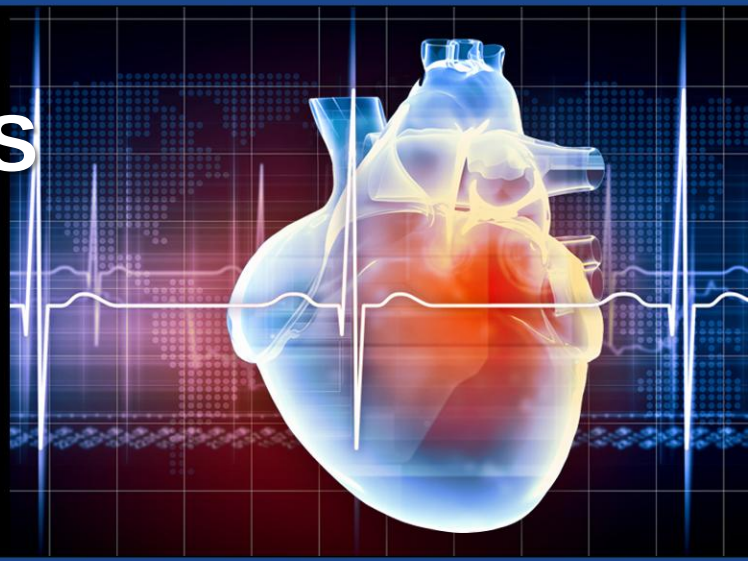
Antiplatelet Therapy in ACS Patients: New P2Y12 Inhibitor is Preferred



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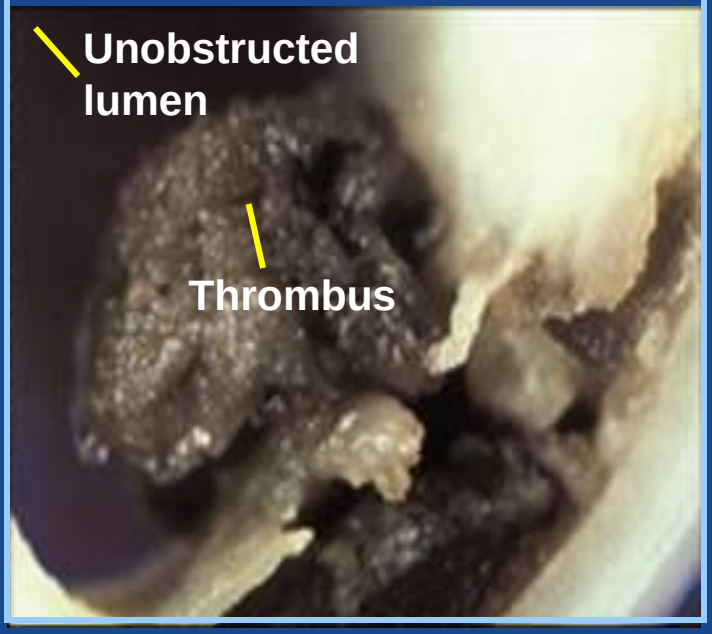
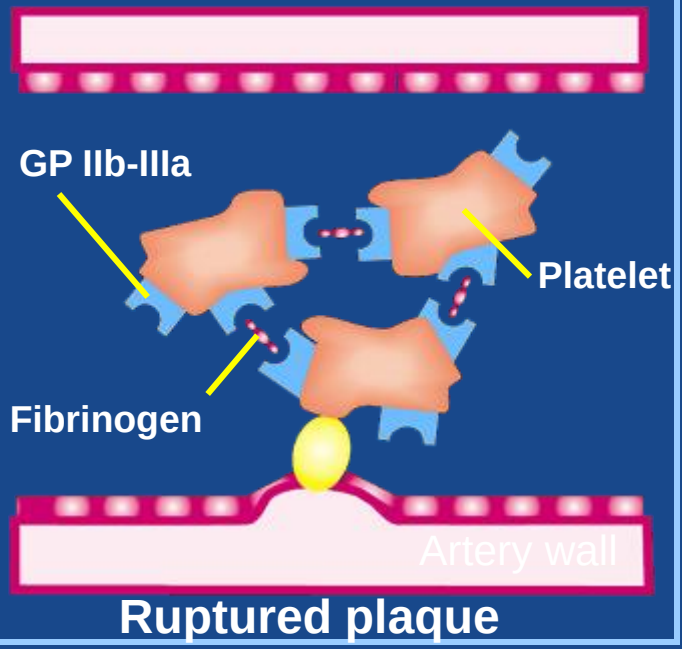
Los Angeles, CA

The Role of the Platelet in Non-ST Elevation Acute Coronary Syndrome

NSTE ACS is generally caused by partially occlusive, platelet-rich thrombus

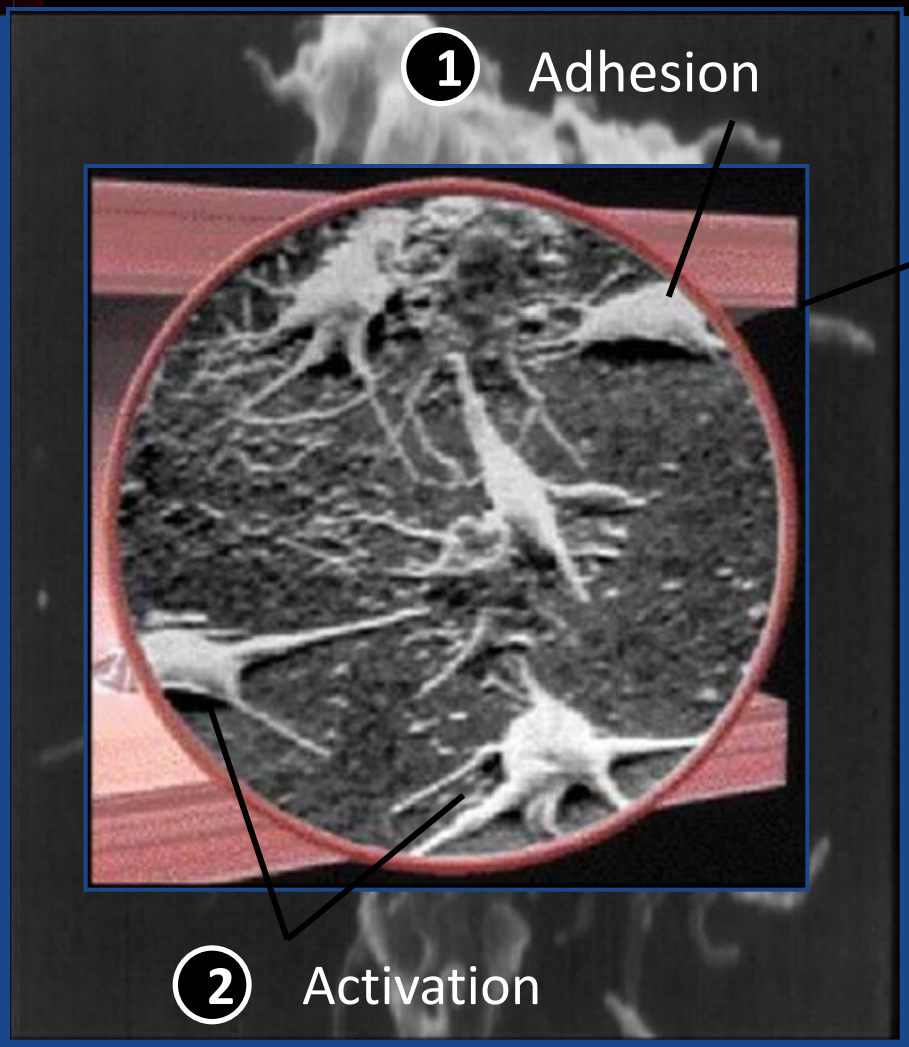


Results from cross-linking of platelets by fibrinogen at platelet receptors GP IIb-IIIa at site of plaque rupture



