PLATO: Impact on the Management of ACS and Personalizing Treatment with Ticagrelor

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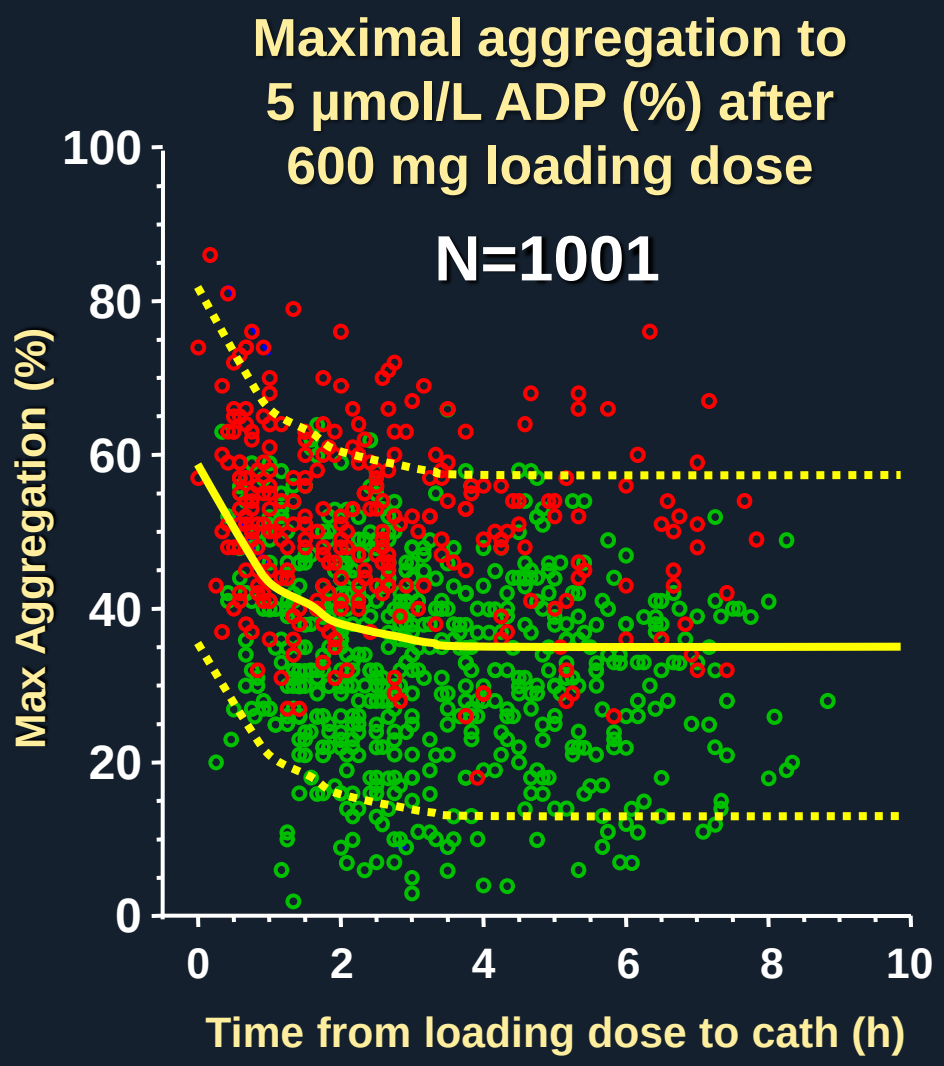
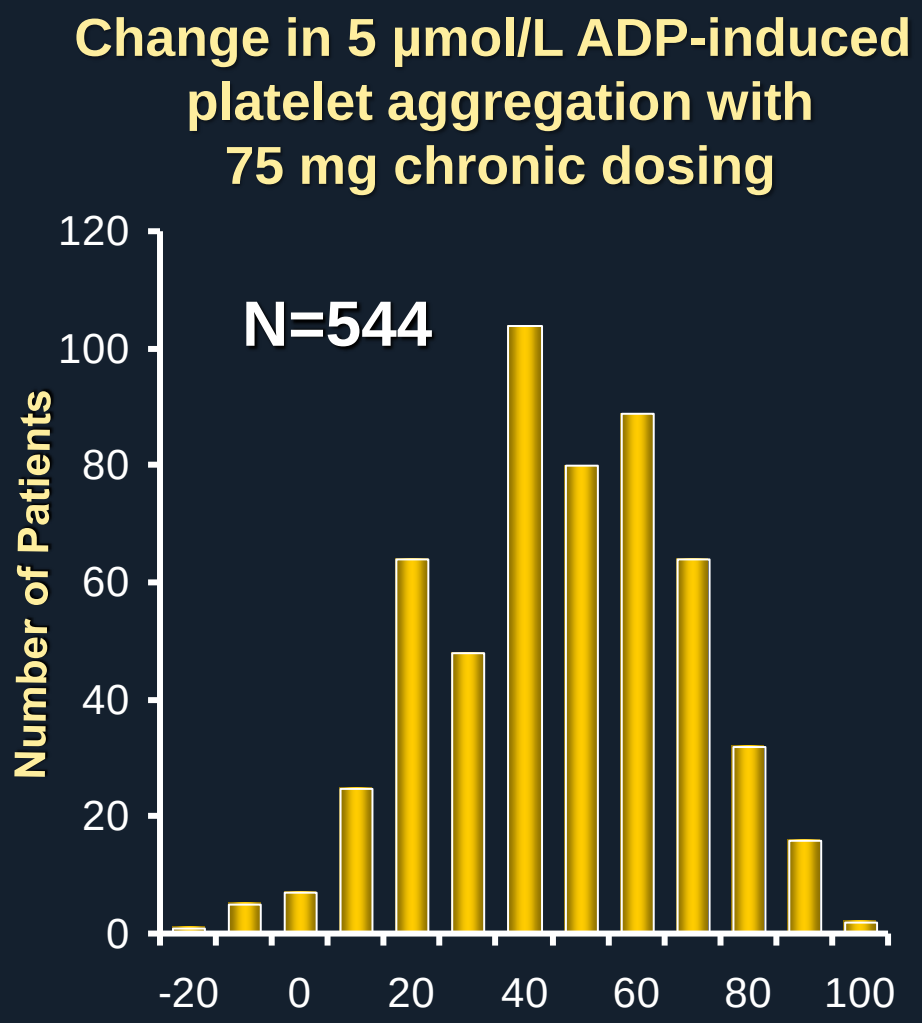
Disclosures

- None

Variability in Clopidogrel Response





Hochholzer W et al. Circ 20051;11:2560-4

Serebruany V et al. JACC 2005;45:246-51

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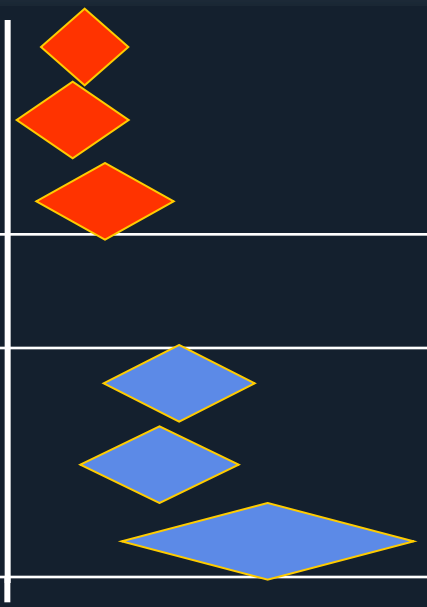
CYP2C19 Genetic Polymorphisms and Outcomes With Clopidogrel

Major Adverse CV Events (N=9,684)	Risk Ratio (95% CI)	*P* Value
Carriers vs Noncarriers	1.61 (1.28-2.02)	<0.001
Heterozygotes vs Wildtype	1.50 (1.08-2.08)	0.016
Homozygotes vs Wildtype	1.81 (1.21-2.71)	0.004
Stent Thrombosis (N=5,772)		
Carriers vs Noncarriers	2.76 (1.77-4.30)	<0.001
Heterozygotes vs Wildtype	2.51 (1.59-3.98)	<0.001
Homozygotes vs Wildtype	4.78 (2.01-11.39)	<0.001



