



ATOLL

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

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K. Huber, C. Pollack, U. Zeymer, E. Vicaut
for the ATOLL investigators

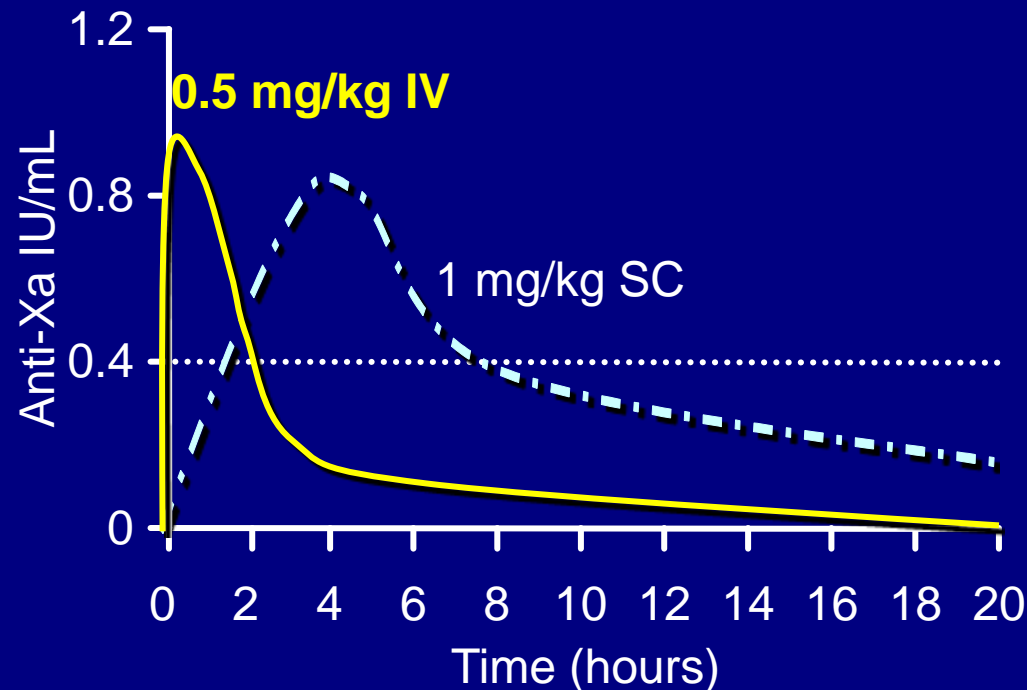
ATOLL: Acute STEMI Treated with primary PCI and intravenous enoxaparin Or UFH to Lower ischemic and bleeding events at short- and Long-term follow-up (Investigator-driven study)

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, Pfizer, 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

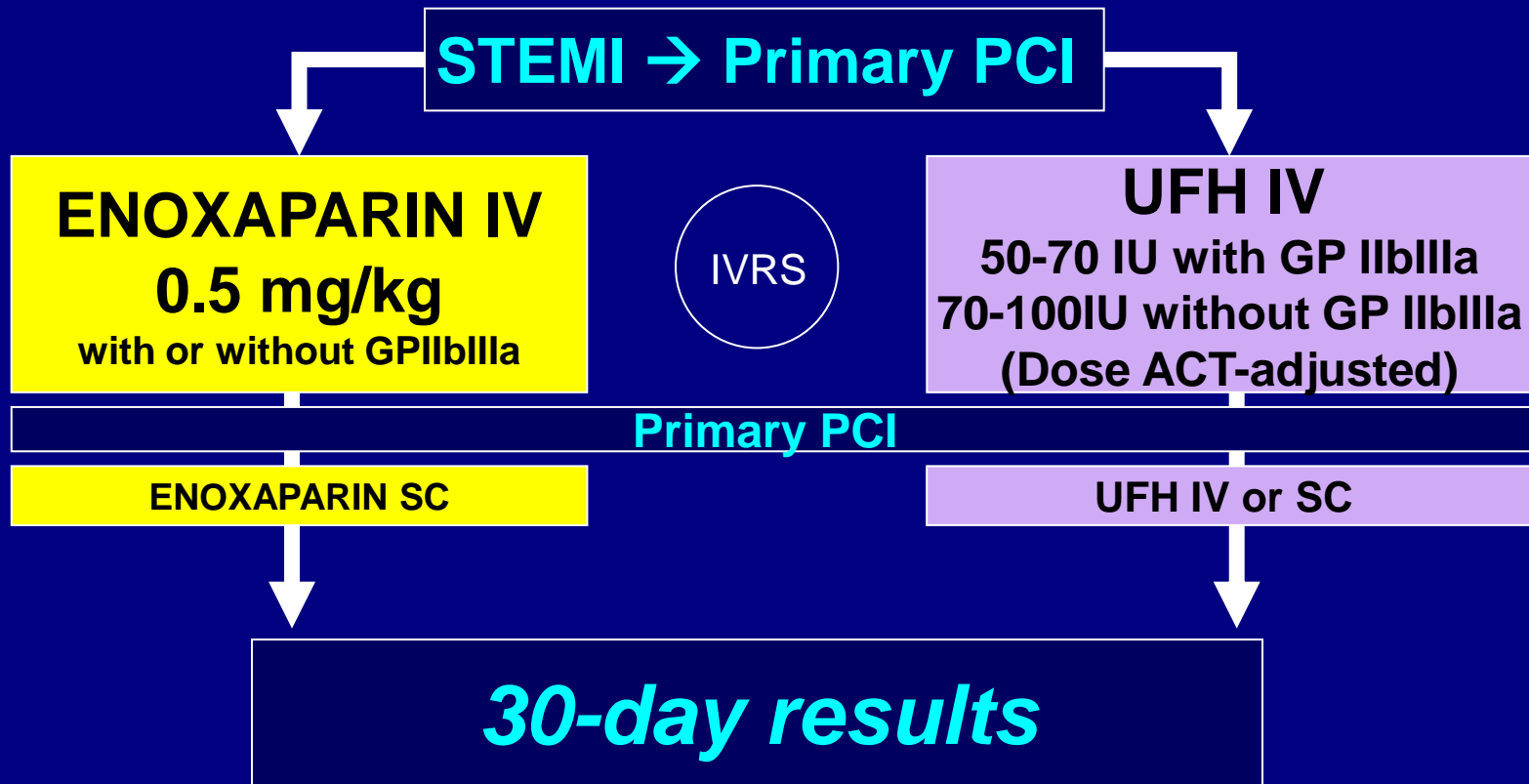
Montalescot et al. JACC Cardiovasc Interv. 2010;3:203-12

