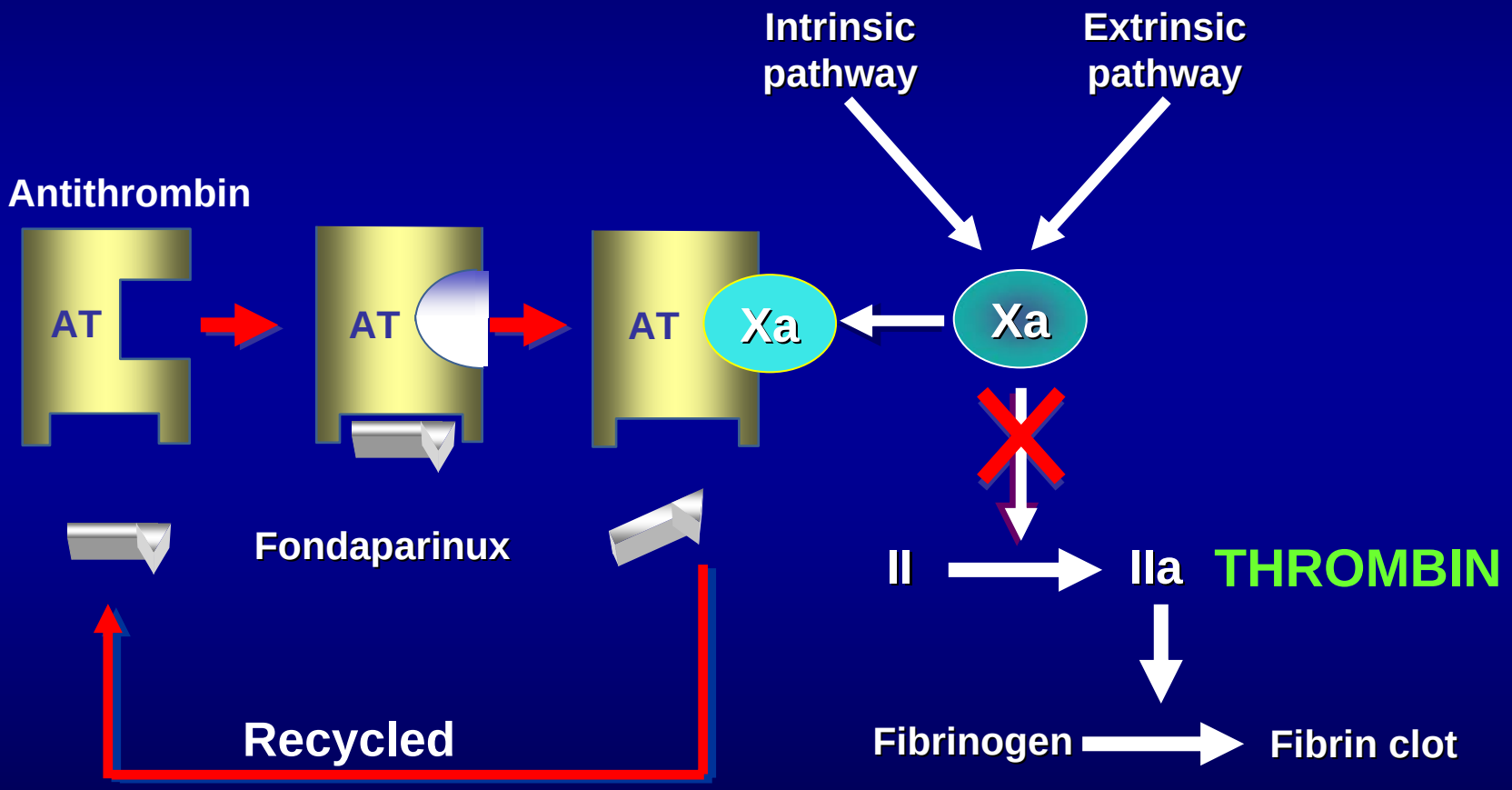
Perspectives on the Use of Fondaparinux in ACS: transitioning to the Cath Lab

Ron Waksman, MD
Professor of Medicine (Cardiology) Georgetown University,
Associate Director Division of Cardiology
Washington Hospital Center, Washington DC

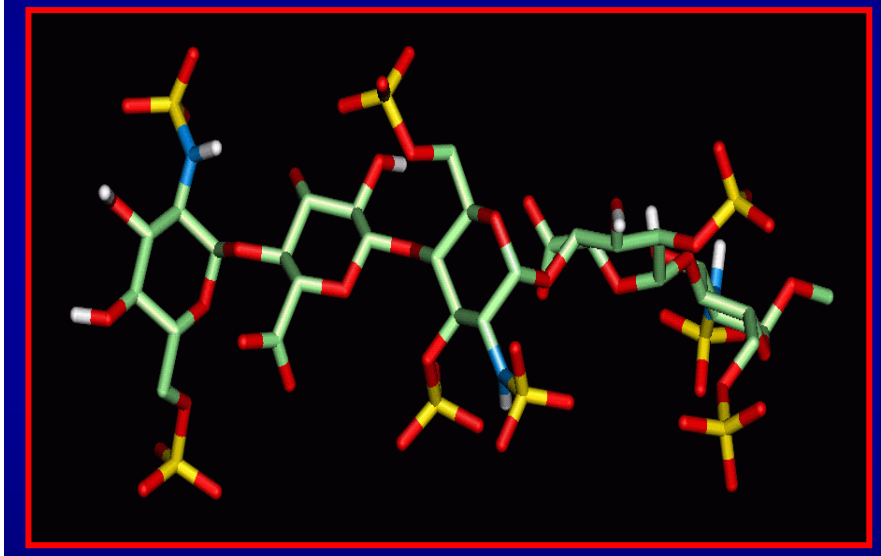
Fondaparinux: Mechanism of Action



It is a synthetic and specific inhibitor of activated Factor X (Xa)

Turpie AGG et al. N Engl J Med. 2001;344:619.

