



Benefit of Fondaparinux on Mortality, Ischemic Events and Bleeding Across the Entire Spectrum of Acute Coronary Syndromes

Michelangelo OASIS 5 and 6 Combined Analysis

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on Behalf of the OASIS 5 and 6 Steering Committee and
Investigators

Disclosures

- Research grant support via the Population Health Research Institute, McMaster University and honoraria GlaxoSmithKline, Sanofi-Aventis, Organon NV and Bristol Myers Squibb
- The OASIS 5 and 6 trials were supported by Sanofi-Synthelabo, Organon NV and GlaxoSmithKline



Introduction

- Fondaparinux is a **pure factor Xa inhibitor** that is given in a once daily subcutaneous dose
- It has **rapid onset of action**, **100% bio-availability** and undergoes **no metabolism or protein binding** (other than its target)
- Unlike the heparins or low molecular weight heparins, it is a **synthetic compound** and **not derived from animal products**
- It has been extensively studied for prevention of VTE where it was superior to enoxaparin



Introduction

- Recently, the OASIS-5 trial of over 20,000 patients with NSTEMI-ACS established non-inferiority of fondaparinux in direct, double blind comparison to enoxaparin at 9 days and a **50% reduction** in major bleeding
- In the OASIS-6 trial of over 12,000 patients with STEMI, fondaparinux reduced death and MI with no increase in bleeding.
- *In both of these trials, there were significant reductions in all cause mortality with fondaparinux*



Objective

To determine the efficacy and safety of fondaparinux across the entire spectrum of acute coronary syndromes (STEMI and NSTEMI) and to further explore its effects versus **UFH/enoxaparin** and versus placebo, separately



Methods

- An intention to treat analysis was used
- Individual patient data for the two trials were combined and the groups compared using the log rank test
- In order to explore the effects of fondaparinux versus active therapy with enox/UFH, data from OASIS 5 was combined with stratum II of OASIS 6
- In order to explore the effects of fondaparinux versus placebo, data from OASIS-6 stratum 1 are presented
- The effect of fondaparinux pre-treatment in patients undergoing PCI was assessed by combining the outcomes in PCI patients from OASIS 5 with the non-primary PCI population in OASIS 6.



Baseline Characteristics

	Control (n=16077)	Fondaparinux (n=16093)
Age, yr	64.7	64.7
Male	65.3	66.0
Heart rate, bpm	74.1	74.2
Systolic blood pressure, mm Hg	135.5	135.6
Diagnosis at study entry		
Unstable angina	28.1	28.5
NSTEMI	34.2	34.0
STEMI	37.7	37.9
CABG	5.4	5.7
PCI	8.3	8.4
Heart Failure	13.8	14.0
Hypertension	62.4	62.5
Diabetes	22.2	22.8

