

OASIS 5: Another guidepost in the treatment of a complex disease

Robert M Califf MD

Vice Chancellor for Clinical Research

Professor of Medicine

Director Duke Clinical Research Institute



Conflicts

- I have worked on many trials with competing and complementary antithrombotic drugs
- Duke University has major research contracts with GSK, Sanofi, The Medicines Company, all of whom have a major interest in interpretation of this trial
- I have cofounded a company, Nitrox, which is partly working on improving the outcomes of blood transfusion



OASIS 5—Key Lessons

- **Bleeding is bad**
- **Dose—outcome relationship cannot be predicted**
 - Must be measured empirically!
- **Enroll enough patients with enough events to get clear answers about outcomes!**
- **Need a clear path to meld understanding of treatment effects with medical tx with the complicated world of the cath lab/surgery**



Bleeding

- Every study done to date shows that patients with bleeding in ACS have a 2-5 fold increase in risk of death and other adverse events
- Possible reasons
 - Anemia itself causing decrease in oxygenation—unlikely to be culprit
 - Blood flow much bigger determinant of oxygenation than Hgb carrying capacity*
 - Hypotension with sympathetic surge
 - Antithrombotics discontinued leading to coronary rethrombosis
 - Blood transfusion causes prothrombotic state with vasoconstriction and NO sink