Fondaparinux: A Synthetic Inhibitor of Factor Xa

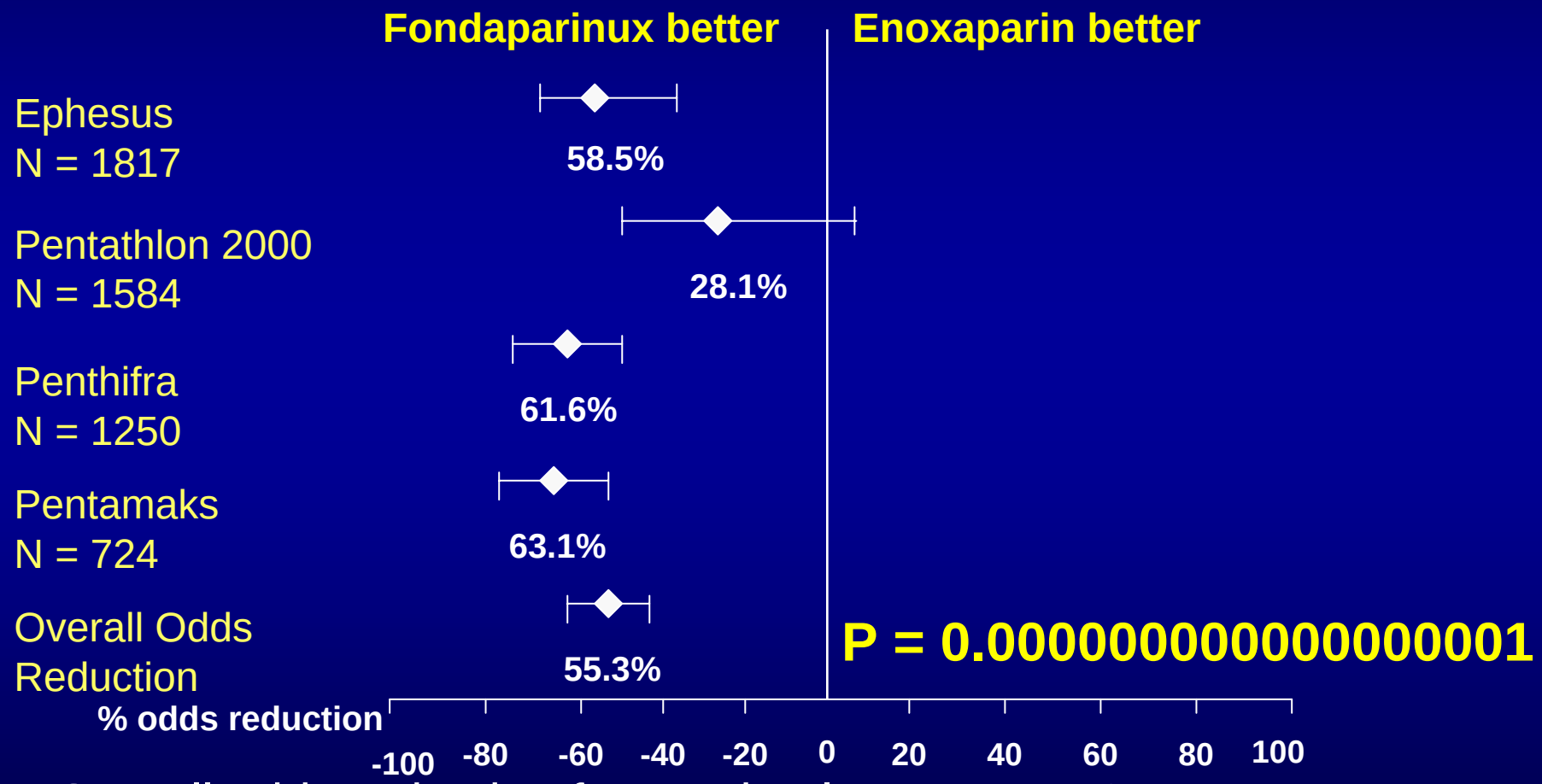


- Once daily administration
- Highly selective for its target
- No risk of pathogen contamination
- Rapid onset ($C_{max}/2$=25 min)
- Effects reversible with administration of activated Factor VII (Novoseven®)
- No liver metabolism
- No protein binding (other than AT)
- No reported cases of HIT
- No dose adjustment necessary in elderly

Herbert JM et al. *Cardiovasc Drug Rev*. 1997;15:1.
van Boeckel CAA et al. *Angew Chem, Int Ed Engl*. 1993;32:1671.

ARIXTRA is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:

Overall Efficacy of Fondaparinux vs Enoxaparin in VTE Prevention: Meta-analysis



Overall odds reduction for proximal DVT = 57.4%
[CI: 72.3 - 35.6]; p = 10^{-6}

Turpie et. al. *Arch Intern Med* 2002: 162: 1833-40

Fondaparinux Across the Spectrum of ACS is not approved in the US

However….

- Fondaparinux has been extensively studied in two large phase III double blind RCT's
- In the NSTE ACS setting fondaparinux reduces major bleeding by 50% vs enoxaparin and lowers both mortality and death/MI/stroke at 6 mo.
- In STEMI, fondaparinux reduces mortality and re-infarction without increasing the risk of bleeding

OASIS 5: A Randomized, Double-Blind, Double-Dummy Trial

20,078 patients with UA/NSTEMI

Aspirin, Clopidogrel, anti-GPIIb/IIIa, planned Cath/PCI as per local practice

Randomization

Fondaparinux

2.5 mg s.c. od up to 8 days

Enoxaparin

1 mg/kg s.c. bid for 2-8 days
1 mg/kg s.c. od if ClCr<30mL/min

1. Michelangelo OASIS 5 Steering Committee. Am Heart J 2005;150:1107.e1-.e10
2. OASIS 5 Investigators. N Engl J Med 1464-76

Study Objectives and Outcomes

Objectives

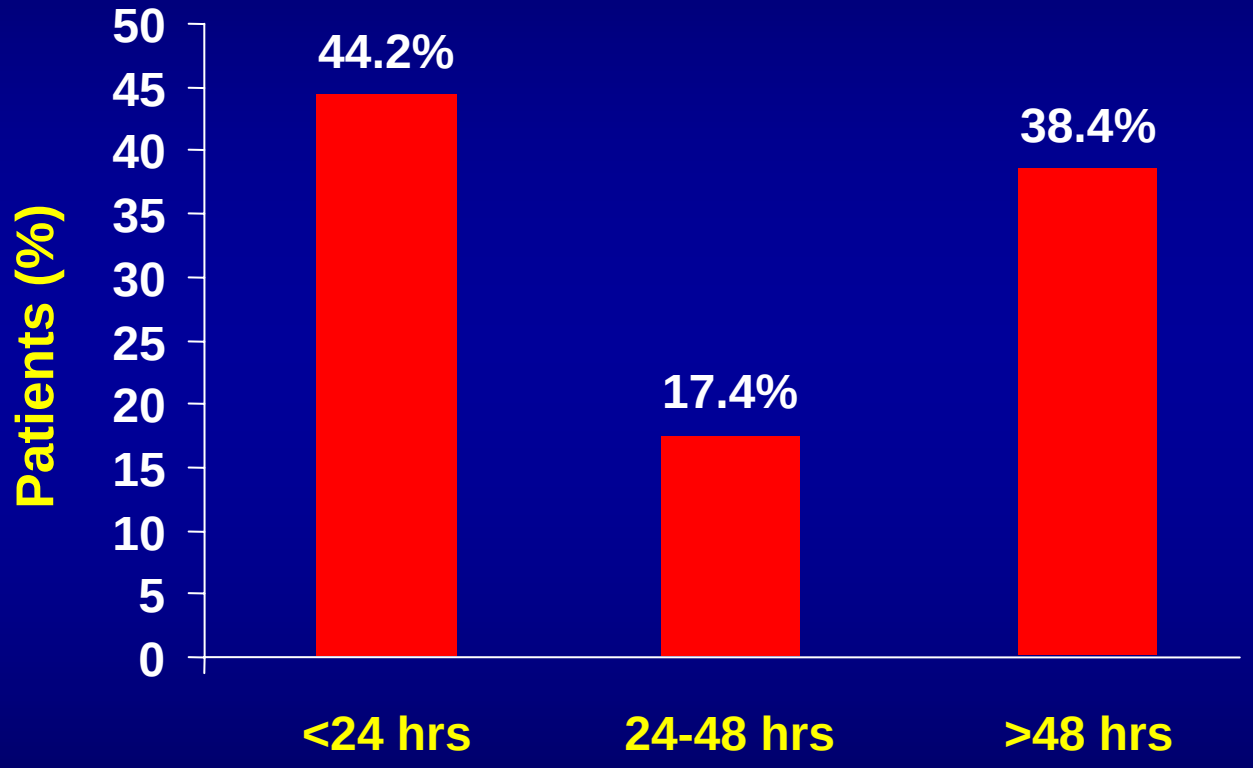
Primary efficacy objective:	**To demonstrate non-inferiority of fondaparinux compared with enoxaparin**
Primary safety objective:	**To determine whether fondaparinux was superior to enoxaparin in preventing major bleeding**

Outcomes (centrally adjudicated)

Primary efficacy:	**1st occurrence of the composite of death, MI, or refractory ischemia (RI) up to day 9**
Primary safety:	**Major bleeding up to day 9**
Risk benefit:	**Death, MI, refractory ischemia, major bleeds up to day 9**
Secondary:	**Above & each component separately at days 30 and 180**

