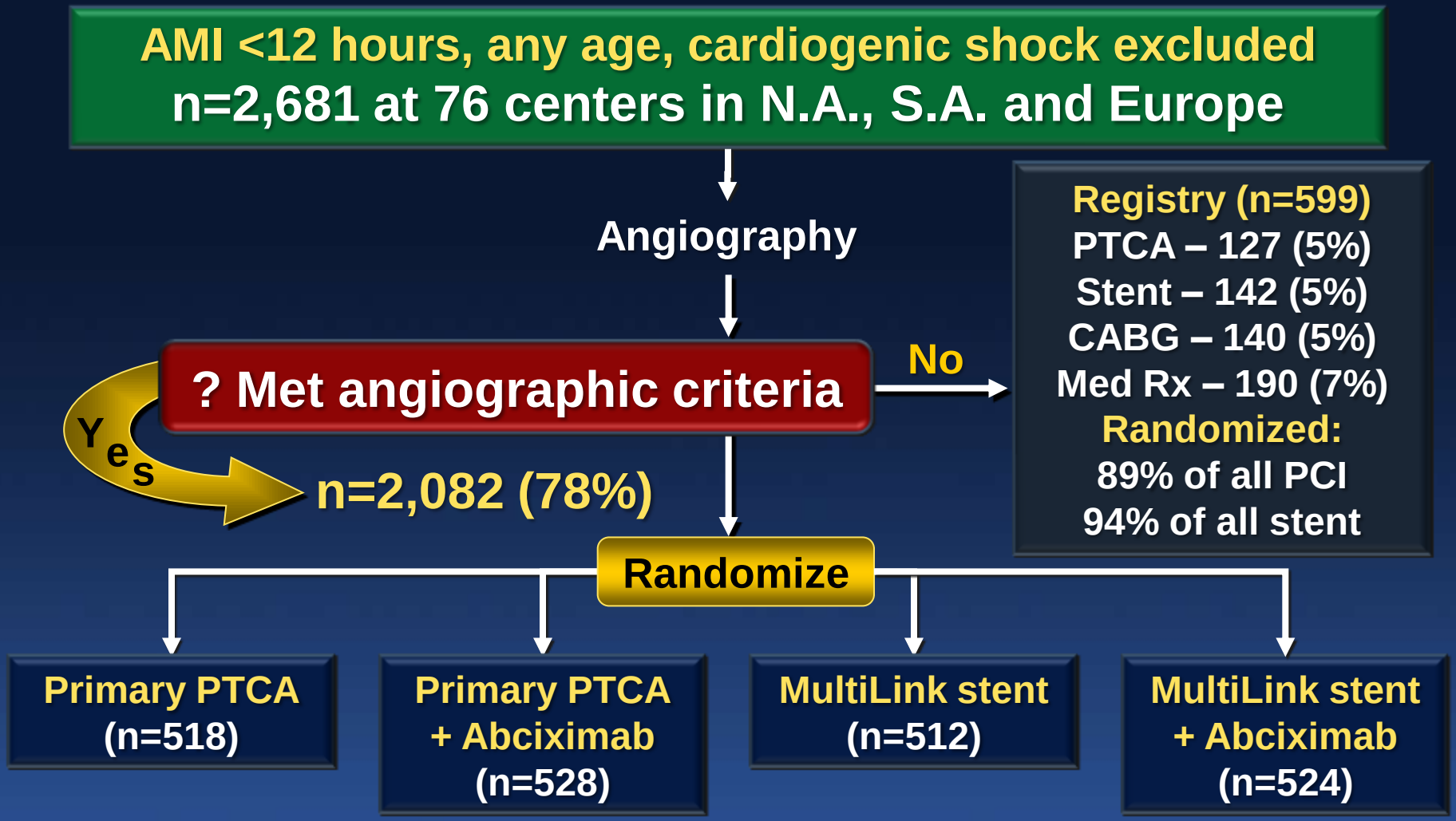
From HORIZONS to EUROMAX: Bivalirudin or UFH + GP IIb/IIIa Inhibitors?

Gregg W. Stone, MD

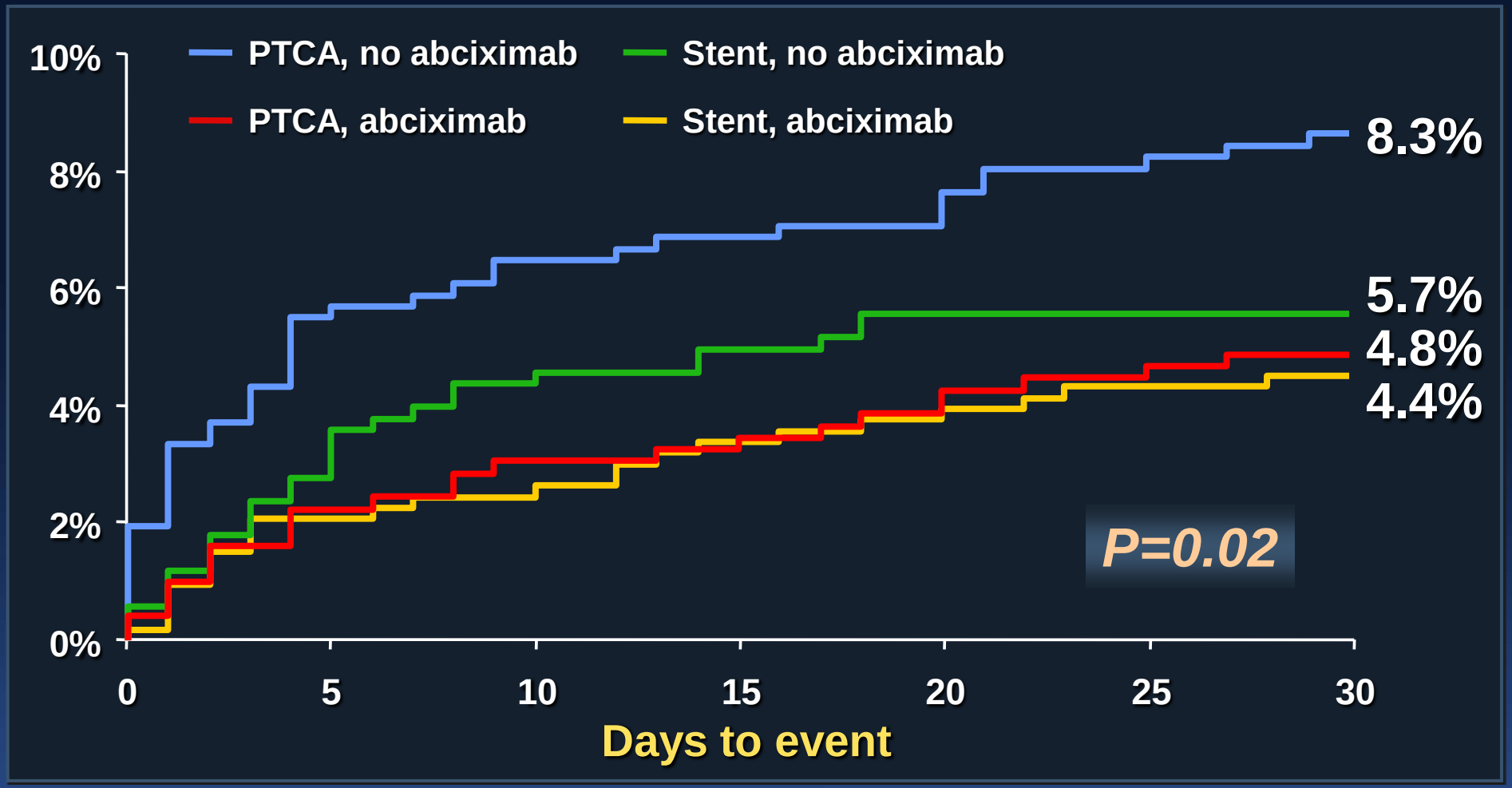
Columbia University Medical Center
NewYork-Presbyterian Hospital
Cardiovascular Research Foundation