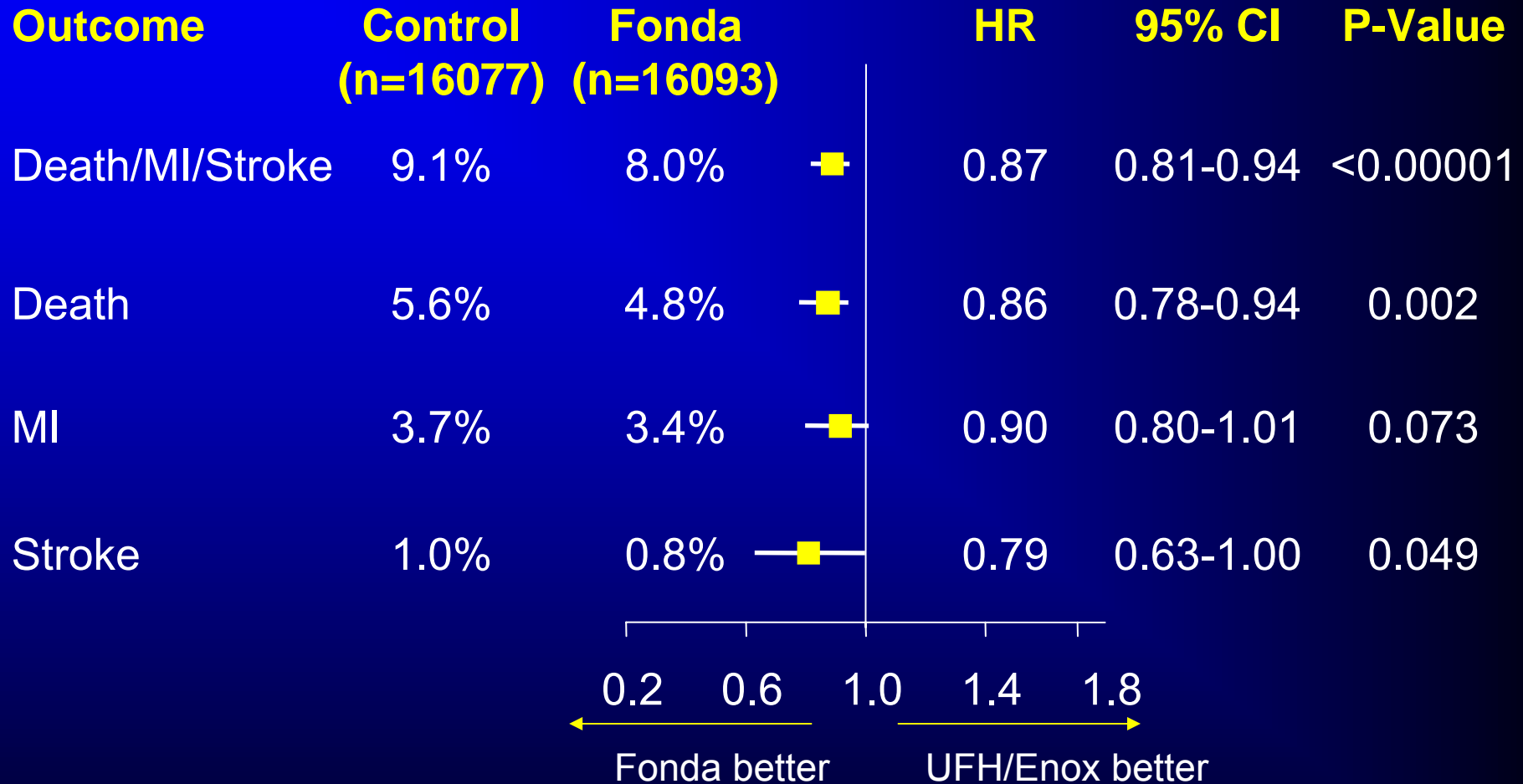
In Hospital Medications and Procedures

	Control (%) (n=16077)	Fondaparinux (%) (n=16093)
Aspirin	97.1	97.3
Clopidogrel or ticlopidine	67.3	67.3
ACE Inhibitors/ARB	73.5	72.5
Beta-blockers	86.2	86.1
Statins	76.2	76.7
Coronary angiography	55.7	56.2
PCI	35.2	35.3
CABG surgery	6.1	6.4



Efficacy Outcomes: All Control vs Fondaparinux

Death, MI, Stroke at 30 Days

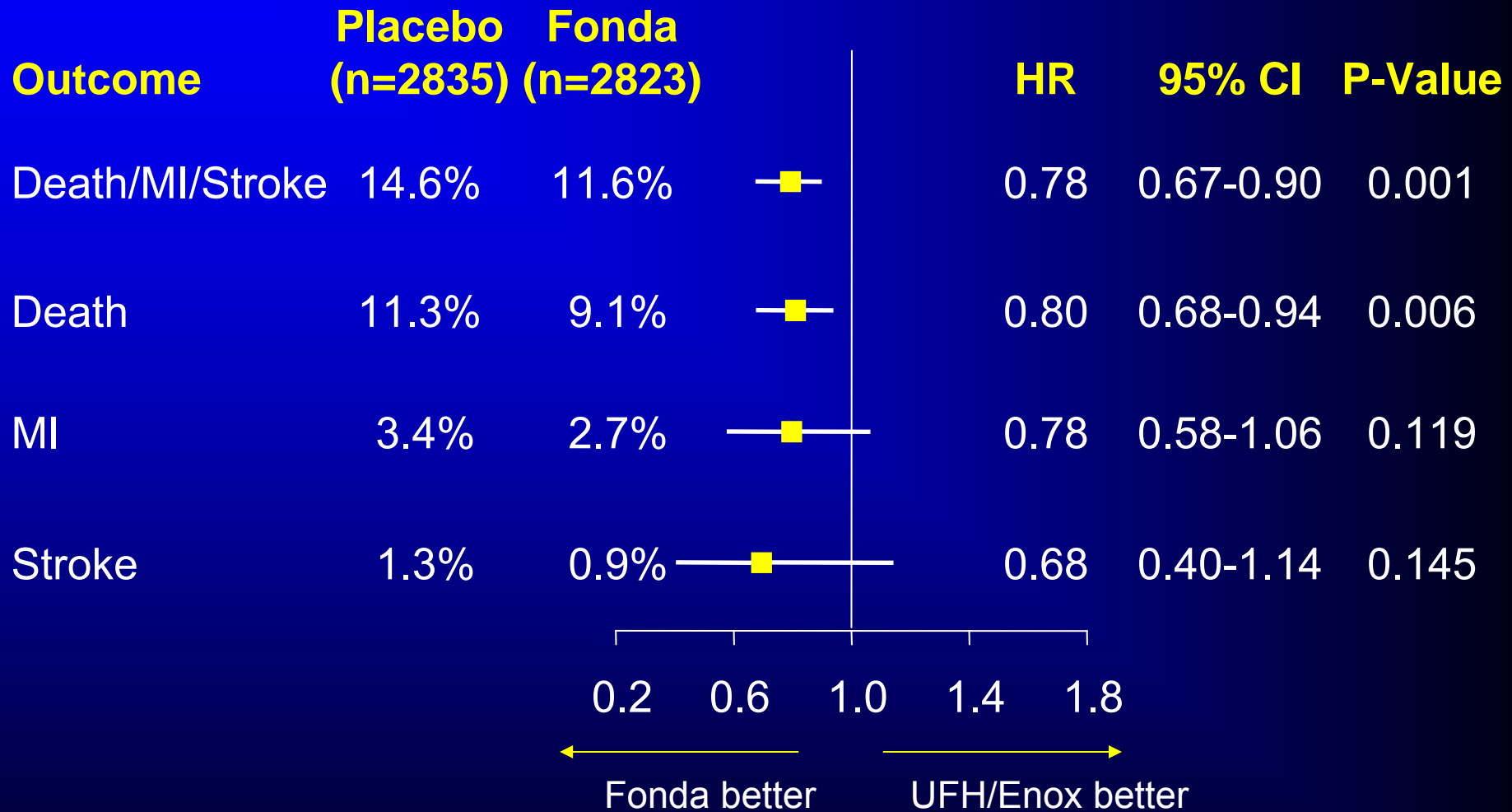


Hazard Ratio (95% CI)