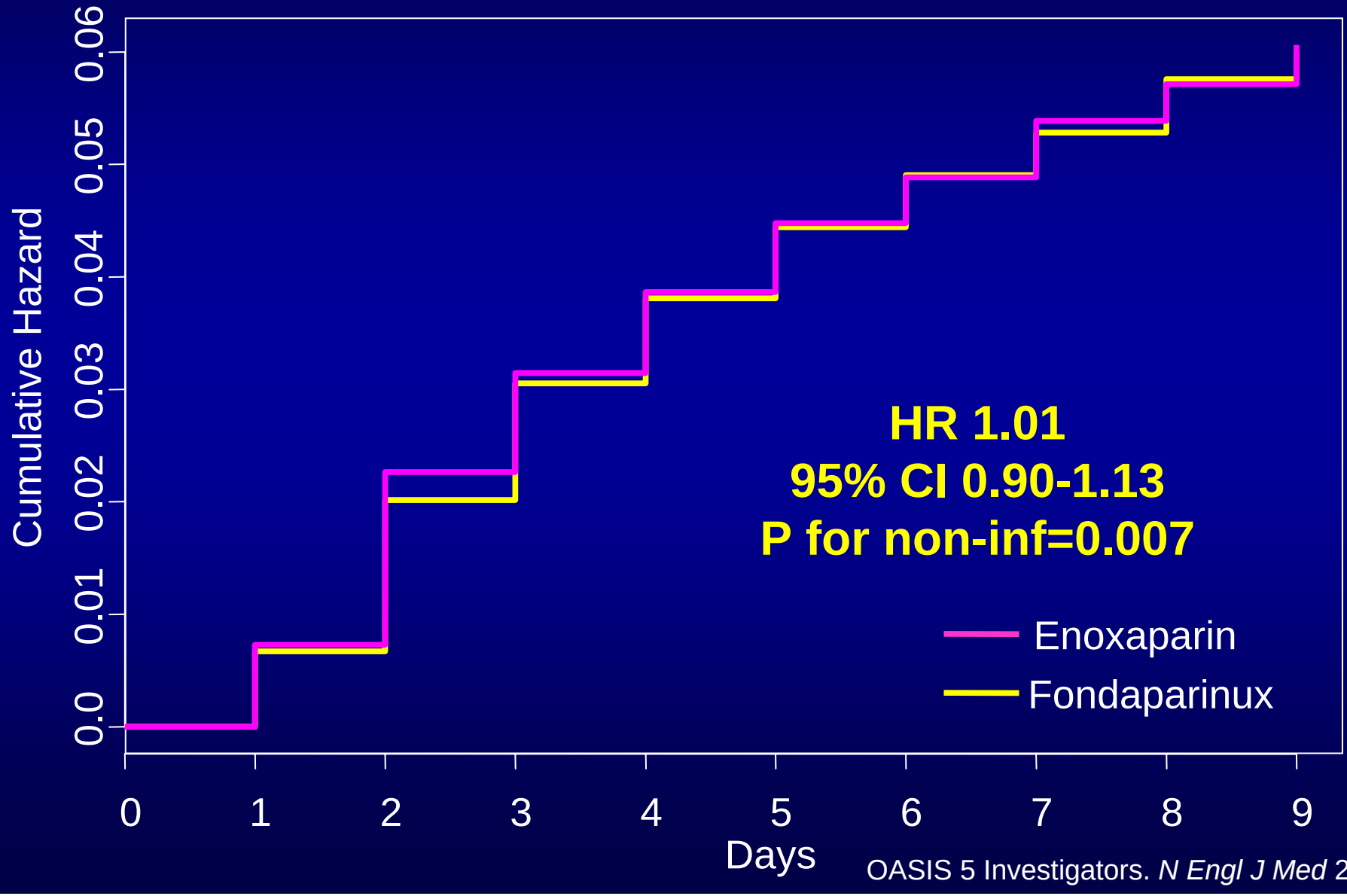
1. Michelangelo OASIS 5 Steering Committee. Am Heart J 2005;150:1107.e1-.e10
2. OASIS 5 Investigators. N Engl J Med 2006;354:1464-76

