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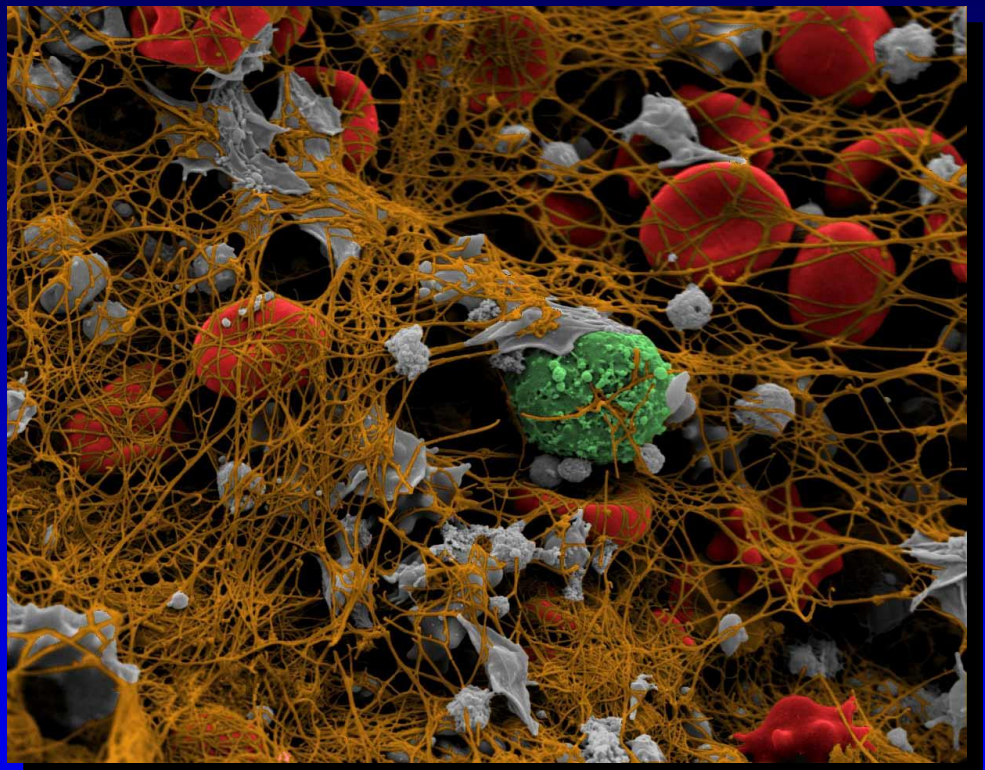
Bridging Hearts and Minds to Enhance Cardiovascular Care

Gaining Experience with New Antiplatelets in ACS-PCI: What Have We Learned

Shaun Goodman

The Plan

- Conflicts of Interest
- ADP receptor inhibitor therapy options
  - Clopidogrel
  - Prasugrel
  - Ticagrelor
- Guideline recommendations



Courtesy of John W. Weisel, University of Pennsylvania

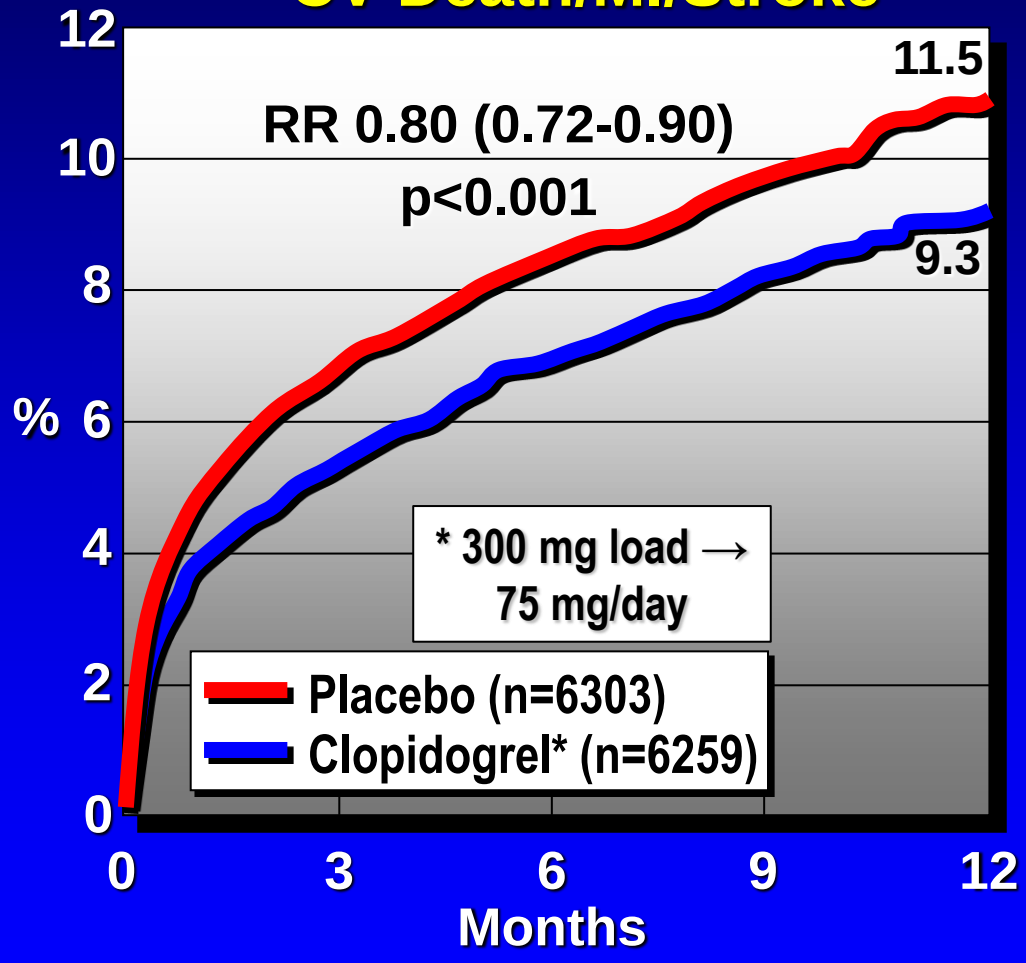
Shaun Goodman: Research Grant Support, Speaker/Consulting Honorarium

Beware of Interest Groups

CURE

Non-ST Elevation ACS patients with ECG changes ± cardiac marker elevation

CV Death/MI/Stroke

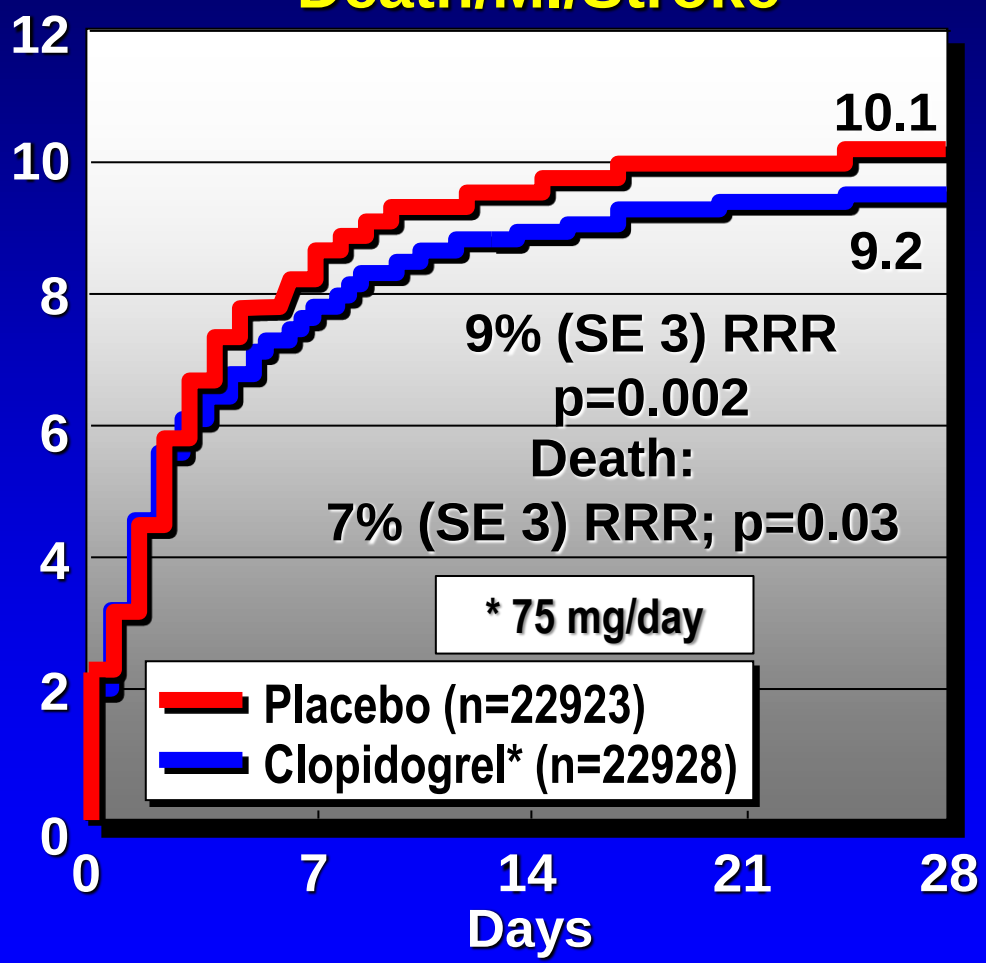


N Engl J Med 2001;345:494-502

commit CCS-2

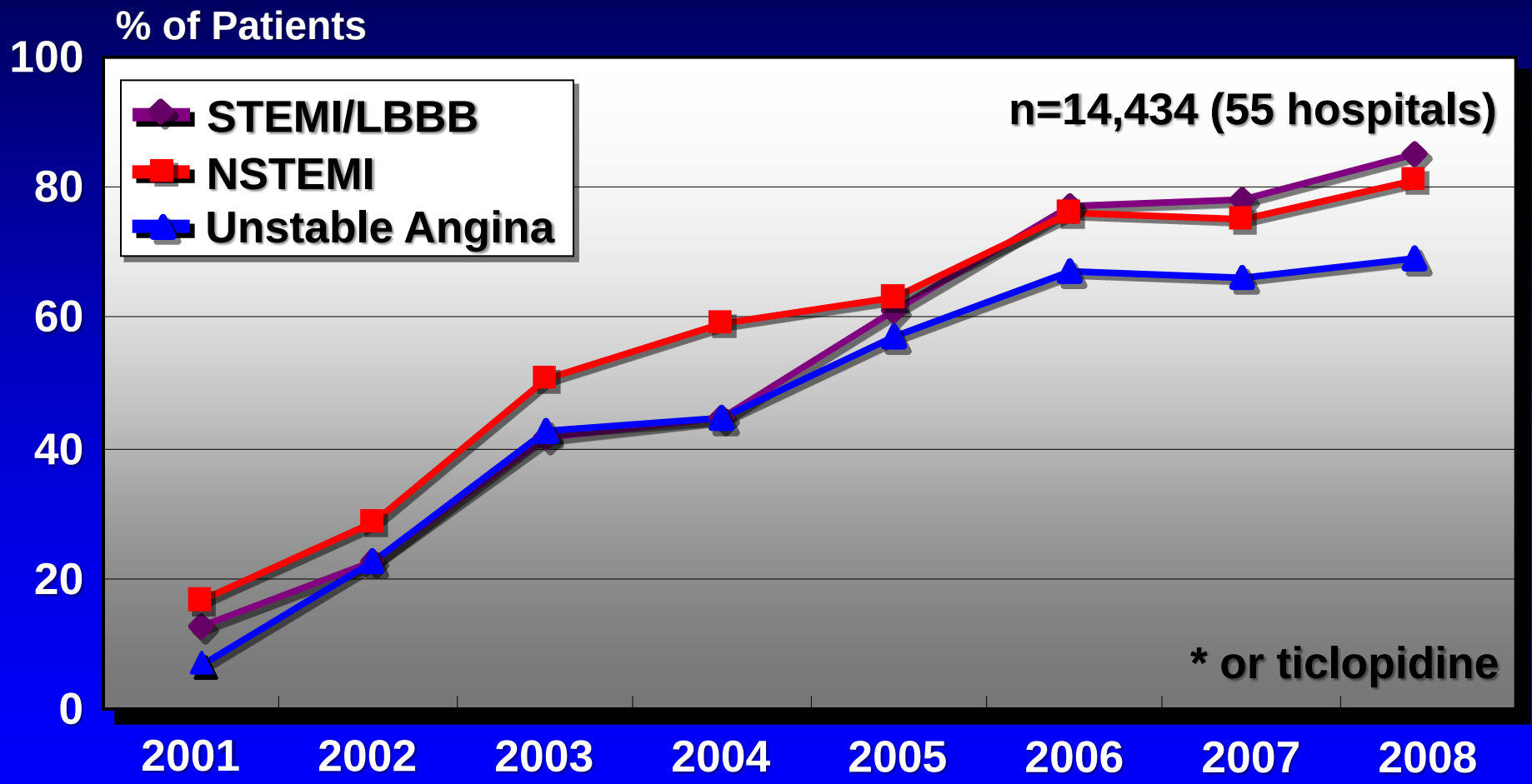
Suspected acute MI (ST change or LBBB) within 24 h of symptom onset

