI = myocardial infarction; UTVR = urgent target-vessel revascularization; OR = odds ratio.

Montalescot G et al. *Eur Heart J,* 2008.

Low-Molecular-Weight Heparin

Advantages

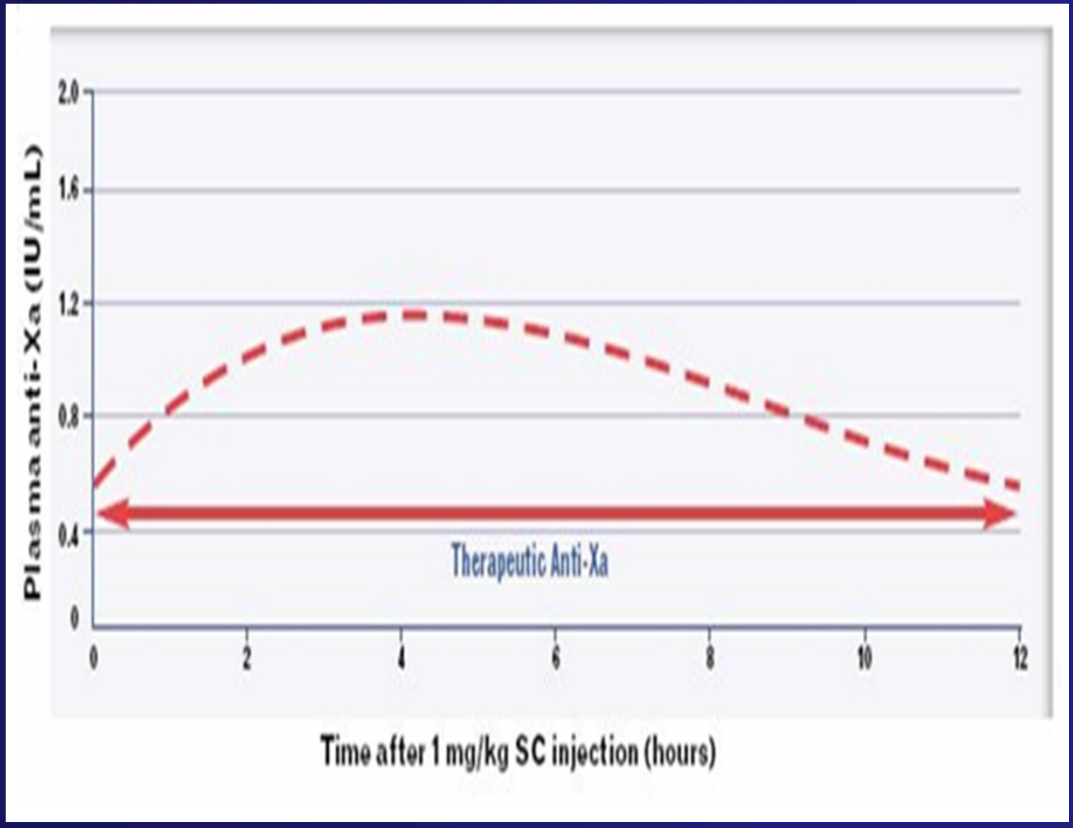
- Increased anti-Xa to anti-IIa activity → inhibits thrombin generation more effectively
- Induces ↑ release of TFPI vs UFH
- Not neutralized by platelet factor 4
- Less binding to plasma proteins (eg, acute-phase reactant proteins) → Predictable anticoagulation with high bioavailability
- Lower rate of HIT vs UFH
- Long history of clinical studies and experience, FDA-approved indications
- Monitoring typically unnecessary
- Easier to use, less resource utilization

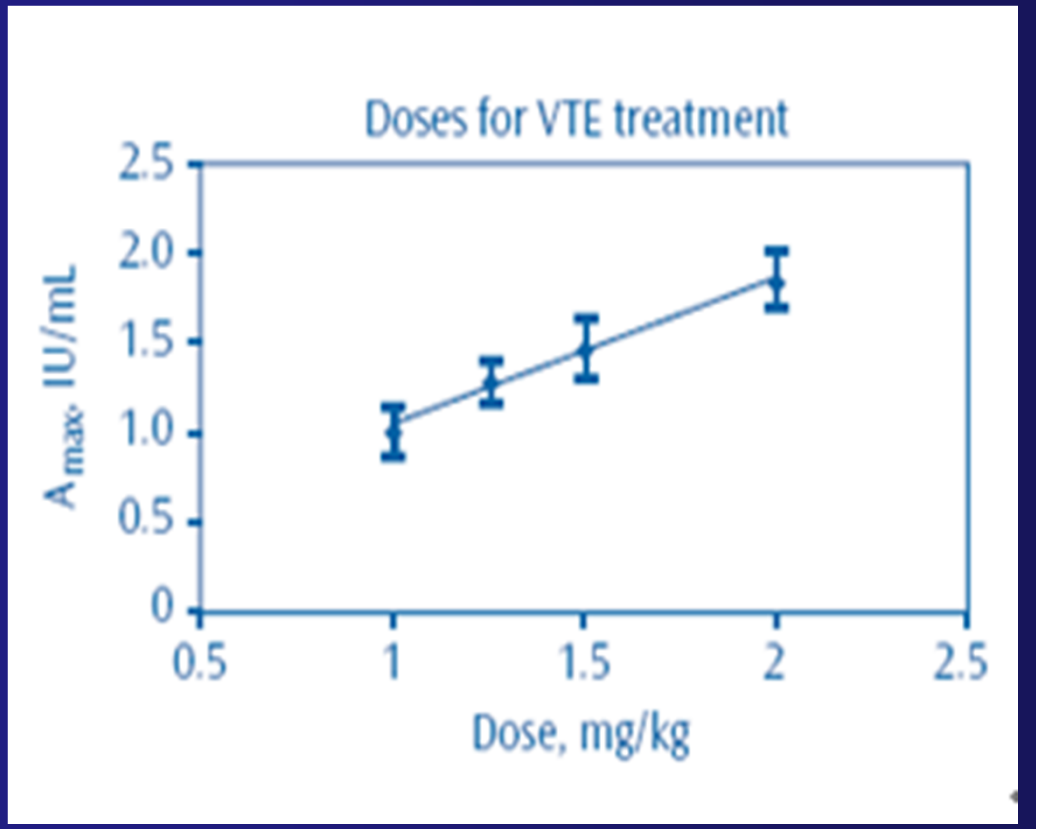
Disadvantages

- Difficult to monitor, but monitoring is typically unnecessary (no aPTT or ACT)

Hirsh J, et al. *Circulation*. 2001;103:2994-3018. TFPI = tissue factor pathway inhibitor; UFH = unfractionated heparin; SC = subcutaneous; aPTT = activated partial thromboplastin time; ACT = activated coagulation time.

Predictable Anti-Xa activity with Enoxaparin ➔ No Monitoring





Data on file. sanofi-aventis, Bridgewater, NJ.

Frydman AM et al. *J Clin Pharmacol.* 1988;28:609-618 *Thromb Haemost.* 1995;73:971

Review of Guidelines and Clinical Data

1. UA/NSTEMI
    1) ACC/AHA updated guideline
    2) Medical Treatment: ESSENCE
    3) Meta-analysis
    4) Elective PCI: STEEPLE

2. STEMI
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    4) Primary PCI: FINESSE, ATOLL
    5) Global registry; FAST-MI, ACOS, KAMIR

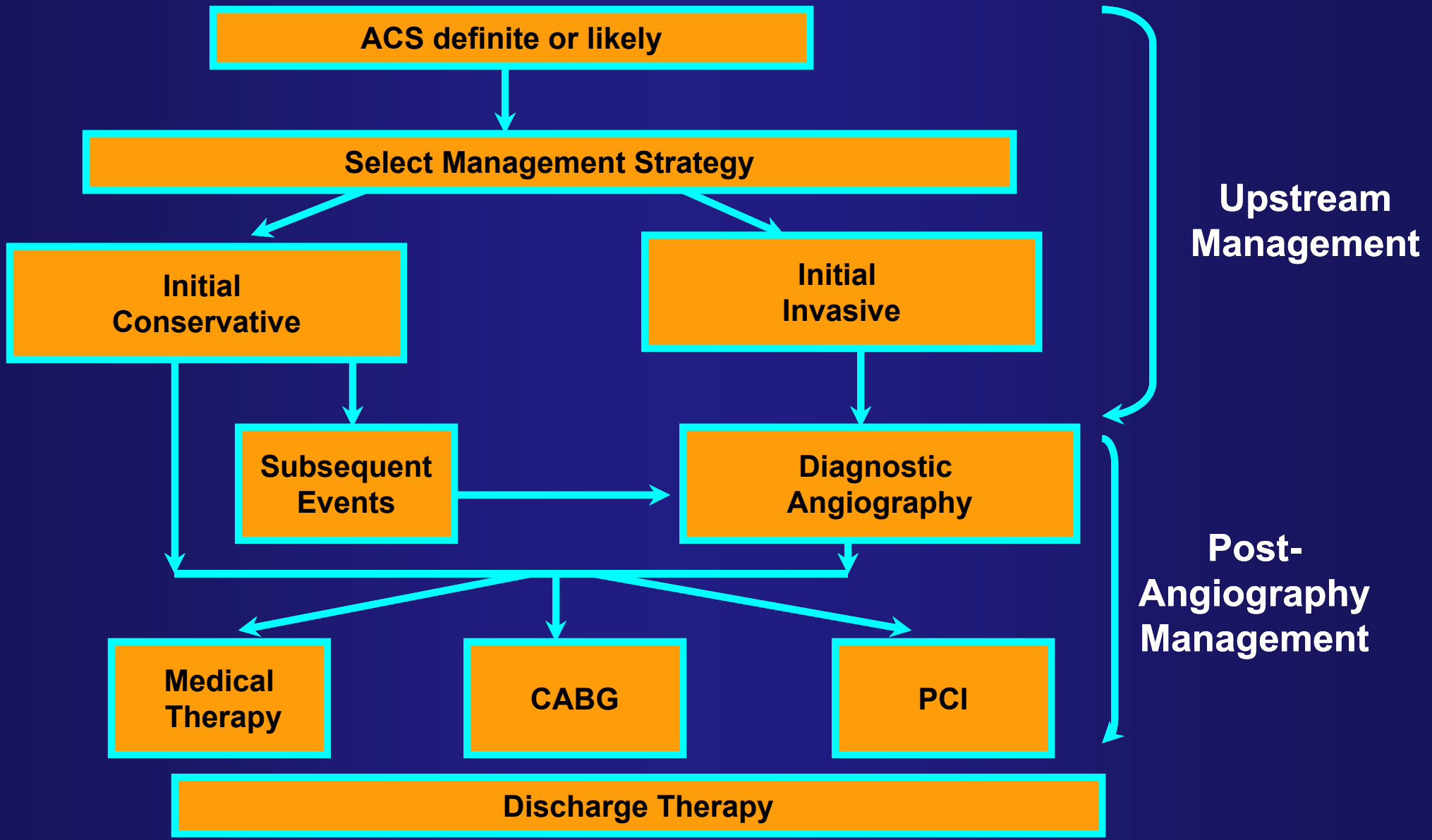
2007 ACC/AHA Guidelines for the Management of Patients with Unstable Angina / Non-ST-Segment Elevation MI

Journal of the American College of Cardiology and Circulation

Released August, 2007

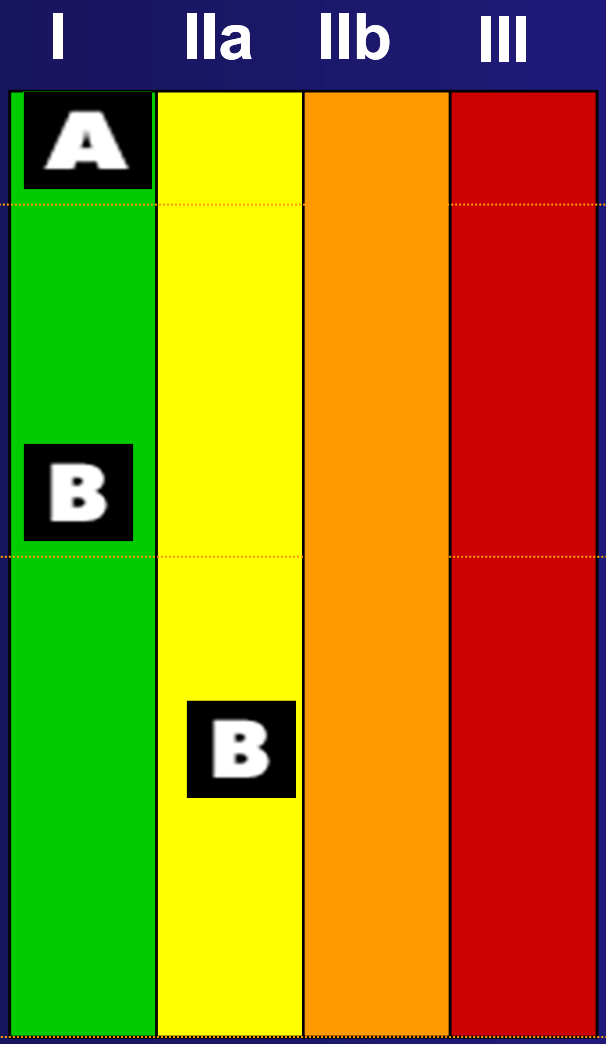
Anderson et al. JACC 2007;50(7):652-726 or at www.acc.org

ACS Management Algorithm



Adapted from Guidelines

Upstream Hospital Care:
Initial Invasive Strategy: Initial Anti-thrombin Tx

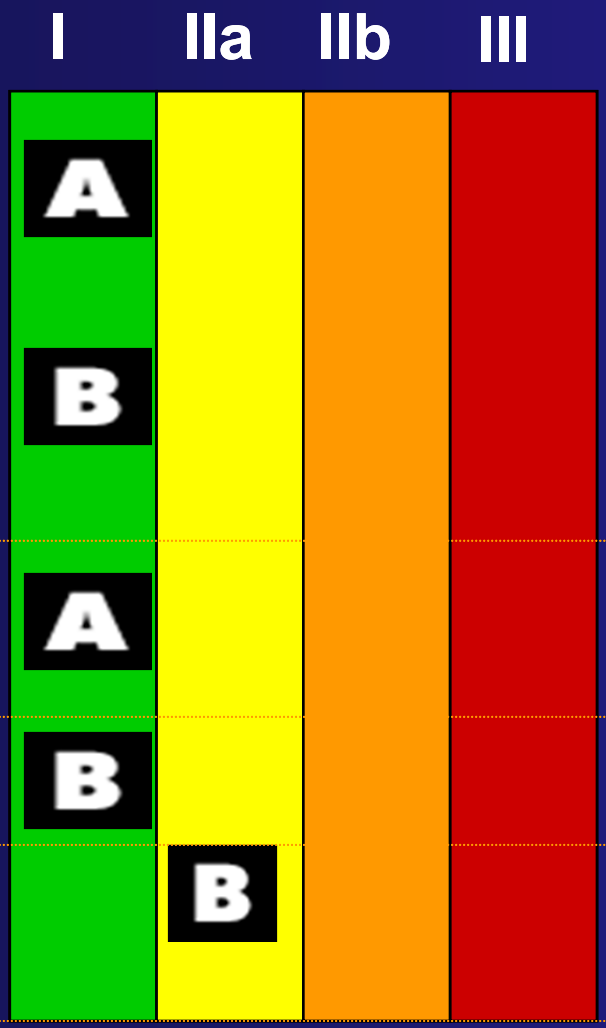


Enoxaparin or UFH

Fondaparinux or Bivalirudin with antiplatelet agents

Bivalirudin instead of GP IIb IIIa inhibitor/Antithrombin upstream only if Clopidogrel is used >6 hrs prior to PCI

Upstream Hospital Care
Initial Conservative Strategy



Clopidogrel with aspirin for at least 1 month

Clopidogrel with aspirin ideally up to 1 year

Enoxaparin or UFH

Fondaparinux

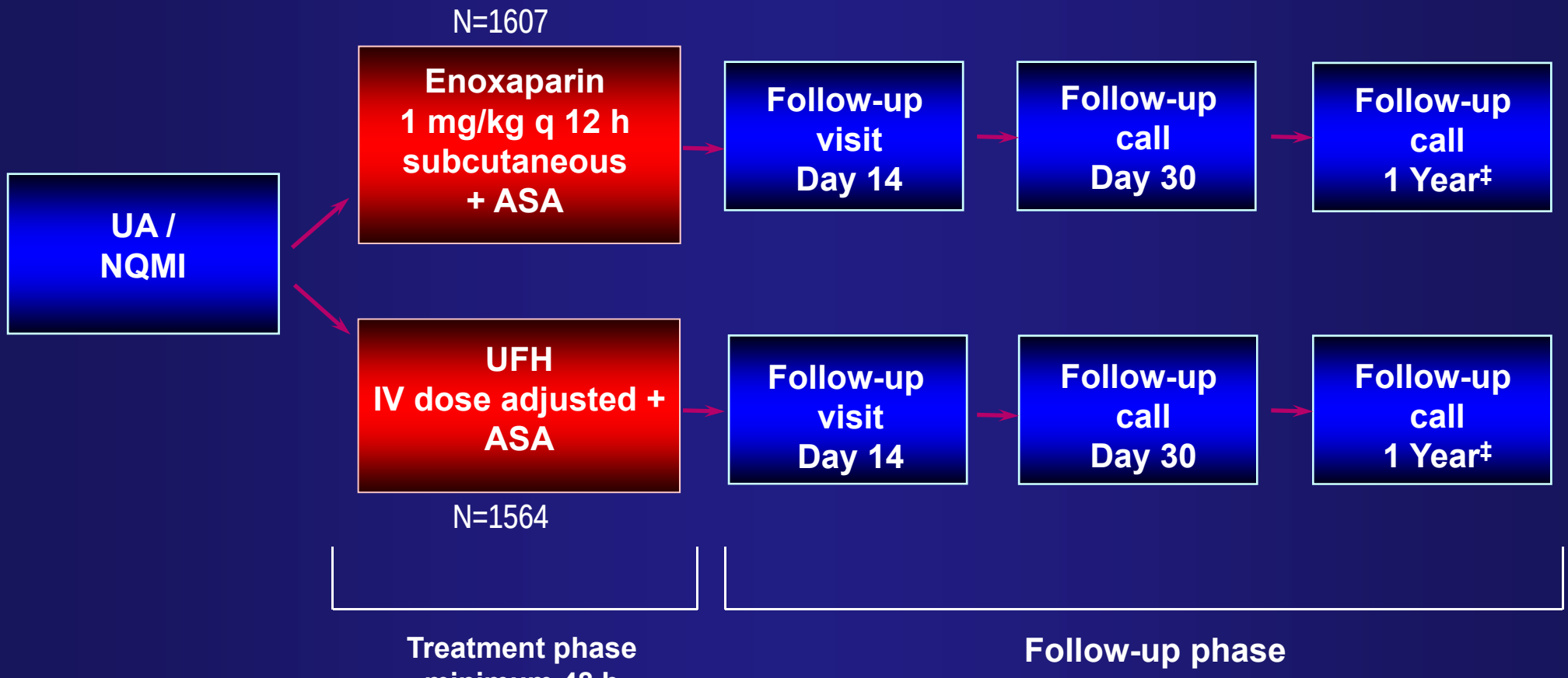
Enoxaparin or Fondaparinux preferred over UFH unless CABG planned <24 hr

The ESSENCE Study:

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (unstable angina and non-Q-wave myocardial infarction)

ESSENCE

The Efficacy and Safety of Subcutaneous Enoxaparin in Non Q wave Coronary Events

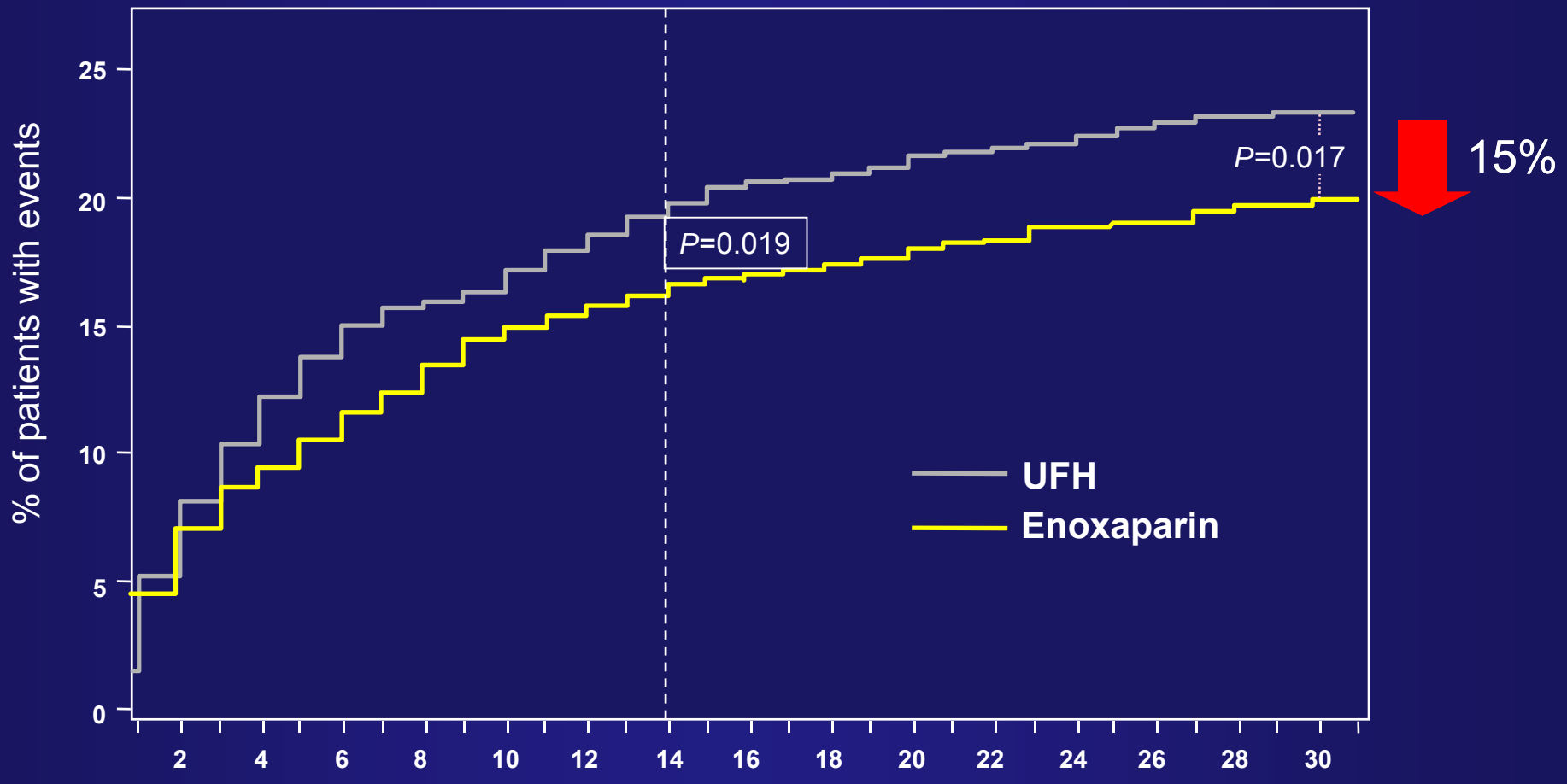


Cohen M, et al. *N Engl J Med* 1997;337:447-52

‡Goodman SG, et al. *J Am Coll Cardiol* 2000

ESSENCE

Time to First Event over 30 Days: Death, MI, RA
Superior efficacy of enoxaparin was maintained to 30 days