Mega JL et al. *JAMA* 2010; 304:1821-30

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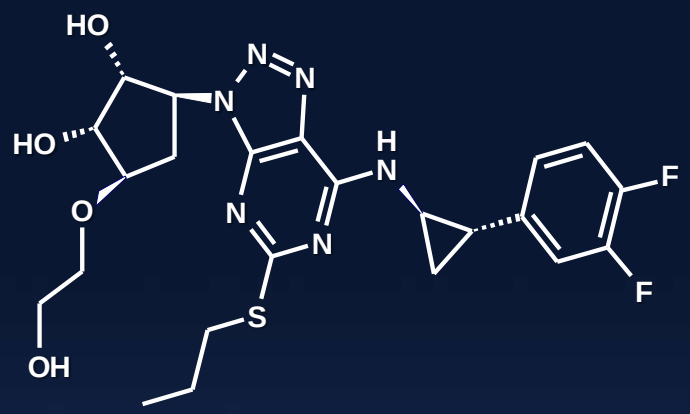
Clopidogrel - Pharmacogenetic Information

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of clopidogrel is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.**

Clopidogrel product information. Revised March 2010

Ticagrelor (AZD 6140):
an Oral Reversible $P2Y_{12}$ Antagonist



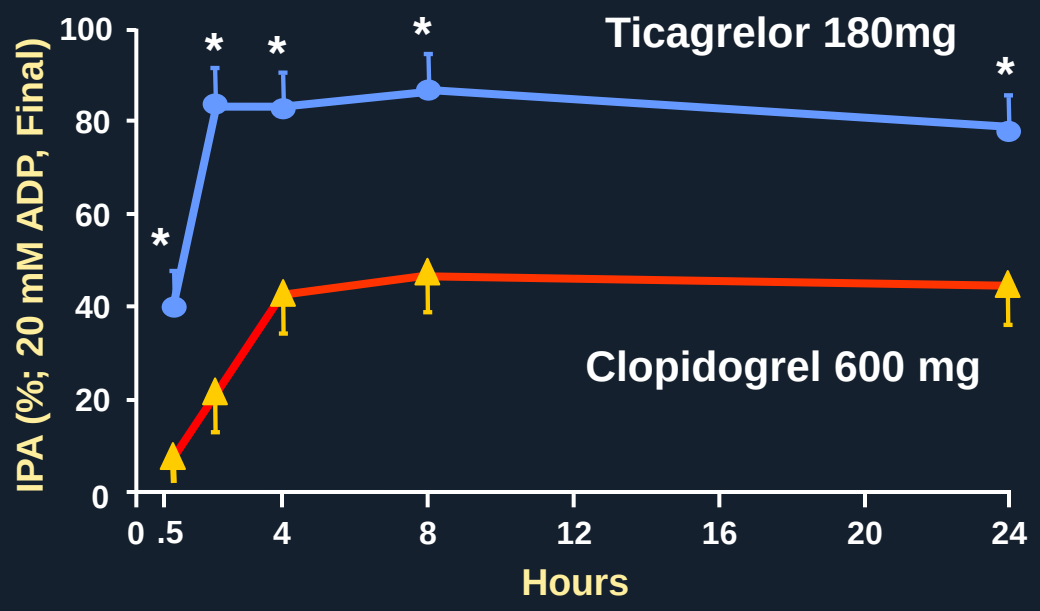
Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- Direct acting
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor
  - Greater inhibition of platelet aggregation than clopidogrel
- Reversibly bound
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of all circulating platelets
- Off-target effects
  - Blocks red blood cell adenosine re-uptake

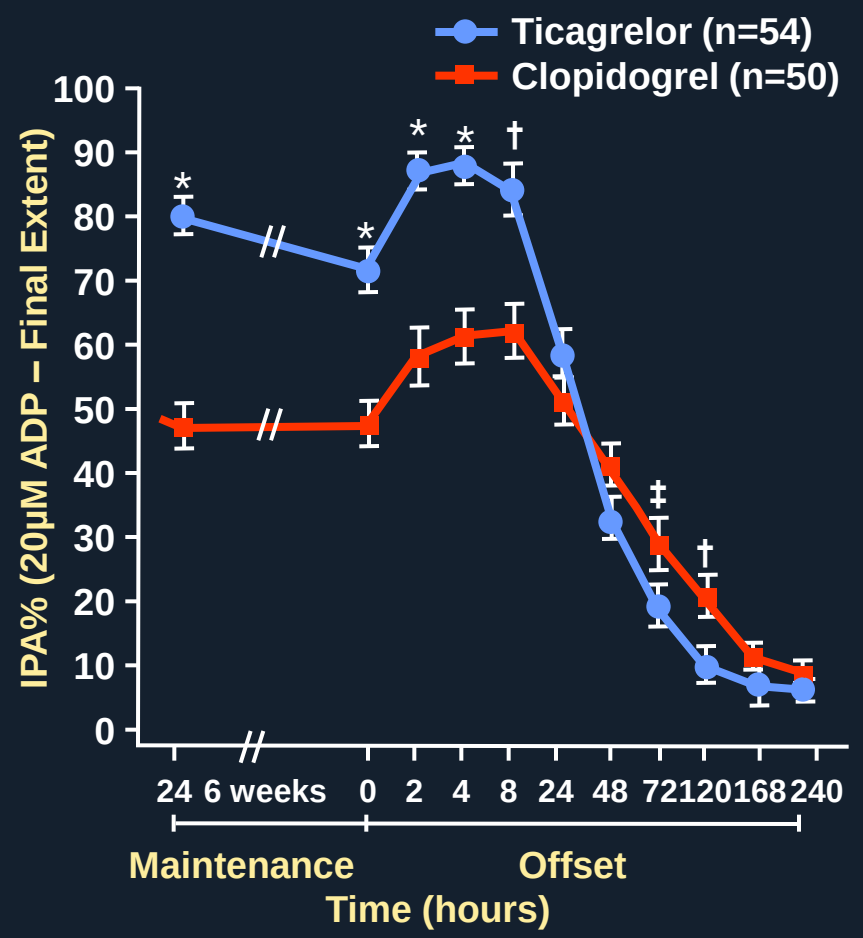
Clopidogrel vs. Ticagrelor

ONSET/OFFSET Study

Loading



Maintenance and Offset



Ticagrelor vs clopidogrel.

* *P*<0.0001; † *P*<0.005; ‡, *P*<0.05

Gurbel PA et al. *Circulation*. 2009;120:2577-85.

PLATO

PLATO Study Design

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

Clopidogrel
If pre-treated, no additional loading dose;
if naive, 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)

Planned invasive 72%
Planned conservative 28%
61% PCI
5% CABG
34% Med Rx

6–12-month exposure (median 9 mos)

Primary endpoint: CV death + MI + Stroke
Primary safety endpint: Total major bleeding