CADILLAC: Trial Design



Stone GW et al. *NEJM* 2002;346:957–66

CADILLAC (n=2,082): 30-Day MACE



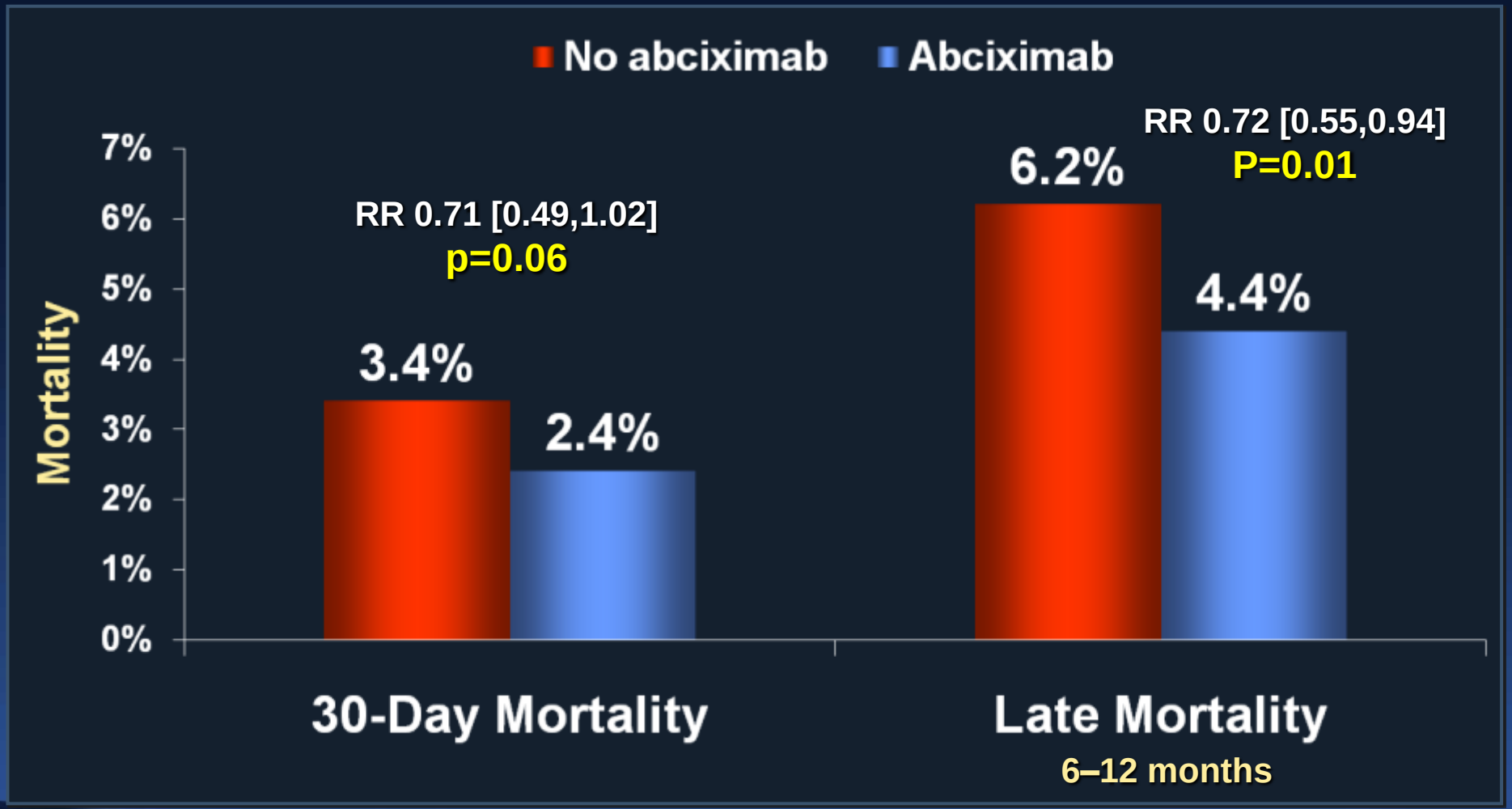
Stent thrombosis:

1.2% with UFH alone vs. 0% with UFH + abciximab **(P=0.01)**

Stone GW et al. *NEJM* 2002;346:957–66

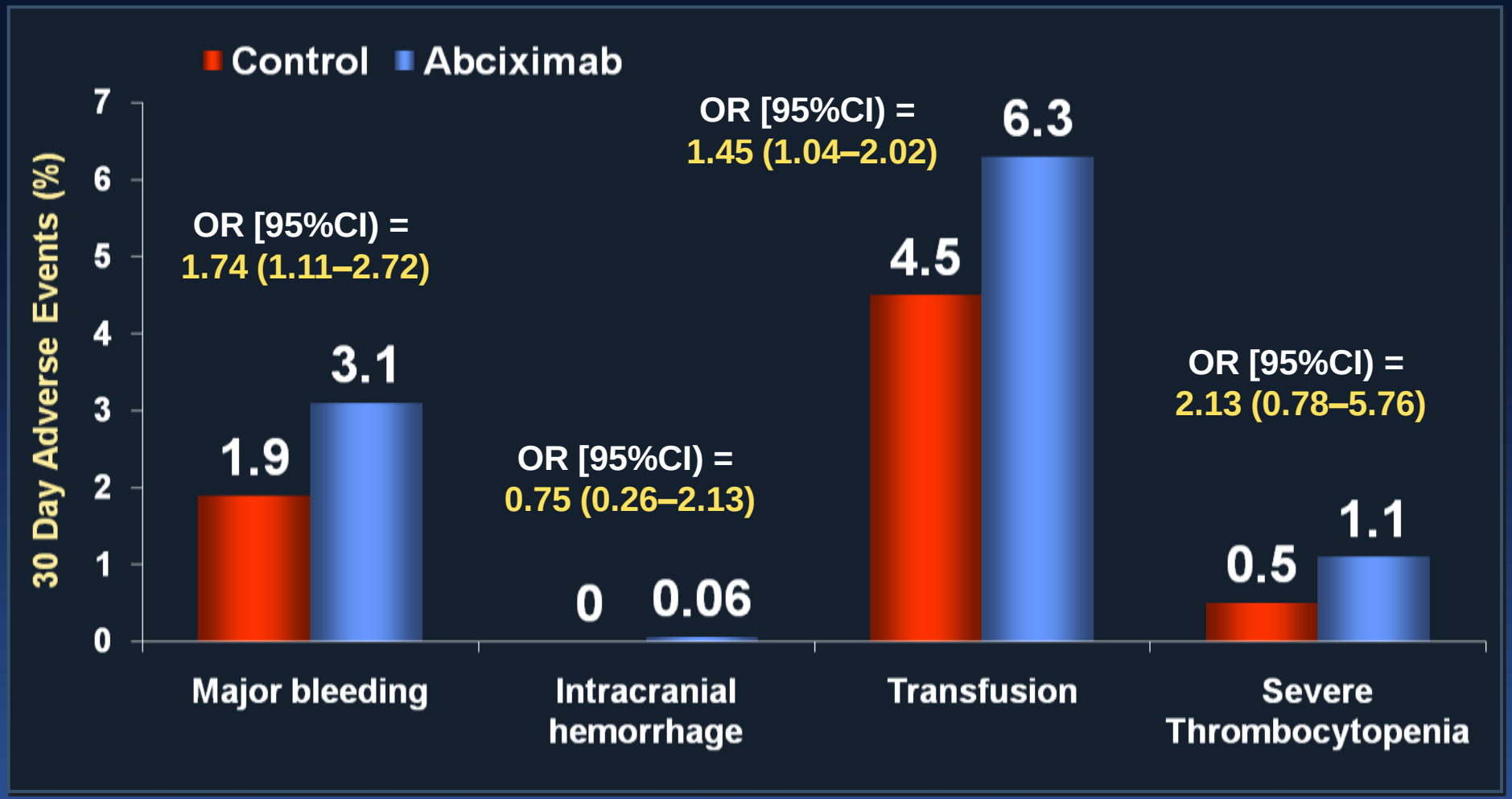
Abciximab in Primary PCI Meta-analysis

8 RCTs, 3,949 pts with AMI w/i 12° undergoing primary PCI (7) or rescue PCI(1) randomized to abciximab vs. placebo or control