Van de Werf F. *Thromb Haemost*. 1997;78(1):210-213; Moser M, et al. *J Cardiovasc Pharmacol*. 2003;41(4): 586-592; Davies MJ. *Heart*. 2000;83(3):361-366.

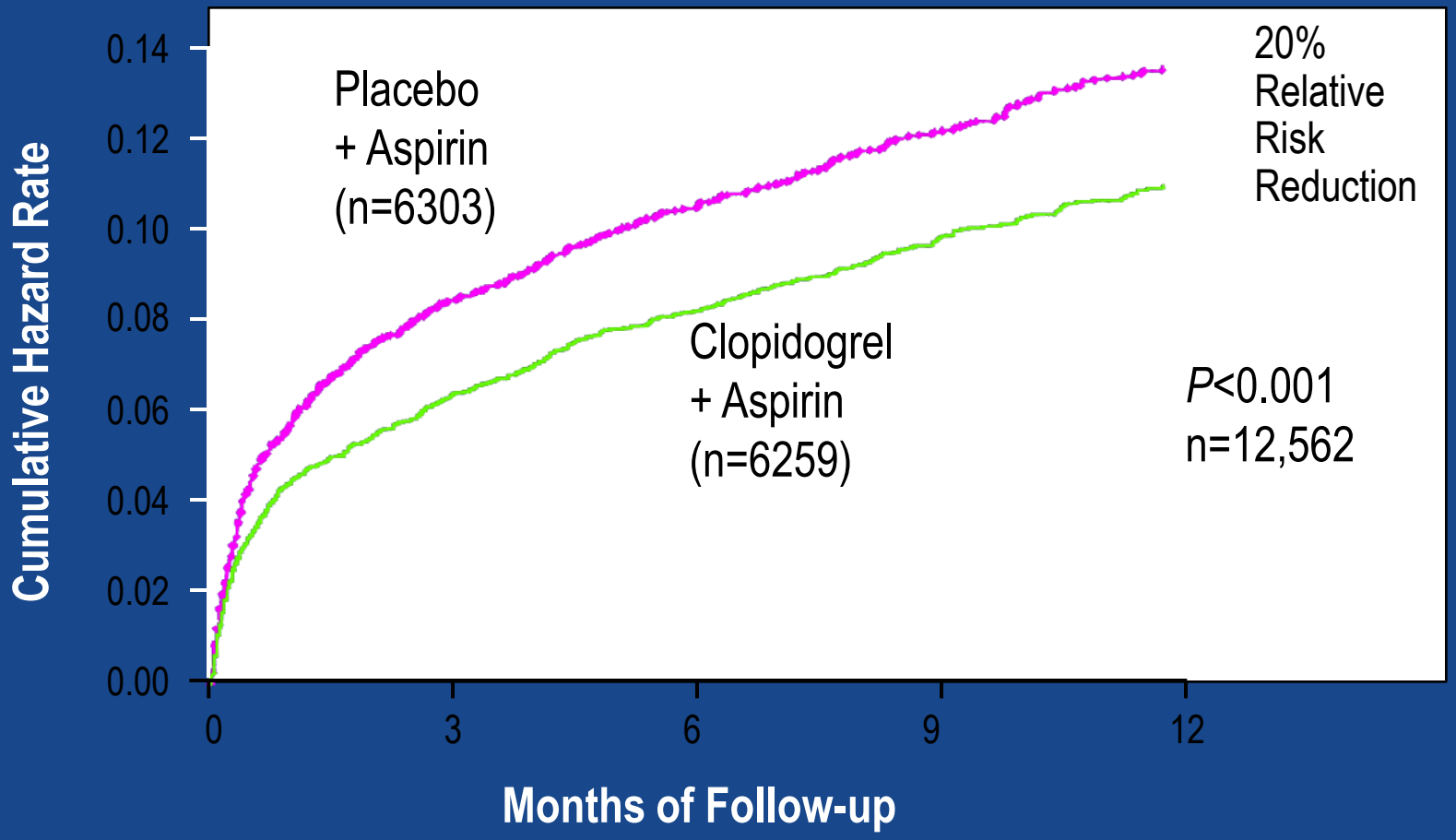
The Role of Platelets in Atherothrombosis



Slide modified from Cannon CP, et al. Available at http://www.theheart.org/viewArticle.do?primaryKey=119759. Accessed April 20, 2005.

