Anticoagulation in acute coronary syndrome

Is there a real need for new agents to optimize efficacy/safety balance

Professor Yoseph Rozenman

The E. Wolfson Medical Center

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Disclosures

I have the following potential conflicts of interest to report:

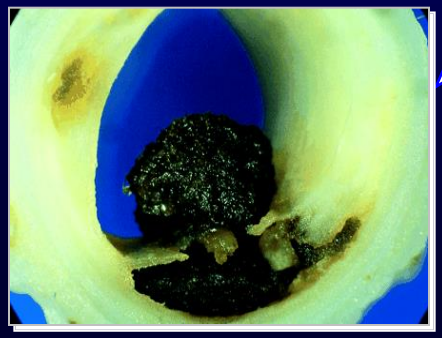
- **Consulting and or lecture fees**: Abott, Boston-Scientific, Medtronic, Pfizer, Sanofi-Aventis, MSD, AstraZeneca, Elli-Lilly, Bayer, Boehringer Ingelheim

Presentation

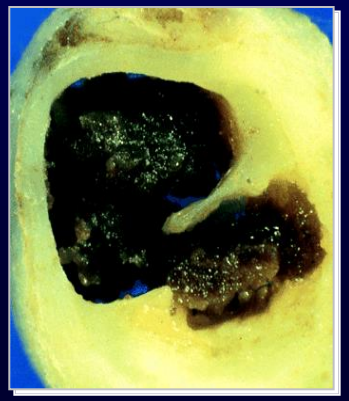
Ischemic Discomfort

Working Dx

Acute Coronary Syndrome



Culprit Plaque



ECG

No ST Elevation

ST Elevation

Biochem. Marker

Myocardial Infarction

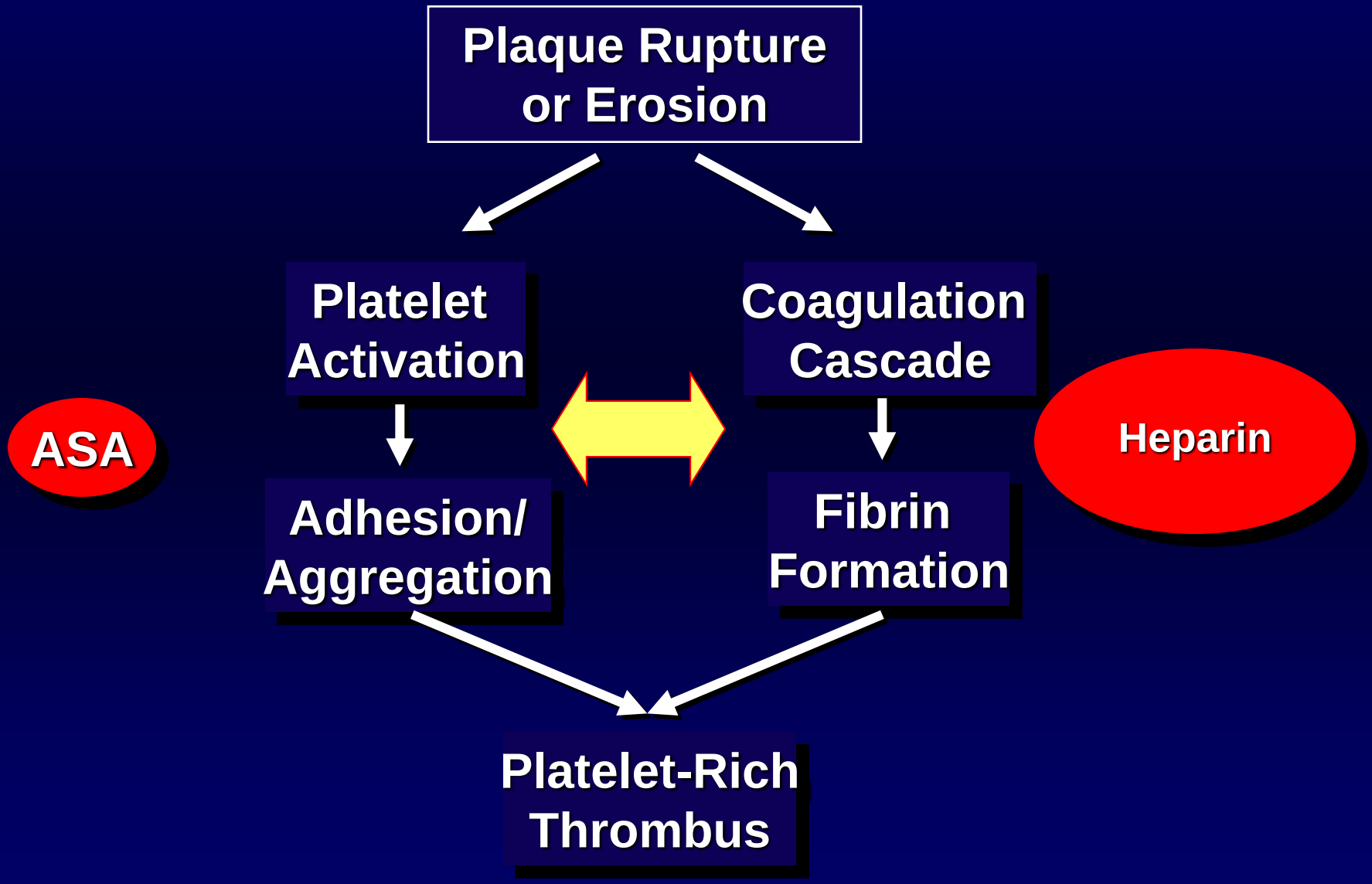
Final Dx

Unstable Angina

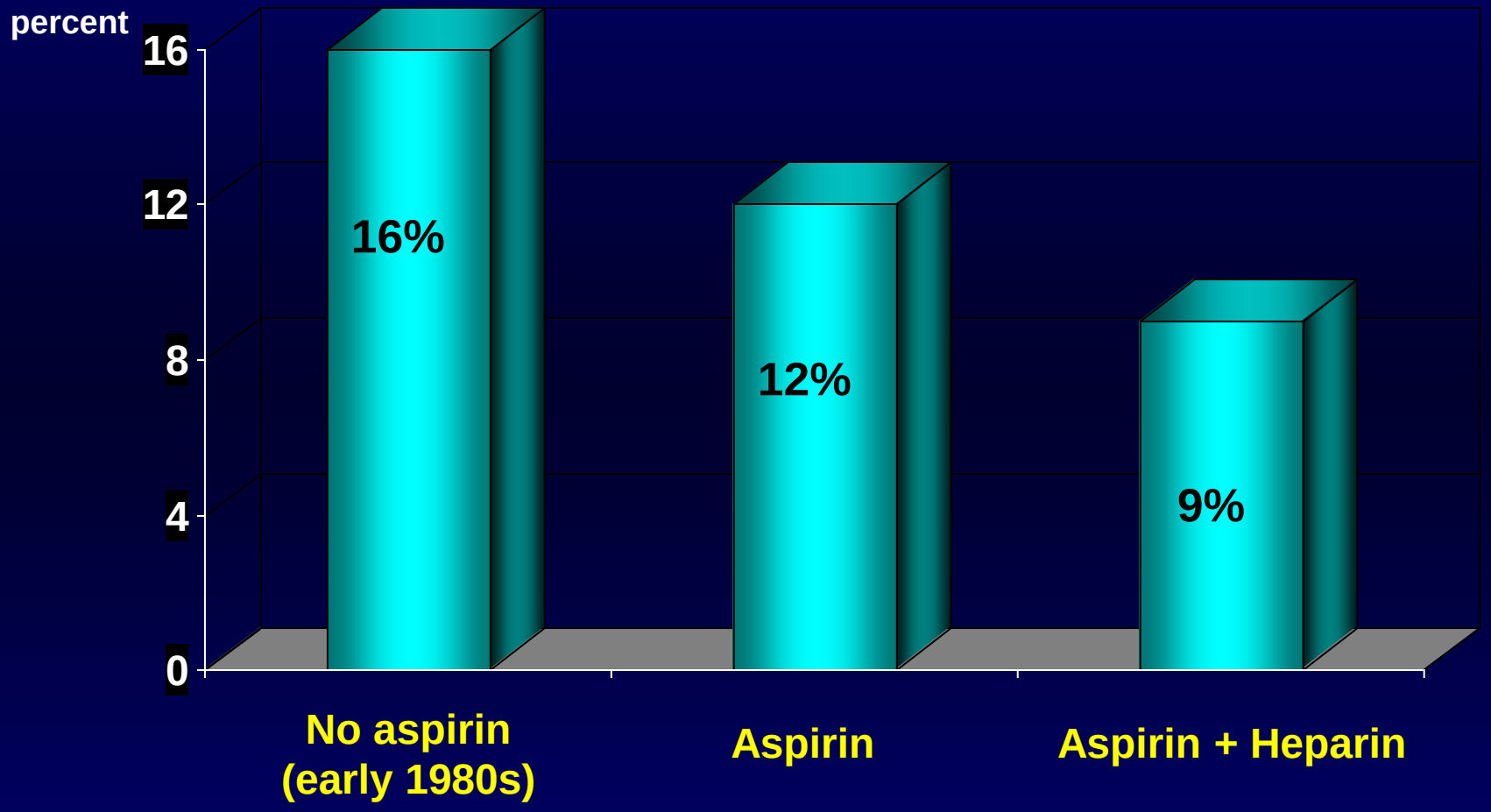
NQMI

Qw MI

Antithrombotic Therapy in ACS

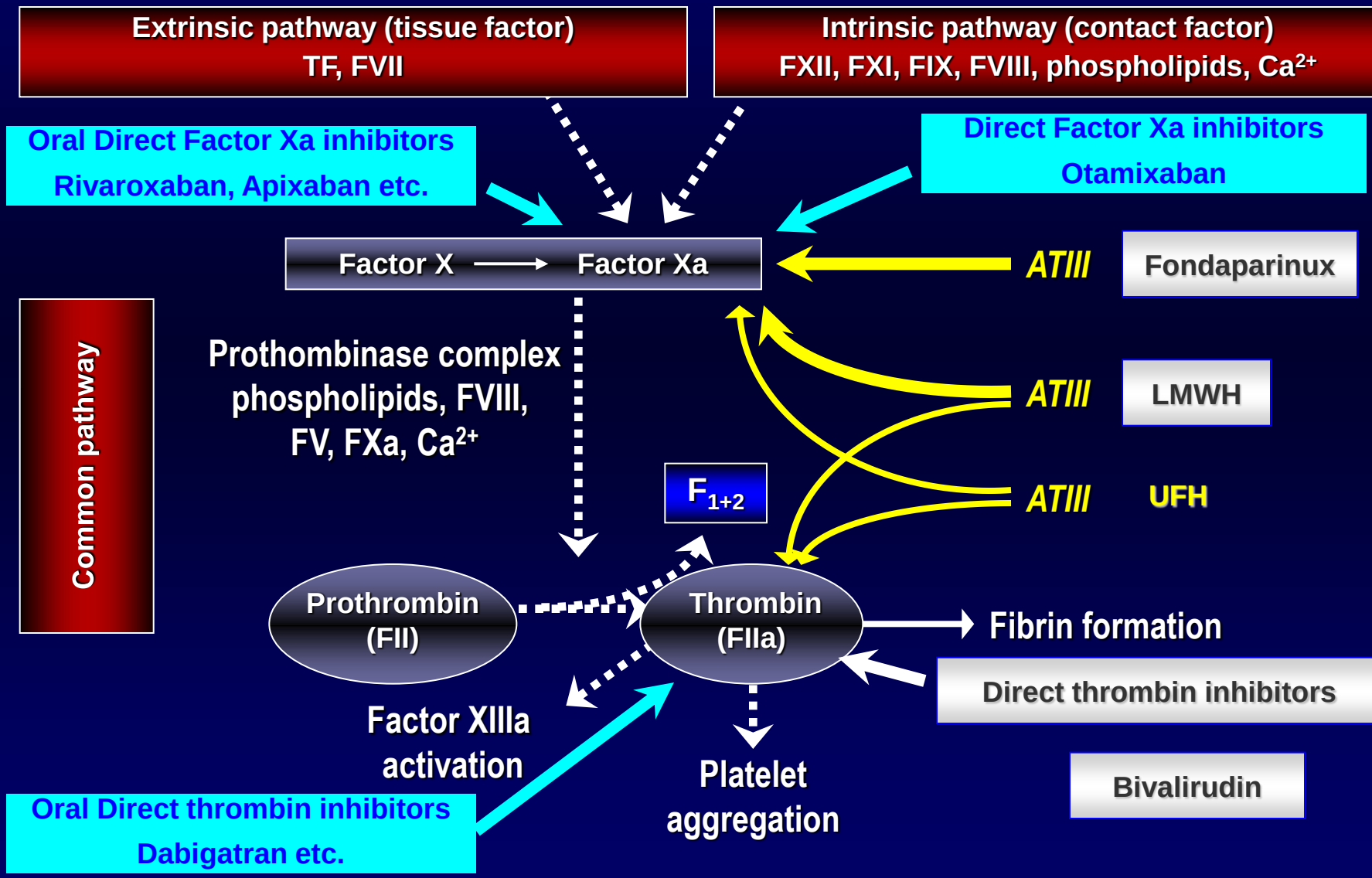


Incidence of death and MI In patients with ACS: Historic perspective



Can we do better with newer antiplatelets and anticoagulants?

