

# Impact of Ischemic vs. Bleeding Endpoints: Lessons from ACUITY and HORIZONS

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Cardiovascular Research Foundation**



CARDIOVASCULAR RESEARCH  
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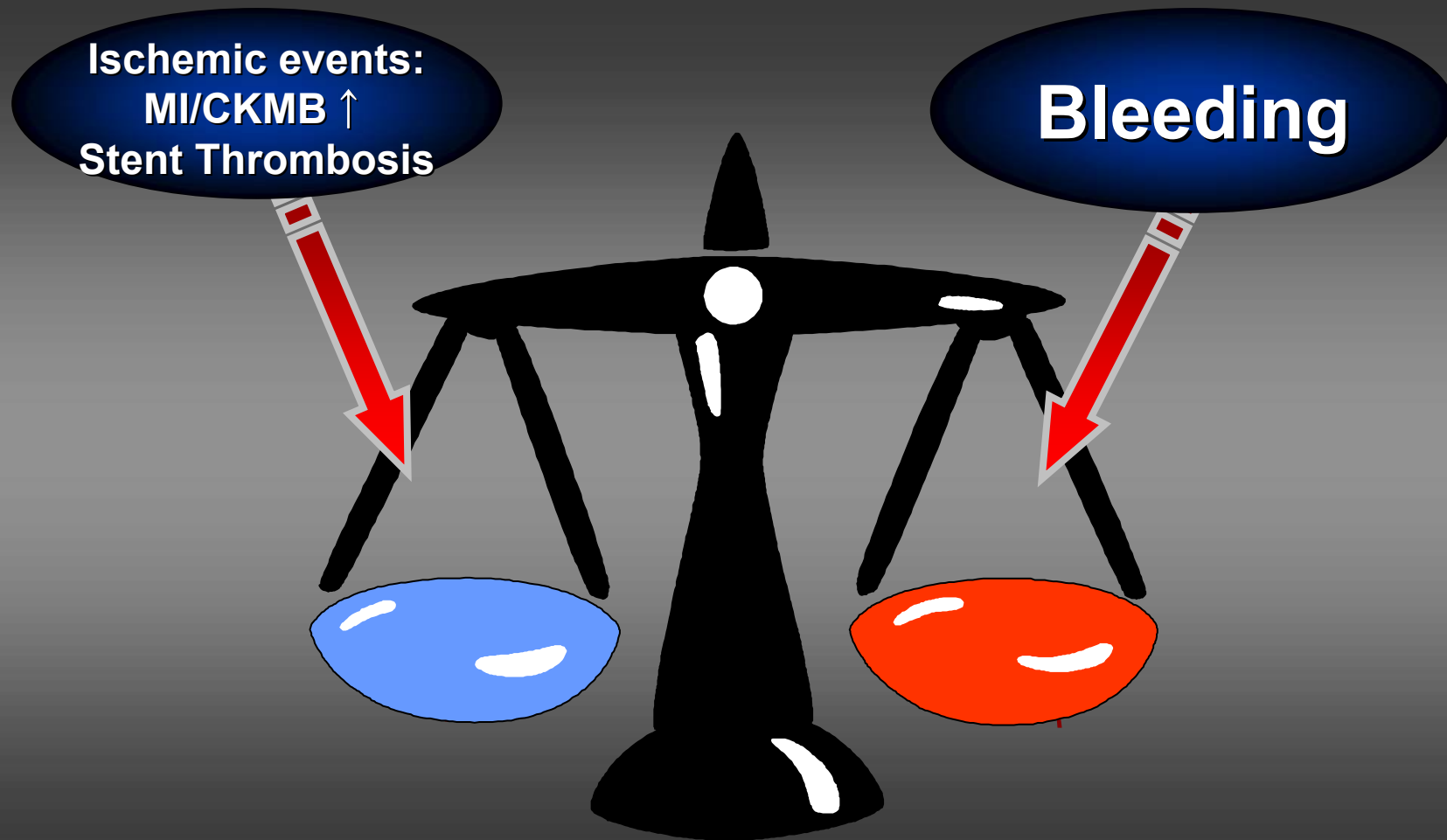
NewYork-Presbyterian

The University Hospital of Columbia and Cornell

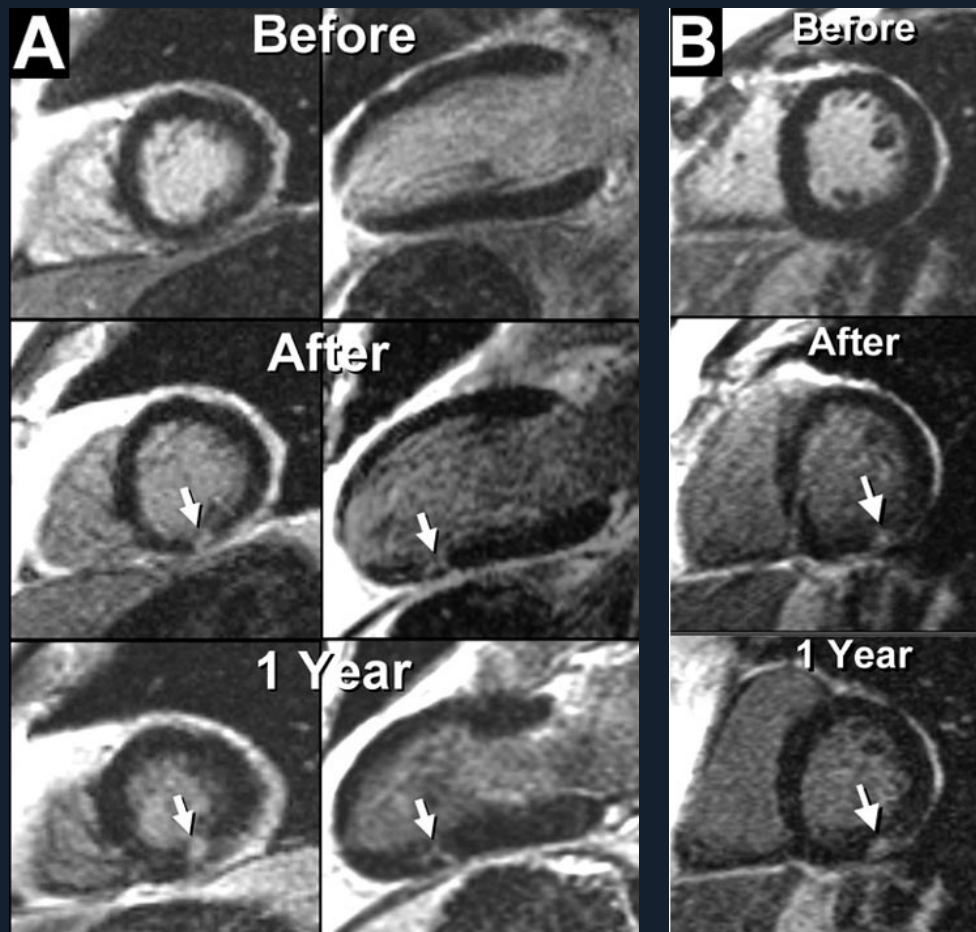
# Disclosures

- **Research support (significant) from: The Medicines Company, Boston Scientific, Cordis, Medtronic Vascular, Abbott Vascular, Sanofi/Aventis**
- **Consultant (Modest): Lilly/Diachi Sankyo, Medtronic Vascular, Abbott Vascular, Cordis, Bracco, The Medicines Company**

# Impact of Procedural Complications of PCI



# Periprocedural CK-MB Elevations After PCI Represent Myonecrosis



**Pt A: RCA stent. Pt B: DLCX stent.**

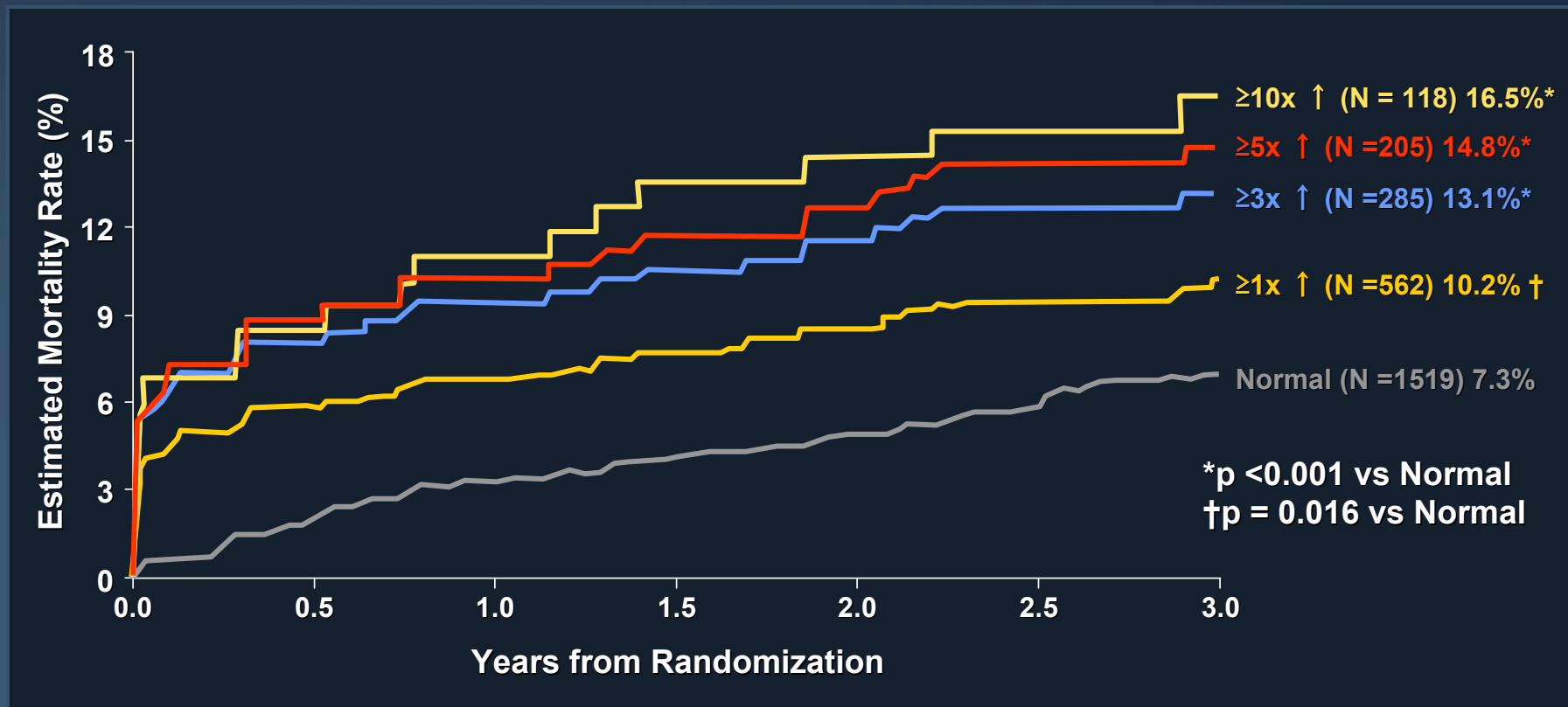
**14 pts with nl LV function underwent successful stent placement without distal embolization, thrombus, transient abrupt closure, or transient slow flow.**

**9 pts had CKMB ↑ (median 21 ng/mL (range, 12 to 93 ng/mL); 5 of these had occlusion of a minor side branch (<1.5 mm dia.); 5 pts had no CKMB ↑**