MI: Myocardial Infarction , RA: Recurrent Angina

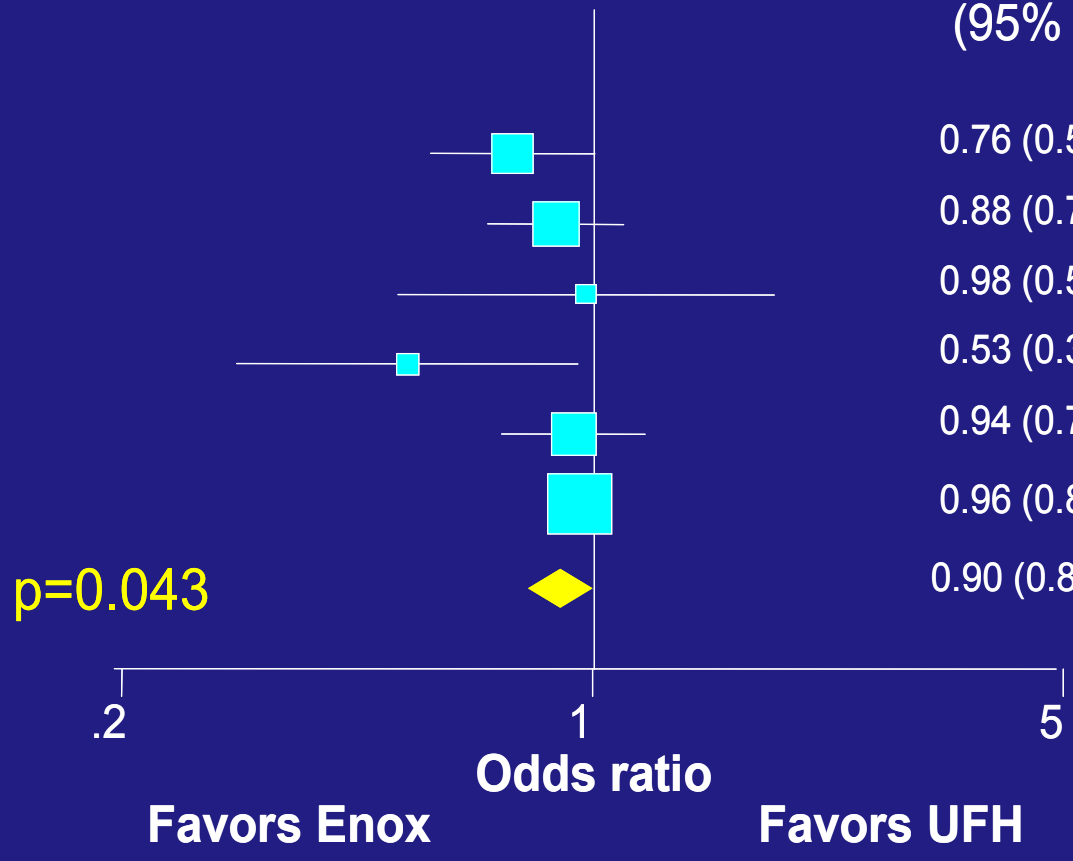
Cohen M, et al. *N Engl J Med* 1997;337:447-52

Meta analysis

UA/NSTEMI

Metaanalysis in NSTE-ACS:

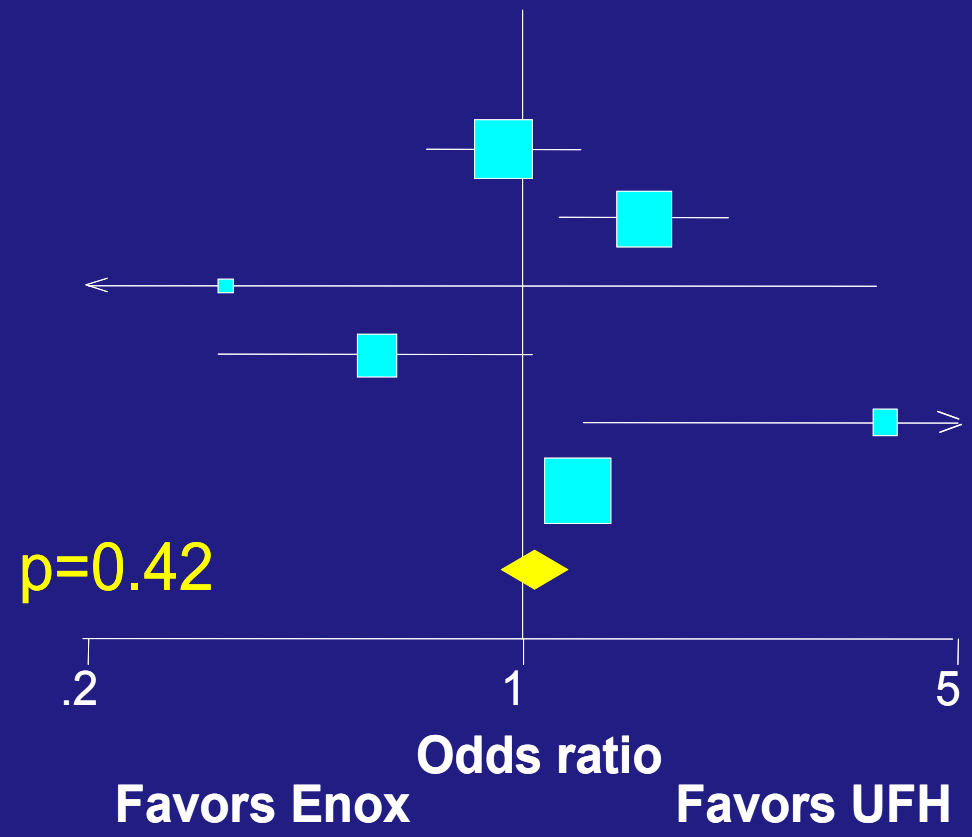
Death or Reinfarction



	Odds ratio (95% CI)	Enox (%)	UFH (%)
ESSENCE	0.76 (0.58,1.01)	5.8	7.5
TIMI 11B	0.88 (0.70,1.11)	7.4	8.3
ACUTE II	0.98 (0.51,1.86)	7.9	8.1
INTERACT	0.53 (0.30,0.95)	5.0	9.0
A TO Z	0.94 (0.73,1.20)	7.4	7.8
SYNERGY	0.96 (0.85,1.07)	13.9	14.5
	0.90 (0.81,0.996)	10.0	11.0

S. Murphy - Eur Heart J. 2007

Major Bleeding



	Odds ratio (95% CI)	Enox (%)	UFH (%)
ESSENCE	0.93 (0.70,1.23)	6.5	6.9
TIMI 11B	1.56 (1.13,2.14)	5.2	3.4
ACUTE II	0.33 (0.03,3.68)	0.3	1.0
INTERACT	0.58 (0.33,1.03)	5.3	8.7
A TO Z	3.78 (1.25,11.41)	0.8	0.2
SYNERGY	1.21 (1.05,1.40)	9.1	7.6
	1.13 (0.84,1.54)	**6.3**	**5.4**

S. Murphy et al. Eur Heart J. 2007

Elective (Scheduled) PCI

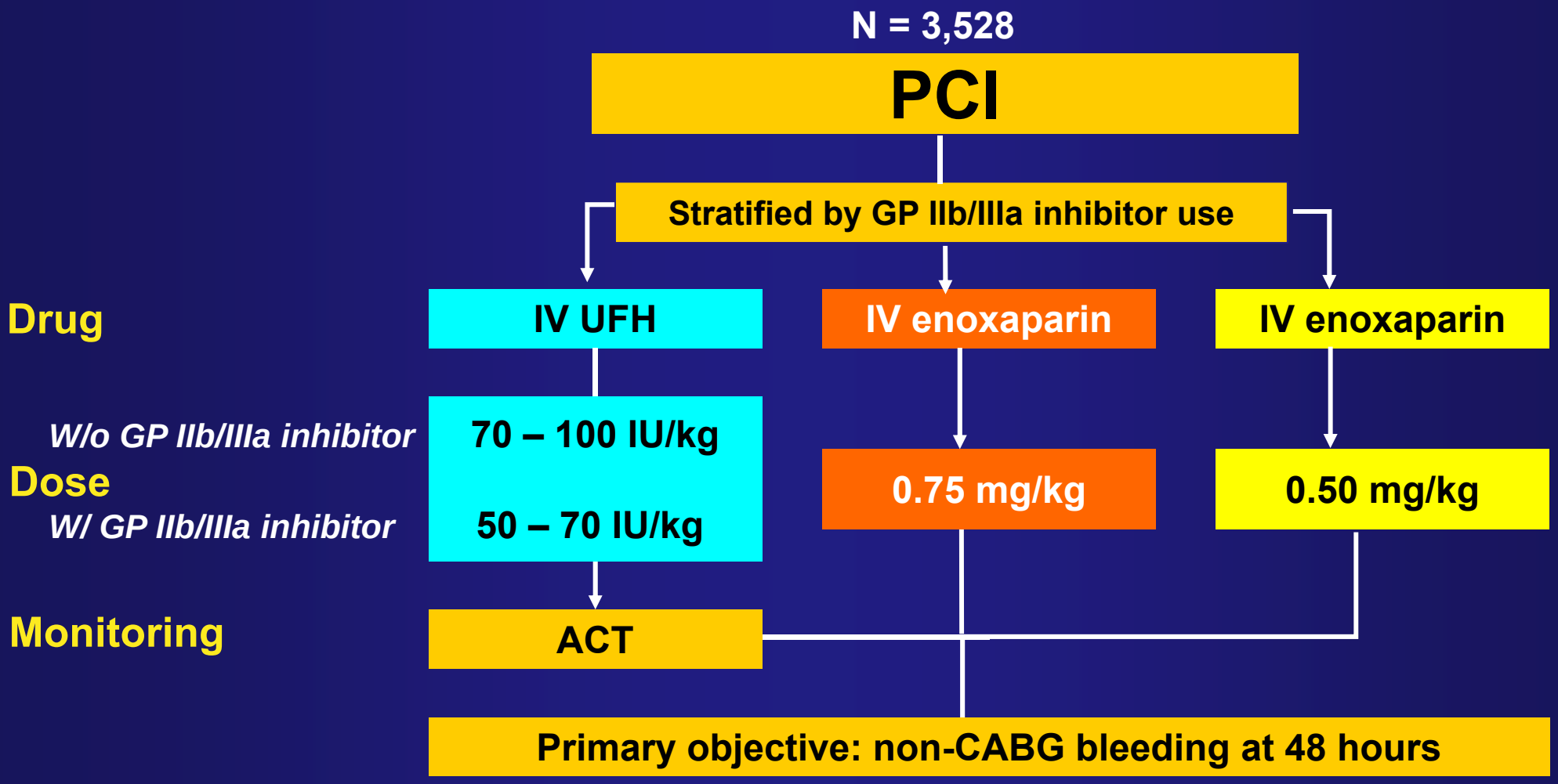
STEEPLE :

Safety and Efficacy of Exoxaparin

in Percutaneous Coronary Intervention (PCI)

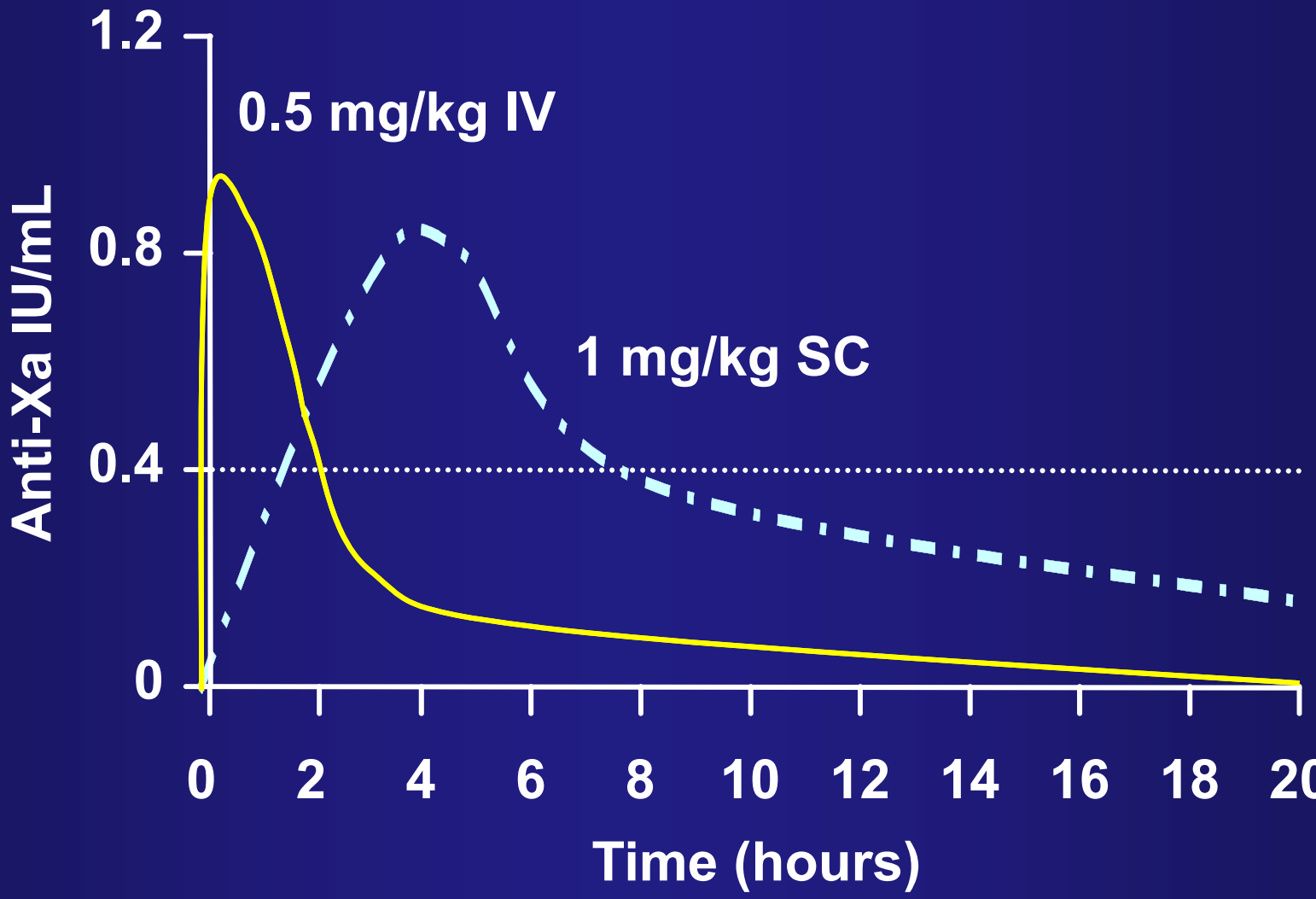
: an International Randomized Evaluation

STEEPLE: Study design



Montalescot G, et al. *N Engl J Med* 2006;355:1006-1017.

Enoxaparin:
Anticoagulation with a single IV injection

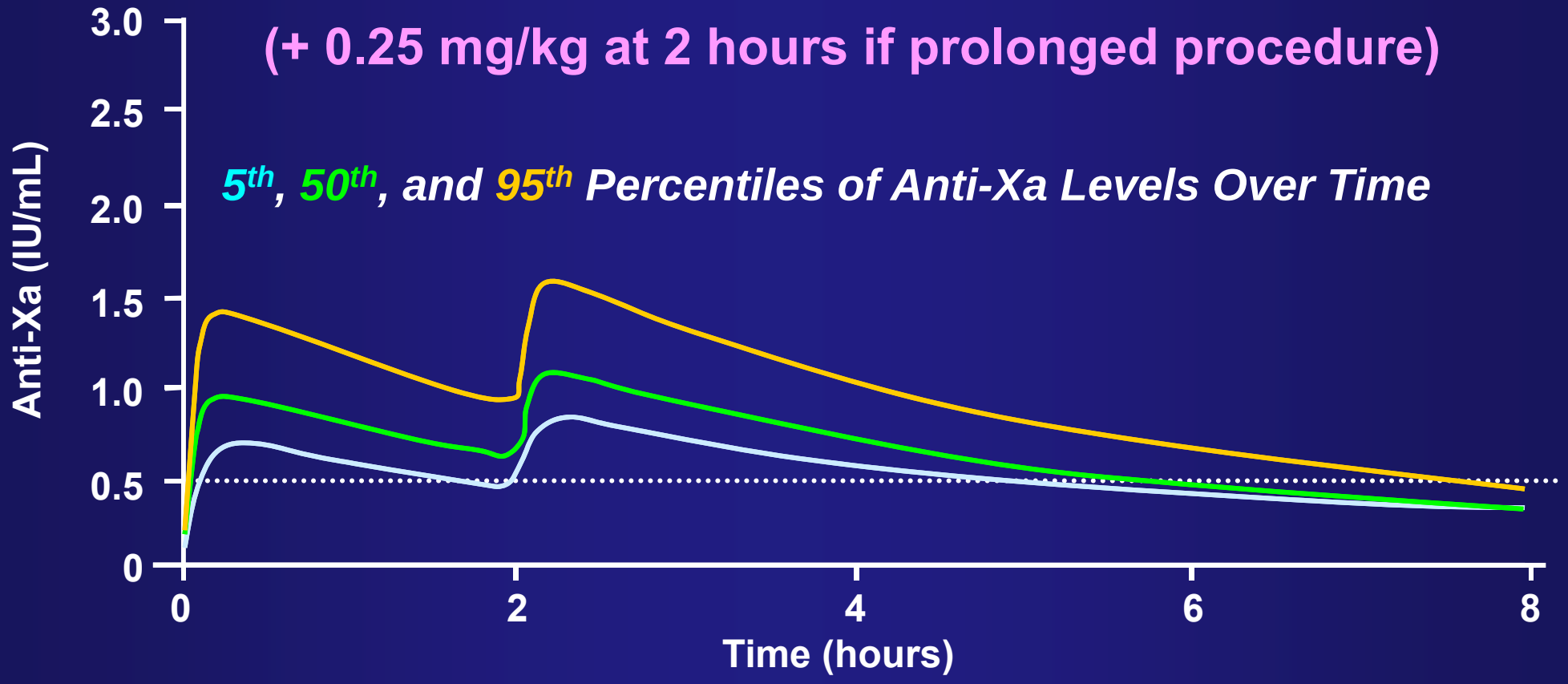


Sanchez-Pena P, et al. *Br J Clin Pharmacol*. 2005;60:364-373.

Enoxaparin: Anticoagulation with additional IV injection after single IV injection

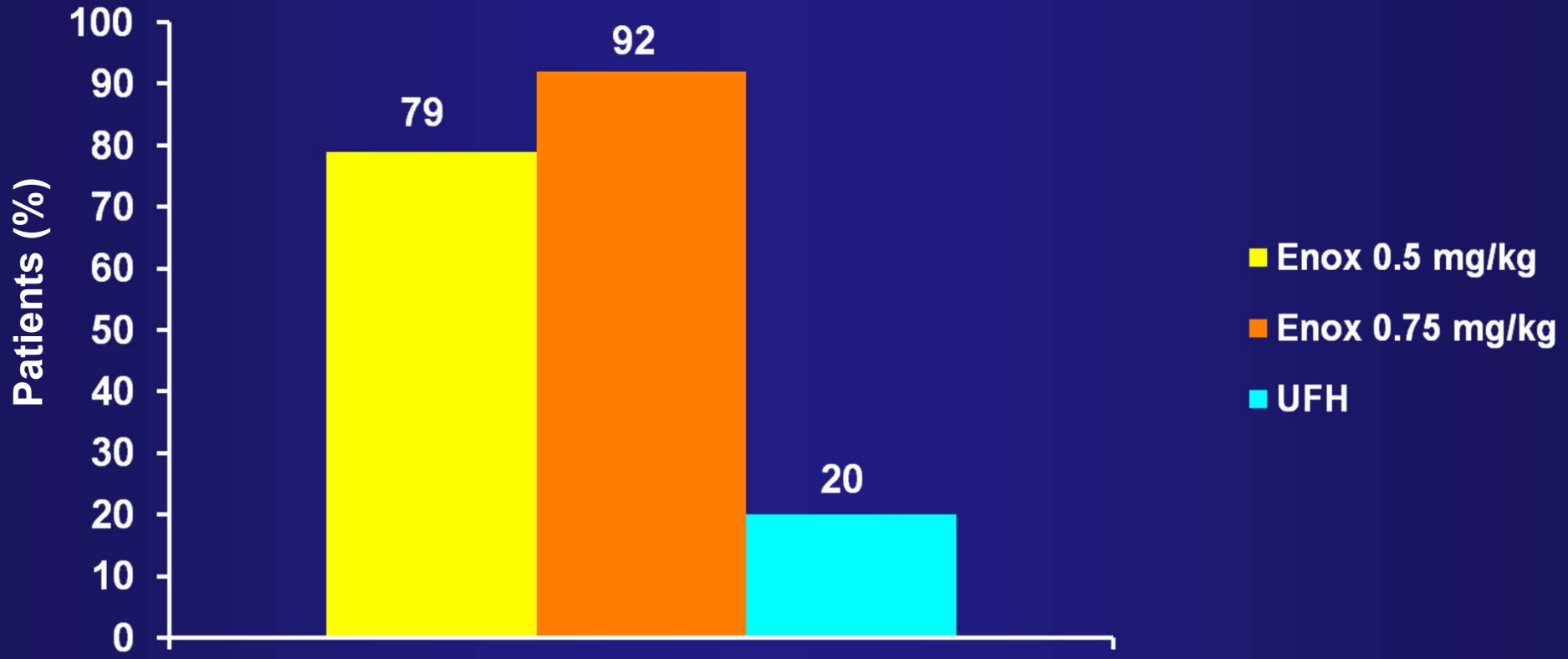
Enoxaparin 0.5 mg/kg IV

(+ 0.25 mg/kg at 2 hours if prolonged procedure)



Sanchez-Pena P, et al. *Br J Clin Pharmacol*. 2005;60:364-373.

Target anticoagulation levels reached in STEEPLE

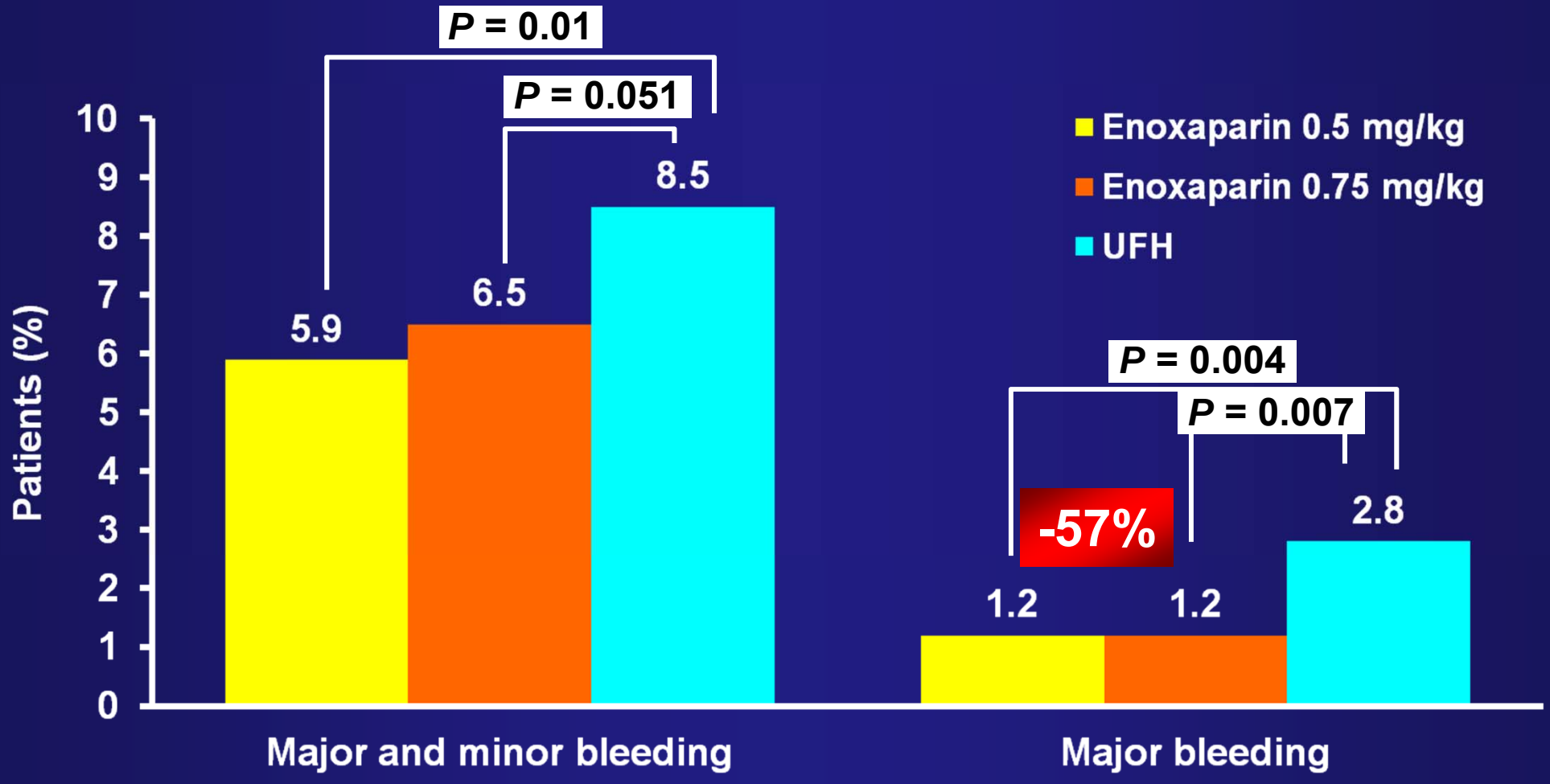


Target anticoagulation levels were pre-specified:

- Enoxaparin: anti-Xa levels 0.5-1.8 IU/ml
- UFH: ACT 200-300 sec if a GP IIb/IIIa inhibitor was used
- or 300-350 sec in the absence of a GP IIb/IIIa inhibitor

Montalescot G, et al. *N Engl J Med* 2006;355:1006-1017.