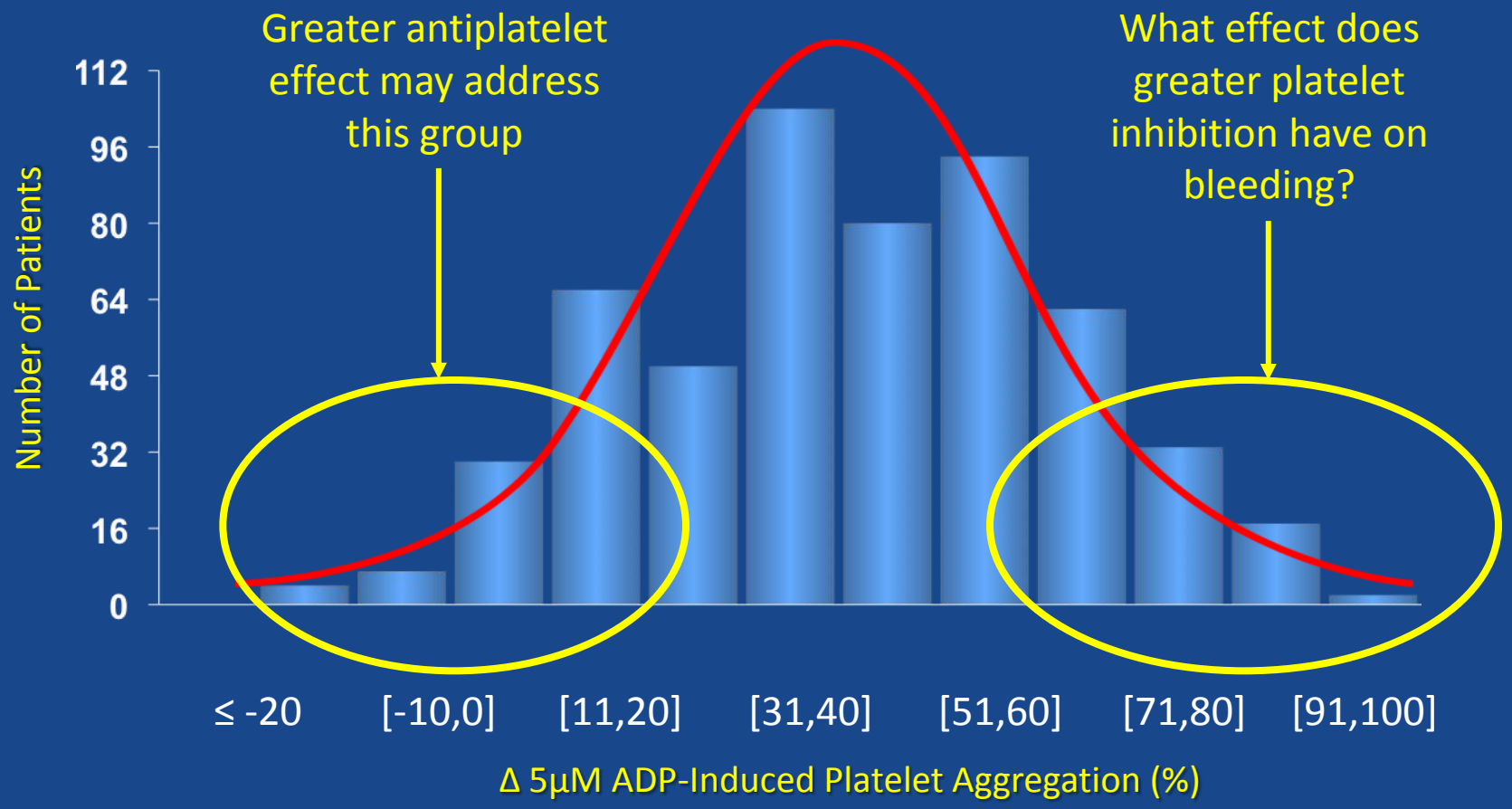
CURE Study

Primary End Point: MI/Stroke/CV Death



Yusuf S et al. *N Engl J Med.* 2001;345:494-502.

IPA Responses to Clopidogrel



Adapted from: Serebruany V et al. J Am Coll Cardiol. 2005.

Biotransformation of Clopidogrel

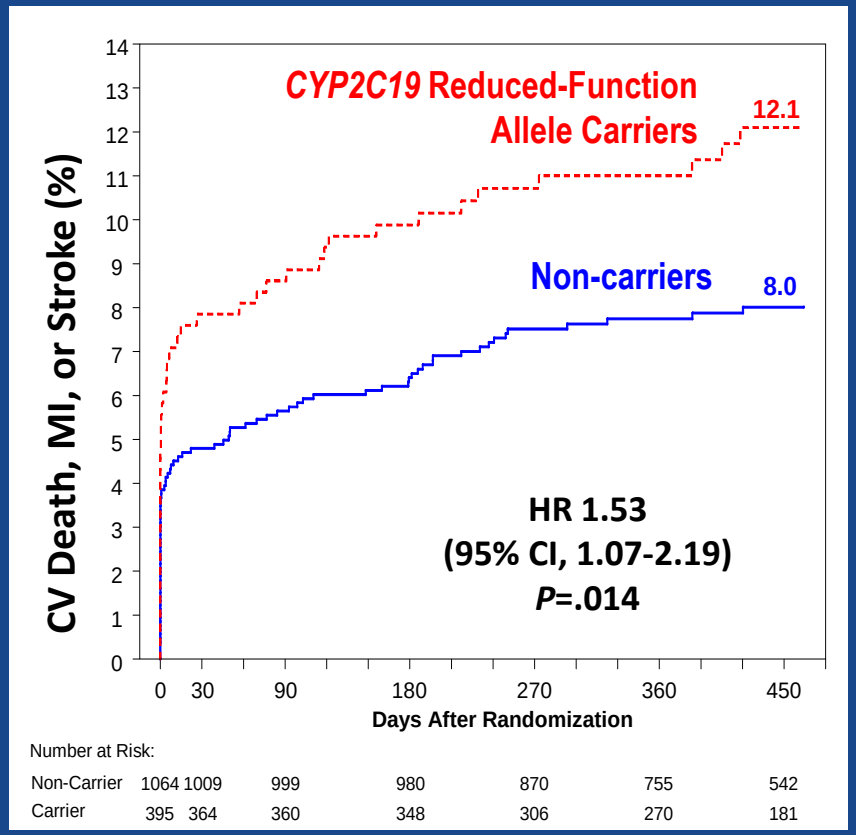
- Clopidogrel is a prodrug that requires conversion to its active metabolite.[1]
  - 2-step process mediated by CYP450s, with CYP2C19 involved in both steps
- A substantial portion of absorbed clopidogrel is shunted into a dead-end pathway by esterases.[2]