Death/MI/Stroke

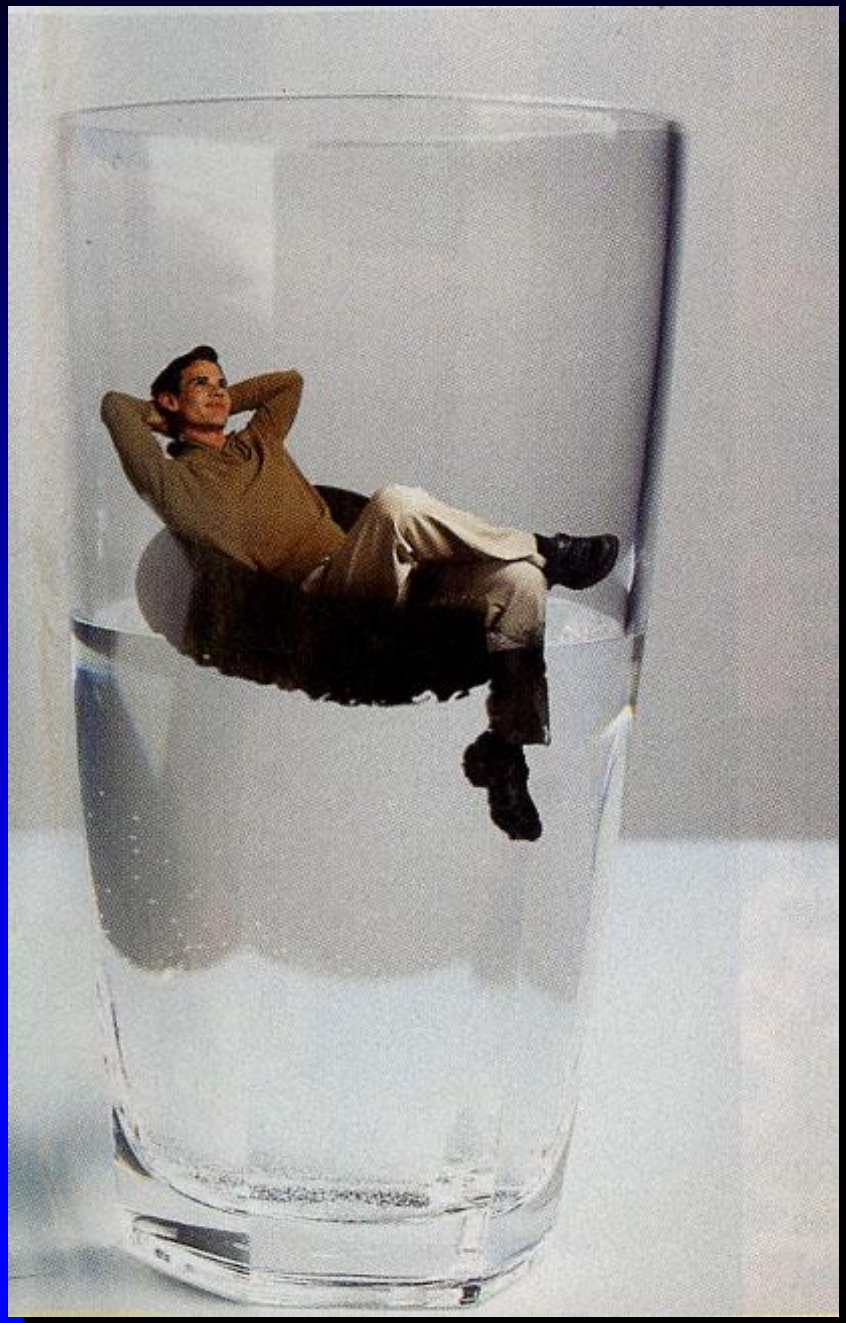


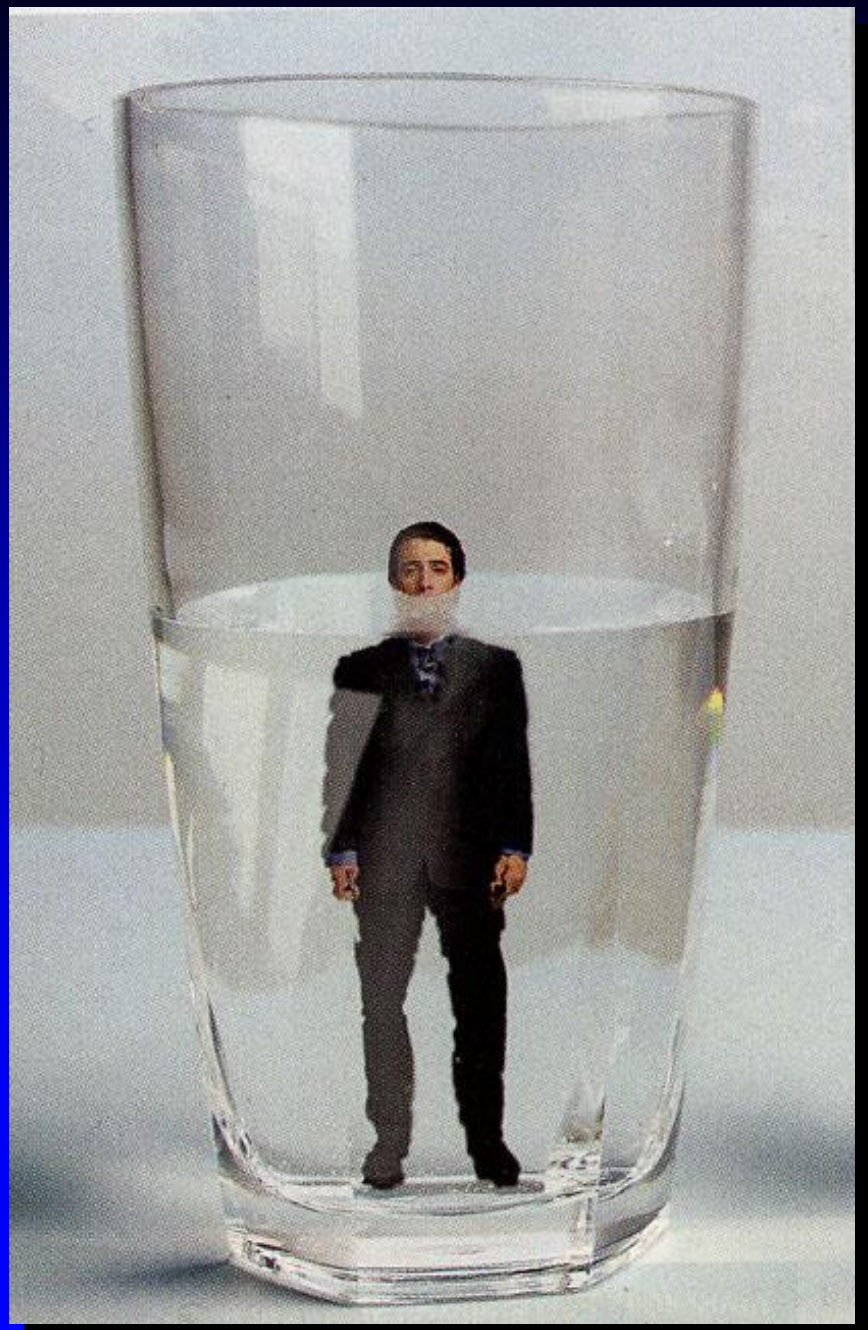
Lancet 2005;366:1607-21

Trends in Clopidogrel* Use at Admission



Adapted from Rao et al *Am Heart J* 2009;157:642-650.e1





Key Limitations of Clopidogrel

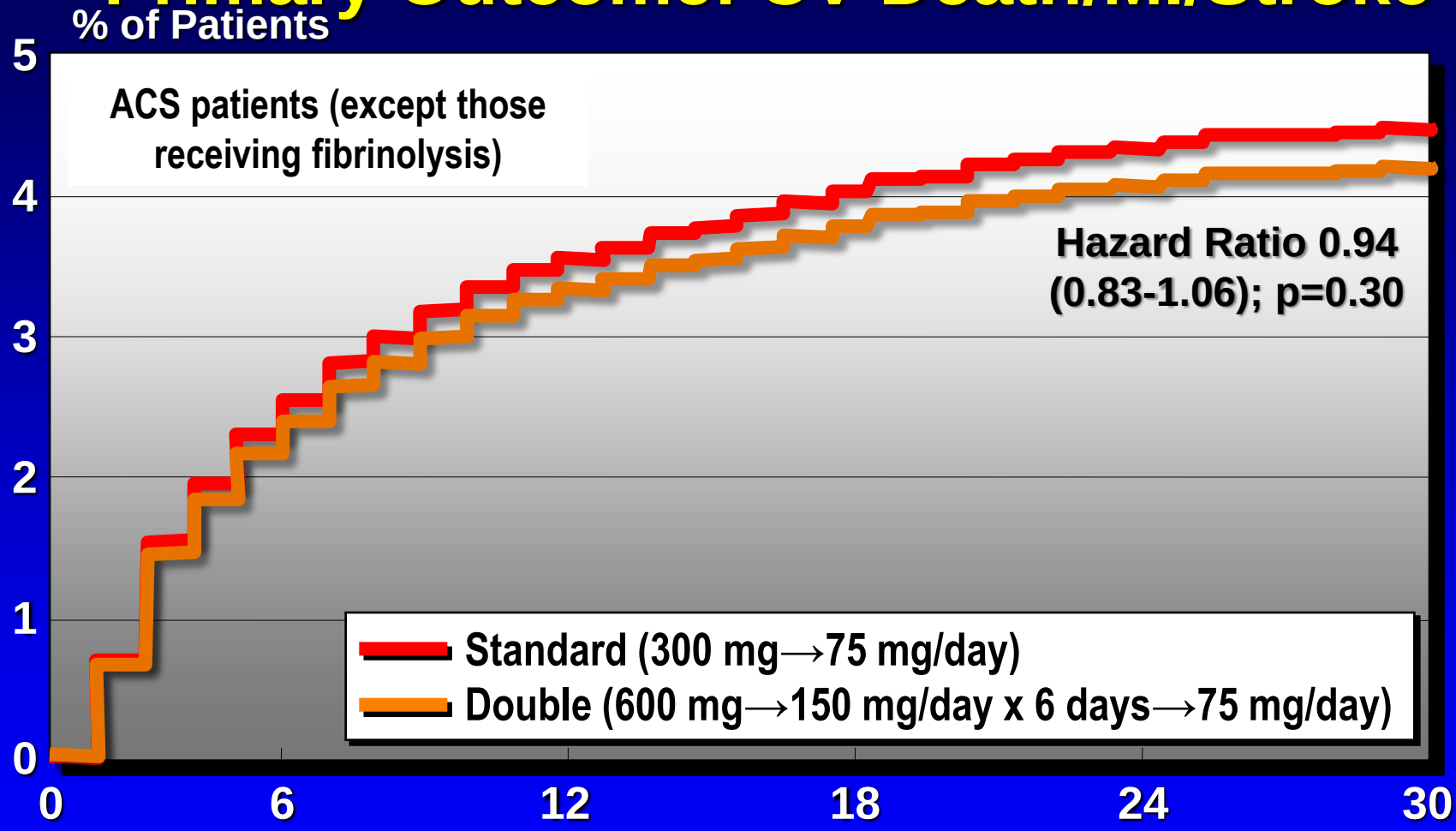
- Delayed onset of action
- Large interindividual variability in platelet response
- Despite significant reduction in cardiovascular events (including mortality) with ASA and clopidogrel → residual risk

Adapated from Schomig *N Engl J Med* 2007;361:1108-11

Limitations of Clopidogrel: Options

- Give more
  - Higher loading (e.g., 600 mg) and maintenance (e.g., 150 mg/day) dose → CURRENT/OASIS 7 trial

Clopidogrel Dose Comparison
Primary Outcome: CV Death/MI/Stroke

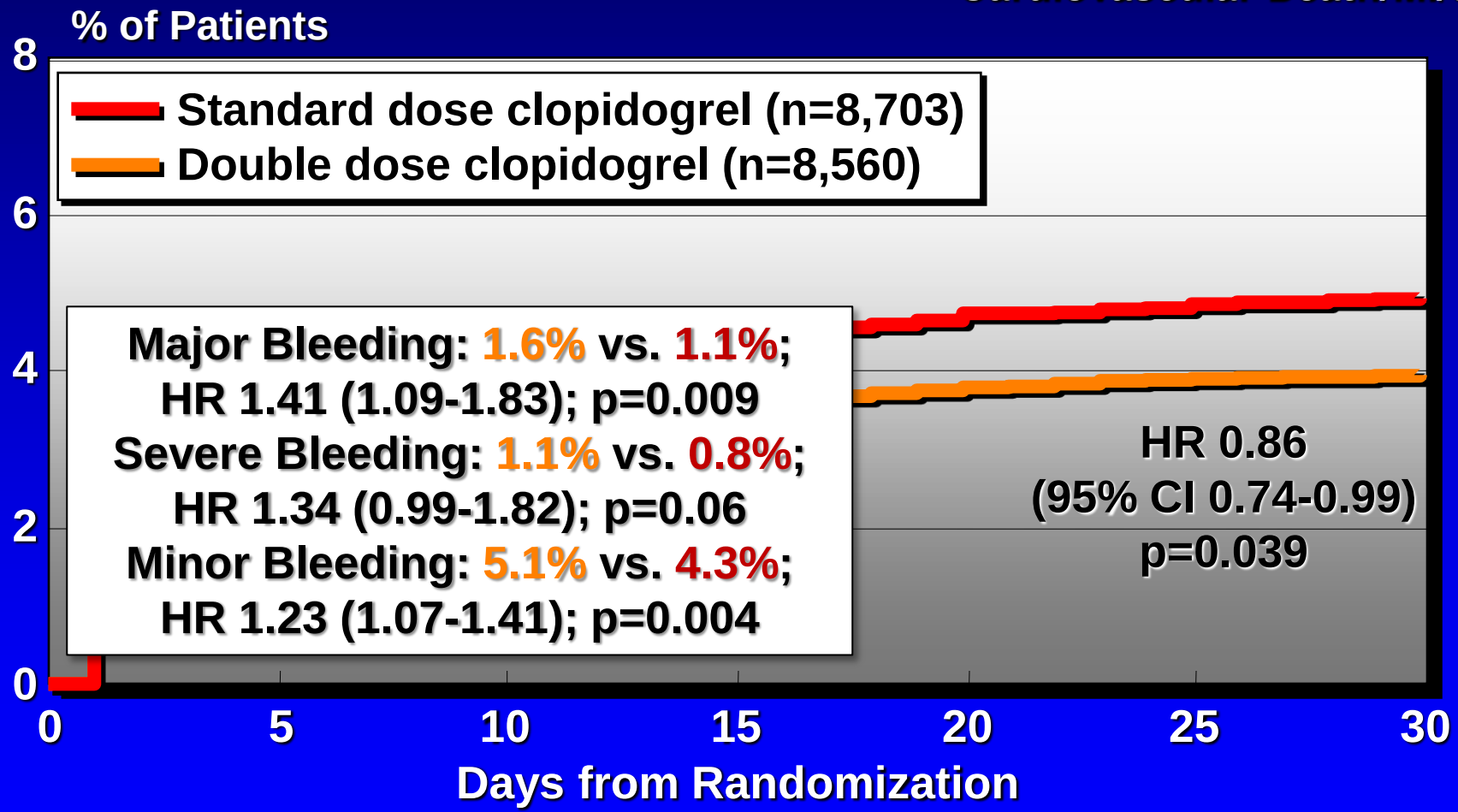


No. at risk						
Double dose	12,520	12,209	12,087	12,032	11,996	11,981
Standard dose	12,566	12,234	12,109	12,045	12,011	11,990