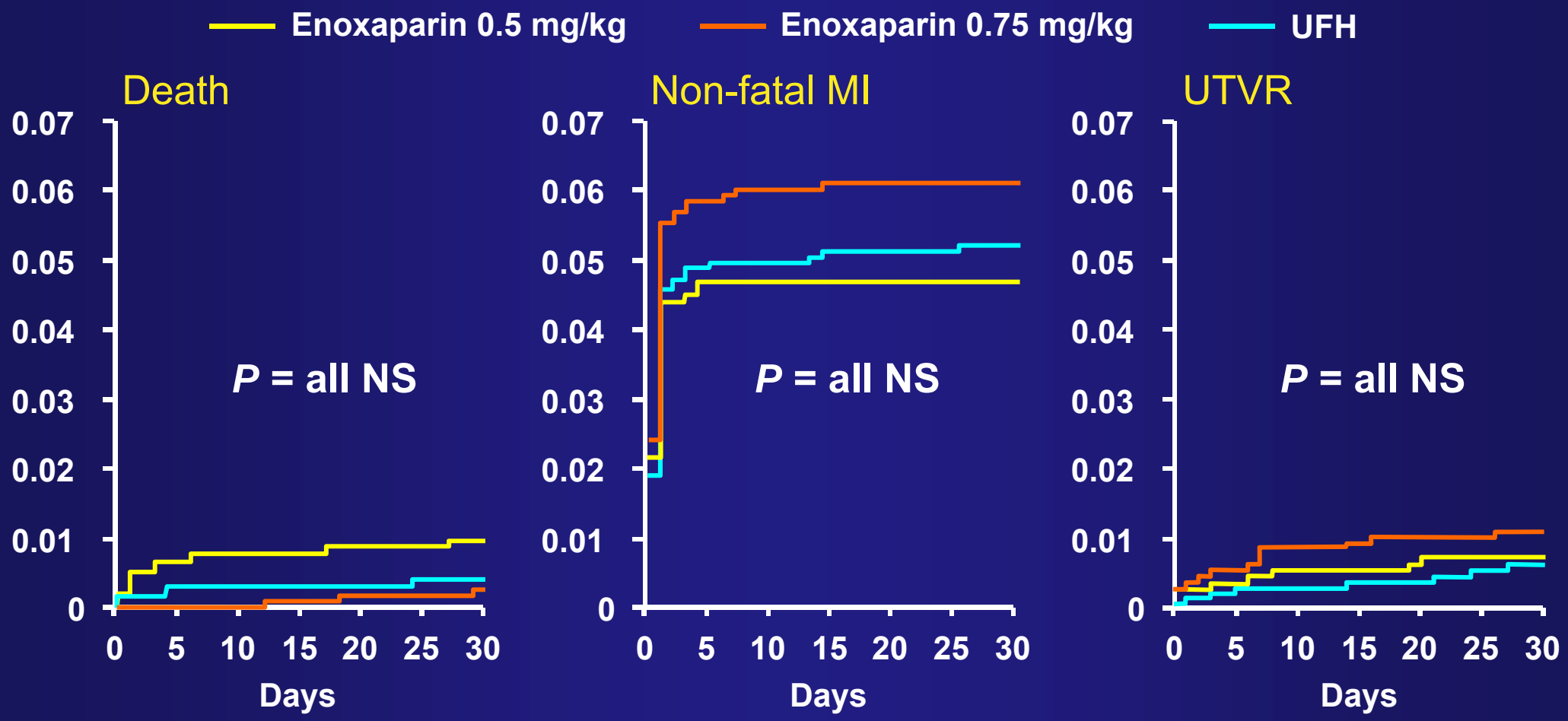
STEEPLE: Non-CABG-related bleeding*



*Primary endpoint.

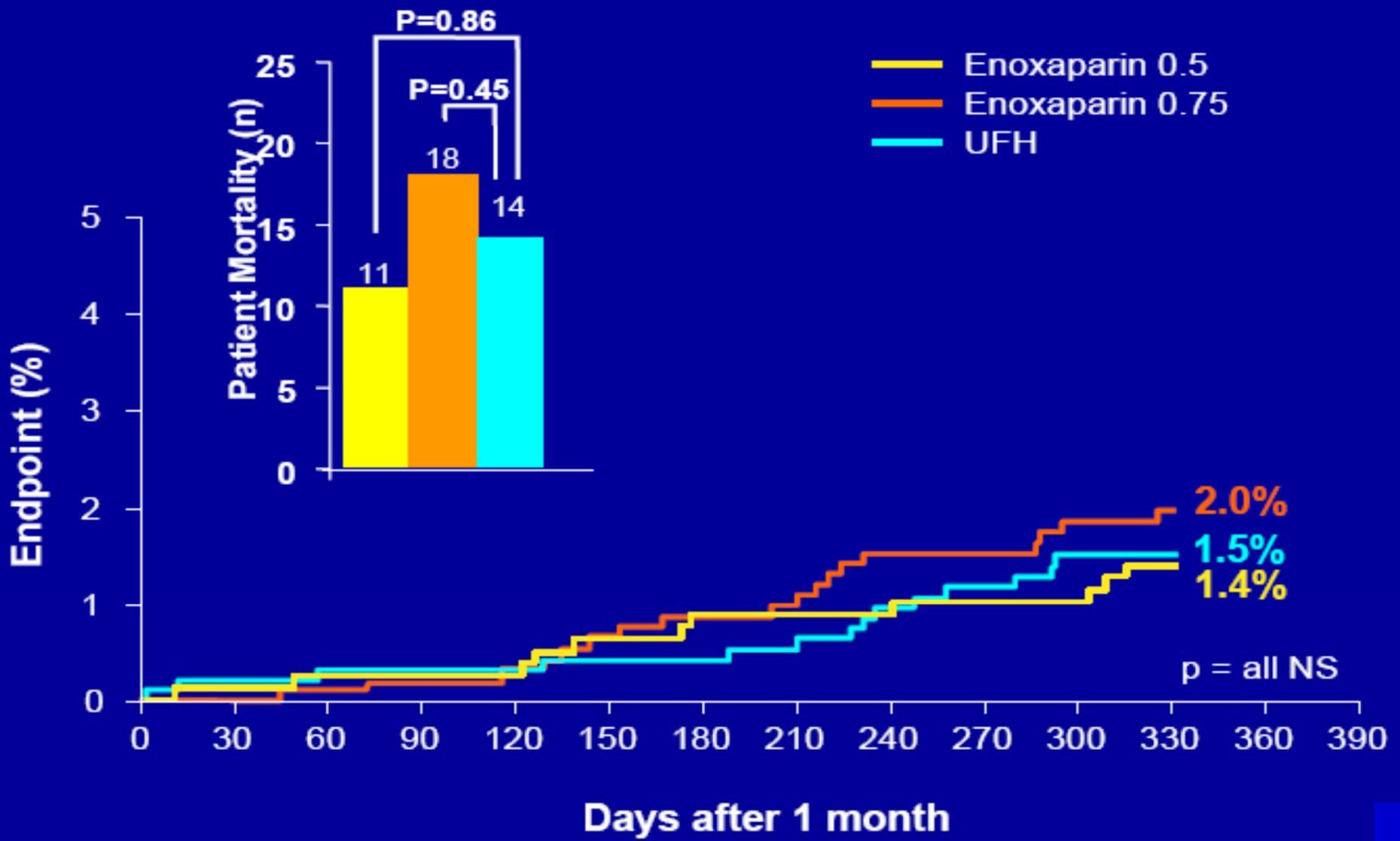
Montalescot G et al. *N Engl J Med* 2006;355:1006-1017.

STEEPLE: Individual ischemic endpoints at 30 Days



Montalescot G et al. *N Engl J Med* 2006;355:1006-1017.

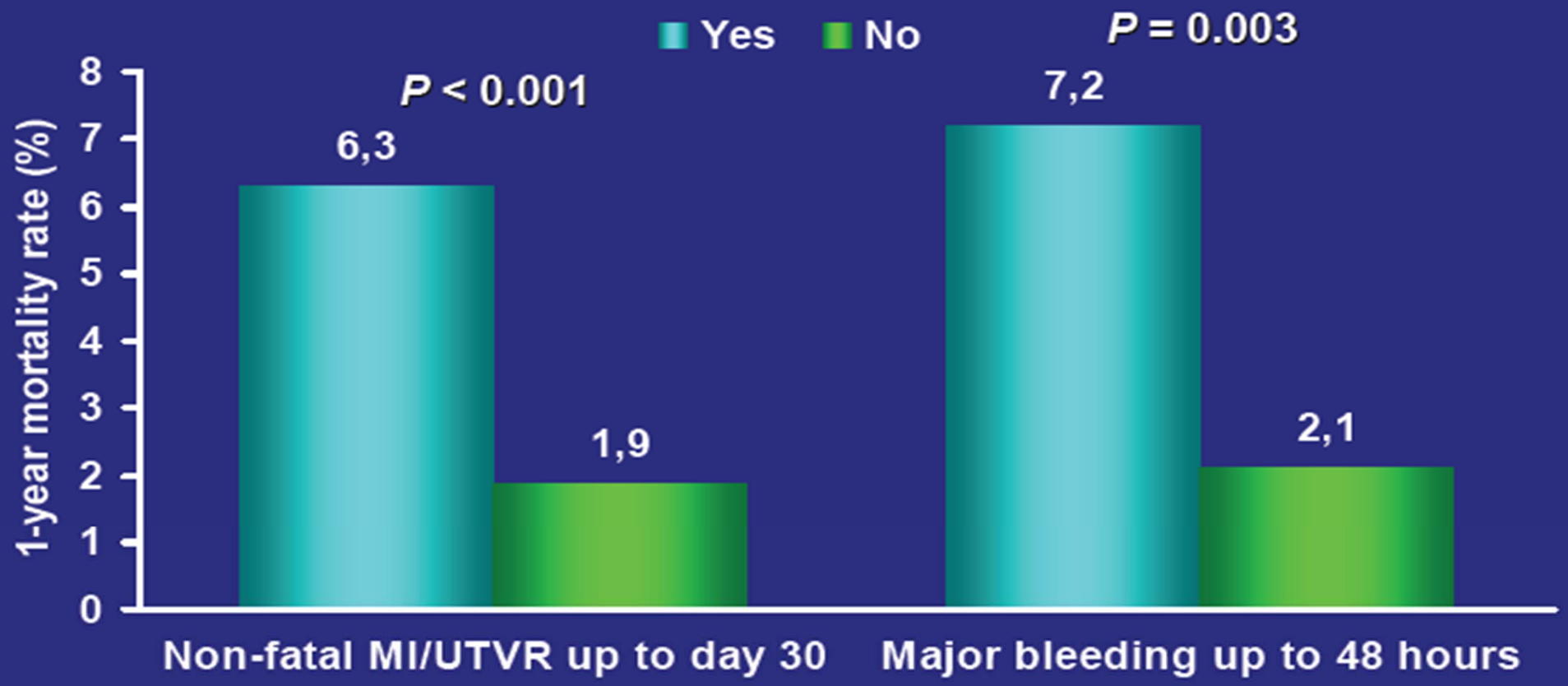
STEEPLE
Mortality: 1 month to 1 year



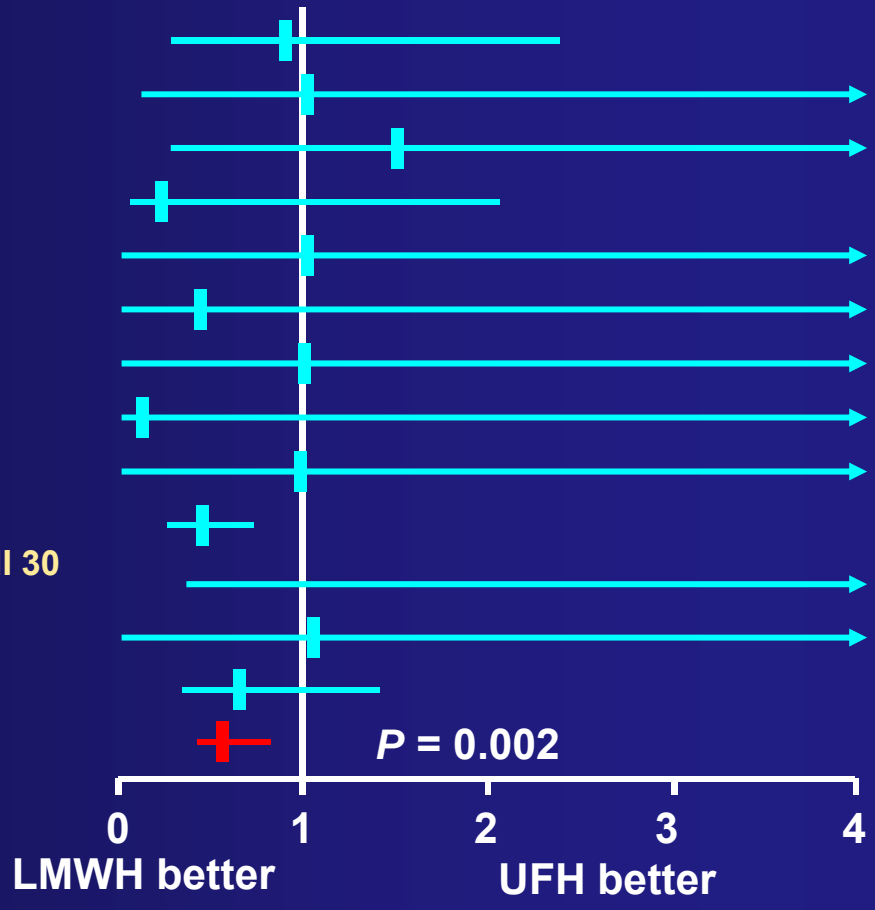
Montalescot G. ESC 2007 presentation

STEEPLE

Effects of Initial Ischemic Events & Major Bleeding on 1-Year Mortality



Meta-Analysis: IV LMWH in PCI (N = 7,318; 13 Studies)



	LMWH	UFH	OR (95% CI)
	——Events/n ——		
REDUCE	7/306	8/306	0.88 (0.32 – 2.41)
Rabah	1/30	1/30	1.00 (0.08 – 12.58)
CRUISE	3/129	2/132	1.49 (0.27 – 8.30)
Galeote	1/50	4/49	0.27 (0.04 – 2.07)
Dudek	0/200	0/200	1.00 (0.00 – 256.80)
Dudek	0/112	0/50	0.45 (0.00 – 115.71)
Drozd	0/50	0/50	1.00 (0.00 – 259.46)
Natarajan	0/160	2/161	0.11 (0.00 – 6.93)
ACTION	0/100	0/100	1.00 (0.00 – 257.69)
STEEPLE	28/2,298	34/1,230	0.43 (0.26 – 0.72)
PROTECT–TIMI 30	4/262	0/298	19.63 (0.35 – ~~~)
Her	0/68	0/71	1.04 (0.00 – 269.83)
ZEUS	11/436	17/440	0.65 (0.30 – 1.39)
Total			0.57 (0.40 – 0.82)

- 43%

Dumaine R, et al. *Arch Intern Med*. 2007;167(22):2423-2430.

STEEPLE: Conclusions

(1) IV enoxaparin in patients to undergo elective PCI

- less bleeding and similar efficacy compared with UFH.

(2) enoxaparin - superior ease of use compared with UFH

- Single IV bolus before the start of PCI
- Similar dose with or without GP IIb/IIIa inhibitors
- No anticoagulation monitoring
- Possibility of immediate sheath pull after PCI with

  Enoxaparin 0.5 mg/kg

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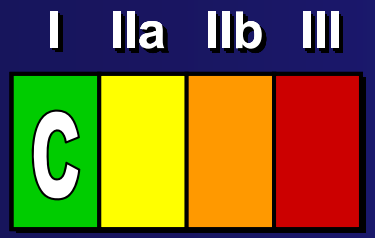
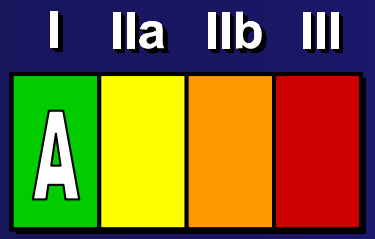
    3) PCI: ExTract TIMI 25 PCI sub-analysis
    4) Primary PCI: FINESSE, ATOLL
    5) Global registry; FAST-MI, ACOS, KAMIR

ACC/AHA 2009 STEMI Guidelines

Focused Update

ACC/AHA – Anticoagulants for STEMI





Patients undergoing reperfusion with fibrinolytics should receive anticoagulant therapy for a minimum of 48 hours *(Level of Evidence: C)* and preferably for the duration of the index hospitalization, up to 8 days

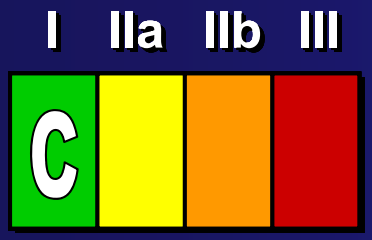
(regimens other than unfractionated heparin [UFH] are recommended if anticoagulant therapy is given for more than 48 hours because of the risk of heparin-induced thrombocytopenia with prolonged UFH treatment). *(Level of Evidence: A)*

Anticoagulant regimens with established efficacy include:

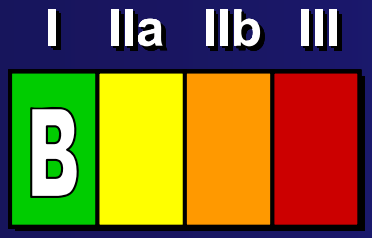
- **UFH *(LOE: C)***
- **Enoxaparin *(LOE:A)***
- **Fondaparinux *(LOE:B)***

ACC/AHA – Anticoagulants for STEMI

For patients proceeding to primary PCI who have been treated with ASA and a thienopyridine, recommended supportive anticoagulant regimens include the following

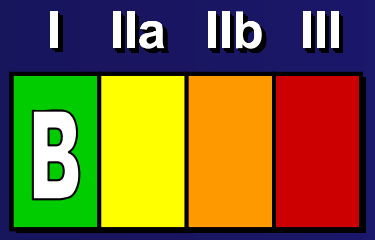


For prior treatment with UFH, additional boluses of UFH should be administered as needed to maintain therapeutic activated clotting time levels, taking into account whether GP IIb/IIIa receptor antagonists have been administered. (*Level of Evidence: C*)

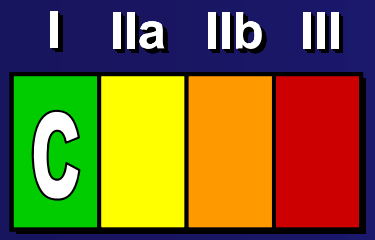


Bivalirudin is useful as a supportive measure for primary PCI with or without prior treatment with UFH (*Level of Evidence: B*)

ACC/AHA – Anticoagulants for STEMI

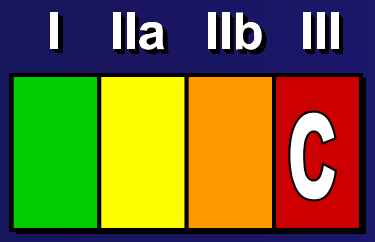


For prior treatment with **Enoxaparin**:
if the last SC dose was administered within the prior 8 hours, no additional enoxaparin should be given;
if the last SC dose was administered at least 8 to 12 hours earlier, an IV dose of 0.3 mg/kg of enoxaparin should be given. (Level of Evidence: **B**)



For prior treatment with **Fondaparinux**:
administer additional intravenous treatment with an anticoagulant possessing anti-IIa activity taking into account whether GP IIb/IIIa receptor antagonists have been administered. (Level of Evidence: **C**)

ACC/AHA – Anticoagulants for STEMI



Because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant to support PCI. An additional anticoagulant with anti-IIa activity should be administered. (Level of Evidence: C)

Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction

ExTRACT-TIMI 25

Background

- **Advantages of ENOX over UFH**

  Greater anti Xa: anti IIa activity

  Reliable A/C without monitoring

  Convenient sc administration

- **Prior trials suggest**

  ENOX may be superior to UFH

- **Pharmacologic reperfusion remains the most common treatment for STEMI**

  Definitive evaluation of ENOX vs. UFH needed

ExTRACT TIMI 25

Protocol Design

N = 20,506
674 sites
48 countries

STEMI < 6 h
Lytic eligible

ASA

Lytic choice by MD
(TNK, tPA, rPA, SK)

Double-blind, double-dummy

ENOX

< 75 y: 30 mg IV bolus
SC 1.0 mg / kg q 12 h (Hosp DC)

≥ 75 y: No bolus
SC 0.75 mg / kg q 12 h (Hosp DC)

CrCl ≤ 30: 1.0 mg / kg q 24 h

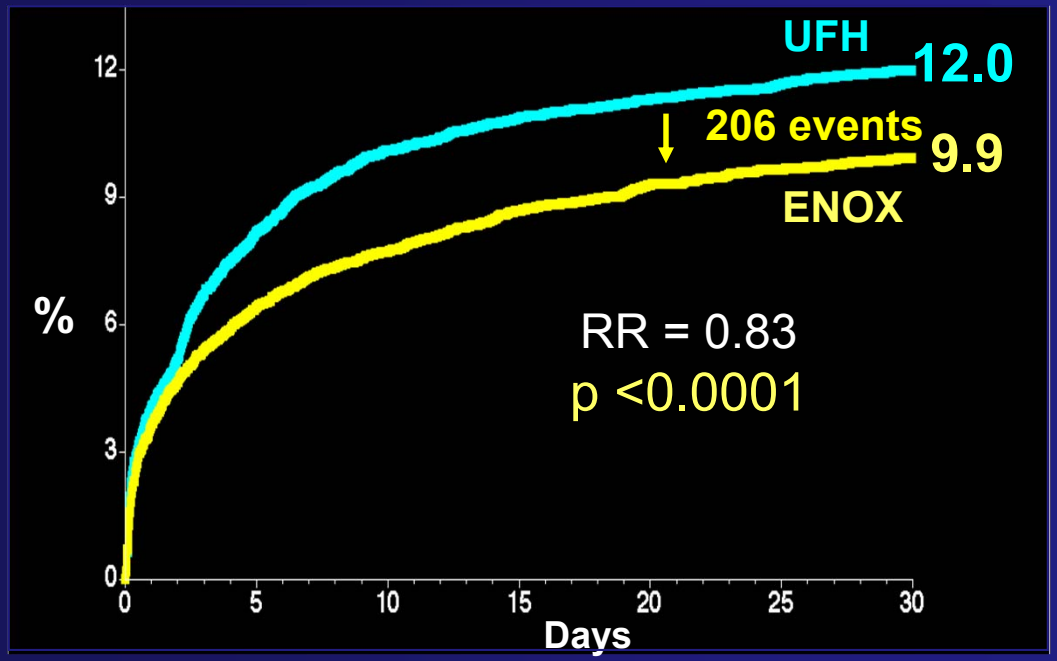
UFH

60 U / kg bolus (4000 U)
Inf 12 U / kg / h (1000 U / h)
Duration: at least 48 h
Cont'd at MD discretion

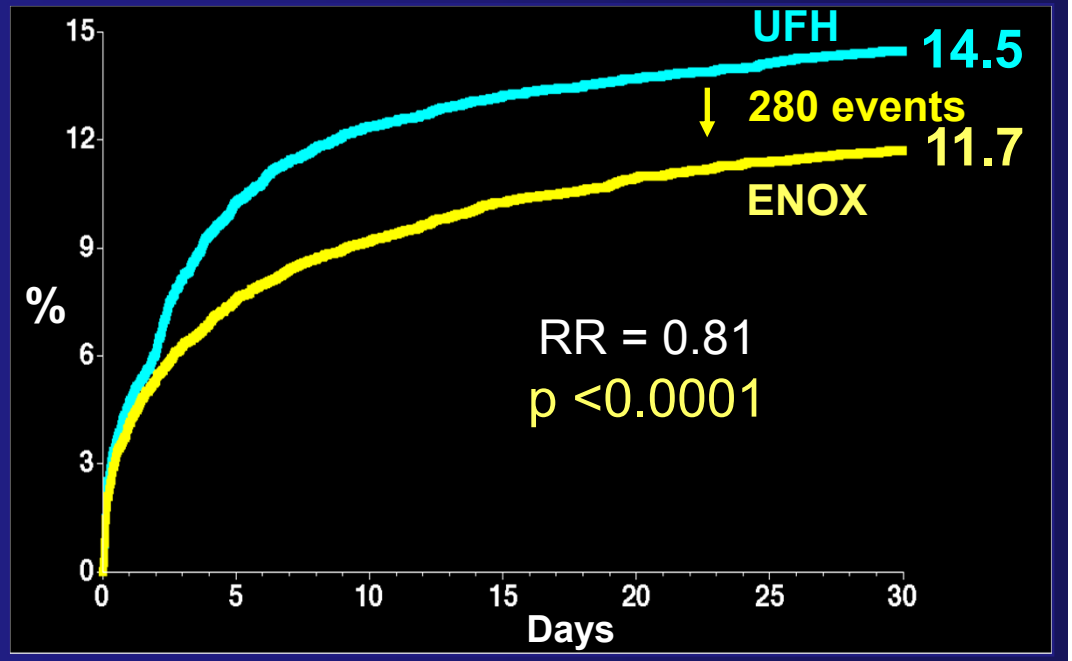
1° Efficacy Endpoint: Death or Nonfatal MI at 30 days
Additional F/U at 6 mo and 1 yr