1. Price MJ, *J Am Coll Cardiol*. 2014;64:1015-1018 2. Tang M et al, *J Pharmacol Exp Ther*. 2006;319:1467-76.

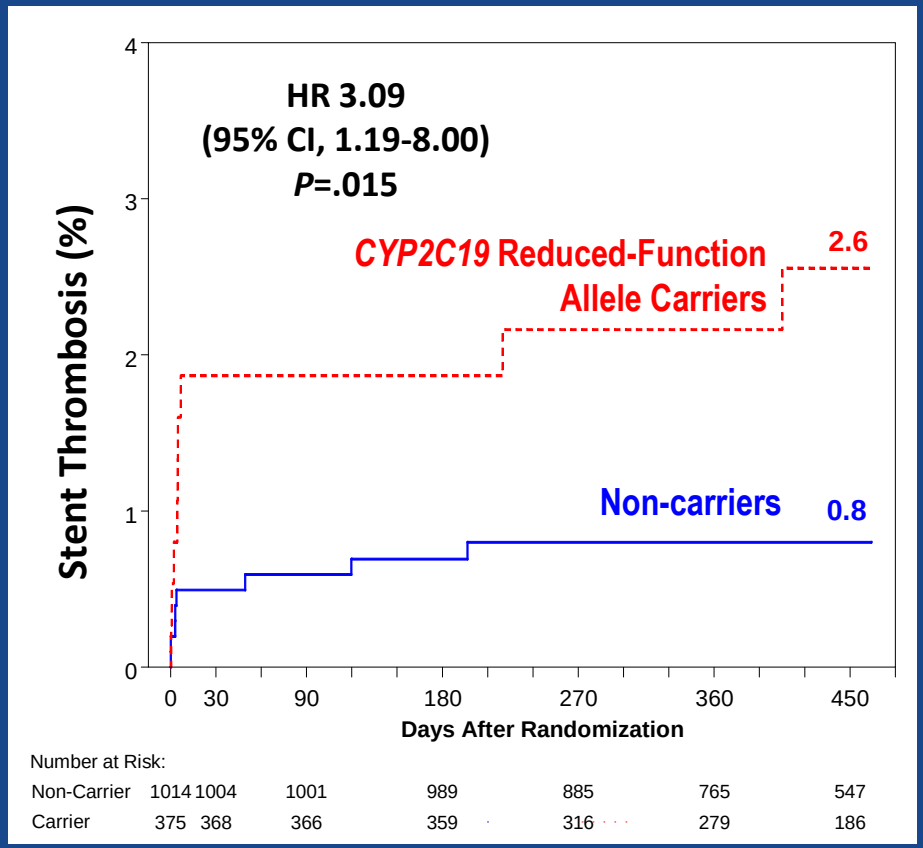
CYP2C19 Genotype, Clinical Outcomes

1477 Patients w/ ACS and planned PCI Rx'd w/ clopidogrel

CV events



Stent Thrombosis



Carriers ~30% of the population

CV, cardiovascular; HR, hazard ratio; CI, confidence interval

TRITON-TIMI 38: Prasugrel vs Clopidogrel

Study Design

STEMI, NSTEMI, or unstable angina with known suitable coronary anatomy scheduled to undergo PCI (N=13,608)

Randomization prior to PCI

Clopidogrel	**Prasugrel**
Standard 300-mg loading dose, after PCI 75-mg qd maintenance	**60-mg loading dose, then after PCI 10-mg qd maintenance**
Aspirin, recommended daily dose 75-162 mg qd	**Aspirin, recommended daily dose 75-162 mg qd**

6-15–month exposure

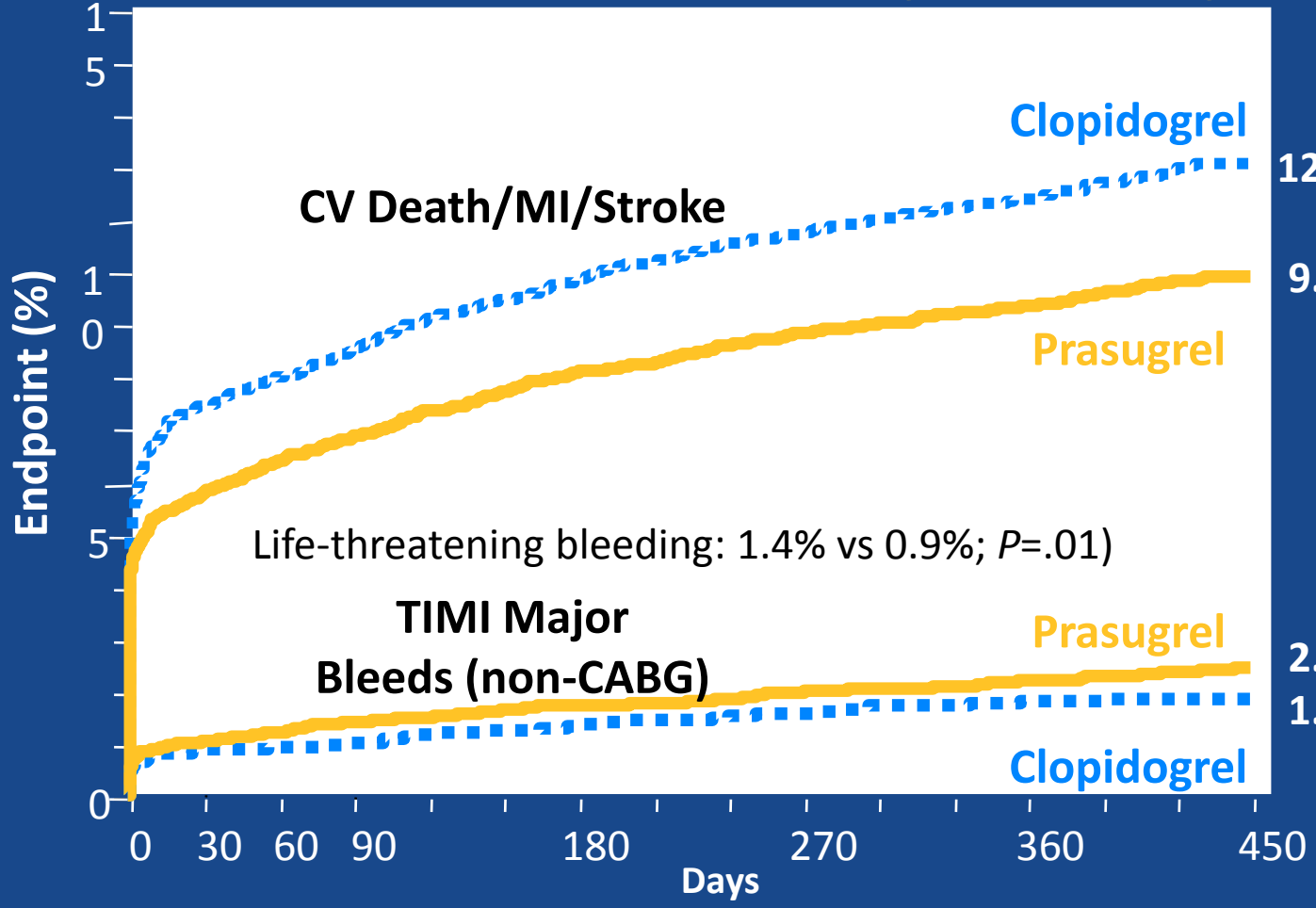
Primary endpoint: CV Death + MI + Stroke
Primary safety endpoint: TIMI Major Bleeding (non-CABG)

TRITON-TIMI, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in MI

Wiviott SD et al. *N Engl J Med.* 2007;357:2001-2015.