CURRENT-OASIS 7 Investigators *N Engl J Med* 2010;363:930-42

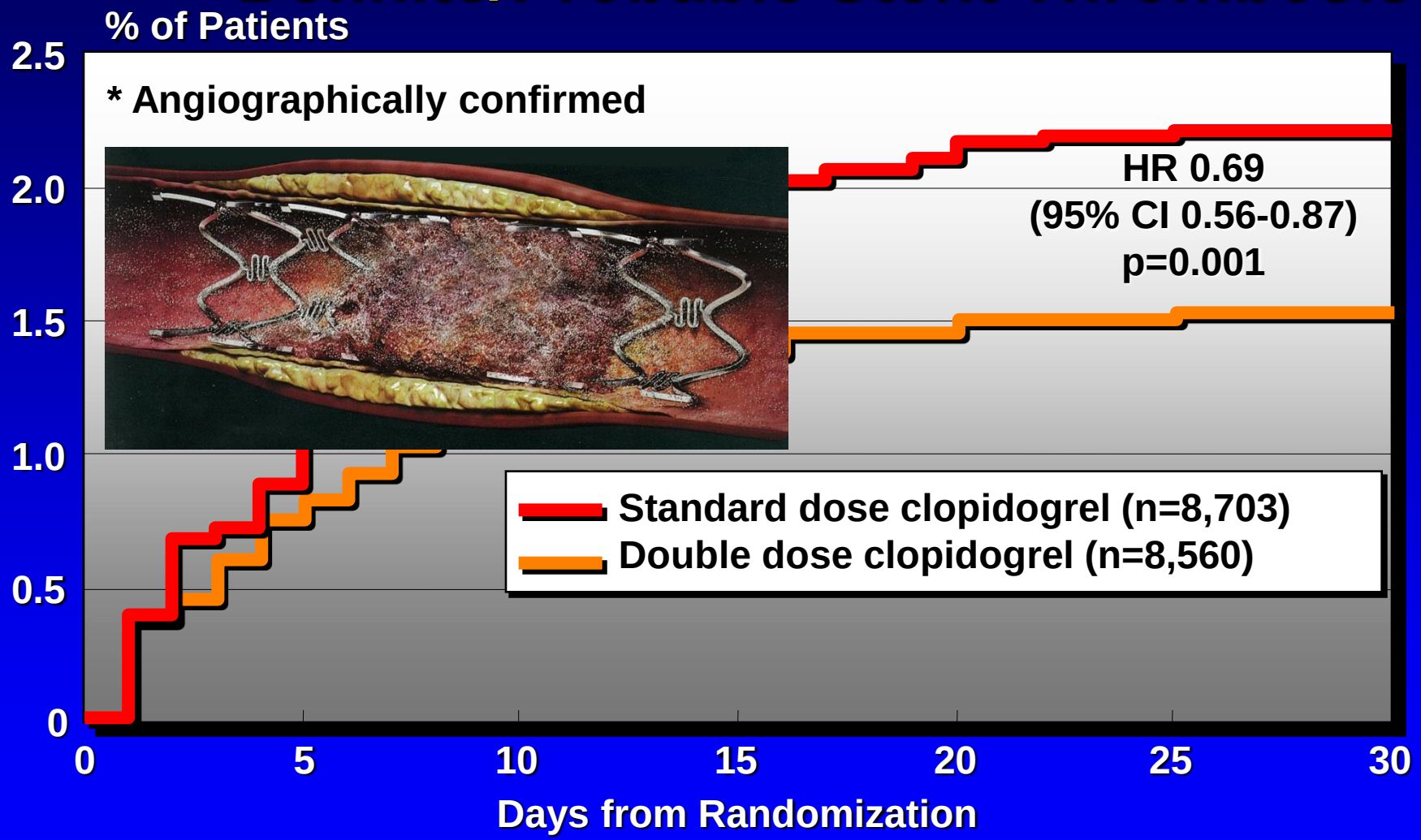
Clopidogrel Standard vs. Double Dose: Primary Outcome* in PCI Patients

* Cardiovascular Death/MI/Stroke



Mehta et al *Lancet* 2010;376:1233-43

Clopidogrel Standard vs. Double Dose: Definite/Probable Stent Thrombosis*



Mehta et al *Lancet* 2010;376:1233-43

The Bottom Line

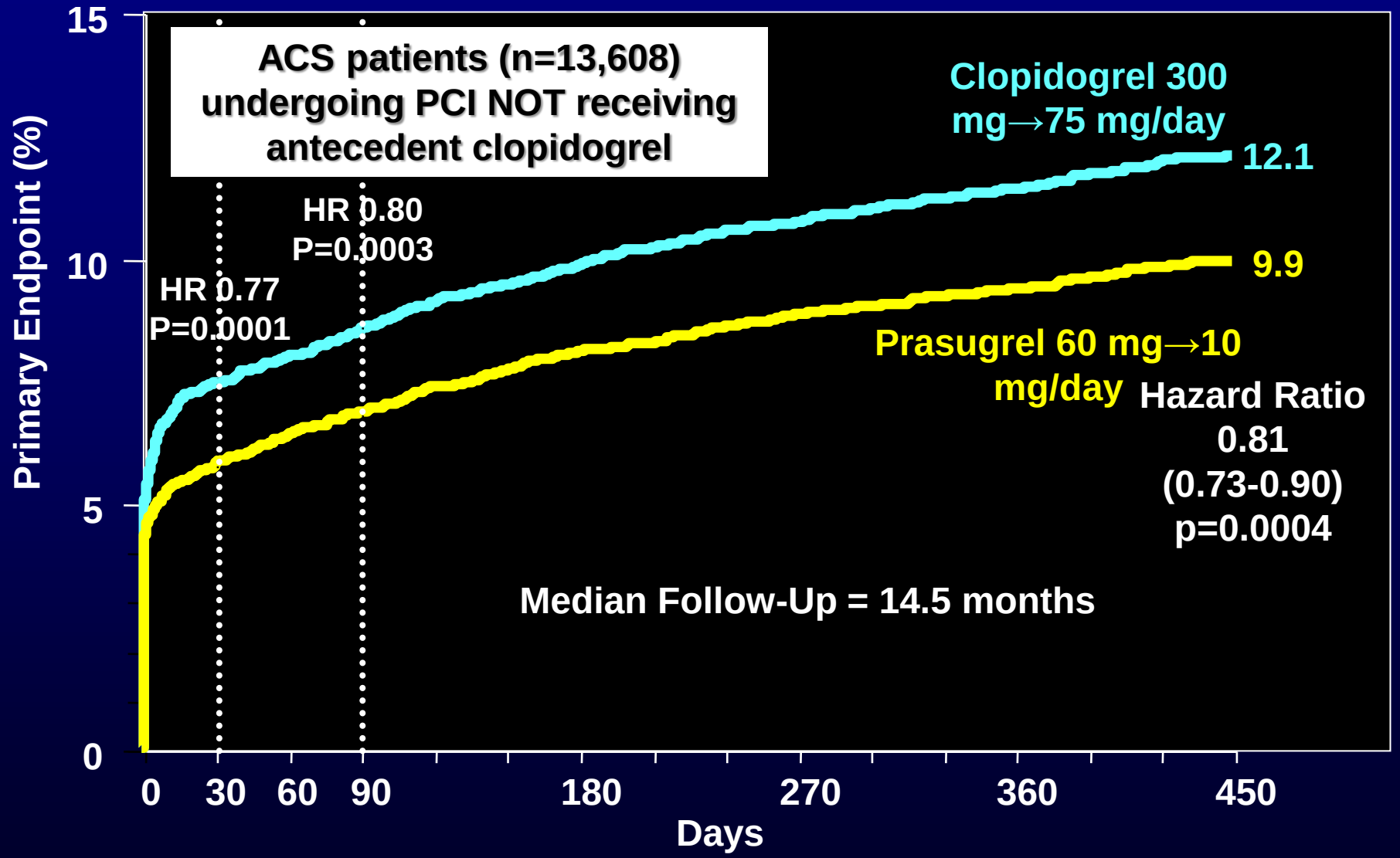
- Clopidogrel
  - Standard dosing (300 mg load
    → 75 mg/day) in ACS patients
    - The *only* ADP receptor inhibitor to be used in combination with fibrinolysis
  - Double dosing (600 mg load → 150 mg/day x 6 days) in ACS patients undergoing PCI (e.g., STEMI undergoing Primary PCI)

…but there are more effective ADP receptor inhibitors than clopidogrel !

Limitations of Clopidogrel: Options

- Give more
  - Higher loading (e.g., 600 mg) and maintenance (e.g., 150 mg/day) dose → CURRENT/OASIS 7 trial
- Find a better inhibitor of $P2Y_{12}$
  - Prasugrel

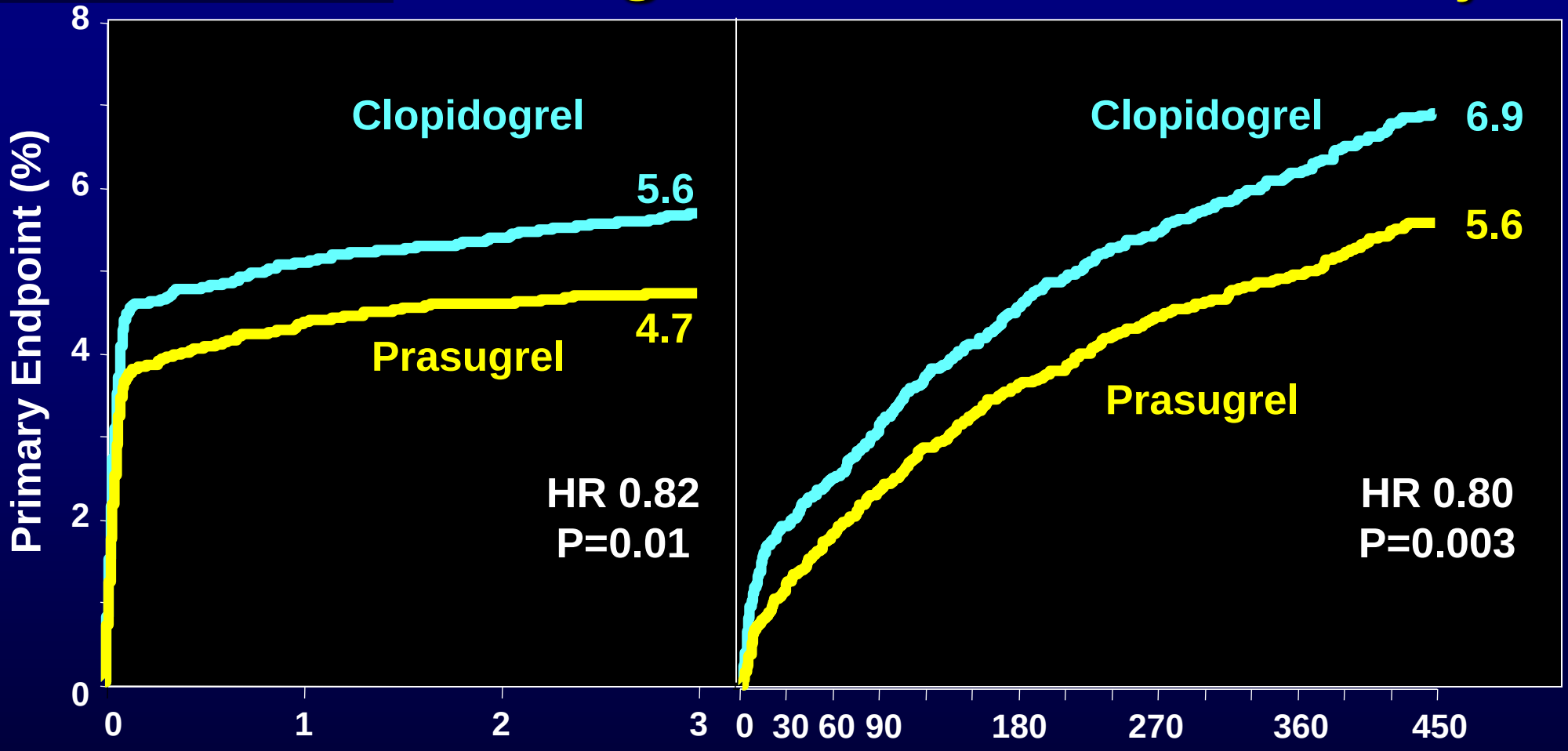
Primary Endpoint
Cardiovascular (CV) Death, MI, or Stroke