Time from Randomization to Catheterization



Mehta et al. JACC 2006;abstract 821-5

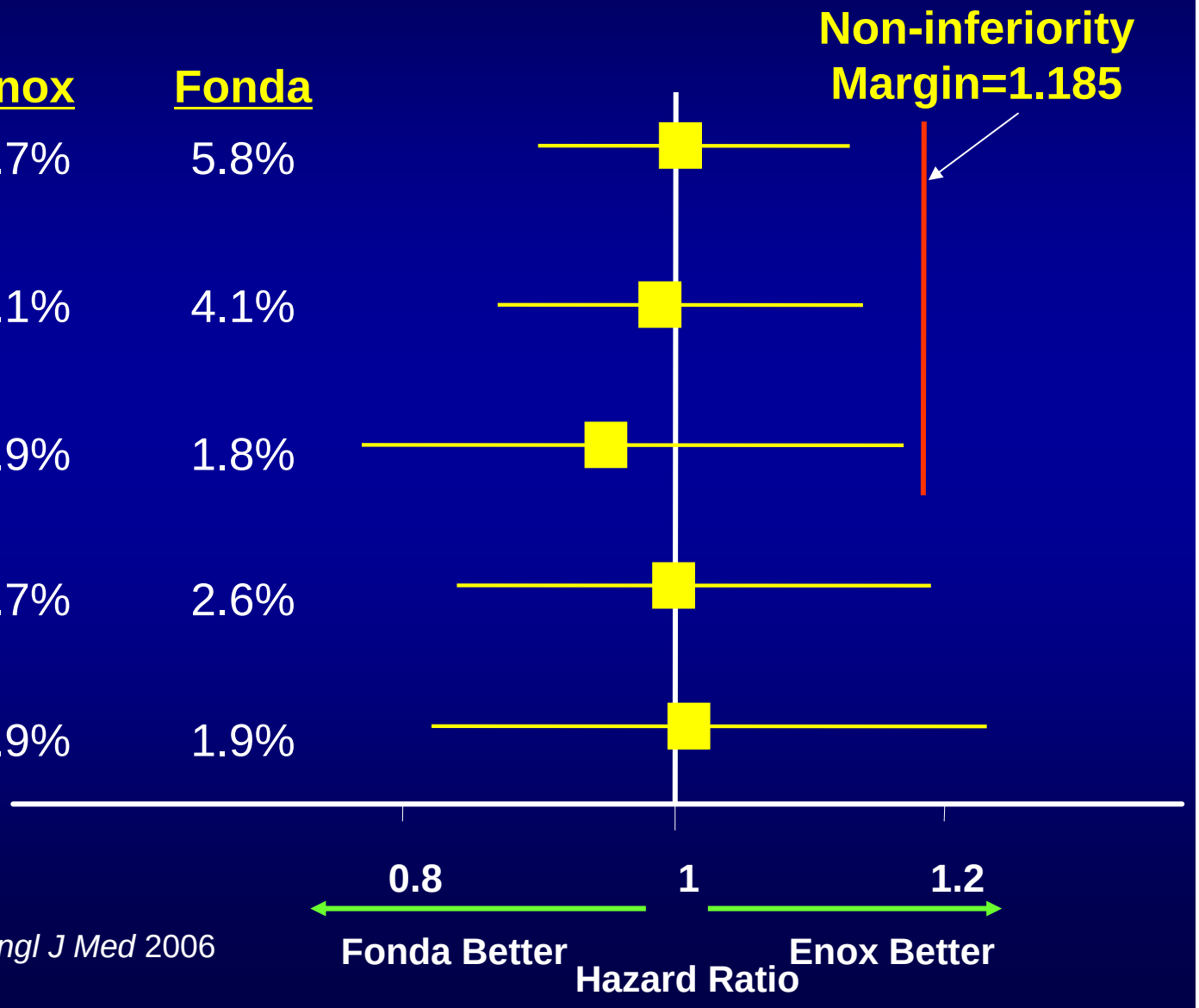
Death/MI/RI: Day 9



OASIS 5 Investigators. *N Engl J Med* 2006

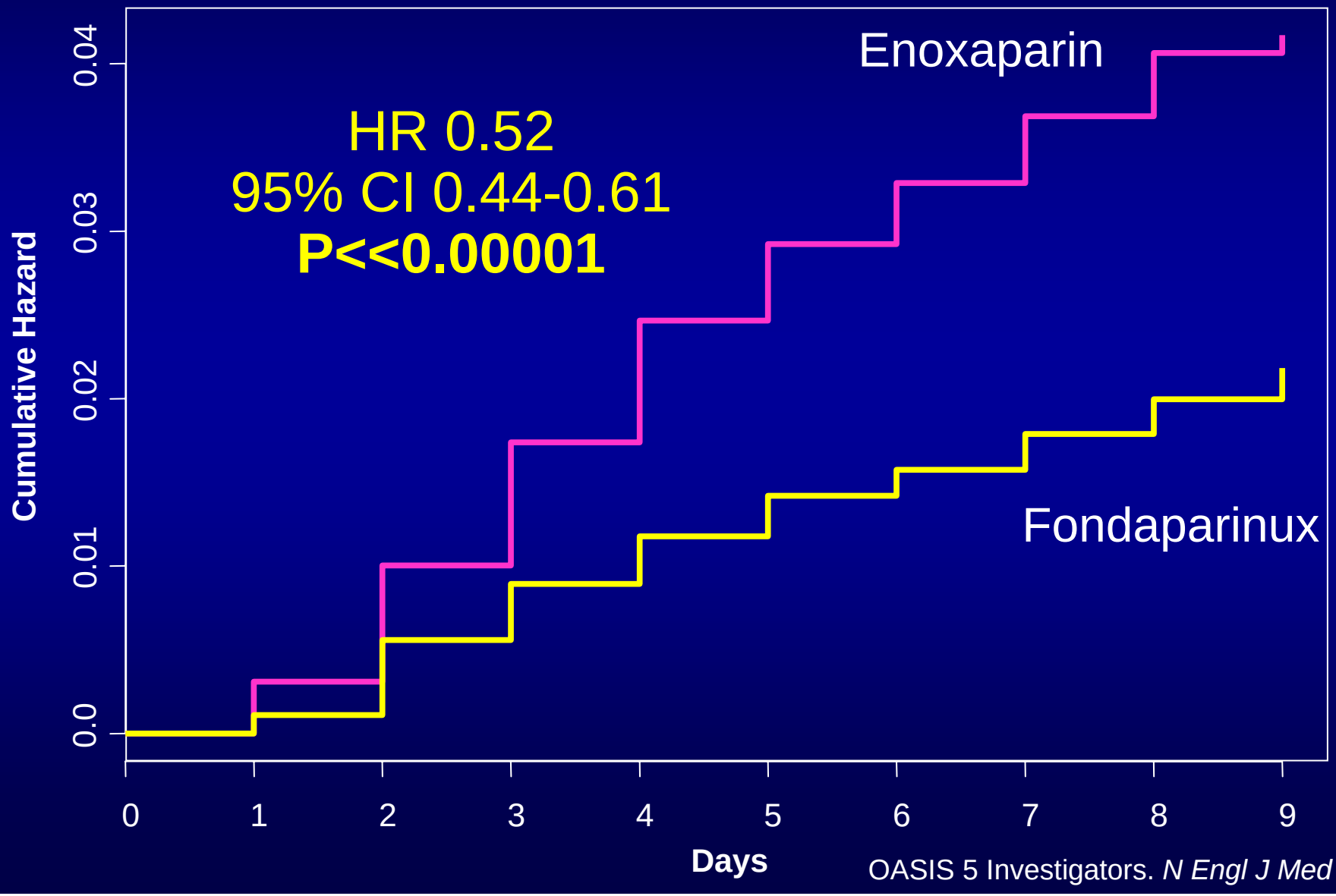
Efficacy Outcomes at Day 9

	Enox	Fonda
Death/MI/RI	5.7%	5.8%
Death/MI	4.1%	4.1%
Death	1.9%	1.8%
MI	2.7%	2.6%
Refract Isch	1.9%	1.9%



OASIS 5 Investigators. *N Engl J Med* 2006

Major Bleeding: 9 Days



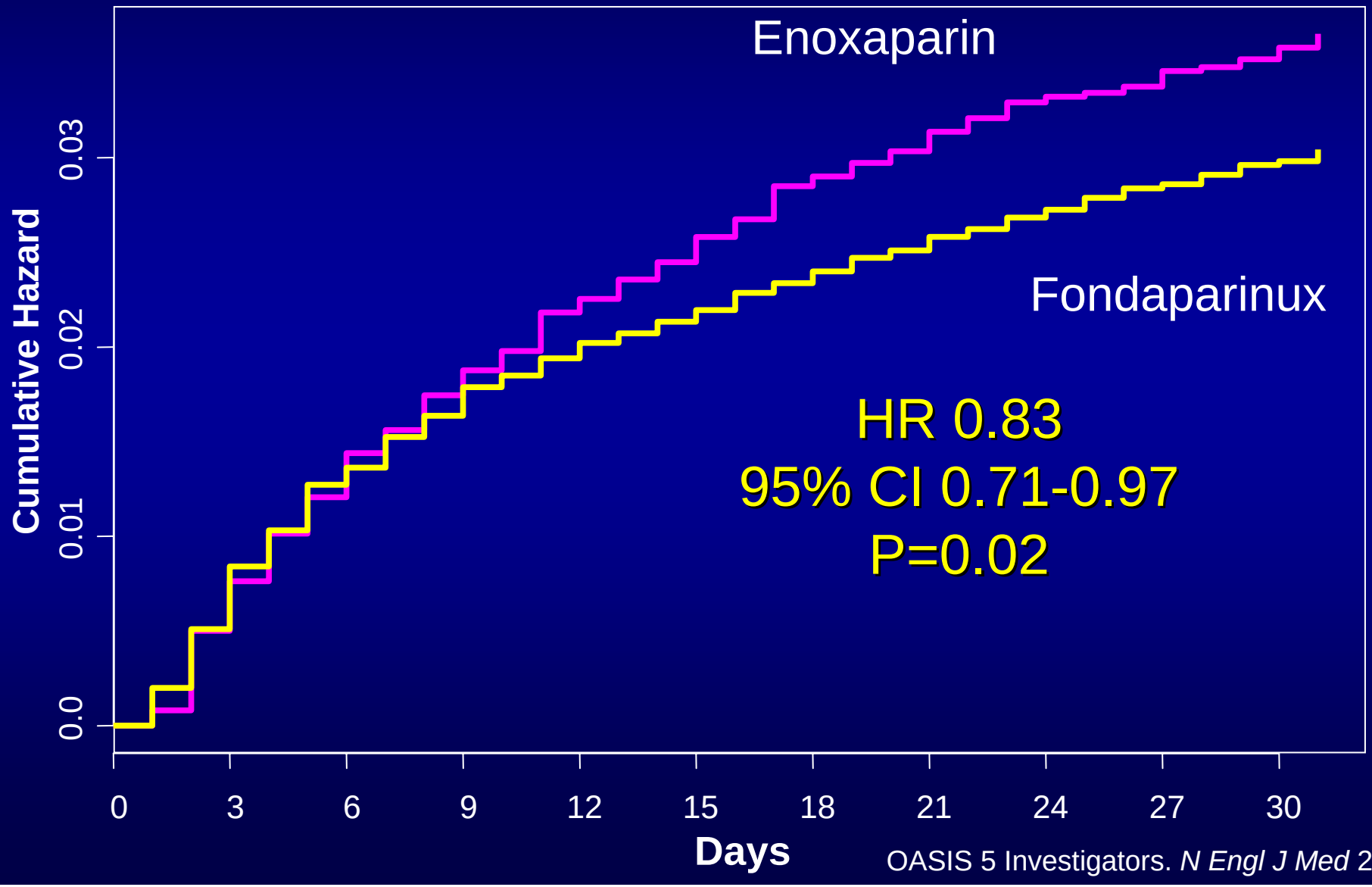
OASIS 5 Investigators. *N Engl J Med* 2006