De Luca G et al. *JAMA* 2005;293:1759–1765

4 RCTs of Abciximab vs. Control in Primary PCI (N=3,266): Safety Events



Kandzari DE et al. *AHJ* 2004;147:457–62

HORIZONS AMI

Harmonizing Outcomes with Revascularization and Stents in AMI

3602 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)**

Emergent angiography, followed by triage to…

CABG – Primary PCI – Medical Rx

3006 pts eligible for stent randomization

R 3:1

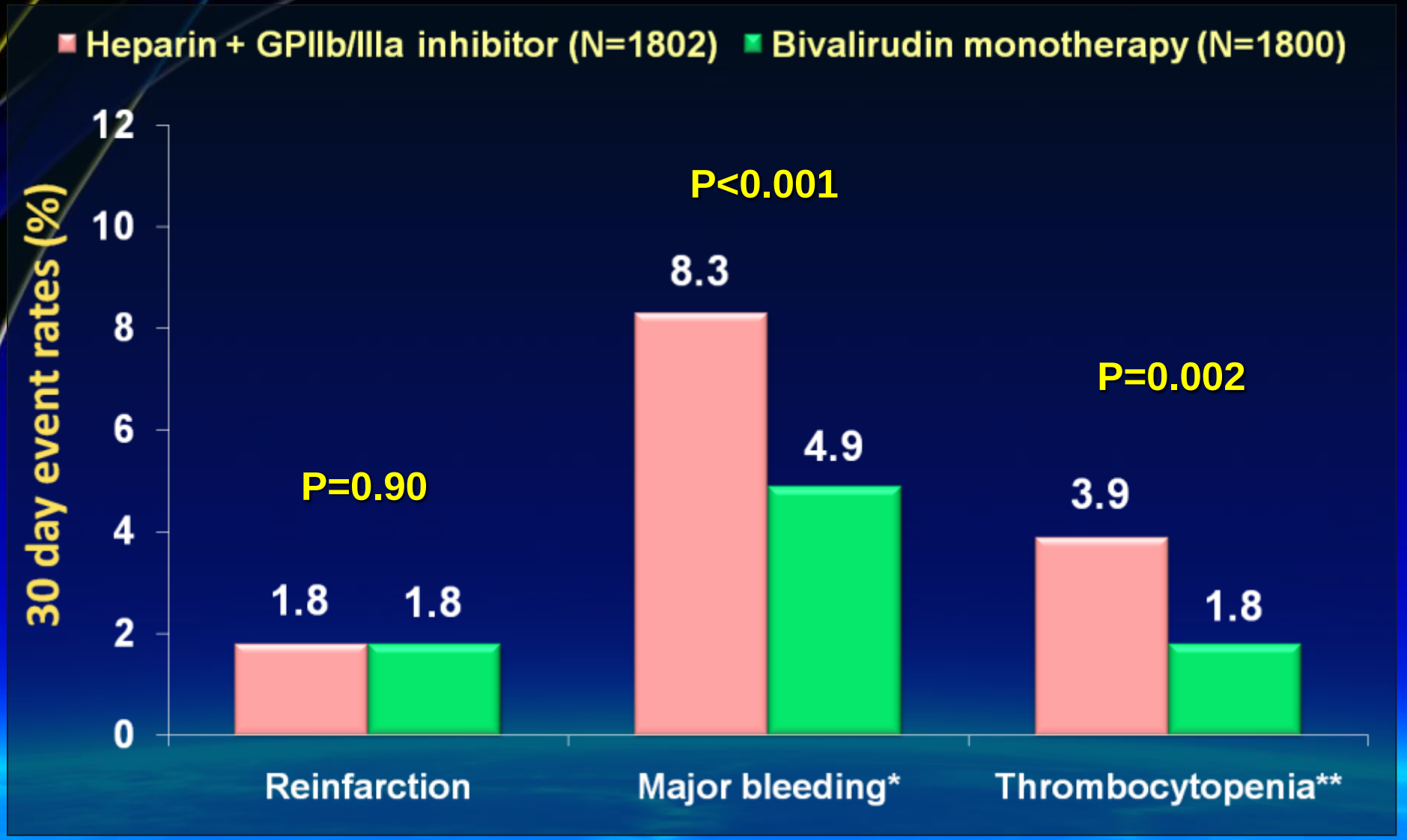
- **Paclitaxel-eluting TAXUS stent**
- **Bare metal EXPRESS stent**