Wiviott et al for the TRITON-TIMI 38 Investigators *N Engl J Med* 2007;357:2001-15

TRÎTON TIMI-38

Timing of Benefit: Landmark Analysis*



* All endpoints occurring before day 3 censored; number at risk includes all pts alive (regardless of whether a nonfatal event had occurred ≤3 days) and had not withdrawn consent for follow-up

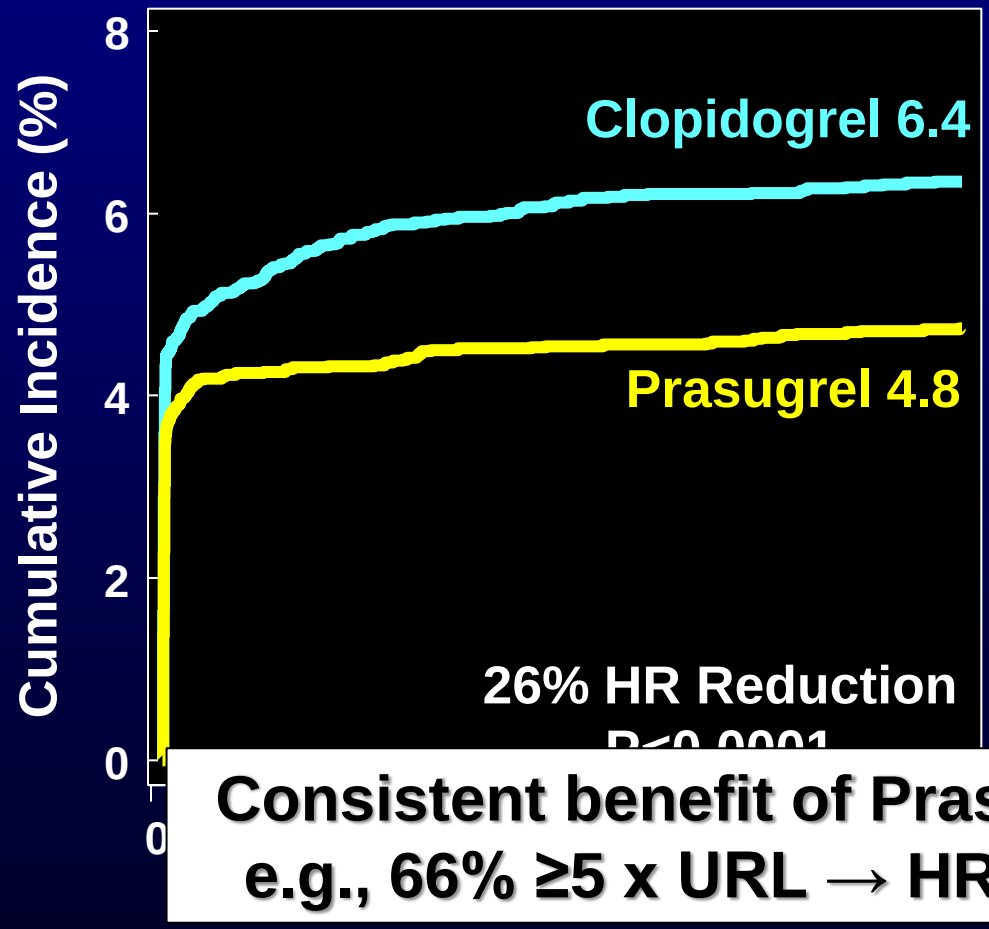
Wiviott et al for the TRITON-TIMI 38 Investigators *N Engl J Med* 2007;357:2001-15

TRÎTON TIMI-38

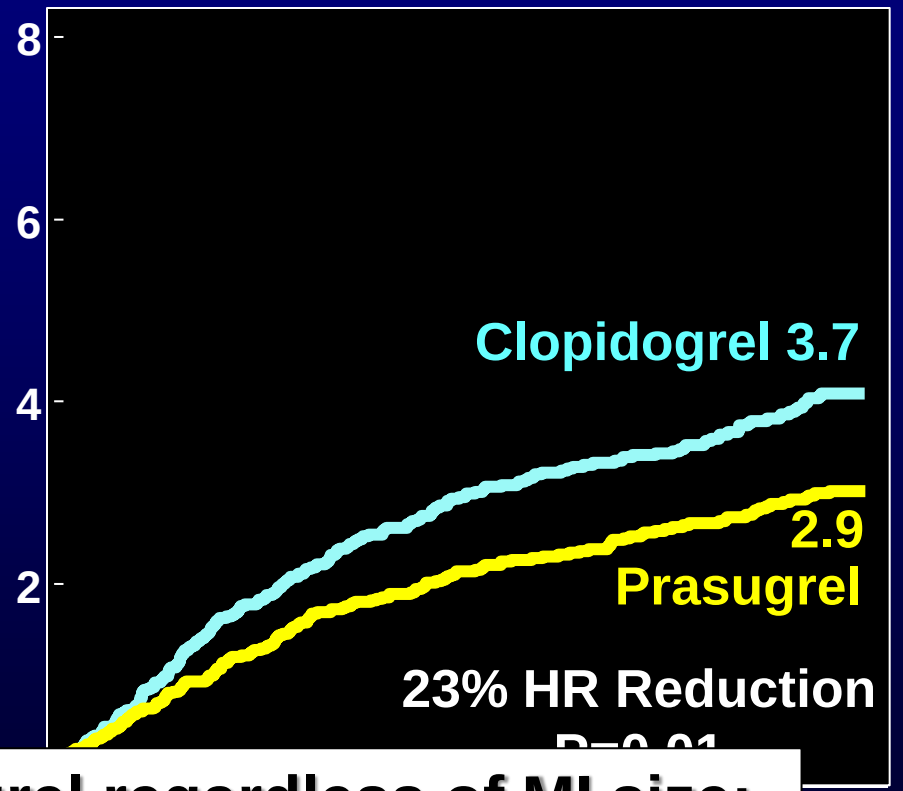
Timing of MI (Landmark Analysis)

*All types by Universal MI Classification: Spontaneous (1), Secondary (2), or Sudden cardiac death (3) [36.6%]; or Procedure-related (PCI-4; CABG=5) [63.2%]

Early MI*: Day 0 - 30



Late MI*: Day 30 - 450

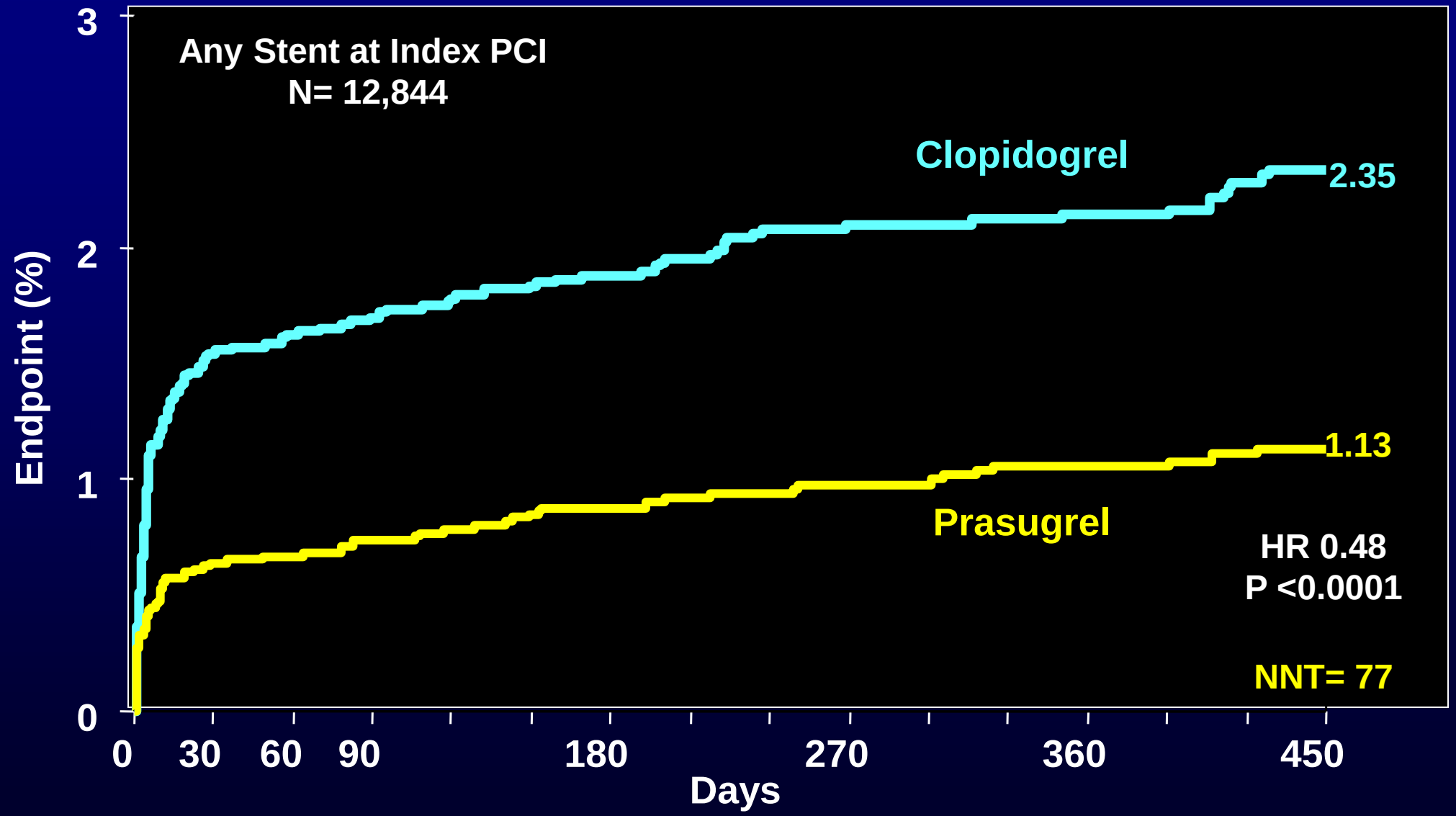


Consistent benefit of Prasugrel regardless of MI size:
e.g., 66% ≥5 x URL → HR. 0.74 (0.64-0.86); P<0.0001