Bleeding Rates: Day 9

Outcome	Enox (%)	Fonda (%)	HR (95% CI)	P value
No. Randomized	10021	10057		
Total Bleed	7.3	3.3	0.44 (0.39-0.50)	<<0.0001
Major Bleed	4.1	2.2	0.52 (0.44-0.61)	<<0.0001
TIMI Major Bleed	1.3	0.7	0.55 (0.41-0.74)	<<0.0001
Minor Bleed	3.2	1.1	0.35 (0.28-0.43)	<<0.0001

OASIS 5 Investigators. *N Engl J Med* 2006

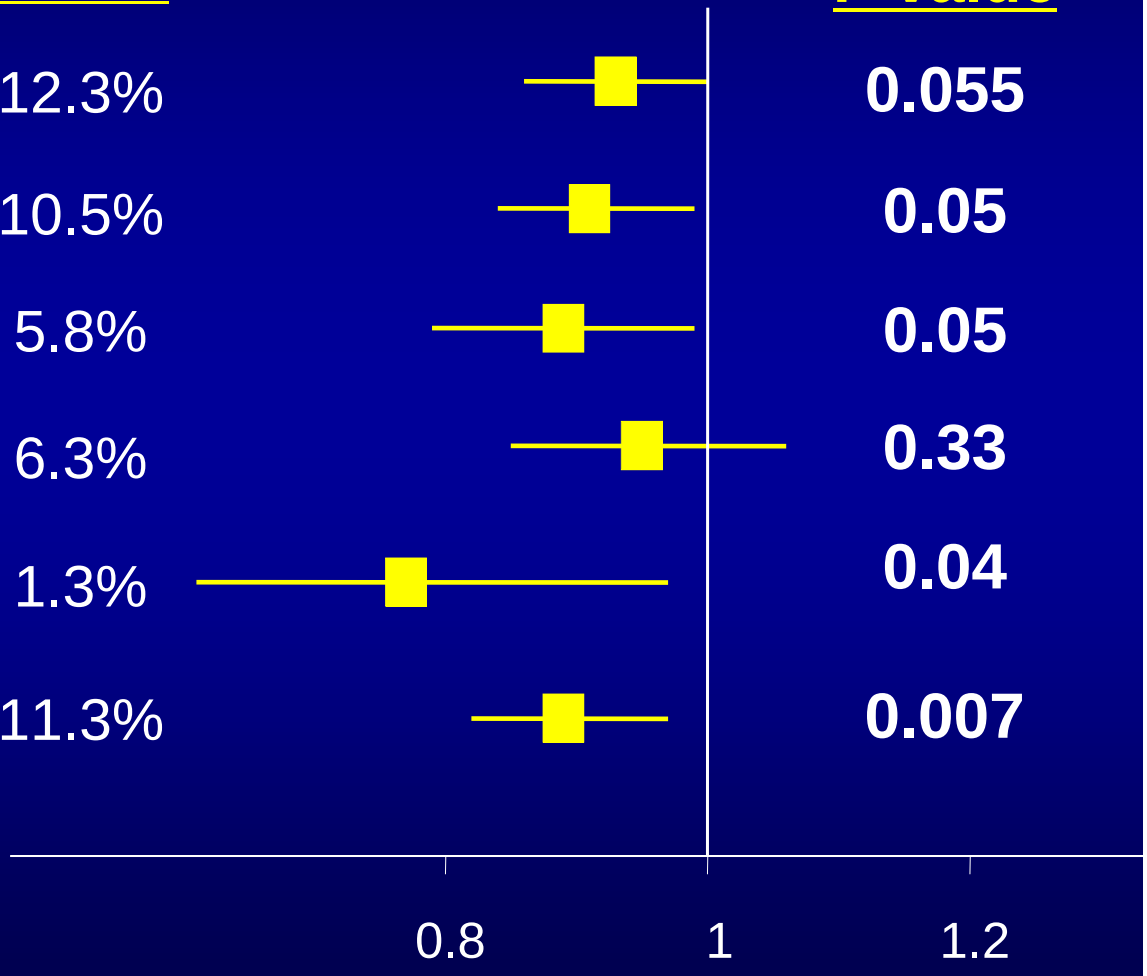
Mortality: Day 30



OASIS 5 Investigators. *N Engl J Med* 2006

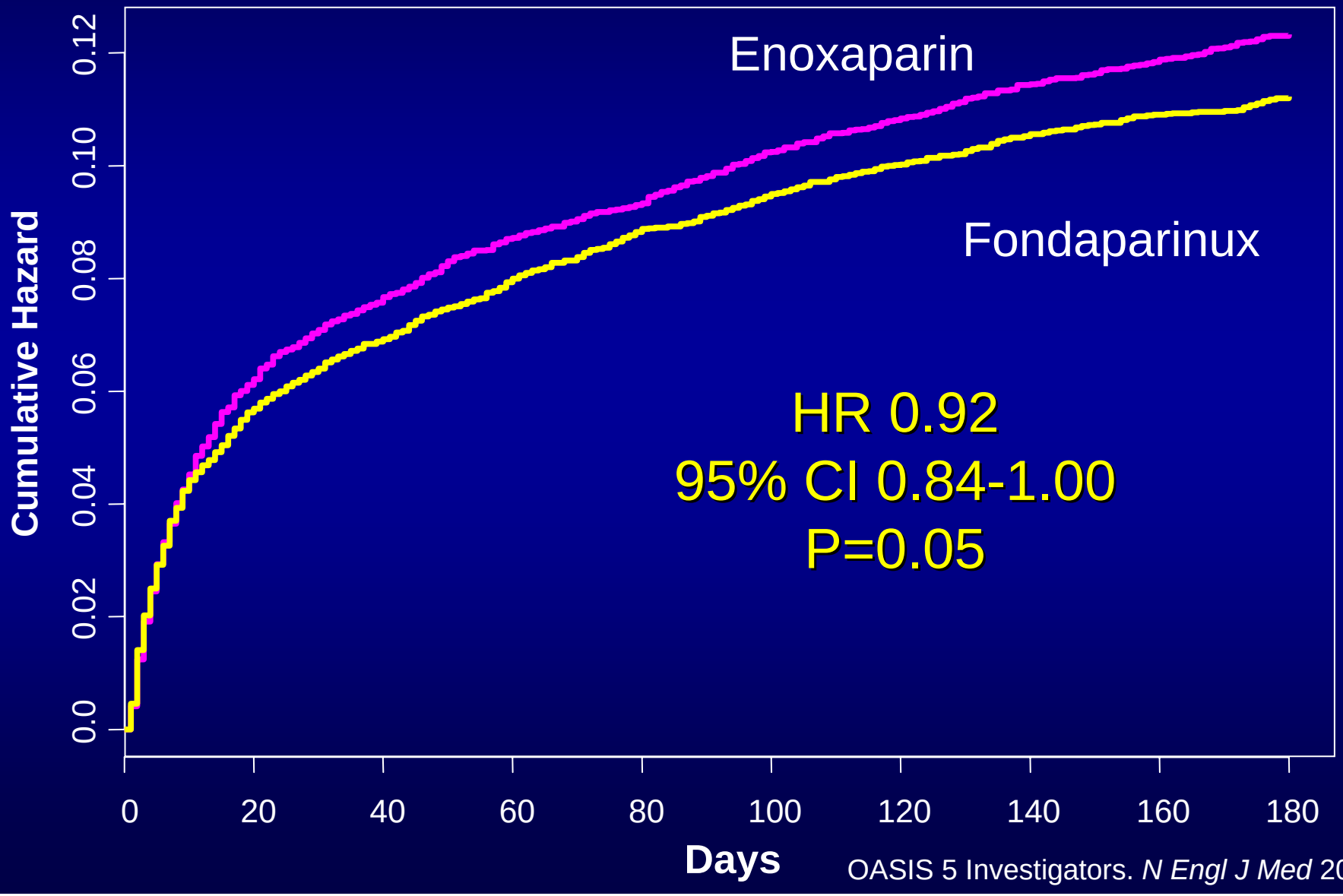
Efficacy at 6 Months

	Enox	Fonda	P value
Death/MI/RI	13.2%	12.3%	**0.055**
Death/MI	11.4%	10.5%	**0.05**
Death	6.5%	5.8%	**0.05**
MI	6.6%	6.3%	**0.33**
Strokes	1.7%	1.3%	**0.04**
Death/MI/Stroke	12.5%	11.3%	**0.007**