**MRI hyperenhancement was seen in all 9 with and none of 5 without CKMB ↑; median 1.5% of the LV (range 0.4% - 6.0%).**

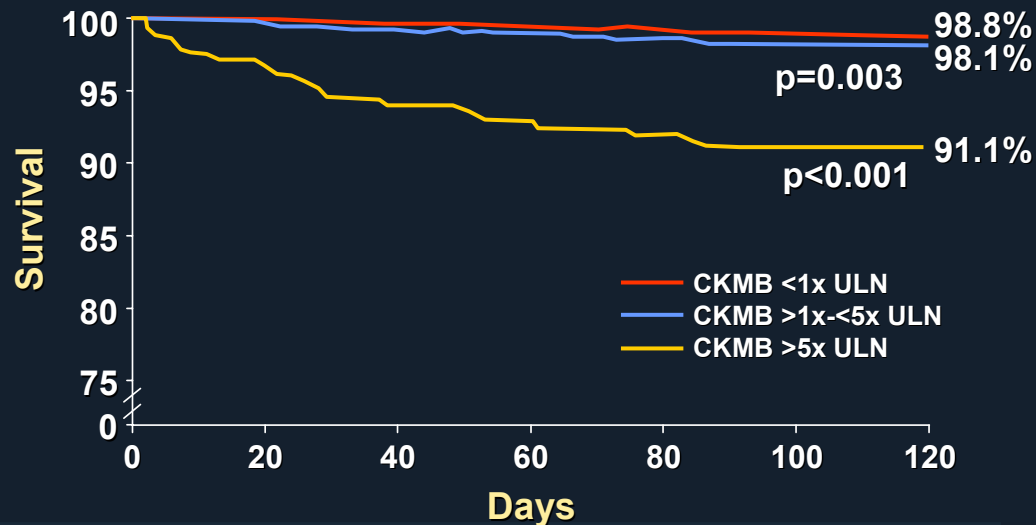
# Impact of Periprocedural CK-MB Elevations After PCI

2099 high risk pts undergoing PTCA in the EPIC trial;  
followed for up to 3 yrs



# Impact of Periprocedural CK-MB Elevations After PCI

**8409 non AMI pts** at CCF underwent successful, uncomplicated PCI; followed for mean ~3 years  
**1446 pts (17.2%) had post-PCI CK-MB > ULN**



**No. at Risk:**

	0	20	40	60	80	100	120
CKMB <1x ULN	6963	6953	5576	5549	5533	5515	5515
CKMB >1x-<5x ULN	1146	1143	1133	1125	1117	1103	1103
CKMB >5x ULN	300	288	282	279	273	269	269

**By multivariate analysis, ↑ CKMB (as a continuous measure) was an independent correlate of death at 4 months (p<0.0001)**

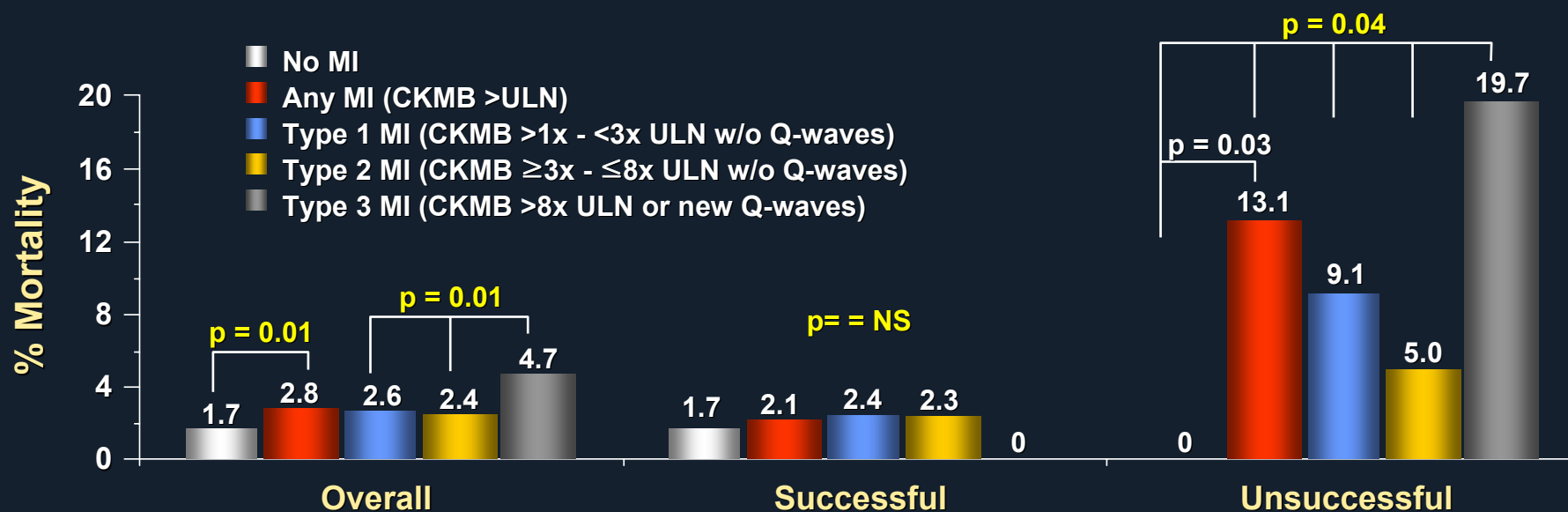


# Impact of Periprocedural CK-MB Elevations After PCI

5850 pts enrolled in 6 stent trials; 1248 (23.1%) had CKMB  $\uparrow$   $>$ ULN. Procedure failure (115 [2.0%] of pts) was defined as final DS  $>$ 50%, TIMI flow  $\leq$ 2, NHLBI dissection  $>$ C, stent thrombosis or urg TVR within 24°. **Unsuccessful vs. successful procedures more commonly had CKMB  $\uparrow$   $>$ ULN (69.6% vs. 20.4%,  $p < 0.0001$ ) and CKMB  $\uparrow$   $\geq$ 8x ULN or Q-MI (32.2% vs. 2.0%,  $p < 0.0001$ ).**

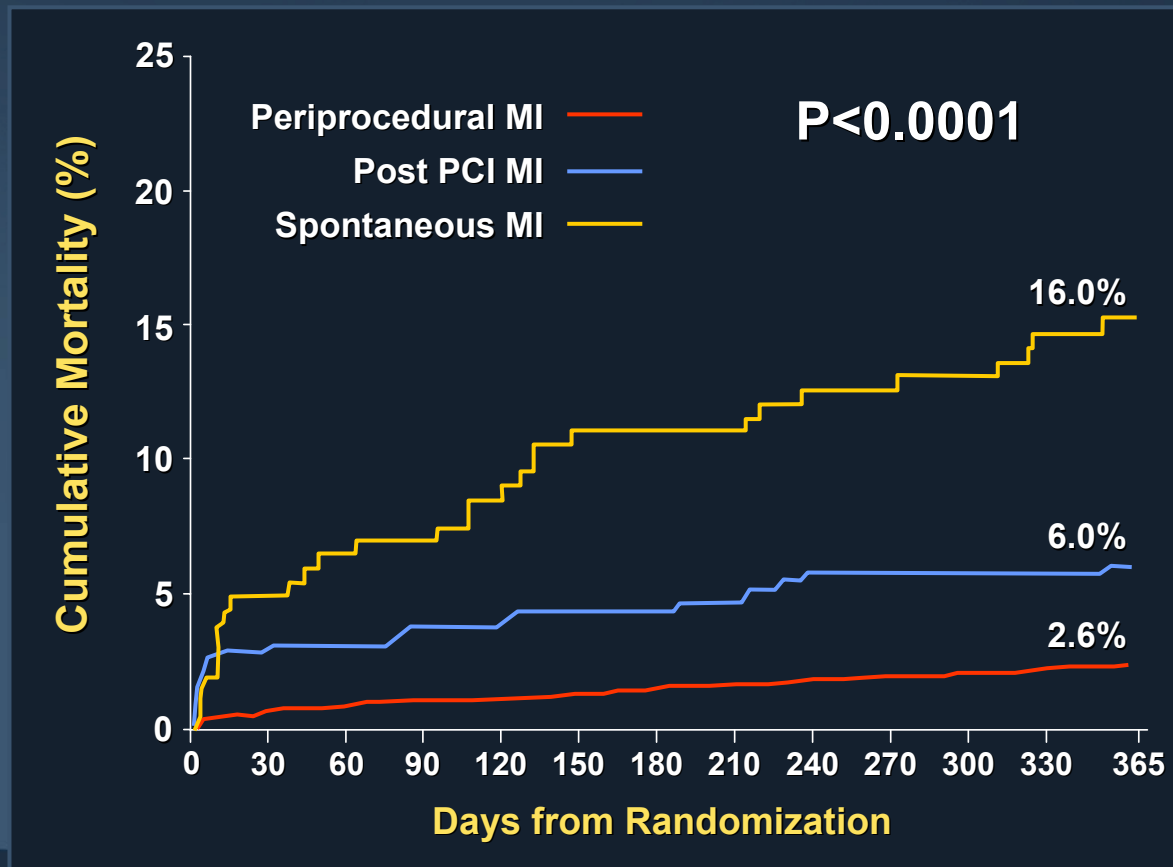
## Mortality as a function of CKMB $\uparrow$ and procedure success

Mean FU 300  $\pm$  90 days



# Prognostic Significance of Periprocedural vs. Spontaneously Occurring MI After PCI

7773 pts with ACS underwent PCI in ACUITY; peri-procedural MI (CK-MB >3x nl) developed in 466 pts (6.0%), and a spontaneous MI unrelated to PCI (troponin >nl) subsequently developed in 200 pts (2.6%)



**Multivariate model  
of 1-yr mortality**

**Spontaneous MI**  
HR = 7.49 [4.95, 11.33],  
 $p < 0.0001$

**Periprocedural MI**  
HR = 1.30 [0.85, 1.98],  
 $p = 0.22$







# Publication of Primary Results

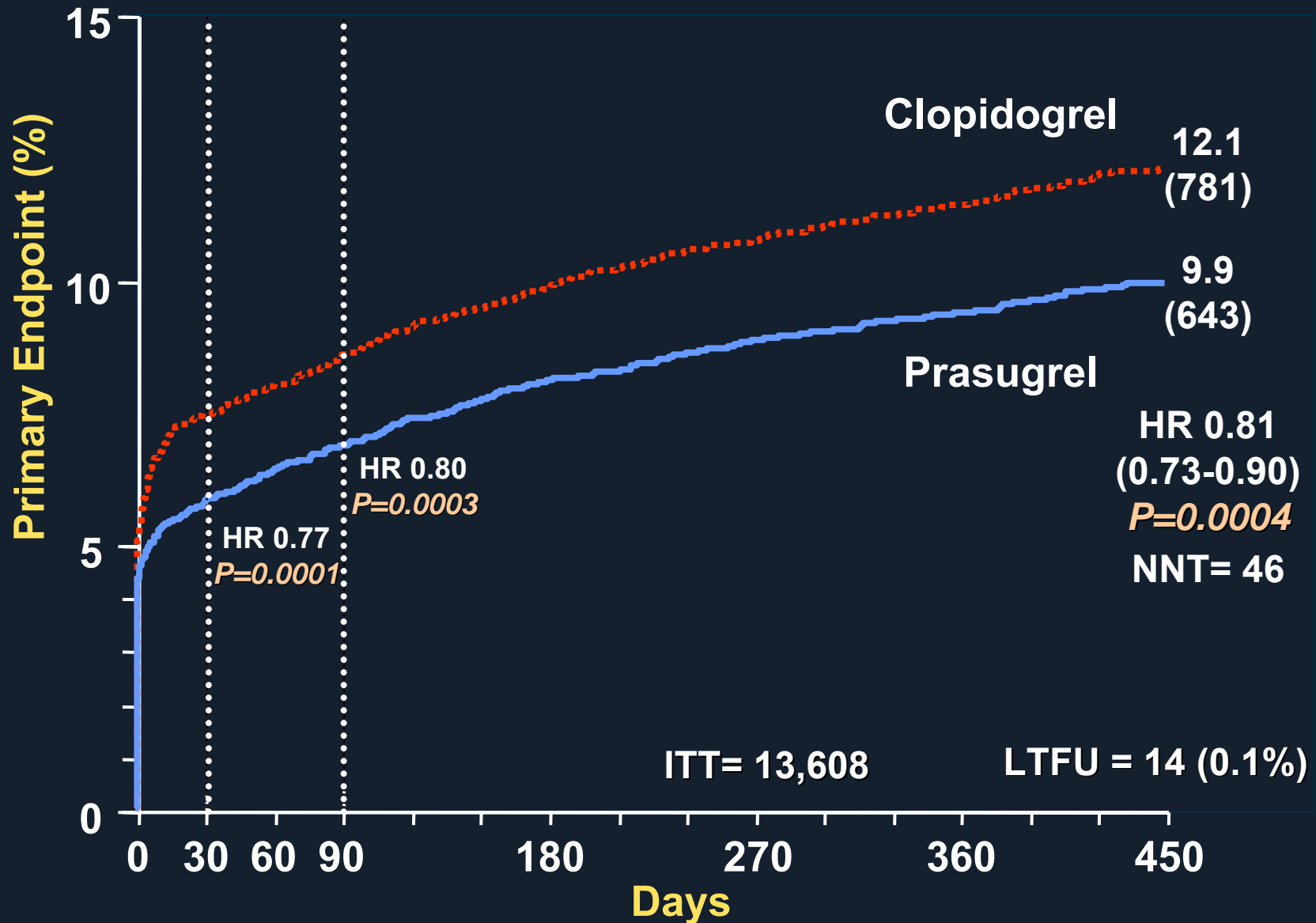
## *The* NEW ENGLAND JOURNAL *of* MEDICINE

### Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

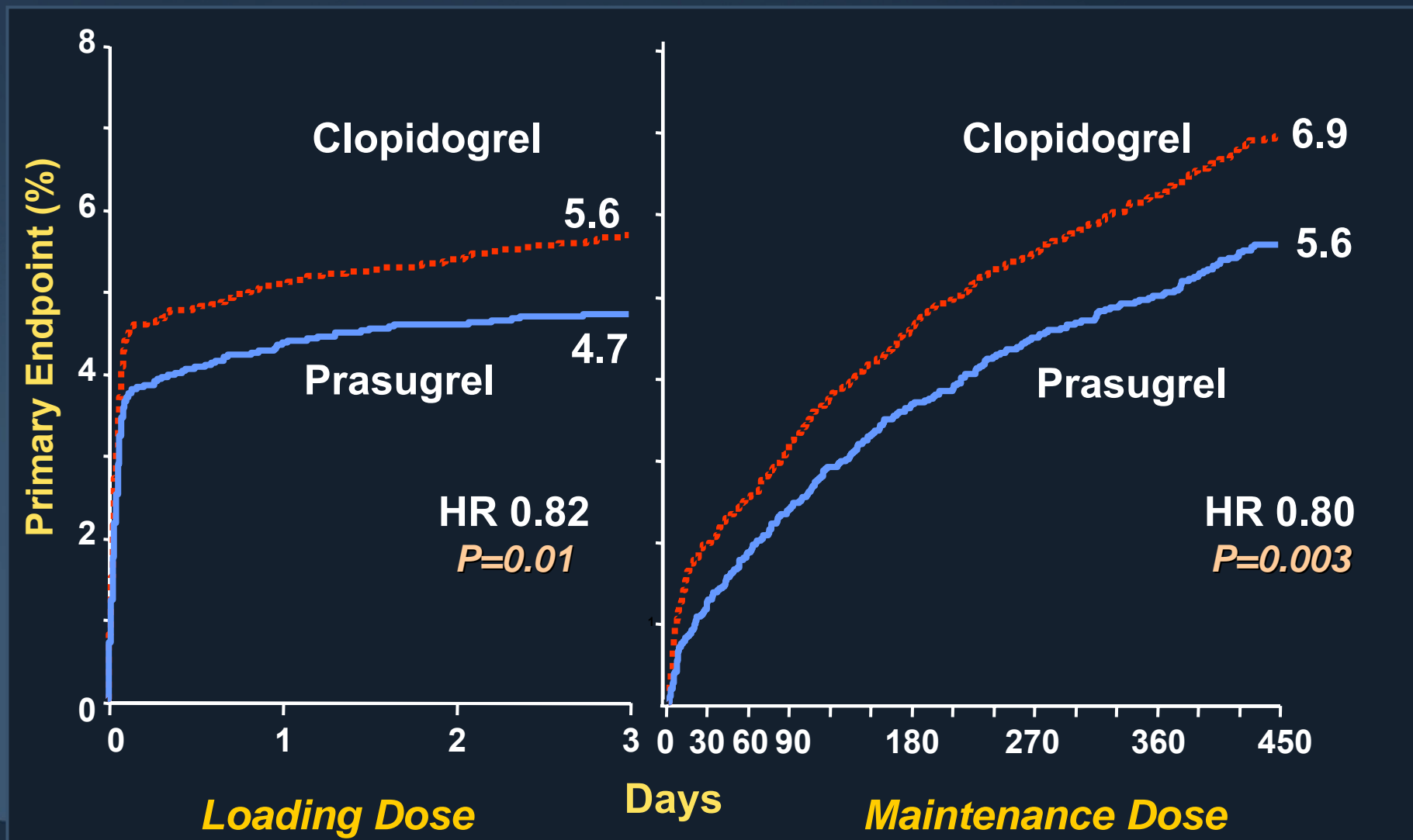
Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D.,  
Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D.,  
Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D.,  
C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON-TIMI 38 Investigators\*



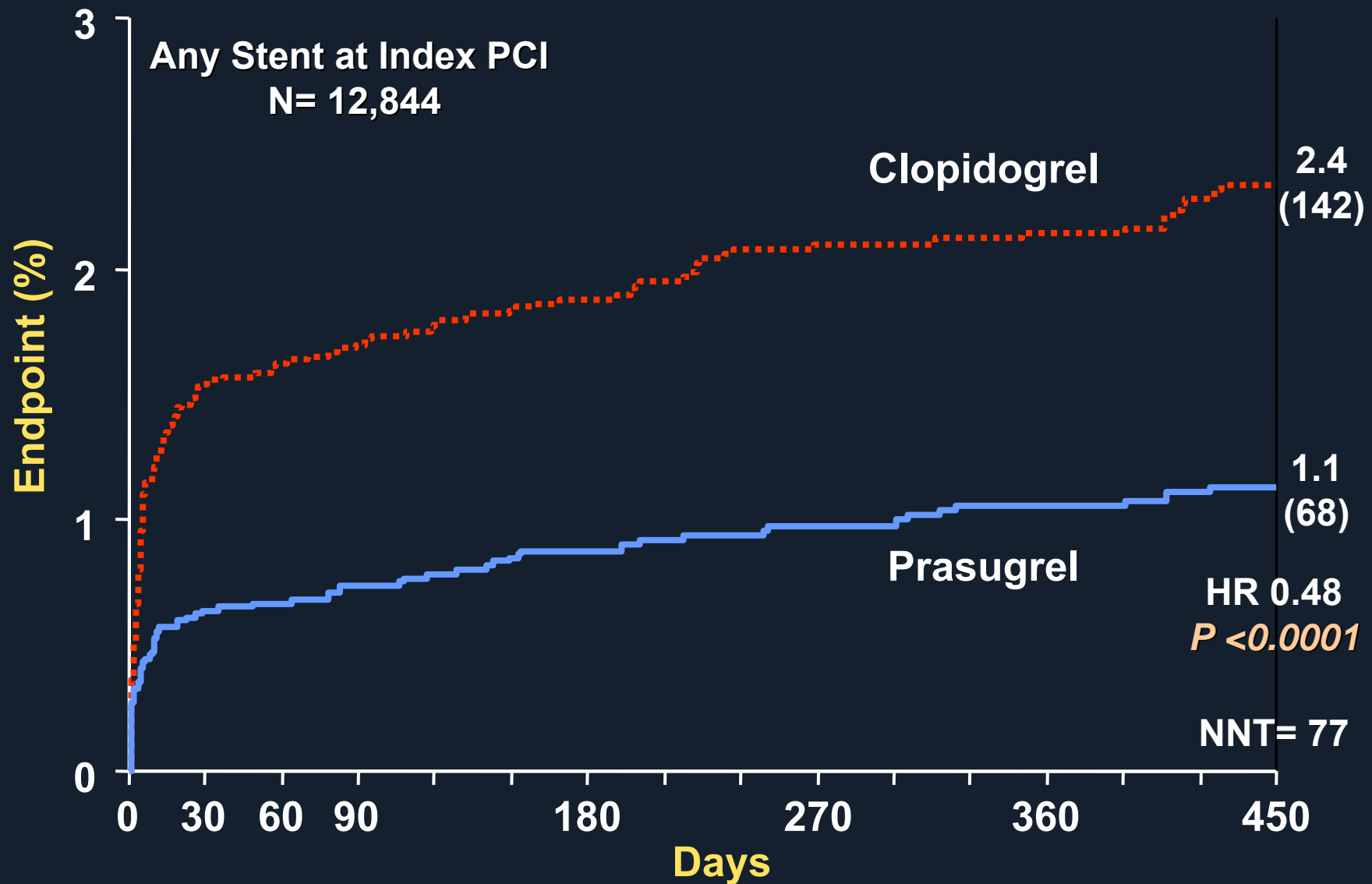
# Primary Endpoint CV Death,MI,Stroke



# Timing of Benefit (Landmark Analysis)



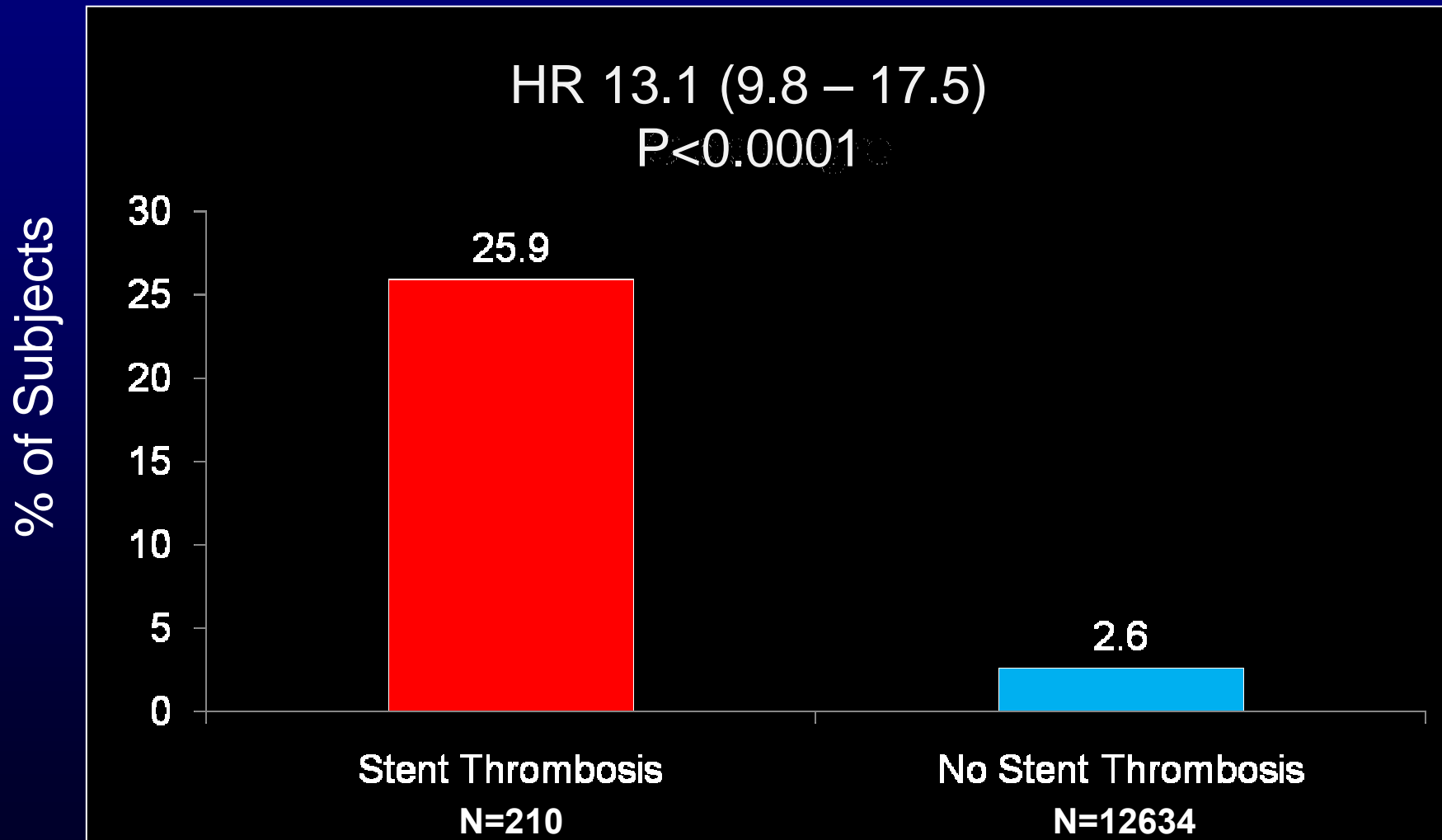
# Stent Thrombosis (ARC Definite + Probable)