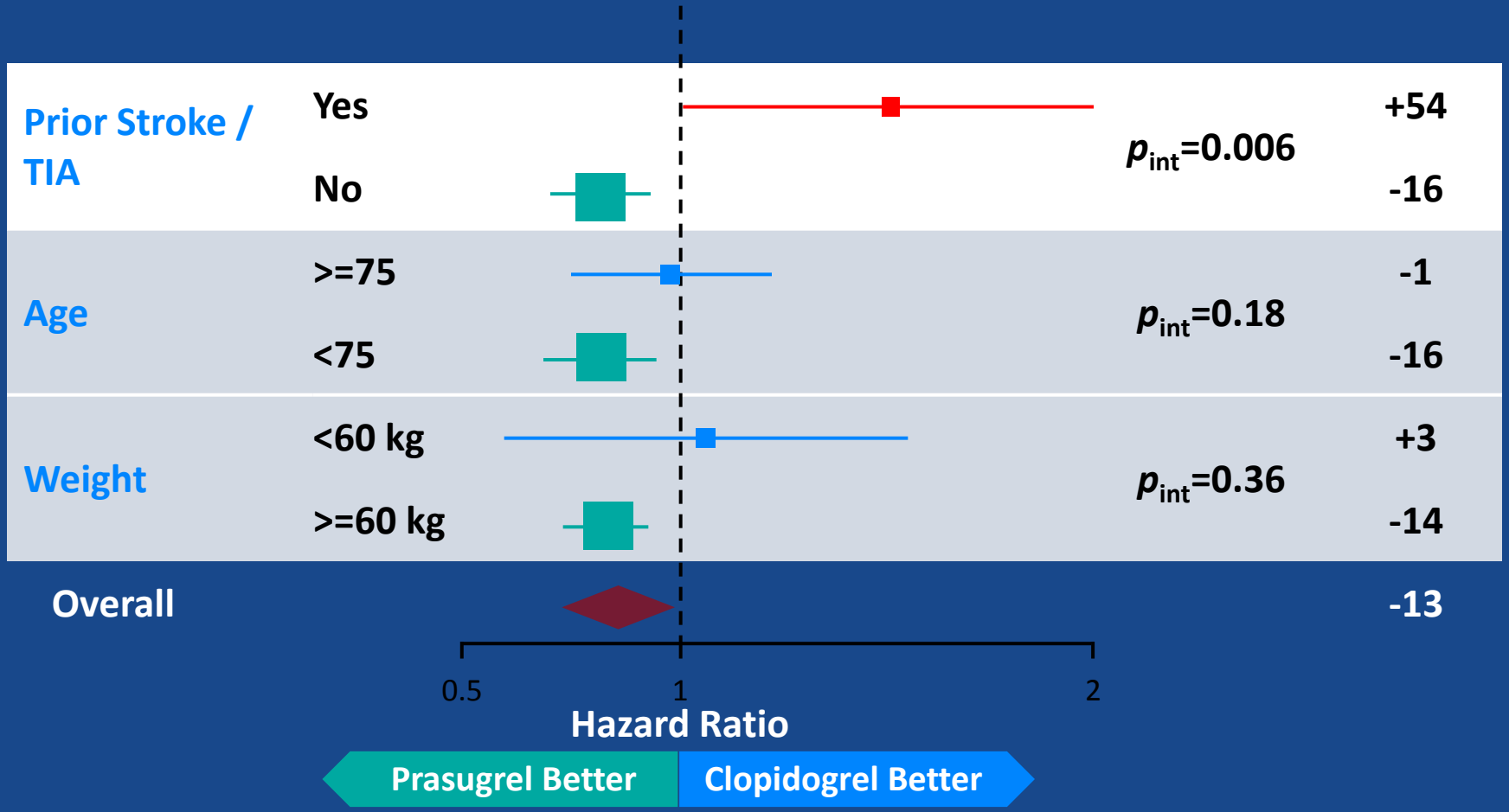
TRITON-TIMI 38: Prasugrel vs Clopidogrel

Balance of Efficacy and Safety



Wiviott SD et al. *N Engl J Med.* 2007;357:2001-2015.

Balancing Efficacy and Bleeding
TRITON TIMI-38: Net Clinical Benefit



TRITON TIMI-38 = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38.

Wiviott SD, et al. *NEJM*. 2007;357:2001-2015.

Prasugrel Summary

- Third-generation oral thienopyridine[1]
- Oral prodrug, hydrolyzed more efficiently vs clopidogrel[1]
  - Faster onset of action
  - More potent antiplatelet effect
  - Reduced variability
  - Less impact of drug-drug interactions, genetic polymorphisms
- **TRITON-TIMI 38:** Significantly reduced rates of ischemic events, but increased risk of major (and fatal) bleeding, in patients with ACS scheduled for PCI[1]
- Contraindicated in patients with history of stroke or TIA[2]
- Consider dose reduction in patients with age >75 or weight <60 kg[2]

1. Capodanno D et al. *J Thromb Haemost.* 2013;11(suppl 1):316-329.
2. Eli Lilly and Co. Effient package insert. 2012.

PLATO: Ticagrelor vs Clopidogrel in ACS

Study Design

NSTE-ACS (moderate-to-high risk), STEMI (if primary PCI)
clopidogrel-treated or -naïve;
randomized within 24 hours of index event
(N=18,624)

Randomization

Clopidogrel
If pretreated, no additional loading dose;
if naïve, standard 300-mg loading dose,
then 75-mg qd maintenance
(additional 300 mg allowed pre-PCI)

Ticagrelor
180-mg loading dose, then
90-mg BID maintenance
(additional 90 mg pre-PCI)

6-12–month exposure

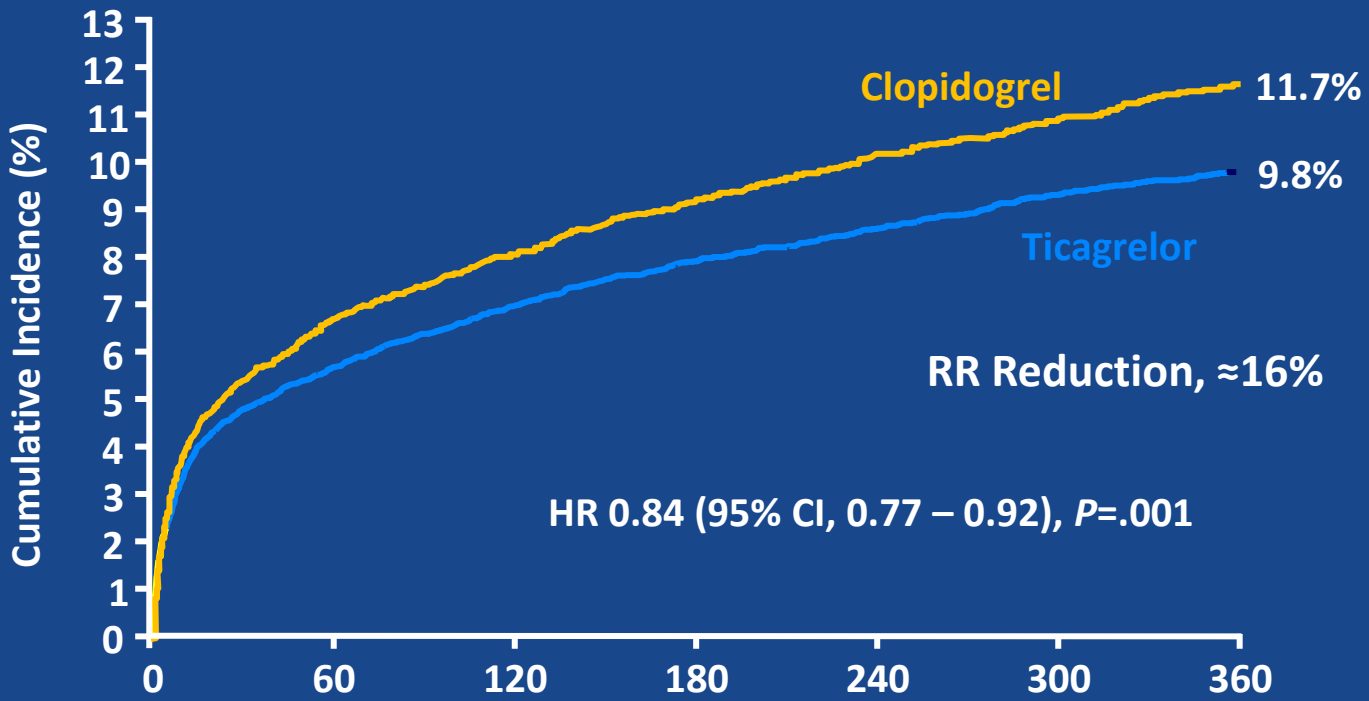
Primary endpoint: CV death + MI + stroke
Primary safety endpoint: total major bleeding