Anticoagulation: Alternatives "beyond" Unfractionated Heparin (UFH)



ACS: Importance of Culprit Plaque Stabilization

ACS

ST Elevation

Reperfusion and culprit plaque stabilization

1. Primary PCI
2. Fibrinolysis + Antithrombotics
   - Early PCI

Non ST Elevation

Culprit plaque stabilization

1. Anti-thrombotic Rx
2. Early PCI

The best way to stabilize a culprit plaque is with a stent

70 YO woman admitted with chest pain ECG changes and mild troponin elevation

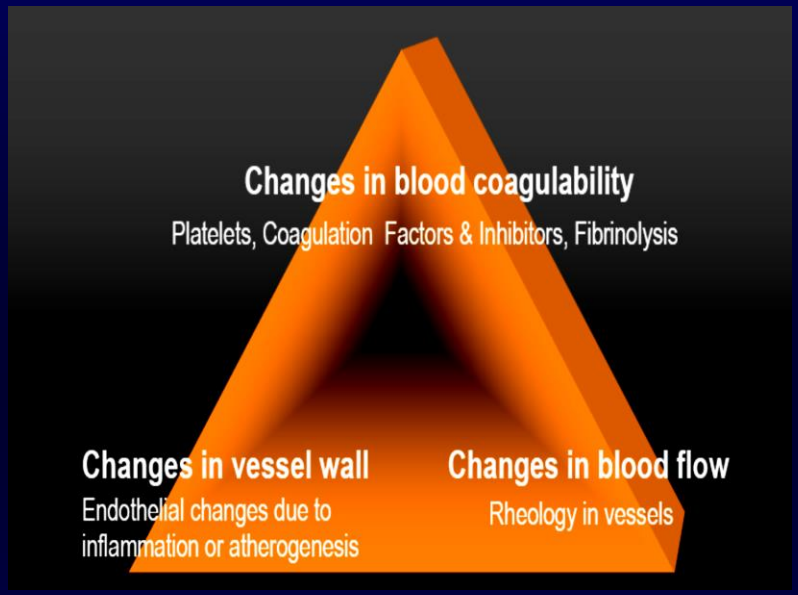
- First manifestation of CAD
- Currently (6PM): stable, in no distress
- Planned for cardiac cath – next morning

Options for anticoagulation (NSTEMI)

- UFH
- Bivalirudin
- Enoxaparin
- Fondaparinux

Virchow's Triad
Implication for therapy in ACS and PCI

When antiplatelet therapy is adequate antithrombins are necessary as long as there is abnormal flow



Rudolf Virchow

1821-1902

Antithrombins in ACS
Basic Principles

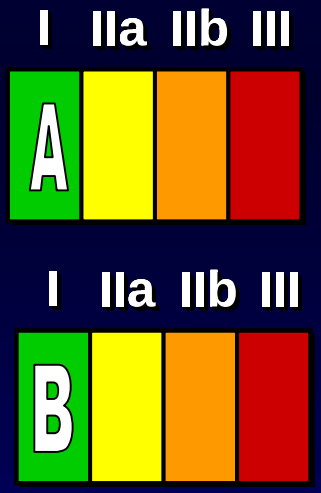
- **Upstream: Before PCI**
  - **Prevent vessel closure**
    - **Low flow condition**

- **During PCI (with optimal antiplatelet therapy)**
  - **Prevent catheter thrombosis**
  - **Careful titration to prevent bleeding**
    - **Puncture site and elsewhere**

- **After PCI**
  - **Not indicated unless:**
    - **Inadequate PCI result – abnormal flow**
    - **Other indications – AFib, LV thrombus etc**

NSTEMI: Initial Invasive Strategy: ACC/AHA Guidelines 2011

Anticoagulant therapy should be added to antiplatelet therapy in UA/NSTEMI patients as soon as possible after presentation.



- For patients in whom an invasive strategy is selected, regimens with established efficacy at a:
  - *Level of Evidence: A*
    - enoxaparin and UFH
  - *Level of Evidence: B*
    - bivalirudin and fondaparinux*

*If fondaparinux is used, it must be coadministered with another anticoagulant with Factor IIa activity, i.e., UFH

Study Design

High-Risk ACS Patients

At least 2 of 3 required:

- Age ≥ 60
- ST ↑ (transient) or ↓
- (+) CK-MB or Troponin

Randomize
(n = 10,000)

Enoxaparin

1 mg/kg SC Q12H

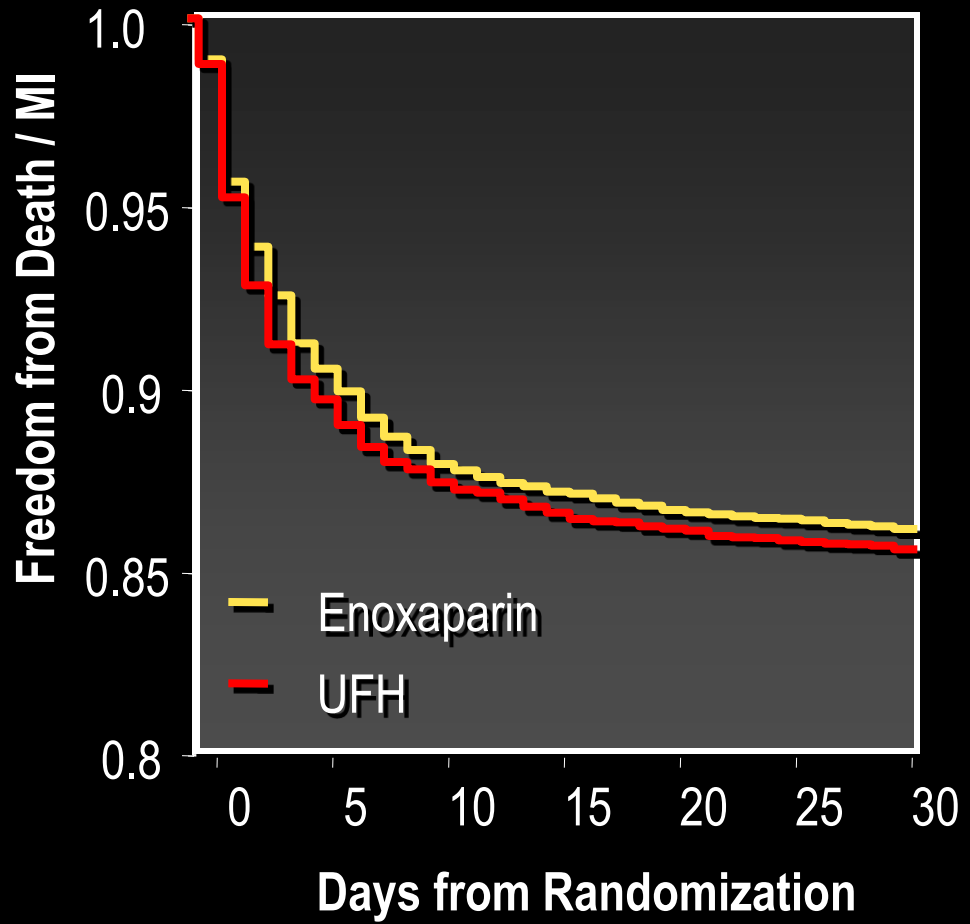
IV Heparin

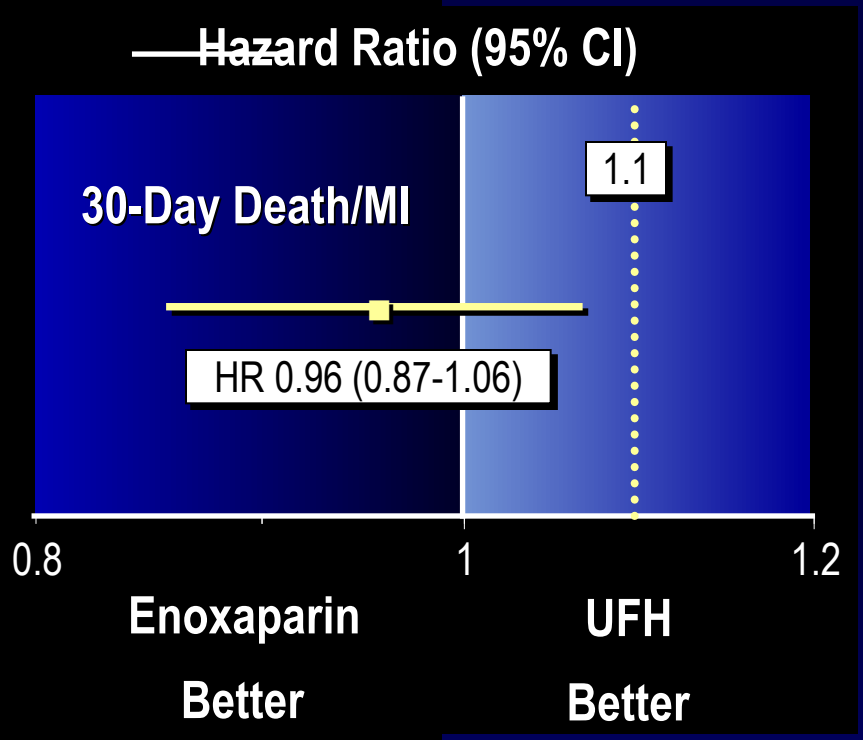
60 U/kg → 12 U/kg/hr
(aPTT 50-70 sec)

Early invasive strategy
Other therapy per AHA/ACC Guidelines
(ASA, β-blocker, ACE, clopidogrel, GP IIb/IIIa)

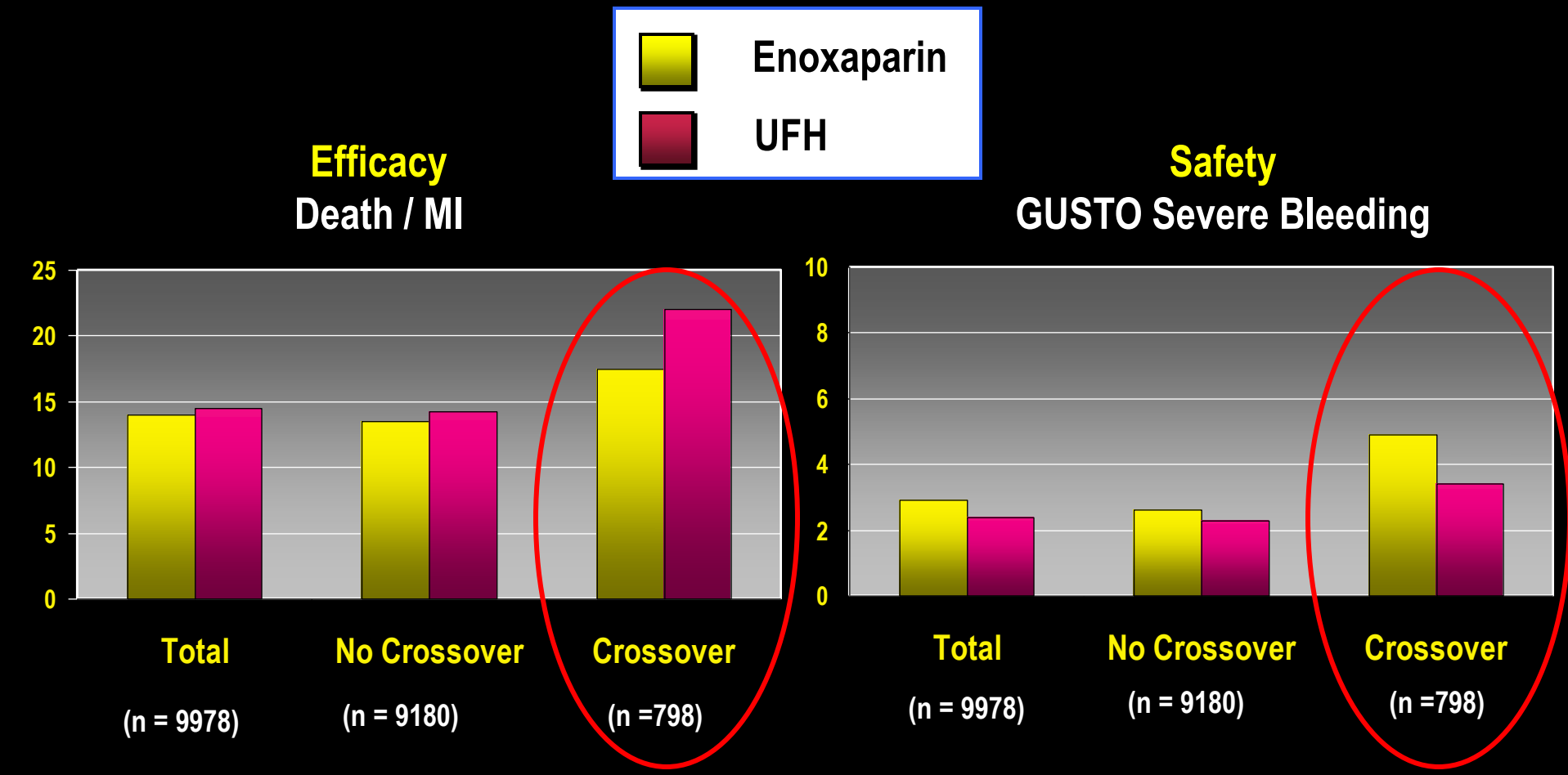
Primary endpoint: Death or MI at 30 days