Brieger et al. Catheter Cardiovasc Interv. 2010 [in press]



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





Trial organization

ACTION Study Group (Academic Research Organization, Paris):

- 1-**Coordinating Center:** Institute of Cardiology, Pitié-Salpêtrière Hospital, Paris
- 2-**Sponsor:** AP-HP (Assistance Publique-Hôpitaux de Paris)
- 3-**Data center, Statistics:** Unité Recherche Clinique, Lariboisière Hospital, Paris
- 4-**International CRO:** Pierrel-Hyperphar
- 5-**Funding:** AP-HP and unrestricted research grant from Sanofi-Aventis Group

Steering Committee: G. Montalescot (*Chair*, France), M. Cohen (USA), P. Goldstein (France), K. Huber (Austria), C. Pollack (USA), E. Vicaut (France), U. Zeymer (Germany)

Data Safety Monitoring Board: A. Cohen (*Chair*, France), M. Cucherat (France), A. Gitt (Germany)

Core Laboratory: R. Dumaine, A. Samadi

Clinical Event Committee: F. Philippe, P. Sabouret, F. Boccara, A. Bellemain, O. Gournay



Main objectives

- **1° EP:**
 - **All-cause mortality at D30,**
 - **Complications of MI at D30** [resuscitated cardiac arrest, recurrent MI/ACS, urgent revascularization, stroke, peripheral or pulmonary embolism],
 - **Procedure failure** [definite stent thrombosis; B.O. use of GpIIb/IIIa; Non-TIMI 3 flow after PCI; ST resolution < 50% after PCI],
 - **Non-CABG major bleeding during hospitalization**
- **Main 2° EP: All-cause mortality, Recurrent MI/ACS or Urgent revascularization at D30**
- **Main safety EP: Non-CABG major bleeding (STEEPLE definition) during hospitalization**



Other objectives

Efficacy

- **Death or complication of MI**
- **Death, re-MI or urgent revascularization**
- **Death; Death or resuscitated cardiac arrest**

Safety

- **Major or minor bleeding**
- **Transfusion**

Net Benefit

- **Death, complication of MI or Major bleeding**



Statistics

- Study had a 80% statistical power to detect a difference between a group UFH proportion of 0.30 and a group enoxaparin proportion of 0.216 (RRR 28%, OR of 0.643) when the sample size in each group is 425.
- Sample size reassessment after 75% recruitment based on conditional power calculation (Addplan software).
- Analysis done on all randomized patients. Multiple imputation procedures for missing values done for sensitivity analysis of the main criteria (Proc MI SAS).
- Chisquare test for frequency comparisons and log-rank for survival analysis (SAS version 9.2).



RESULTS



Baseline characteristics

	UFH (n=460)	ENOXAPARIN (n=450)
Male sex	78% (359)	78% (353)
Age, median (Q1;Q3)	60 (52; 70)	59 (52; 71)
Age > 75	17% (80)	19% (85)
Pre-hospital randomization	71% (325)	70% (318)
Current smoker, % (n)	47% (218)	44% (199)
Diabetes, % (n)	15% (69)	14% (63)
Hypertension, % (n)	45% (207)	46% (205)
Hyperlipidemia, % (n)	40% (184)	40%(180)
Prior myocardial infarction, % (n)	10% (44)	6% (28)
Prior stroke, % (n)	2% (10)	3% (12)
Shock and/or cardiac arrest before sheath, % (n)	5% (24)	4% (17)
Time from symptom onset to randomization—hr, median (Q1;Q3)	2h19 (1h26; 4h37)	2h33 (1h29; 4h50)