Clinical FU at 30d, 6 mo, 1 yr, and then yearly through 3 yrs; angio FU at 13 mo

Stone GW et al
NEJM 2008;358:2218-30 &
NEJM 2009;360:1946-1459

HORIZONS AMI

HORIZONS-AMI: 30-Day Adverse Events



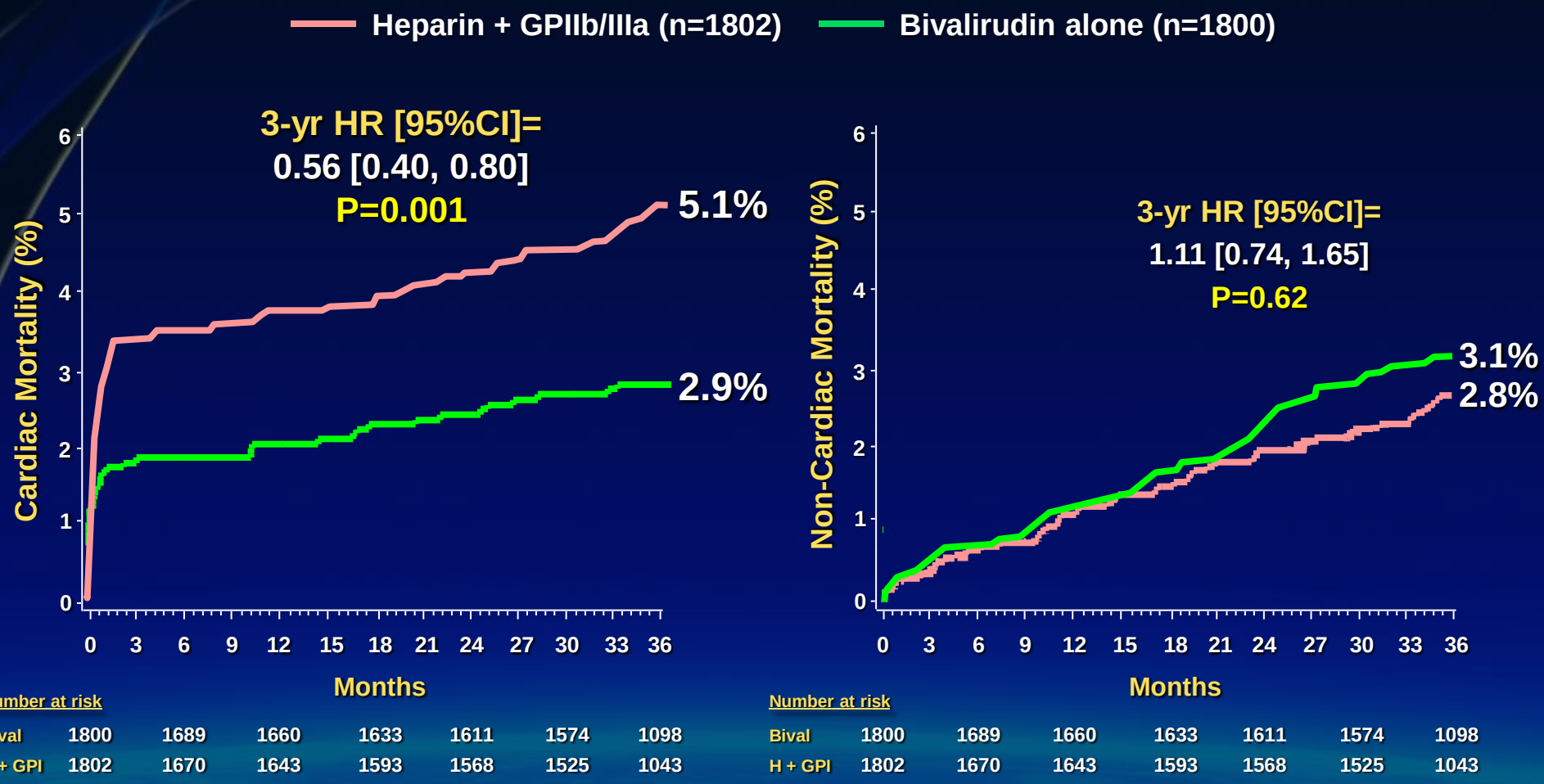
*Not related to CABG

** Plat cnt <100,000 cells/mm^3

Stone GW et al. NEJM 2008;358:2218-30

HORIZONS-AMI

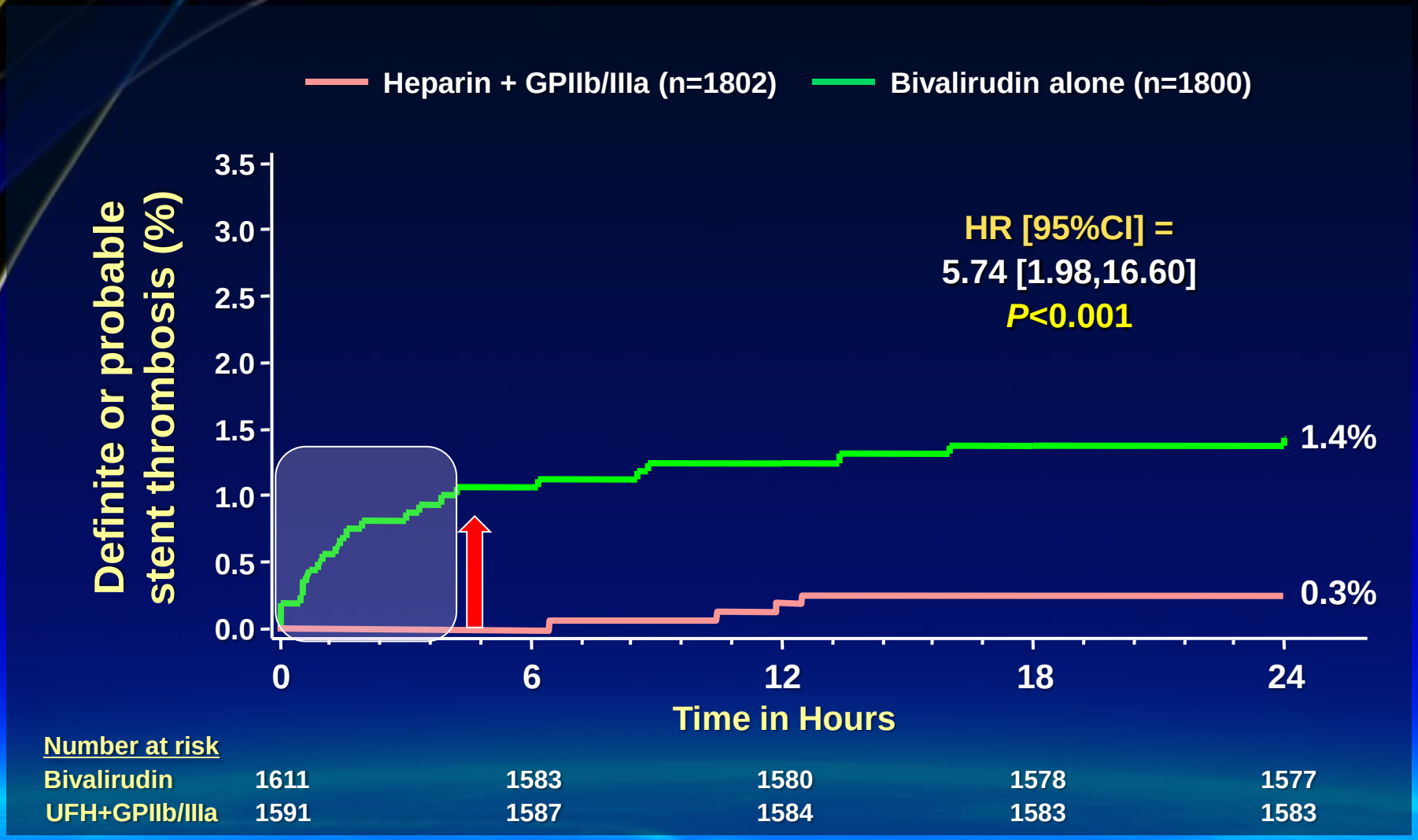
3-Year Mortality: Cardiac and Non Cardiac