Main Results - 30 days

Primary Endpoint:
Death or non-fatal re-MI by 30 days



Main Secondary Endpoint:
Death, non-fatal re-MI, urgent revascularization by 30 days



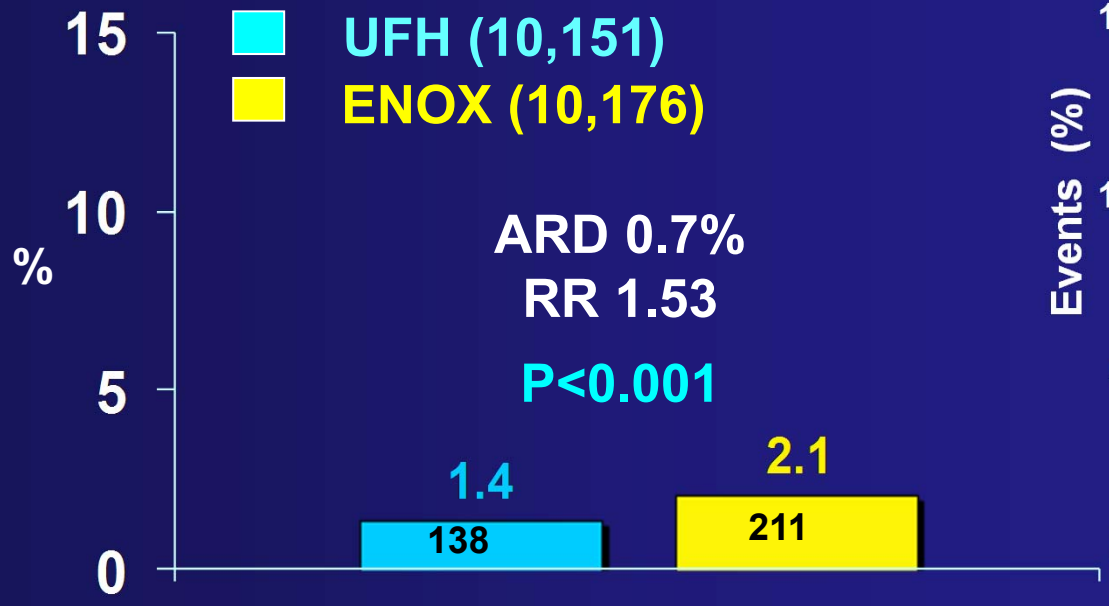
33% RRR in reMI by 48 h (P=0.002)
19% RRR in Death/MI by 72 h (P<0.001)

12% RRR in by 48 h (P=0.02)

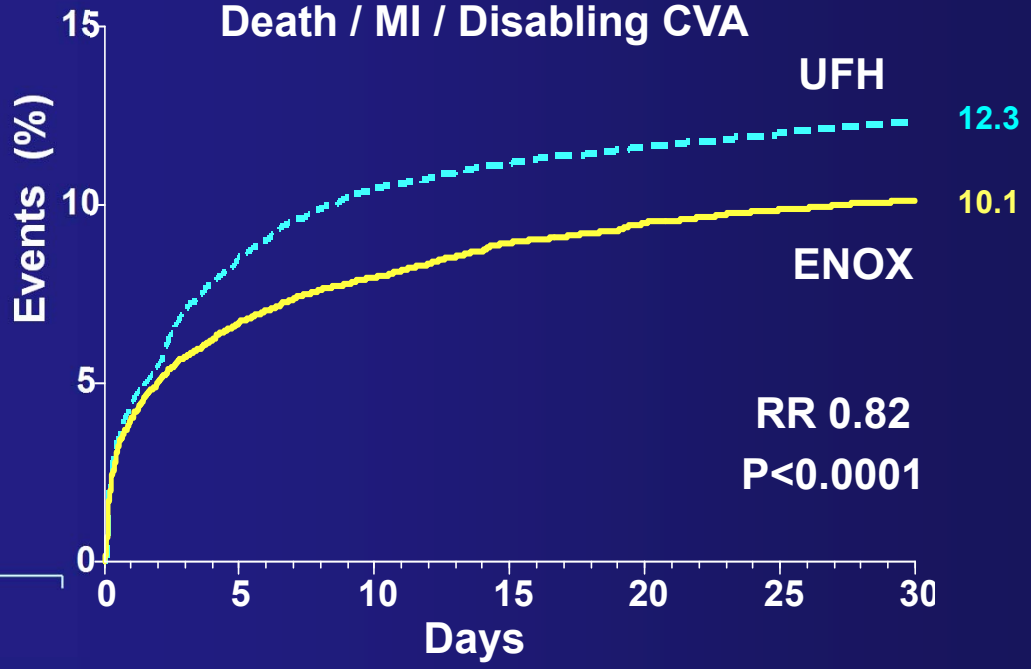
N Engl J Med 2006;354:1477-88.

30 days: Major Bleeds and Net Clinical Benefit

Major Bleeds (TIMI)



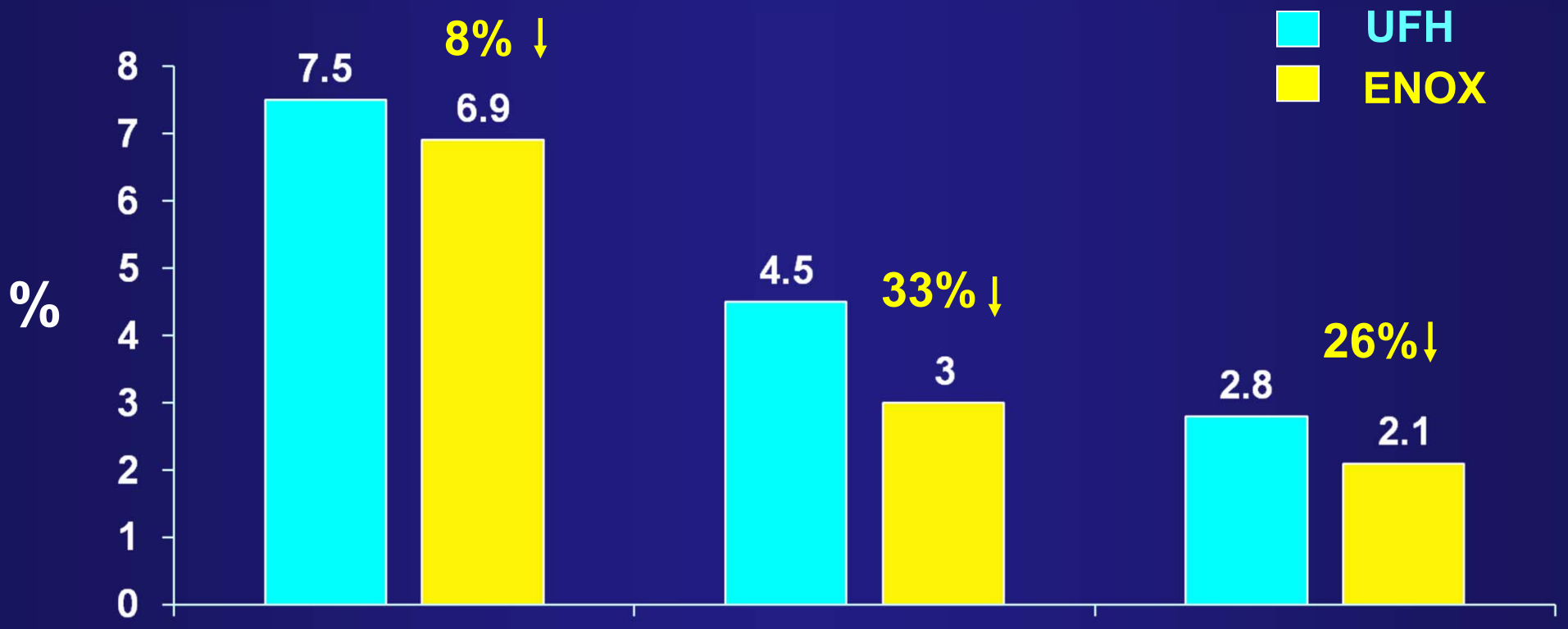
Net Clinical Benefit



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

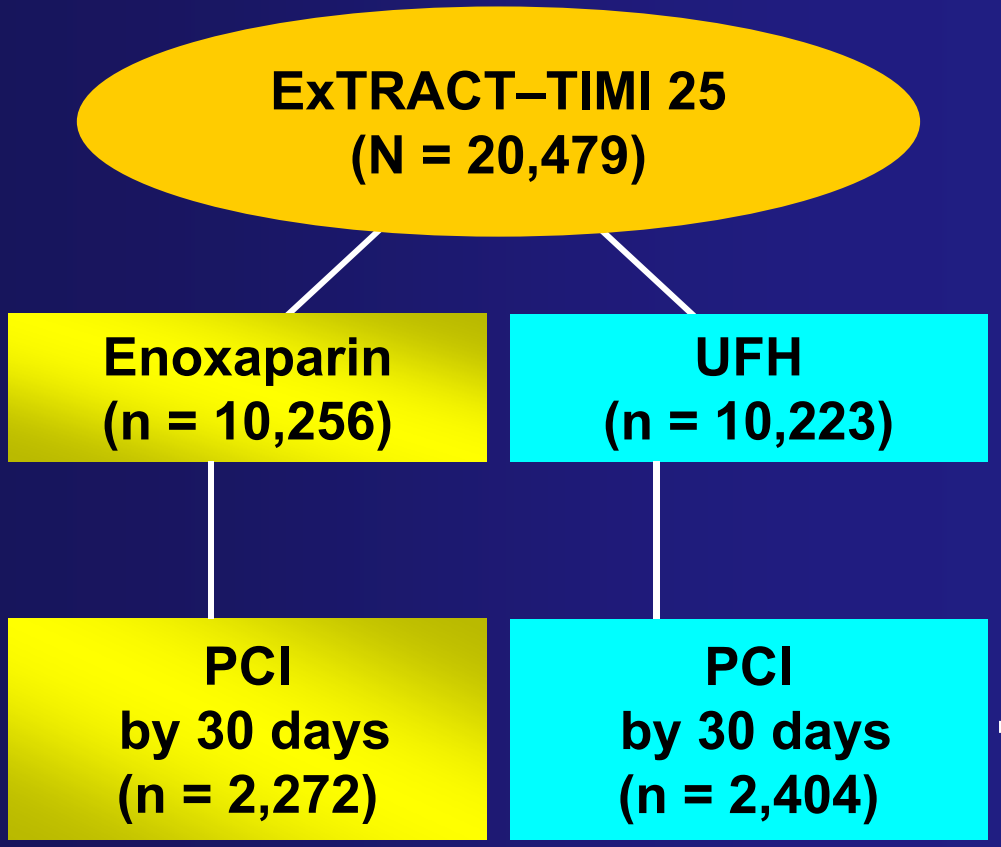
ExTRACT TIMI 25

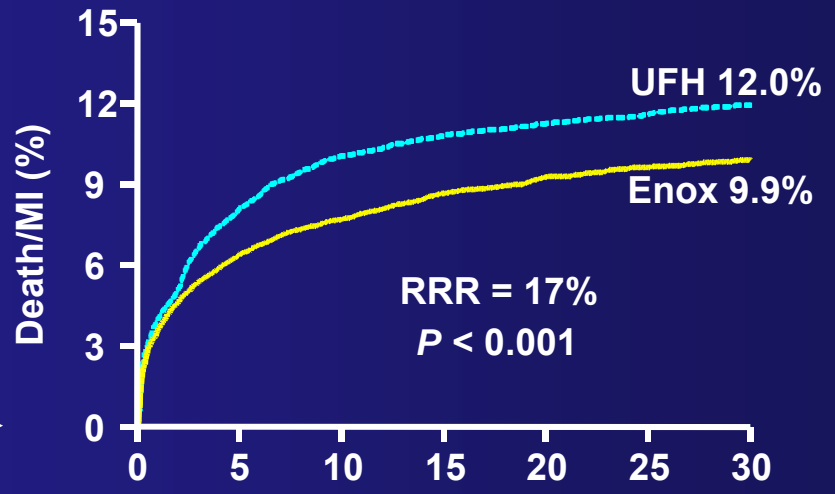
Outcomes at 30 Days (ITT)

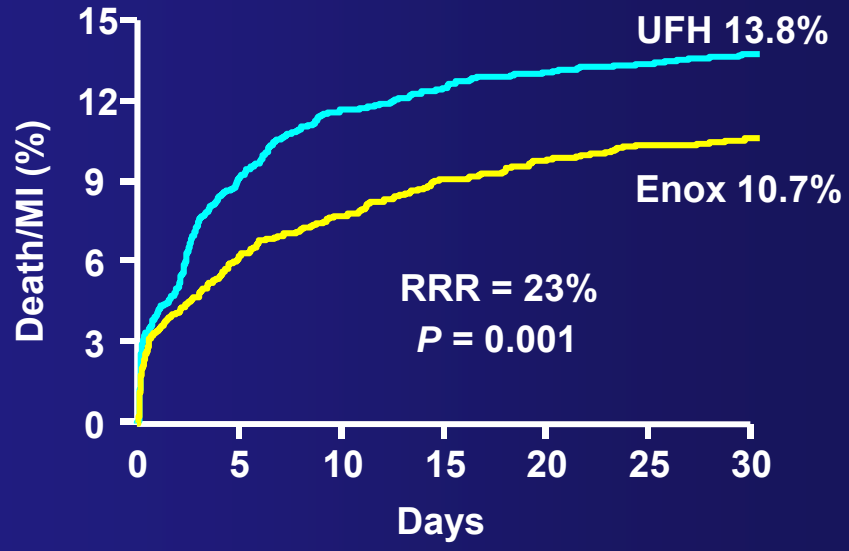


	Death	Nonfatal MI	Urg Revasc
RR	0.92	0.67	0.74
P value	0.11	<0.0001	0.0008

ExTRACT–TIMI 25: whole & PCI subgroup

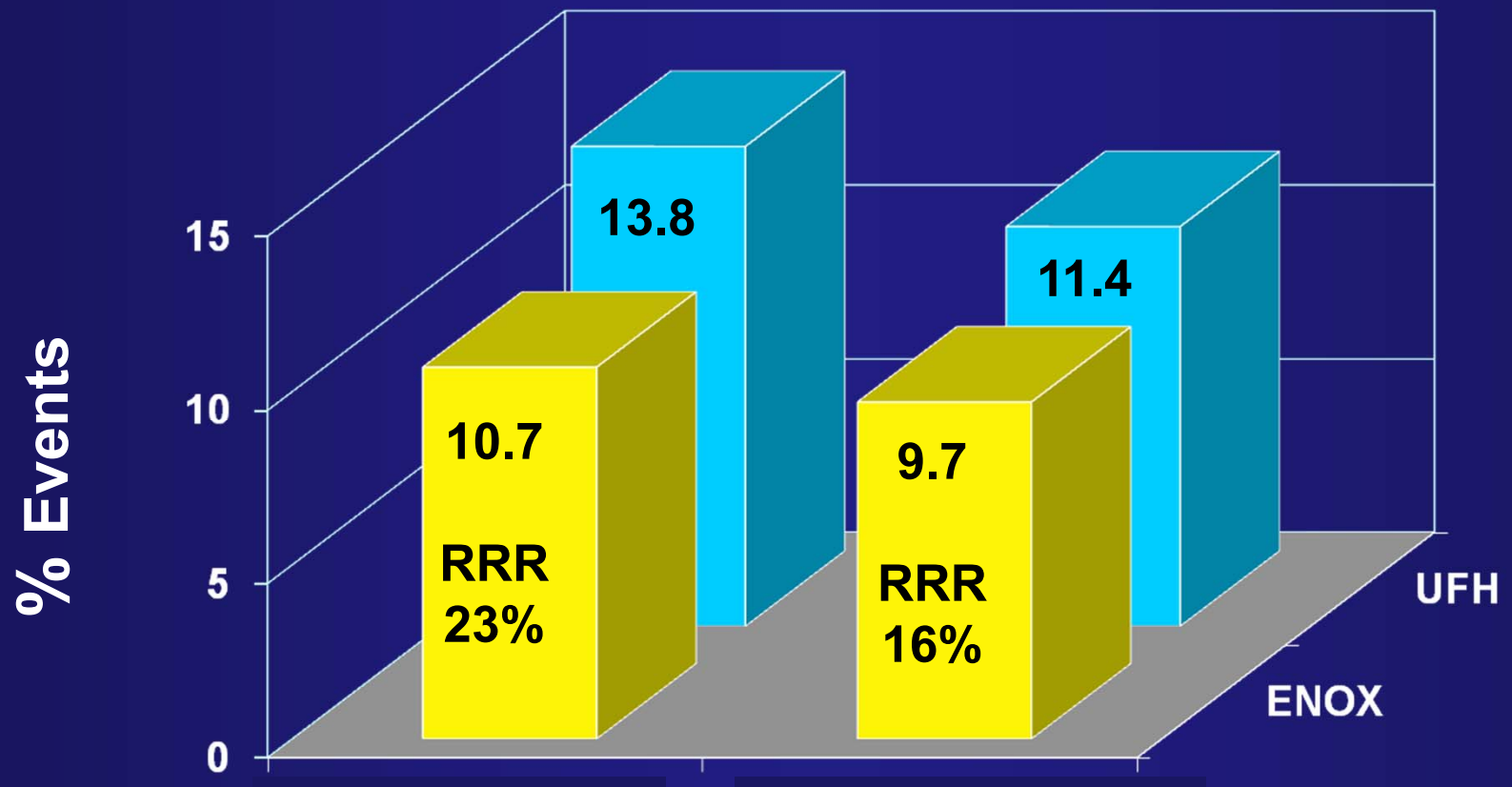






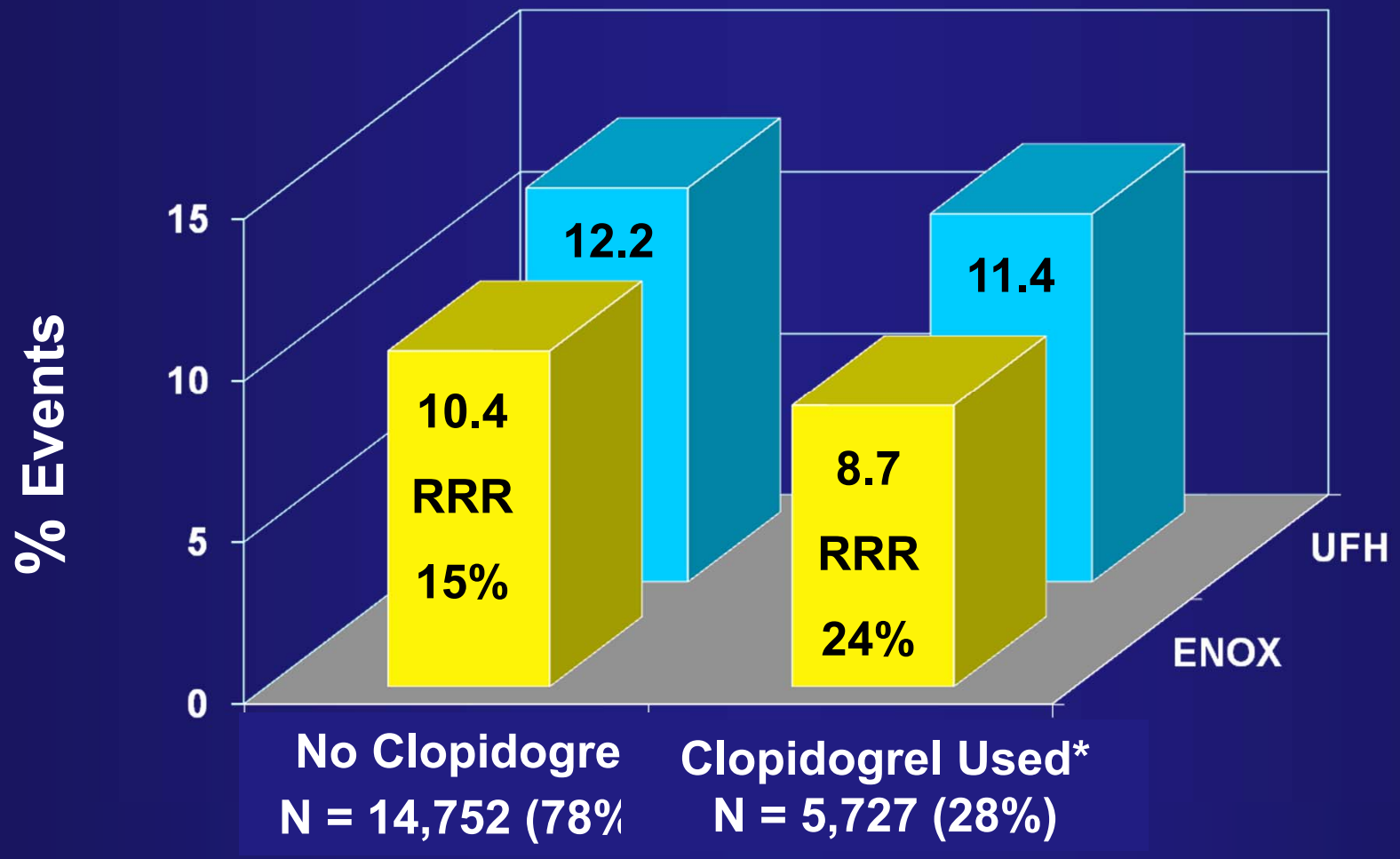
Antman EM, et al. *N Engl J Med* 2006;354:1477-1488.
Gibson CM, et al. *J Am Coll Cardiol* 2007;49:2238-2246.

Death or Nonfatal MI - Day 30
Medical Rx vs Any PCI



P Value 0.001 0.0004

Death or Nonfatal MI - Day 30 depending on Clopidogrel Use



P Value 0.0005 0.0006

* 2546 clopidogrel treated patients did not undergo PCI

ExTRACT-TIMI 25: Conclusions

- In > 20,000 STEMI patients,
- Enoxaparin : reduction of death / MI at 30 days by 17%

  vs. IV UFH (9.9% vs. 12.0%, p=0.0001).

- This effect is seen early (48 hours) and is consistent across all subgroups.