Death and MI at 30 Days

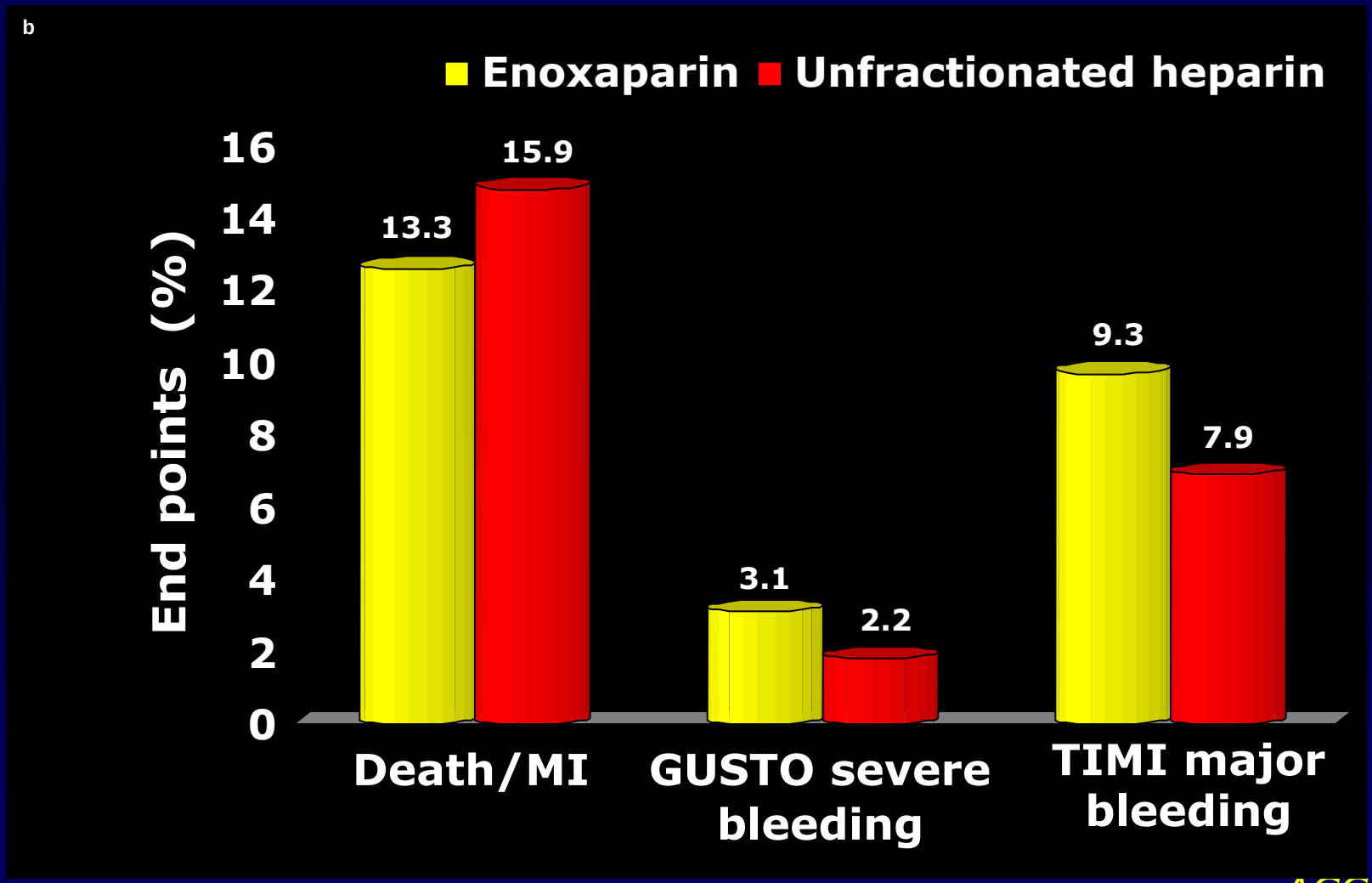




Crossovers: Relation to Outcome Efficacy and Safety



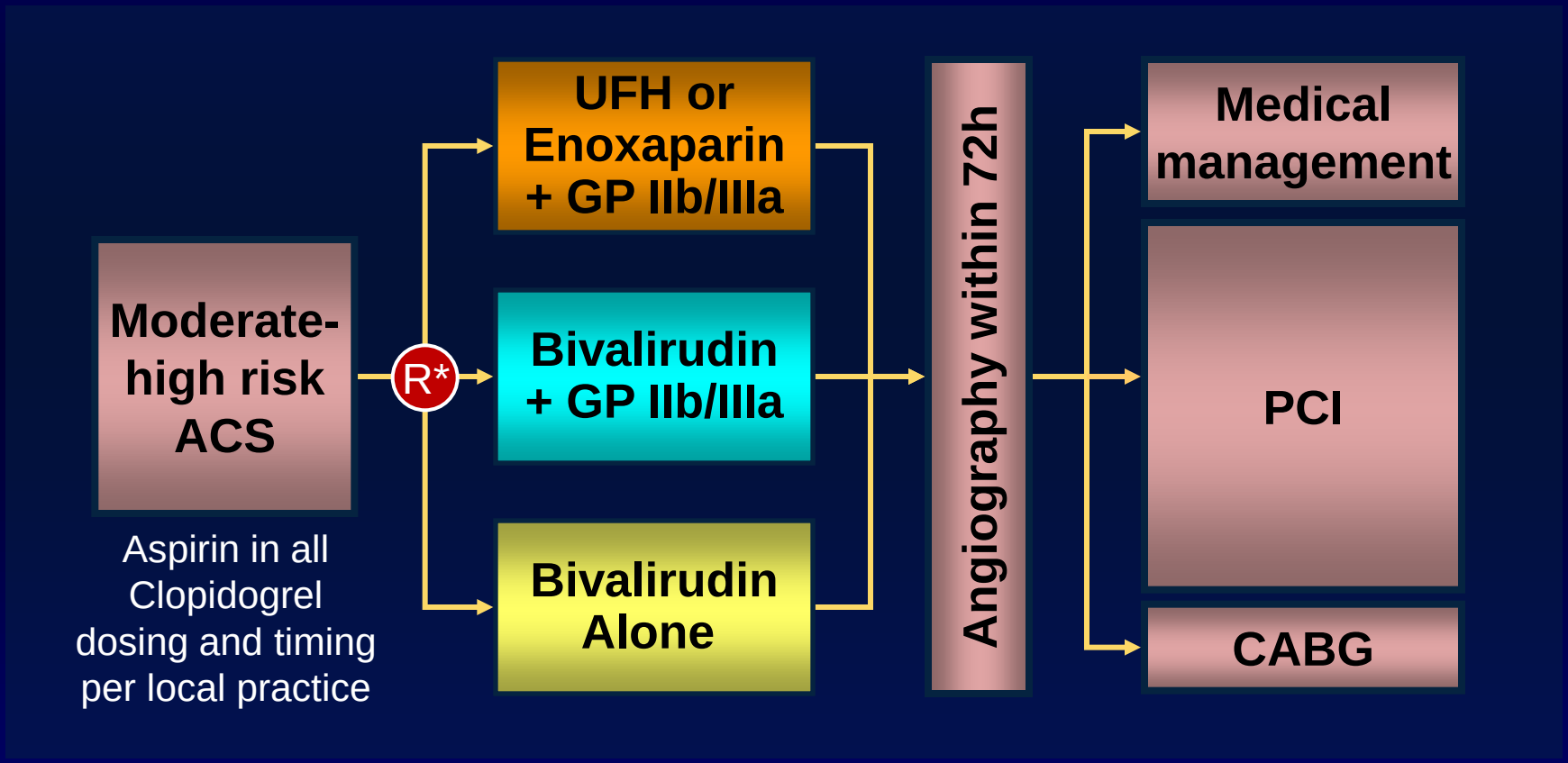
SYNERGY: Consistent antithrombotic treatment



ACC 2004

ACUITY: Study Design

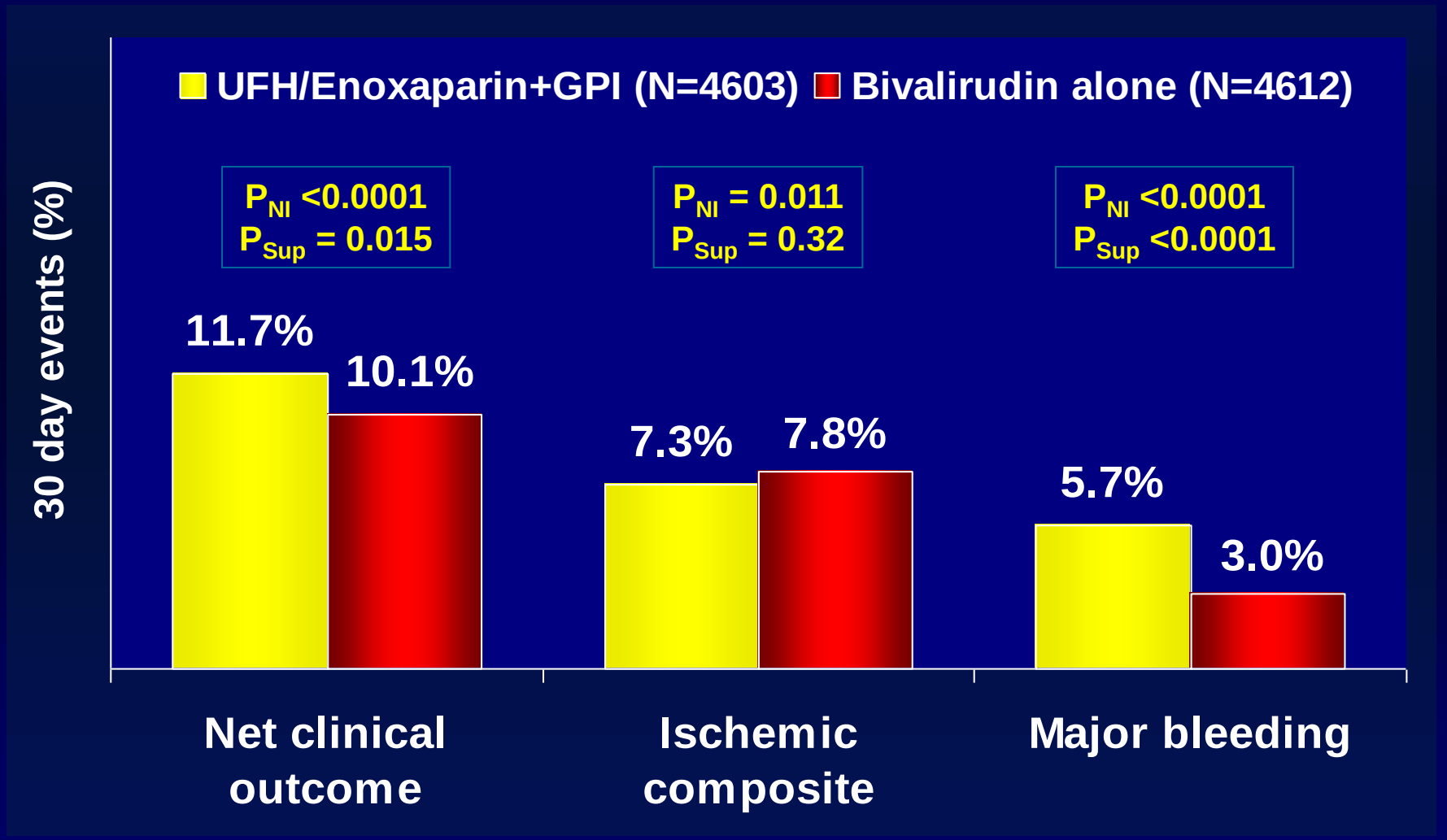
Moderate-high risk unstable angina or NSTEMI undergoing an invasive strategy (N = 13,800)