PLATO, Platelet Inhibition and Patient Outcomes

Wallentin L et al. *N Engl J Med*. 2009;361(11):1045-1057.

PLATO: Ticagrelor vs Clopidogrel in ACS

Time to Primary Efficacy Endpoint*



Number at risk:

Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6650	5096	4047

*Composite of CV death, MI, or stroke

Wallentin L et al. *N Engl J Med*. 2009;361(11):1045-1057.

PLATO: Clopidogrel vs Ticagrelor

Major Efficacy Endpoints at 12 Months, Total Cohort

ENDPOINT*	Ticagrelor (n=9333)	Clopidogrel (n=9291)	Ticagrelor HR (95% CI)	*P* value†
Primary endpoint, %				
Death from vascular causes/MI/ stroke	9.8	11.7	0.84 (0.77–0.92)	<.001
Secondary endpoints, %				
Death from any cause/MI/stroke	10.2	12.3	0.84 (0.77–0.92)	<.001
Death vascular cause/MI/ stroke/SRI/TIA/arterial thrombotic events	14.6	16.7	0.88 (0.81–0.95)	<.001
MI	5.8	6.9	0.84 (0.75–0.95)	.005
Death vascular causes	4.0	5.1	0.79 (0.69–0.91)	.001
Stroke	1.5	1.3	1.17 (0.91–1.52)	.22
All-cause mortality	4.5	5.9	0.78 (0.69–0.89)	<.001

*Percentages are K-M estimates of the rate of the endpoint at 12 mo; patients could have had >1 type of endpoint

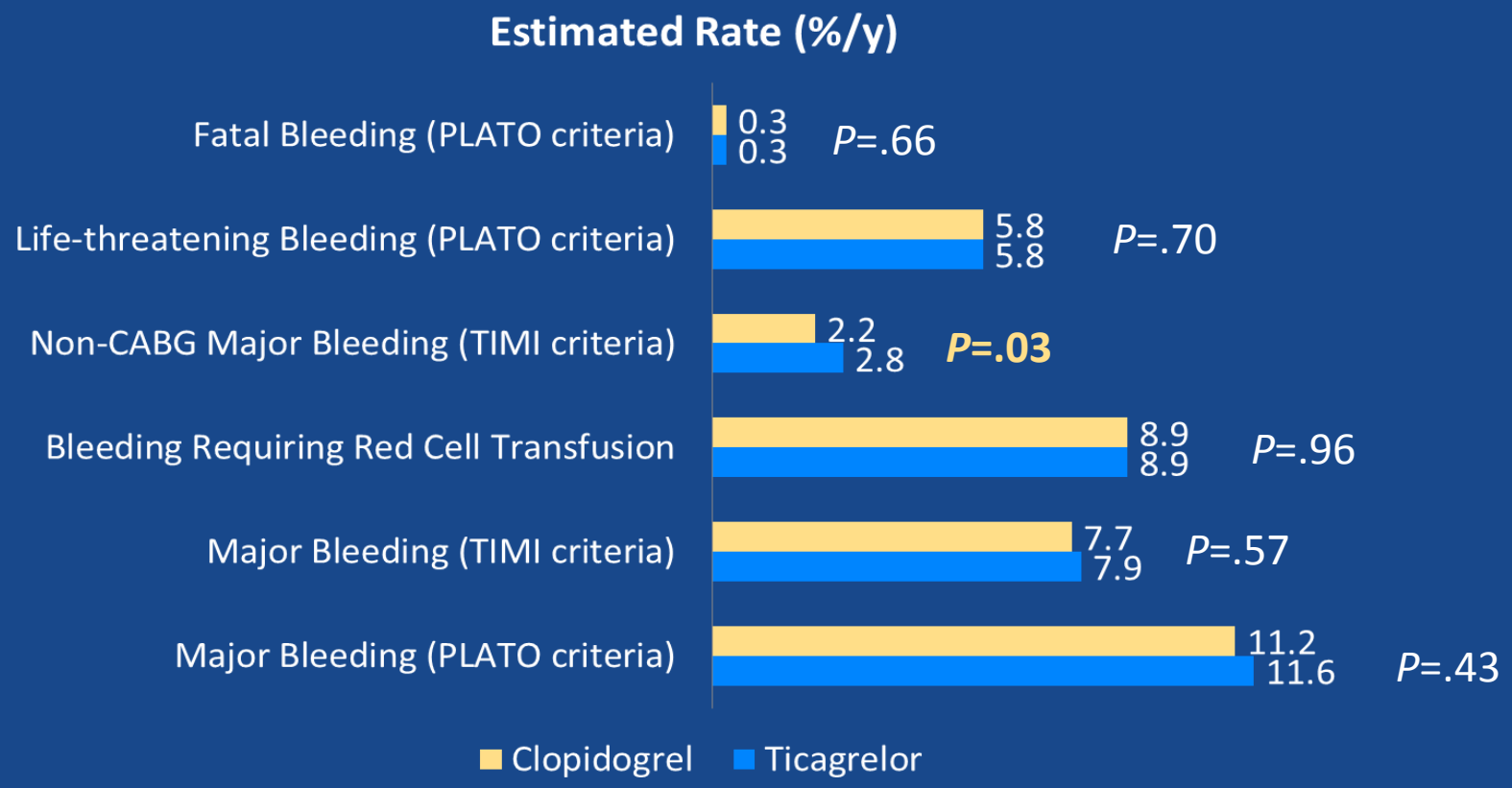
†By Cox regression analysis

SRI, severe recurrent ischemia

Wallentin L et al. *N Engl J Med*. 2009;361(11):1045-1057.