Stone GW et al. Lancet 2011;377:2193-204

HORIZONS AMI

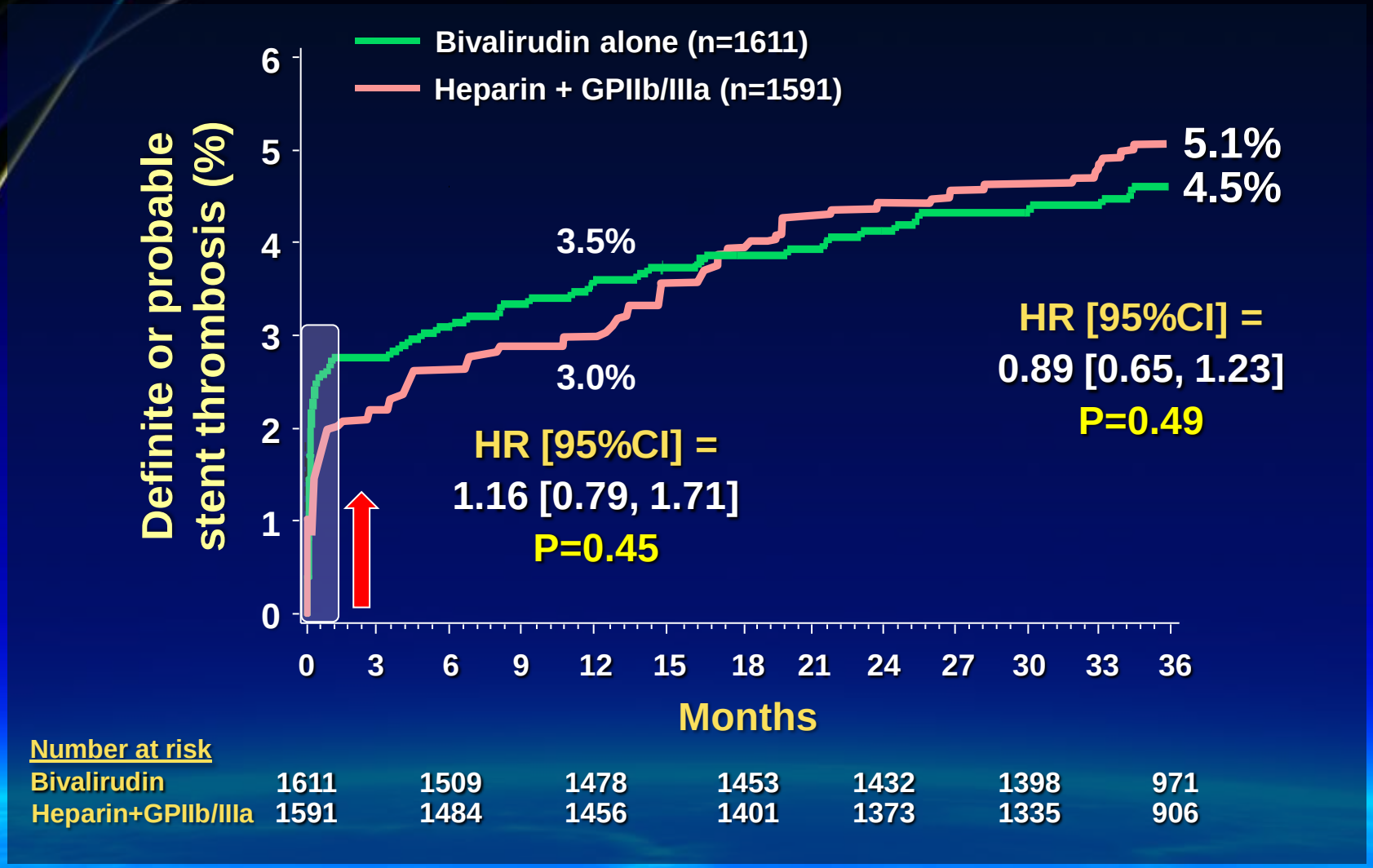
HORIZONS-AMI: Acute Stent Thrombosis



Dangas G et al. *Circulation*. 2011;123:1745-56

HORIZONS-AMI

HORIZONS-AMI: 3-Year Stent Thrombosis



Stone GW et al. Lancet 2011;377:2193-204

HORIZONS-AMI

Randomized Trials of Bivalirudin During Primary PCI in STEMI

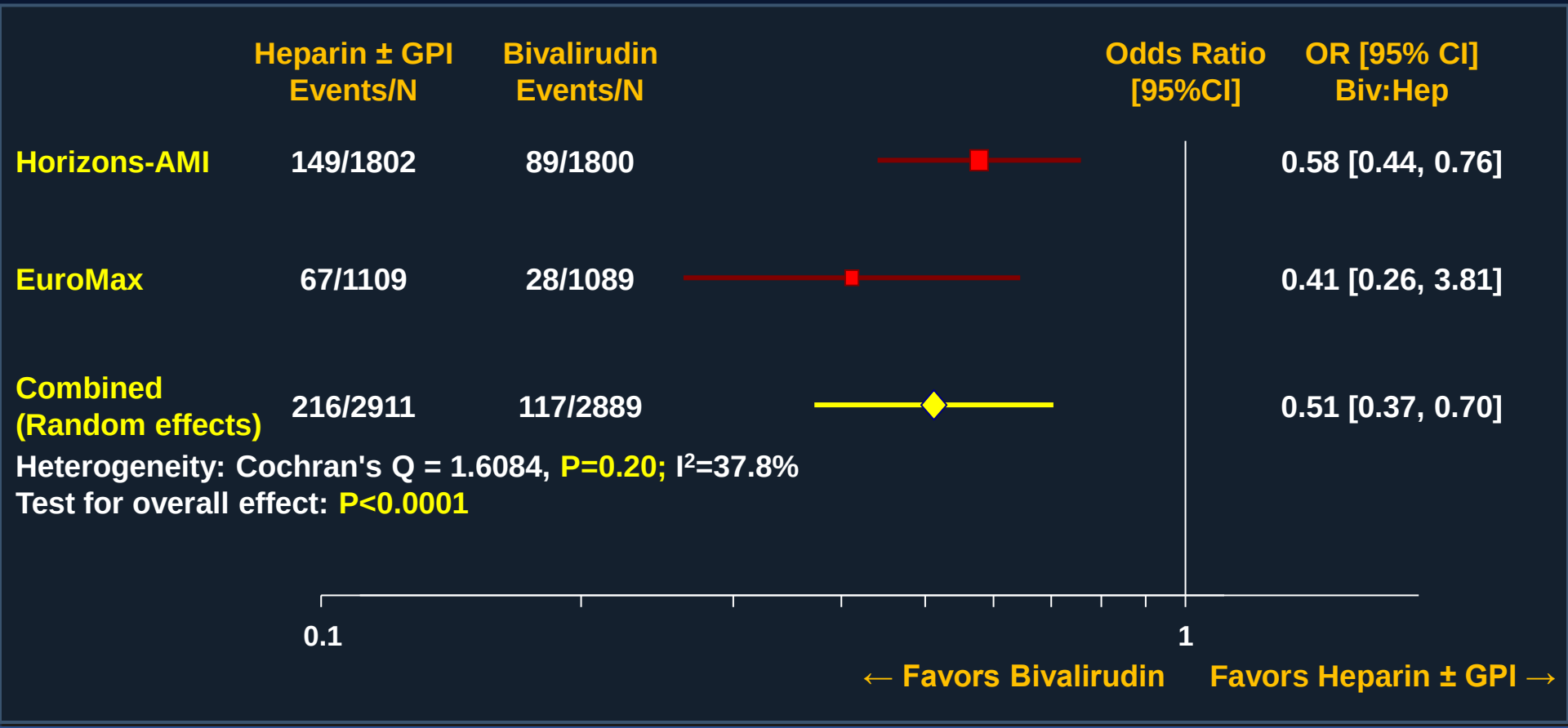
	HORIZONS-AMI	EuroMax
N patients, center, countries, geographies	3,602 pts at 123 sites in 13 counties (USA, EU, SA)	2,198 pts at 65 sites in 9 counties (EU)
Primary PCI performed	92.9%	88.1%
Pre-hospital study drug	0%	100%
UFH prior to bivalirudin	65.8%	2.2%
GPIIb/IIIa use (heparin arm)	94.5%	58.5% routine (69.1% including bailout)
Post-PCI bivalirudin (biv arm)	12.6%	93.0% (≥2 hrs)
Prasugrel/ticagrelor at d/c*	0%	58.9%
Radial artery access	6.0%	47.0%