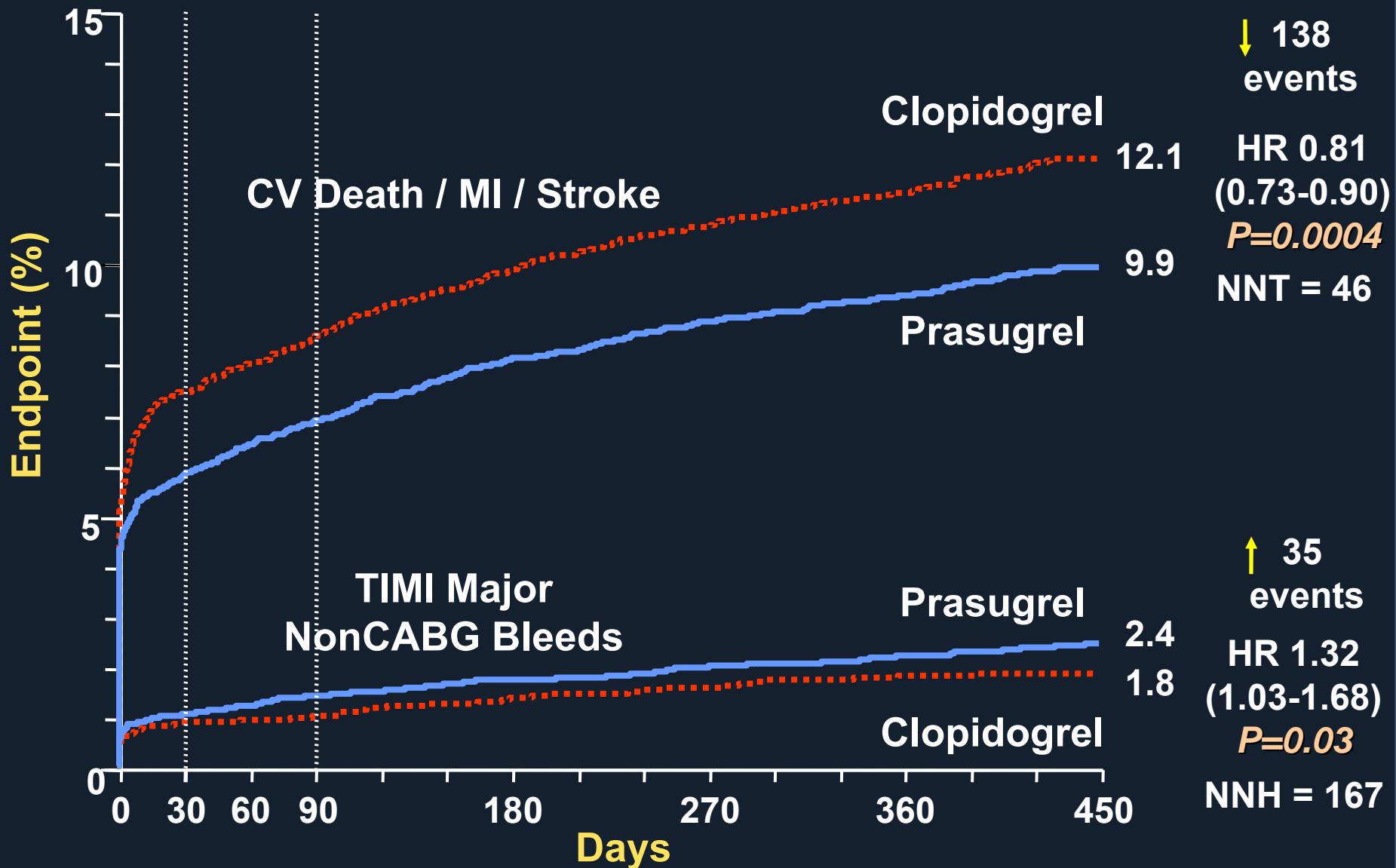


# Death Following ST

Mortality During Follow up (%) Post-Stent Thrombosis

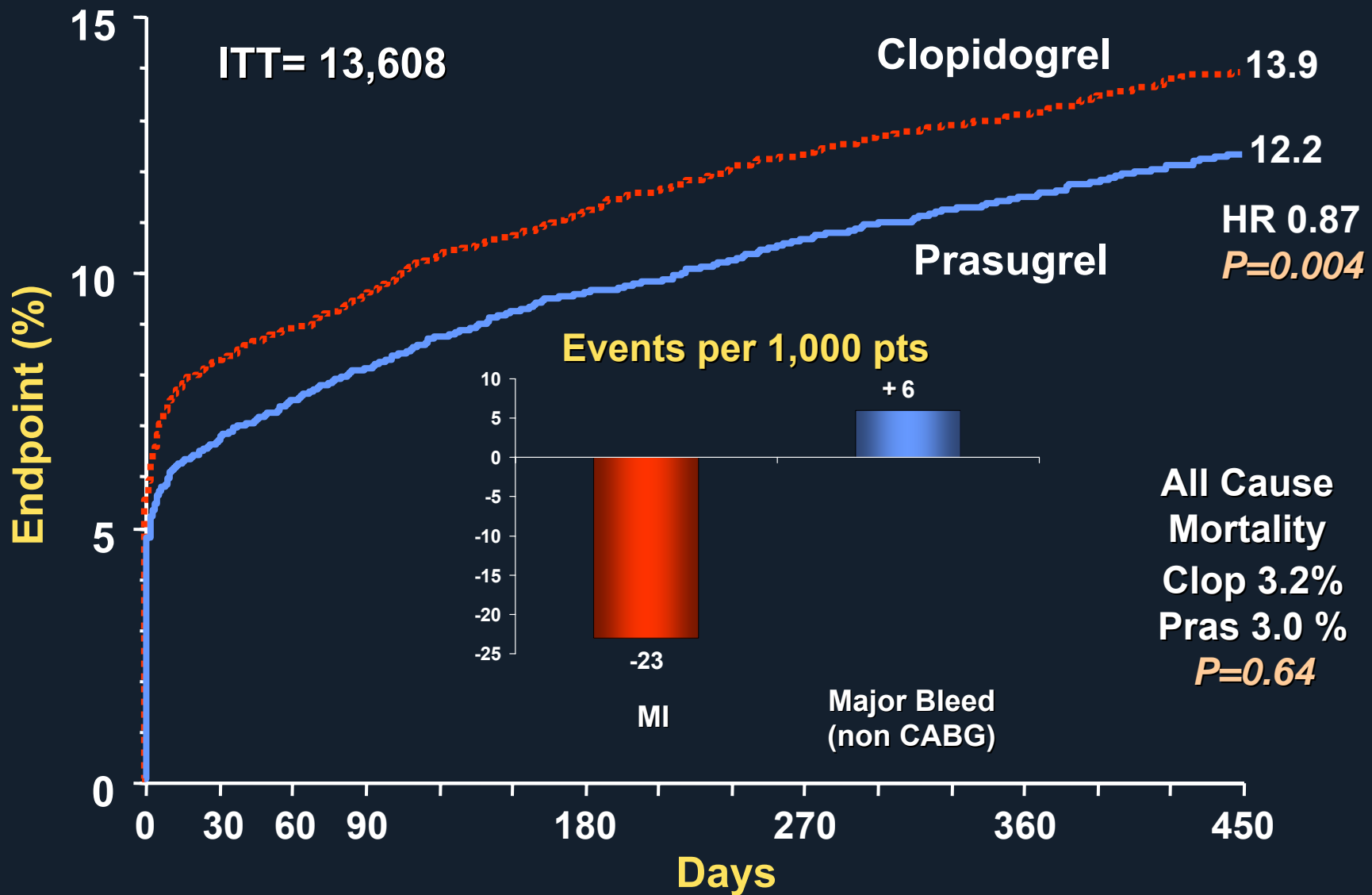


# Balance of Efficacy and Safety



# Net Clinical Benefit

## Death, MI, Stroke, Major Bleed (non CABG)



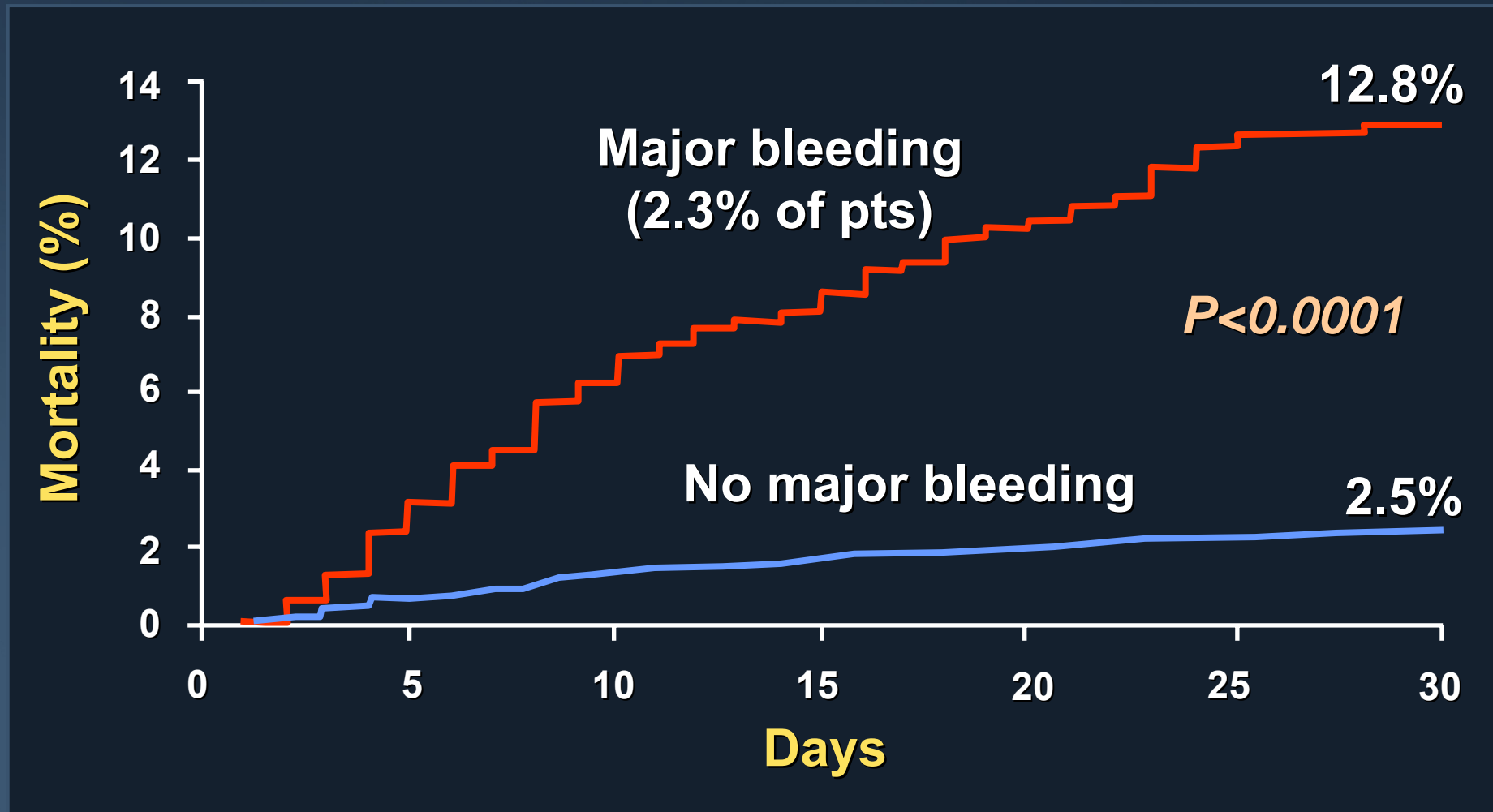
**Major bleeding** (with or without blood product transfusions) has emerged as a **powerful independent predictor of early and late mortality** in pts with NSTEMI, STEMI and in those undergoing PCI