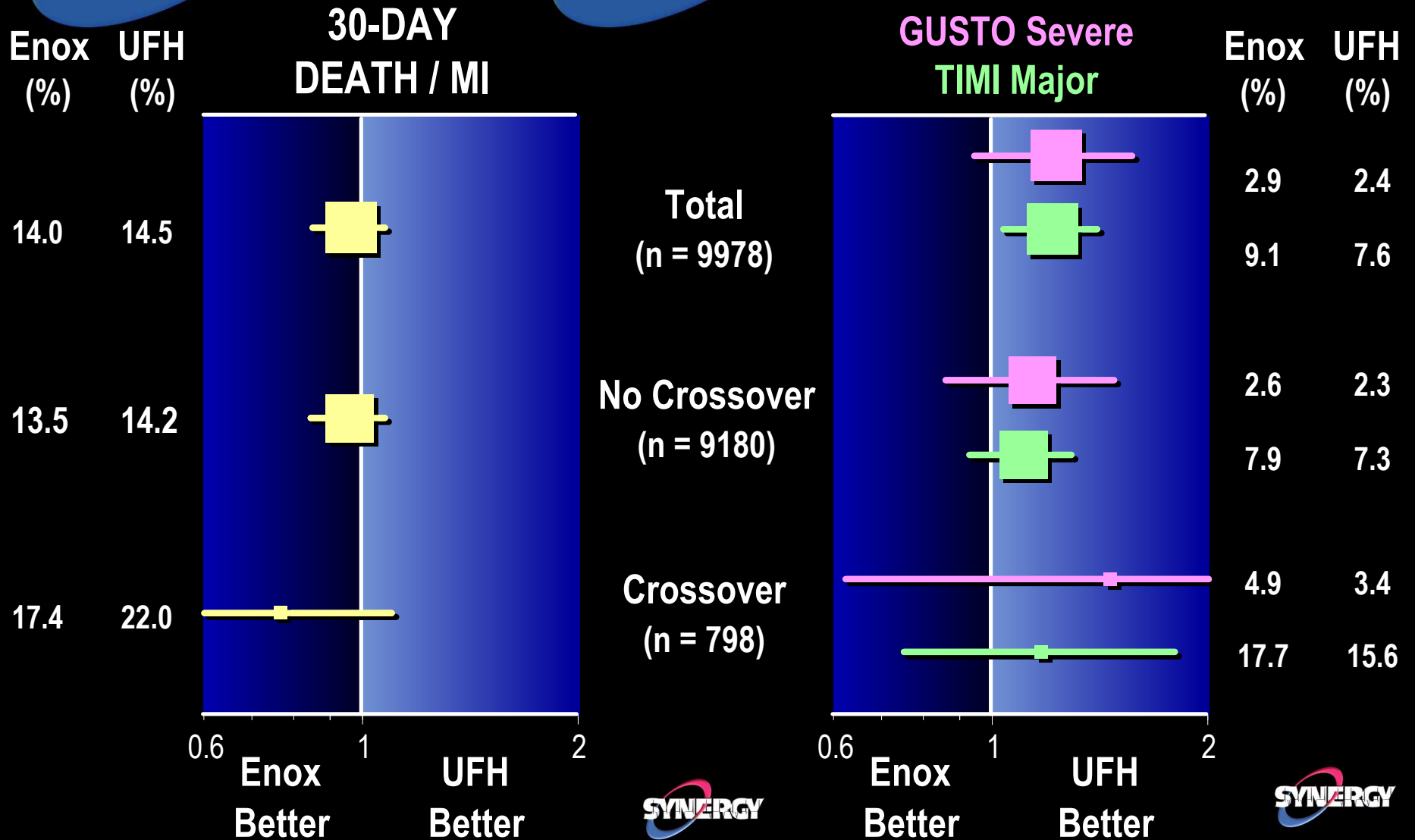


How did they pick that dose?

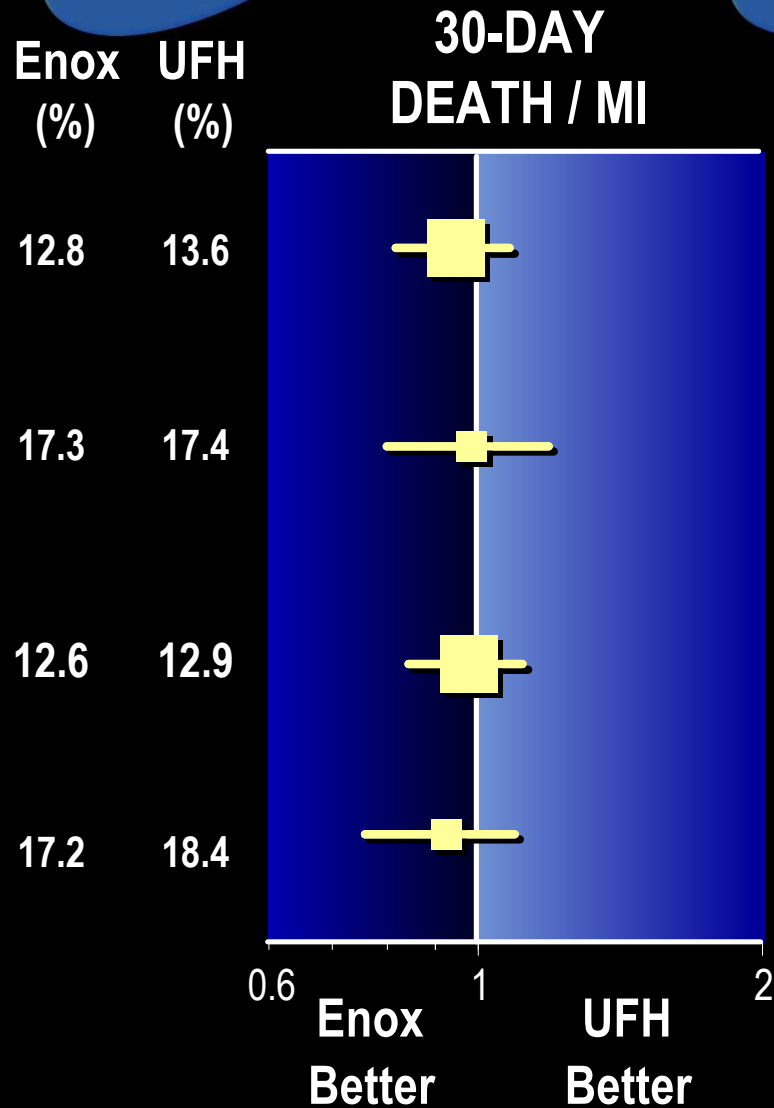
- **All previous antithrombotics**
 - Dose related increase in bleeding and decrease in ischemic events (classic tradeoff)
- **Fondaparinox (apparently)**
 - Dose related increase in bleeding
 - No dose related reduction in ischemic events
 - Lowest effective dose is most effective dose!?
- **Enoxaparin**
 - Package insert: adjust dose for Cr Cl < 30
 - Excess bleeding in older and women—very similar to SYNERGY findings