*Among pts treated with an ADP antagonist

Stone GW et al. NEJM 2008;358:2218-30
Steg PG et al. NEJM 2013:on-line

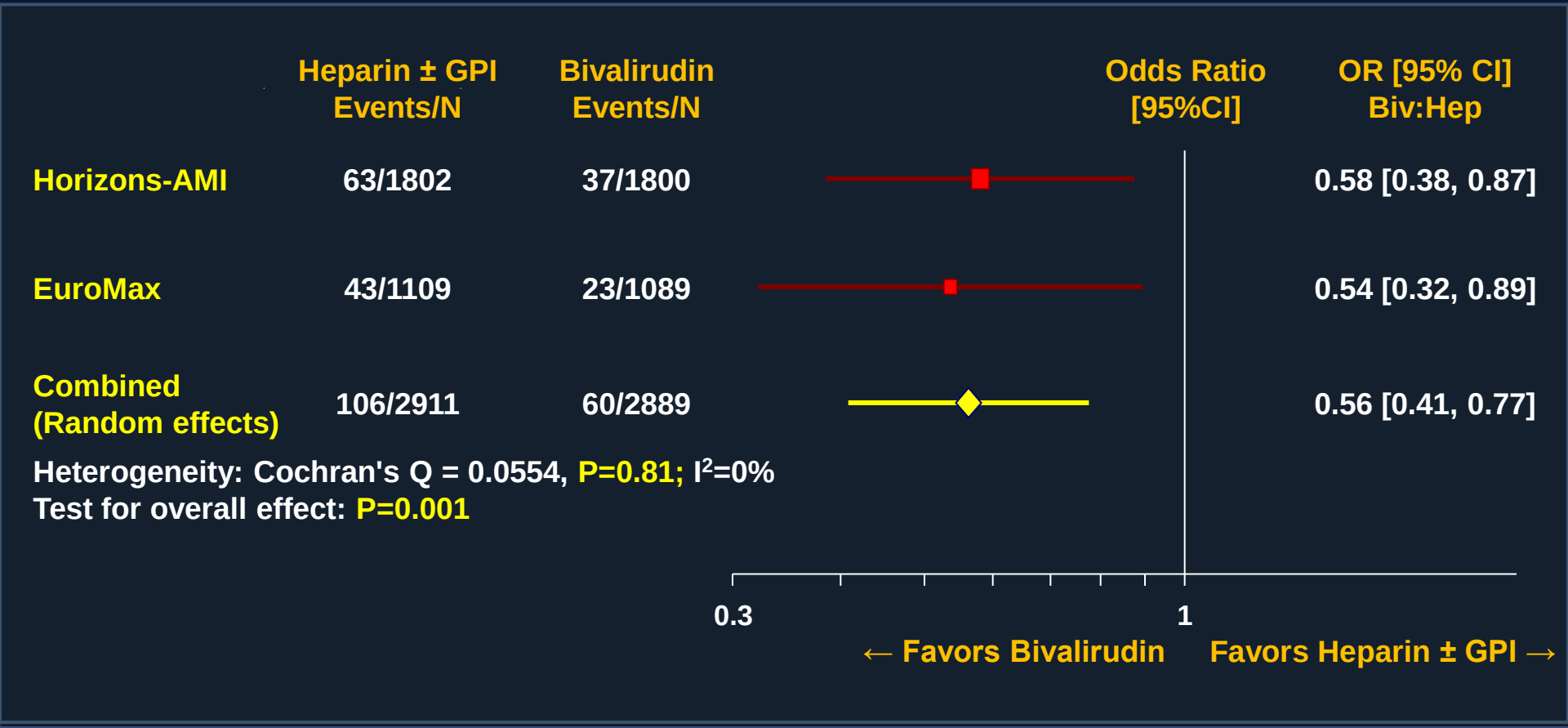
Meta-analysis of Bivalirudin During Primary PCI in STEMI