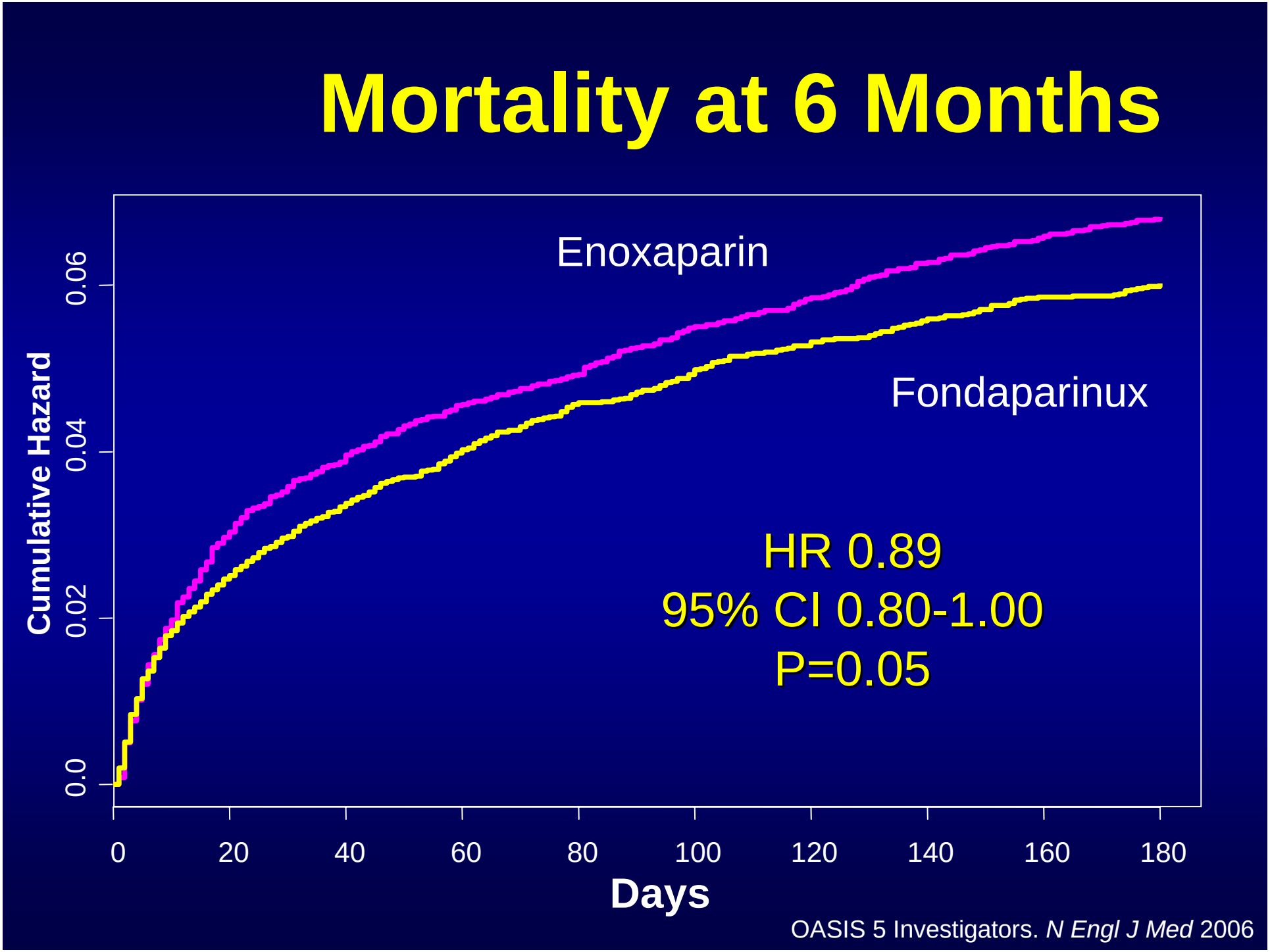
OASIS 5 Investigators. *N Engl J Med* 2006

Death or MI: 6 Months



OASIS 5 Investigators. *N Engl J Med* 2006

Mortality at 6 Months



OASIS 5 Investigators. *N Engl J Med* 2006

Open-Label UFH Usage in PCI Patients♦

	ARIXTRA	Enoxaparin
# patients receiving PCI during initial hospitalization*	2854	2741
# PCI procedures	2888	2781
# patients receiving open-label UFH before *and/or* during PCI	480 (16.8%)	444 (16.2%)
# procedures with open-label UFH before *and/or* during PCI	481 (16.7%)	447 (16.1%)
Median UFH dose (IU/kg)	48.4	44.8

* Subset 2: subjects who underwent PCI during initial hospitalization and within 8 days of randomization and who were receiving study drug at the time of procedure.

Data on File, ZM2005/00083/00 AR1103420, GlaxoSmithKline

♦Unapproved Use
Not For Affirmative Use

Coronary Complications During PCI with Pre-Procedural, Open-label UFH♦

	ARIXTRA	Enoxaparin
Total number of patients receiving pre-procedural open-label UFH	54	58
Total number of PCI procedures associated with pre-procedural open-label UFH	54	58
Coronary complications during PCI	7 (13.0%)	4 (6.9%)
Abrupt closure of coronary artery	1 (1.9%)	0
New angiographic thrombus	0	1 (1.7%)
Catheter thrombus confirmed by adjudication	1 (1.9%)*	0

* The ARIXTRA treated patient who experienced catheter thrombus received open-label UFH prior to PCI at a dose of 5 IU/kg. This patient recovered without sequelae.

Data on File, ZM2005/00083/00 AR1103420, GlaxoSmithKline

♦Unapproved Use
Not For Affirmative Use

Catheter-Related Thrombus with Enoxaparin and Fondaparinux

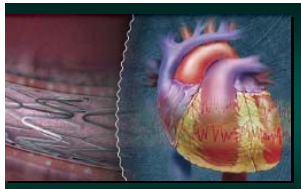
Enoxaparin

- 8 cases total: 6 when PCI performed within 6 h of last enox dose where no UFH was given
- Rate is 6/1431=0.42%
- In Enoxaparin patients receiving study UFH, there was 1 case.
- 1 case time of PCI not ascertained

Fondaparinux

- 29 cases (UFH was not routinely given to fonda group)
- Rate is 29/3135=0.9%
- When open label UFH was used prior to PCI (5000 U mean), only 1 case of catheter thrombus was reported

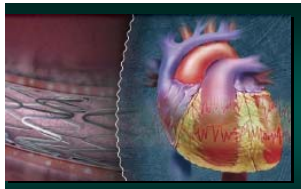
Mehta SR et al. *ACC* 2006



SWITCH III

(Switching from Arixtra® (fondaparinux) to Angiomax® (bivalirudin) or unfractionated heparin in patients with acute coronary syndromes without ST-segment elevation undergoing percutaneous coronary intervention (PCI))

Principal Investigator: Ron Waksman, MD



SWITCH III Study Design

Patient Presents to ER/Cath Lab

Arixtra Administration
2.5 mg SubQ QD

Catheterization
≤ 24 hours of Arixtra

No PCI
"Screen Failure"

Requires PCI

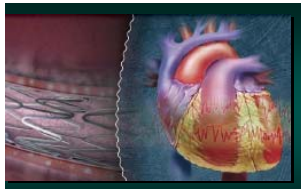
300 patients will be randomized

All patients are followed through the duration of the hospitalization or until CABG

Bivalirudin

1:1 Randomization

UFH



SWITCH III Study Endpoints

- **Primary Endpoint:**
  - **Major bleed defined as clinically overt bleeding that is:**
    - **Fatal**
    - **Symptomatic intracranial hemorrhage**
    - **Retroperitoneal hemorrhage**
    - **Intraocular hemorrhage leading to significant vision loss**
    - **Decrease in hemoglobin of at least 3.0 g/dL**
      ***with each blood transfusion unit counting for 1 g/dL of Hb)**
    - **Bleed requiring transfusion of two or more units of RBCs or equivalent whole blood**
- **Secondary Endpoint:**
  - ***in-hospital death (non-hemorrhagic related),***
  - ***vascular access site complications,***
  - ***myocardial infarction,***
  - ***need for repeat revascularization,***
  - ***procedural complication and***
  - ***catheter thrombosis***

Study Design: Randomized, Double Blind, Double Dummy

12,000 Patients with STEMI < 12 h of symptom onset

Inclusion: ST ↑ ≥ 2 mm prec leads or ≥ 1 mm limb leads

Exclusion: Contra-ind. for anticoagulant, INR>1.8, pregnancy, ICH<12 mo.