Crossovers: Efficacy and Safety



Age and Creatinine: Efficacy and Safety



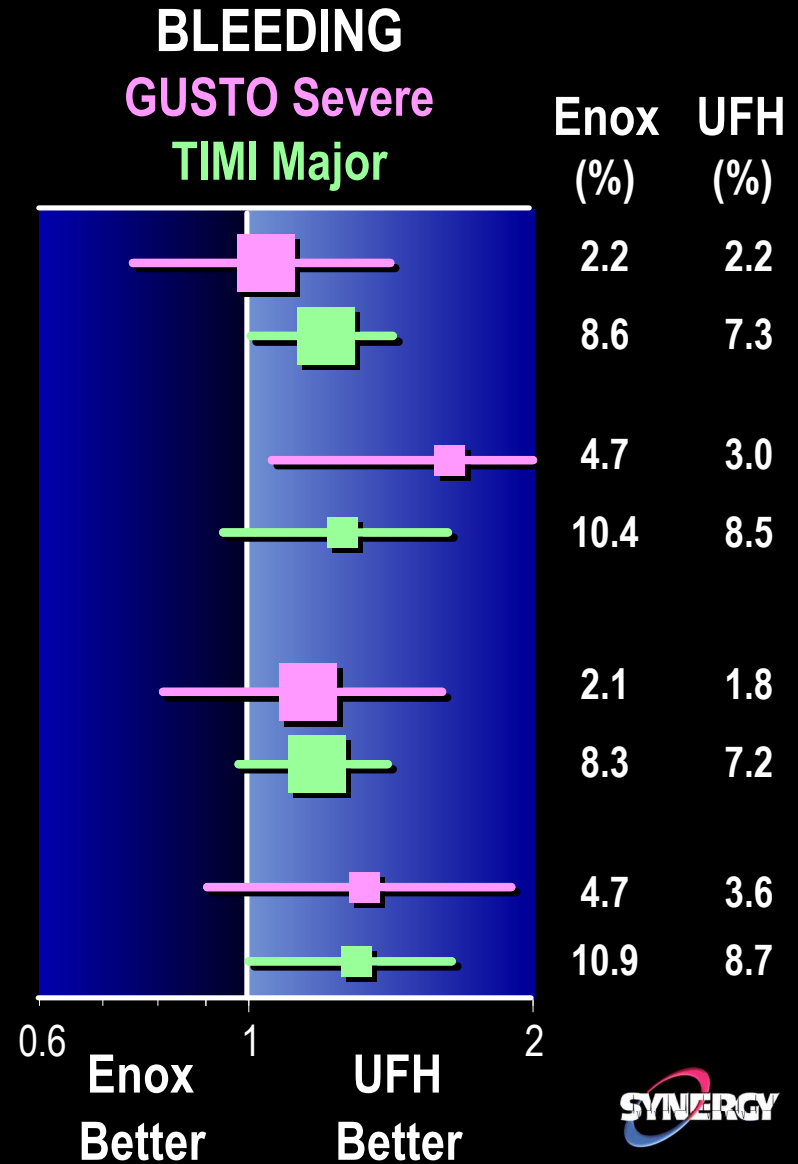
Age < 75
(n = 7438)

Age ≥ 75
(n = 2540)

CrCl ≥ 60
(n = 7019)

CrCl < 60
(n = 2959)

SYNERGY



SYNERGY

Enroll enough patients with enough events

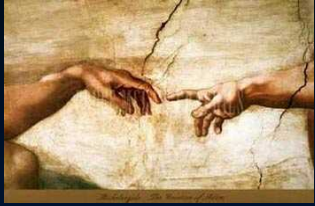
- The search for surrogates that will radically reduce sample size continues
- Given that literally millions of people will be treated with mainstream CV drugs
 - Biomarkers for risk stratification is sensible
 - This will not obviate the need for large trials
 - Every biomarker creates a subgroup needing validation in independent sample*
- A better approach is to reduce the use of unnecessary trial procedures (thereby reducing cost) and enroll 10X patients