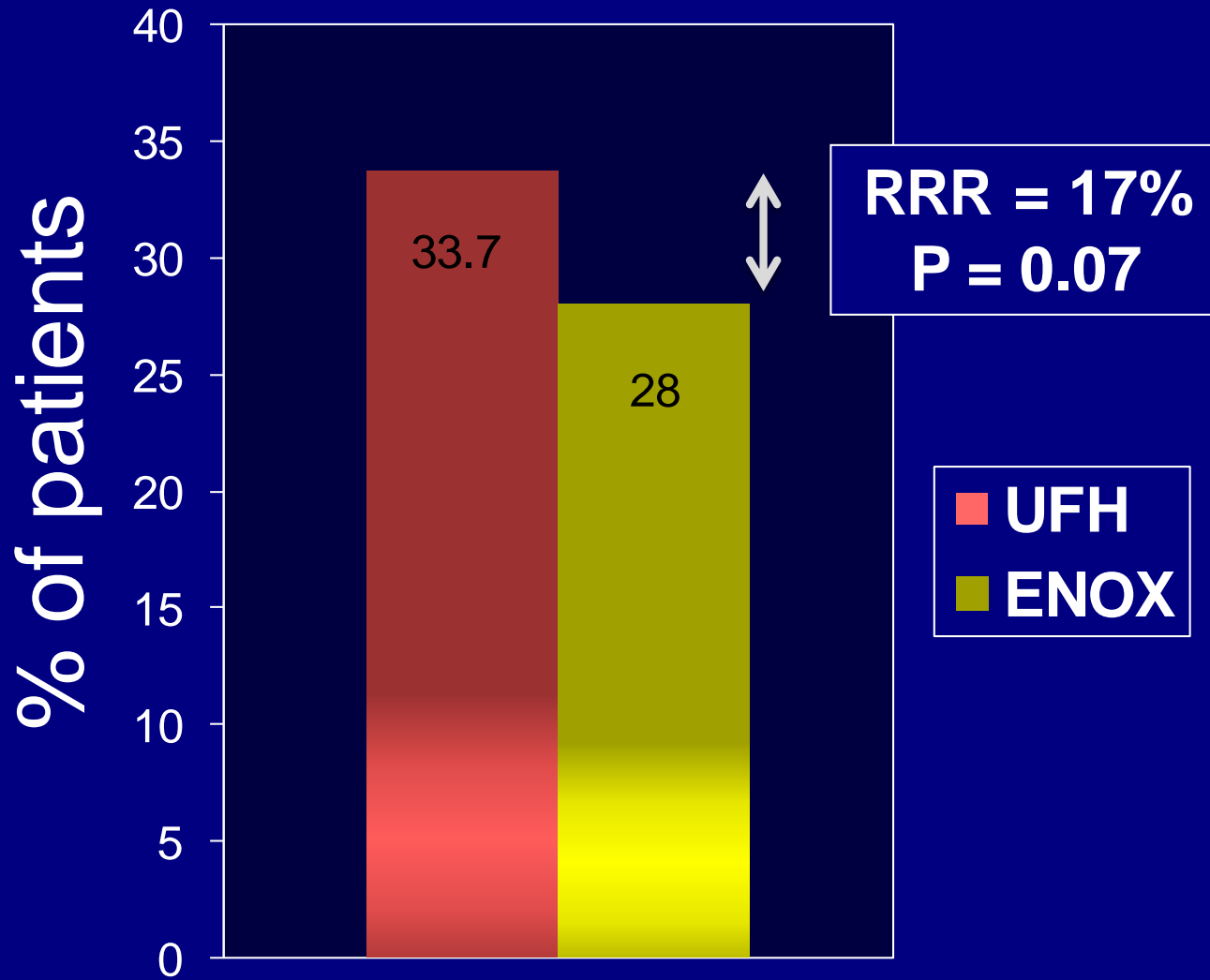
Procedure and study medications

	UFH (n=460)	ENOXAPARIN (n=450)
Radial artery access, % (n)	66% (305)	69% (309)
Other artery access, % (n)	34% (155)	31% (141)
Stent implanted (among PCI patients) , % (n)	94% (366)	96% (364)
Thrombectomy (among PCI patients) , % (n)	44% (173)	48% (184)
Glycoprotein IIb/IIIa before start of PCI,% (n)	77% (357)	71% (313)
Abciximab	64% (295)	62% (277)
Eptifibatide	11% (54)	8% (34)
Tirofiban	2% (8)	0.4% (2)
Medications before/during hospitalization — % (n)		
Aspirin	94% (434)	96% (431)
Clopidogrel	93% (427)	94% (422)
≤ 300mg	37% (171)	37% (168)
> 300 and ≤ 600mg	37% (172)	39% (174)
> 600 and ≤ 900mg	25% (113)	22% (101)
> 900mg	1% (4)	2% (7)
Beta-blockers	84% (385)	88% (398)
ACE-inhibitors	72% (333)	75% (336)
Statins	83% (382)	87% (392)



Primary Endpoint

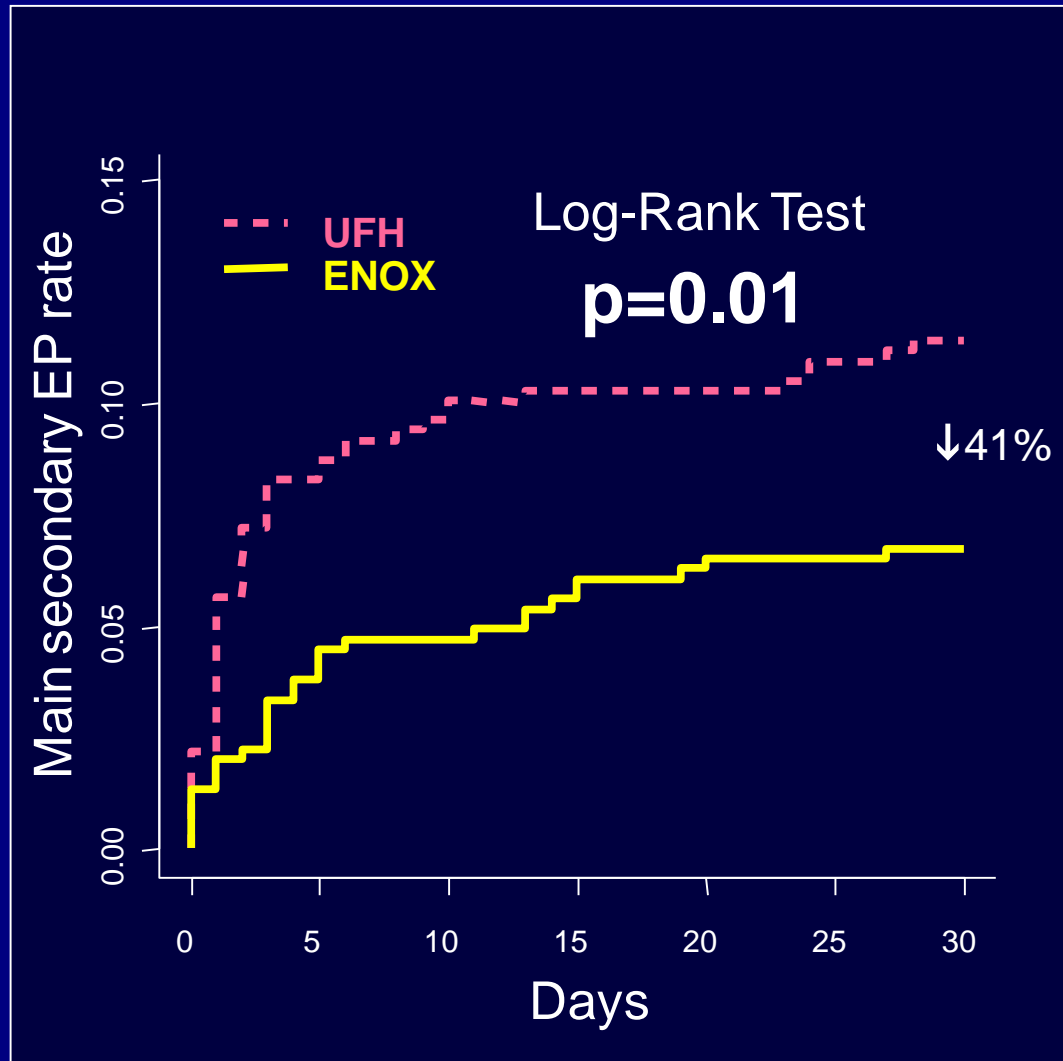
Death, Complication of MI, Procedure Failure or Major Bleeding





Main Secondary Endpoint (ischemic)

Death, Recurrent MI/ACS or Urgent Revascularization



30d rate (%)