***Stratified by pre-angiography thienopyridine use or administration**

ACUITY Design. Stone GW et al. AHJ 2004;148:764–75

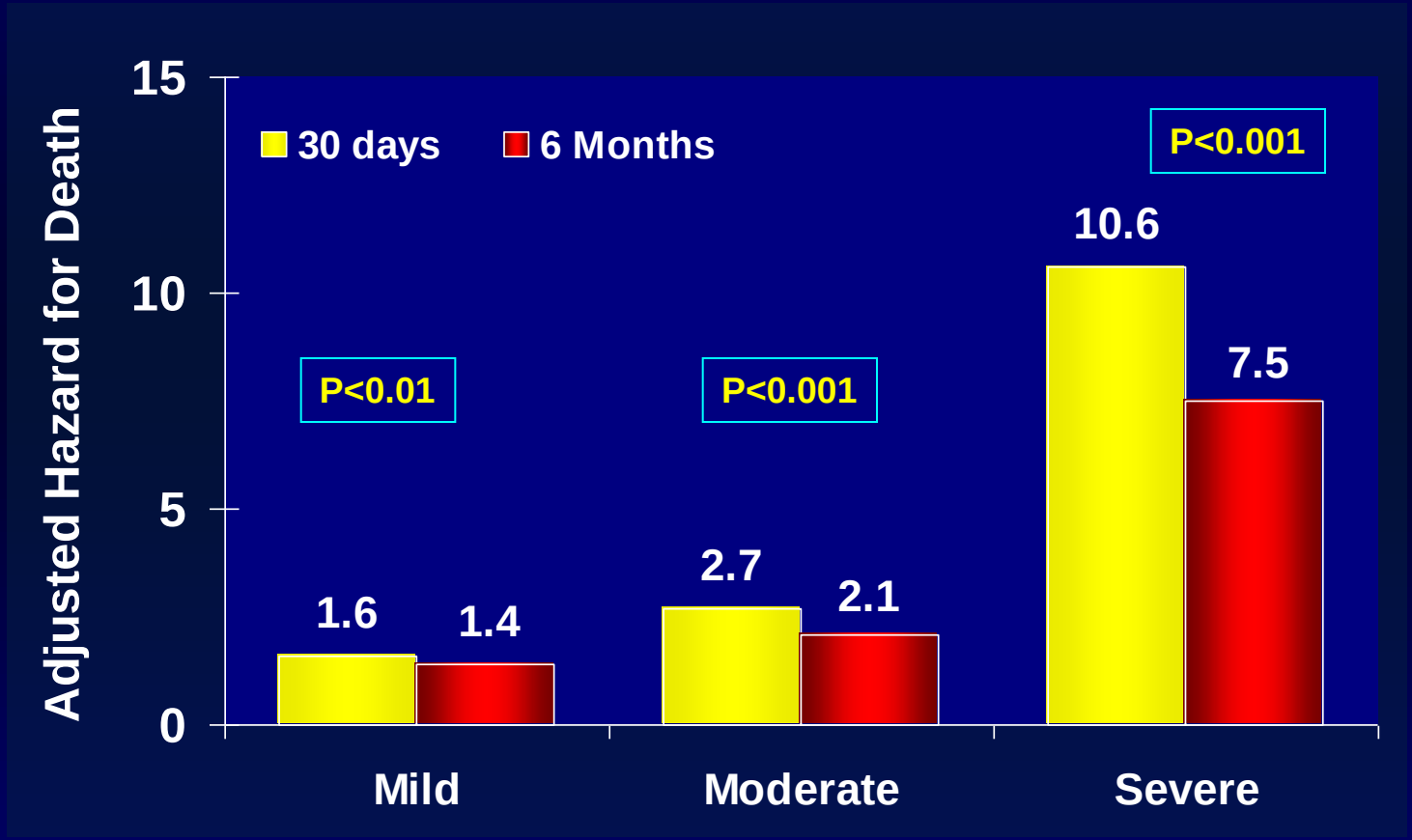
UFH/Enoxaparin + GPI vs. Bivalirudin Alone



Bleeding and Outcomes in ACS

26,452 patients from PURSUIT, PARAGON A, PARAGON B, GUSTO IIb NST

Adjusted Hazard Ratios for Mortality by Bleeding Severity



Bleeding as a time-dependent covariate

Adapted from Rao SV, et.al. *AJC* 2005

Change in PCI Practice after ACUITY

- Radial approach is becoming more common
  - Only 5.8% in ACUITY
  - Impact on bleeding and outcome
- New antiplatelet agents are available
  - Upstream GP IIb/IIIa blockers are rarely used

70 YO woman admitted with chest pain ECG changes and mild troponin elevation

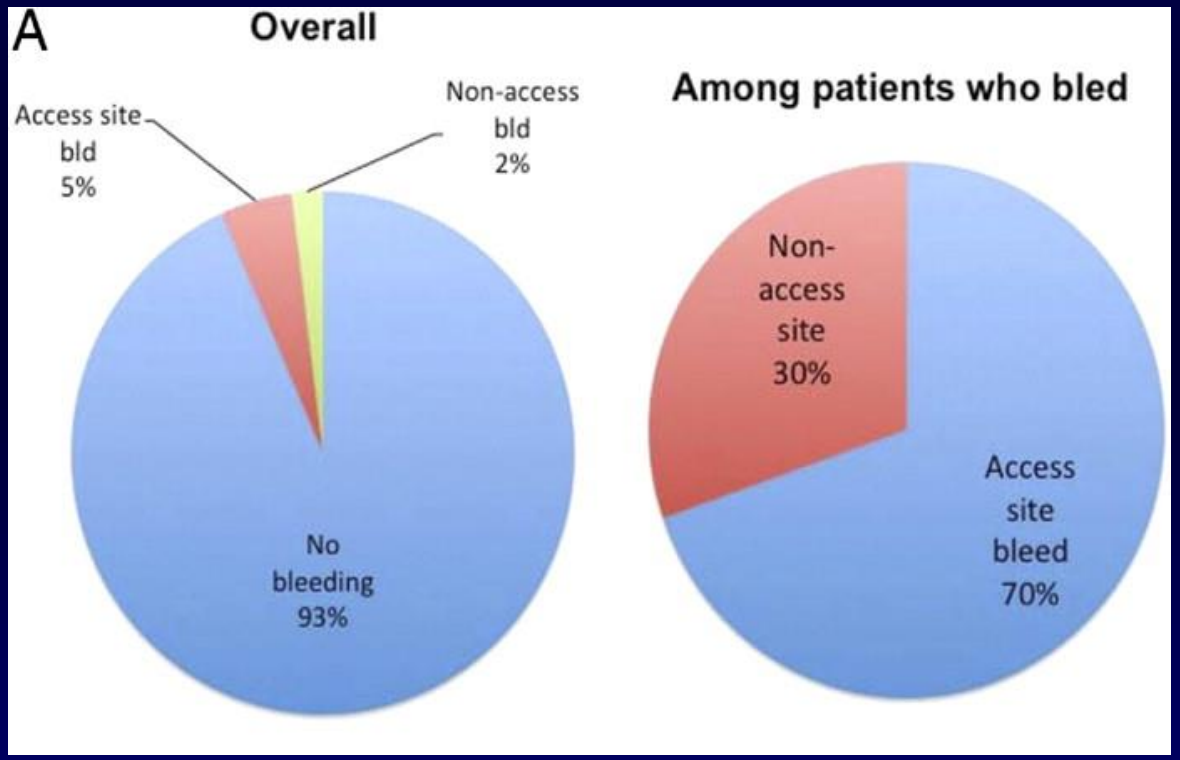
- First manifestation of CAD
- Currently (6PM): stable, in no distress
- Planned for cardiac cath – next morning

Challenge for Anticoagulation

- Safe effective and convenient therapy before catheterization
- Easy transition to cath lab
  - Minimizing bleeding complications

Is Bleeding Still Relevant With Radial Approach to PCI?

Meta-analysis of trials of PCI in ACS

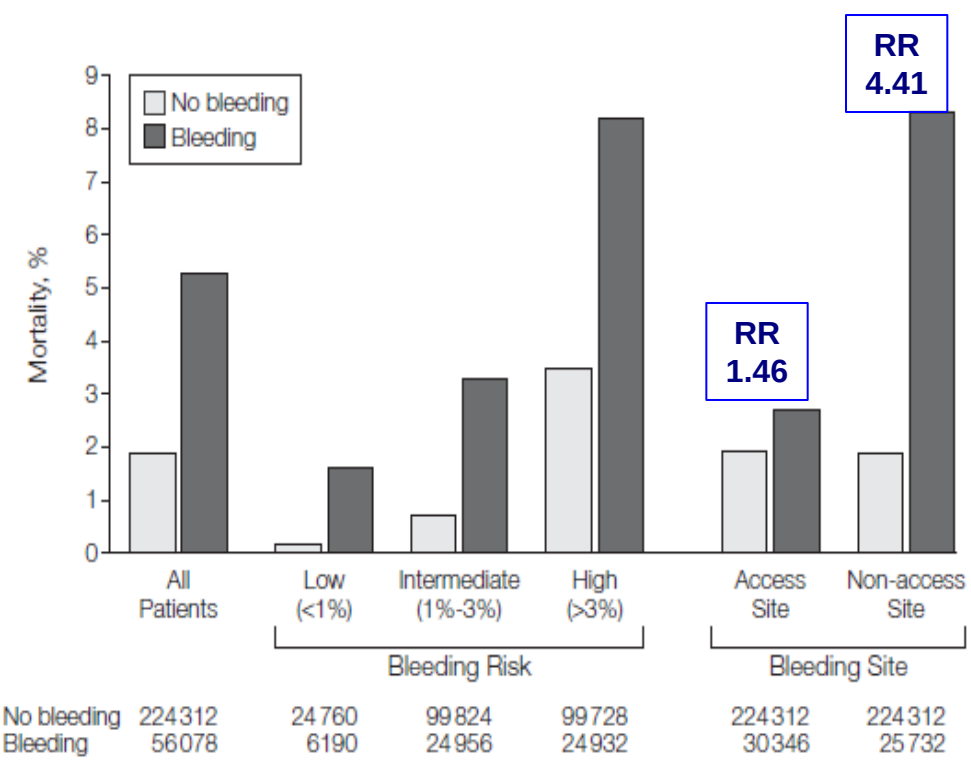


Rao et al. JACC 2010 55: 2187

Bleeding and Mortality in PCI for ACS (NCDR)

- 3 386 688 PCI procedures
- 57 246 bleeding events (1.7%)
- 22 165 in-hospital deaths (0.65%)

Figure 1. In-hospital Mortality in the Propensity-Matched Cohort



- Bleeding is associated with marked increase in mortality
- Risk of bleeding is associated with risk of death
- Non-access site is associated with much higher RR for mortality as compared to access site bleeding

JAMA 2013;309(10):1022-1029

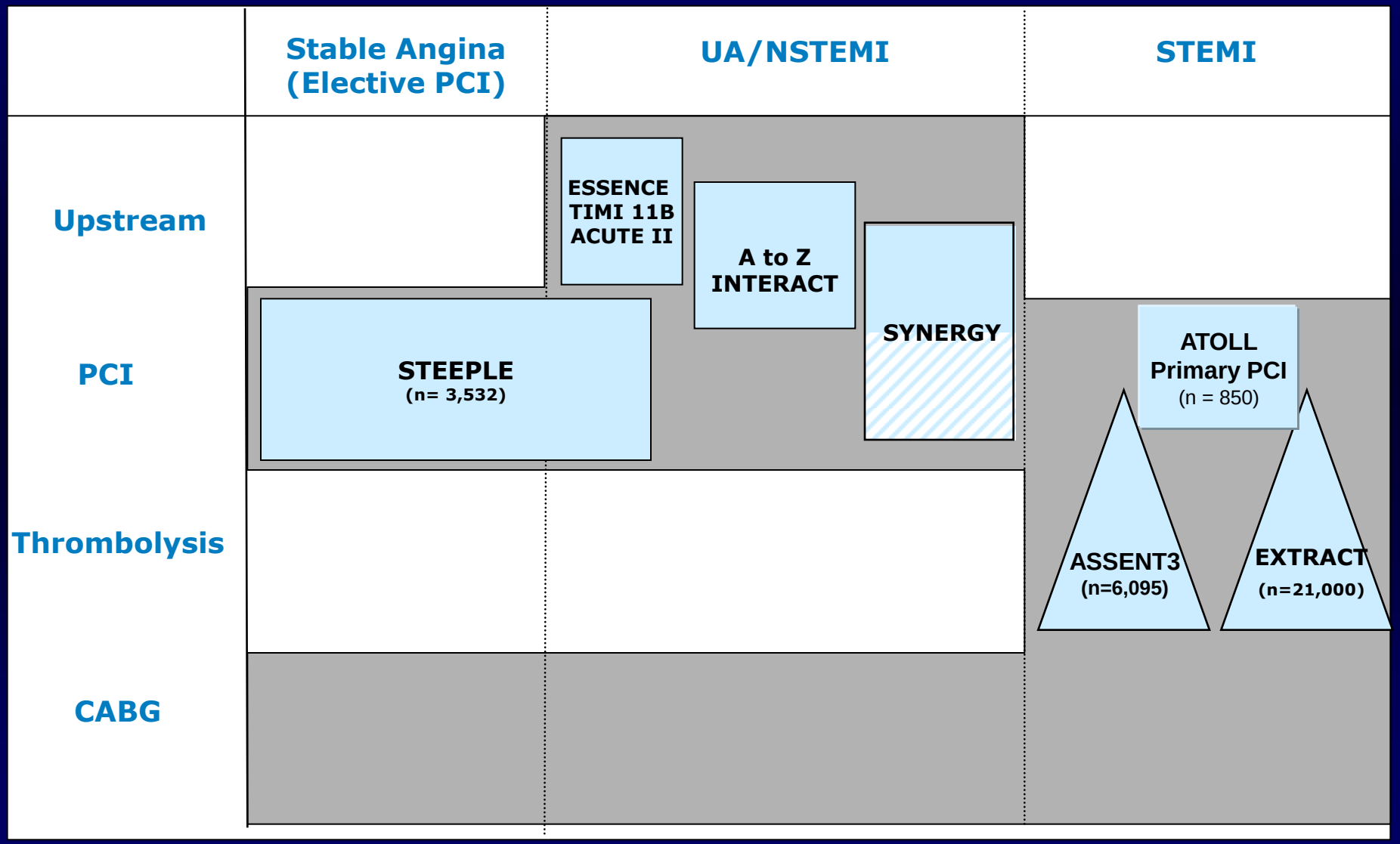
70 YO woman admitted with chest pain ECG changes and mild troponin elevation