Morrow et al for the TRITON-TIMI 38 Investigators *Circulation* 2009:119;2758-64

TRITON TIMI-38

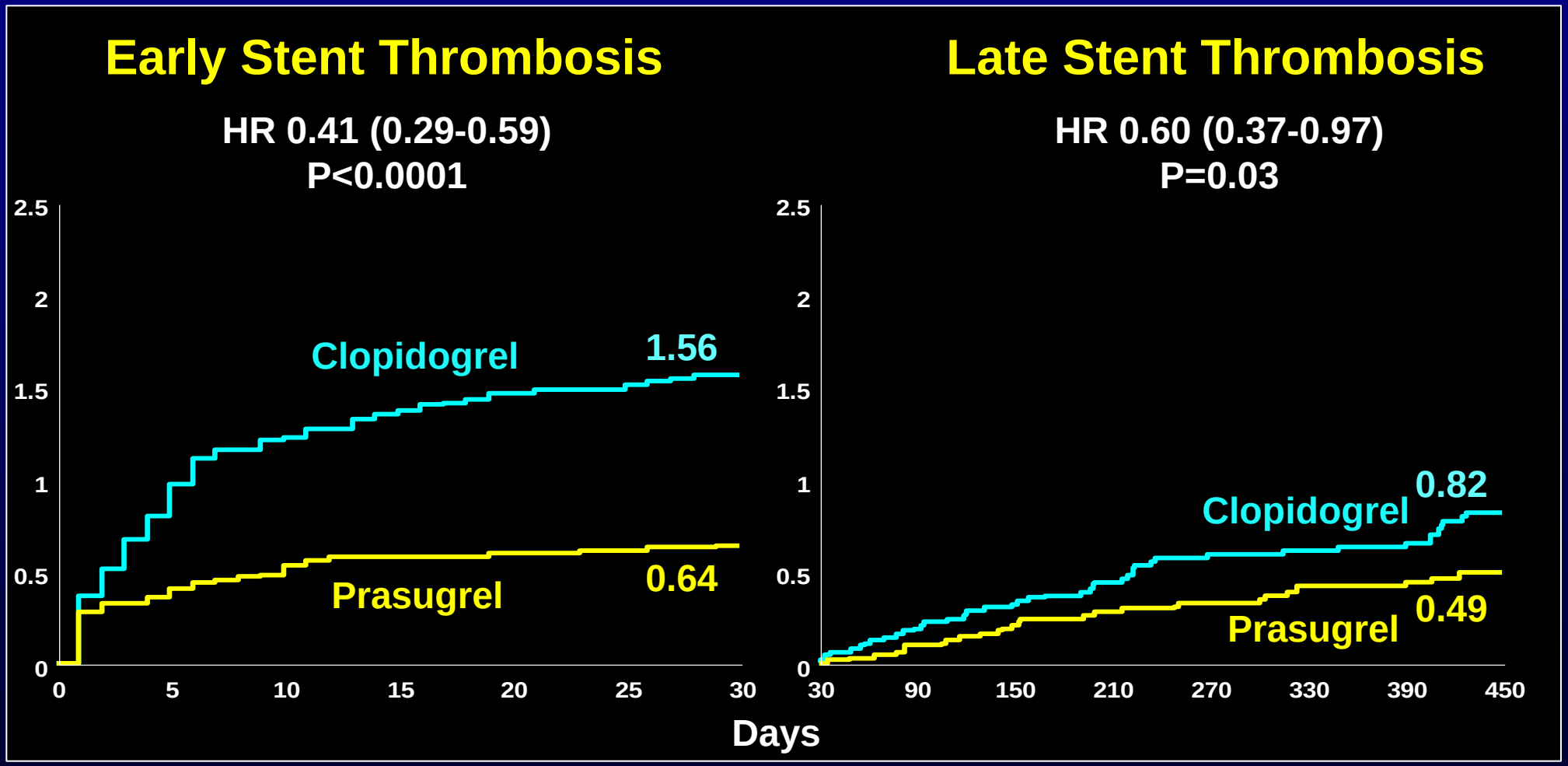
Stent Thrombosis



Wiviott et al *N Engl J Med* 2007;357:2001-15 and *Lancet* 2008;371:1353-63

TRÎTON TIMI-38

Stent Thrombosis: Timing

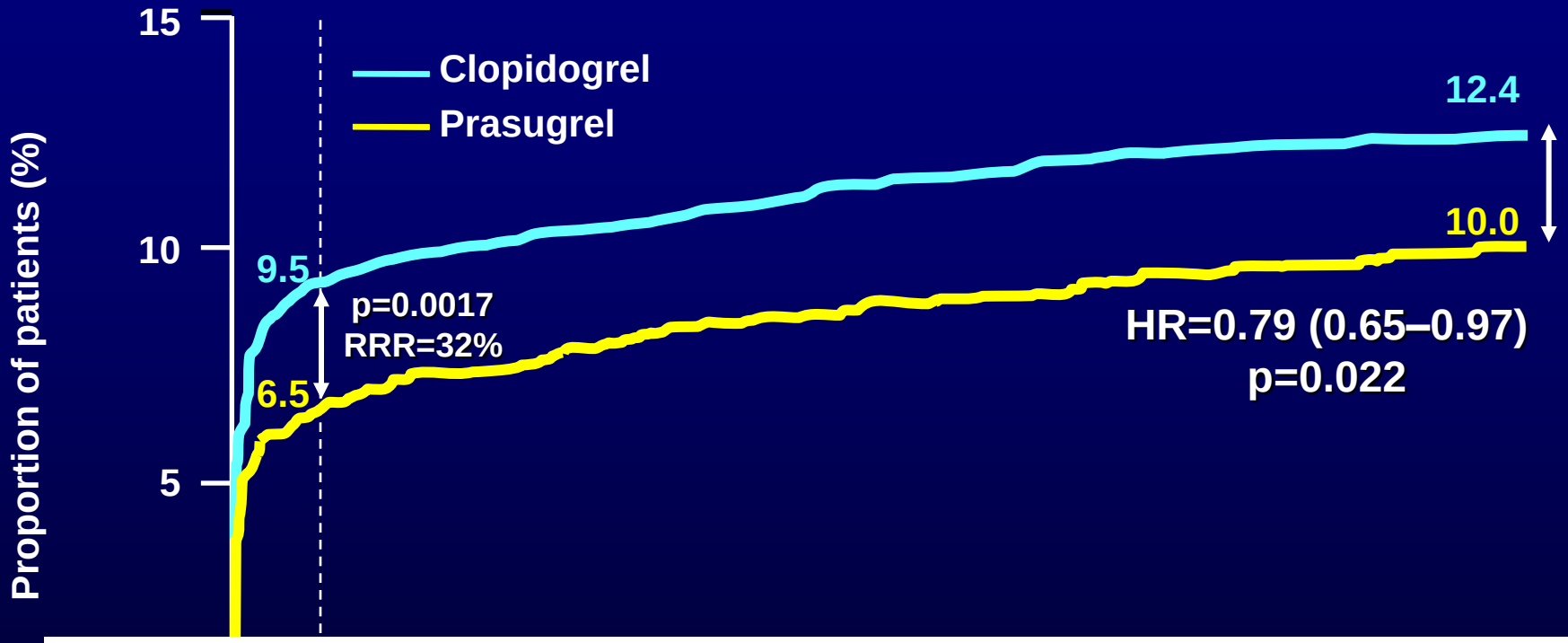


Wiviott et al for the TRITON-TIMI 38 Investigators *Lancet* 2008;371:1353-1363

TRÎTON TIMI-38

CV Death, MI or Stroke

STEMI Cohort: Primary (n=2,438) or Secondary PCI (n=1094)

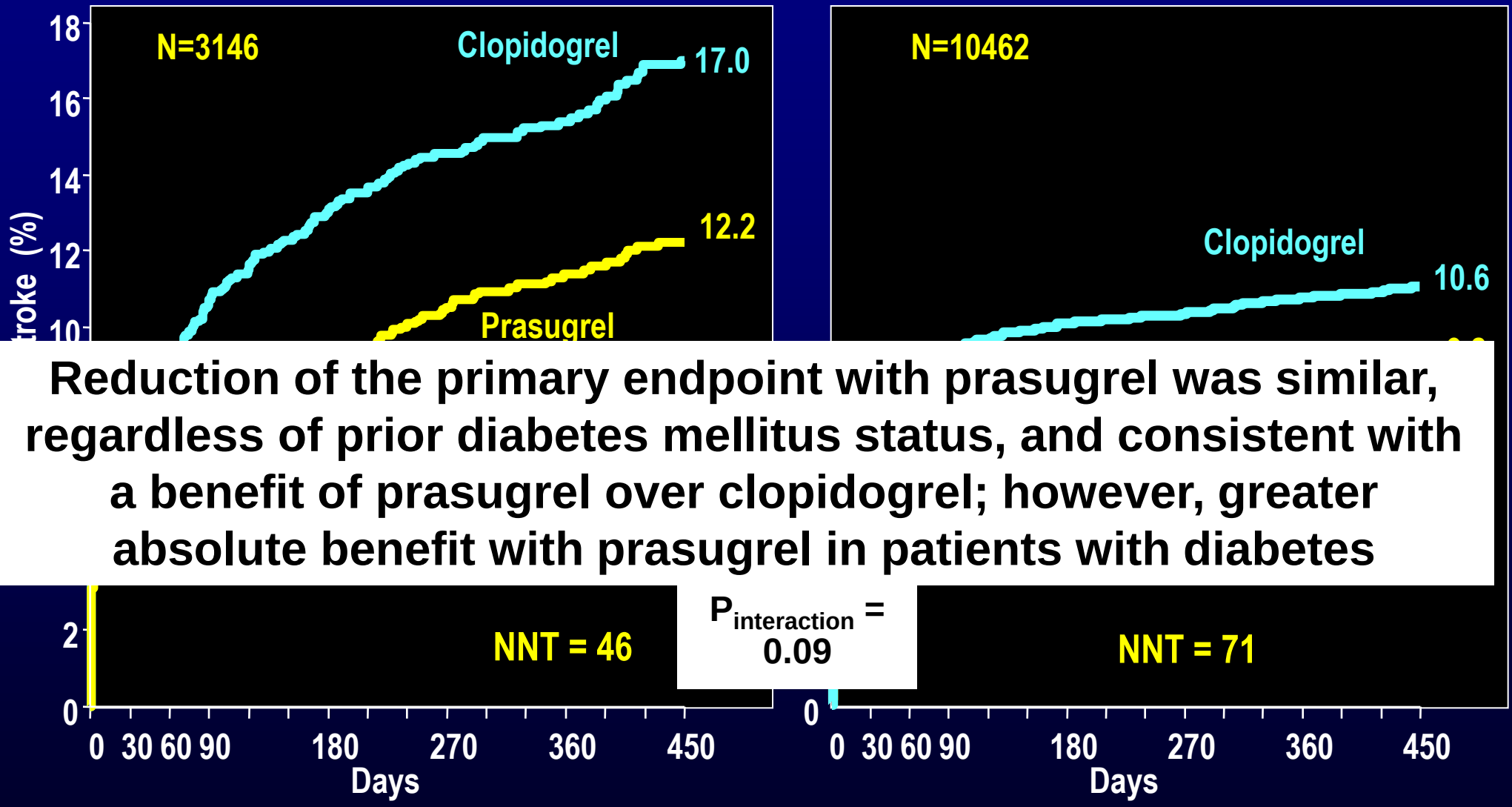


	30 Days	15 months
Cardiovascular Death:	2.4% vs. 1.4%, p=0.047	3.4% vs. 2.4%, p=0.13
All-cause Death:	2.6% vs. 1.6%, p=0.045	4.3% vs. 3.3%, p=0.11

Montalescot et al *Lancet* 2009;373:723-31

TRÎTON TIMI-38

Diabetes Mellitus and No Diabetes Mellitus Subgroups

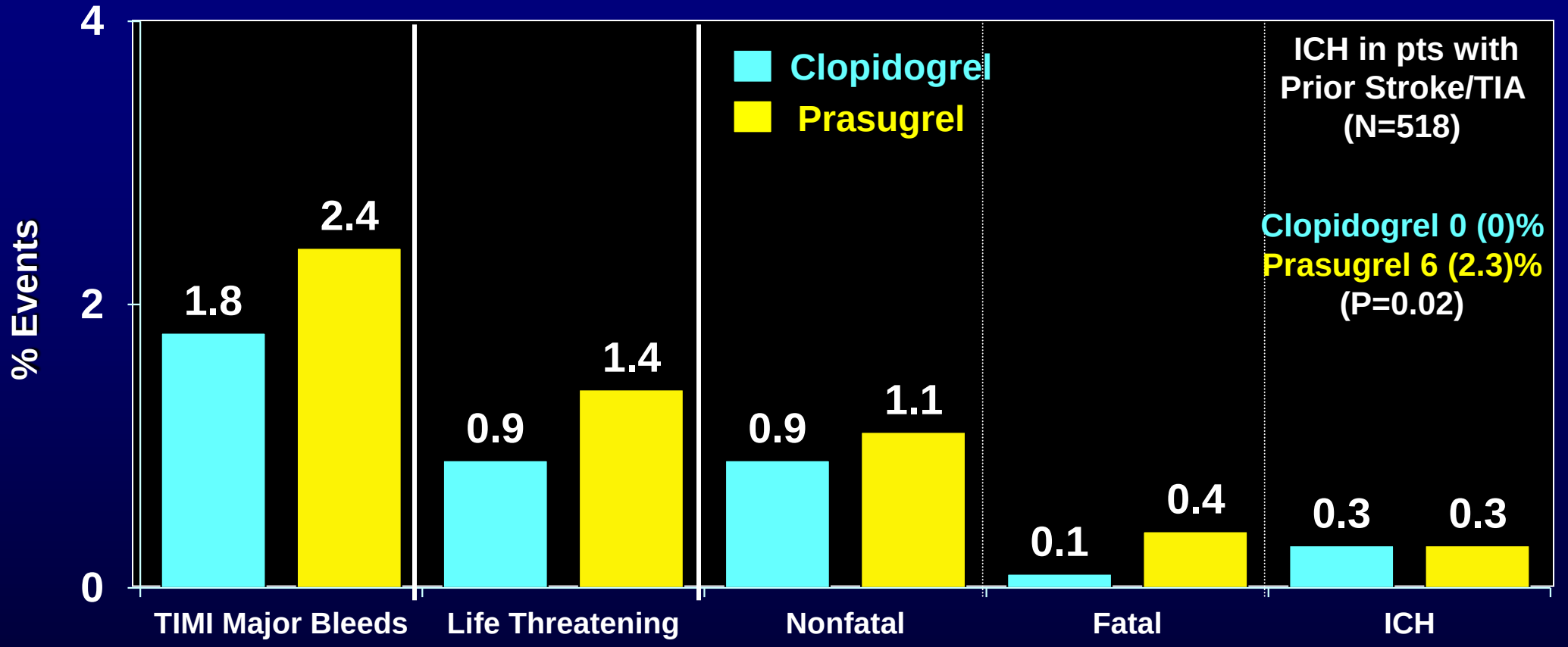


Reduction of the primary endpoint with prasugrel was similar, regardless of prior diabetes mellitus status, and consistent with a benefit of prasugrel over clopidogrel; however, greater absolute benefit with prasugrel in patients with diabetes

Wiviott et al *Circulation* 2008;118:1626-36

"Nurse Wright, when I give the signal, you slap that Band-Aid on him as fast as possible."

Bleeding Events
Safety Cohort (N=13,457)