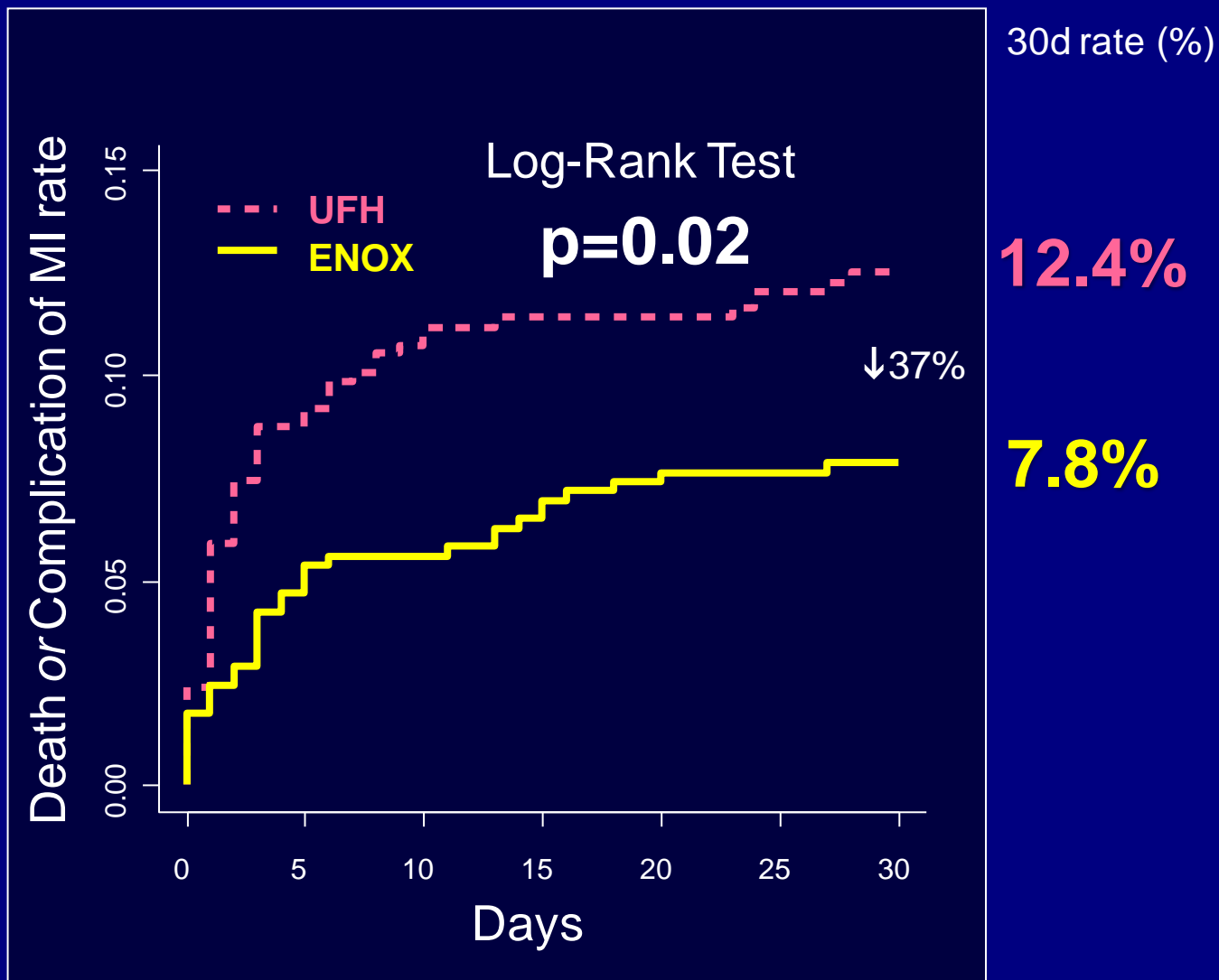
11.3%

6.7%



Death or Complication of MI

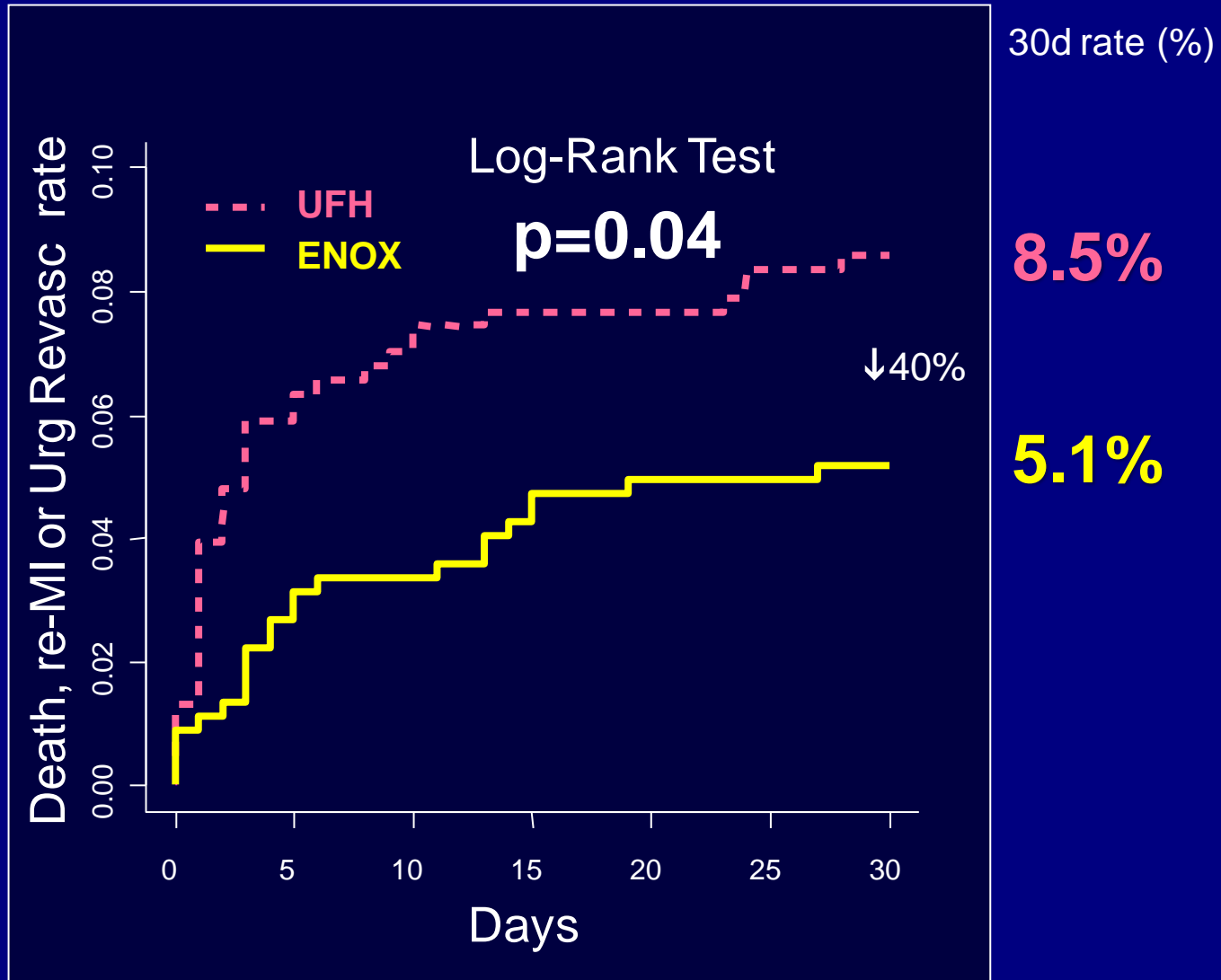
Death, resuscitated cardiac arrest, recurrent MI/ACS, Urg Revasc, stroke, peripheral or pulmonary embolism