- First manifestation of CAD
- Currently (6PM): stable, in no distress
- Planned for cardiac cath – next morning

Immediate therapy (until PCI)

- UFH
  - Theoretically inferior
  - Inconvenient
    - Narrow therapeutic window, dose adjustment etc.
- Bivalirudin
  - Effective, expensive
- Enoxaparin (S.Q)
  - Effective, cheap, simple
  - Commonly used

Enoxaparin vs. UFH: Clinical Trials



70 YO woman admitted with chest pain ECG changes and mild troponin elevation

- First manifestation of CAD
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Anticoagulation during PCI

- Heparin
  - UFH
  - Enoxaparin IV
- Bivalirudin

UNIVERSITY OF GOTHENBURG

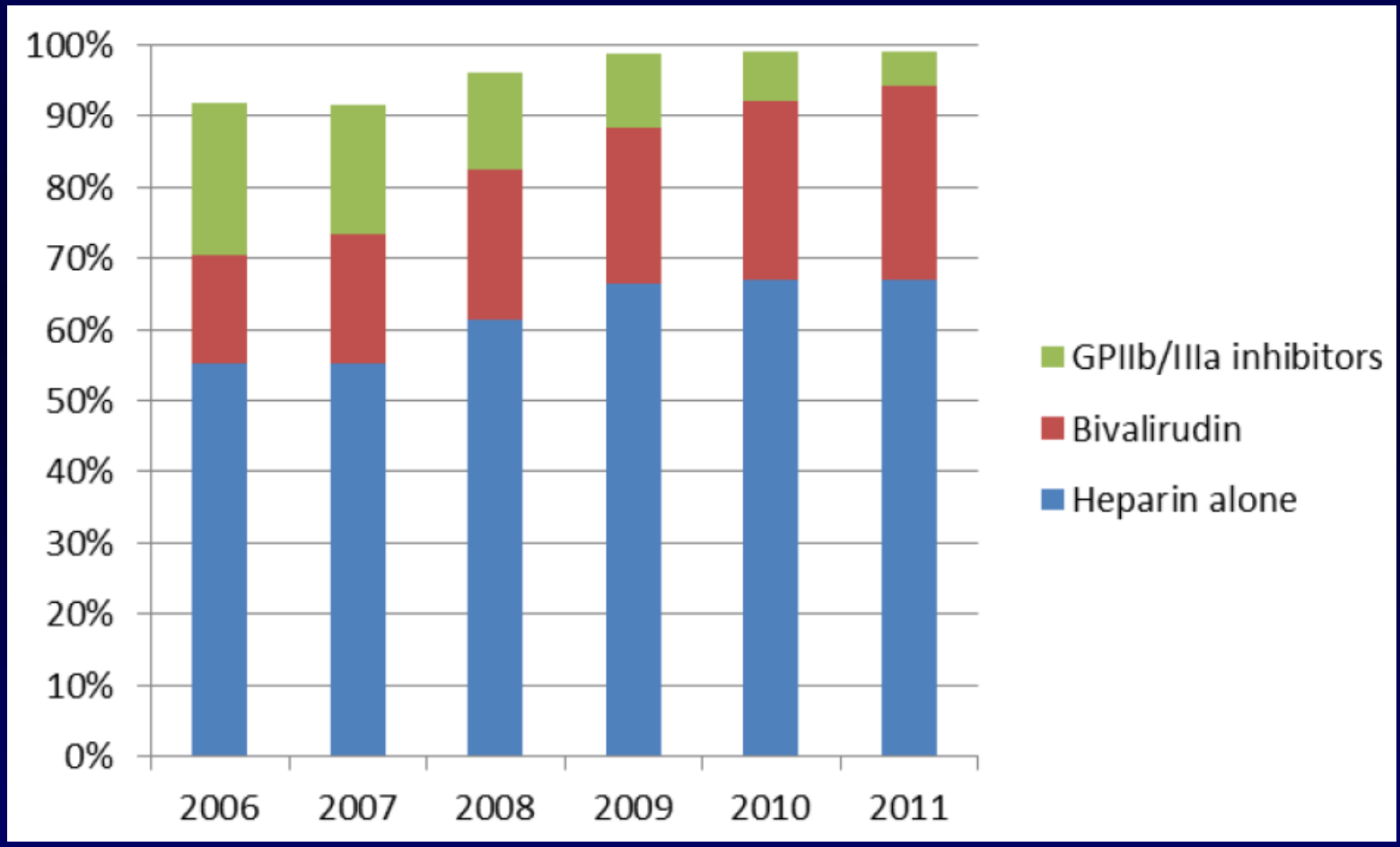
Heparin versus bivalirudin in patients with non ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention

- a report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR)

Oskar Angerås[1], Sasha Koul[2], Måns Söderbom[3], Per Albertsson[1], Truls Råmunddal[1], Göran Matejka[1], Fredrik Scherstén[2], Jonas Oldgren[4], Stefan James[4], Bo Lagerqvist[4], Ole Fröbert[5], Hans Wedel[6], David Erlinge[2], Elmir Omerovic[1]

[1]Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden
[2]Department of Cardiology, Lund University, Lund, Sweden
[3]Department of Economics, University of Gothenburg, Gothenburg, Sweden
[4]Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden
[5]Department of Cardiology, Örebro University Hospital, Örebro, Sweden
[6] Nordic School of Public Health, Gothenburg, Sweden

Antithrombotic Therapy In Sweden PCI for NSTE- ACS

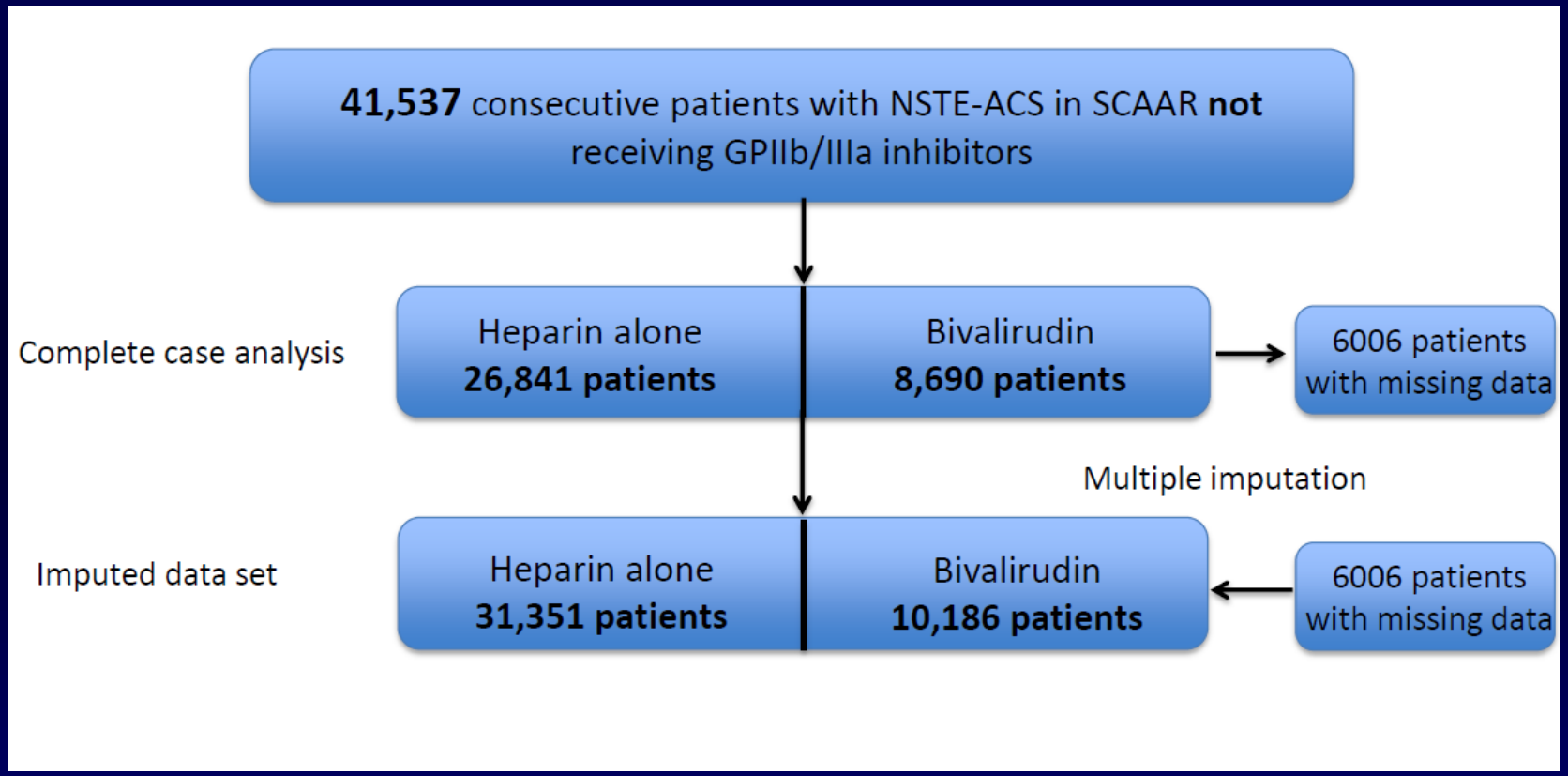


UFH therapy in the cath lab

- UFH is theoretically inferior to modern anticoagulants however it is still very popular in the cath lab due to:
  - Easily titrated with ACT
  - Short acting
  - Has an antidote
  - Familiar to medical staff

Is it really inferior to bivalirudin?