Absolute diff.: 0.6%
Hazard Ratio 1.32
P=0.03
Number Needed to Harm=167

0.5%
HR 1.52
P=0.01

0.2%
P=0.23

0.3%
P=0.002

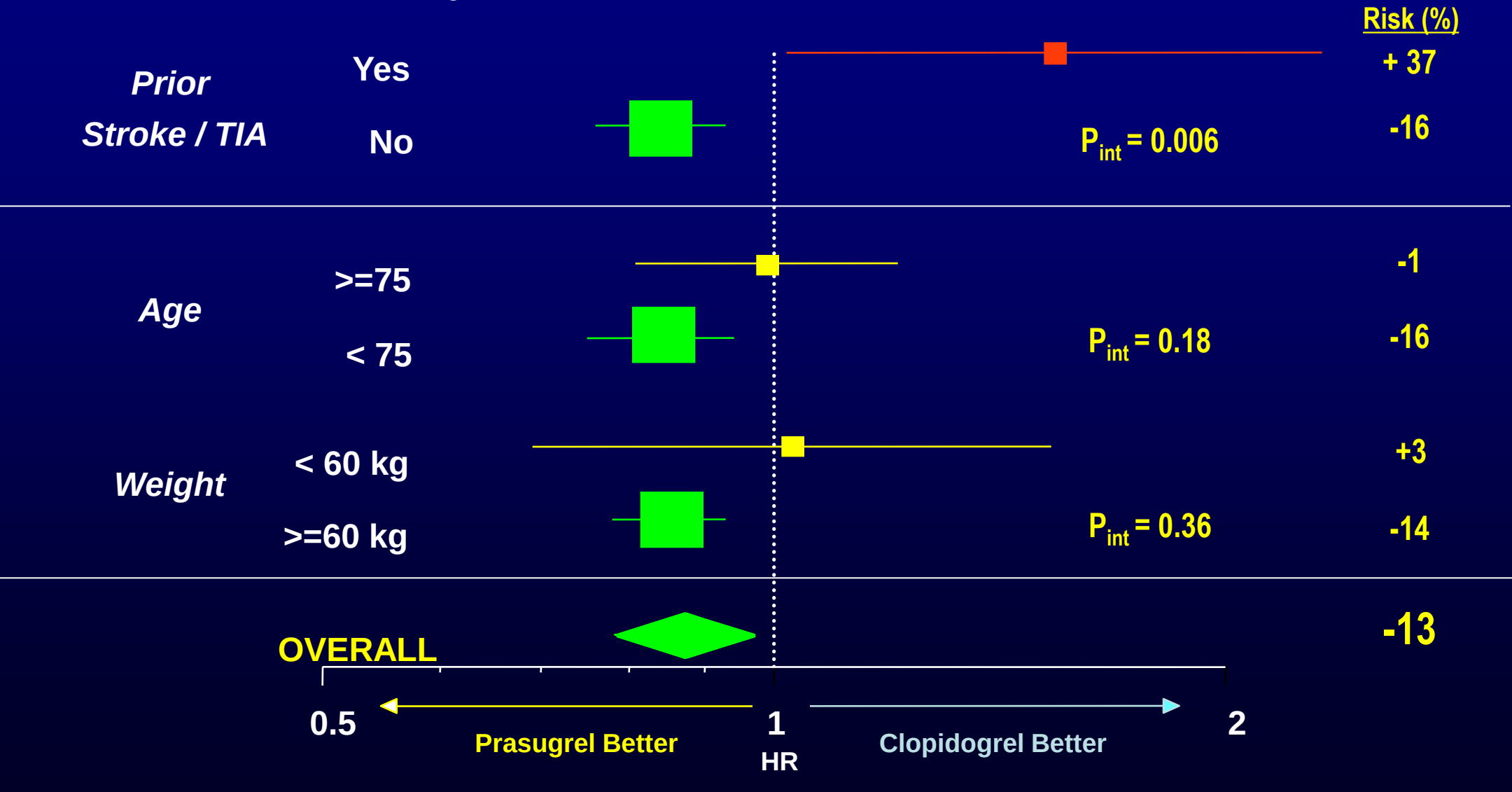
0%
P=0.74

Wiviott et al *N Engl J Med* 2007;357:2001-15

TRITON TIMI-38

Net Clinical Benefit
Bleeding Risk Subgroups
Post-hoc analysis

n=2,667: 19.6% of study population



TRILOGY ACS Study Design

Medically Managed Non-STEACS pts with ≥1 of age ≥60 yrs, prior MI, diabetes, prior revascularization

Randomization Stratified by:
Age, Country, Prior Clopidogrel Treatment
(Primary analysis cohort — Age < 75 years)

Median Time to Enrollment = 4.5 Days (2.6, 6.7)

Medical Management Decision ≤72 hrs
(No prior clopidogrel given) — 4% of total

- **Clopidogrel** 300 mg LD + 75 mg MD
- **Prasugrel** 30 mg LD + 5* or 10 mg MD

Medical Management Decision ≤ 10 days
(Clopidogrel started ≤ 72 hrs in-hospital OR on chronic clopidogrel) — 96% of total

- **Clopidogrel** 75 mg MD
- **Prasugrel** 5* or 10 mg MD

Minimum Rx Duration: 6 months; Maximum Rx Duration: 30 months

Primary Efficacy Endpoint: CV Death, MI, Stroke

All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended
* For patients <60 kg or ≥75 years, 5 mg maintenance dose (MD) of prasugrel was given.

Adapted from Chin et al *Am Heart J* 2010;160:16-22.e1

TRILOGY ACS Enrollment:

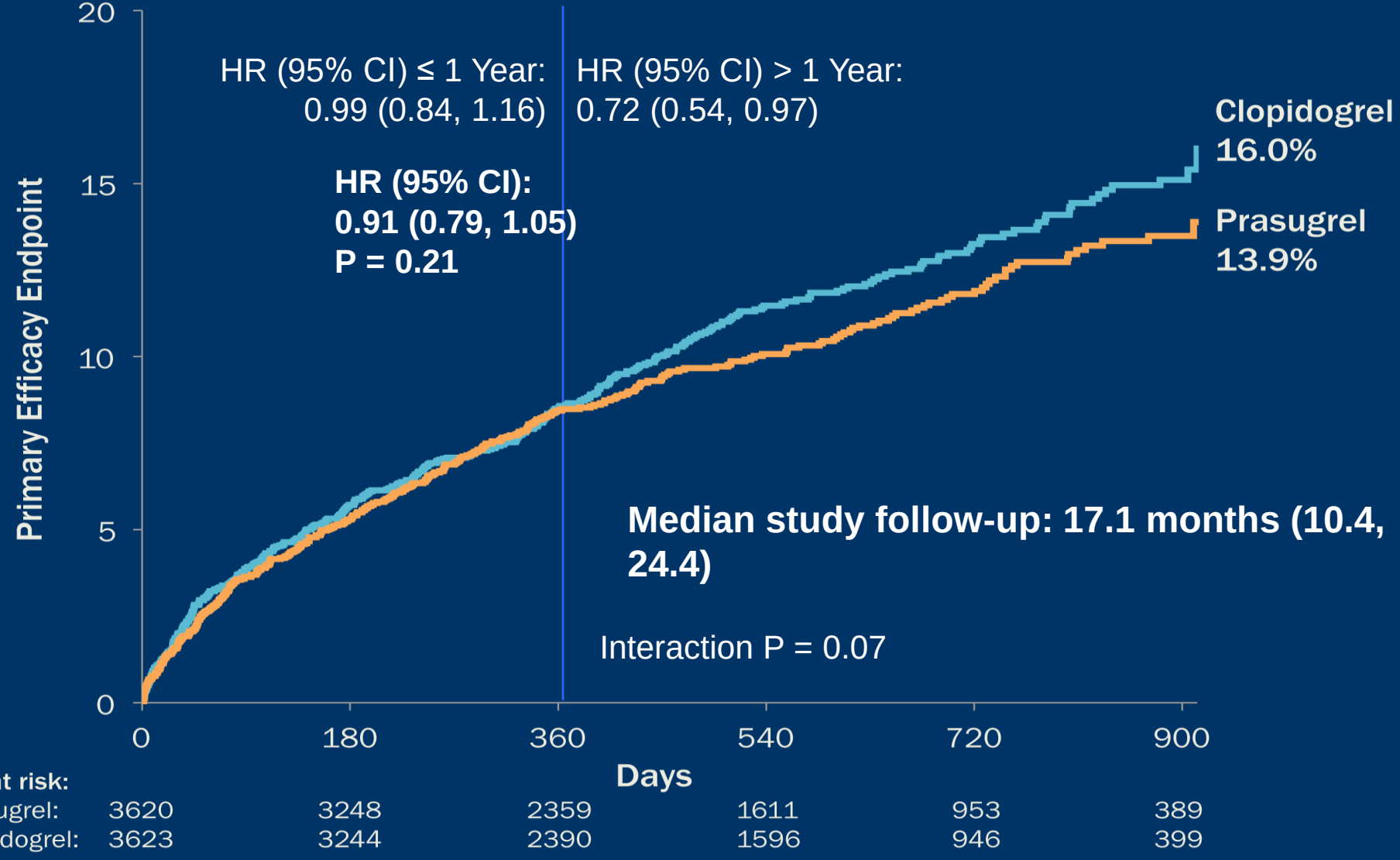
9,326 patients in 8 regions, 52 Countries

(7,243 patients < 75 years old; 2,083 patients ≥ 75 years old)

Roe et al for the TRILOGY ACS Investigators *N Engl J Med* 2012;367:1297-309

Primary Efficacy Endpoint to 30 Months

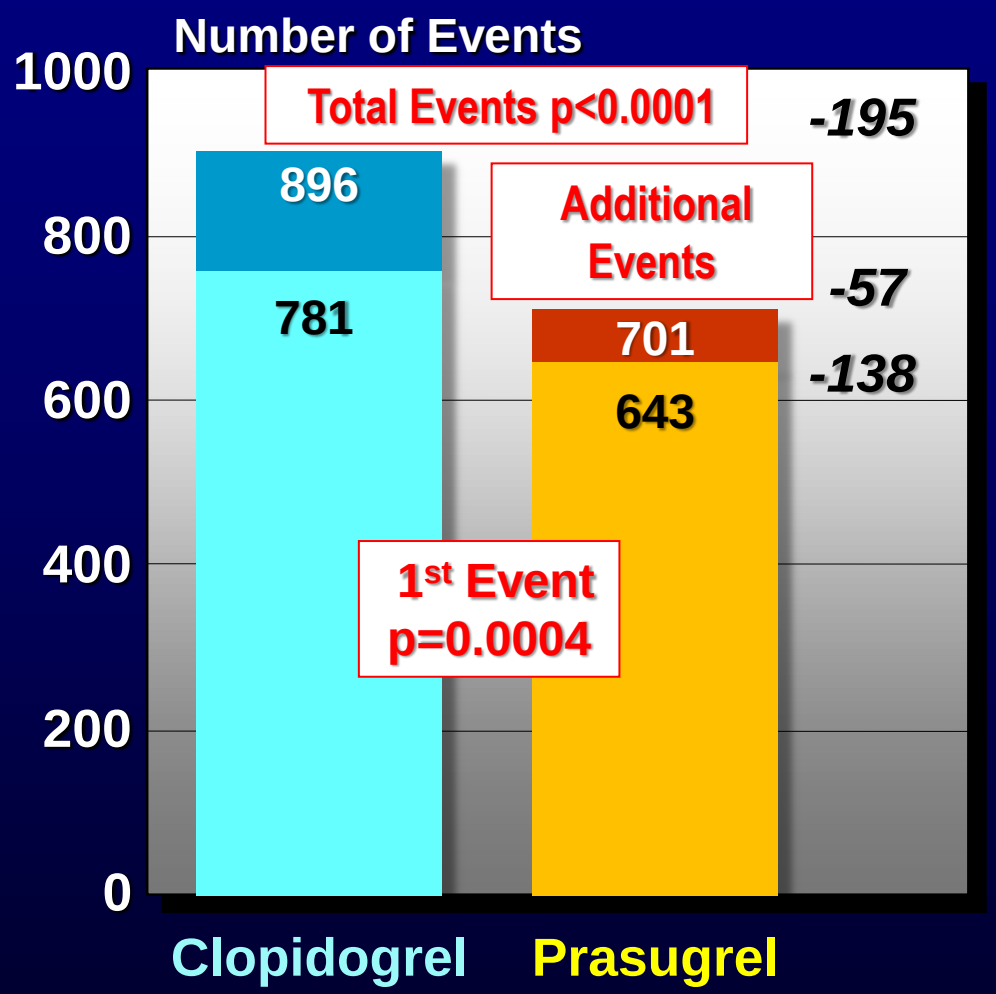
(Age < 75 years)

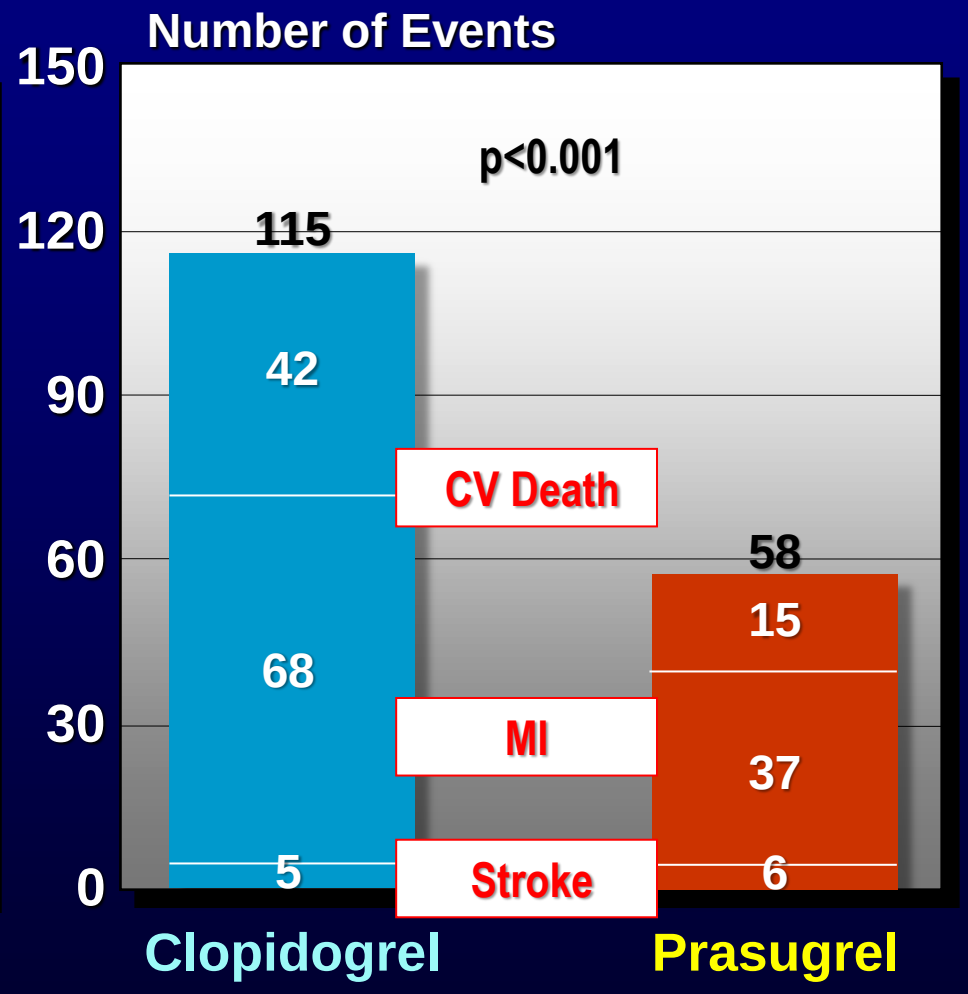


Roe et al for the TRILOGY ACS Investigators *N Engl J Med* 2012;367:1297-309

TRÎTON TIMI-38

Primary Endpoint Events Prevented





Adapted from Murphy et al *Eur Heart J* 2008;29:2473-9

Evaluation of All Ischemic Events Over Time*

(Age < 75 years)