# Impact of In-hospital Bleeding in ACS

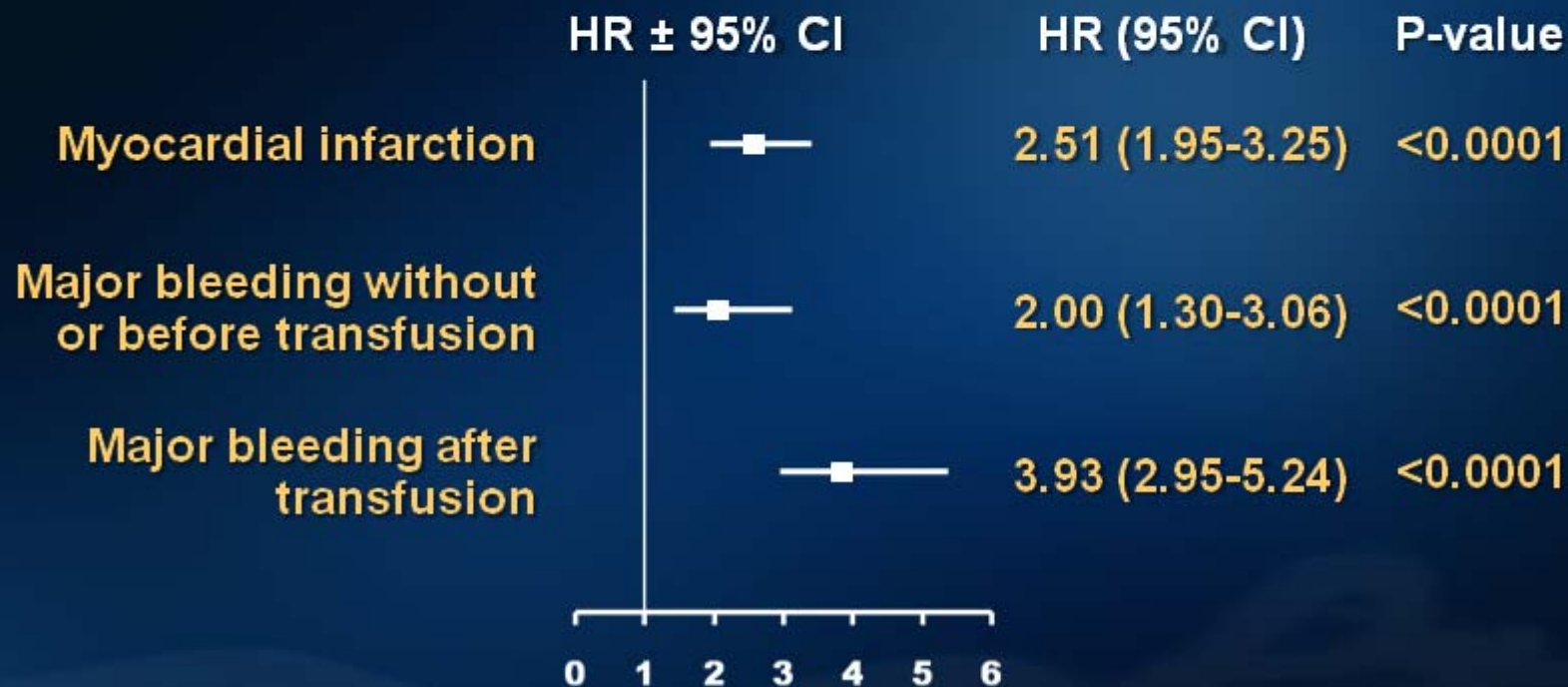
## 34,146 Pts with ACS in the OASIS-1/2 and CURE



# **ACUITY: Influence of Major Bleeding and MI in the First 30 Days on Risk of Death Over 1 Year**

**Of 13,819 enrolled pts, 524 (3.8%) died within 1 year**

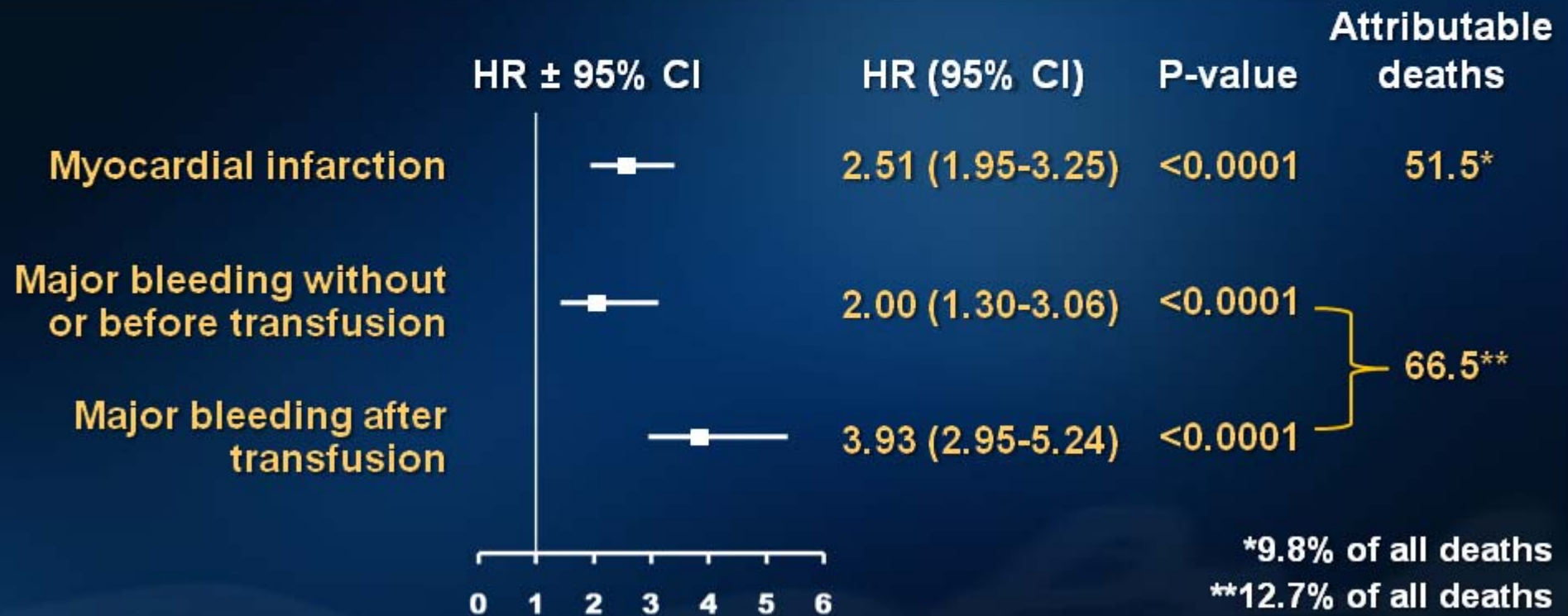
Cox model adjusted for 36 baseline predictors, with MI and major bleeding (non-CABG) as time-updated covariates



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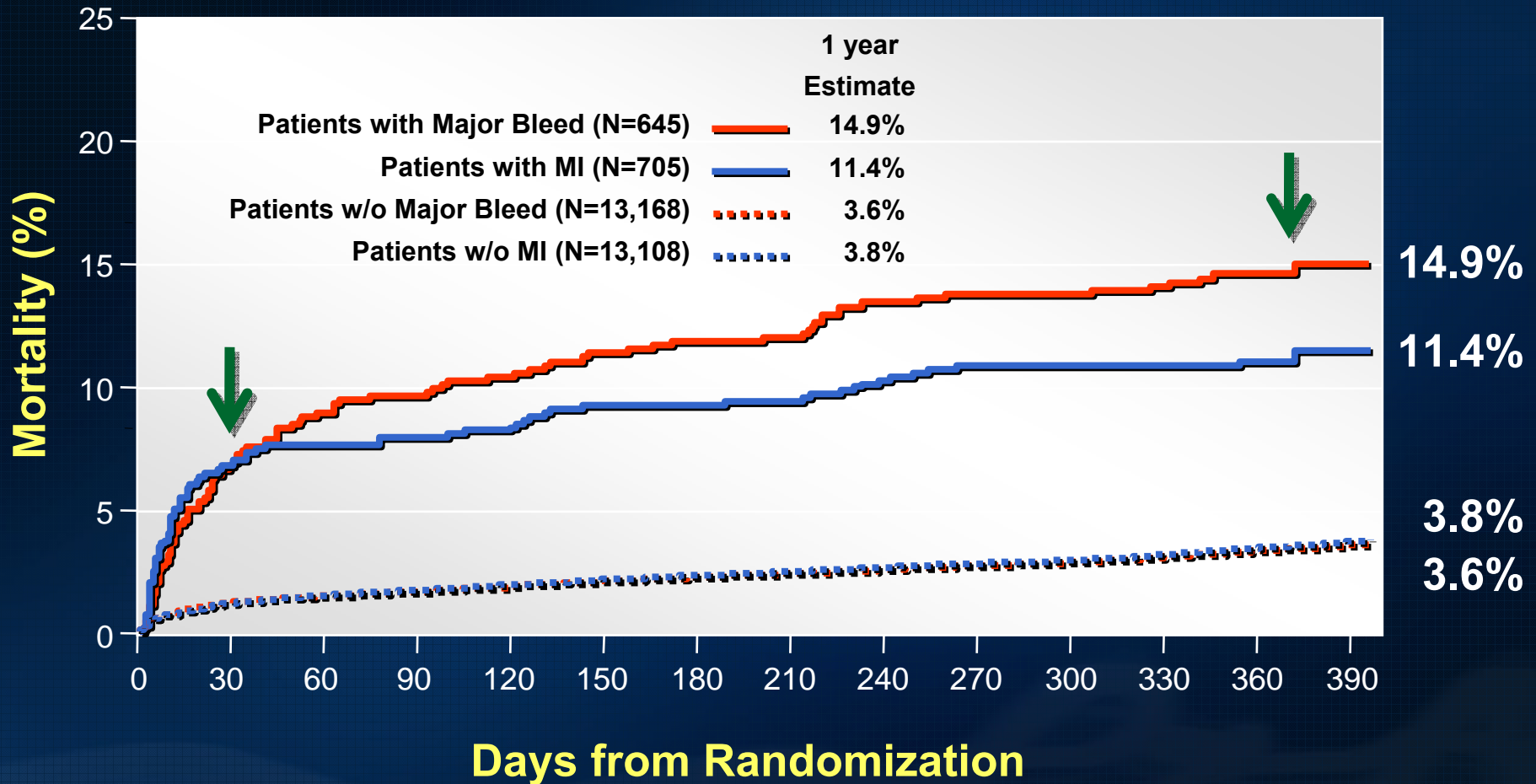
Attributable deaths = N deaths among pts with the time updated event (attribute) X (adj. HR - 1)/adj. HR