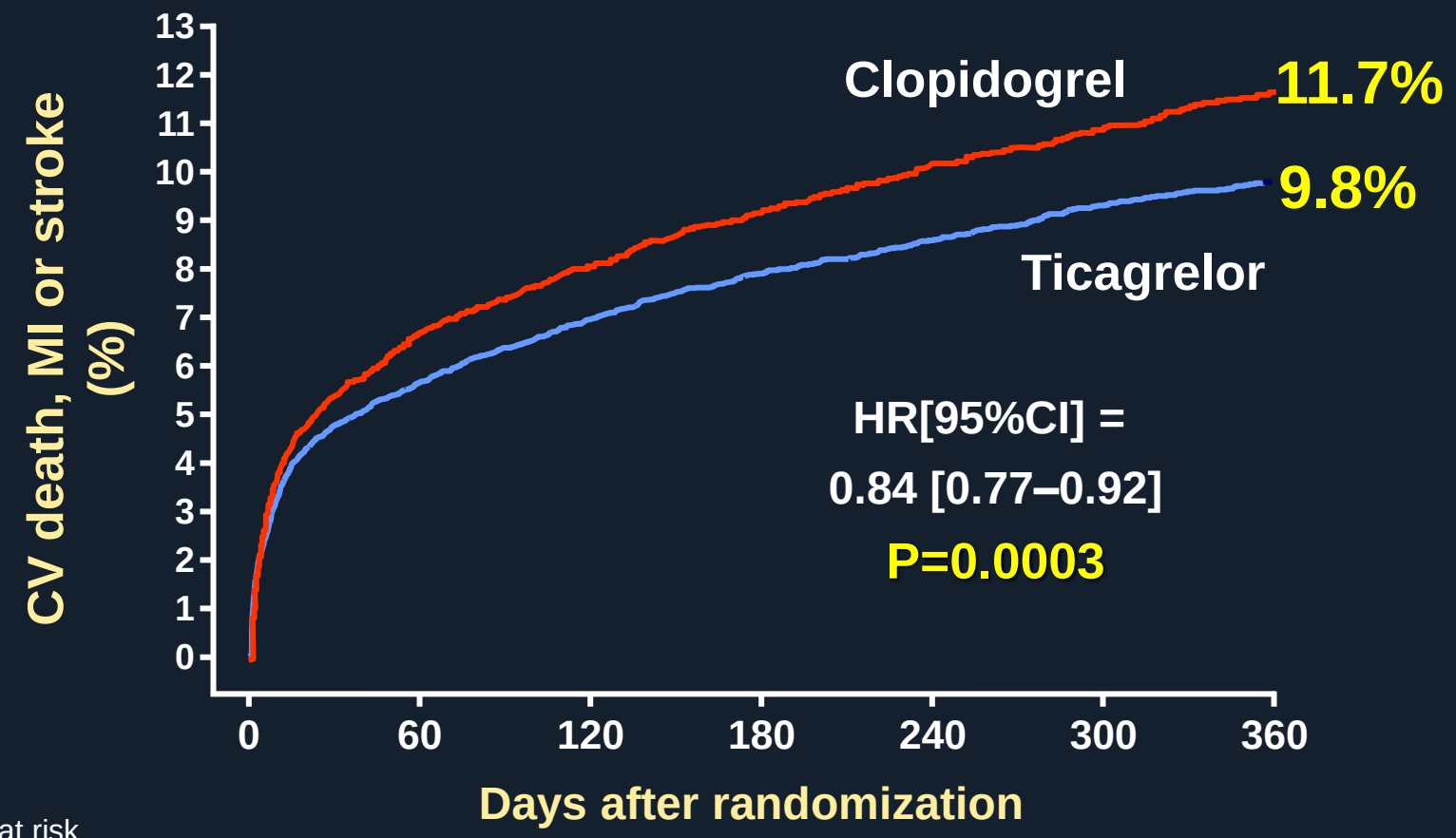
Note: ASA 325 mg load, then 75-100 mg QD (325 mg x6 mo permitted if stented)

Wallentin L et al. *NEJM* 2009;361:1045-57

PLATO

Primary Efficacy Endpoint

Composite of CV Death, MI or Stroke



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 L et al. *NEJM* 2009;361:1045-57

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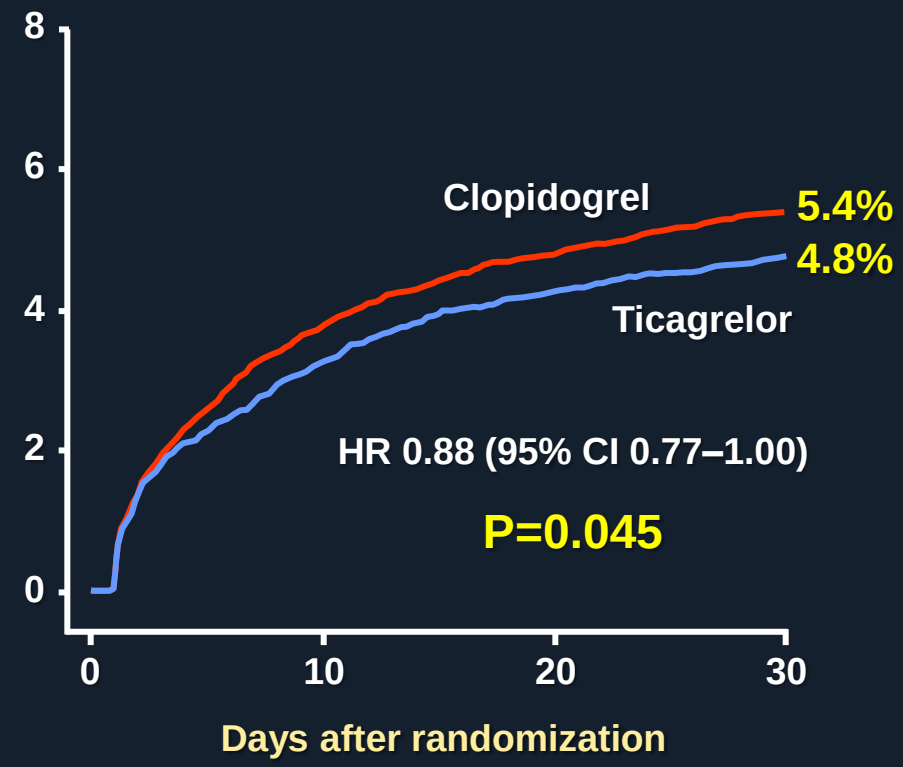
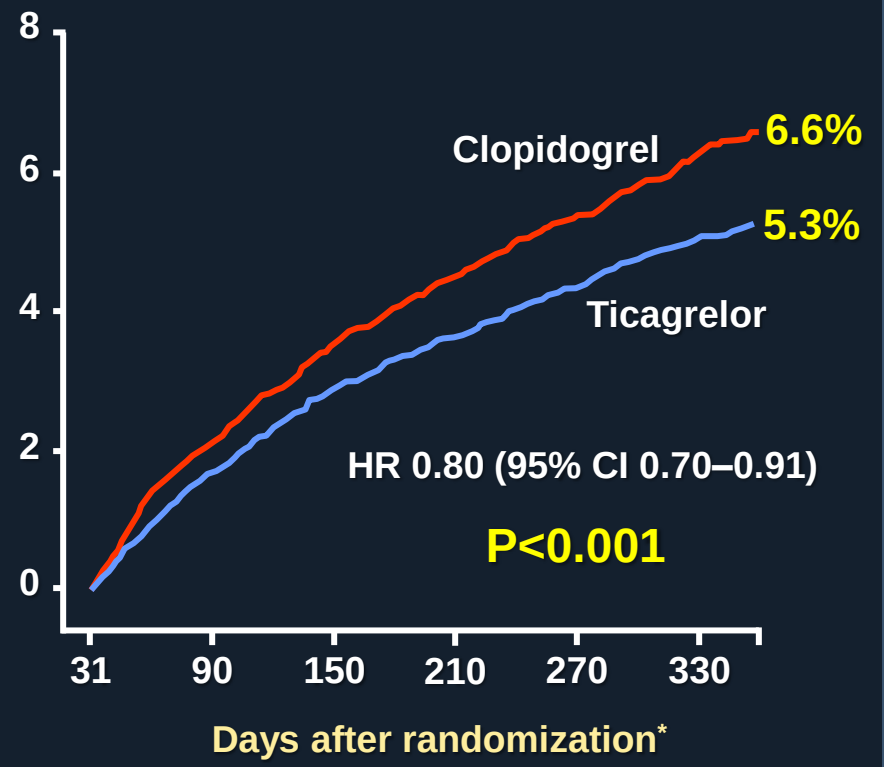
Primary Efficacy Endpoint (Composite of CV Death, MI or Stroke)





No. at risk										
Ticagrelor	9,333	8,942	8,827	8,763	8,673	8,543	8,397	7,028	6,480	4,822
Clopidogrel	9,291	8,875	8,763	8,688	8,688	8,437	8,286	6,945	6,379	4,751