Lytics (SK, TPA, TNK, RPA), Primary PCI or no reperfusion (eg. late)

Stratification

UFH not indicated

Randomization

Fondaparinux 2.5 mg

Placebo

UFH indicated

Randomization

Fondaparinux 2.5 mg

UFH

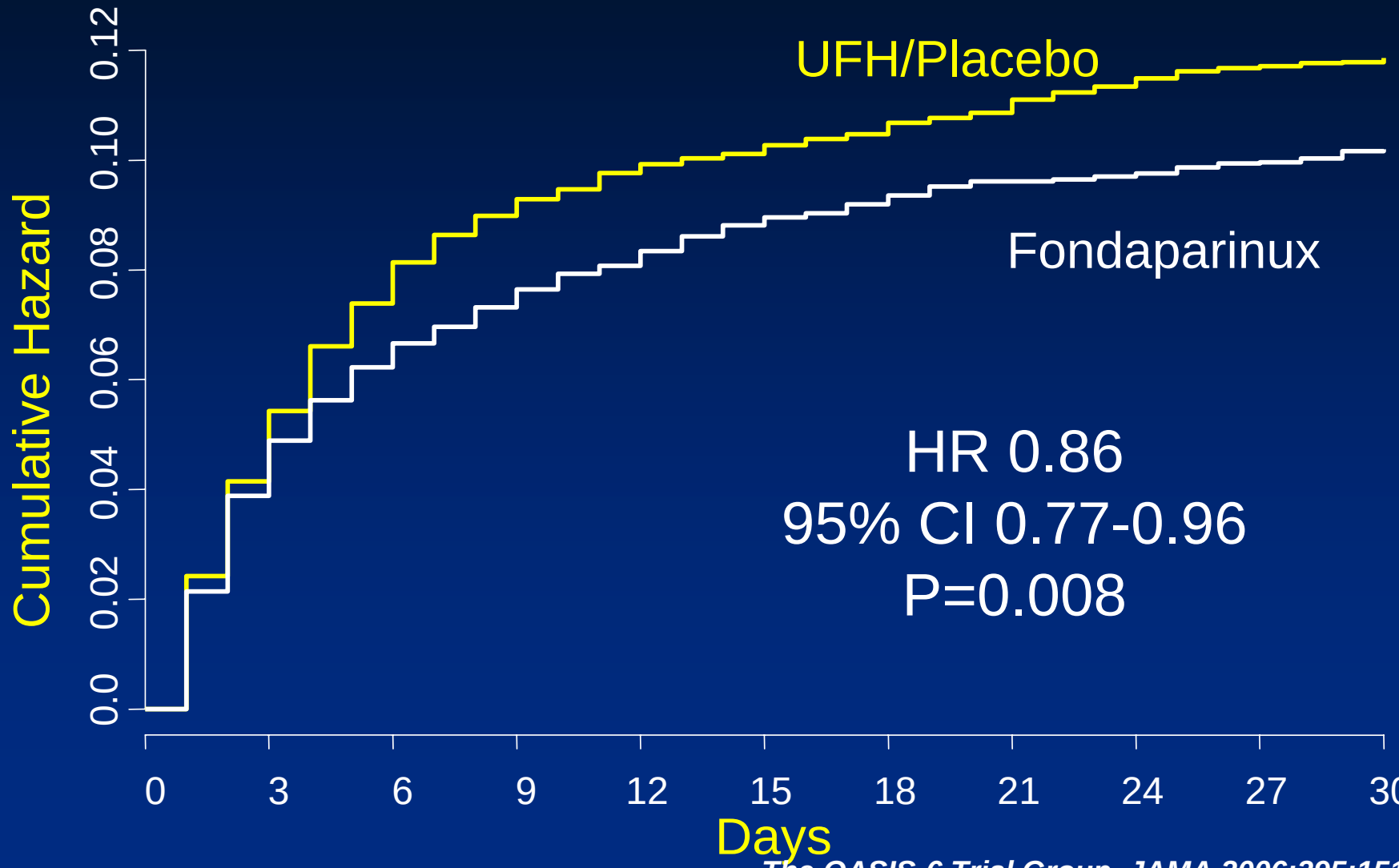
The OASIS-6 Trial Group. JAMA 2006;295:1519-30

Primary Efficacy Outcome Death/MI at 30 Days

	No. of Events (%)				
	Control	Fonda	HR	95% CI	P
No. of Patients	6056	6036			
Death or Re-MI	11.2	9.7	0.86	0.77-0.96	0.008
Death	8.9	7.8	0.87	0.77-0.98	0.026
Reinfarction	3.0	2.5	0.81	0.65-1.01	0.057

The OASIS-6 Trial Group. JAMA 2006;295:1519-30

Primary Efficacy Outcome
Death/MI at 30 Days



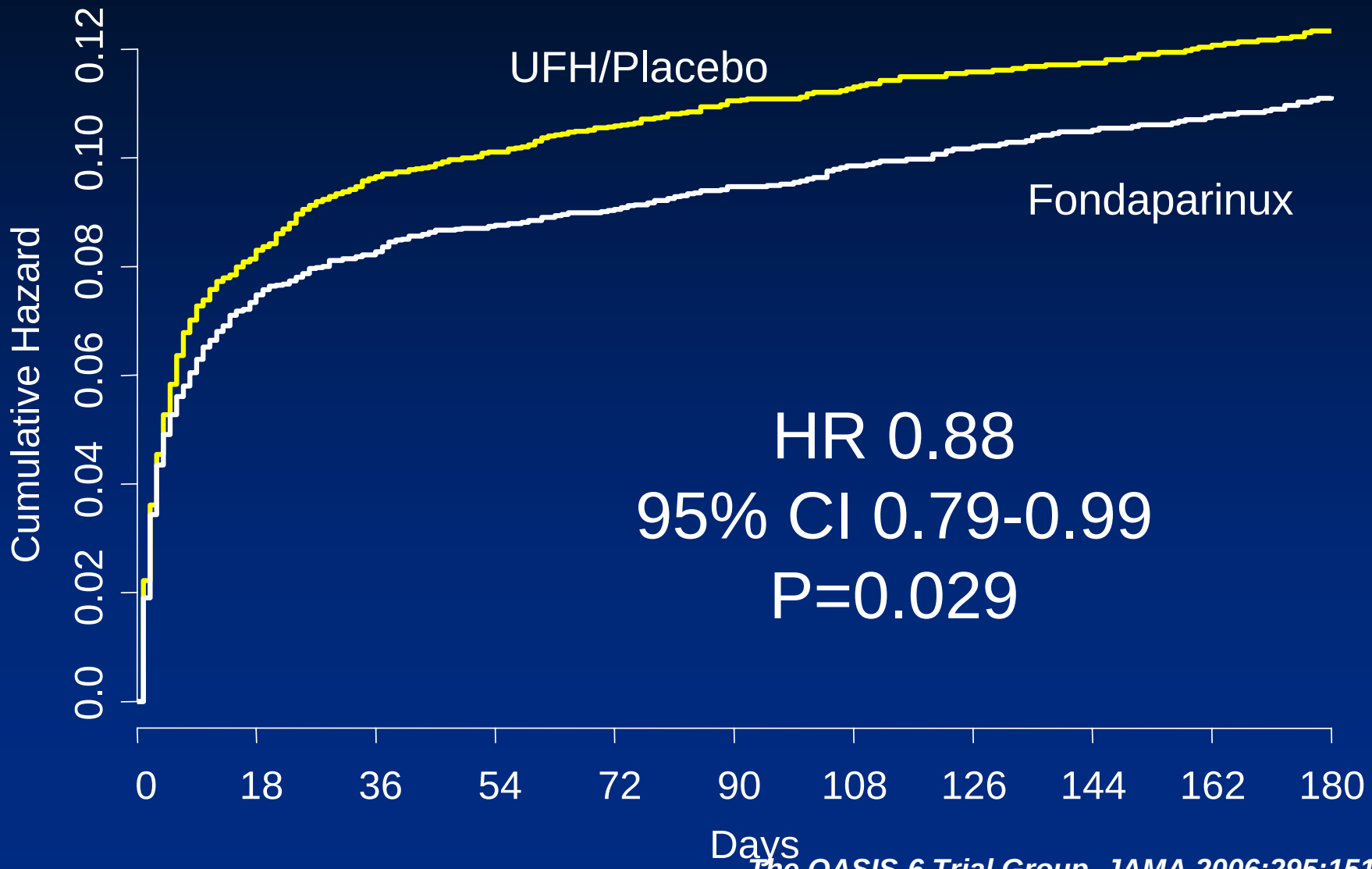
The OASIS-6 Trial Group. JAMA 2006;295:1519-30