- Lower risk multiple recurrent ischemic events suggested with prasugrel using the pre-specified Andersen-Gill model (HR = 0.85, 95% CI: 0.72–1.00, P=0.04)
- Significant interaction with treatment and time (HR for >12 months = 0.64, 95% CI: 0.48–0.86, Interaction P=0.02)

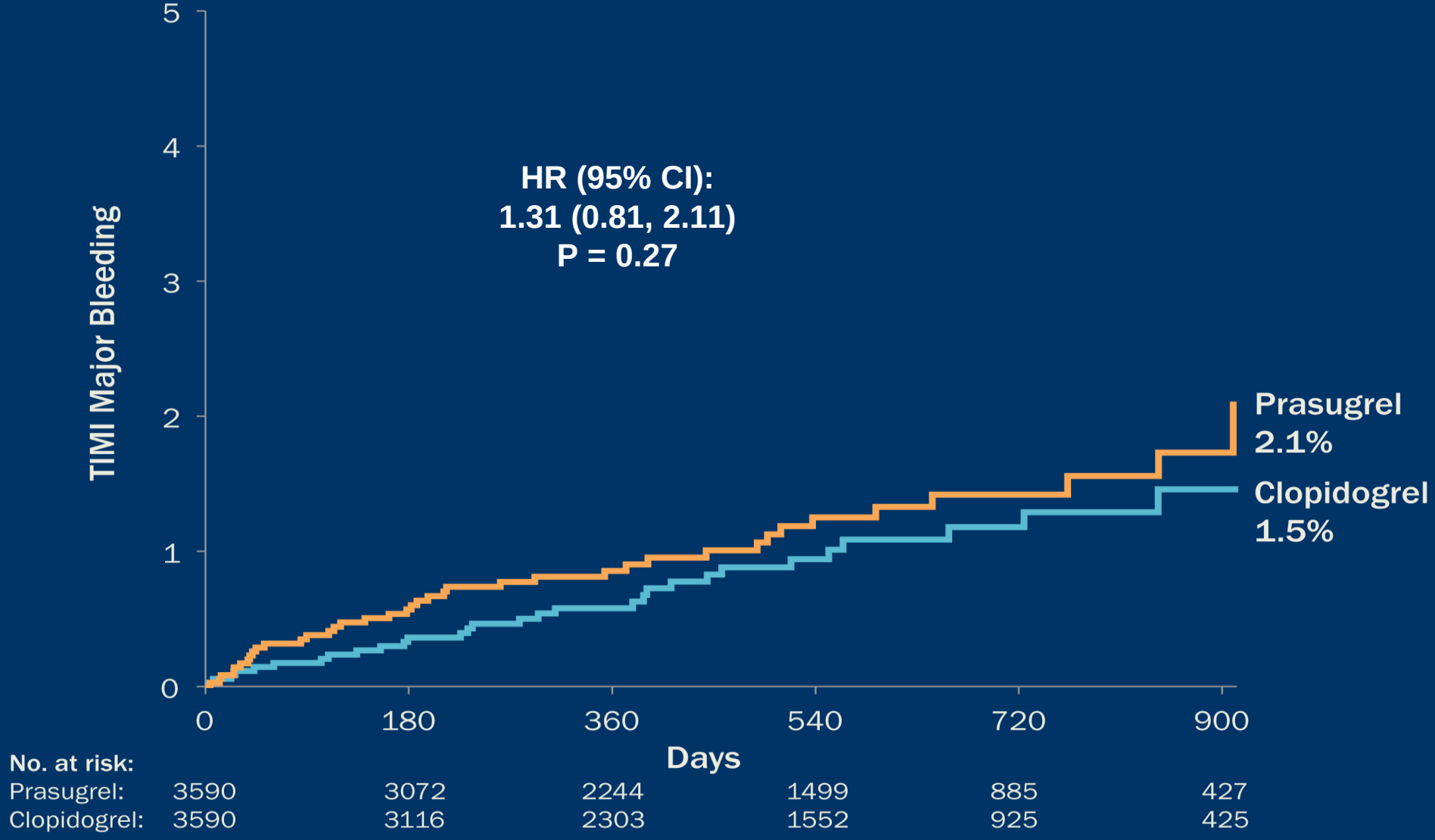
	Prasugrel	Clopidogrel
≥ 1 event	364	397
≥ 2 events	77	109
3–7 events	18	24

*** Pre-specified evaluation of all CV death, MI, or stroke events by treatment**

Roe et al for the TRILOGY ACS Investigators *N Engl J Med* 2012;367:1297-309

TIMI Major Bleeding to 30 Months

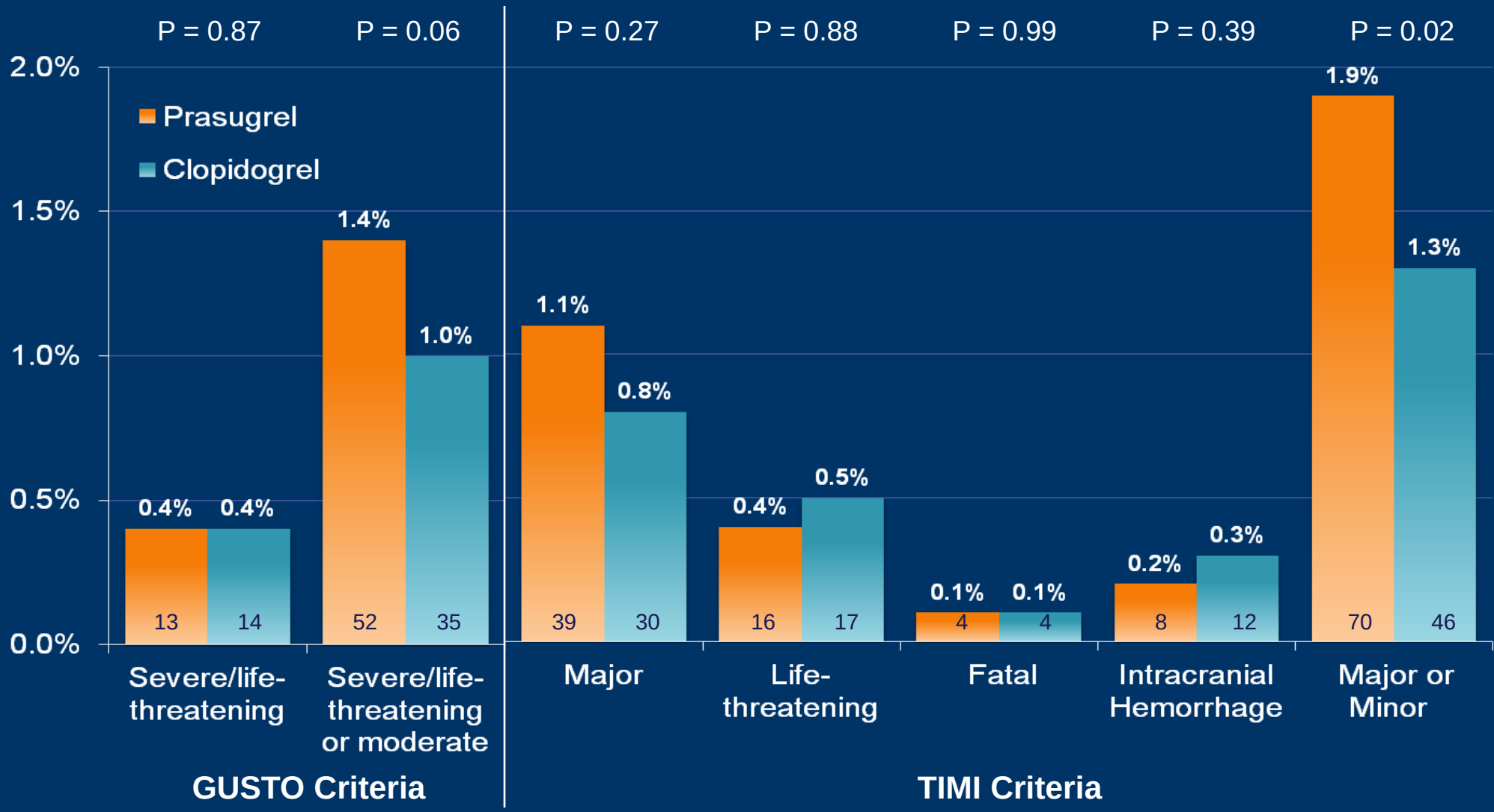
(Age < 75 years)



Roe et al for the TRILOGY ACS Investigators *N Engl J Med* 2012;367:1297-309

Incidence of Bleeding Outcomes

(Age < 75 years)



Roe et al for the TRILOGY ACS Investigators *N Engl J Med* 2012;367:1297-309

The Bottom Line

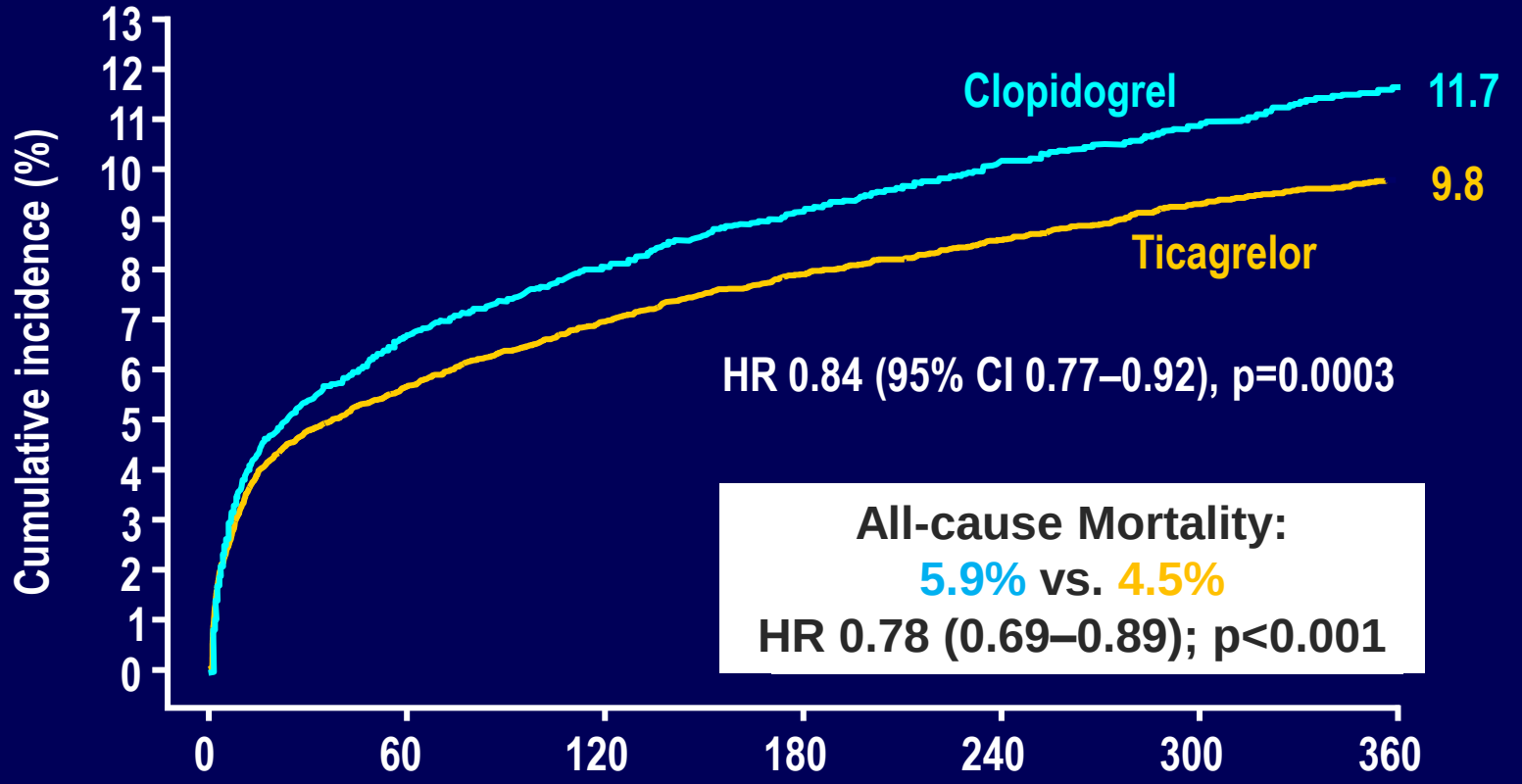
- **Prasugrel**
  - **60 mg load → 10 mg/day in ACS patients undergoing PCI x 12-15 months**
  - **Better efficacy**
  - **Higher bleeding: contraindicated in prior stroke/TIA; caution in elderly, low body weight**
  - **Which patients?**
    - **Primary PCI**
    - **Non-ST Elevation ACS (NSTEMI and UA) and STEMI (≥24 hrs post-lysis or no reperfusion therapy) patients undergoing PCI**
    - **No definitive benefit over clopidogrel in post-NSTEACS patients managed *without* revascularization**

Limitations of Clopidogrel: Options

- Give more
  - Higher loading (e.g., 600 mg) and maintenance (e.g., 150 mg/day) dose → CURRENT/OASIS 7 trial
- Find a better inhibitor of $P2Y_{12}$
  - Prasugrel
- Find a different type of $P2Y_{12}$ inhibitor
  - Ticagrelor

Time to First Primary Efficacy Event: Composite of Cardiovascular Death, MI or Stroke