* Excludes patients with any primary event during the first 30 days

Wallentin L et al. *NEJM* 2009;361:1045-57

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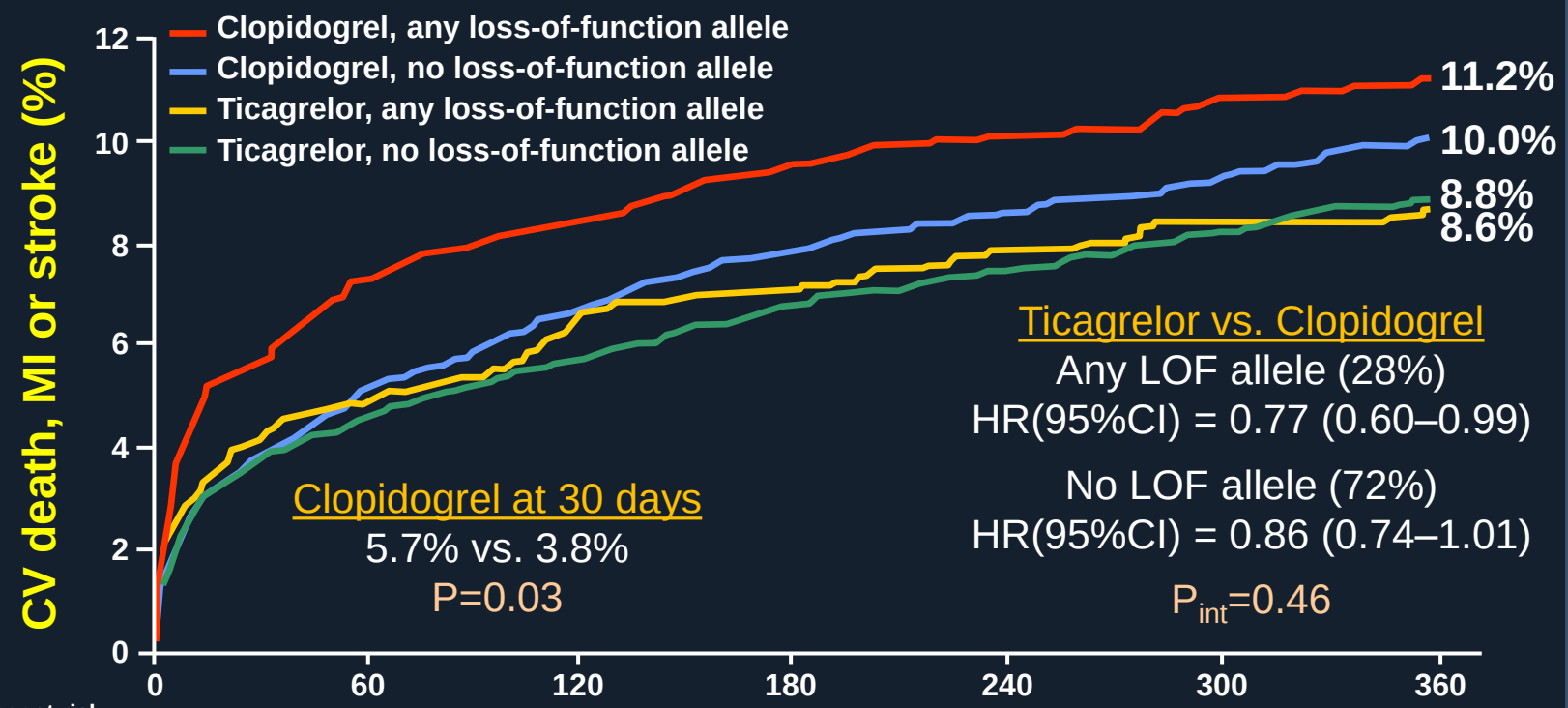
PLATO Genetics (N=10,285)

Assays were performed for CYP2C19 loss-of-function alleles (*2, *3, *4, *5, *6, *7, and *8), gain-of-function allele (*17) and the ABCB1 SNP 3435C→T.

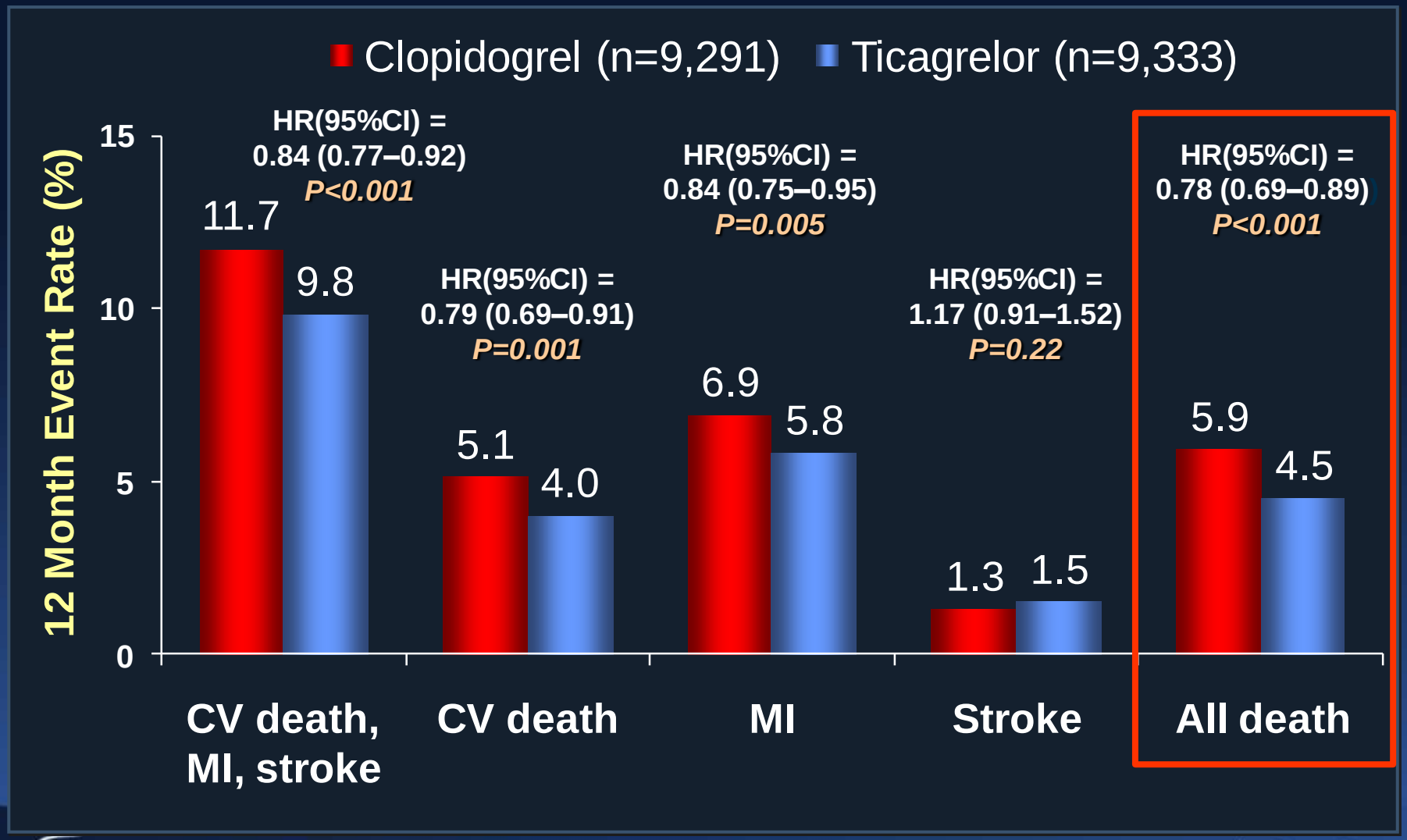


Number at risk	0	60	120	180	240	300	360
Clopidogrel							
Any loss-of-function allele	1388	1275	1259	1226	1027	801	658
No loss-of-function allele	3516	3321	3256	3186	2691	2123	1757
Ticagrelor							
Any loss-of-function allele	1384	1305	1274	1250	1053	834	683
No loss-of-function allele	3554	3352	3301	3222	2718	2127	1761