Primary / Facilitated PCI

FINESSE: LMWH substudy

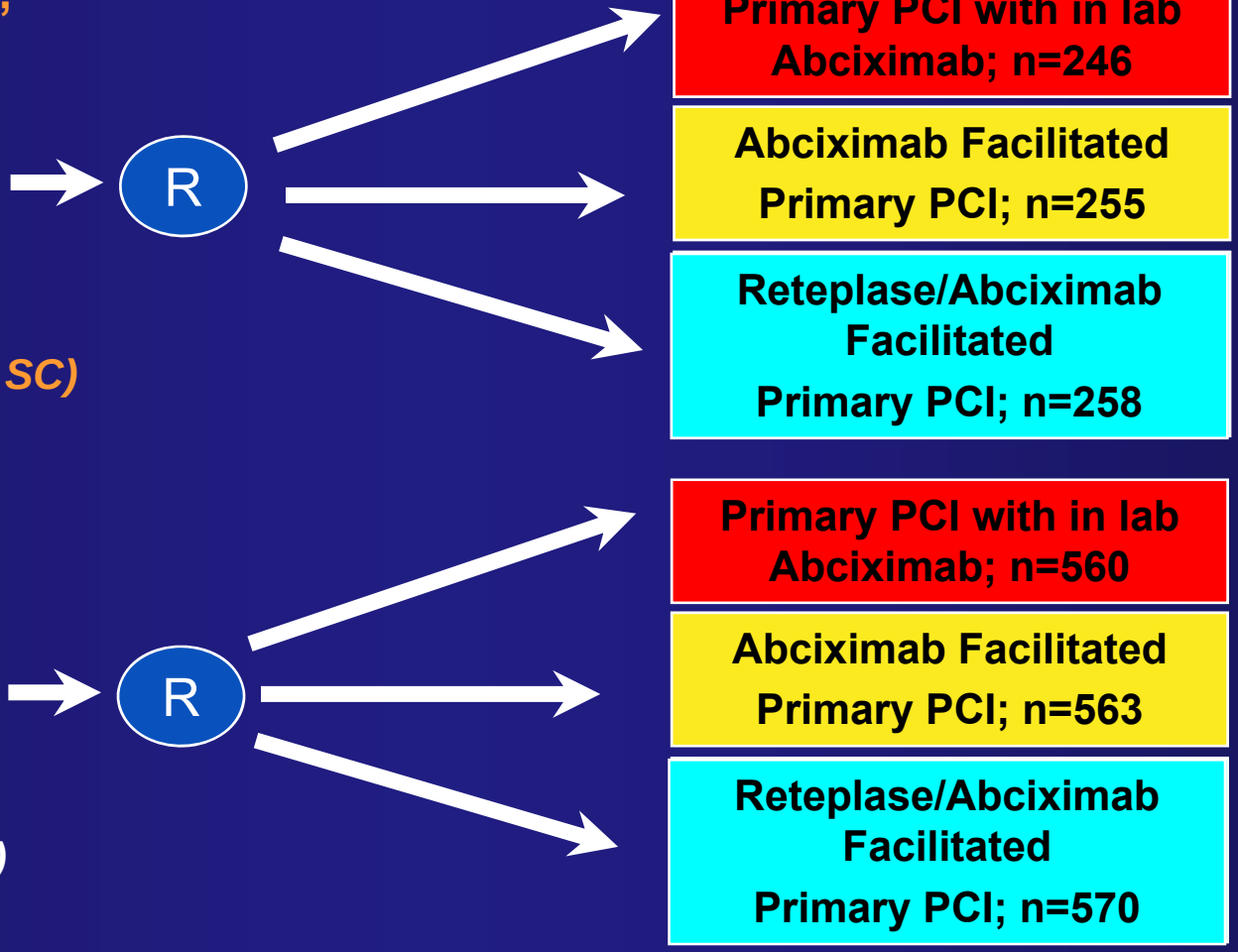
To compare safety and efficacy between LMWH and UFH

"LMWH Substudy"
N=759

With Enoxaparin
(0.5 mg/kg IV, 0.3 mg/kg SC)

"Main Study"
N=1693

Heparin
(40U/kg, 3000U max)



Montalescot G. Presented at TCT 2007.

Montalescot G et al. *JACC Cardiovasc Interv* 2010; 3:203–212.

FINESSE LMWH substudy: Bleeding results

Outcome	Enoxaparin (%)	Heparin (%)	Adjusted OR	p
Major bleeding	2.6	4.4	0.55	0.0451
Minor bleeding	9.5	5.4	1.68	0.009
Major or minor bleeding	12.0	9.9	1.17	0.334

Montalescot G et al. *JACC Cardiovasc Interv* 2010; 3:203–212.

FINESSE- LMWH substudy ; efficacy

Outcome	Enoxaparin (%)	Heparin (%)	Adjusted OR	p
Death, MI, urgent revascularization, refractory ischemia through 30 d	5.3	8.0	0.47	0.0005
All cause mortality at 90 d	3.8	5.6	0.59	0.0462
Death/MI at 30 d	4.0	5.6	0.58	0.0356

Montalescot G et al. *JACC Cardiovasc Interv* 2010; 3:203–212.

Net adverse clinical outcome

Enoxaparin (%)	Heparin (%)	Adjusted OR	Adjusted p
8.2	11.7	0.64	0.0134

1. Enoxaparin was associated with a 30% lower relative risk of death or MI through 30 days.
2. Intravenous enoxaparin over UFH was associated with a lower risk of both major TIMI bleeding and ischemic events in primary PCI of STEMI."

Montalescot G et al. *JACC Cardiovasc Interv* 2010; 3:203–212.

ESC, Stockholm - August 30, 2010 – Hotline session

ATOLL

An international randomized study comparing IV enoxaparin to IV UFH in primary PCI

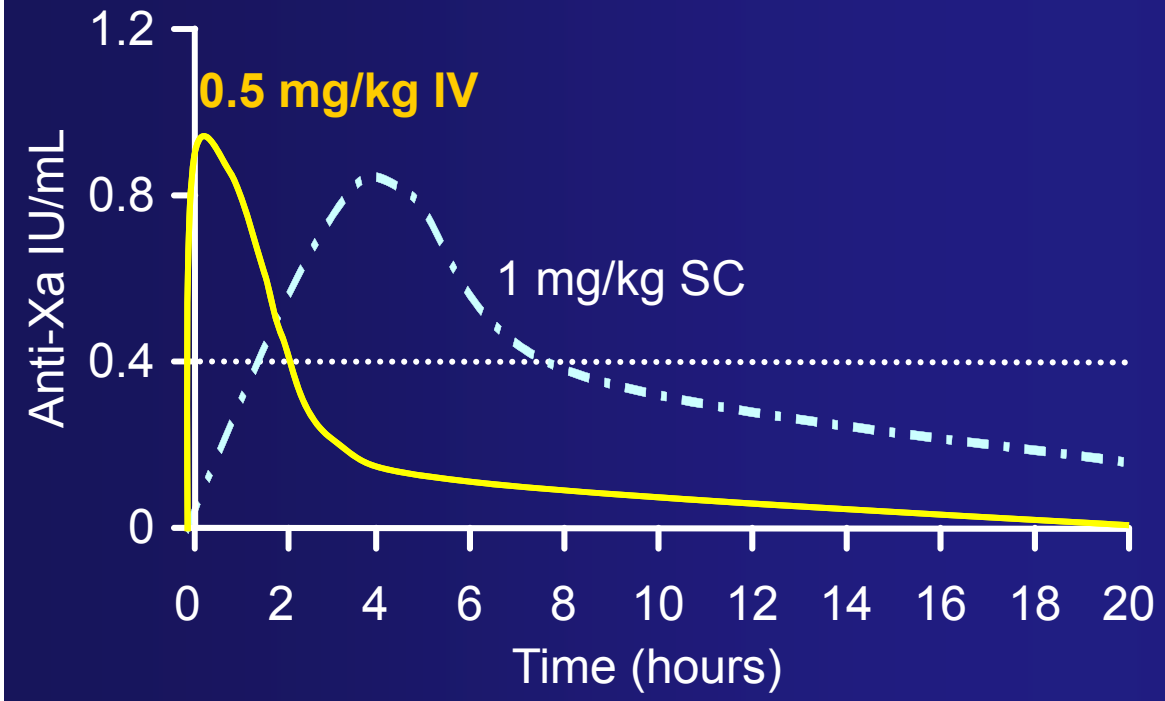
G. Montalescot, M. Cohen, P. Goldstein,
K. Huber, C. Pollack, U. Zeymer, E. Vicaut
for the ATOLL investigators

ATOLL: **A**cute STEMI **T**reated with primary PCI and intravenous enoxaparin **O**r UFH to **L**ower ischemic and bleeding events at short- and **L**ong-term follow-up (Investigator-driven study)

G. MONTALESCOT, DISCLOSURE: **Research Grants (to the Institution)** from Abbott Vascular, Bristol Myers Squibb, Boston Scientific, Centocor, Cordis, Eli-Lilly, Fédération Française de Cardiologie, Fondation de France, Guerbet Medical, INSERM, Medtronic, Pfizer, Sanofi-Aventis Group, Société Française de Cardiologie; **Consulting or Lecture Fees** from Accumetrics, Astra-Zeneca, Bayer, Biotronik, Boehringer-Ingelheim, Bristol-Myers Squibb, Daichi-Sankyo, Eisai, Eli-Lilly, Menarini, MSD, Novartis, Portola, Sanofi-Aventis Group, Schering-Plough , Servier and The Medicines Company.

Intravenous 0.5mg/kg Enoxaparin

PD experience



Sanchez-Pena P. Br J Clin Pharmacol. 2005;60:364-73.

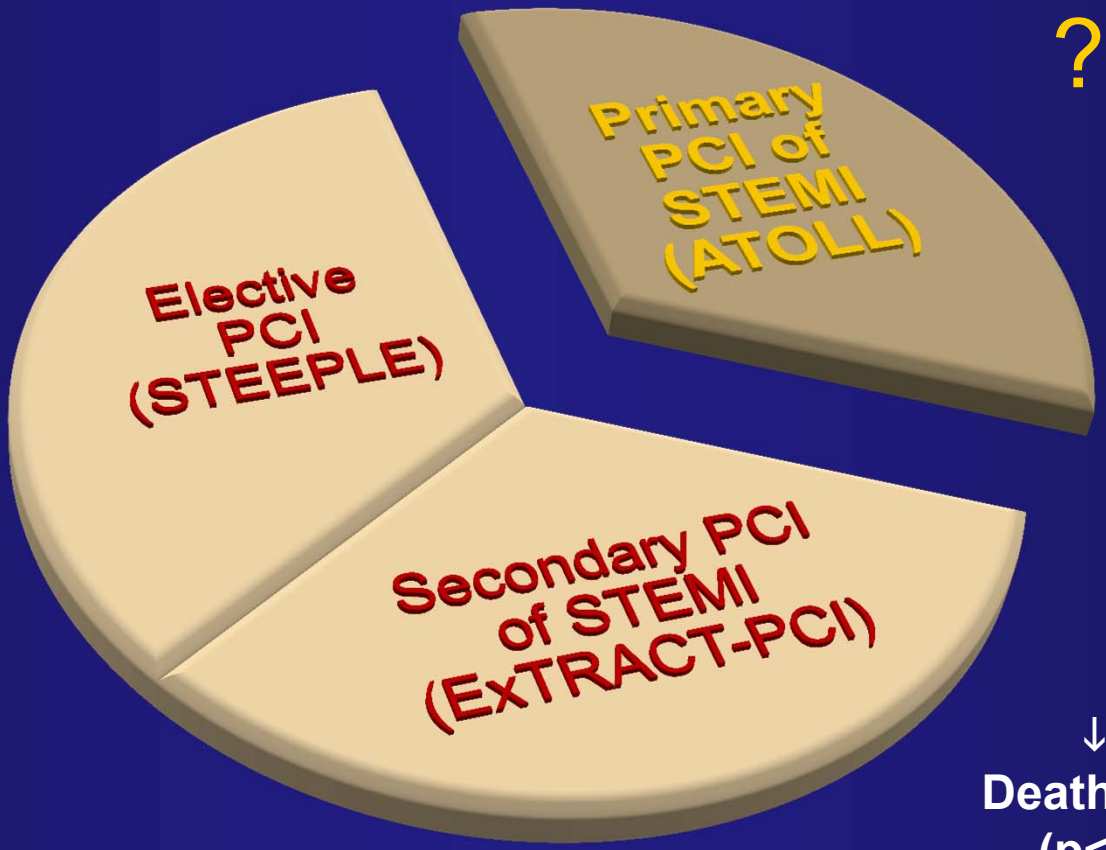
Clinical experience

- Choussat et al (elective PCI)
- Miller et al (ACS-PCI)
- Carnendran et al (elective PCI)
- STEEPLE (elective PCI)
- PROTECT –TIMI30 (ACS-PCI)
- Silvain et al (elective PCI)
- FINESSE (primary PCI)
- Brieger et al. (Primary PCI)

Choussat et al. JACC. 2002;40:1943-50.
Miller L. J Invasive Cardiol. 2002;14:247-50
Carnendran et al. J Invasive Cardiol. 2003;15:235-8.
Montalescot et al. N Engl J Med. 2006;355:1006-17.
Gibson et al. JACC. 2006;47:2364-2373
Silvain et al. JACC. 2010;55:617-25
Montalescot et al. JACC Cardiovasc Interv. 2010;3:203-12
Brieger et al. Catheter Cardiovasc Interv. 2010 [in press]

Intravenous enoxaparin *vs.* UFH in PCI

↓57%
Major Bleeding
(p=0.004)

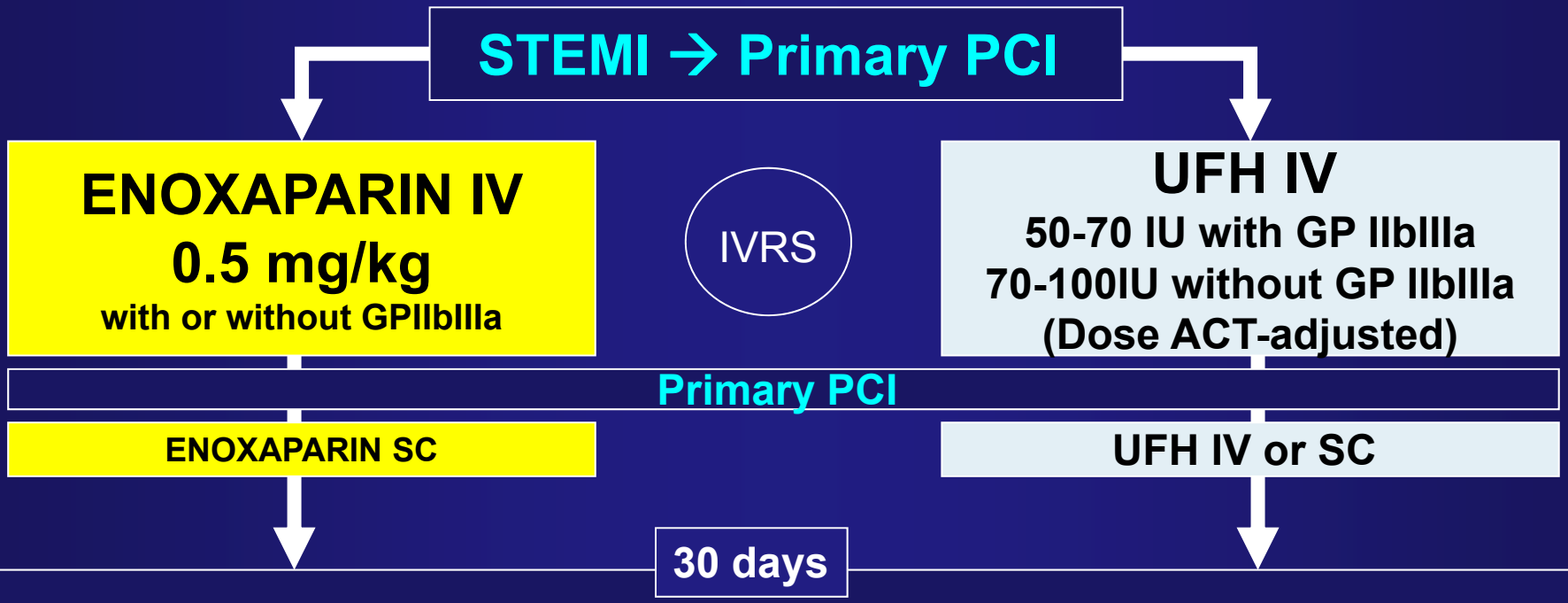


↓23%
Death or re-MI
(p<0.001)

Montalescot G et al. N Engl J Med 2006;355:1006 –17
Gibson MC et al. J Am Coll Cardiol 2007;49:2238–46

ATOLL Trial design

Randomization as *early* as possible (MICU +++)
Real life population (shock, cardiac arrest included)
No anticoagulation and no lytic **before** Rx
Similar antiplatelet therapy in both groups

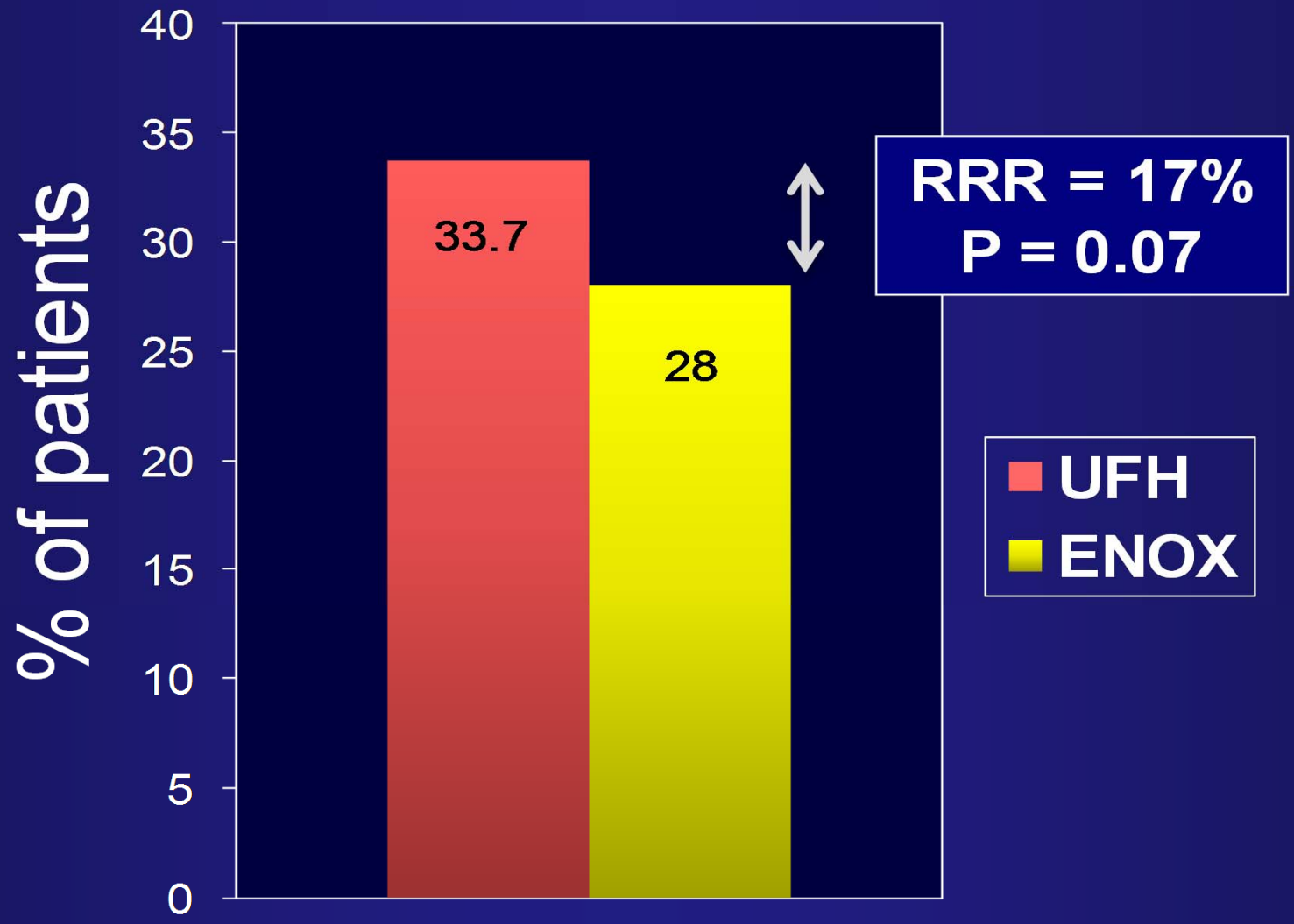


1°EP: **Death, Complication of MI, Procedure Failure, Major Bleeding**

Main 2°EP: **Death, recurrent MI/ACS, Urgent Revascularization**

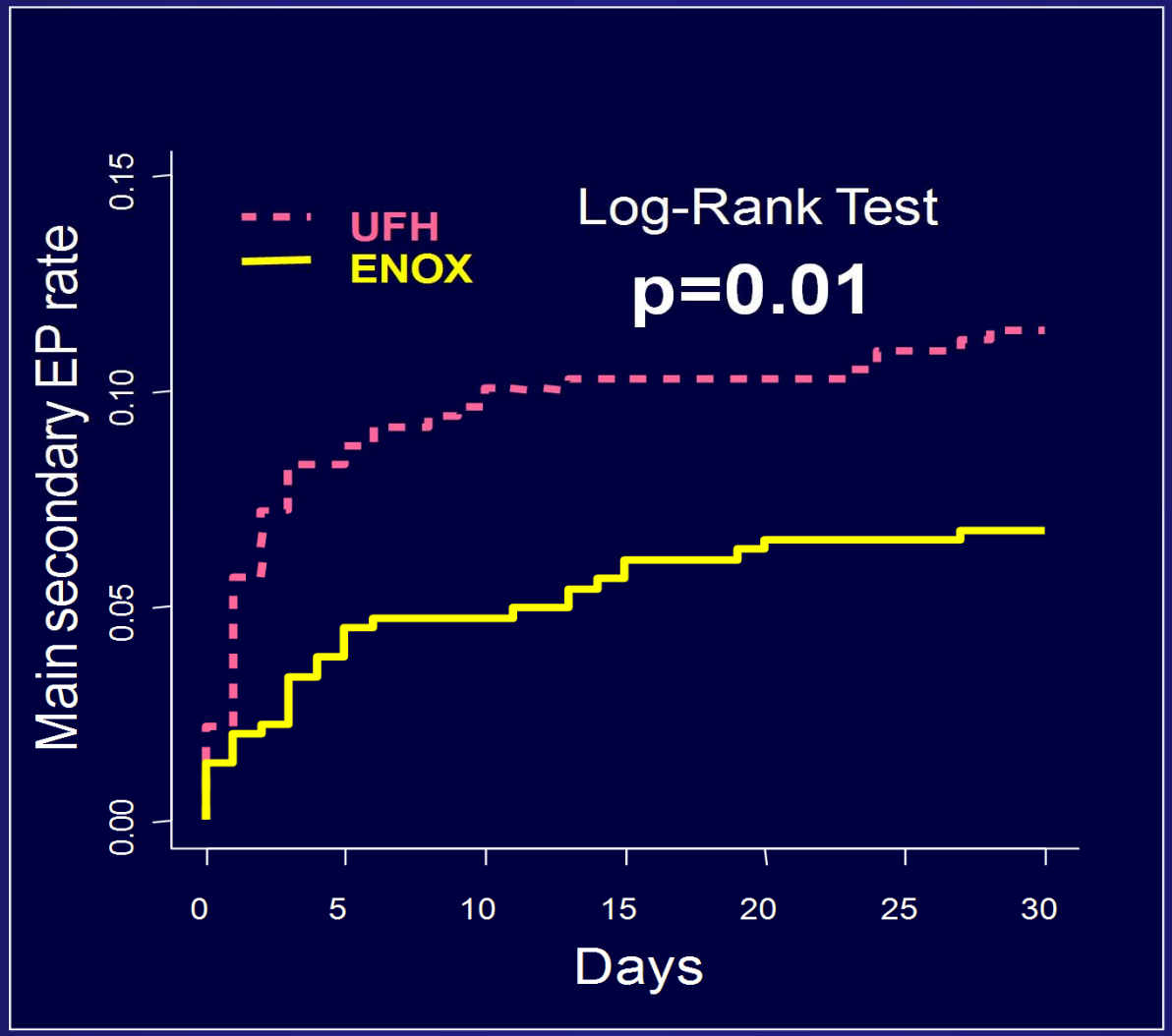
Primary Endpoint

Death, Complication of MI, Procedure Failure or Major Bleeding



Main Secondary Endpoint (ischemic)