Mehran RM et al. In press EHJ

ACUITY

# ACUITY (N=13,819)

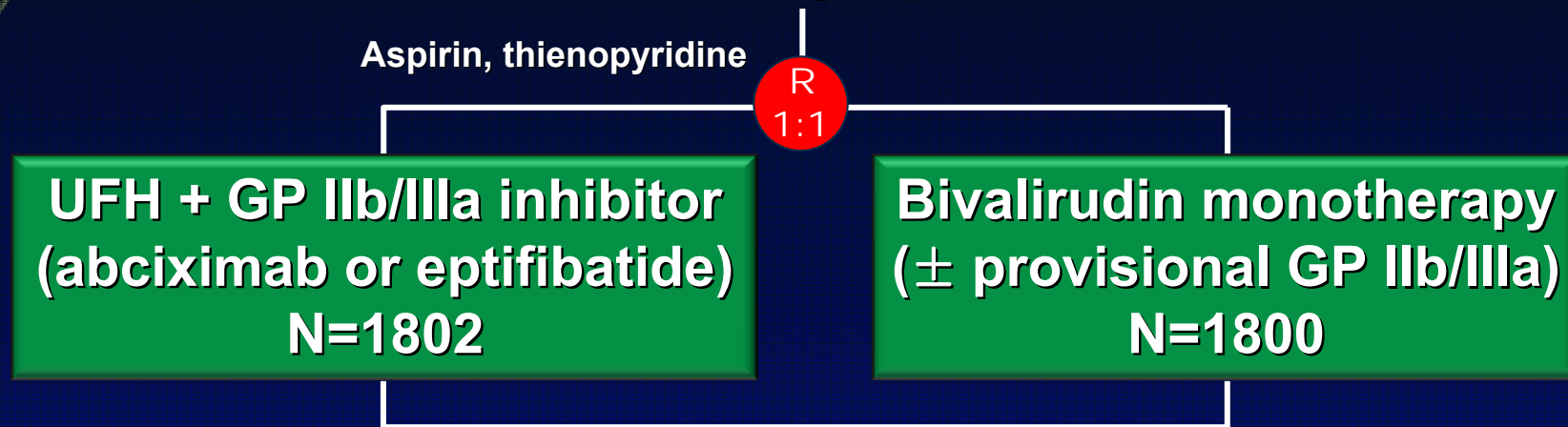
## Impact of MI and Major Bleeding in the First 30 Days on Risk of Death Over 1 Year



# HORIZONSAMI

Harmonizing Outcomes with Revascularization and Stents in AMI

3602 pts with STEMI with symptom onset  $\leq 12$  hours



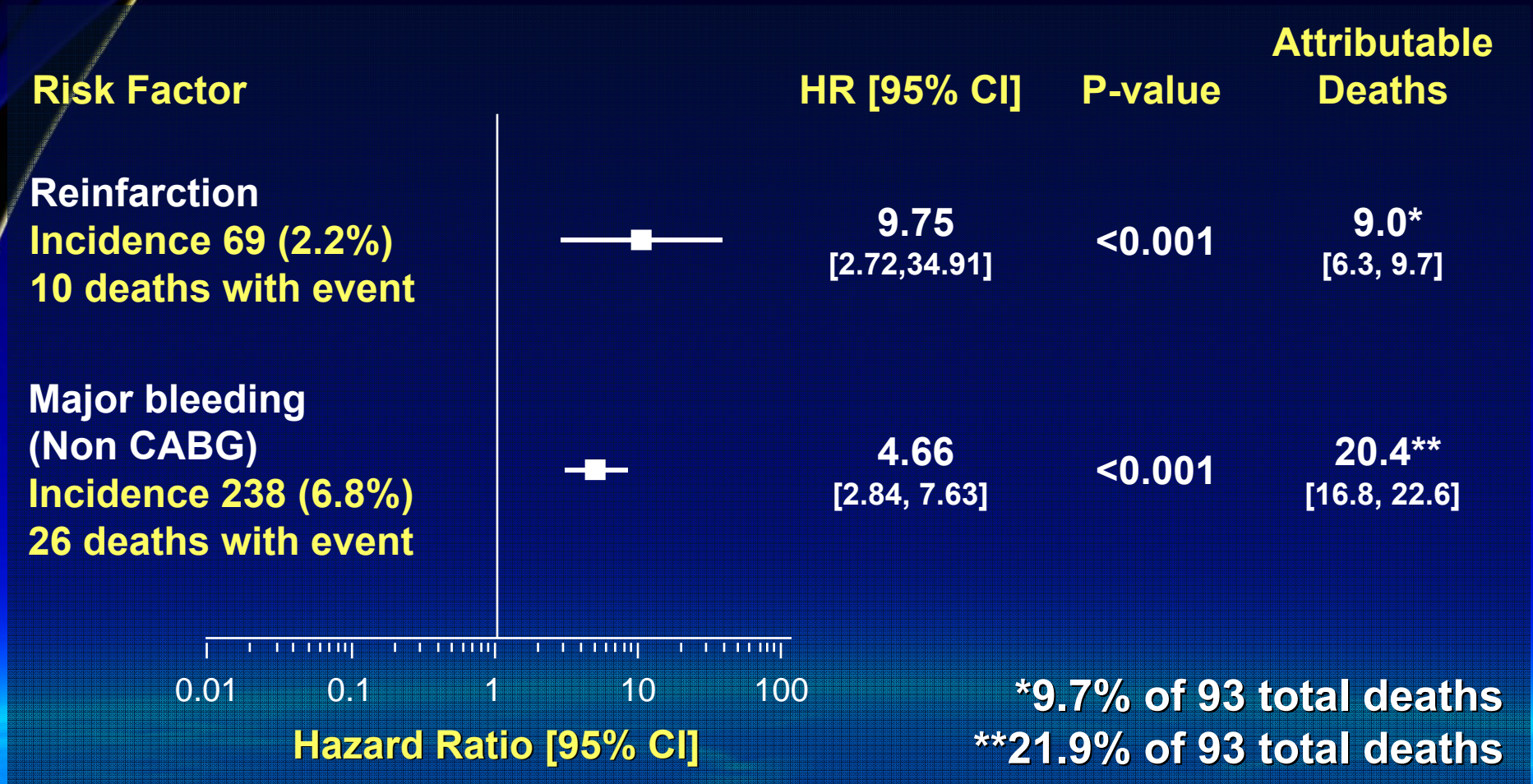
Emergent angiography, followed by triage to primary PCI (93%), CABG (2%) or medical therapy (5%)

**Primary Endpoints**

30 Days by ITT

# Time-updated covariate adjusted Cox model relating 30-day events to 30-day mortality

- Complete model with MACE components and major bleeding -

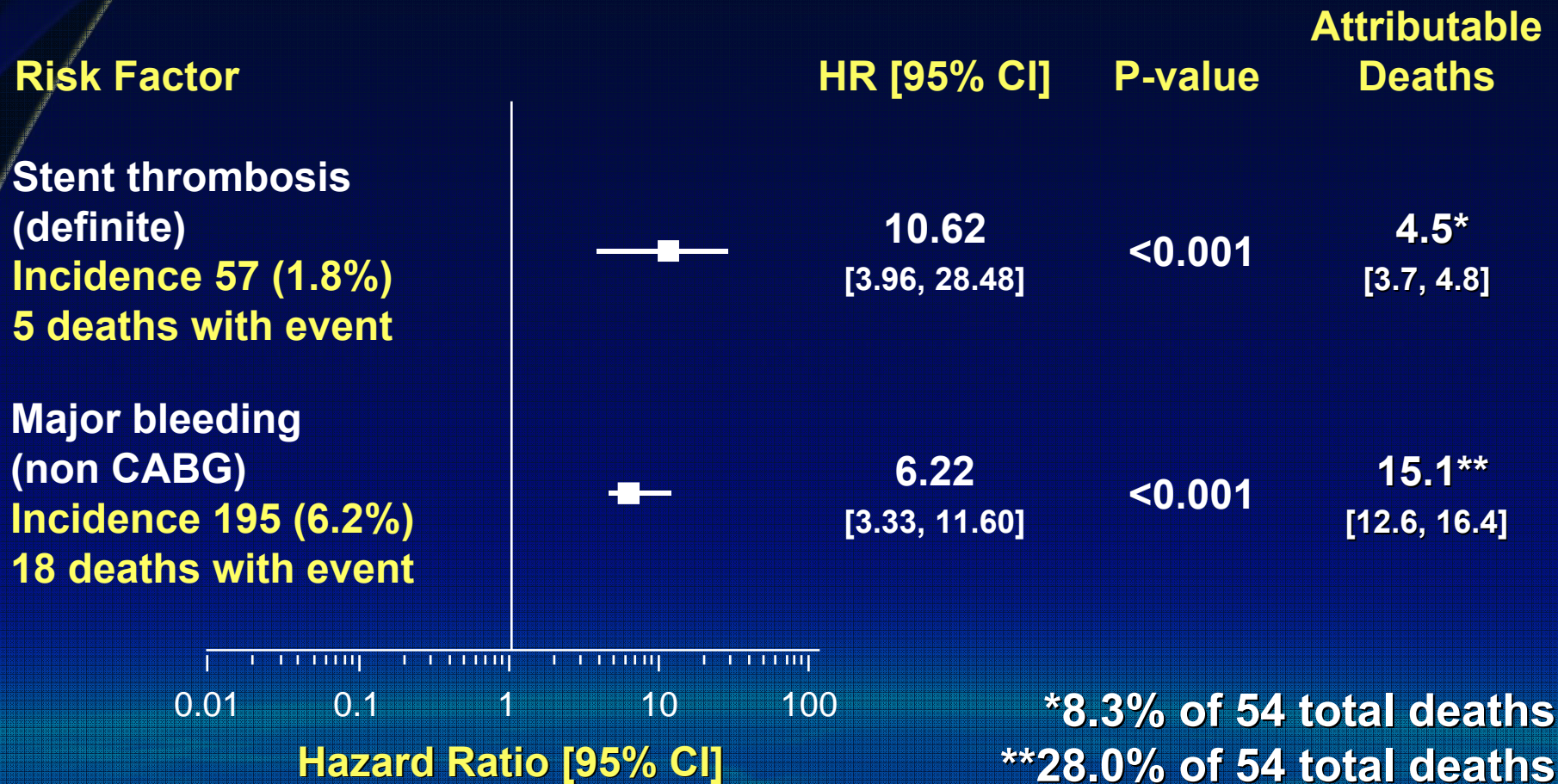


**C-statistic = 0.87.** Attributable deaths = N deaths among pts with the time updated event (attribute) X (adj. HR - 1)/adj. HR