Triple Ischemic Endpoint

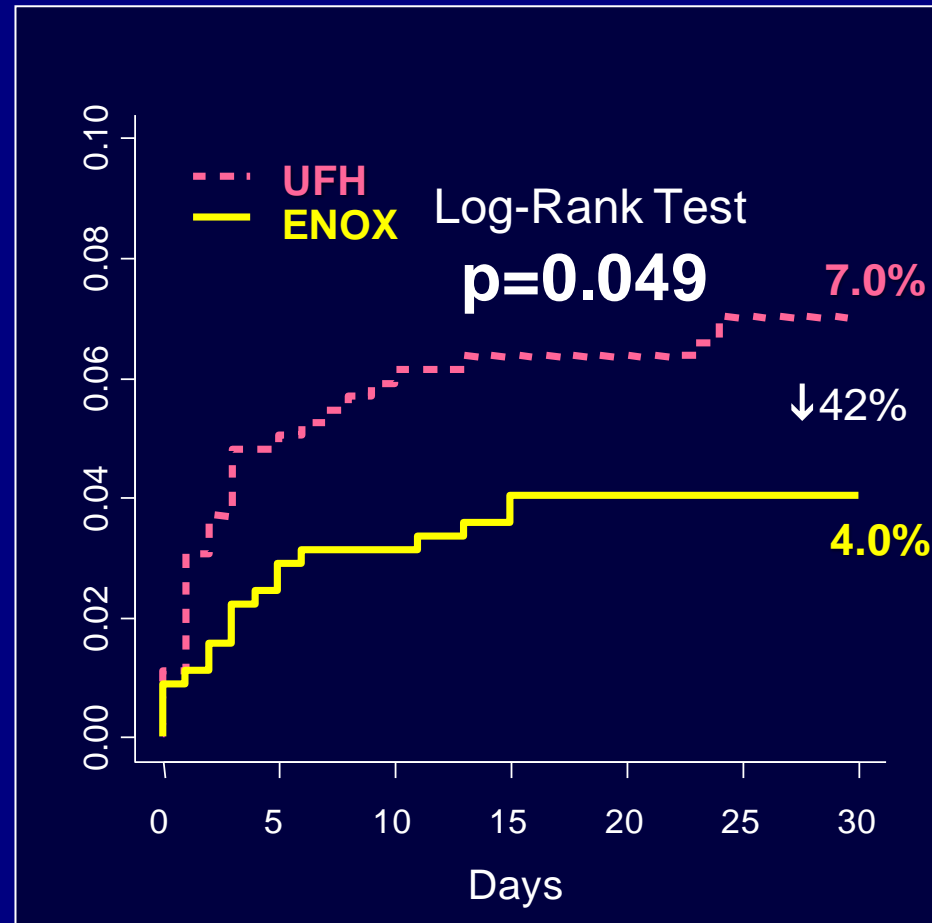
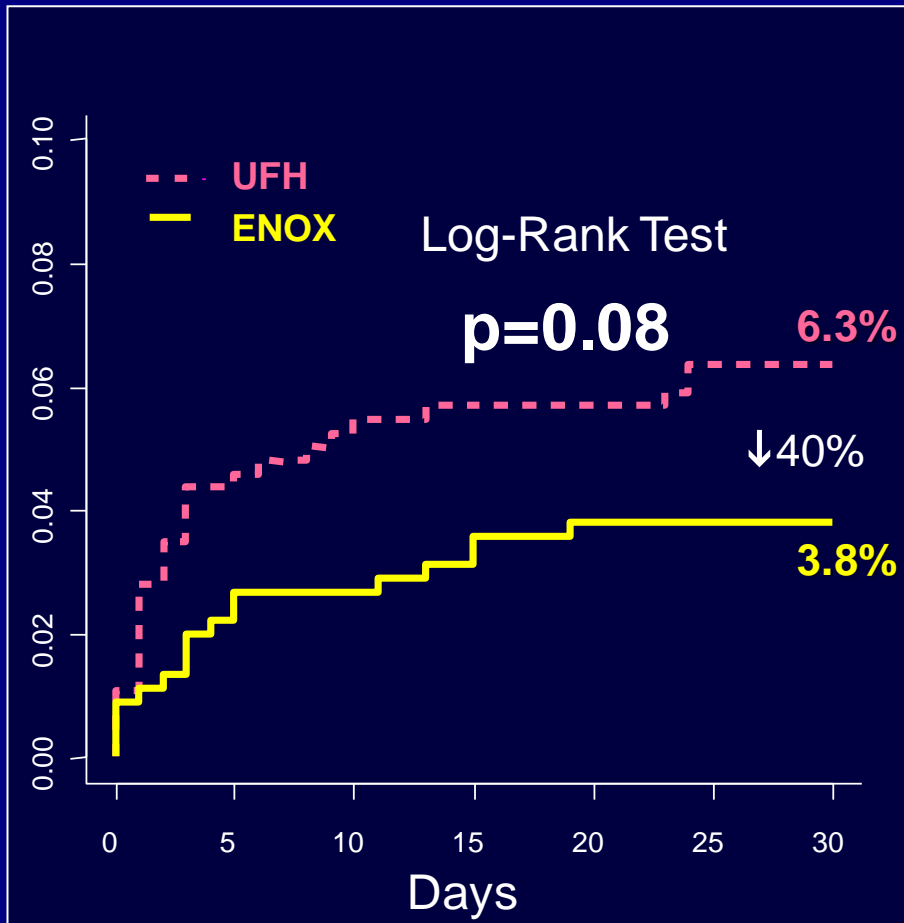
Death, re-MI or Urgent Revascularization