Death, Recurrent MI/ACS or Urgent Revascularization



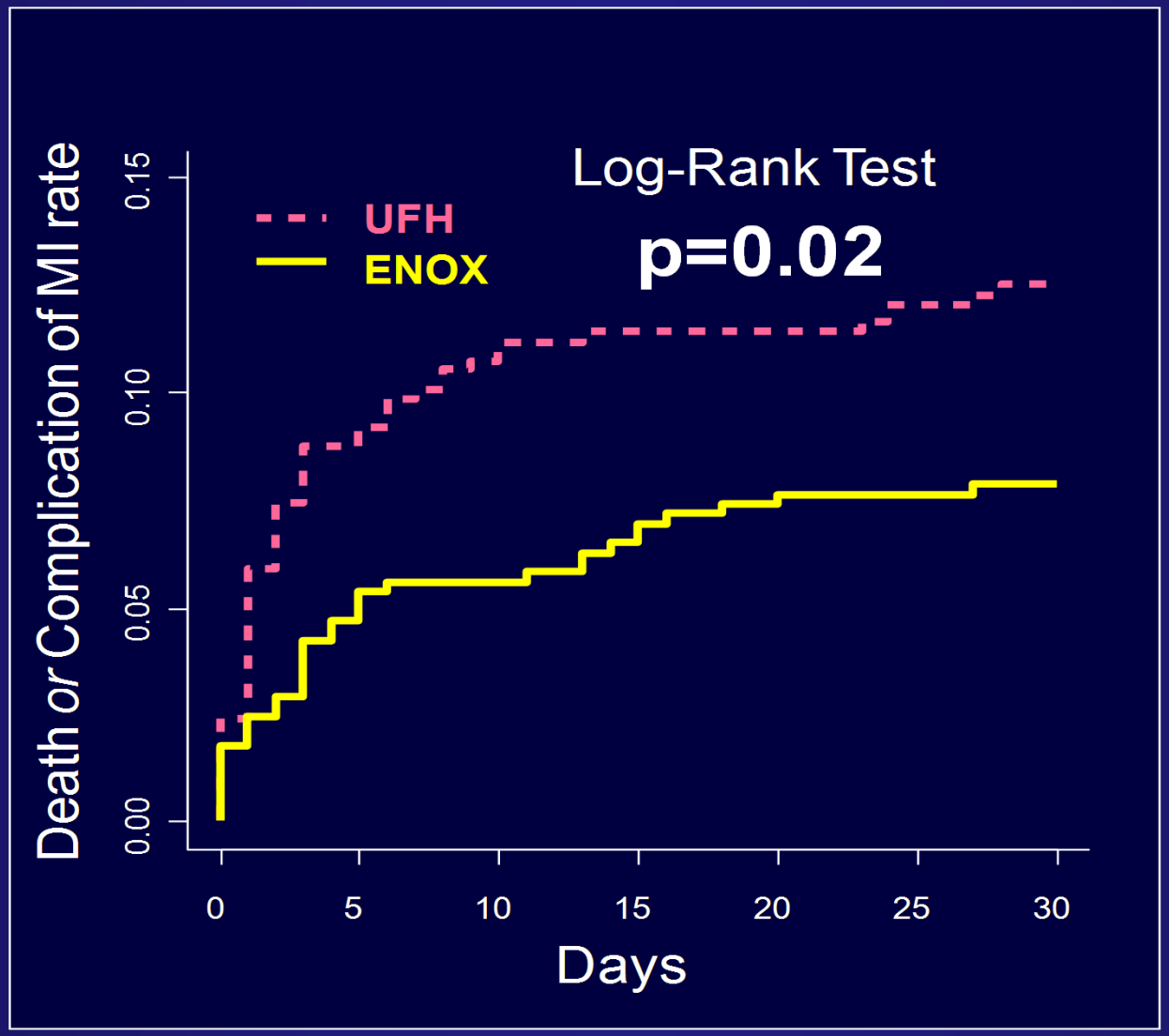
30d rate (%)

11.3%

6.7%

Death or Complication of MI

Death, resuscitated cardiac arrest, recurrent MI/ACS, Urg Revasc, stroke, peripheral or pulmonary embolism



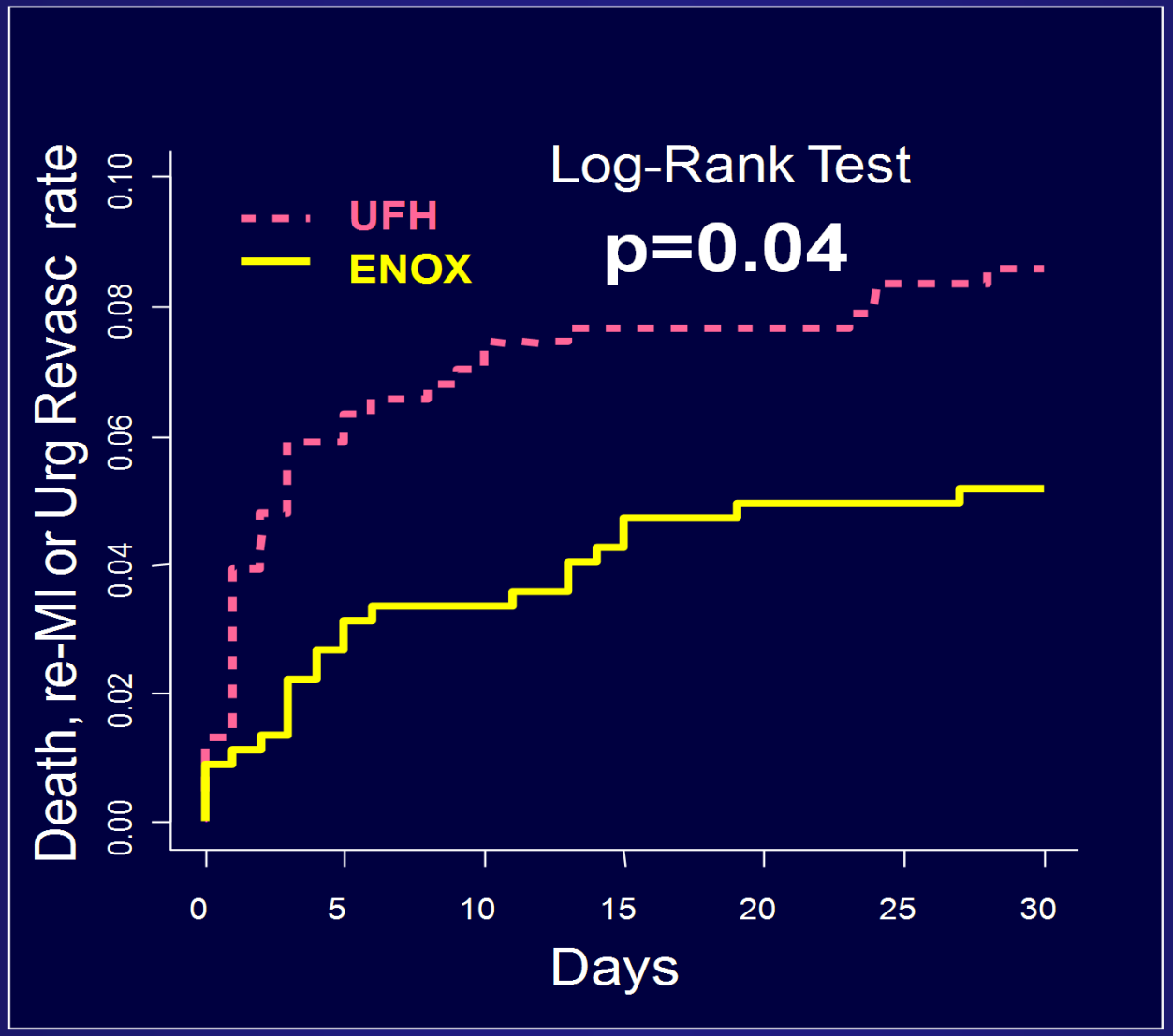
30d rate (%)

12.4%

7.8%

Triple Ischemic Endpoint

Death, re-MI or Urgent Revascularization

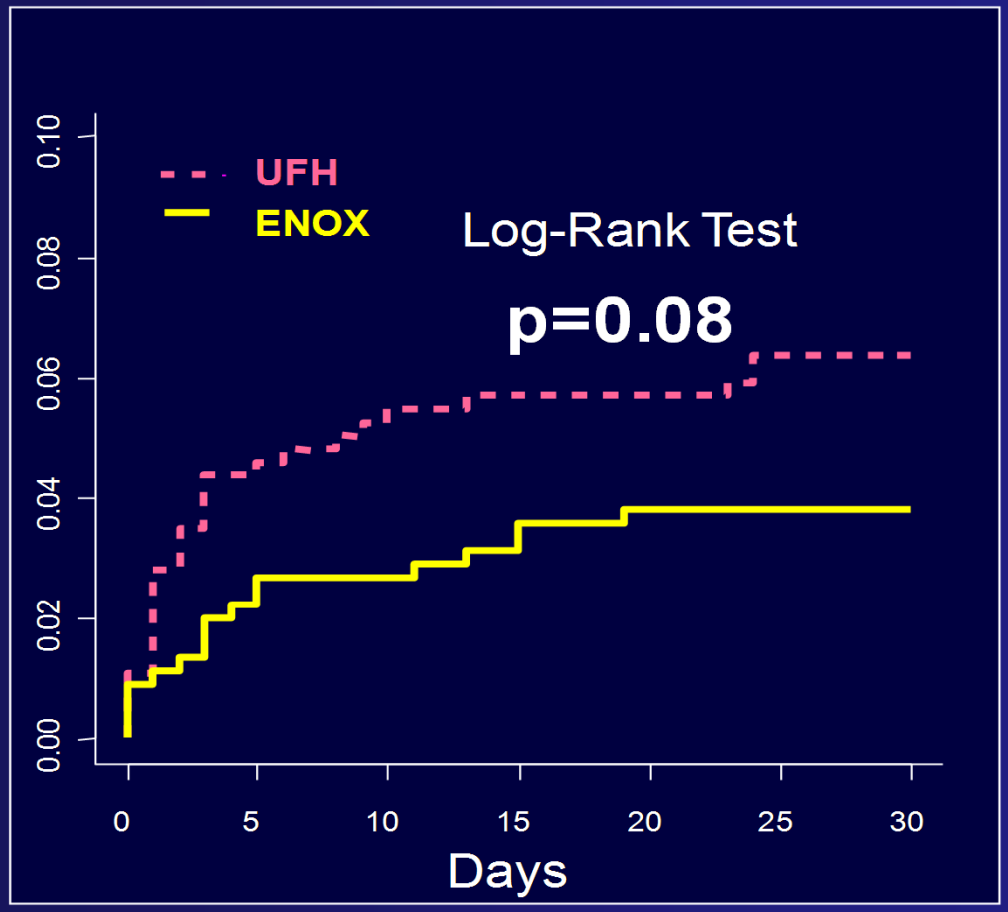


30d rate (%)

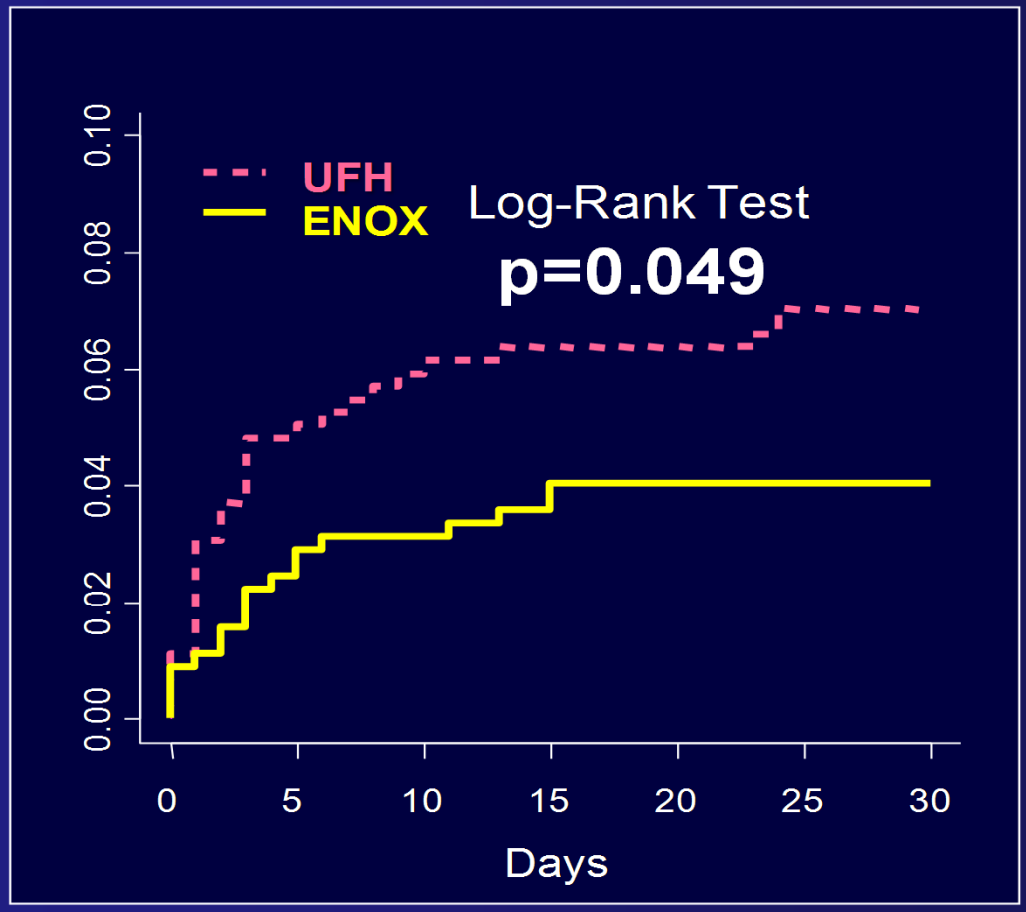
8.5%

5.1%

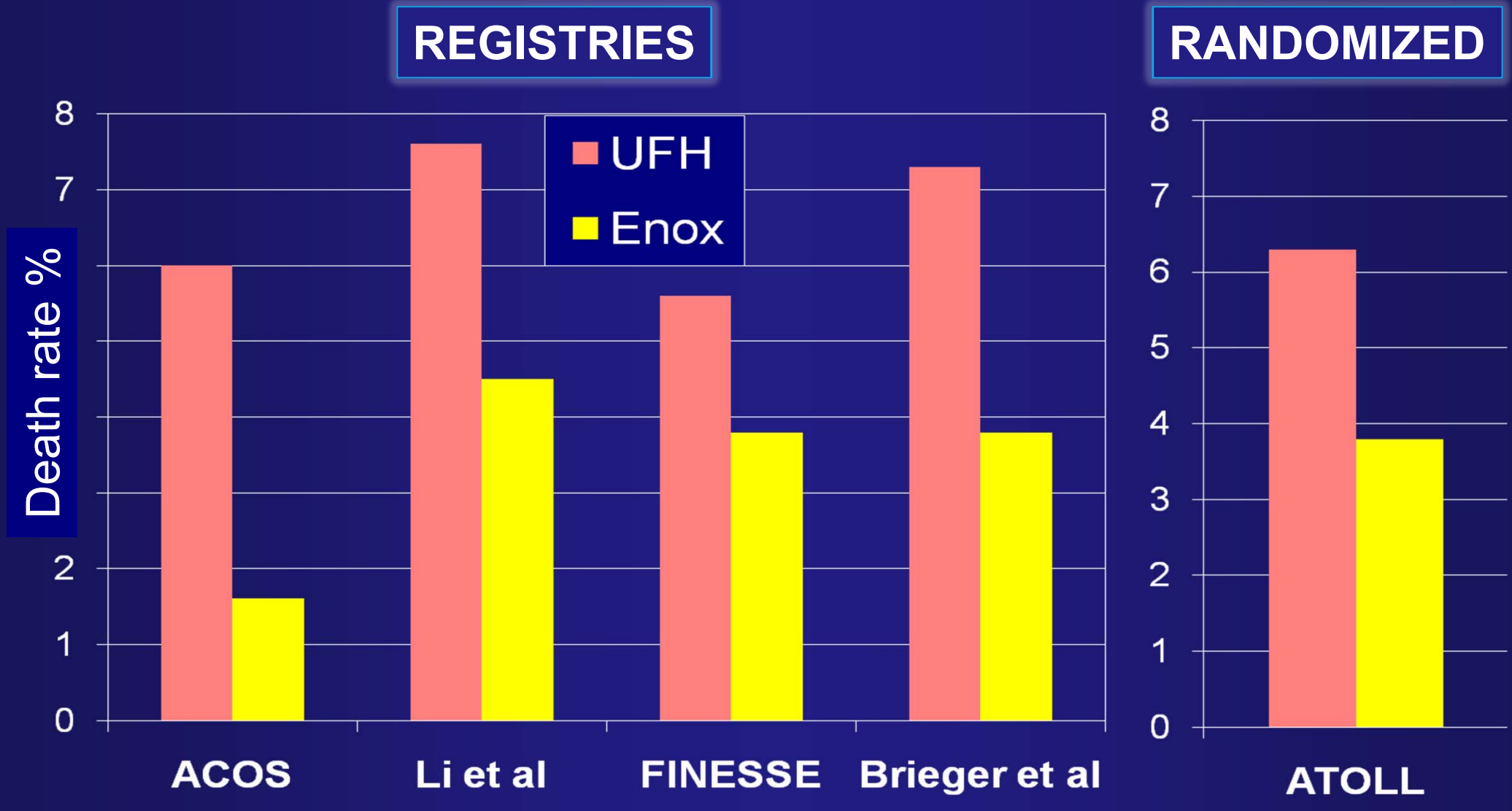
Death (any)



Death *or* resuscitated cardiac arrest



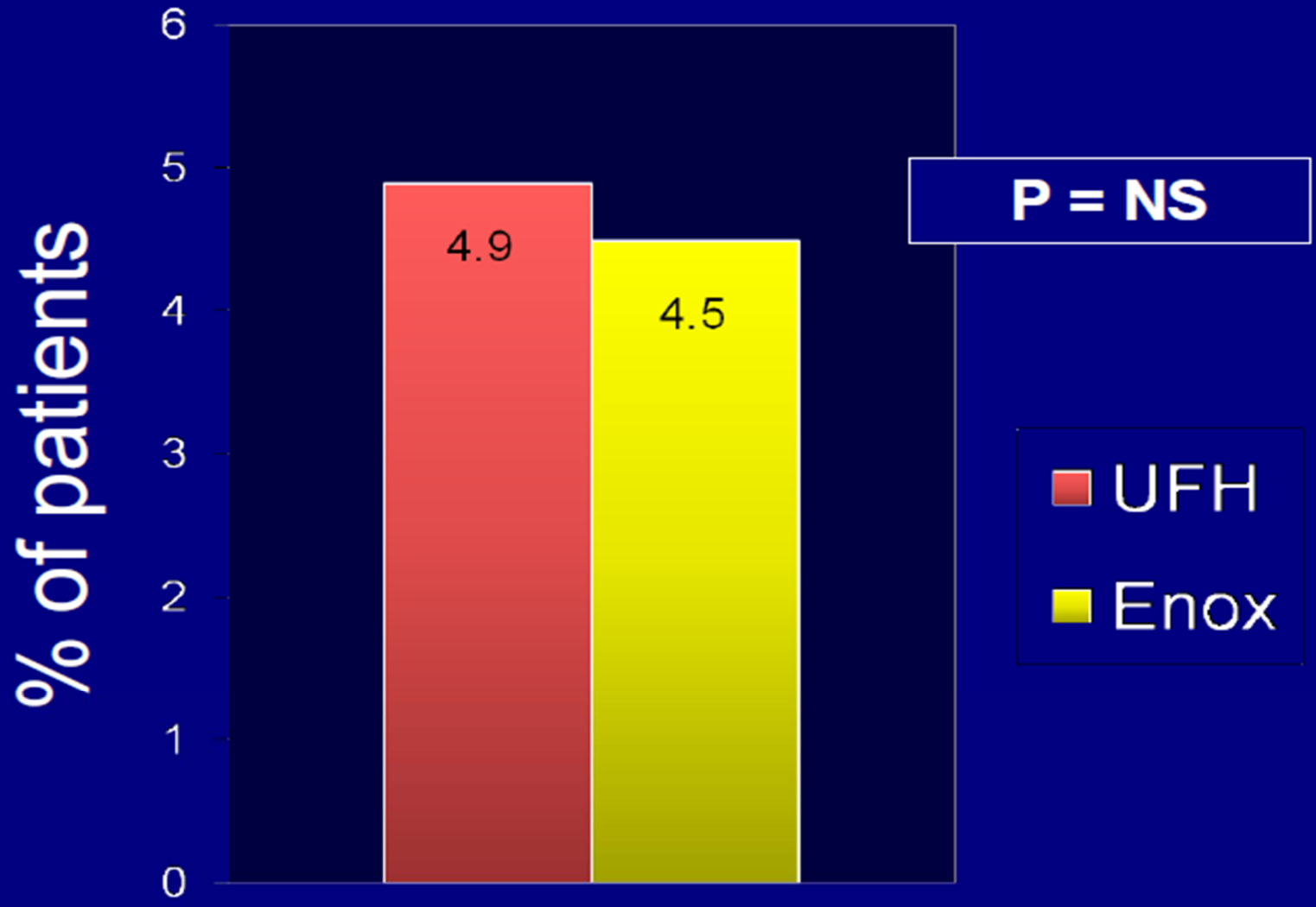
Death finding → Chance finding?