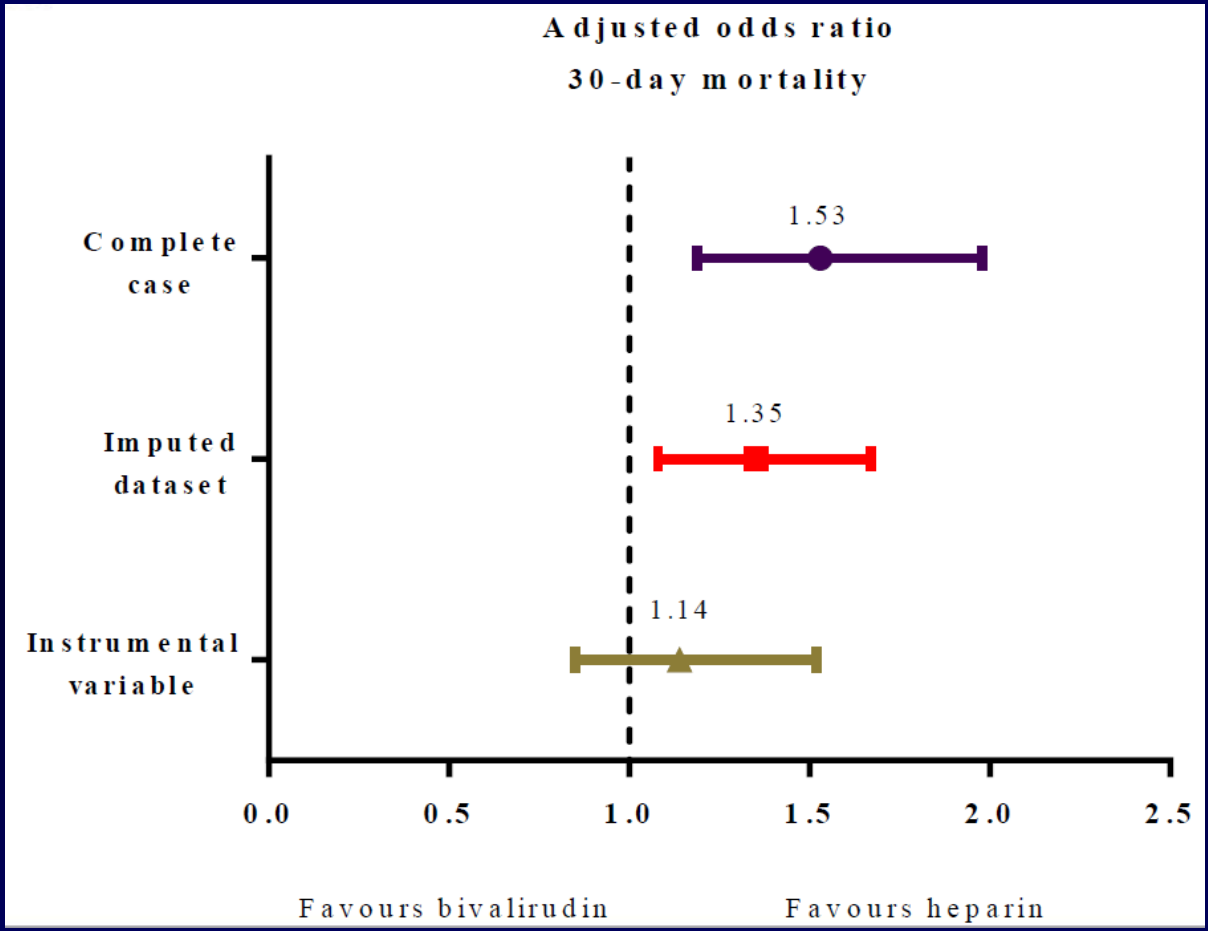
Study Design – Treatment During PCI



Procedural Characteristics

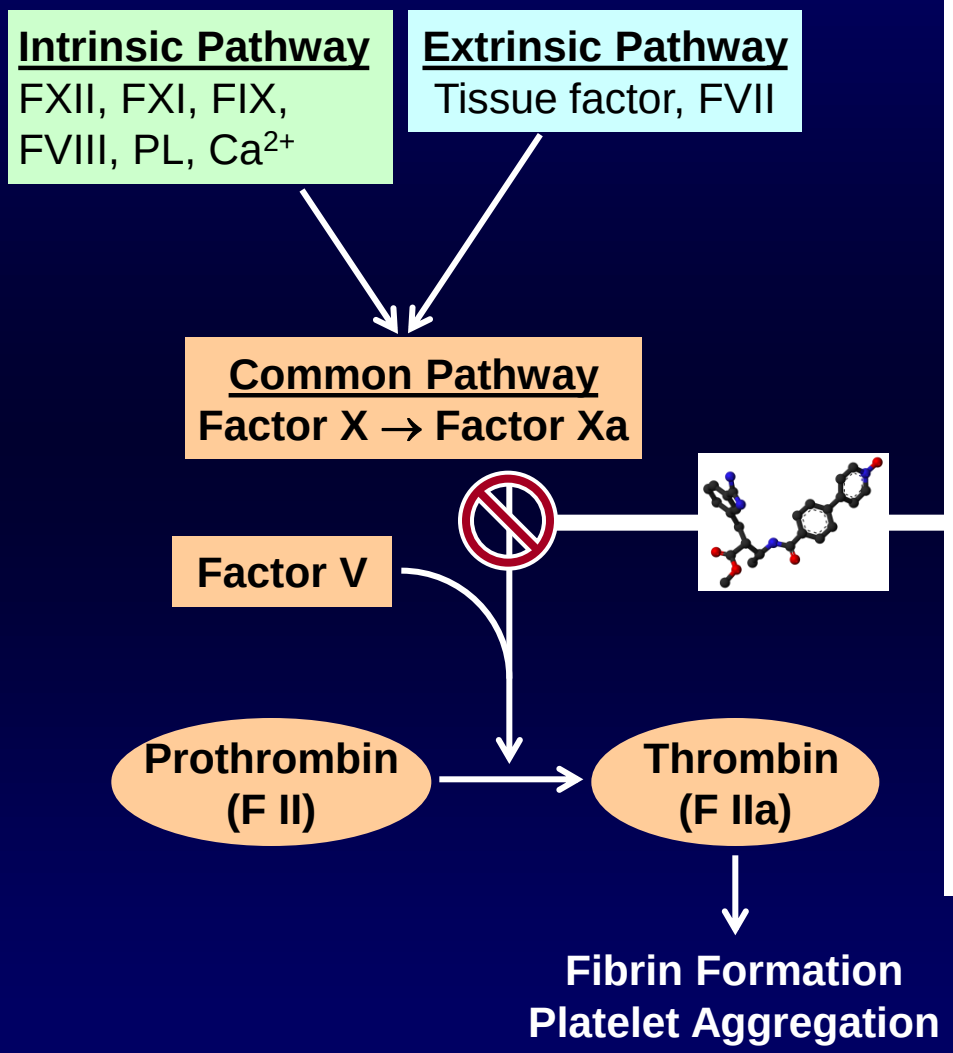
	UFH/LMWH (n=31,351)	Bivalirudin (n=10,186)	P-value	p-value after ps-score adjustment	Missing (n)
UH/LMWH/Fondaparinux (%)	100	22	<0.001		0
Access site					
Femoral (%)	52	54	0.01	1.00	0
Radial (%)	48	46	0.01	1.00	0
Angiographical findings					
One vessel disease (%)	47	43	<0.001	0.70	172
Two vessel disease (%)	30	31	0.11	0.99	172
Three vessel disease (%)	18	20	<0.001	0.91	172
Left main stem disease (%)	4.6	6.0	<0.001	0.42	172
Complete revascularization (%)	65	59	<0.001	0.52	320
Use of stent (%)	92	94	<0.001	0.94	0
Use of DES (%)	42	32	<0.001	0.37	0
No of stents used (mean±SD)	1.4±0.9	1.5±1.0	<0.001	<0.001	0
Mean stent diameter, mm (mean±SD)	2.98±0.49	3.03±0.53	<0.001	0.74	17

Results and Conclusion



A large RCT is planned in Sweden comparing Heparin to bivalirudin in ACS patients treated with new antiplatelet agents

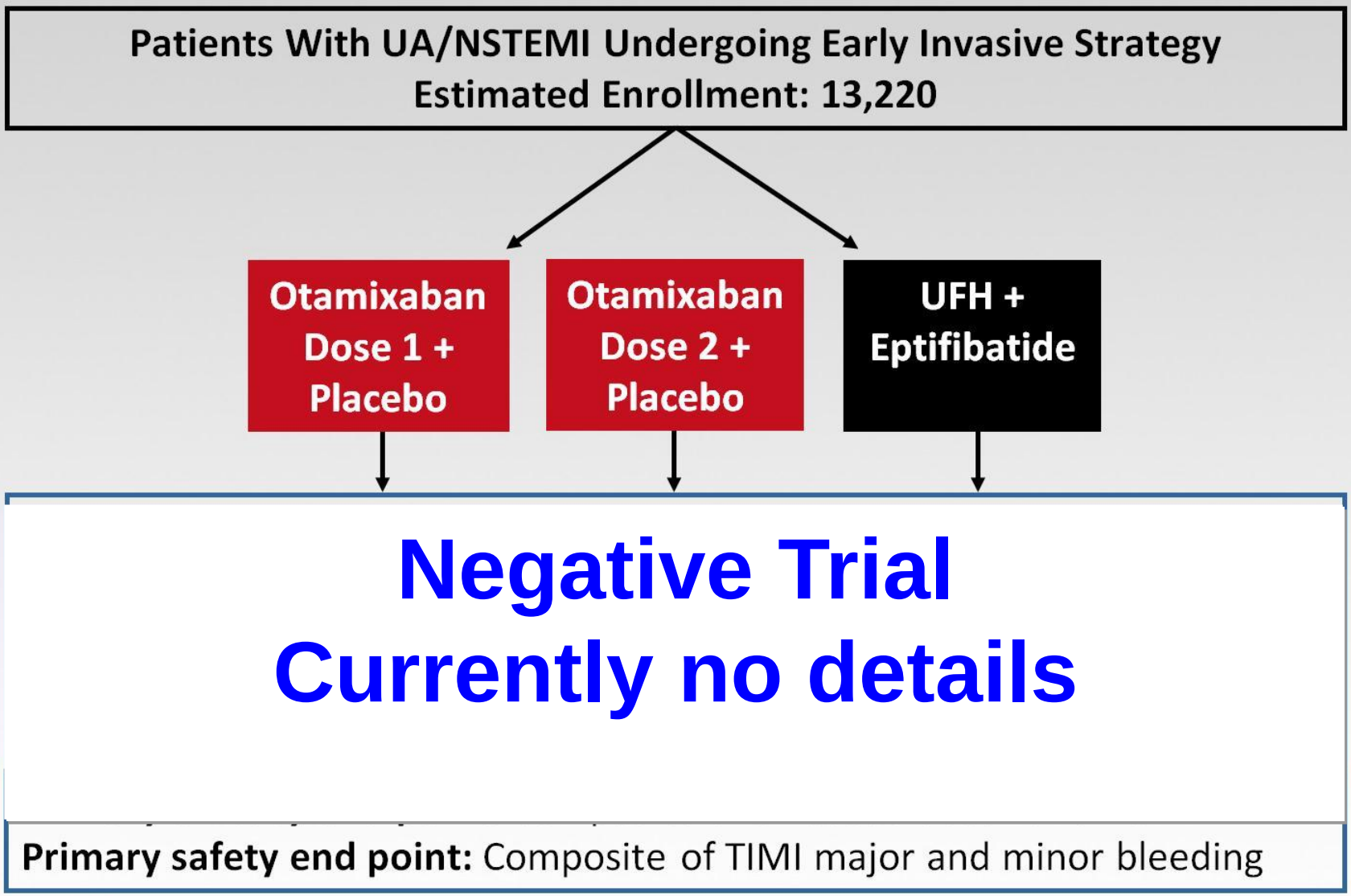
Coagulation Cascade



OTAMIXABAN

- Specific, Direct, IV, Factor Xa Inhib
  - Proximal inhib of coag cascade
- Small molecule
  - Inhibits clot-bound factor Xa, which is inaccessible to large molecule & indirect inhibitors
- Favorable PK/PD profile
  - Short-acting (half-life 30 min)
  - Wt-based bolus & infusion
  - No need for monitoring
  - No significant renal elimination

TAO: Study Design



70 YO woman admitted with chest pain ECG changes and mild troponin elevation

- First manifestation of CAD
- **Currently (6PM):** stable, in no distress
- Planned for cardiac cath – next morning

Anticoagulation for NSTEMI

Future trials will examine alternatives for heparin on top of current background antiplatelet therapy and increasing use of transradial approach

72 years old male in the cath lab with ant. STEMI

- 3 hours of pain
- First presentation of CAD
- No prior therapy

Options for anticoagulation in the cath lab

- UFH
- Bivalirudin
- Enoxaparin

HORIZONS AMI

Harmonizing Outcomes with Revascularization and Stents in AMI

≥3400* pts with STEMI with symptom onset ≤12 hours

Aspirin, thienopyridine

R 1:1

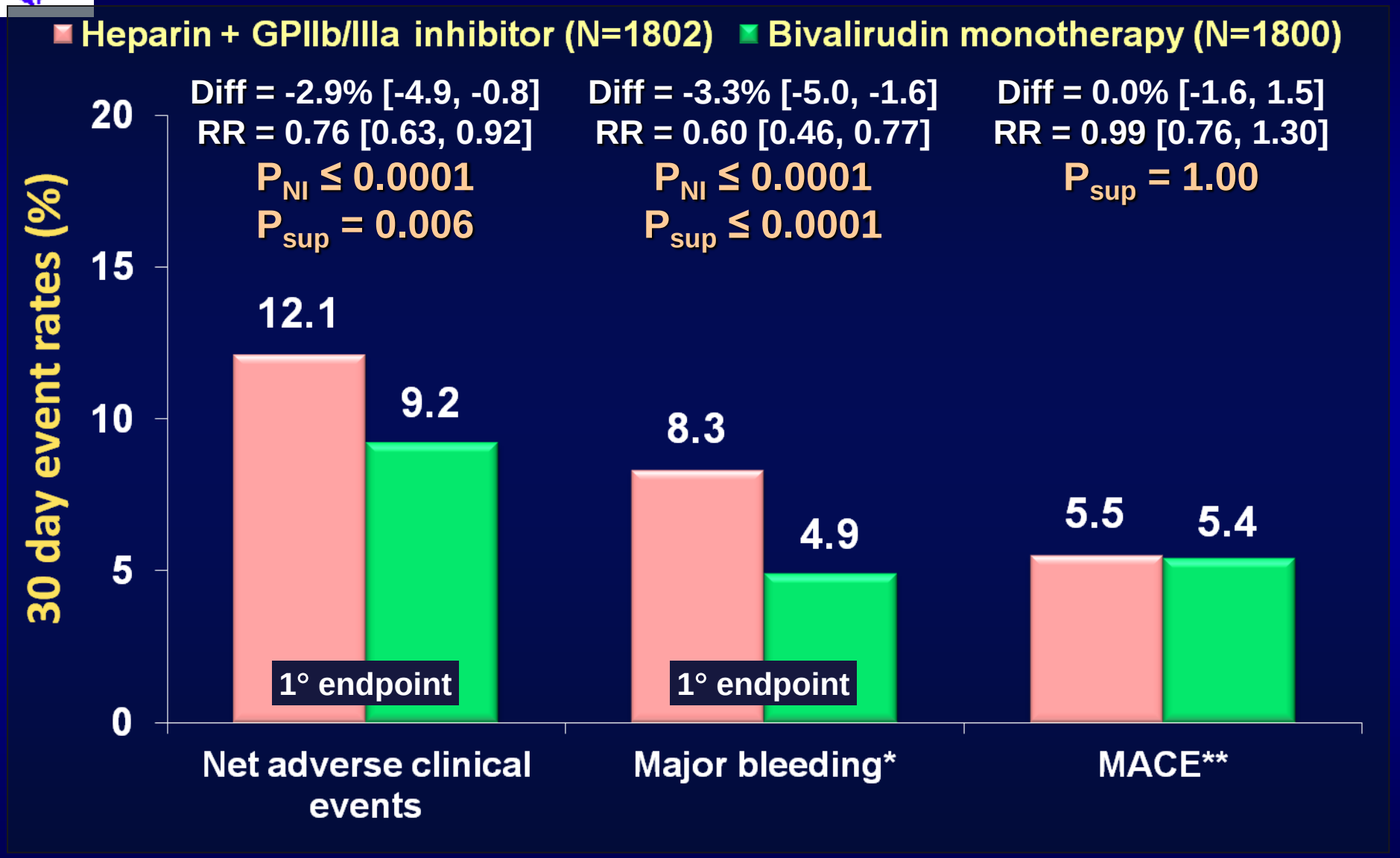
- UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide)
- Bivalirudin monotherapy (± provisional GP IIb/IIIa)