Efficacy Outcomes: Placebo vs Fondaparinux

Death, MI, Stroke at 30 Days



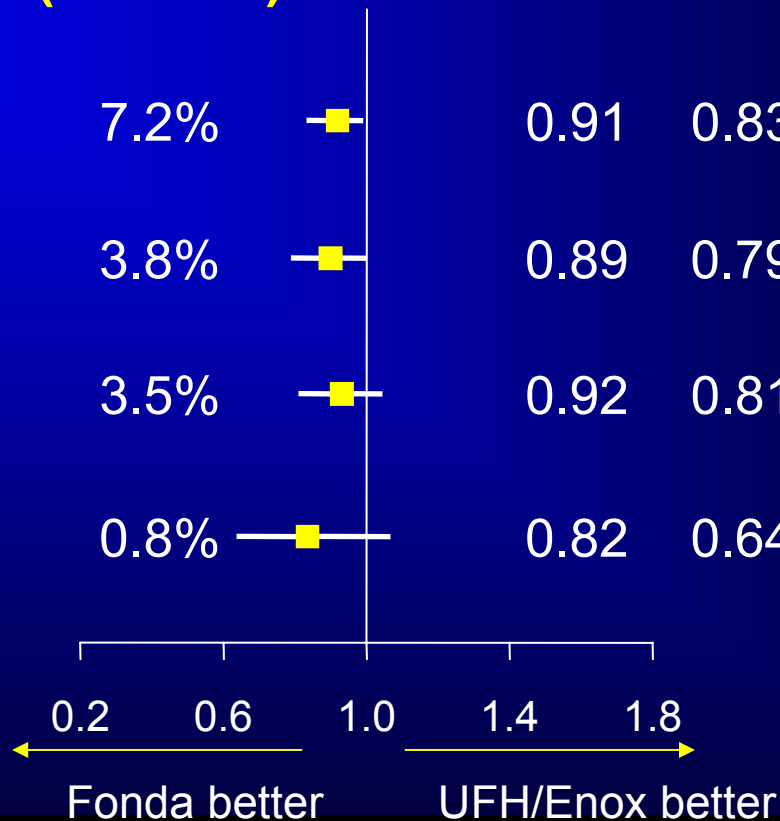
Hazard Ratio (95% CI)



Efficacy Outcomes: UFH/Enox vs Fondaparinux

Death, MI, Stroke at 30 Days

Outcome	UFH/Enox (n=13242)	Fonda (n=13270)	HR	95% CI	P-Value
Death/MI/Stroke	8.0%	7.2%	0.91	0.83-0.99	0.030
Death	4.3%	3.8%	0.89	0.79-1.00	0.052
MI	3.8%	3.5%	0.92	0.81-1.04	0.196
Stroke	1.0%	0.8%	0.82	0.64-1.07	0.143