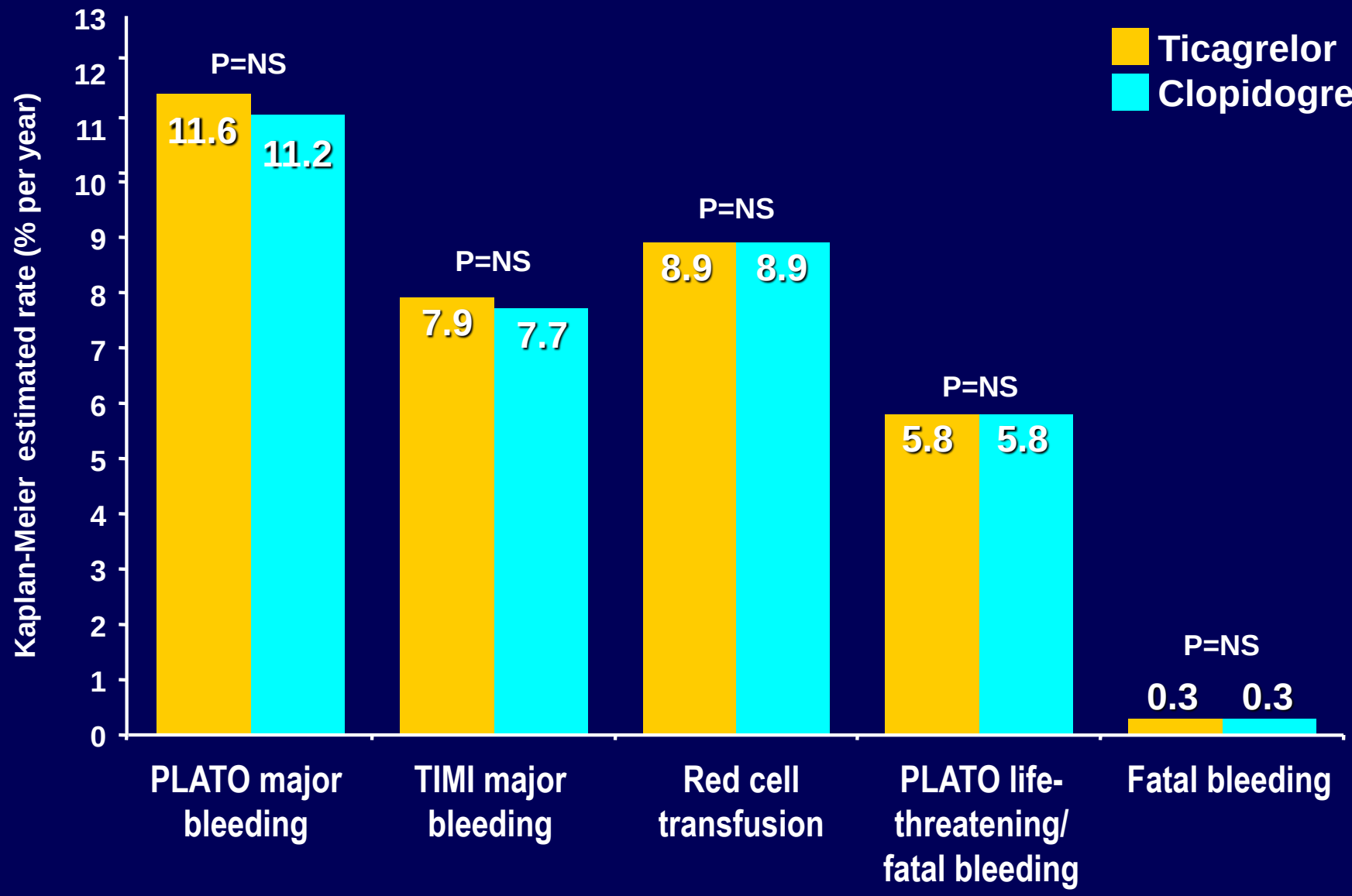
PLATO



No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

Wallentin et al for the PLATO Investigators *N Engl J Med* 2009;361:1045-57

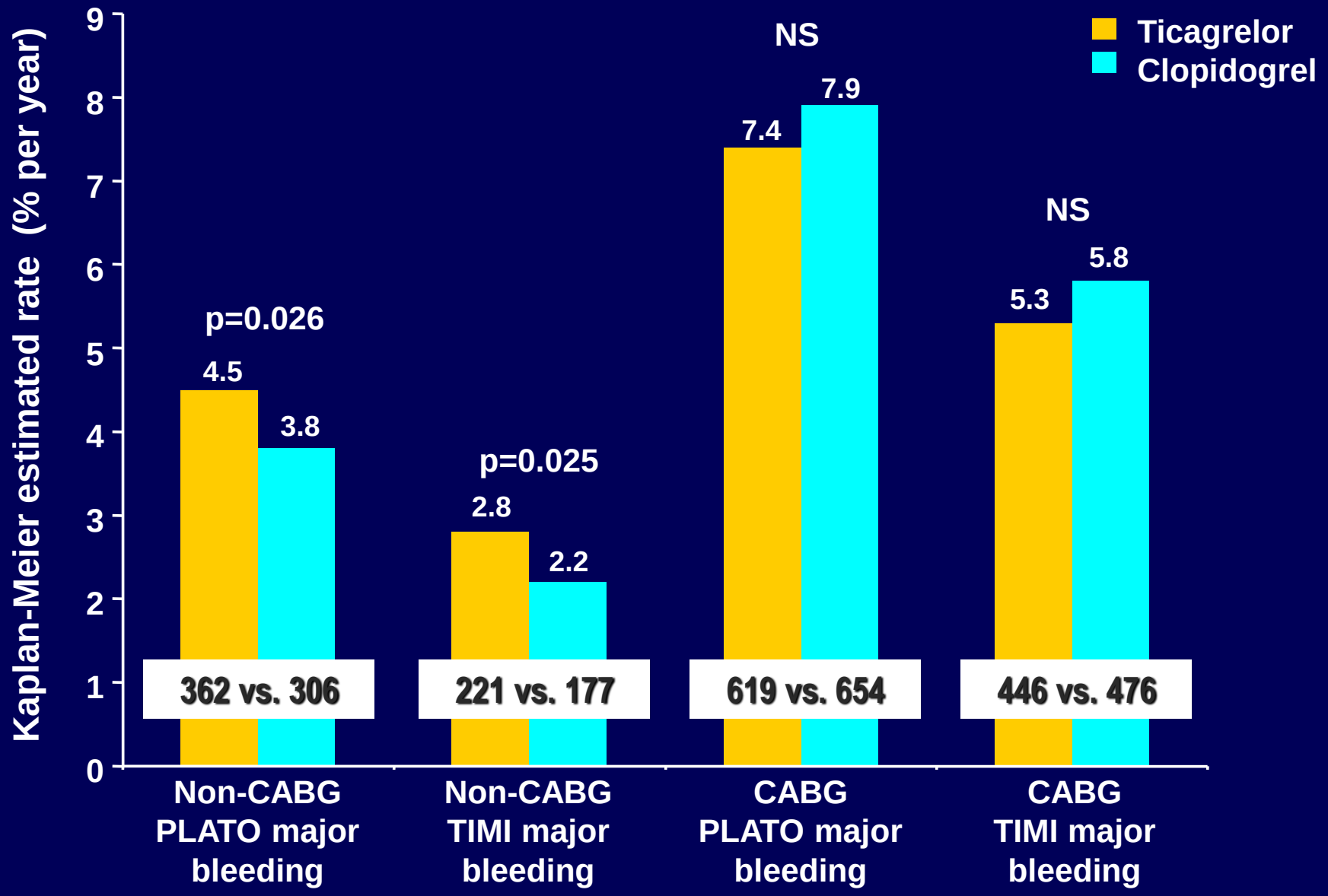
Total major bleeding



Wallentin et al *N Engl J Med* 2009;361:1045-57

Non-CABG and CABG-related Major Bleeding

PLATO



Wallentin et al *N Engl J Med* 2009;361:1045-57

Dyspnea

PLATO

Dyspnea	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value
Any	13.8	7.8	<0.001
With discontinuation of study treatment	0.9	0.1	<0.001

Wallentin et al *N Engl J Med* 2009;361:1045-57

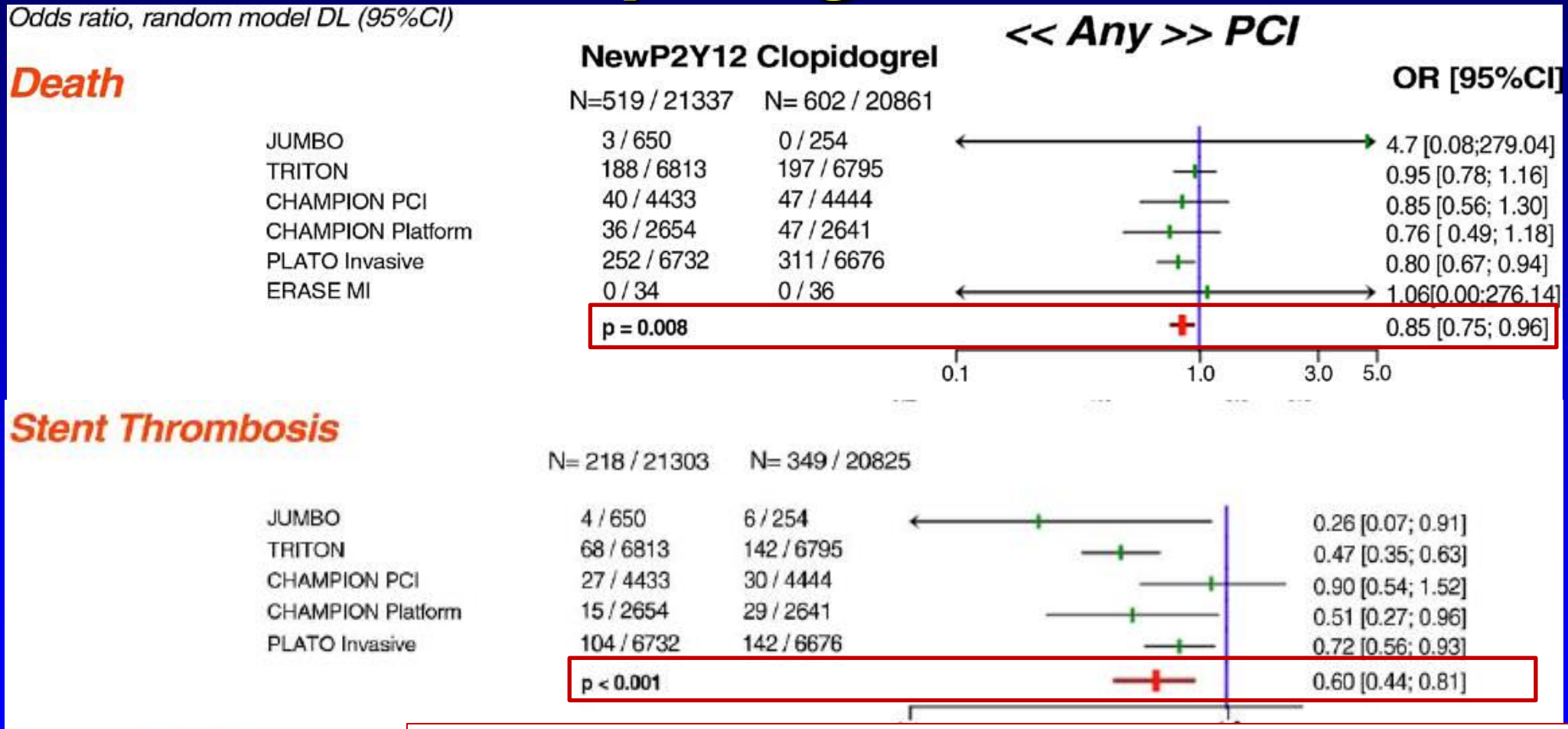
- Dyspnea classified as severe in 0.4% vs. 0.3%[1]
- Ticagrelor-induced dyspnea is "reversible" upon discontinuation[1]
- No significant changes in cardiopulmonary function parameters[2,3]
- Dyspnea not related to heart failure (HF) or respiratory disease[1]
- Likely due to alteration of adenosine metabolism[4]: ticagrelor inhibits reuptake[4], increases ATP production[5] → increased adenosine concentrations

[1] Storey et al *Eur Heart J* 2011;32;2945-53; [2]Storey et al *J Am Coll Cardiol* 2010;56:185-93
[3] Storey et al *Am J Cardiol* 2011;108:1542-46; [4]Wittfeldt et al *J Am Coll Cardiol* 2013;61:723-7
[5]Van Giezen et al *J Cardiovasc Pharmacol Therapeut* 2011;17:164-72;
[5]Ohman et al *J Am Coll Cardiol* 2012;59:E556

The Bottom Line

- Ticagrelor
  - 180 mg → 90 mg twice daily x 1 year
    - BID dosing but antiplatelet effect 24 hours after last dose is similar to clopidogrel
  - Better efficacy (including mortality reduction) with modest increase in bleeding
  - Increased rates of dyspnea
    - No significant changes in cardiopulmonary function, usually mild/transient and reversible in PLATO; however, more patients will discontinue therapy
  - Which patients?
    - Entire spectrum of ACS pts that would otherwise be considered for clopidogrel (except for fibrinolytic-treated STEMI pts)

New ADP Receptor Antagonists vs. Clopidogrel in PCI



STEMI subgroup: significant decrease in death (22%), MACE (16%), and stent thrombosis (33%)

ESC Guideline Recommendations

In Primary PCI (STEMI)

An ADP-receptor blocker is recommended in addition to aspirin. Options are:	I	A
• Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age <75 years.	I	B
• Ticagrelor.	I	B
• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C

Steg et al *Eur Heart J* 2012;33:2569-619

In NSTEACS (NSTEMI/UA)

Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins) , regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.[d]	I	B
Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A

New ADP Receptor Inhibitors recommended over Clopidogrel


IN CASE OF EMERGENCY
PANEL OF EXPERTS