PLATO: Ticagrelor vs Clopidogrel in ACS

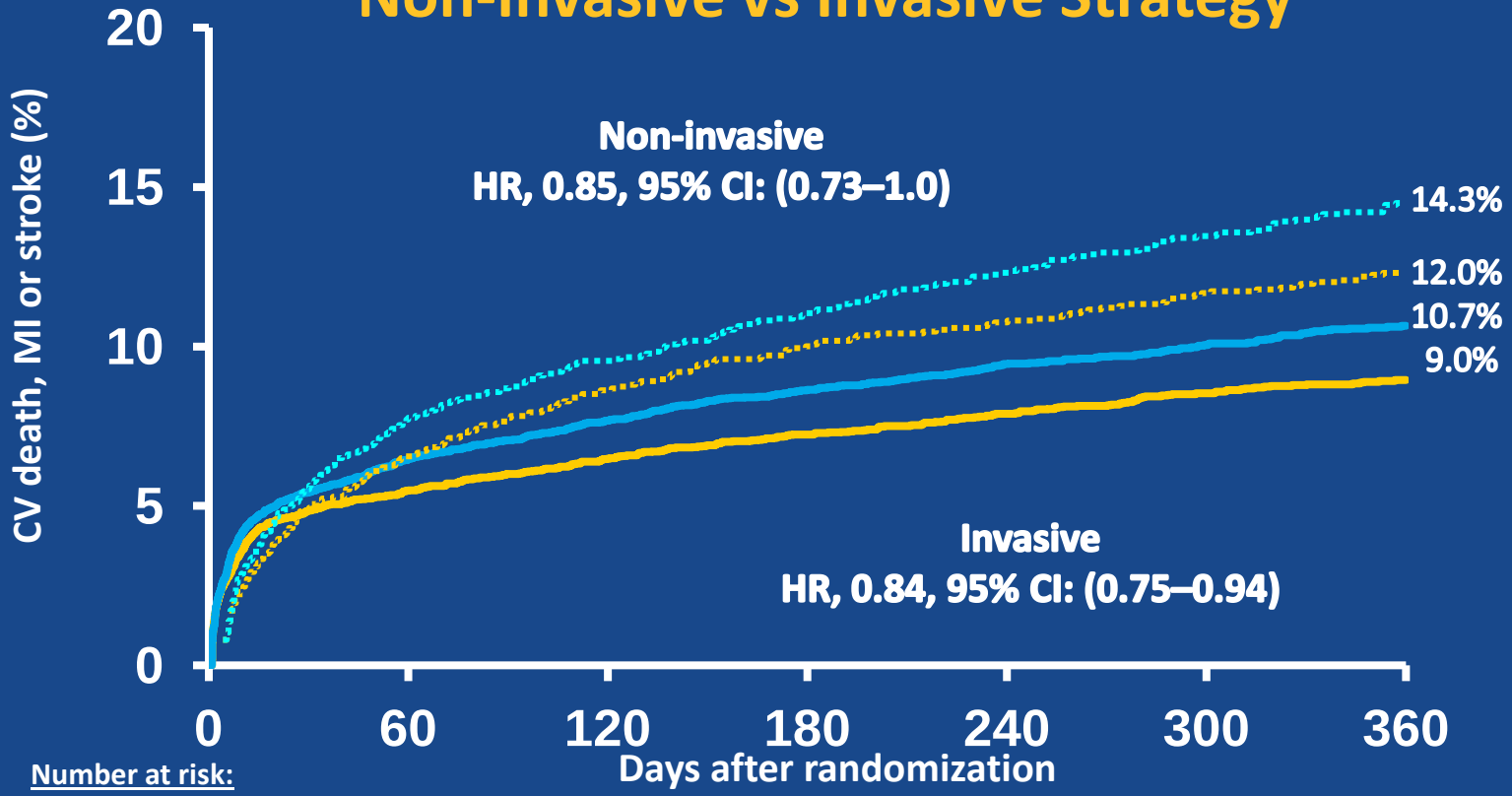
Major Bleeding



Wallentin L et al. *N Engl J Med*. 2009;361(11):1045-1057.