Medical Treatment and Cath Lab

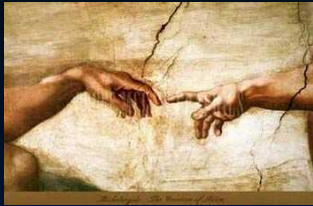
- **Medical stabilization calls for different doses and combinations than cath lab**
- **SYNERGY pointed out that mixing antithrombotics without adequate empirical testing could be dangerous**
 - Empirical testing means measuring outcomes in thousands of people with randomized dosing regimens
- **Catheter thrombosis will bother cath lab people even though death/MI no different!**
- **STEEPLE is evaluating enoxaparin with no UFH vs UFH alone in PCI (bleeding is primary concern)**
 - To be presented this week by Prof Montalescot





Death, MI, Refractory Ischemia or Major Bleed at Day 30 by Age

	Enox	Fonda	HR (95% CI)	P-value
<65	7.5%	7.4%	0.99 (0.84, 1.16)	0.883
>65 yrs	15.4%	12.1%	0.77 (0.70, 0.85)	0.000
				P for interaction = 0.011



Efficacy & Bleeding by Cath Lab vs No Cath Lab: Day 30

Efficacy

With Cath Lab

No Cath Lab

Bleeding

With Cath Lab

No Cath Lab

Efficacy+Bleeding

With Cath Lab

No Cath Lab

Interaction P

0.246

0.745

0.808

0.4

0.6

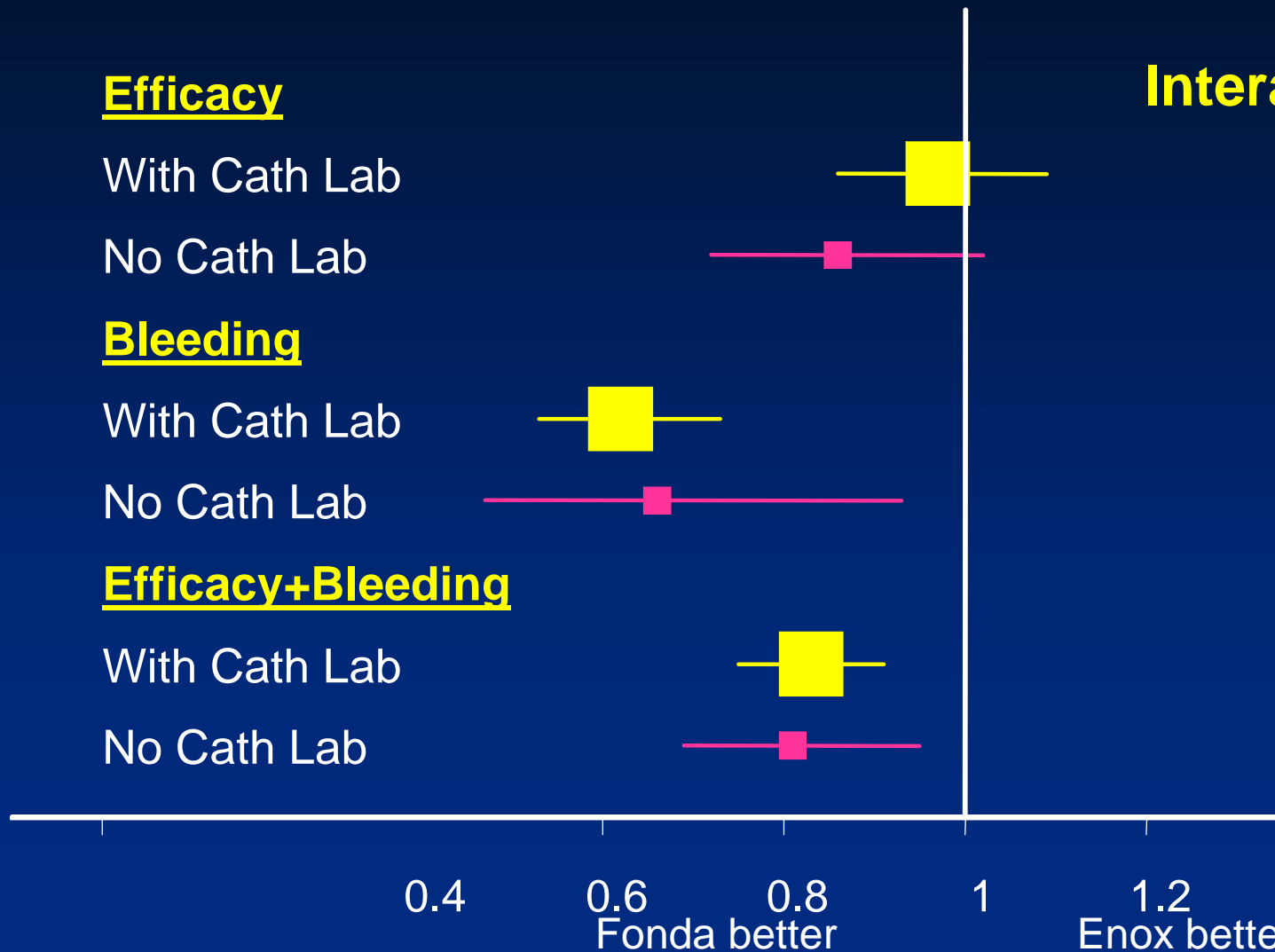
0.8

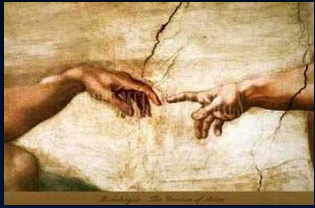
1

1.2

Fonda better

Enox better





Efficacy & Bleeding by Prior Heparin: Day 30