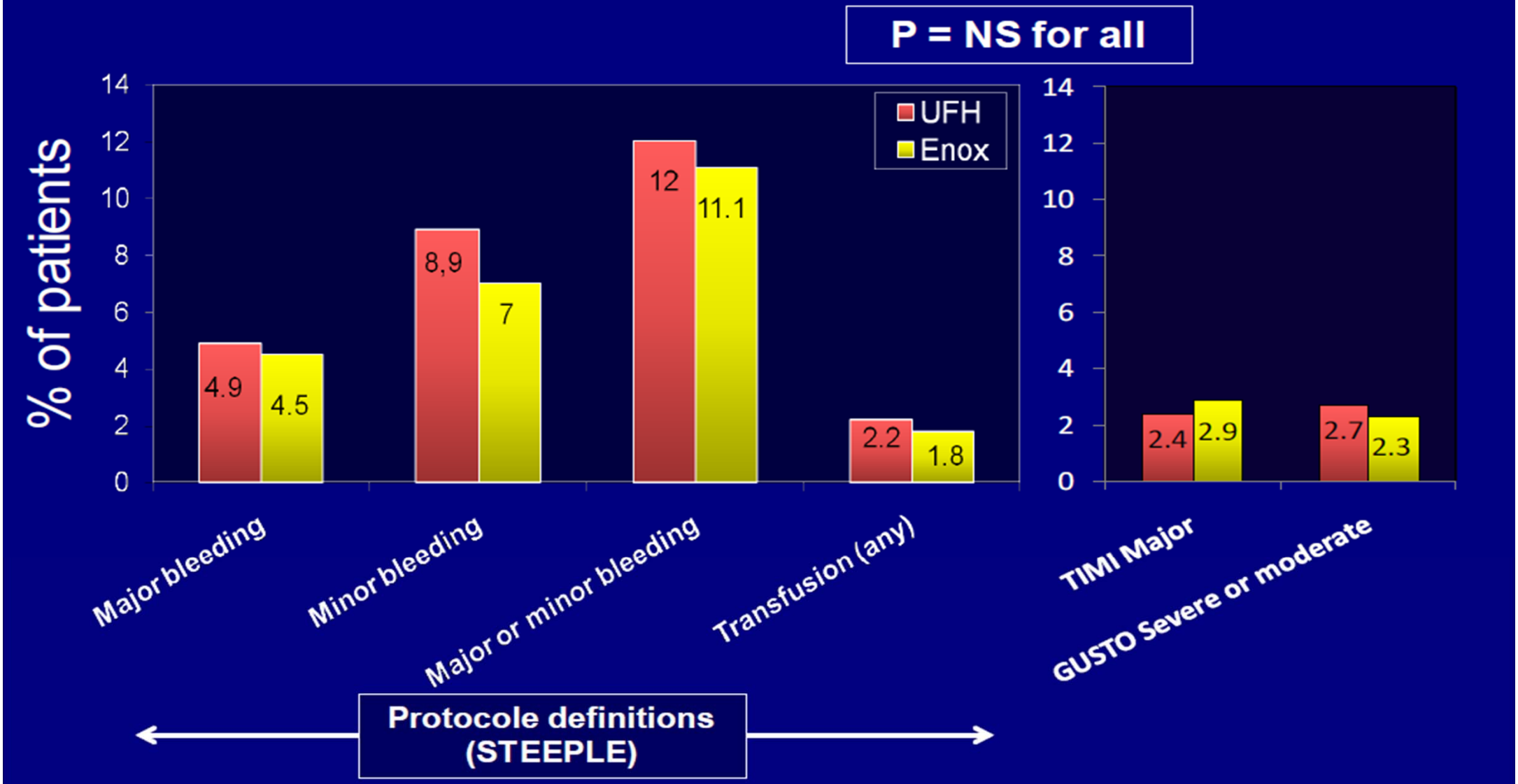
Zeymer et al. Eurointervention 2009;4:524-8. Li YJ, Rha SW et al. Am Heart J 2010;159:684-90. Montalescot et al. JACC CI 2010;3:203-12. Brieger et al. CCI 2010 (in press)

Main Safety Endpoint

Non-CABG Major Bleeding (STEEPLE definition)

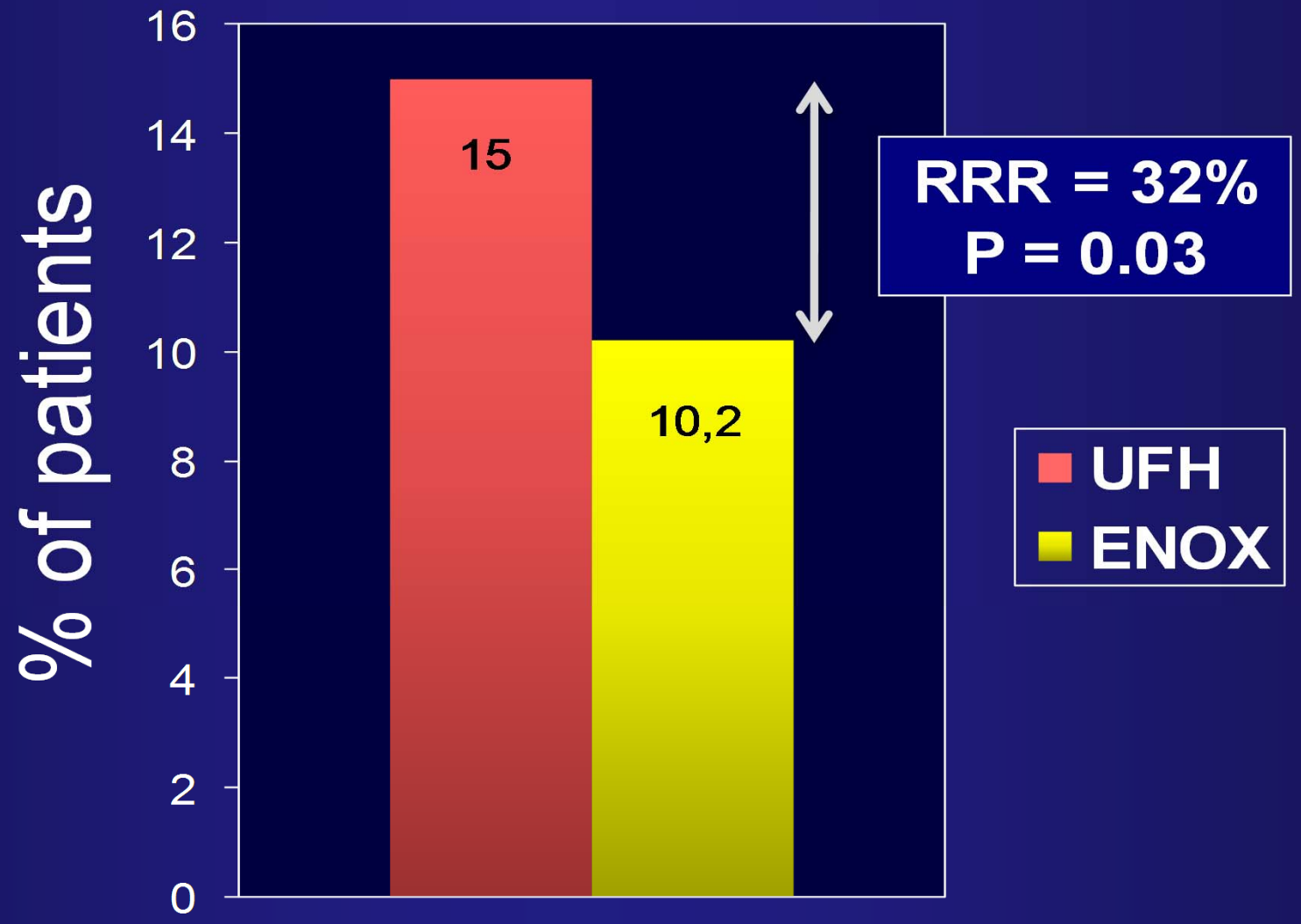


All Safety Endpoints



Death, Complication of MI or Major bleeding

Net clinical benefit



Conclusions

In this 1st pure head-to-head comparison between 2 anticoagulants in primary PCI, i.v. enoxaparin:

- **Did not reduce procedural failure, in particular low TIMI flow and non ST-segment resolution**
- **Reduced serious ischemic events on top of intense antiplatelet therapy**
- **Had a good safety profile with a superior net clinical benefit**

The Lancet
Manuscript Draft

Manuscript Number: THELANCET-D-11-02305

Title: Intravenous Enoxaparin or Unfractionated Heparin in Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction

Article Type: Fast Track (Randomised Controlled Trial)

Intravenous Enoxaparin or Unfractionated Heparin in Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction

Gilles Montalescot, MD, PhD, Uwe Zeymer, MD, PhD, Johanne Silvain, MD, PhD, Bertrand Boulanger, MD, Marc Cohen, MD, Patrick Goldstein, MD, Patrick Ecollan, MD, Xavier Combes, MD, Kurt Huber, MD, PhD, Charles Pollack Jr., MD, Jean-François Bénezet, MD, Olivier Stibbe, MD, Emmanuelle Filippi, MD, Emmanuel Teiger, MD, PhD, Guillaume Cayla, MD, Simon Elhadad, MD, Frédéric Adnet, MD, Tahar Chouihed, MD, Sébastien Gallula, MD, Agnès Greffet, MD, Mounir Aout, PhD, Jean-Philippe Collet, MD, PhD, Eric Vicaut, MD, PhD for the ATOLL Investigators

ATOLL: **A**cute STEMI **T**reated with primary angioplasty and intravenous enoxaparin **O**r UFH to **L**ower ischemic and bleeding events at short- and **L**ong-term follow-up

ClinicalTrials.gov: NCT00718471

Reviewer's (Dr Rha) Comments (1)

Dr Montalescot and his co-workers report the results from Acute STEMI Treated with primary angioplasty and intravenous enoxaparin Or UFH to Lower ischemic and bleeding events at short- and Long-term follow-up (ATOLL) study.

In ATOLL study, Dr Montalescot and his co-workers compared enoxaparin and UHF in patients undergoing primary PCI, predominantly performed with a radial artery access. The authors found that anticoagulation with enoxaparin resulted in a lower rate of the primary end point that was not statistically significant, and in a significantly lower rate of the main secondary end point. Death or complication of MI was also reduced with enoxaparin. The incidence of bleeding events was not different between groups. They concluded that intravenous enoxaparin as compared with unfractionated heparin did reduce ischemic end points although the reduction of the primary end point failed to reach statistical significance. The good ischemic and safety profile of enoxaparin led to an improved net clinical benefit. Notably, in this study, they enrolled a broad risk, real world population managed with current, guidelines supported drugs and techniques.

Reviewer's (Dr Rha) Comments (2)

Major comment:

We congratulate Dr. Montalescot and his coworkers on this elegant study because the ATOLL study has been nicely designed and well preformed. This manuscript also has been nicely written and the statistics analysis was properly conducted. The conclusions were proper and strongly supported by the results.

Minor comments:

1. Intravenous bolus of 0.5mg/kg of enoxaparin was used before primary PCI, and subcutaneous enoxaparin 40mg was given once a day, subsequently. Actually, the superior effects from enoxaparin come from this composite drug use regime. Therefore, we suggest the authors should mention this in the methods section of the abstract.

2. The reference 22 was wrongly edited in the text with double occuring numbers on page 17-18. And the reference 16 should be superscript on page 18.

THELANCET-D-11-02305
“Intravenous Enoxaparin or Unfractionated Heparin in Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction”
Original Submission

Seung Woon Rha (Reviewer 5)

Reviewer Recommendation Term: Accept with Minor Revision

Manuscript Rating Question(s):	Scale	Rating
The subject addressed in this article is worthy of investigation?	[1-5]	5
The hypothesis is clearly stated?	[1-5]	5
The most important previous studies are cited as far as I know?	[1-5]	4
The data presented are new (or deserved to be replicated)?	[1-5]	4
The research design is suitable?	[1-5]	5
The methods are described specifically enough to be evaluated?	[1-5]	4
The discussion addresses sources of systematic and random error?	[1-5]	4
The conclusions are supported by the data?	[1-5]	4
The summary accurately reflects the content of the paper?	[1-5]	4
Overall Score	[1-5]	4

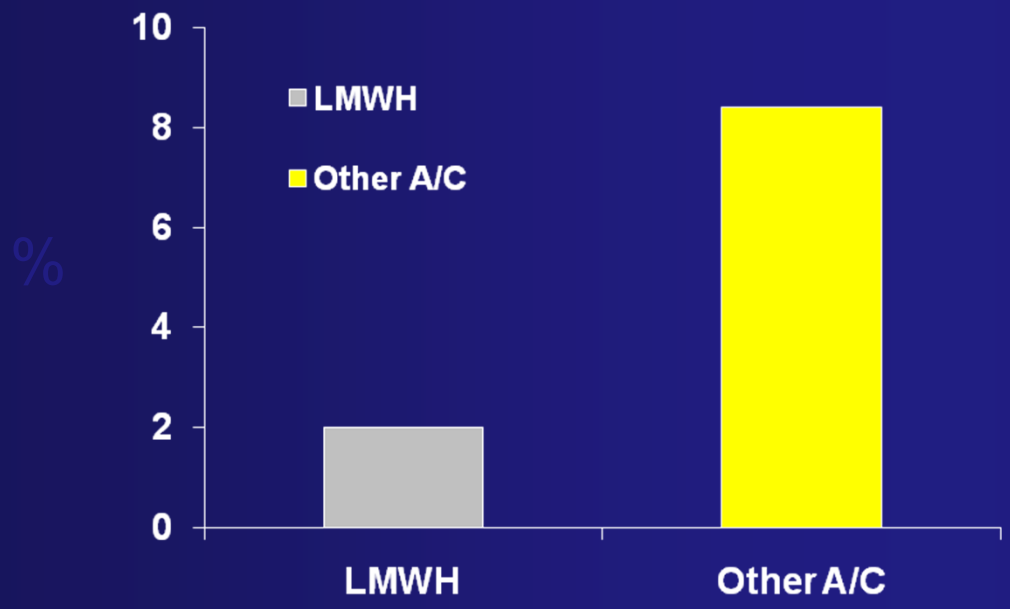
Global Registry

FAST-MI (STEMI) registry

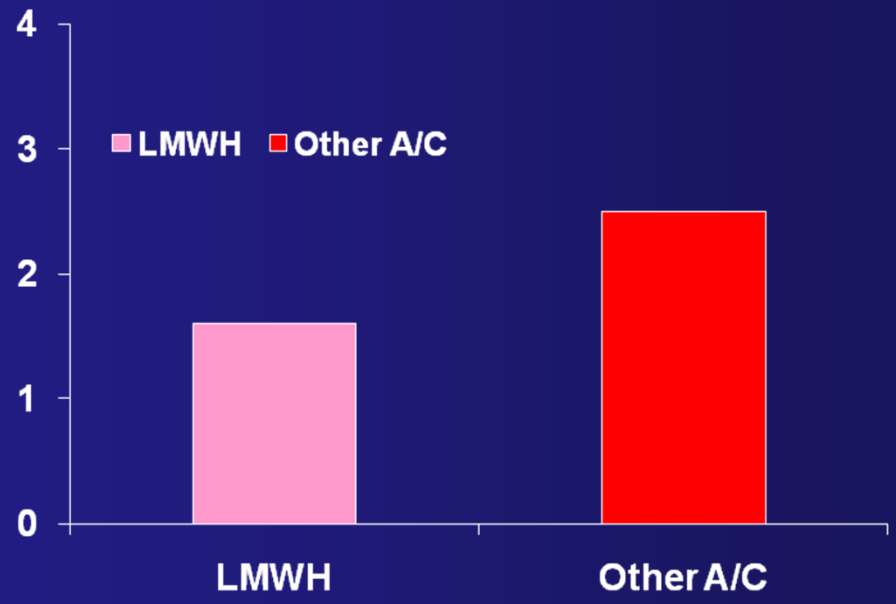
1711 STEMI patients: 1025 with reperfusion

- 45% lysis
- 55% 1° PCI

DEATH



MAJOR BLEED



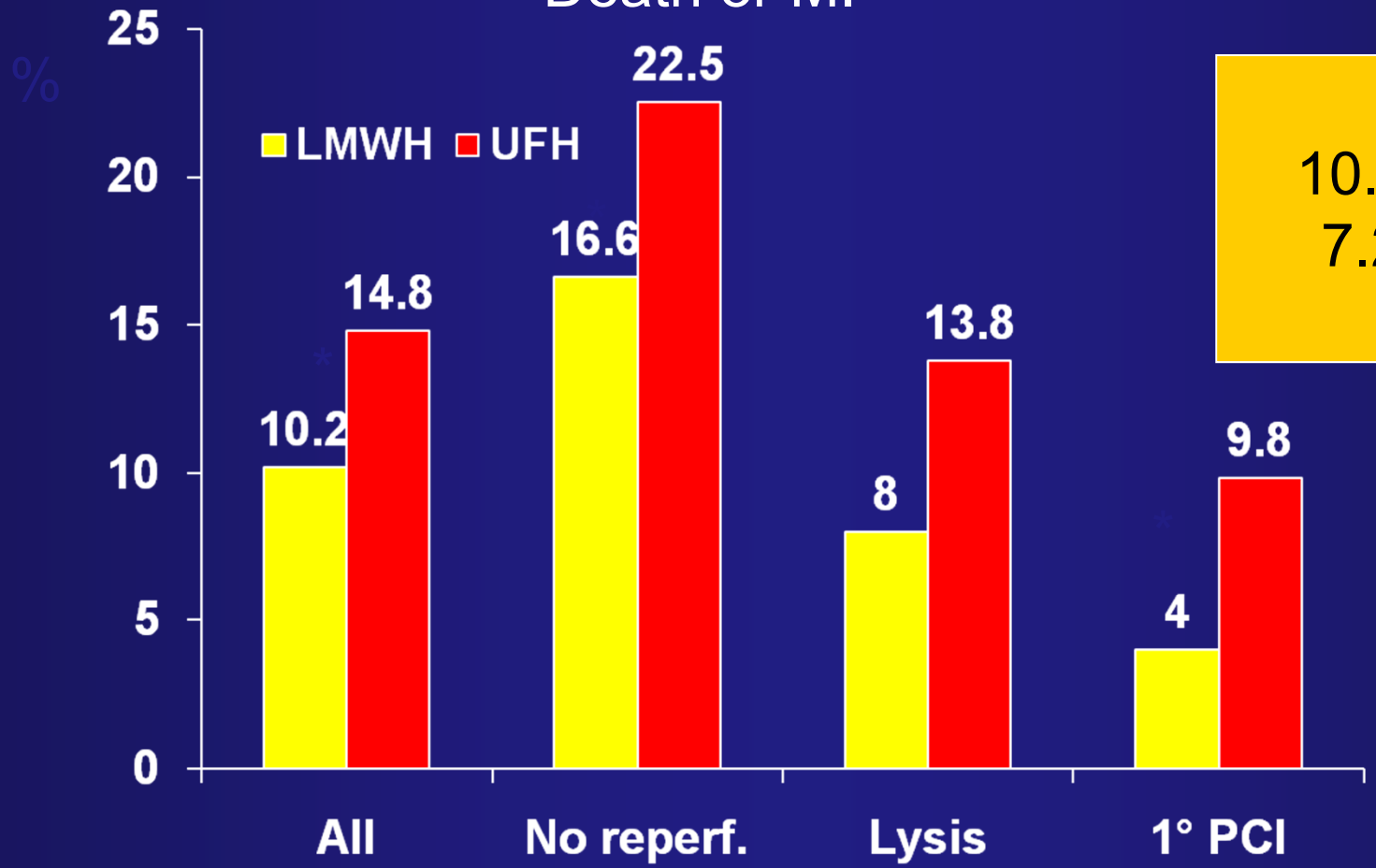
Multivariate analysis: LMWH predicts survival

Danchin N et al. Presented at: ACC 2007 Annual Meeting; March 24–27, 2007; New Orleans, La. Abstract 1025-94.

ACOS (STEMI) Registry

6299 STEMI patients:

- 2683 No Rx
- 2021 lysis
- 2371 1° PCI



Death
10.0% UFH *vs.* 7.2% LMWH, $p<0.05$

Zeymer U, et al. *Thromb Haemost* 2008;99:150-154.

P < 0.05, univariate analysis

Low Molecular Weight Heparin versus Unfractionated Heparin in Acute ST-Segment Elevation Myocardial Infarction Patients undergoing Primary PCI with Drug-eluting Stents

Kang-Yin Chen, *Seung-Woon Rha*, Yong-Jian Li, Kanhaiya L. Poddar, Jae Hyoung Park, Jin Oh Na, Cheol Ung Choi, Hong Euy Lim, Jin Won Kim, Eung Ju Kim, Chang Gyu Park, Hong Seog Seo, Dong Joo Oh, Young Keun Ahn*, Myung Ho Jeong*

Cardiovascular Center,
Korea University Guro Hospital, Seoul, Korea
***Chonnam National University Hospital, Gwangju, Korea**

KSC 2008

Low-molecular-weight heparin versus unfractionated heparin in acute ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention with drug-eluting stents

Yong-Jian Li, MD,[a,b] Seung-Woon Rha, MD,[a] Kang-Yin Chen, MD,[c] Kanhaiya L. Poddar, MD,[a] Zhe Jin, MD,[b] Yoshiyasu Minami, MD,[a] Lin Wang, MD,[a] Qun Dang, MD,[b] Guang-Ping Li, MD,[c] Sureshkumar Ramasamy, MD,[a] Ji-Young Park, MD,[a] Chol Ung Choi, MD,[a] Jin-Won Kim, MD,[a] Eung Ju Kim, MD,[a] Chang Gyu Park, MD,[a] Hong Seog Seo, MD,[a] Dong Joo Oh, MD,[a] Myung Ho Jeong, MD,[d] Young Keun Ahn, MD,[d] Taek Jong Hong, MD,[e] Jong-Seon Park, MD,[f] Young Jo Kim, MD,[f] Seung Ho Hur, MD,[g] In Whan Seong, MD,[h] Jei Keon Chae, MD,[i] Myeong Chan Cho, MD,[j] Jang Ho Bae, MD,[k] Dong Hoon Choi, MD,[l] Yang Soo Jang, MD,[l] In Ho Chae, MD,[m] Hyo Soo Kim, MD,[n] Chong Jin Kim, MD,[o] Jung Han Yoon, MD,[p] Tae Hoon Ahn, MD,[q] Seung-Jea Tahk, MD,[r] Wook Sung Chung, MD,[s] Ki Bae Seung, MD,[s] and Seung Jung Park, MD,[t] other Korea Acute Myocardial infarction Registry Investigators[u] *Seoul, Gwangju, Pusan, Daegu, Daejeon, Jeonju, Chongju, Bundang, Wonju, Korea; and Tianjin, China*

Background Whether low-molecular-weight heparin (LMWH) is superior to unfractionated heparin (UFH) in acute ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) remains unclear.

Methods A total of 3,372 STEMI patients who underwent primary PCI with DESs received either LMWH (n = 1,531 patients, subcutaneous enoxaparin 1 mg/kg, bid for 3-5 days plus reduced dose of UFH [50 U/kg] during PCI) or UFH alone (n = 1,841 patients, intravenous bolus injection of 5,000 U, followed by 24,000 U/d infusion for at least 48 hours). The bleeding events and clinical outcomes during in-hospital and at 8 months were compared.

Results The incidences of major and minor bleeding events were similar between the 2 groups. Multivariable Cox regression analysis showed that LMWH group had lower incidences of cardiac death (adjusted odds ratio [OR] 0.55, 95% CI 0.39-0.77, $P < .001$), total death (adjusted OR 0.50, 95% CI 0.37-0.68, $P < .001$), and total major adverse cardiac events (adjusted OR 0.77, 95% CI 0.62-0.95, $P = .017$) at 8 months as compared with UFH group. Similar results were obtained across different subgroups including different DESs, age, and sex.

Conclusions The LMWH enoxaparin combined with reduced dose of UFH (50 U/kg) administration as an adjunctive antithrombotic therapy in STEMI patients undergoing primary PCI with DESs seems to be safe and efficacious. However, randomized clinical trials are needed to confirm this conclusion. (Am Heart J 2010;159:684-690.e1.)

Table IV. Cumulative clinical outcomes up to 8 months

Variables, n (%)	UFH (n = 1841)	Enoxaparin (n = 1531)	P
In-hospital outcomes			
Cardiac death	87 (4.7)	34 (2.2)	<.001
Total death	116 (6.3)	45 (2.9)	<.001
Recurrent MI	8 (0.4)	2 (0.1)	.106
Major bleeding events	11 (0.6)	8 (0.5)	.772
Minor bleeding events	21 (1.1)	16 (1.0)	.790
Outcomes at 8 m			
Cardiac death	103 (5.6)	55 (3.6)	.006
Total death	140 (7.6)	69 (4.5)	<.001
Recurrent MI	11 (0.6)	5 (0.3)	.254
CABG	2 (0.1)	1 (0.1)	1.000
TLR	26 (1.4)	27 (1.8)	.414
Re-PCI	60 (3.3)	73 (4.8)	.025
Total MACE	213 (11.6)	149 (9.7)	.086

CABG, Coronary artery bypass grafting; *re-PCI*, repeated percutaneous coronary intervention.

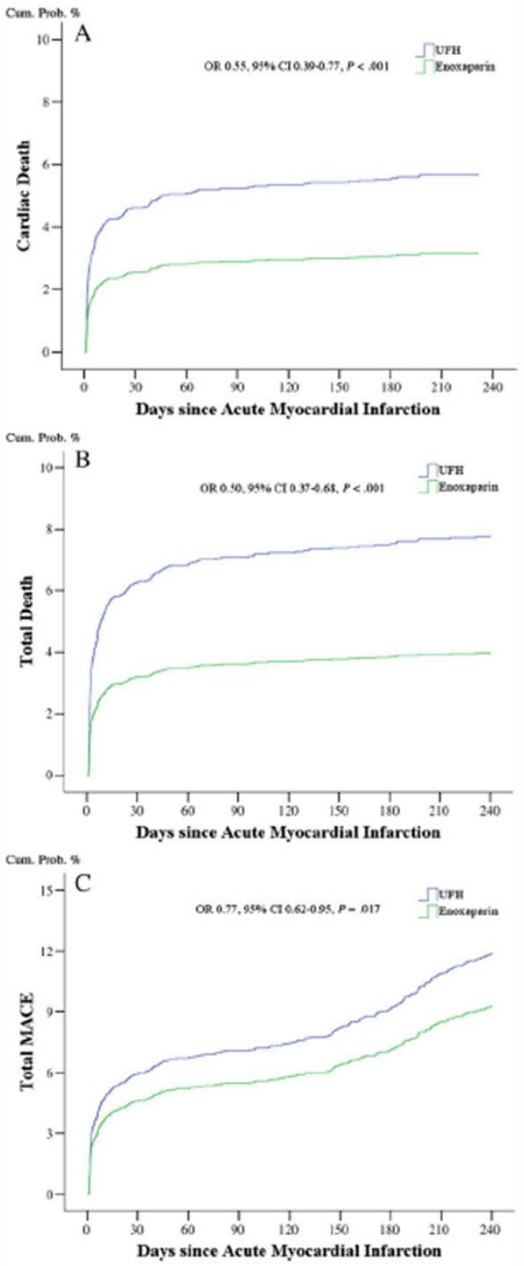
Li YJ, Rha SW et al. Am Heart J 2010; 159:684-690.e1.