Wallentin L et al. *Lancet* 2010:on-line

PLATO

Primary and Secondary Endpoint Events



Wallentin L et al. *NEJM* 2009;361:1045-57

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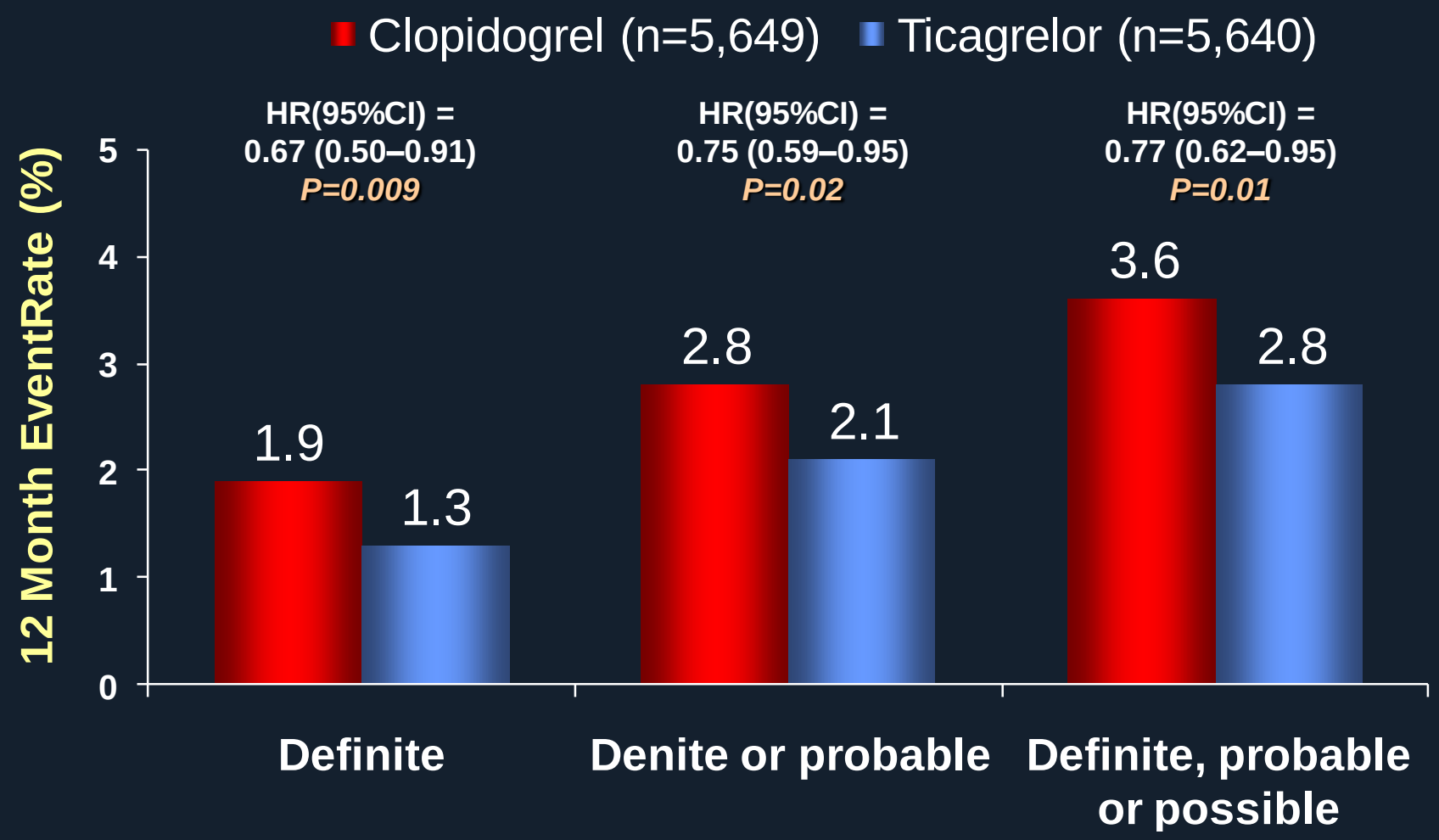
PLATO

Stent Thrombosis



Wallentin L et al. *NEJM* 2009;361:1045-57

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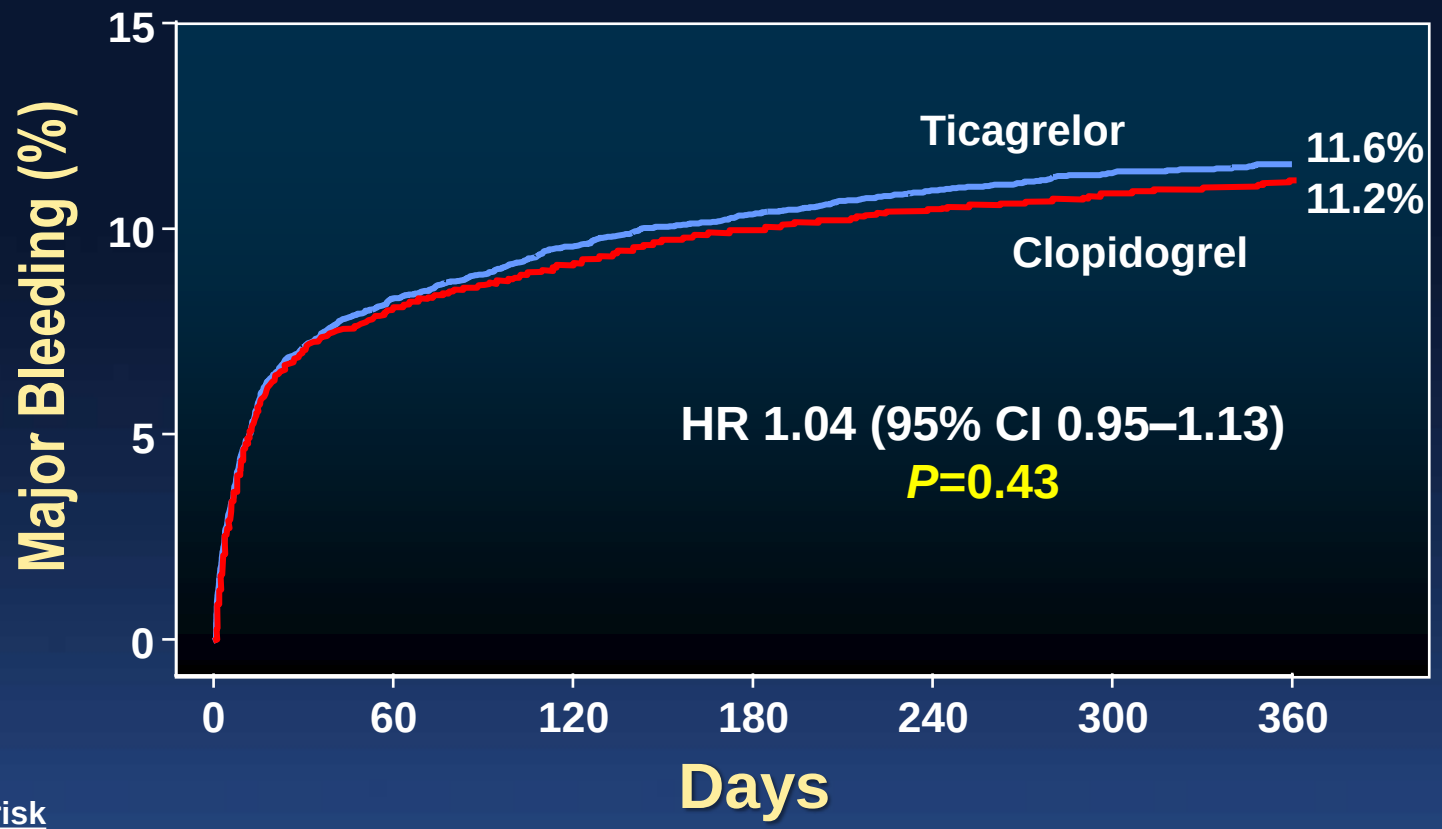
PLATO
Total Major Bleeding