Efficacy

Prior Hep

No Prior Hep

Bleeding

Prior Hep

No Prior Hep

Efficacy+Bleeding

Prior Hep

No Prior Hep

Interaction P

0.727

0.538

0.767

0.4

0.6

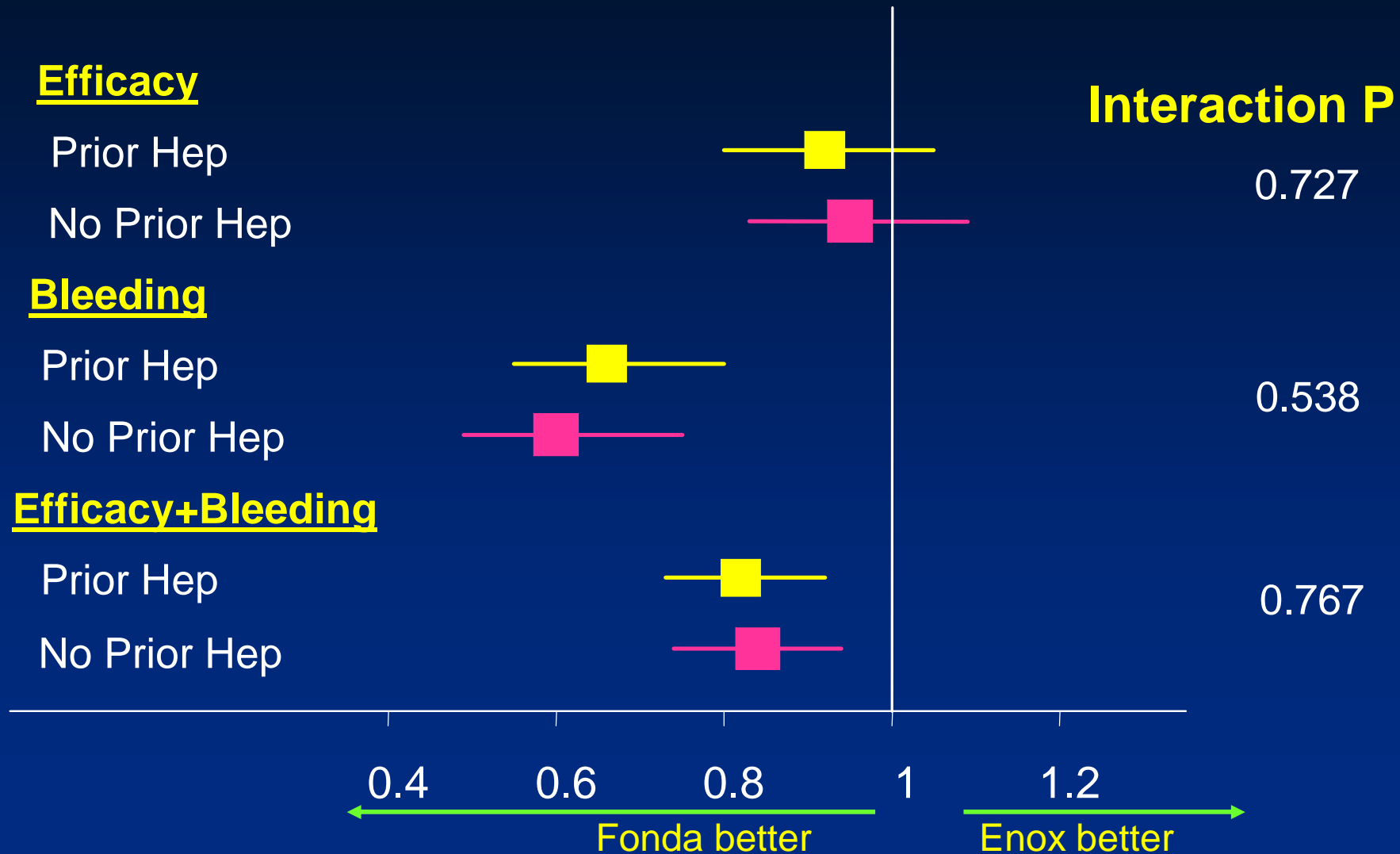
0.8

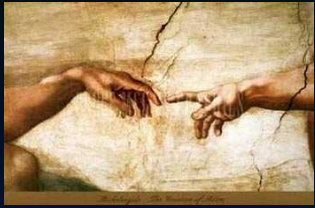
1

1.2

Fonda better

Enox better





Bleeds at 9 Days Based on Open Label Heparin Use in Hospital

No Heparin

Bleeding	Enox	Fonda	HR (95% CI)	P-value
Total	5.8%	2.2%	0.37 (0.31-0.45)	<<0.0001
Major	3.1%	1.3%	0.41 (0.32-0.52)	<<0.0001
Minor	2.8%	0.9%	0.33 (0.25-0.44)	<<0.0001
TIMI Major	0.9%	0.4%	0.44 (0.28-0.69)	<0.0003

With Heparin

Total	10.4	5.7	0.54 (0.44-0.65)	<<0.0001
Major	6.5%	4.3%	0.66 (0.52-0.83)	0.0004
Minor	4.0%	1.5%	0.37 (0.26-0.53)	<<0.00001
TIMI Major	2.4%	1.5%	0.63 (0.43-0.93)	0.021



PCI During Study Treatment Period Procedural Complications

Events at 30 days	Enox (%)	Fonda (%)	HR (95% CI)	P value
No. Rand.	3089	3118		
Any UFH during PCI	53.8	18.8		
Coronary--Any Complicat ⁿ	8.6	9.6	1.11 (0.95-1.30)	0.18
Abrupt Closure	1.1	1.5	1.33 (0.86-2.06)	0.20
Vasc. Access Site	8.1	3.3	0.40 (0.32-0.50)	<<0.0001
Pseudo-aneurysm	1.6	1.0	0.63 (0.40-0.98)	0.039
Large Hematoma	4.4	1.6	0.35 (0.26-0.49)	<<0.0001
Catheter thrombus*	0.5	1.3*	2.76 (1.50-5.07)	0.001*

*Following institution of routine UFH prior to PCI, only one case of cath thrombus in 330 patients given fonda.

Personal Current Bottom Line

- OASIS 5 has identified an excellent regimen for anticoagulation in ACS
- Can't tell if bleeding difference due to intrinsic differences in physical properties of comparative drugs or better dosing with Fonda
 - Enox disadvantaged by **cath lab switching—DON'T DO IT!**
 - Enox dosing probably wrong with CrCl of 30-60
- **Catheter thrombosis will be a pragmatic issue**
- **We must redouble efforts to deal with bleeding**
 - Decrease number of bleeds with better dosing regimens
 - Deal more effectively with bleeding when it occurs
- **Further analyses will be fascinating and will lead to refinement of views of comparative strategies**



A Proposal

- **Develop professionally driven CQI process to optimize patient outcomes through constant iterative clinical trials**
- **This approach could immediately take lessons from trials and incorporate them into new protocols**
- **Far superior for patients than product dependent approach we currently use**
- **ONLY ONE PROBLEM—WHO WOULD FUND IT?**