Death/MI at Study End (3 or 6 months)

	No. of Events (%)				
	Control	Fonda	HR	95% CI	P
No. of Patients	6056	6036			
Death or Re-MI	14.8	13.4	0.88	0.79-0.97	0.008
Death	11.6	10.5	0.88	0.79-0.99	0.029
Reinfarction	4.6	3.8	0.81	0.67-0.97	0.026

The OASIS-6 Trial Group. JAMA 2006;295:1519-30

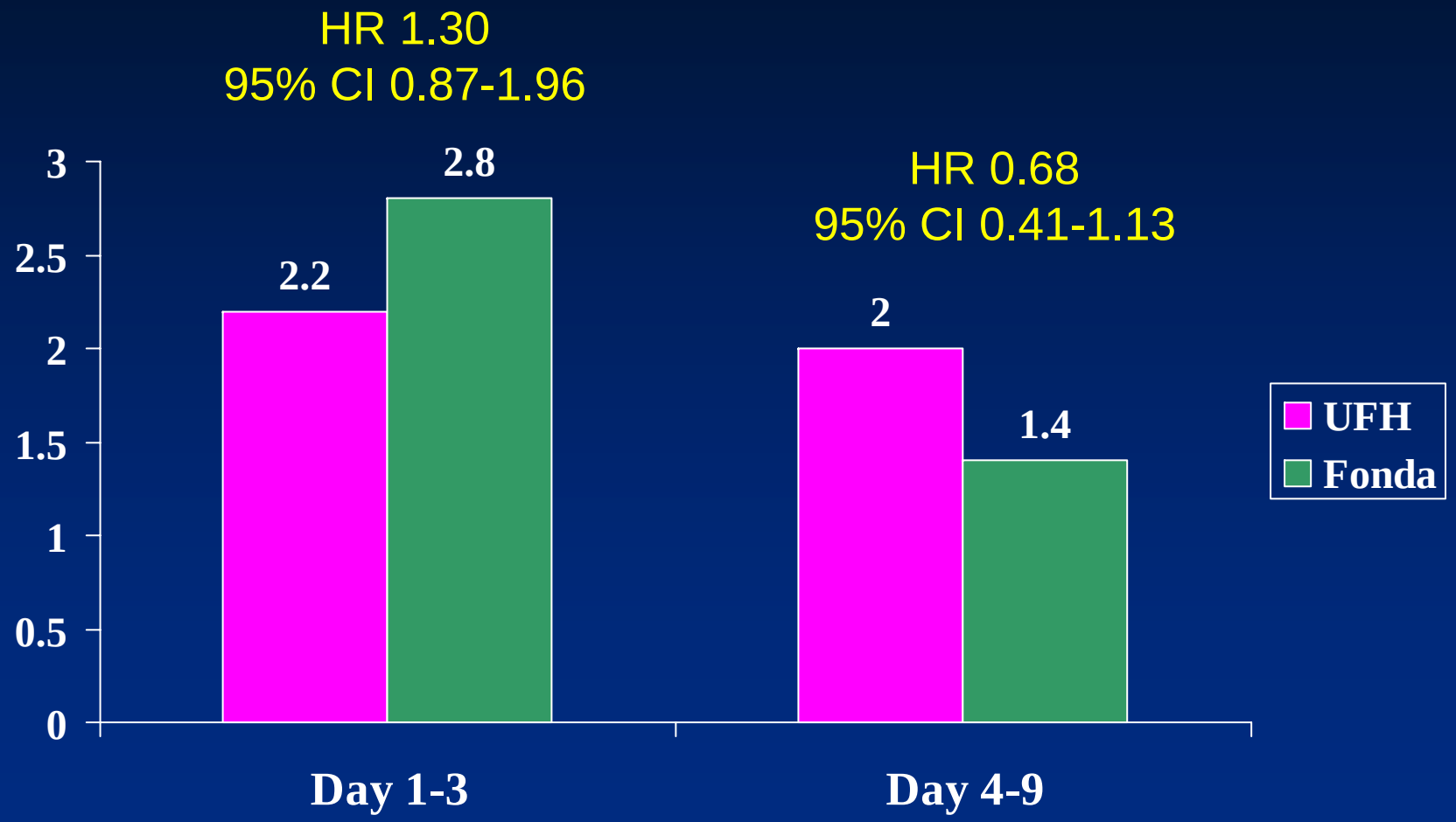
Death at Study End (3 or 6 months)



HR 0.88
95% CI 0.79-0.99
P=0.029

The OASIS-6 Trial Group. JAMA 2006;295:1519-30

Primary PCI Results: Death/MI in 1-3 days and 4-9 days



The OASIS-6 Trial Group. JAMA 2006;295:1519-30

OASIS 6 Conclusions:

1. Fondaparinux significantly reduces mortality and re-MI in STEMI without increasing bleeding compared to placebo or UFH.

2. Benefits emerge at 9 days and are sustained to 180 days.

3. In primary PCI, UFH should remain the treatment of choice. Consider fonda after primary PCI.

4. The benefits are marked in those receiving no reperfusion therapy and those receiving thrombolytics (21% RRR at 30 days), with lower severe bleeding.

5. Mortality is significantly reduced

Enoxaparin and Fondaparinux in STEMI

	Enoxaparin	Fondaparinux
Mortality	neutral	↓
Re MI	↓	↓
Major Bleeding	↑	neutral or ↓
Fatal Bleeding	↑	neutral or ↓
ICH	trend to ↑	neutral

Enoxaparin and Fondaparinux
Other Practical Considerations

	Enoxaparin	Fondaparinux
Cost (red book)	US$123.82/day*	$45.86/day
Regimen	Twice daily	Once daily
Formulation	Animal Byproducts	Synthetic
Dose Adjustment	needed in elderly and renal dysfunction	Not necessary

***80 mg syringe**

Conclusions

1. Fondaparinux is non-inferior compared with enoxaparin at 9 days, with substantially lower rates of important bleeds. The net benefit-risk balance clearly favors fondaparinux.
2. Bleeding increases the risk of death significantly.
3. At one month and at 6 months there is a significant reduction in mortality with fondaparinux.
4. Strokes are also significantly reduced, so that there is a clear reduction in death, MI, and strokes with fondaparinux
5. Consistent results are observed in those undergoing PCI (including early PCI) and in every other subgroup examined.

Fondaparinux Across the Spectrum of ACS

From both an efficacy and safety perspective, fondaparinux is a very attractive choice across the full spectrum of ACS

Wait for FDA approval