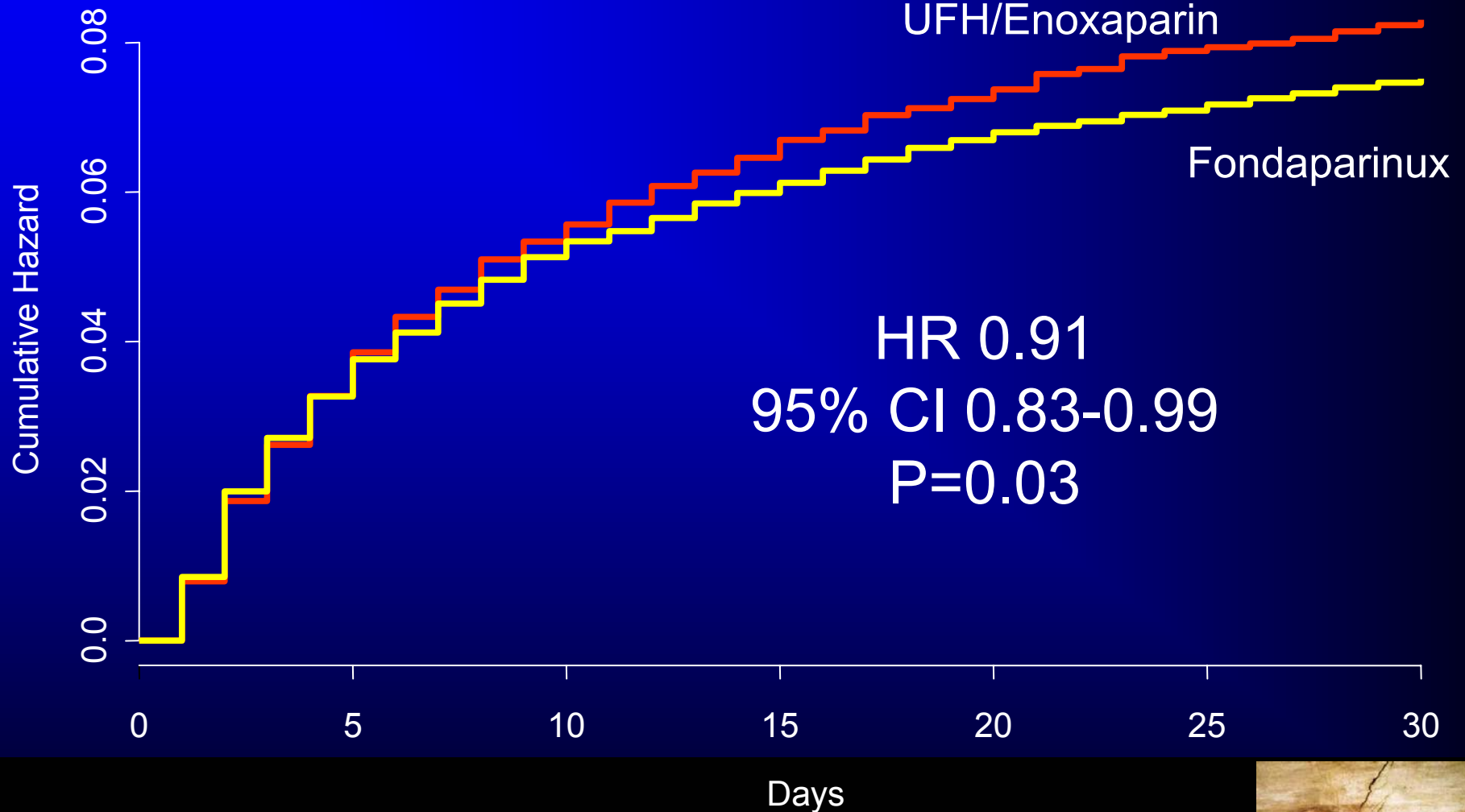


Hazard Ratio (95% CI)



UFH/Enox versus Fondaparinux

Death/MI/Stroke at 30 days



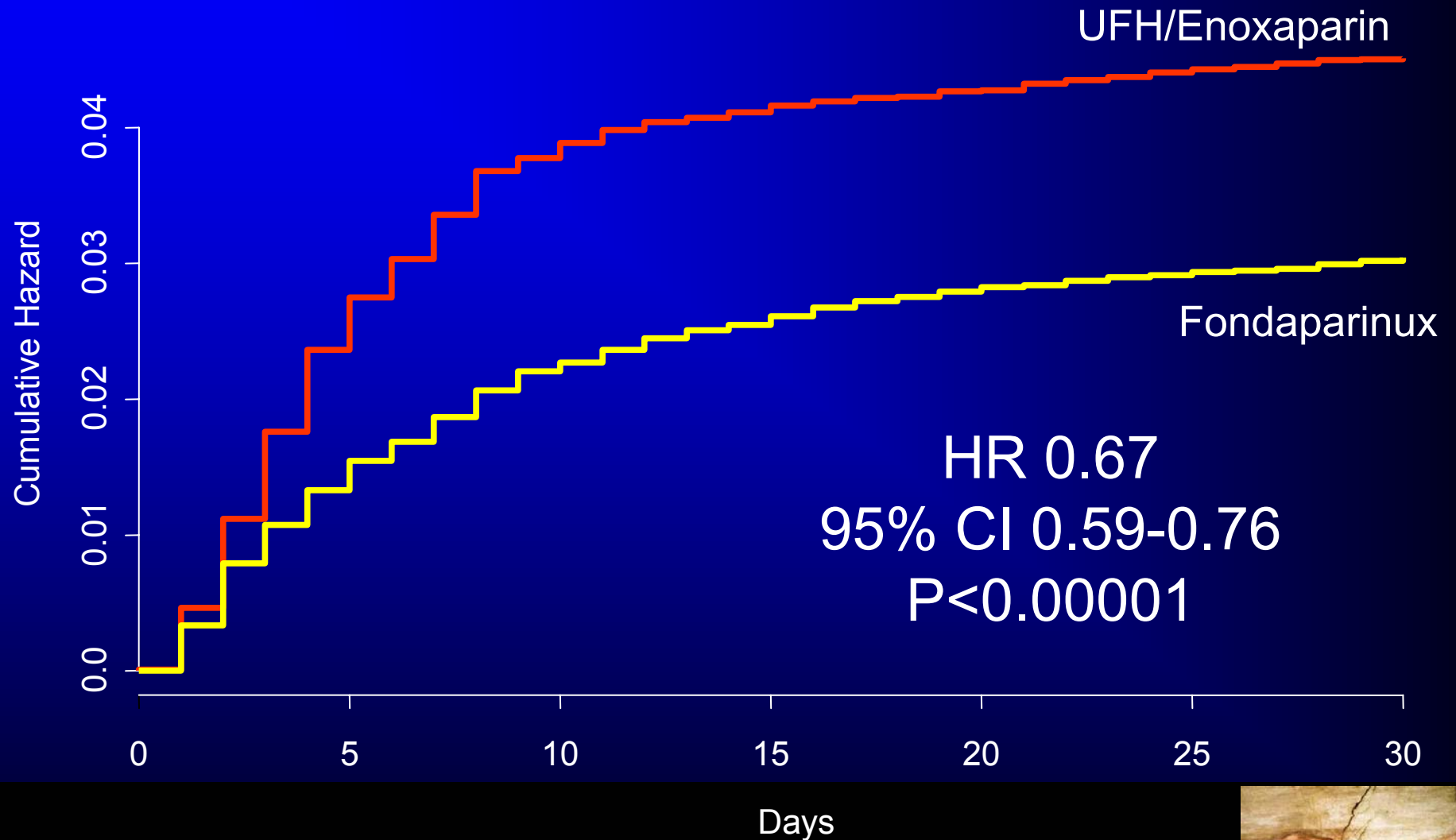
Major Bleeding

	Control	Fonda	HR	95% CI	P value
At 9 days					
Overall	3.4	2.1	0.59	0.52-0.68	<0.00001
Vs Placebo	2.1	1.4	0.68	0.45-1.02	0.065
Vs UFH/Enox	3.7	2.2	0.58	0.50-0.68	<0.00001
At 30 days					
Overall	4.0	2.8	0.67	0.60-0.76	<0.00001
Vs Placebo	2.3	1.6	0.69	0.47-1.02	0.062
Vs UFH/Enox	4.4	3.0	0.67	0.59-0.76	<0.00001
At 6 months					
Overall	4.8	3.7	0.76	0.68-0.84	<0.0001
Vs Placebo	2.5	2.2	0.81	0.57-1.16	0.26
Vs UFH/Enox	5.2	4.0	0.75	0.67-0.84	<0.00001

n=16077 (overall) and 16093 (fonda); n=2835 (placebo) and 2823 (fonda);
n=13242 (UFH/Enox) 13270 (fonda)