Pharmacology Arm
Primary Endpoints*
30 Day
Intention to Treat Population

* All stent randomization results are still blinded

HORIZONS AMI

Primary Outcome Measures (ITT)

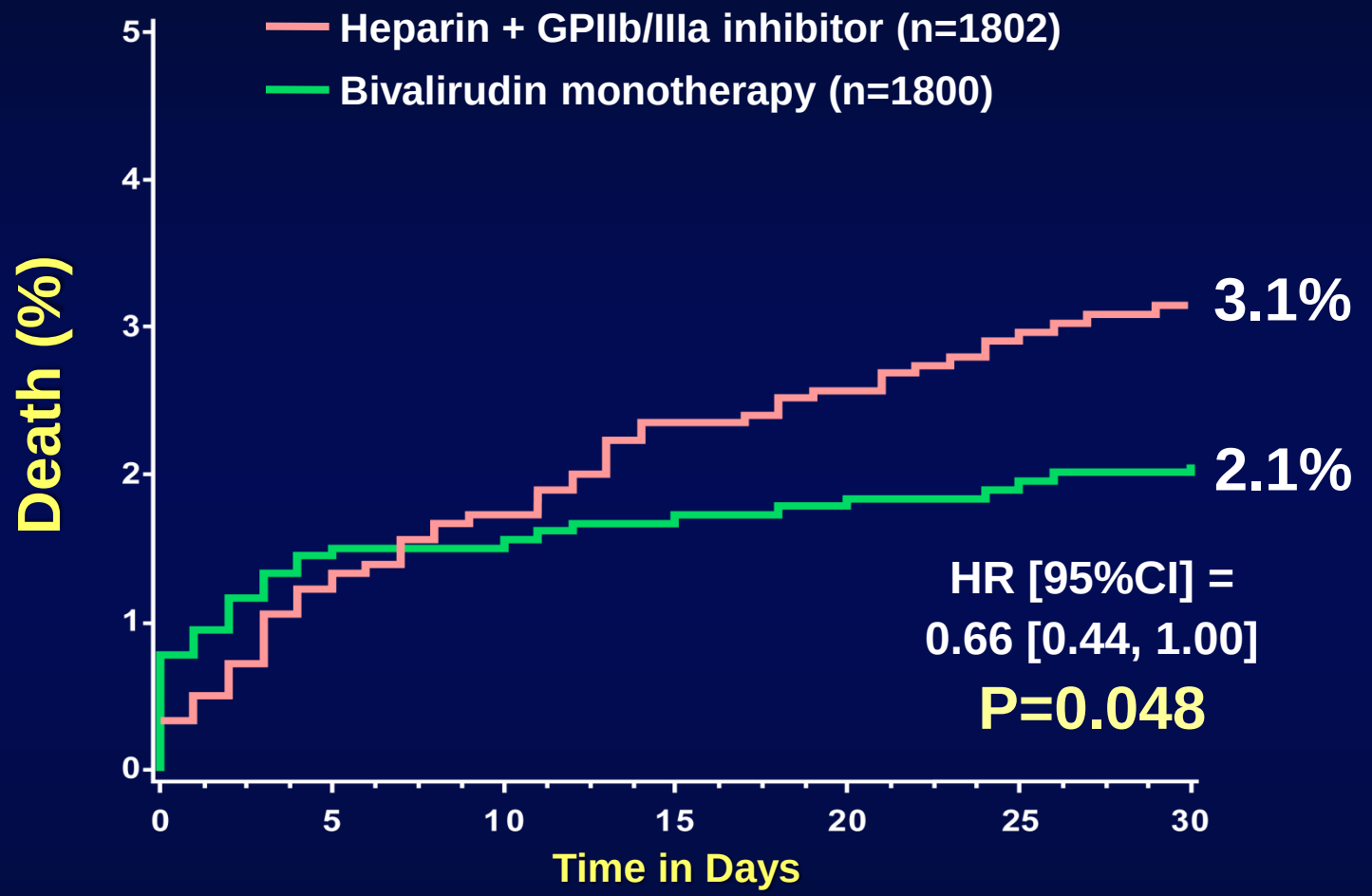


*Not related to CABG

**MACE = All cause death, reinfarction, ischemic TVR or stroke

HORIZONSAMI

HORIZONS AMI: 30 Day Mortality



Number at risk							
Bivalirudin	1800	1758	1751	1746	1742	1729	1666
Heparin + GPIIb/IIIa	1802	1764	1748	1736	1728	1707	1630

HORIZONS AMI

30 Day Stent Thrombosis (N=3,124)

	UFH + GP IIb/IIIa (N=1553)	Bivalirudin (N=1571)	P Value
ARC definite or probable*	1.9%	2.5%	0.33
- definite	1.4%	2.2%	0.11
- probable	0.5%	0.3%	0.26
- acute (≤24 hrs)	0.3%	1.3%	0.0009

Unlike NSTEMI when pre-treatment with plavix may provide adequate antiplatelet therapy during PCI in STEMI (primary PCI) plavix is ineffective at the time of intervention

Independent Predictors of Acute ST (Cox Model)

Variable	HR [95% CI]	P-value
Pre-PCI TIMI flow 0/1	6.10 [1.43, 26.04]	0.01
Lesion ulceration	4.80 [1.41, 16.37]	0.01
Bivalirudin (v. UFH+GPI)	4.65 [1.59, 13.54]	0.005
Number of stents	1.50 [1.06, 2.12]	0.02
Pre-rand heparin	0.27 [0.12, 0.60]	0.002

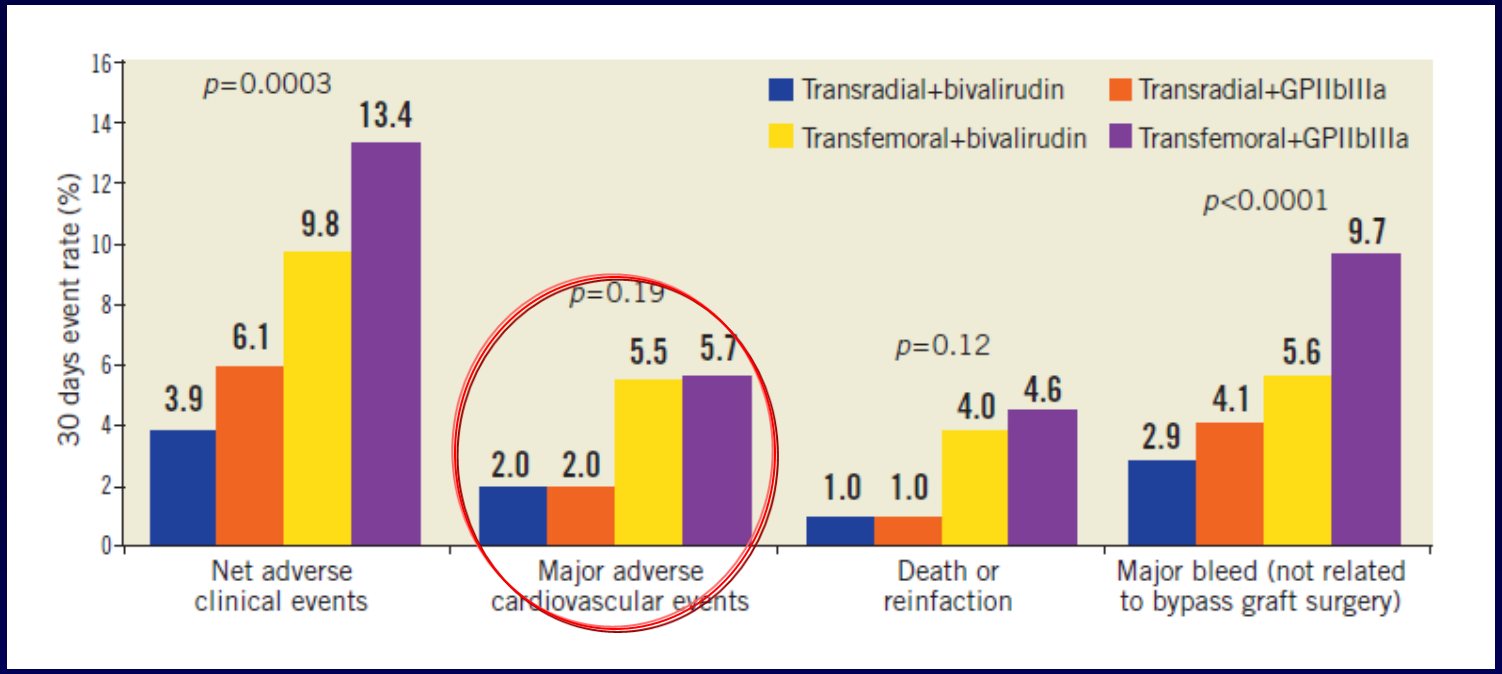
Dangas ACC 2009

HORIZONS AMI

HORIZONS: Impact of access site on outcome

Généreux et al. Eurointervention 2011

Radial –	**200 (6%)**
Femoral –	**3134 (94%)**



Limitations:

- **Very small number of patients treated with radial approach**
- **Significant bias in selection of radial vs. femoral**

72 years old male in the cath lab with ant. STEMI

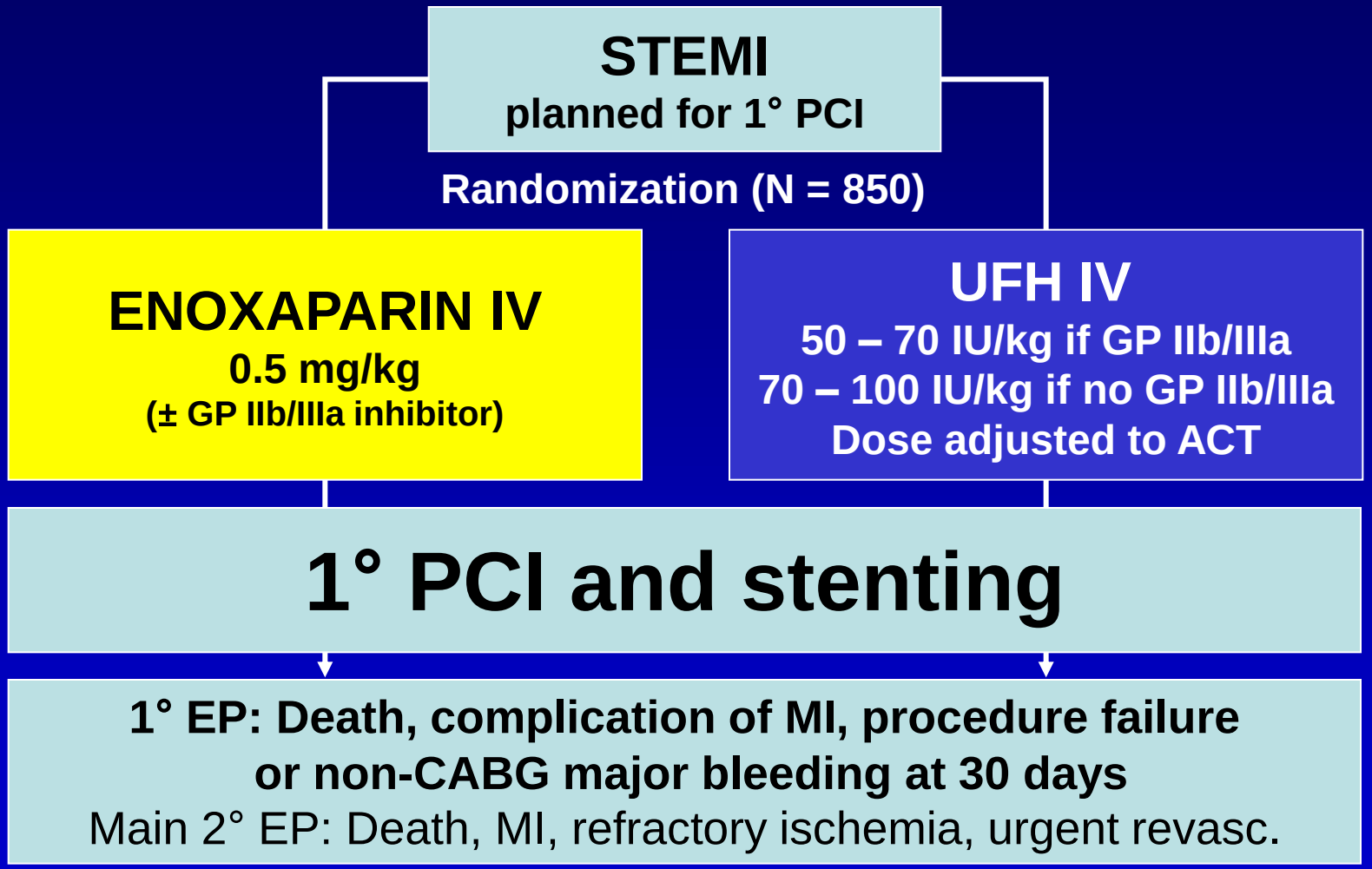
- 3 hours of pain
- First presentation of CAD