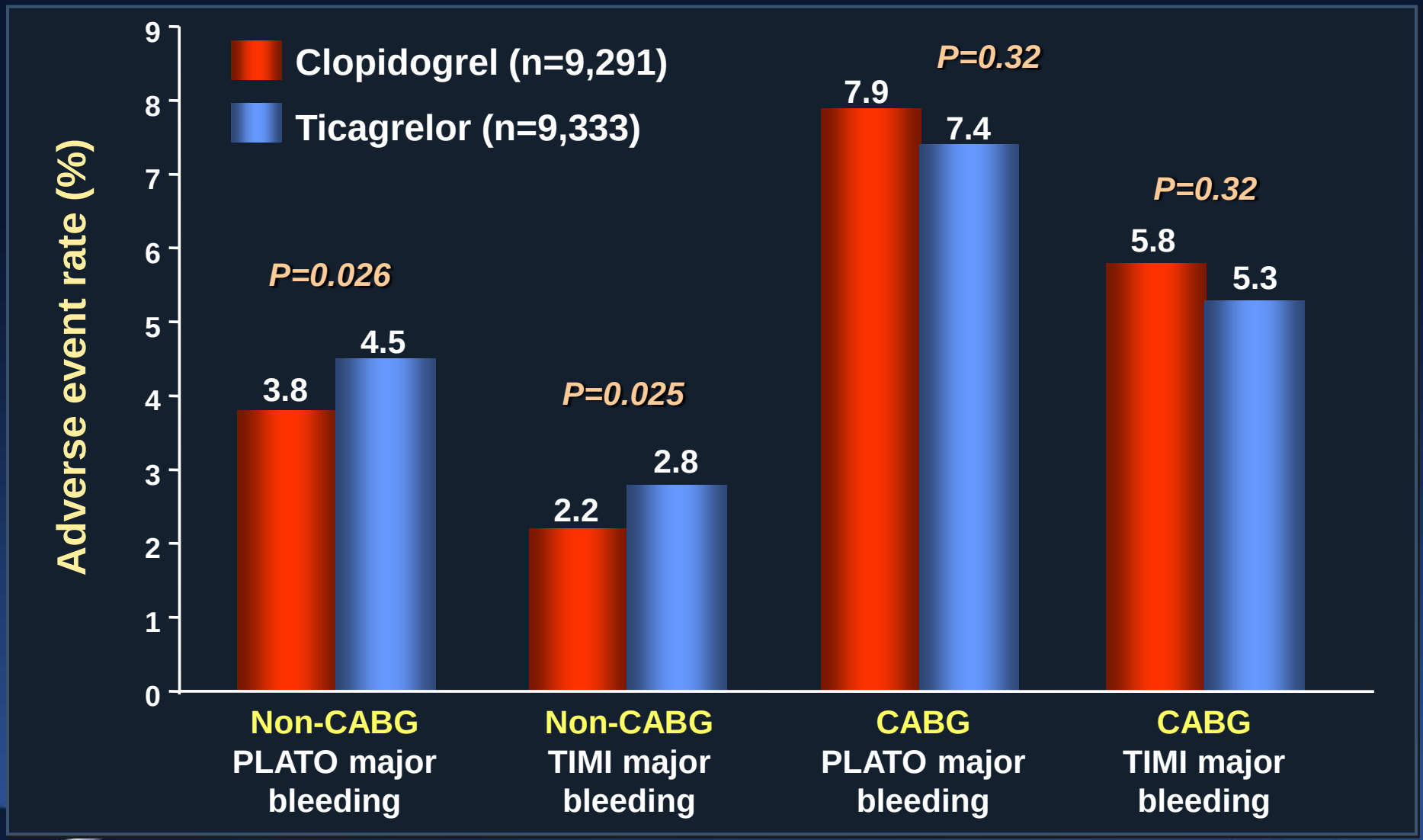


No. at risk

Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

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

PLATO: Non-CABG and CABG-related Major Bleeding



Wallentin L et al. *NEJM* 2009;361:1045-57

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PLATO

Major Bleeding, 12 Months

End Point	Ticagrelor (n=9235)	Clopidogrel (n=9186)	HR (95% CI)	*P*
Primary safety endpoints				
PLATO major bleeding	11.6%	11.2%	1.04 (0.95-1.13)	0.43
TIMI major bleeding	7.9%	7.7%	1.03 (0.93-1.15)	0.57
Bleeding requiring red cell transfusion	8.9%	8.9%	1.00 (0.91-1.11)	0.96
Life-threatening or fatal bleeding	5.8%	5.8%	1.03 (0.90-1.16)	0.70
Fatal bleeding	0.3%	0.3%	0.87 (0.48-1.59)	0.66
- Non-intracranial	0.1%	0.3%		0.03
Intracranial bleeding	0.3%	0.2%	1.87 (0.98-3.58)	0.06
- Fatal	0.1%	0.01%		0.02
- Nonfatal	0.2%	0.2%		0.69

Wallentin L et al. *NEJM* 2009;361:1045-57

PLATO

Intracranial hemorrhage in pts with history of TIA or stroke

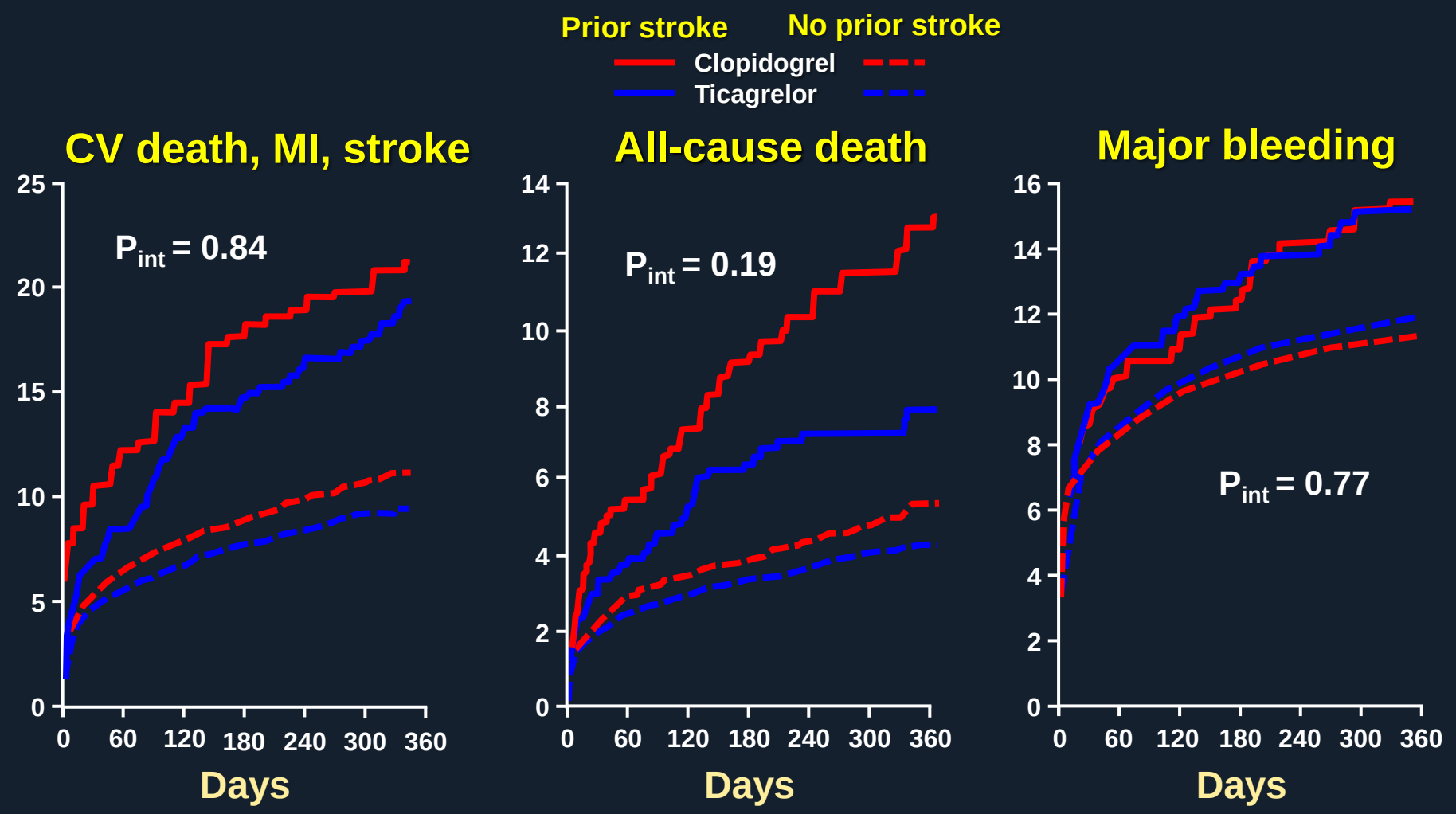
Adverse effect	Pts without prior TIA or nonhemorrhagic stroke		Pts with prior TIA or nonhemorrhagic stroke	
	Ticagrelor N=8762	Clopidogrel N=8700	Ticagrelor N=564	Clopidogrel N=588
Intracranial hemorrhage	22 (0.3%)	11 (0.0%)	4 (0.7%)	4 (0.7%)*
- Non-fatal	11 (0.1%)	9 (0.1%)	4 (0.7%)	4 (0.7%)
- Fatal	11 (0.1%)	2 (0.0%)	0	0