# Time-updated covariate adjusted Cox model relating 30-day events to 30-day mortality

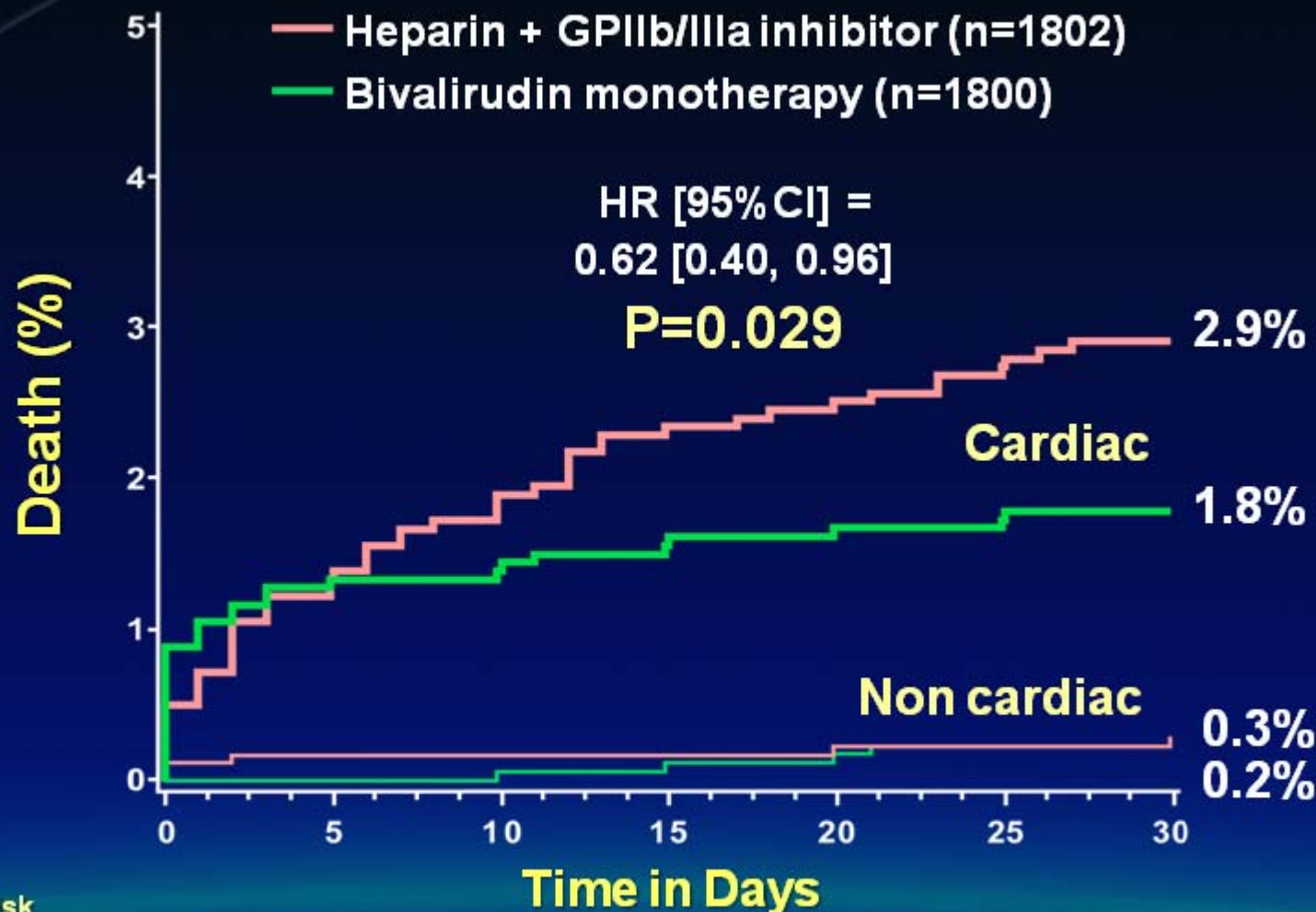
- Complete model in 3,124 pts with successfully implanted stents -



**C-statistic = 0.87.** Attributable deaths = N deaths among pts with the time updated event (attribute) X (adj. HR - 1)/adj. HR

HORIZONSAMI

# 30 Day Mortality: Cardiac and Non Cardiac

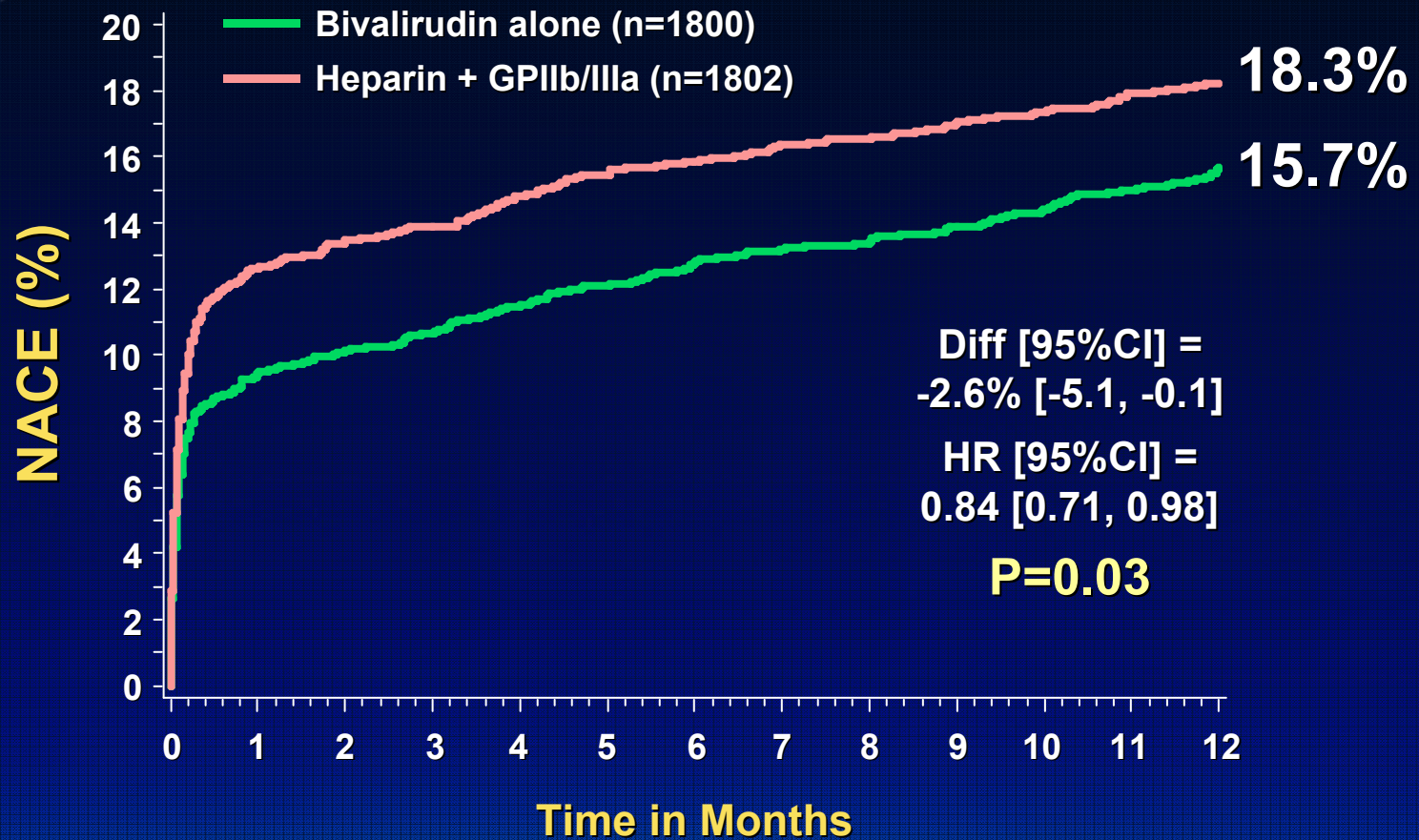


Number at risk

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



# 1-Year Net Adverse Clinical Events\*



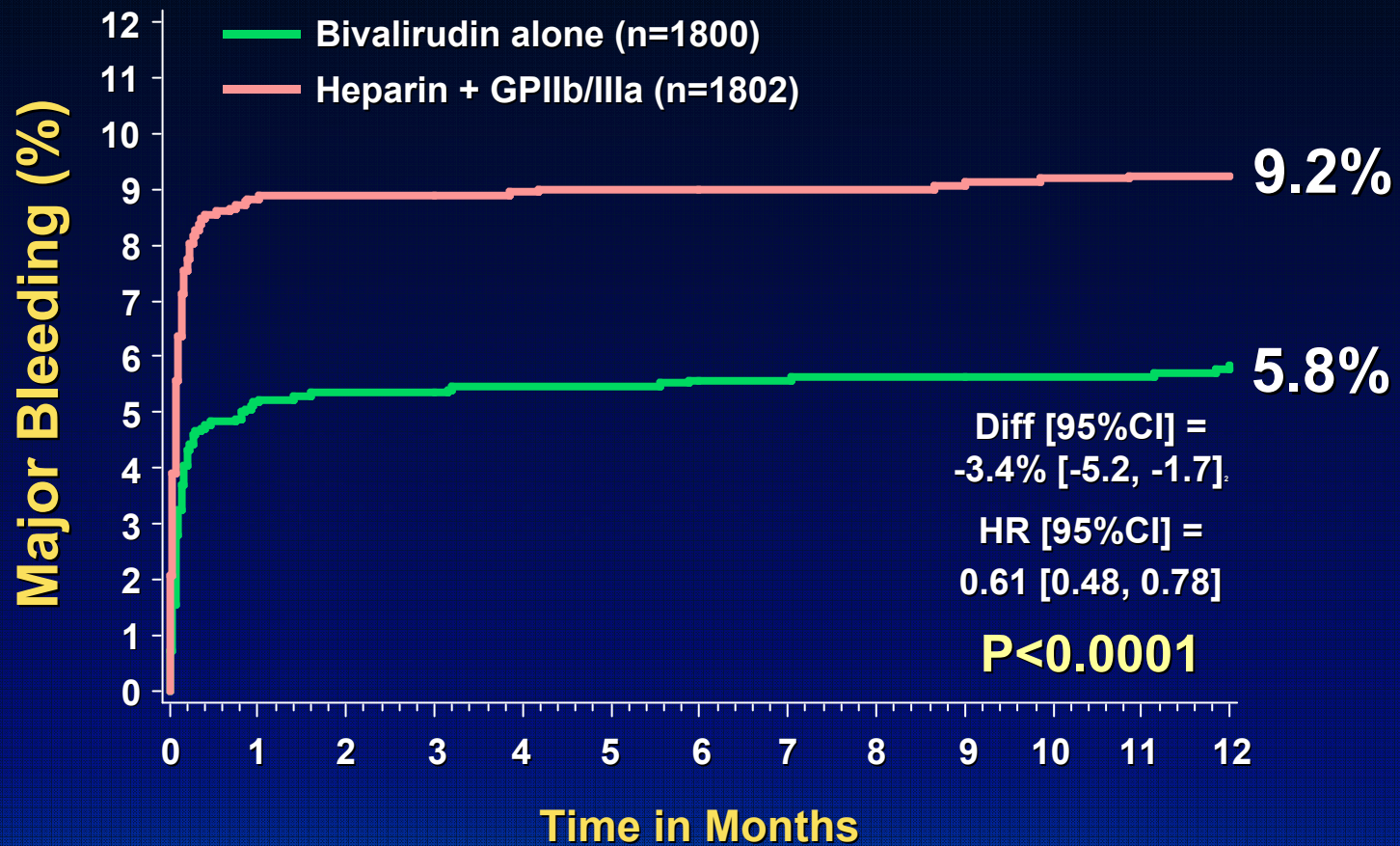
Number at risk

<b>Bivalirudin alone</b>	1800	1559	1514	1483	1343
<b>Heparin+GPIIb/IIIa</b>	1802	1499	1459	1427	1281

\*MACE or major bleeding (non CABG)