Death (any)

Death *or* resuscitated cardiac arrest

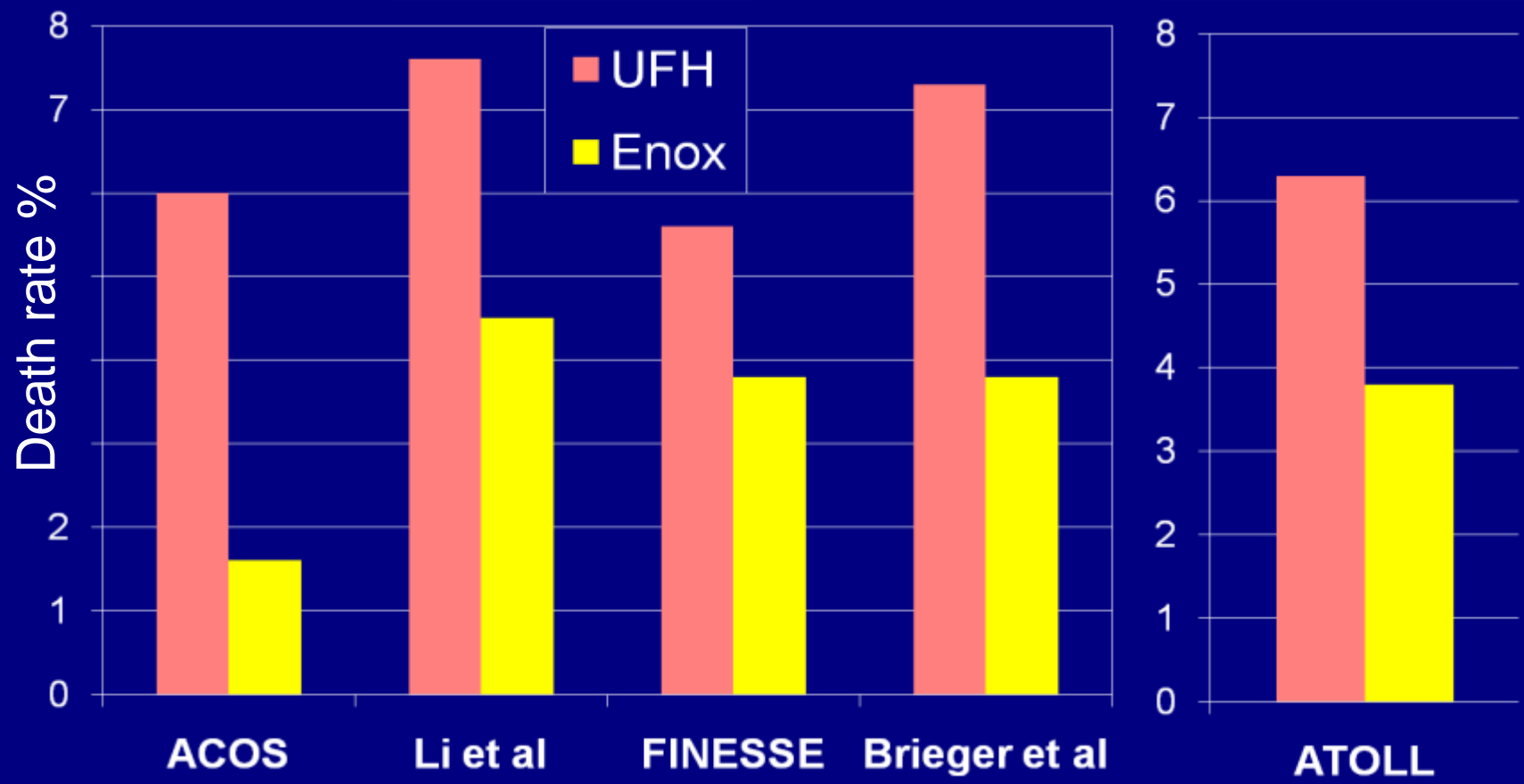




Death finding → Chance finding?