*One pt in the clopidogrel group had a procedural ICH

AstraZeneca core slides for the July 28, 2010 Meeting of the Cardiovascular and Renal Drugs Advisory Committee
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm221382.htm

Pts with Prior Stroke or TIA

1,152/18,624 pts (6.2%) had a history of stroke or TIA

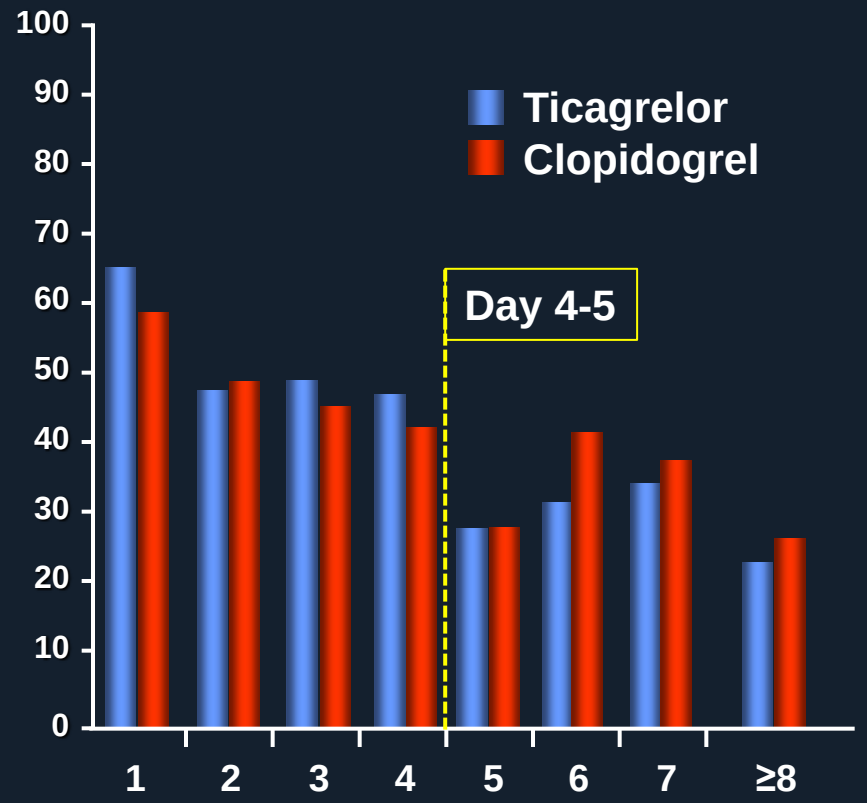


James SK et al. *Circulation* 2012;125:2914-21

PLATO CABG (n=1849):

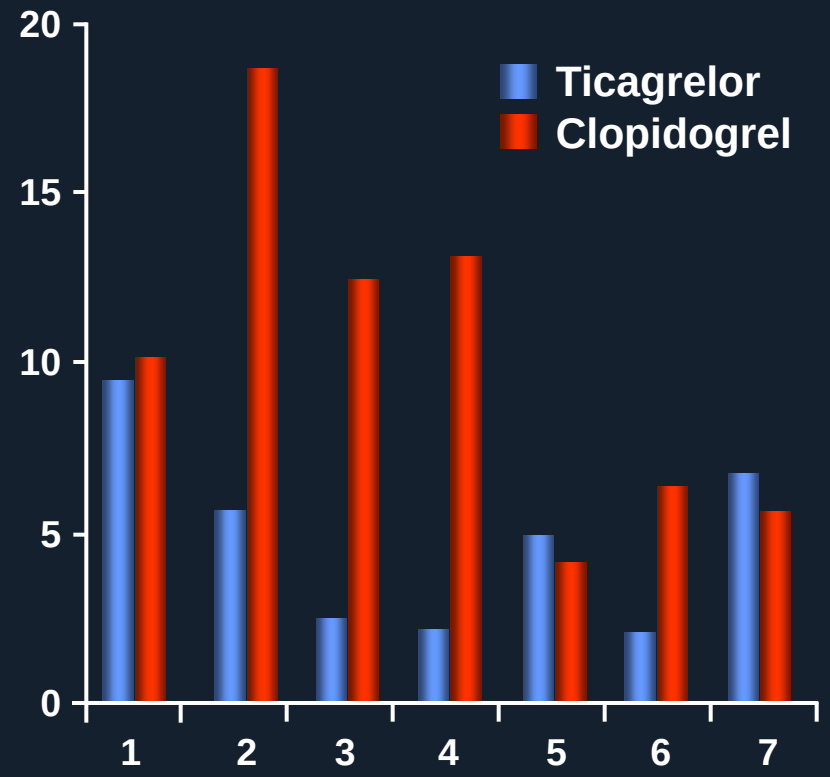
Bleeding and Death by Days From Last Study Drug

Fatal or life-threatening bleed



No. of Pts:	1	2	3	4	5	6	7	≥8
Ticagrelor	84	106	114	84	79	91	74	228
Clopidogrel	88	86	73	69	96	110	107	274