**HORIZONSAMI**

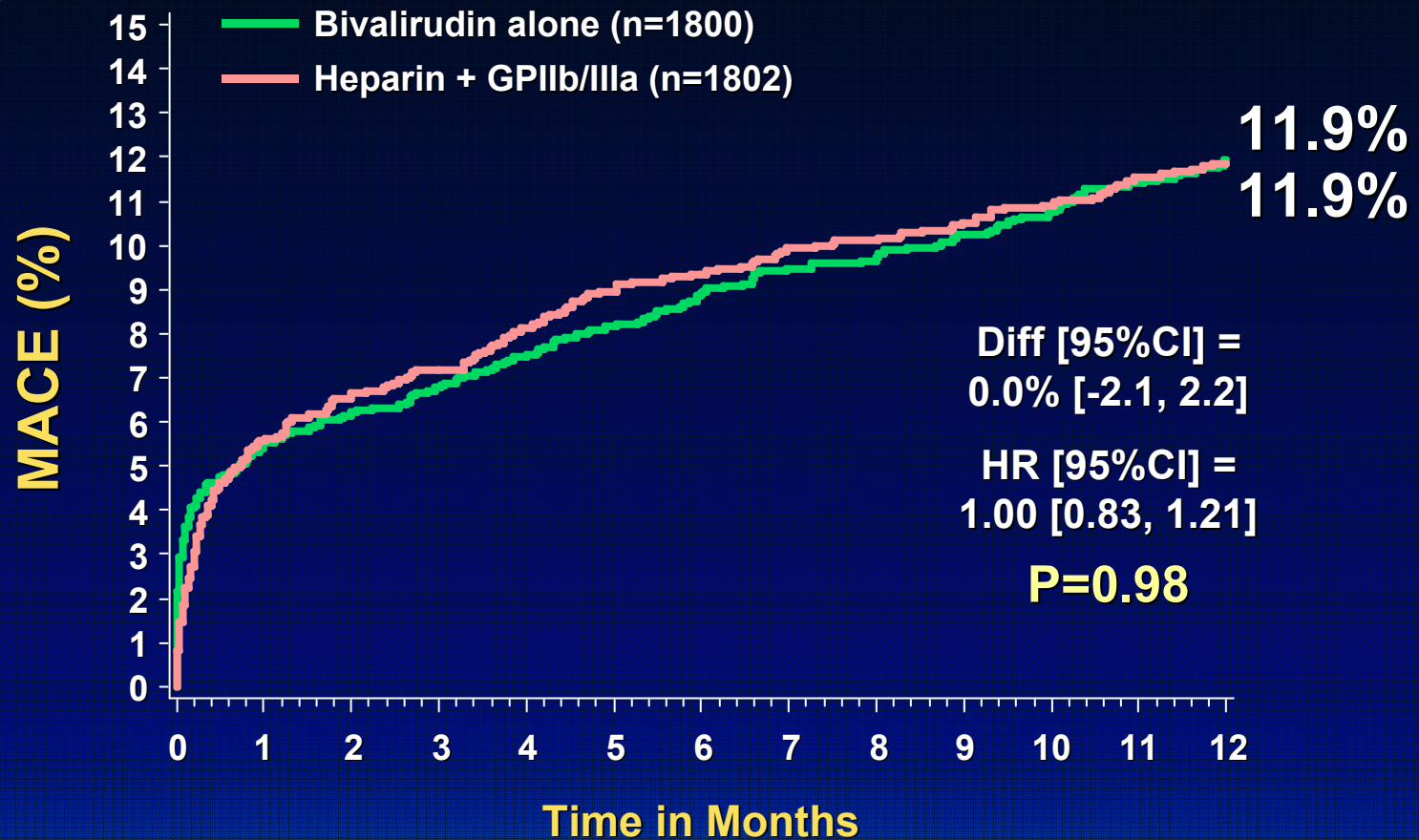
# 1-Year Major Bleeding (non-CABG)



## Number at risk

Bivalirudin alone	1800	1621	1601	1586	1448
Heparin+GPIIb/IIIa	1802	1544	1532	1515	1368

# 1-Year Major Adverse CV Events\*



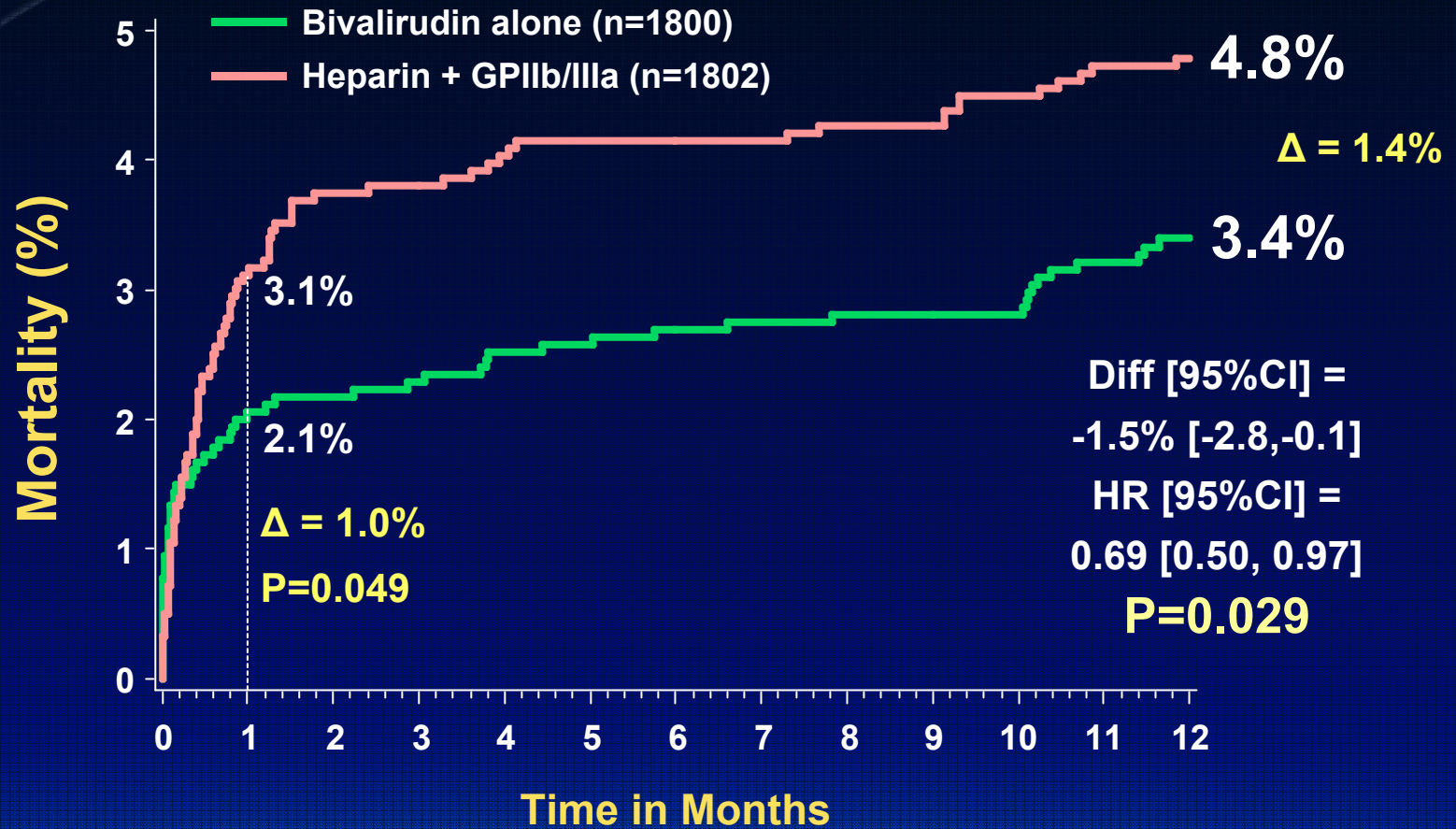
**Number at risk**

<b>Bivalirudin alone</b>	1800	1627	1579	1544	1394
<b>Heparin+GPIIb/IIIa</b>	1802	1619	1573	1540	1380

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

**HORIZONSAMI**

# 1-Year All-Cause Mortality



## Number at risk

	0	1	2	3	4	5	6	7	8	9	10	11	12
Bivalirudin alone	1800	1705	1684	1669	1669	1669	1669	1669	1669	1669	1669	1520	1520
Heparin+GPIIb/IIIa	1802	1678	1663	1663	1663	1663	1663	1663	1663	1663	1663	1486	1486

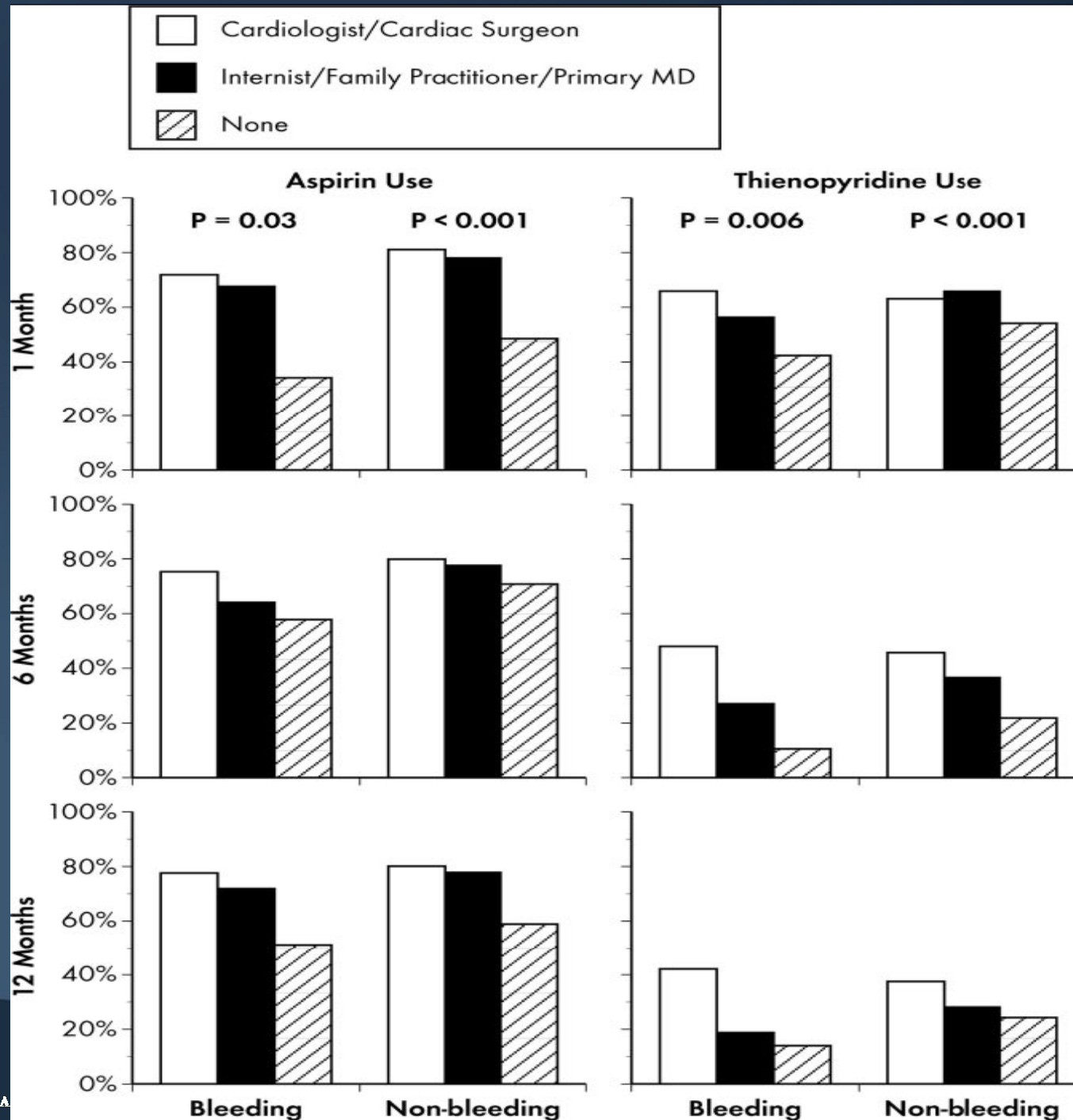
# Possible Mechanisms Linking Hemorrhagic Complications to Mortality

1. Fatal hemorrhage (e.g. intracranial bleed)
2. Vol. depletion  $\Rightarrow$  Hypotension, ischemia, arrhythmias
3. Complications from procedures to manage bleeding
4. Discontinuation of lifesaving medications (antiplatelet agents, beta blockers, statins)
5. Blood transfusions depleted in NO  $\Rightarrow$  systemic vasoconstriction, inflammation, apoptosis
6. Unmeasured confounders



# Post AMI Meds in bleeding patients

*Wang et al.  
Circulation.  
2008;118:000-  
000*



# Conclusions

- ❖ Pharmacologic treatment of patients with ACS undergoing PCI has improved over the years to decrease ischemic and bleeding complications
- ❖ As most drugs which ↓ ischemia also ↑ bleeding, the offsetting impact of adverse ischemic and hemorrhagic events must be carefully examined
- ❖ **The net balance of ischemia and bleeding may vary tremendously with the risk profile of the individual pt for each complication, and the follow-up duration**
- ❖ Models are needed to assess a patient's risk for bleeding as well as ischemic complications to further enhance treatment of the patients with therapies that are efficacious and also safe



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