30-day non-CABG major bleeding



Meta-analysis of Bivalirudin During Primary PCI in STEMI

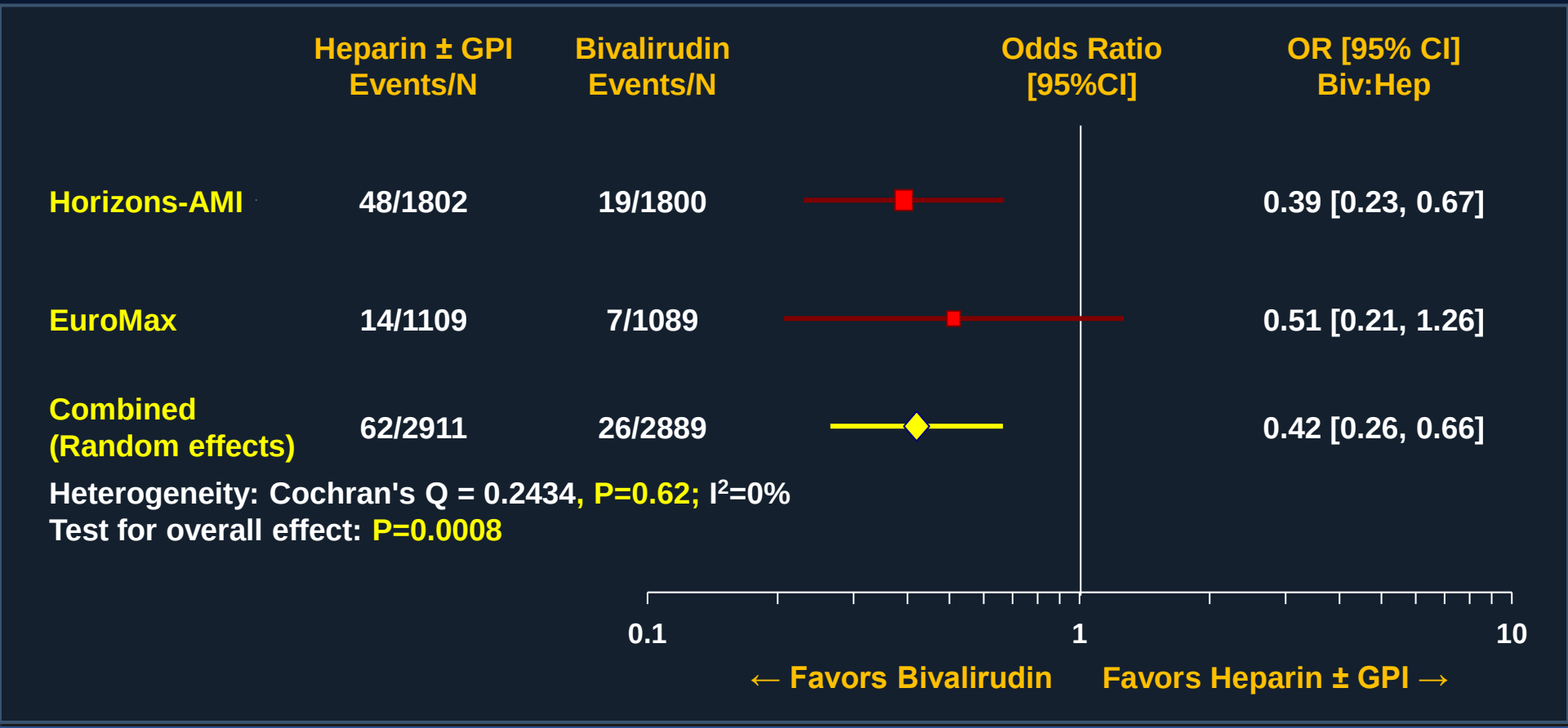
30-day transfusion



Stone GW et al. NEJM 2008;358:2218-30
Steg PG et al. NEJM 2013:on-line

Meta-analysis of Bivalirudin During Primary PCI in STEMI

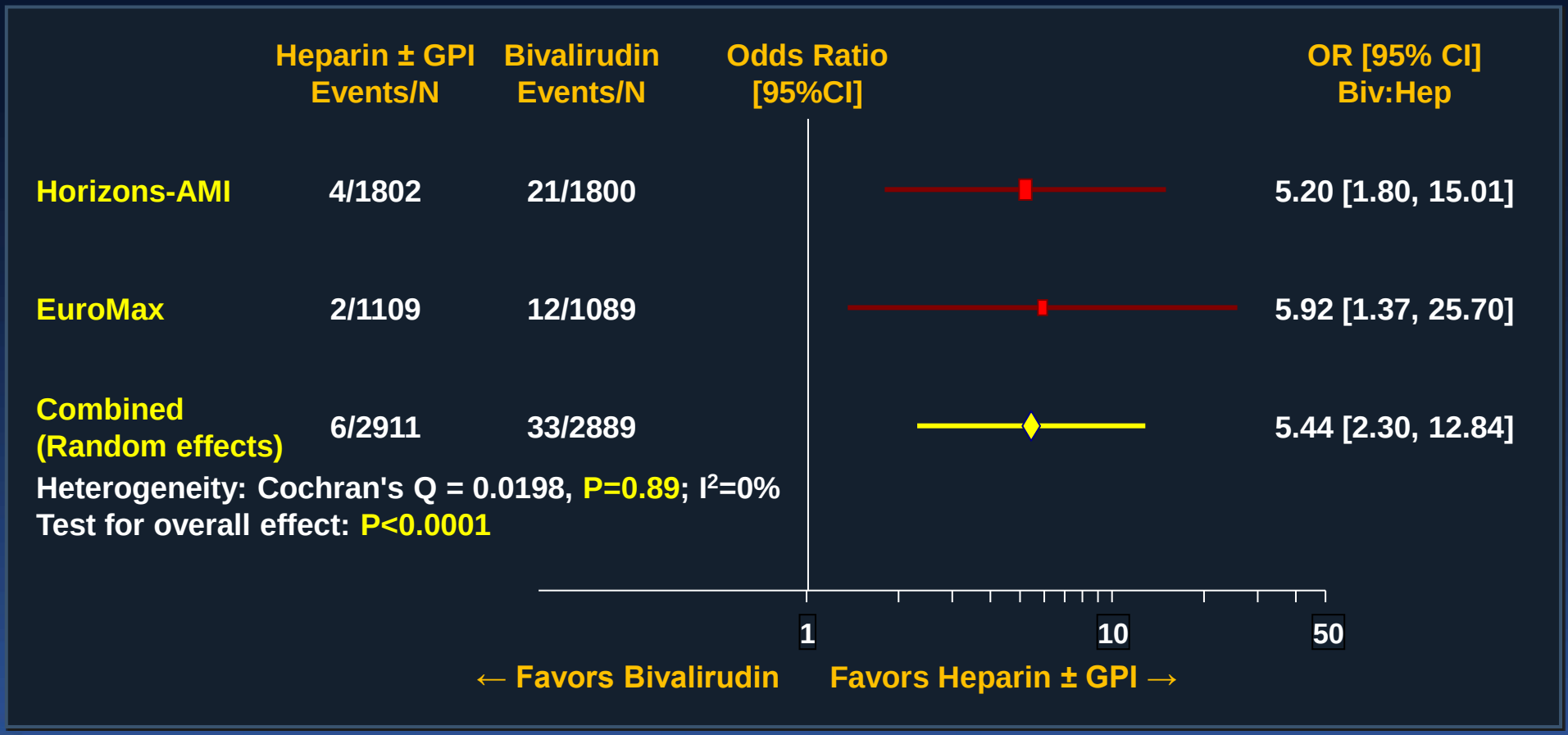
30-day thrombocytopenia



Stone GW et al. NEJM 2008;358:2218-30
Steg PG et al. NEJM 2013:on-line

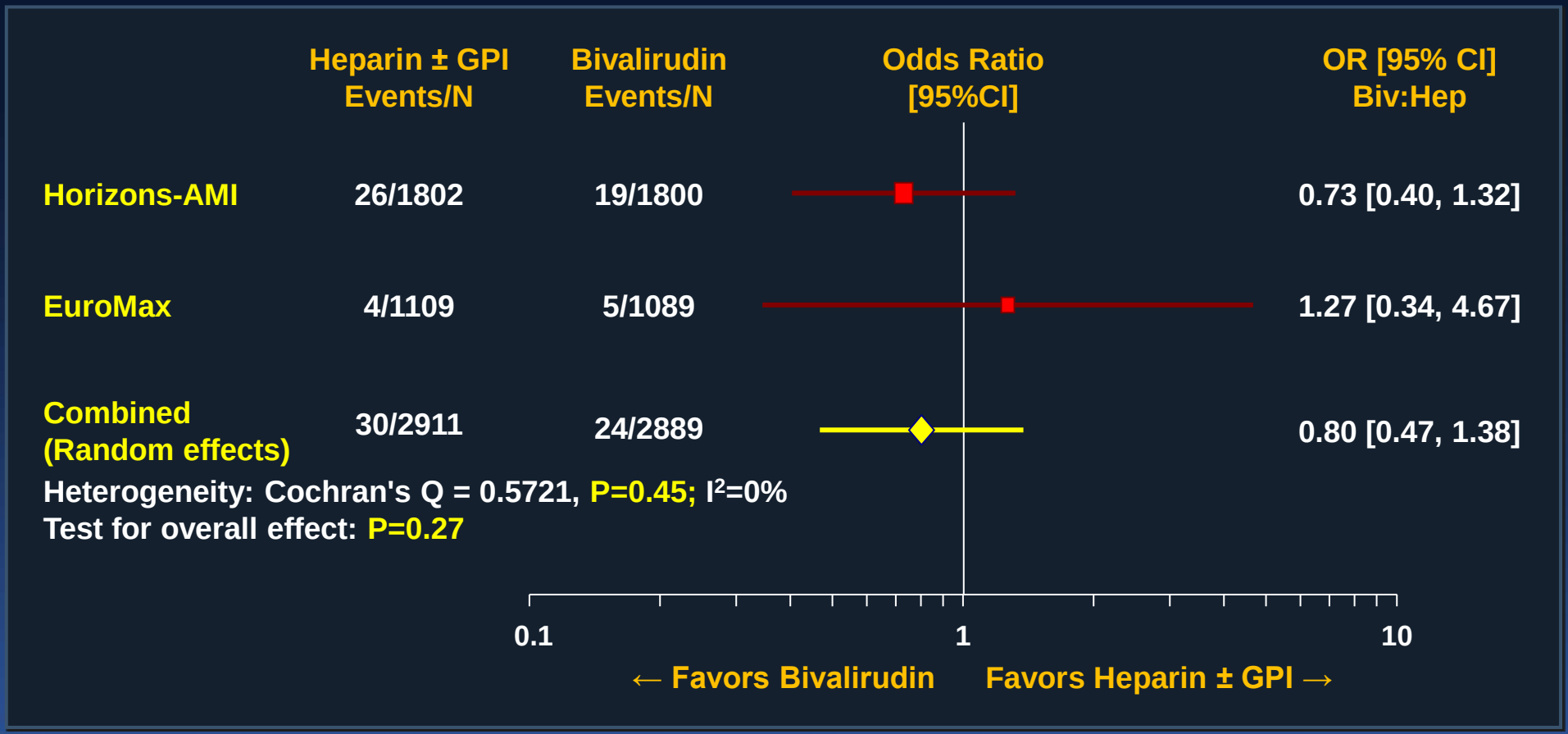
Meta-analysis of Bivalirudin During Primary PCI in STEMI

30-day acute stent thrombosis (<24 hrs)