Major Bleeding at 30 days

UFH/Enox versus Fondaparinux



Outcomes in PCI Patients According to Anticoagulant Used for PCI

(PCI for UA/NSTEMI or Rescue/Facilitated/Routine PCI for STEMI)

	Control	Fonda	HR	95% CI	P value
Death/MI/Stroke					
Enox/UFH vs Fonda	8.0	8.0	1.00	0.84-1.20	0.97
Enox alone vs Fonda*	8.0	6.9	0.86	0.67-1.10	0.23
UFH vs Fonda†	8.0	9.2	1.17	0.91-1.49	0.21
Major Bleeding					
Enox/UFH vs Fonda	5.5	2.9	0.52	0.41-0.67	<0.0001
Enox alone vs Fonda*	5.5	3.0	0.54	0.38-0.76	0.0005
UFH vs Fonda†	5.6	2.9	0.51	0.35-0.73	0.0003
Death/MI/Maj. Bleed					
Enox/UFH vs Fonda	11.9	9.9	0.82	0.84-1.20	0.010
Enox alone vs Fonda*	11.8	9.0	0.75	0.61-0.93	0.010
UFH vs Fonda†	12.1	10.8	0.89	0.72-1.10	0.30

*Enoxaparin alone vs Fonda: PCI performed < 6 hours of last sc enoxaparin dose in OASIS 5

†UFH vs Fonda: PCI performed ≥ 6 hours from last sc enoxaparin dose in OASIS 5 and all non-Primary PCI's in OASIS 6

Enox/UFH vs Fonda N=3136 & 3154, respectively; Enox alone vs Fonda n=1633 & 1648, respectively; UFH vs Fonda n=1503 & 1506, respectively

Efficacy, Safety and Catheter Thrombus According to Use of Open Label UFH Prior to PCI

PCI for UA/NSTEMI and Rescue, Facilitated or Routine PCI for STEMI

	UFH/Enox	Fonda	HR	95% CI
Major Bleed at Day 30				
All non-primary PCI	5.4	3.0	0.54	0.42-0.69*
UFH Prior to PCI	5.2	3.6	0.69	0.32-1.46
Death/MI/Stroke at Day 30				
All non-primary PCI	7.9	7.9	0.99	0.84-1.18
UFH Prior to PCI	12.7	11.8	0.92	0.60-1.41
Catheter Thrombus				
All non-primary PCI	0.2	0.9	3.58	1.64-7.83
UFH Prior to PCI	0	0.3†	--	--

*P<0.0001

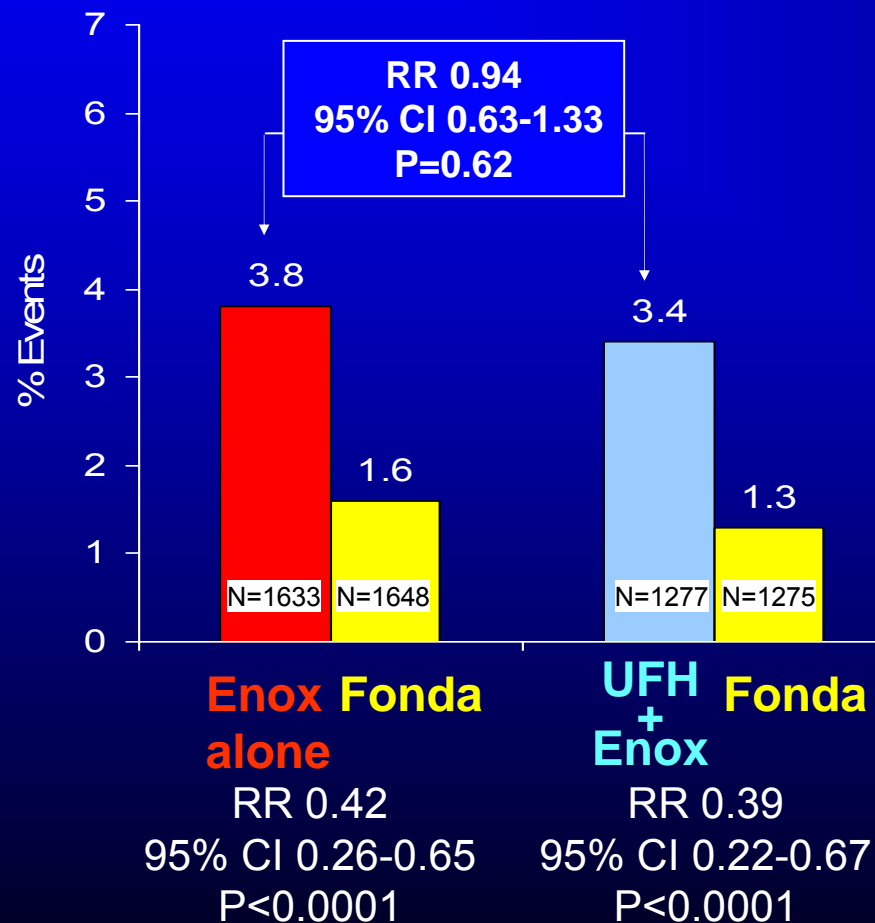
All non-primary PCI, N=3298 UFH/enox and N=3336 fonda