Table V. Adjusted cumulative clinical outcomes up to 8 months of enoxaparin as compared with UFH (Cox regression analysis using propensity score)

Variables	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
In-hospital outcomes				
Cardiac death	0.46 (0.31-0.68)	<.001	0.28 (0.16-0.48)	<.001
Total death	0.45 (0.32-0.64)	<.001	0.27 (0.17-0.43)	<.001
Recurrent MI	0.30 (0.06-1.41)	.128	0.28 (0.06-1.38)	.117
Outcomes at 8 m				
Cardiac death	0.63 (0.45-0.88)	.007	0.55 (0.39-0.77)	<.001
Total death	0.57 (0.43-0.77)	<.001	0.50 (0.37-0.68)	<.001
Recurrent MI	0.54 (0.19-1.57)	.262	0.66 (0.22-1.95)	.452
CABG	0.60 (0.05-6.63)	.678	0.36 (0.03-4.23)	.417
Re-PCI	1.49 (1.05-2.11)	.026	1.47 (1.03-2.09)	.033
TLR	1.25 (0.73-2.16)	.415	1.27 (0.73-2.22)	.392
Total MACE	0.82 (0.66-1.03)	.086	0.77 (0.62-0.95)	.017

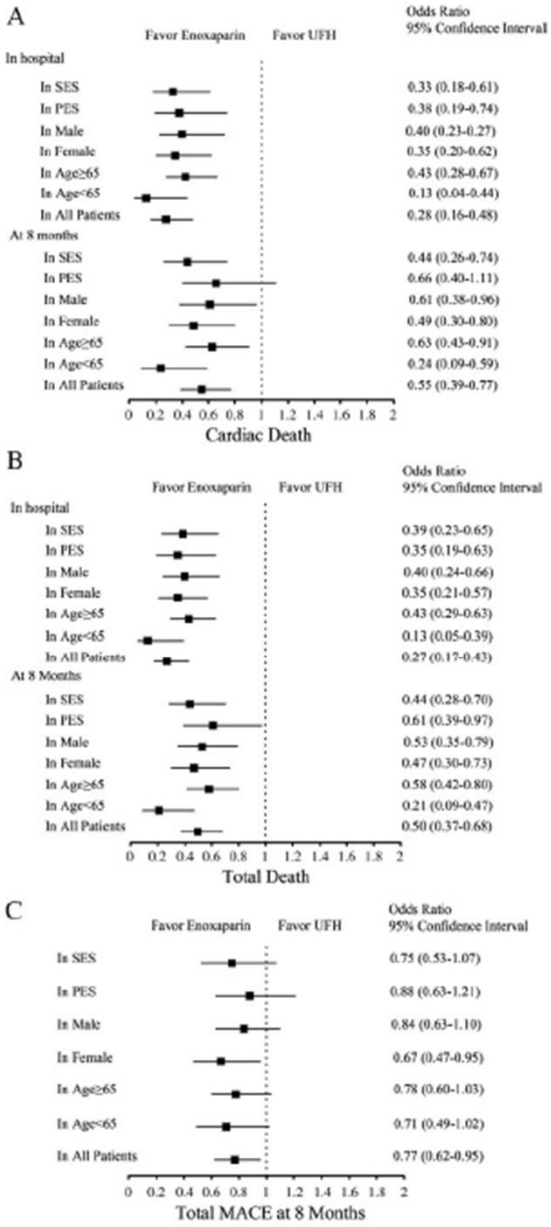
Li YJ, Rha SW et al. Am Heart J 2010; 159:684-690.e1.

Figure 1



Adjusted cumulative incidences in patients received enoxaparin or UFH of cardiac death (**A**), total death (**B**), and total MACE (**C**) at 8 months. Cum prob, cumulative probability; OR, odds ratio.

Figure 2



Adjusted odds ratios for incidences of cardiac death (**A**), total death (**B**), and total MACE (**C**) associated with enoxaparin therapy in all study population and various subgroups of patients according to different stents, sex, and age.

1. Early Divergence

2. Same results among different subgroups

Low Molecular Weight Heparin versus Unfractionated Heparin in the Off-Label Use of Drug-Eluting Stents in Acute Non-ST-Segment Elevation Myocardial Infarction

Kang-Yin Chen, *Seung-Woon Rha*, Yong-Jian Li, Kanhaiya L. Poddar, Jae Hyoung Park, Jin Oh Na, Cheol Ung Choi, Hong Euy Lim, Jin Won Kim, Eung Ju Kim, Chang Gyu Park, Hong Seog Seo, Dong Joo Oh, Young Keun Ahn*, Myung Ho Jeong*

Cardiovascular Center,
Korea University Guro Hospital, Seoul, Korea
***Chonnam National University Hospital, Gwangju, Korea**

CEPP 2011 submitted

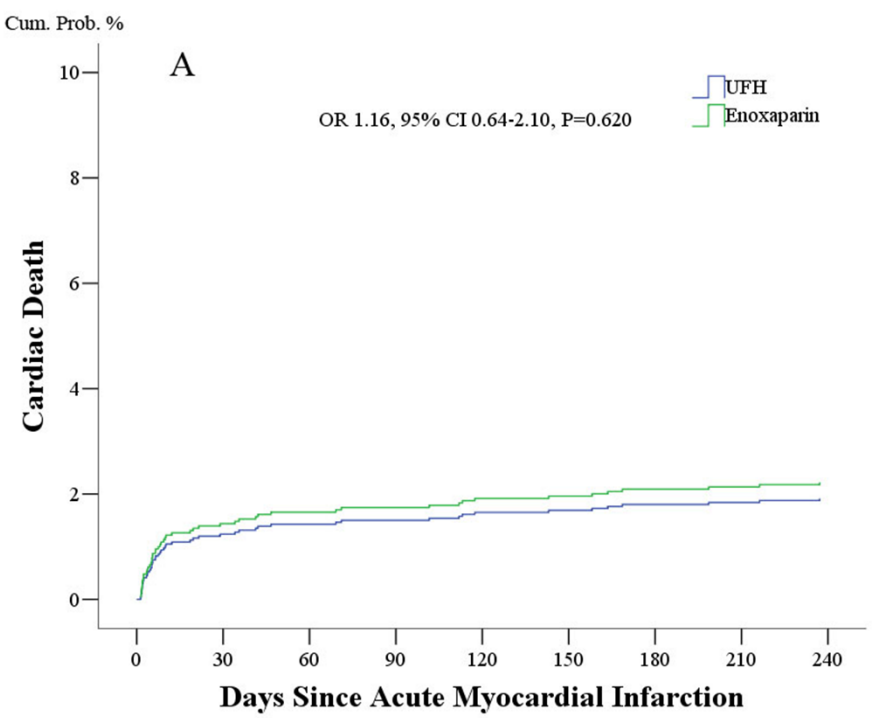
KSC 2008

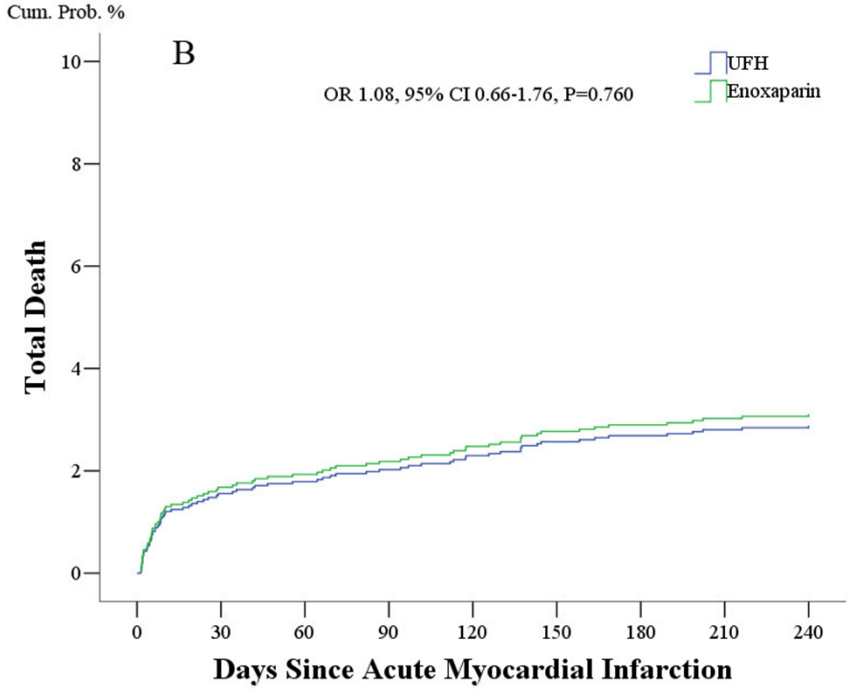
Cumulative Clinical Outcomes up to 8 Months

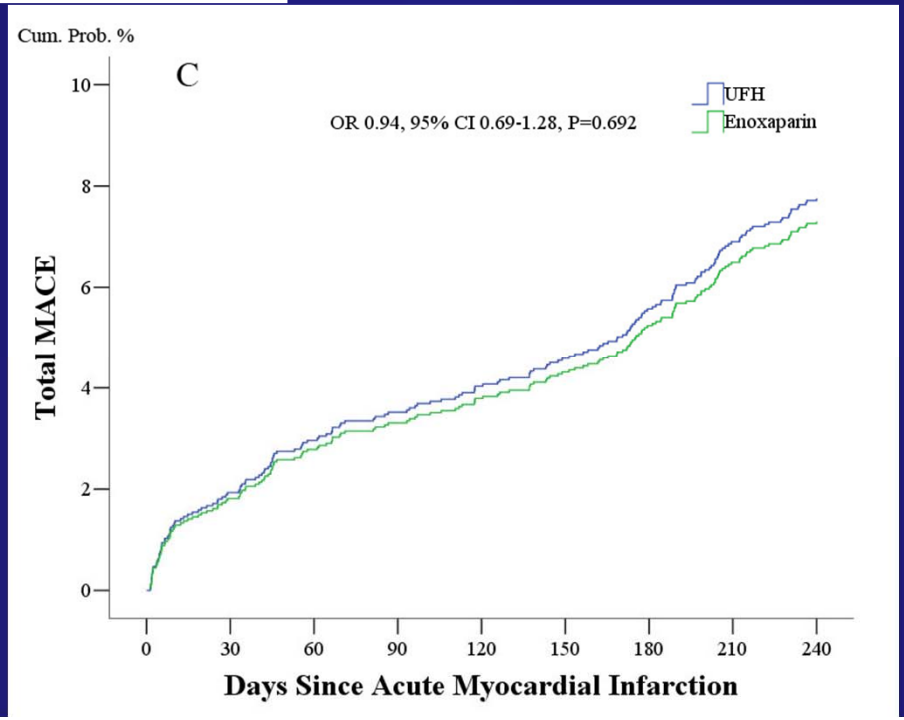
Variables, n (%)	UFH (n=1,219)	Enoxaparin (n=1,178)	*P* value
In-hospital outcomes			
Cardiac death	12 (1.0)	15 (1.3)	0.503
Total death	16 (1.3)	20 (1.7)	0.438
Recurrent MI	0 (0)	2 (0.2)	0.150
Major bleeding events	3 (0.2)	4 (0.3)	0.672
Minor bleeding events	11 (0.9)	13 (1.1)	0.621
Outcomes at 8 months			
Cardiac death	22 (1.8)	29 (2.5)	0.265
Total death	33 (2.7)	41 (3.5)	0.274
Recurrent MI	12 (1.0)	3 (0.3)	0.024
CABG	3 (0.2)	3 (0.3)	1.000
Repeated PCI	43 (3.5)	42 (3.6)	0.960
TLR	25 (2.1)	10 (0.8)	0.014

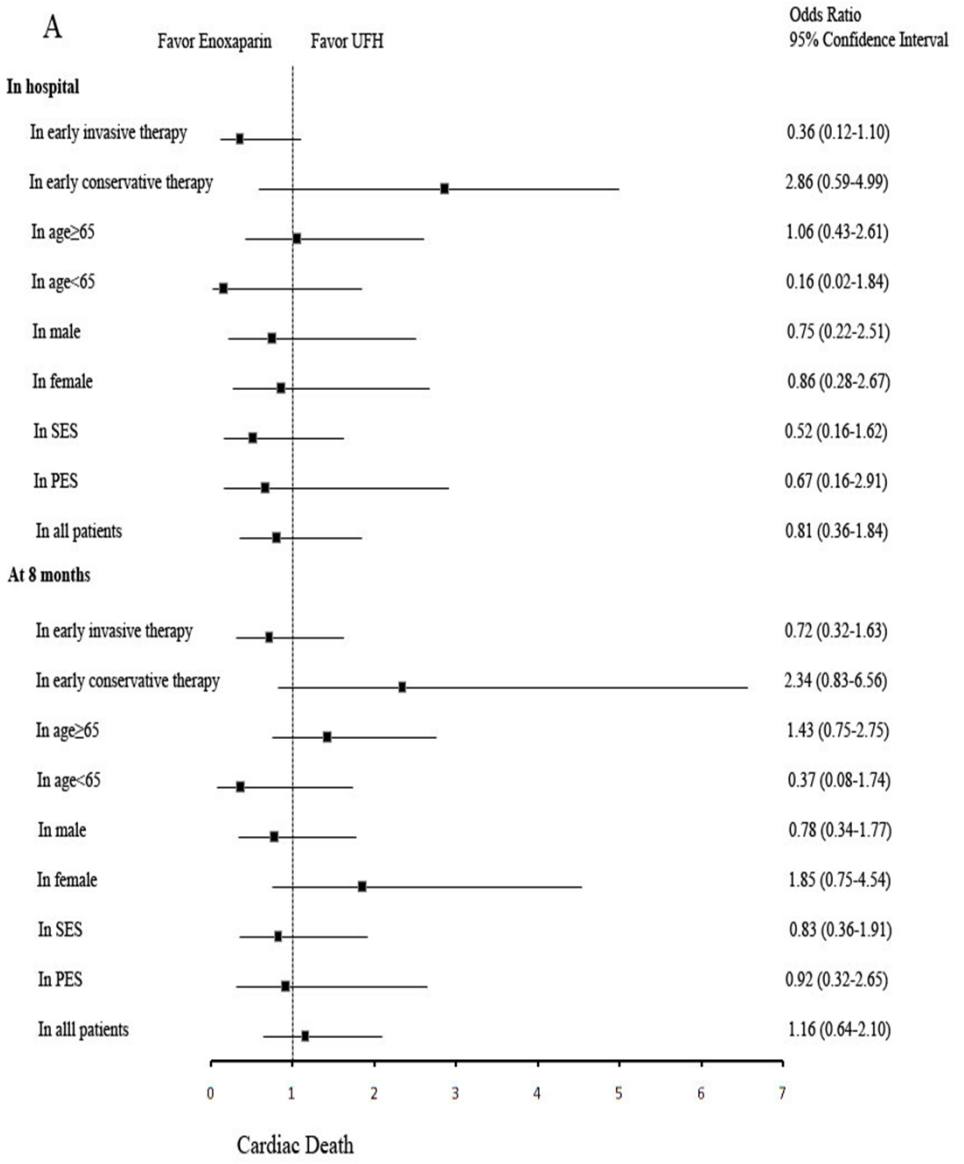
Adjusted Cumulative Clinical Outcomes up to 8 Months of Enoxaparin as Compared with Unfractionated Heparin (Cox Regression Analysis Using Propensity Score)

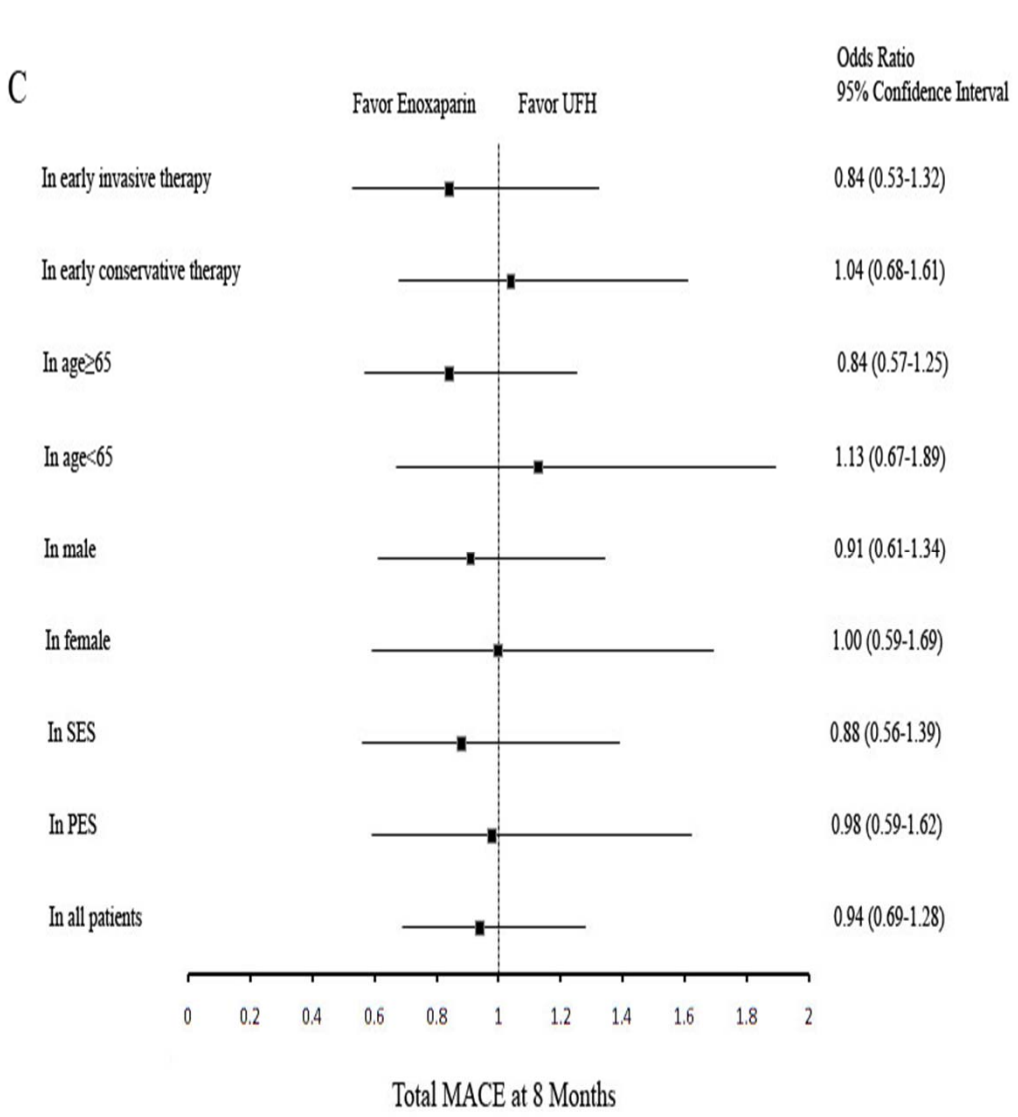
Variables	Unadjusted OR (95% CI)	*P* value	Adjusted OR* (95% CI)	*P* value
In-hospital outcomes				
Cardiac death	1.30 (0.61-2.78)	0.504	0.81 (0.36-1.84)	0.614
Total death	1.30 (0.67-2.52)	0.439	0.84 (0.41-1.71)	0.631
Outcomes at 8 months				
Cardiac death	1.37 (0.78-2.40)	0.267	1.16 (0.64-2.10)	0.620
Total death	1.30 (0.81-2.06)	0.275	1.08 (0.66-1.76)	0.760
Recurrent MI	0.26 (0.07-0.91)	0.036	0.33 (0.09-1.22)	0.096
CABG	1.03 (0.21-5.14)	0.967	0.61 (0.11-3.46)	0.578
Re-PCI	1.01 (0.66-1.56)	0.960	1.04 (0.66-1.64)	0.872
TLR	0.41 (0.20-0.85)	0.018	0.45 (0.21-0.99)	0.046
Total MACE	1.00 (0.74-1.36)	0.994	0.94 (0.69-1.28)	0.692


Cum. Prob. %
A
OR 1.16, 95% CI 0.64-2.10, P=0.620
UFH
Enoxaparin
Cardiac Death
10
8
6
4
2
0
0
30
60
90
120
150
180
210
240
Days Since Acute Myocardial Infarction


Cum. Prob. %
B
OR 1.08, 95% CI 0.66-1.76, P=0.760
UFH
Enoxaparin
Total Death
10
8
6
4
2
0
0
30
60
90
120
150
180
210
240
Days Since Acute Myocardial Infarction


Cum. Prob. %
C
OR 0.94, 95% CI 0.69-1.28, P=0.692
UFH
Enoxaparin
Total MACE
10
8
6
4
2
0
0
30
60
90
120
150
180
210
240
Days Since Acute Myocardial Infarction


A
Favor Enoxaparin
Favor UFH
Odds Ratio
95% Confidence Interval
In hospital
In early invasive therapy
0.36 (0.12-1.10)
In early conservative therapy
2.86 (0.59-4.99)
In age≥65
1.06 (0.43-2.61)
In age<65
0.16 (0.02-1.84)
In male
0.75 (0.22-2.51)
In female
0.86 (0.28-2.67)
In SES
0.52 (0.16-1.62)
In PES
0.67 (0.16-2.91)
In all patients
0.81 (0.36-1.84)
At 8 months
In early invasive therapy
0.72 (0.32-1.63)
In early conservative therapy
2.34 (0.83-6.56)
In age≥65
1.43 (0.75-2.75)
In age<65
0.37 (0.08-1.74)
In male
0.78 (0.34-1.77)
In female
1.85 (0.75-4.54)
In SES
0.83 (0.36-1.91)
In PES
0.92 (0.32-2.65)
In alll patients
1.16 (0.64-2.10)
0
1
2
3
4
5
6
7
Cardiac Death


C
Favor Enoxaparin
Favor UFH
Odds Ratio
95% Confidence Interval
In early invasive therapy
0.84 (0.53-1.32)
In early conservative therapy
1.04 (0.68-1.61)
In age≥65
0.84 (0.57-1.25)
In age<65
1.13 (0.67-1.89)
In male
0.91 (0.61-1.34)
In female
1.00 (0.59-1.69)
In SES
0.88 (0.56-1.39)
In PES
0.98 (0.59-1.62)
In all patients
0.94 (0.69-1.28)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Total MACE at 8 Months

KAMIR-NSTEMI Conclusion

Enoxaparin combined with UFH as an adjunctive antithrombotic therapy in NSTEMI patients undergoing PCI with DES was safe and showed comparable clinical outcomes at 8 months as compared with UFH alone.

Research Fellow 2008

At e-CTO Live

Dr Yong-Jian Li from Tianjin Medical Universtiy

At Teacher's Day 2008

Research Fellow 2008

Research Fellow 2011

Amro Elnagar, Benha University Hospital, Egypt

Conclusions: enoxaparin in the cath-lab

Antman EM, et al. N Engl J Med. 2006
Harrington RA et al. Chest 2008
Hulot JS, et al. Ther Drug Monit. 2004
King SB 3rd , et al. Circulation. 2008

30mg IV bolus
+ 1 mg/kg s.c. every 12h*

CATH LAB

PCI
Last SC < 8 H:
No additional LMWH

PCI
Last SC > 8 H:
0.3mg/kg IV bolus

* 30mg IV bolus: Optional by patients

75 yo or older; No bolus, Enoxaparin 0.75mg/kg SC every 12h

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

Summary & Conclusion

1. Introduction; LMWH in ACS
2. Clinical Data from Western Countries & KAMIR

- 1) UA/NSTEMI
  - : ESSENCE, Meta-analysis, STEEPLE
- 2) STEMI
- : ExTract TIMI 25, FINESSE, ATOLL
- Global registry (FAST-MI, ACOS, KAMIR)

3. Summary & Conclusion

Conclusion

1. LMWH enoxaparin (Clexane) is a suitable substitute for UFH in across the spectrum of ACS in all treatment settings/strategies.

2. Given the wealth of prior data showing the benefits in the management of UA/NSTEMI & STEMI patients, its newly demonstrated benefits in Primary PCI and convenience of use, enoxaparin should be considered a treatment of choice across the spectrum of Acute Coronary Syndrome (ACS) patients.