Options for anticoagulation (in addition to antiplatelet therapy)

- UFH
- Bivalirudin – role of UFH pre-treatment?
- Enoxaparin

ATOLL: Study Design

Lancet 2011; 378:693



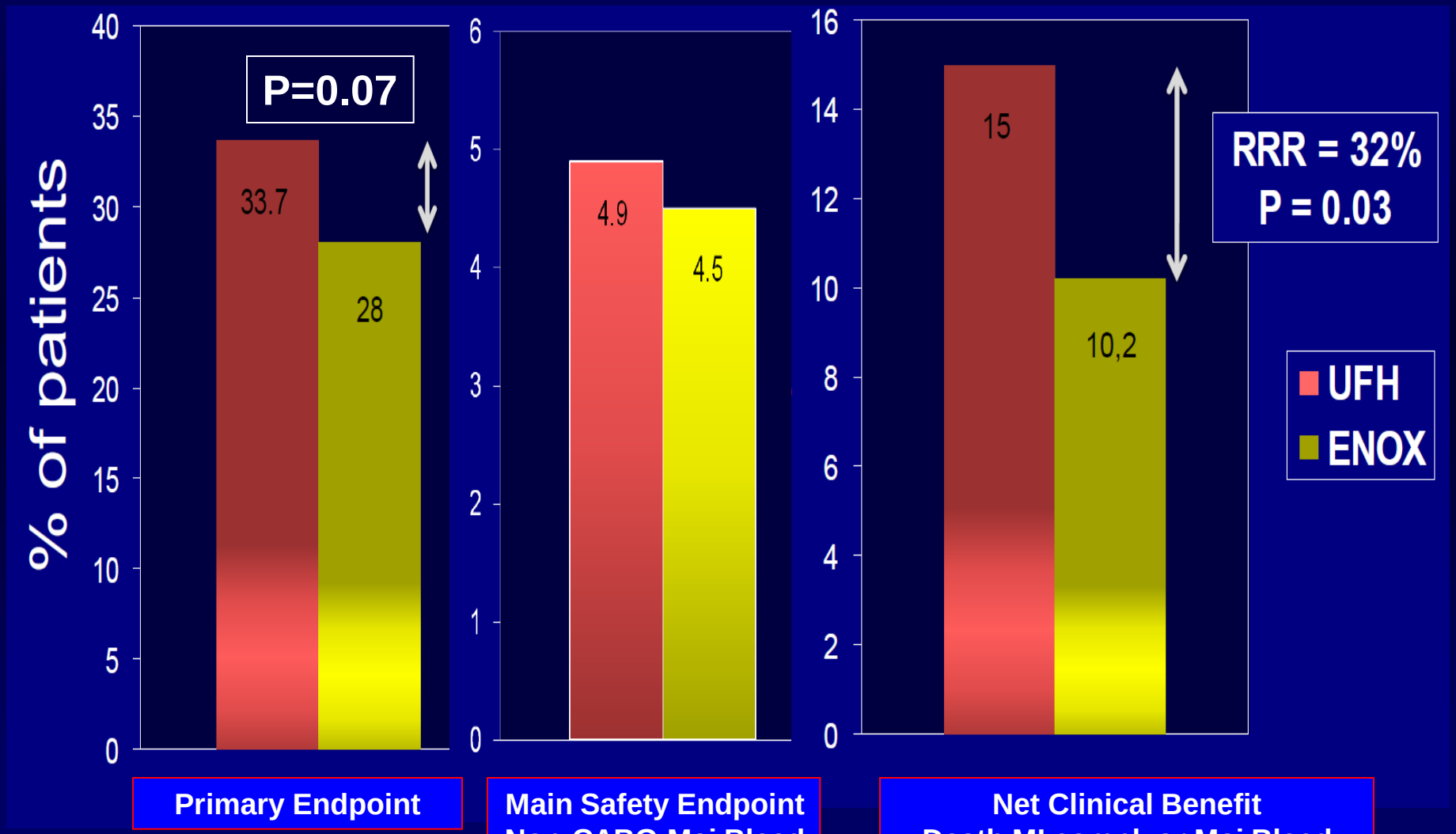
6-month follow-up

Patients who have already received UFH or LMWH or any other anticoagulant are excluded.
All concomitant drugs accepted, except lytics; cross-over to other anticoagulant NOT accepted.

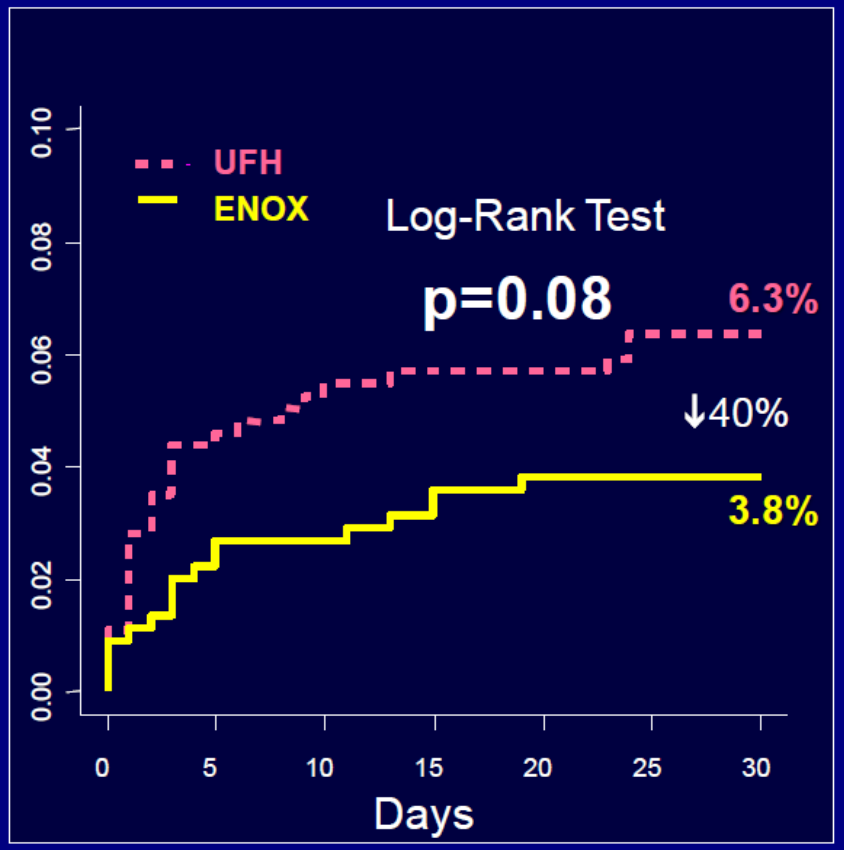
ATOLL: Procedure and Study Medication

	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)

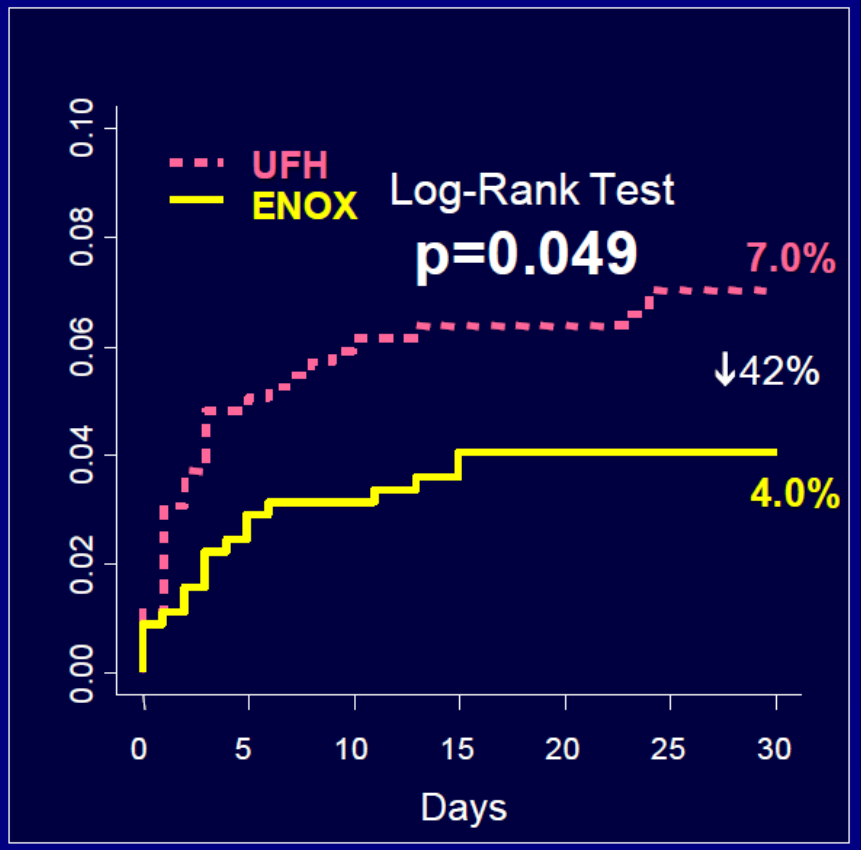
ATOLL: Primary Endpoint, Safety and Net Clinical Benefit



ATOLL: Mortality



Death

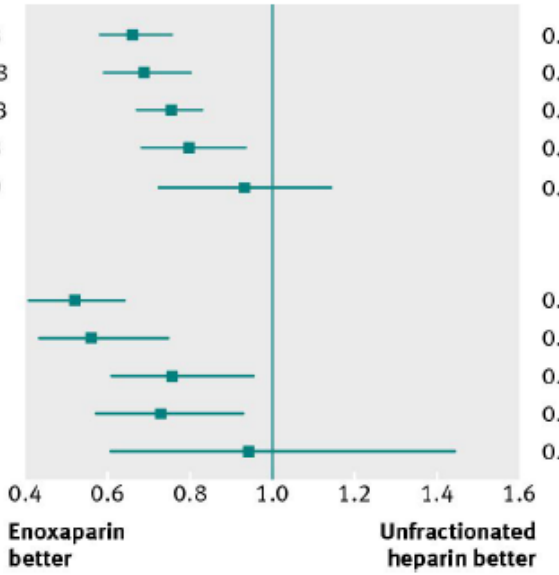


Death or Resuscitated cardiac arrest

Meta-analysis: Enoxaparin vs. UFH in the cath lab
Efficacy and safety (including mortality)

23 trials, 30966 patients

Study	Number needed to treat	No of events/No in group: Enoxaparin	No of events/No in group: Unfractionated heparin	Relative risk (95% CI) random	P value
All PCIs					
Death	60	278/13 943	622/17 023	0.66 (0.57 to 0.76)	<0.001
Death or myocardial infarction	50	836/11 924	1351/14 968	0.68 (0.57 to 0.81)	<0.001
Complications of myocardial infarction	66	765/13 943	1135/17 023	0.75 (0.66 to 0.85)	<0.001
Major bleeding	83	295/13 852	564/16 923	0.80 (0.68 to 0.95)	0.009
Minor bleeding	-	718/13 150	793/13 669	0.92 (0.74 to 1.14)	0.45
Primary PCI for STEMI					
Death	34	112/3590	401/6653	0.52 (0.42 to 0.64)	<0.001
Death or myocardial infarction	28	139/3590	499/6653	0.56 (0.42 to 0.76)	<0.001
Complications of myocardial infarction	68	96/3590	275/6653	0.76 (0.60 to 0.96)	0.022
Major bleeding	53	92/3499	298/6553	0.72 (0.56 to 0.93)	0.01
Minor bleeding	-	138/3216	177/4372	0.94 (0.60 to 1.47)	0.78



Highly significant reduction of death:

- **34% - all PCIs**
- **48% - Primary PCI for STEMI**

Silvain et al. BMJ, 2012

Conclusions

- Modern treatment of patients with ACS utilizes a combination of PCI and antithrombotic therapy.
- Despite increasing use of transradial approach, bleeding remains an important problem that is associated with poor outcome.
- Ideal anticoagulation in the setting of modern antiplatelet therapy will have to be clarified in future trials.
- A simple, easy to use new anticoagulant may offer advantage over UFH.

Thank You