UFH Prior to PCI, N=306 fonda and N=306 UFH/Enox

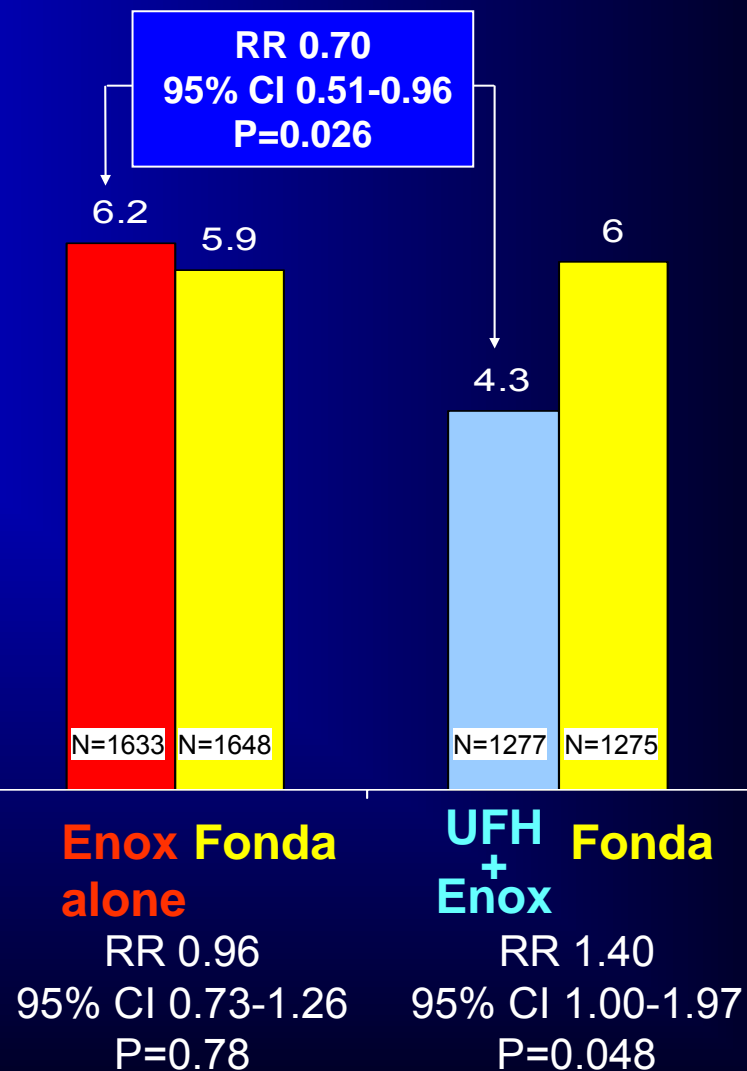
†represents 1 patient who received a very low UFH dose prior to PCI (570 IU or 5.0 IU/kg)