REGISTRIES

RANDOMIZED

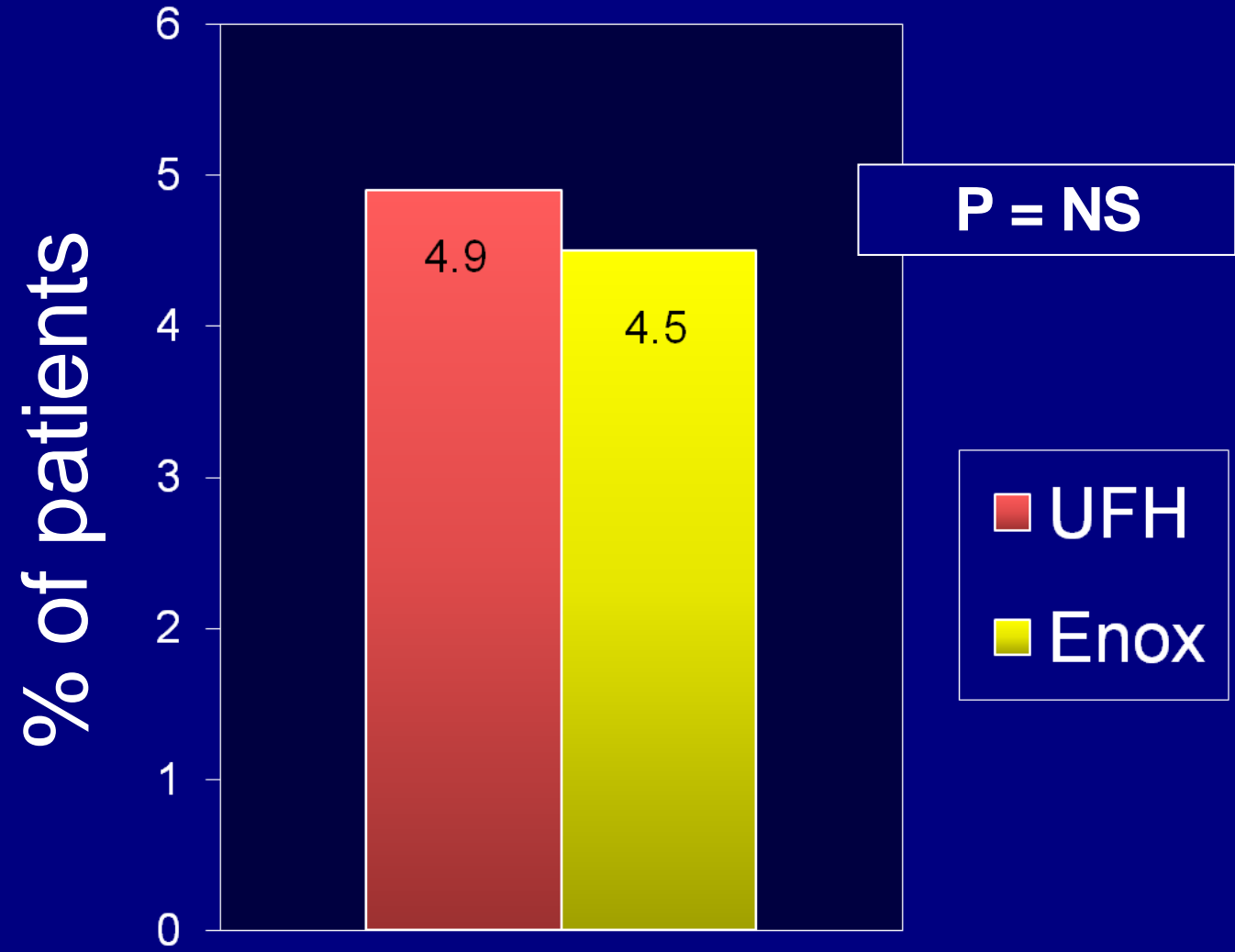


Zeymer et al. Eurointervention 2009;4:524-8. Li et al. Am Heart J 2010;159:684-90.
Montalescot et al. JACC CI 2010;3:203-12. Brieger et al. CCI 2010 (DOI:10.1002/ccd.22674)



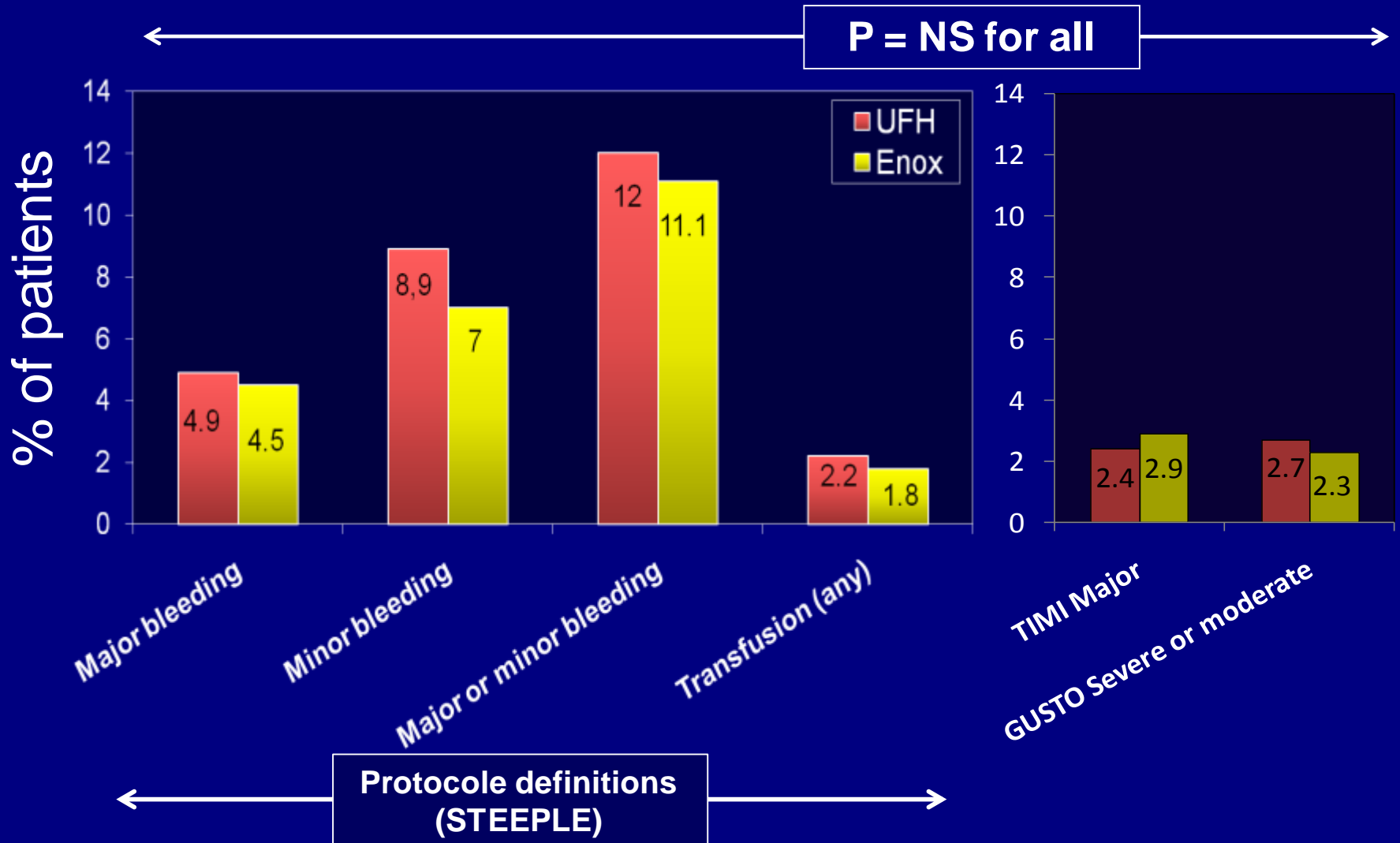
Main Safety Endpoint

Non-CABG Major Bleeding (STEEPLE definition)