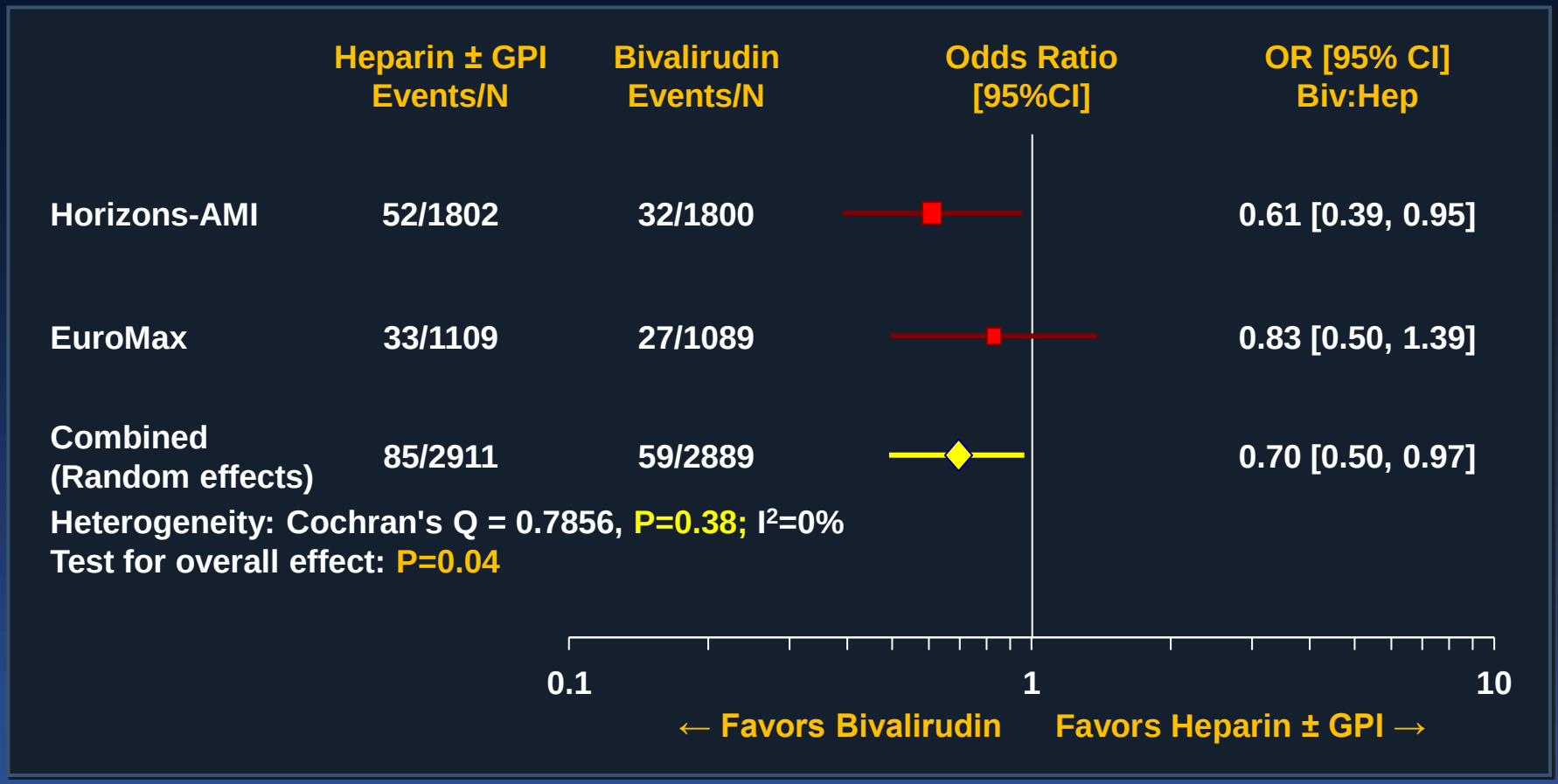
Meta-analysis of Bivalirudin During Primary PCI in STEMI

30-day subacute stent thrombosis (1-30d)



Meta-analysis of Bivalirudin During Primary PCI in STEMI

30-day cardiac mortality



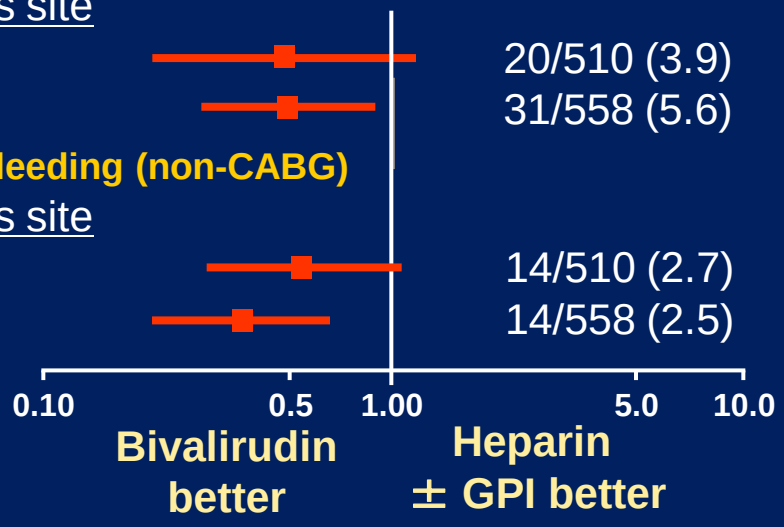
Stone GW et al. NEJM 2008;358:2218-30
Steg PG et al. NEJM 2013:on-line

Beyond HORIZONS-AMI:

What New Insights has EuroMax Provided?

1. Does use of radial access eliminate the benefits of bivalirudin in reducing bleeding?

	Bivalirudin (N=1089) n/N (%)	Heparin ±GPI (N=1109) n/N (%)	Relative risk (95% CI)	Interaction *P* value
30-day death or major bleeding (non-CABG)				
Arterial access site				
Radial	20/510 (3.9)	33/502 (6.6)	0.60 [0.35, 1.03]	0.97
Femoral	31/558 (5.6)	53/582 (9.1)	0.61 [0.40, 0.94]	
30-day major bleeding (non-CABG)				
Arterial access site				
Radial	14/510 (2.7)	25/502 (5.0)	0.55 [0.29, 1.05]	0.35
Femoral	14/558 (2.5)	40/582 (6.9)	0.37 [0.20, 0.66]	



Beyond HORIZONS-AMI: What New Insights has EuroMax Provided?

2. Are the benefits of bivalirudin reduced when compared to heparin alone (GPI for bailout only)?

30-day endpoint	Bivalirudin	Heparin ± routine GPI	RR (95%CI)	P value
Death or major bleeding				
- Routine GPI	5.1%	7.6%	0.67 (0.46, 0.97)	0.03
- No routine GPI	5.1%	9.8%	0.52 (0.35, 0.75)	<0.001
Major bleeding				
- Routine GPI	-	-	0.44 (0.27, 0.71)	<0.001
- No routine GPI	-	-	0.41 (0.25, 0.68)	<0.001

117/460 pts (25.4%) in the control arm treated with heparin alone required bailout GPIIb/IIIa inhibitor !

Steg PG et al. NEJM 2013:on-line

Beyond HORIZONS-AMI: What New Insights has EuroMax Provided?

3. Does prasugrel or ticagrelor reduce acute stent thrombosis?

	Prasugrel/Ticagrelor (N=1135)	Clopidogrel (N=784)
Definite ST*	13 (1.1%)	8 (1.0%)
Acute (<24h)†‡	8 (0.8%)	5 (0.5%)
Subacute (24 h to 30 d)*	4 (0.4%)	5 (0.6%)

* According to maintenance $P2Y_{12}$ inhibition;
† According to loading $P2Y_{12}$ inhibition;
‡ 1 pt with acute ST did not have a maintenance dose, 1 patient had missing data

Clemmensen P et al. ACC 2014

Beyond HORIZONS-AMI: What New Insights has EuroMax Provided?

4. Might a prolonged bivalirudin infusion reduce acute stent thrombosis without increasing bleeding?

	Heparins ± GPI (n=1109)	Bivalirudin + 0.25 mg/kg/hr infusion* (n=670)‡	Bivalirudin + 1.75 mg/kg/hr infusion* (n=244)§
Acute ST	2 (0.2%)	11 (1.6%)	1 (0.4%)
Major bleeding	57 (6.0%)	16 (2.4%)	7 (2.9%)

Data on a post-PCI infusion is not available for 35 patients
* Median [95%CI] infusion duration was 4.5 [4.2, 4.9] hours
‡ 659 of these received at least 2 hours infusion post-PCI
§ 191 of these received at least 2 hours infusion post-PCI

Clemmensen P et al. ACC 2014

Conclusions: Bivalirudin vs. Heparin + GPI

- Prior to bivalirudin, heparin + GPI was the standard of care for primary PCI in STEMI, and resulted in lower rates of stent thrombosis, reinfarction and death compared to heparin alone
- Bivalirudin compared to heparin + GPI has been shown in 2 large multicenter RCTs to reduce major bleeding, thrombocytopenia and cardiac mortality, at the cost of a 1% absolute increase in acute stent thrombosis
  - **As a result of this favorable trade-off, bivalirudin has emerged as the new standard of care for primary PCI**
- A prolonged high-dose bivalirudin infusion and the potent rapidly acting IV ADP antagonist cangrelor may reduce acute stent thrombosis after bivalirudin