OASIS 5: Fonda vs Enox alone and vs UFH+Enox in PCI Patients

Major Bleeding 48 hours after PCI

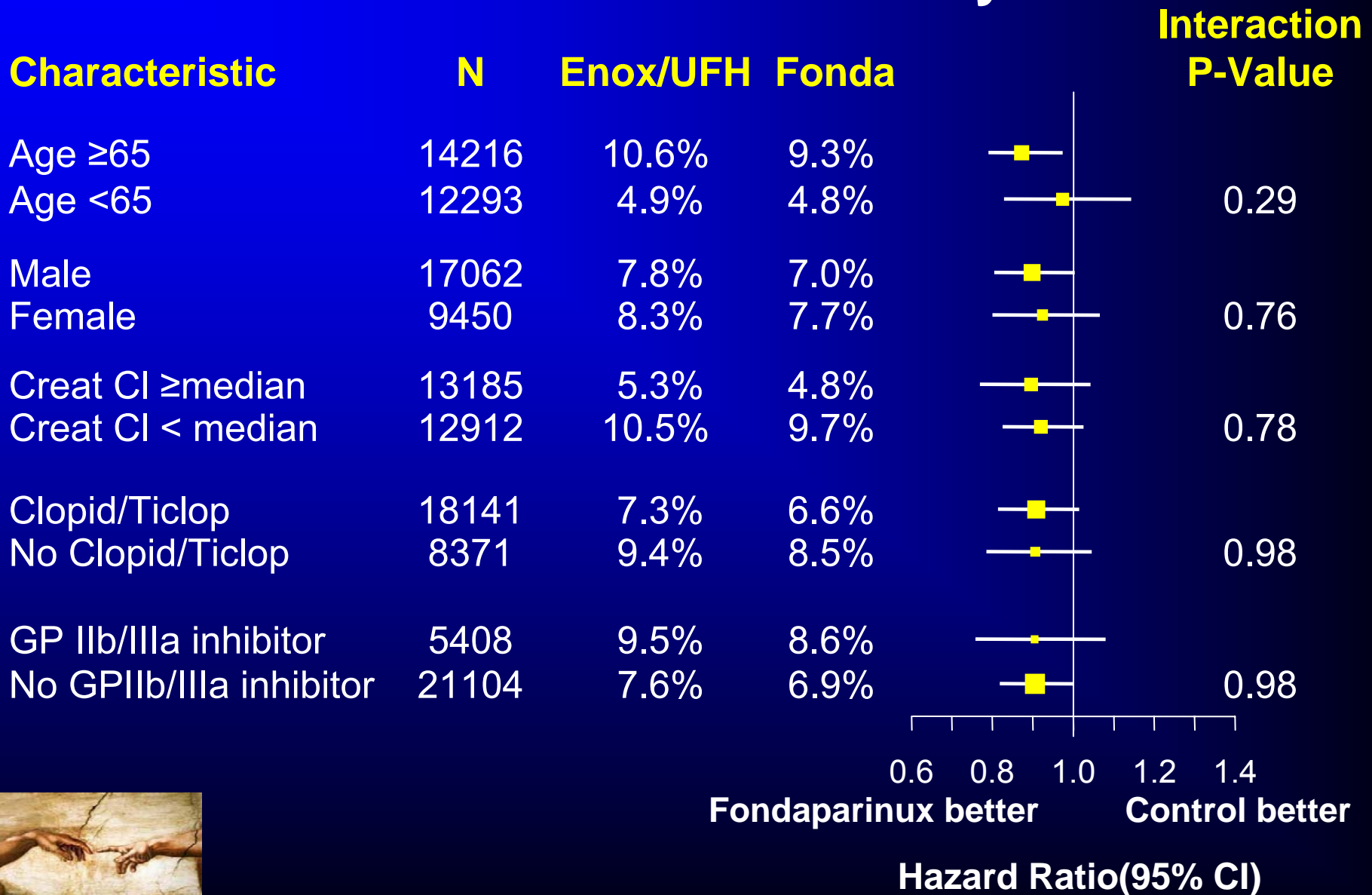


Abrupt/threatened abrupt closure



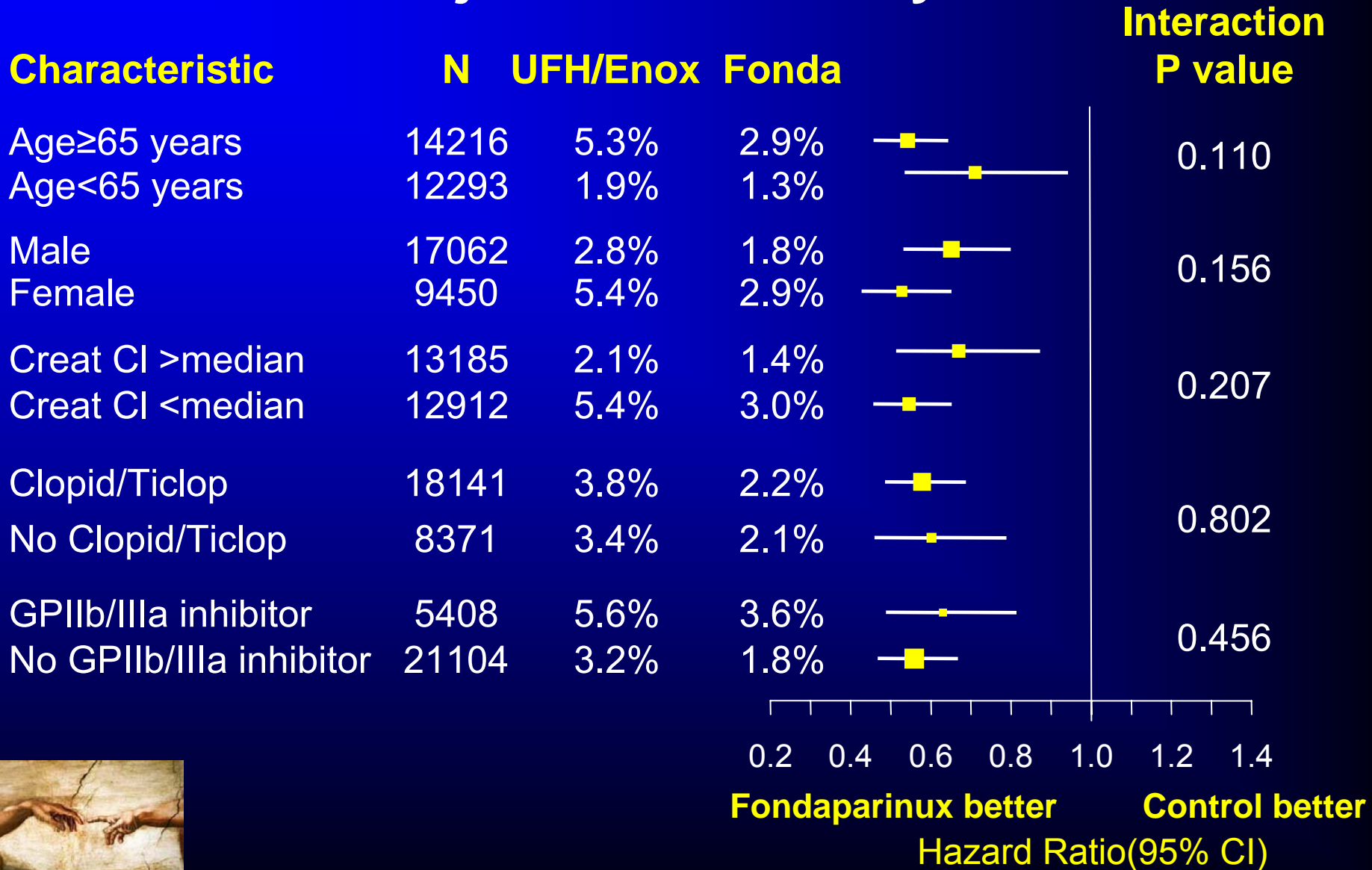
Fonda vs Enox/UFH: Subgroups

Death/MI/Stroke at 30 days



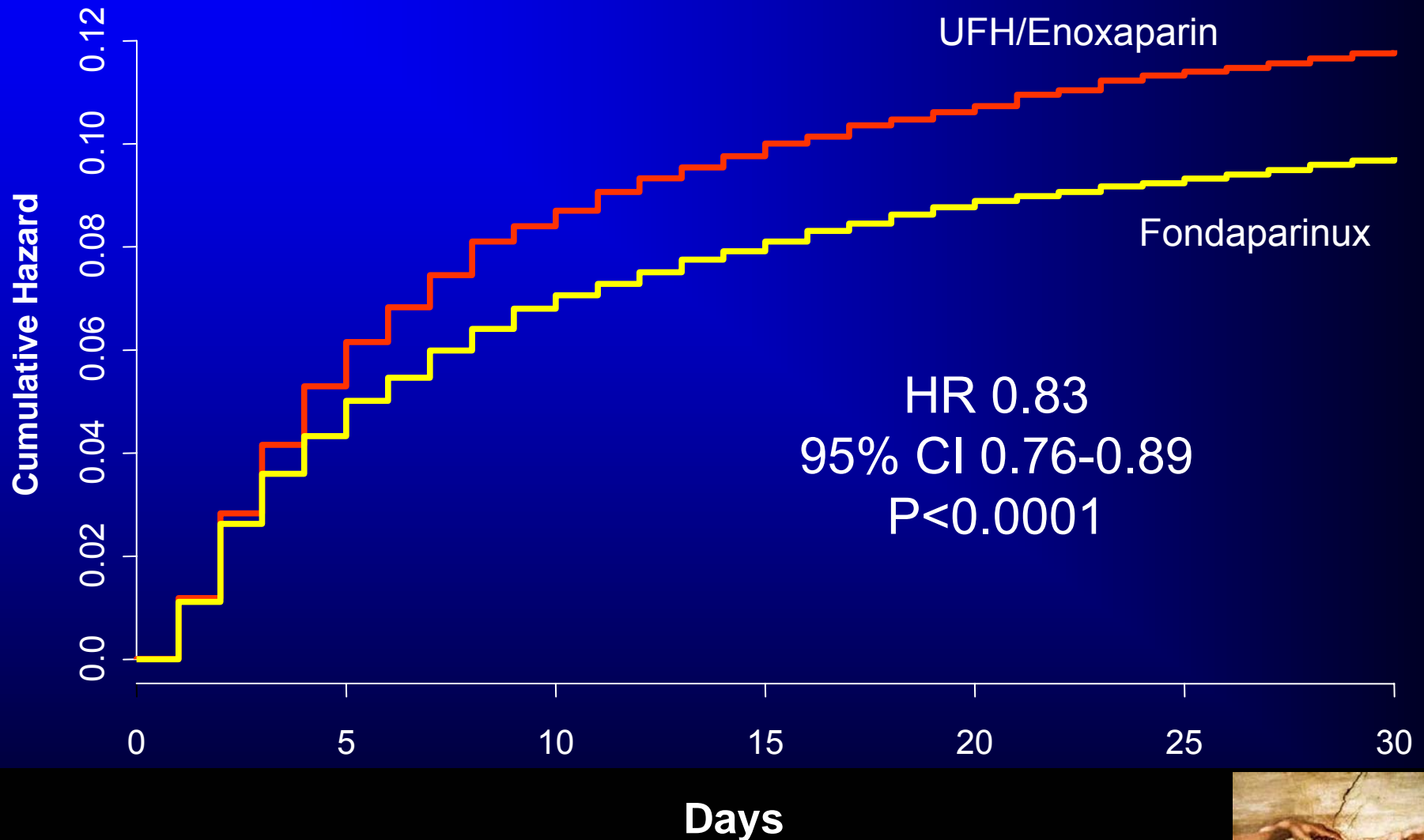
UFH/Enox vs Fonda: Subgroups

Major bleed at 9 days



Net Clinical Benefit at 30 Days

Death/MI/Major bleed



Conclusions

1. Fondaparinux is superior to UFH/enoxaparin in reducing death/MI/stroke across the whole spectrum of patients with ACS
2. Fondaparinux is associated with markedly lower rates of major bleeding than UFH/enoxaparin
3. Upstream therapy with fondaparinux is safe and effective in patients undergoing PCI
4. Catheter thrombus occurs very rarely in comparison with death or re-MI and appears to be avoided with standard UFH for the PCI itself without increasing major bleeding



Implications

- Fondaparinux is the only antithrombotic agent that reduces mortality and major bleeding compared with heparin/LMWH
- Patients who are treated upstream with fondaparinux can be managed safely with a variety of management strategies, including PCI
- If PCI is performed in a patient receiving fondaparinux, standard UFH should be used as the anticoagulant for the procedure itself



Implications

A tailored strategy of using fondaparinux in all ACS patients followed by UFH for the PCI procedure itself is a very attractive strategy for the management of patients with ACS that has substantial benefits over standard treatment with enoxaparin or UFH alone