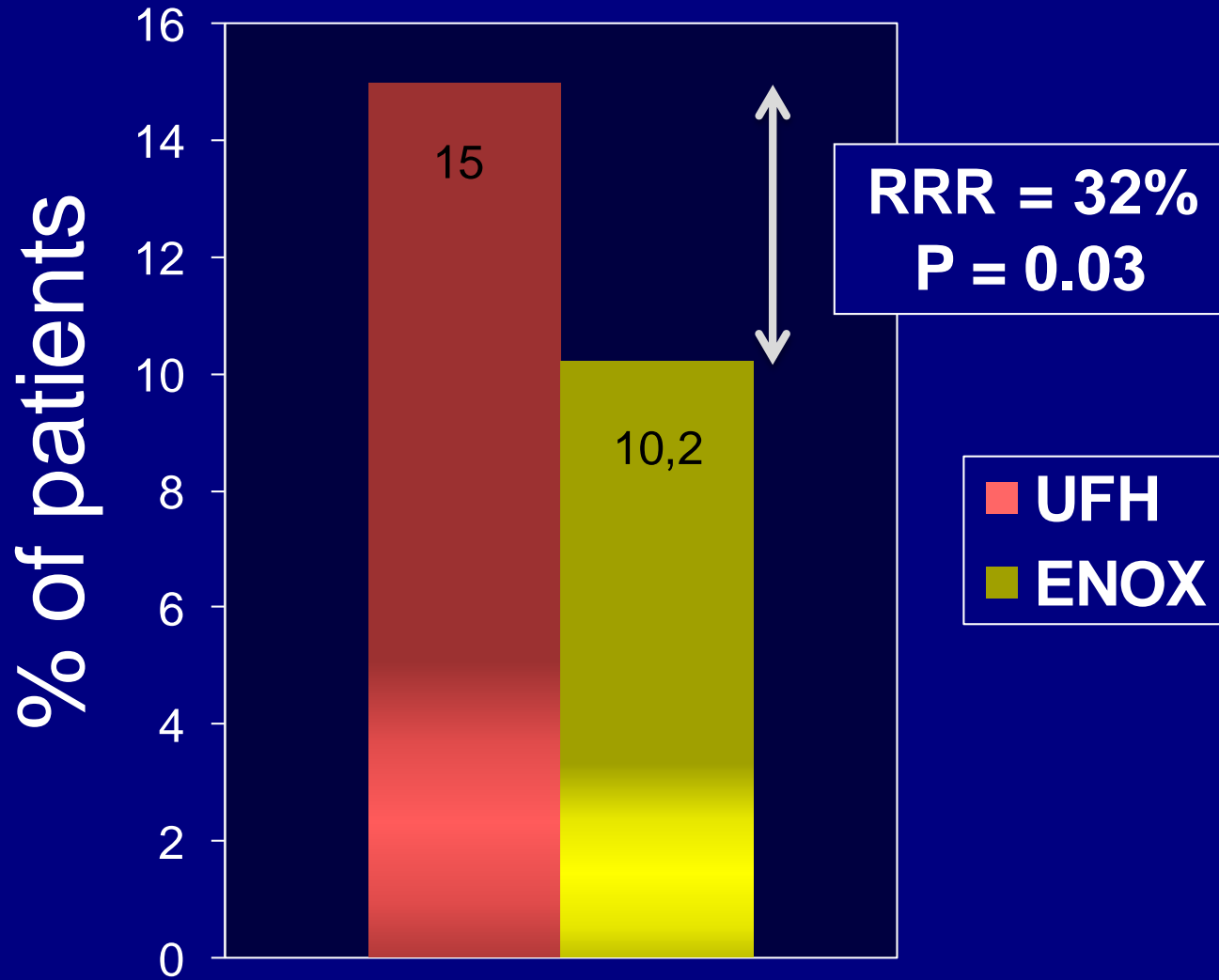
All Safety Endpoints





Death, Complication of MI or Major bleeding

Net clinical benefit





Study Limitations

- Not a pivotal registration trial → Independent trial led by the investigators
- Medium size trial → « Real life » population (>70% Rx in the field) and no prior anticoagulation
- Misses its primary EP, a mix of ischemic, safety and « classic » surrogate EP → Effective on hard ischemic EP
- Reflects practice in a limited number of countries → Contemporary study (>70% of GIIbIIIa, >60% high dose clopidogrel, >66% radial)



Conclusions

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

- Did not reduce procedural failure
- **Reduced serious ischemic events**, on top of intense antiplatelet therapy
- Had a good safety profile, with a **superior net clinical benefit**



Special Thank to:

INVESTIGATORS – **Austria**: WR. Benzer, K. Huber, F. Leisch, F. Weidinger –
France: F. Adnet, M. Angioi, B. Barberon, JF. Benezet, JL. Bonnet, J. Boschhat, B. Boulanger, D. Carrie, T. Chouihed, P. Coste, Y. Cottin, H. Courcoux, C. Cuvier, N. Danchin, JL. Ducasse, F. Duclos, P. Ecollan, S. Elhadad, E. Filippi, M. Freysz, F. Funck, S. Gallula, B. Gelée, A. Greffet, P. Henry, A. Jacquemin, T. Joseph, JM. Lablanche, H. Lardoux, H. Le Breton, B. Lederman, A. Margenet, G. Mehu, O. Nallet, F. Paganelli, M. Pansieri, L. Payot, C. Pougues, E. Salengro, C. Spaulding, G. Steg, O. Stibbe, E. Teiger, M. Thicoipe, C. Thuaire, J. Treuil, O. Wittenberg, O. Wolf – **Germany**: D. Andresen, C. Axthelm, Fischer, E. Girth, E. Hauptmann, U. Zeymer – **USA**: M.Cohen, F. Shamoon

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PIERREL Research– L. Basso, L. Merlini, M. Mazzoleni

ACTION study Group – ME. Assossou, M. Aout, B. Bertin, D. Brugier, JP. Collet, M. Courreges-Viaud, V. Gallois, P. Gallula, V. Jouis, S. Kabla, C. Misse, G. Ngouala, A. Pena, S. Paulsrud, N. Vignolles