PLATO: Ticagrelor vs Clopidogrel in ACS

Non-Invasive vs Invasive Strategy

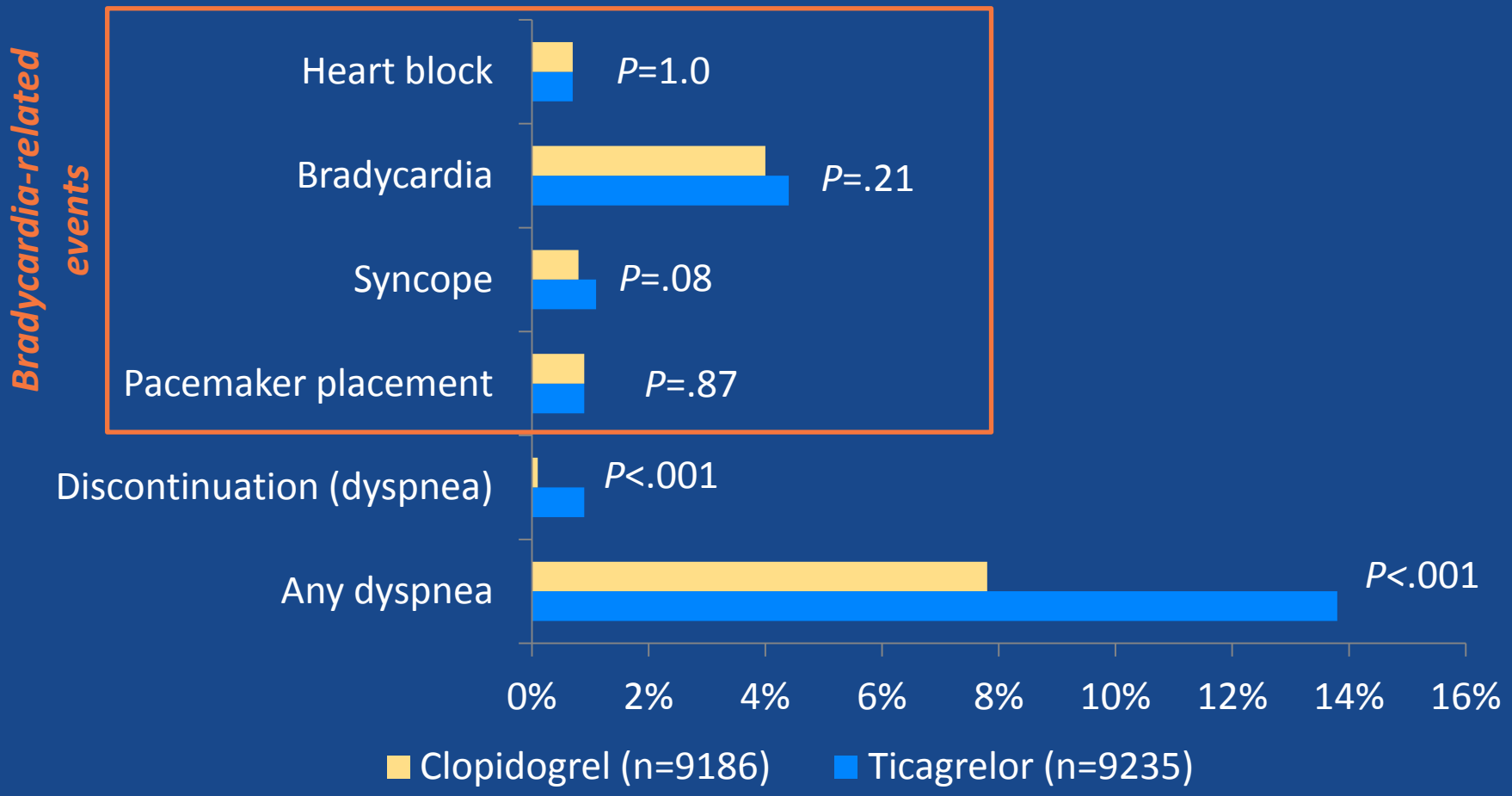


Number at risk:							
Invasive							
Ticagrelor	6732	6236	6134	5972	4889	3735	3048
Clopidogrel	6676	6129	6034	5881	4815	3680	2965
Non-Invasive							
Ticagrelor	2601	2392	2326	2247	1854	1426	1099
Clopidogrel	2615	2392	2328	2243	1835	1416	1109

James S et al. *BMJ.* 2011;342:d3527.

PLATO: Clopidogrel vs Ticagrelor

Other Safety Endpoints*



*Percentages are K-M estimates of the rate of the endpoint at 12 mo; patients could have had >1 type of endpoint

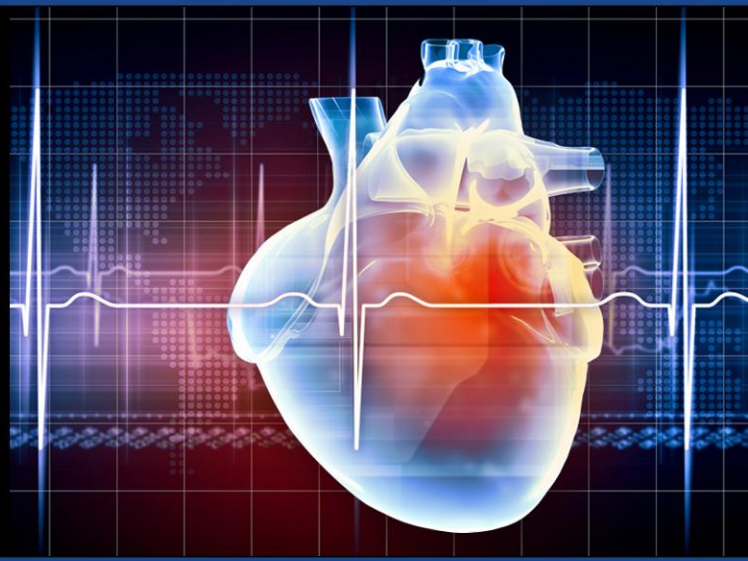
Wallentin L et al. *N Engl J Med*. 2009;361(11):1045-1057.

Ticagrelor Summary

- Directly, reversibly inhibits $P2Y_{12}$ receptor[1]
  - More potent, consistent antiplatelet effect
  - Requires twice-daily dosing
- In PLATO, ticagrelor resulted in improved ischemic benefit, decreased CV mortality in patients with ACS; significant increase in non-CABG bleeding, but not CABG-related bleeding.[2]
  - High-dose ASA (≥300 mg) associated with possible harm in combination with ticagrelor[3]; recommended ASA dose ≤100mg QD
  - Demonstrated less efficacy in US population in PLATO; may be related to higher ASA dose in US or play of chance[3]

1. Capodanno D et al. *J Thromb Haemost* . 2013;11(suppl 1):316-329. 2. Wallentin L et al. *N Engl J Med*. 2009;361(11):1045-1057.
3. Mahaffey KW et al. *Circulation.* 2011;124:544-554.

CURRENT GUIDELINES FOR DUAL ANTIPLATELET THERAPY IN ACS



Guidelines for Antiplatelet Therapy in NSTEMI

2014 AHA/ACC Guideline for the Management of NSTE-ACS

Recommended LD of $P2Y_{12}$ inhibitors at the time of PCI:

- Clopidogrel 600 mg (LOE: B), *or*
- Prasugrel* 60 mg (LOE: B) who are not at high risk of bleeding (LOE: B), *or*
- Ticagrelor† 180 mg (LOE: B)

Duration and maintenance dose of $P2Y_{12}$ receptor inhibitors after stent placement:

- In NSTE-ACS patients:
  - Either clopidogrel 75 mg/d, prasugrel 10 mg/d, or ticagrelor 90 mg BID, ≥12 mo (LOE: B)
- If risk of morbidity due to bleeding outweighs anticipated benefits afforded by $P2Y_{12}$ receptor inhibitor therapy, consider earlier discontinuation (LOE: C)

*Loading dose of prasugrel indicated if not pretreated with another $P2Y_{12}$ receptor inhibitor; should not be used in patients with a h/o stroke or TIA
†The recommended dose of aspirin to be used with ticagrelor is 81 mg/d
LOE, level of evidence

Amsterdam EA et al. *Circulation*. 2014;Epub ahead of print Sept 23.

Adjunctive Antiplatelet Therapy to Support Reperfusion with Primary PCI for STEMI

2013 ACCF/AHA Guidelines

Aspirin:

- 162 to 325 mg given before primary PCI (LOE: B), *and*
- 81 mg to 325 mg maintenance dose continued indefinitely after PCI (LOE: A)
- Preferred maintenance dose is 81 mg/d (Class IIa, LOE: B)*

*The recommended dose of aspirin to be used with ticagrelor is 81 mg/d

O'Gara PT et al. *Circulation*. 2013;127:e362-425.

Adjunctive Antiplatelet for Primary PCI for STEMI

2013 ACCF/AHA Guidelines

$P2Y_{12}$ receptor inhibitors:

- Loading dose as early as possible or at time of PCI
  - Clopidogrel, 600 mg
  - Prasugrel, 60 mg
  - Ticagrelor, 180 mg
- Maintenance therapy for 1 y (minimum 1 mo with BMS) in patients who receive a stent (DES or BMS)*
  - Clopidogrel, 75 mg/d (LOE: B)
  - Prasugrel, 10 mg/d (LOE: B)
  - Ticagrelor, 90 mg BID (LOE: B)
- Prasugrel contraindicated in patients with history of stroke or TIA

BMS, bare-metal stent; DES, drug-eluting stent

*Balloon angioplasty without stent placement may be used in selected patients. It might be reasonable to provide $P2Y_{12}$ inhibitor therapy to patients with STEMI undergoing balloon angioplasty alone per recommendations listed for BMS .

O'Gara PT et al. *Circulation*. 2013;127:e362-425.

THANK YOU!