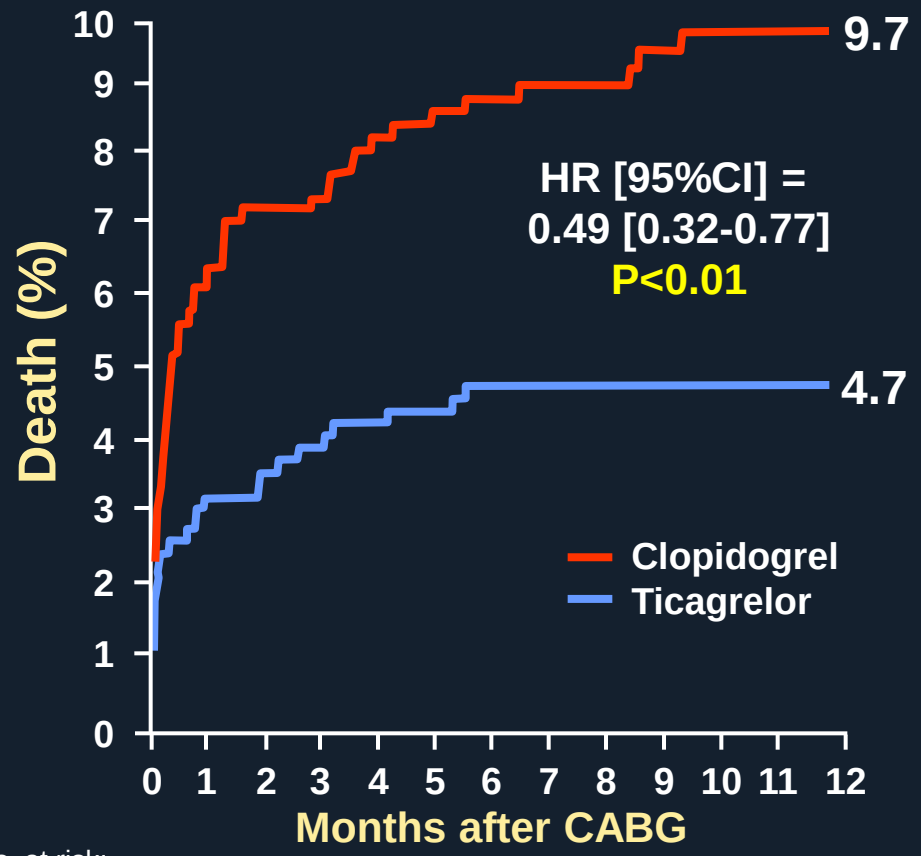
Death



No. of Pts:	1	2	3	4	5	6	7
Ticagrelor	84	106	114	84	79	91	74
Clopidogrel	88	86	73	69	96	110	107

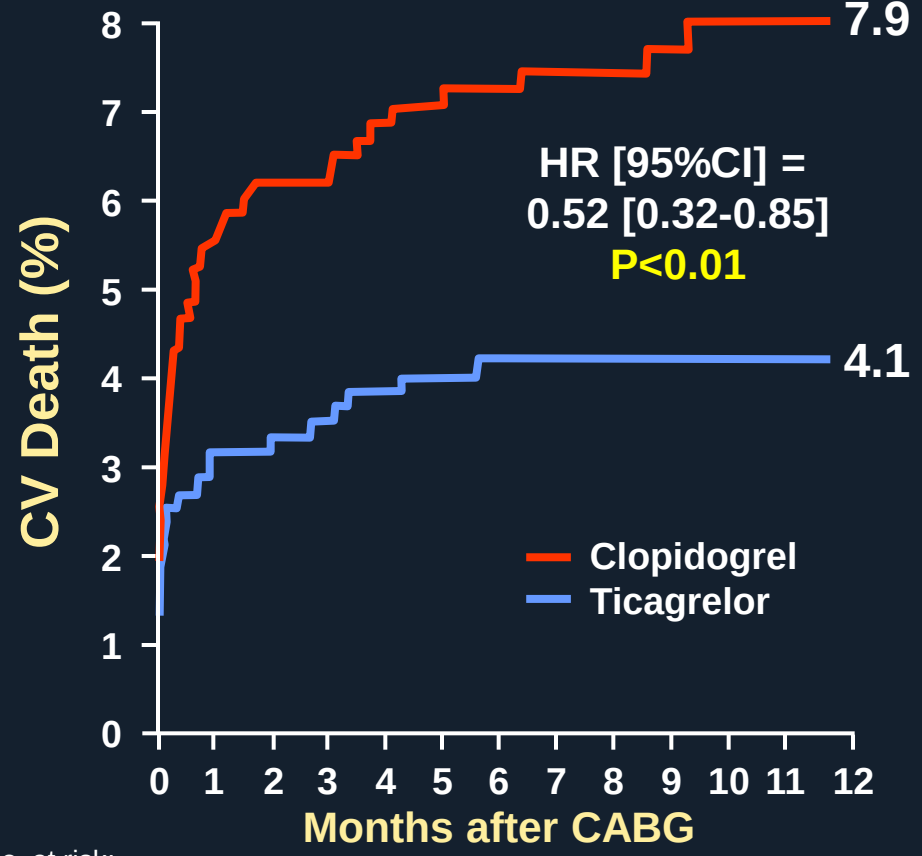
Held C et al. *JACC* 2011;57;672-84

PLATO CABG (n=1849)
1-year Mortality after CABG



No. at risk:

Ticagrelor	629	583	567	491	415	291	119
Clopidogrel	629	565	530	472	404	289	130



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Clopidogrel	629	565	529	472	404	289	130

Held C et al. *JACC* 2011;57;672-84

Ticagrelor vs. Clopidogrel: Relative Benefit and Safety in NSTEACS vs STEMI

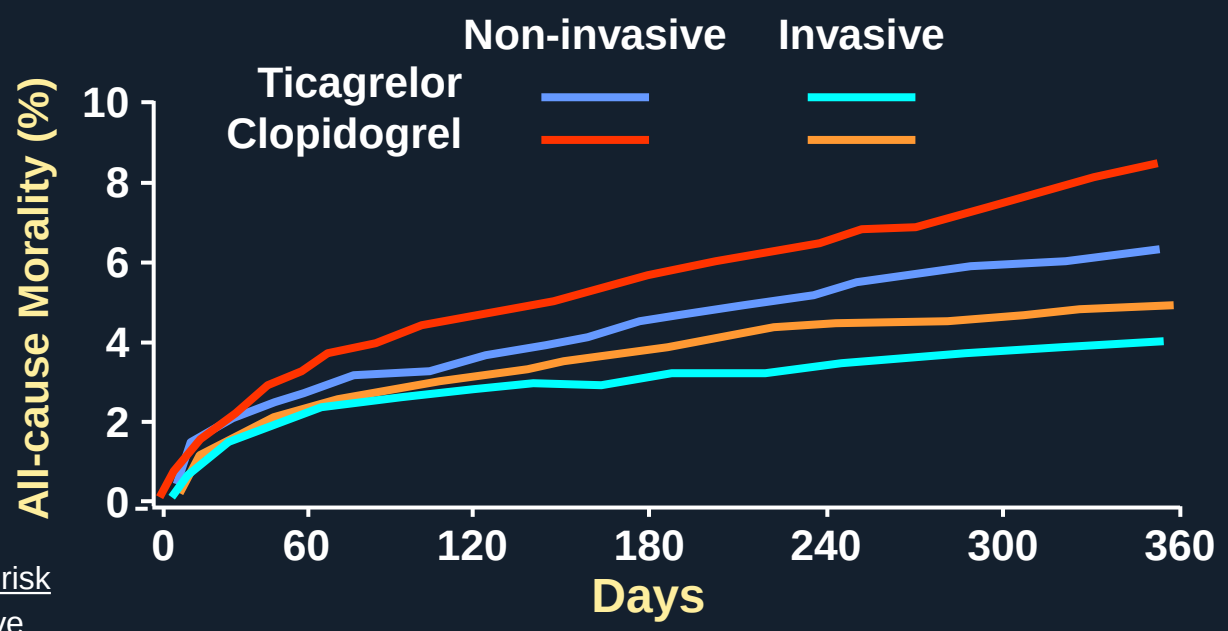
	Ticagrelor	Clopidogrel	HR (95%CI)	P_{INT}
CV death, MI, stroke				
NSTEACS (N=11,074)	10.1%	12.3%	0.83 (0.74, 0.93)	0.68
STEMI/LBBB (N=7,544)	9.4%	10.8%	0.87 (0.75, 1.01)	
Major bleeding				
NSTEACS (N=10,949)	13.4%	12.6%	1.07 (0.95, 1.19)	0.30
STEMI/LBBB (N=7,471)	9.0%	9.1%	0.98 (0.83, 1.14)	

Wallentin L et al. *NEJM* 2009;361:1045-57

Substudy: Pts Intended for Medical Rx

5216 (28%) of 18,624 ACS pts specified for non-invasive management before rand. UA in 35.4%, NSTEMI in 55.9%; STEMI in 8.7%. In-hosp: 20.4% PCI, 4.0% CABG

All-cause mortality according to management



No. at risk							
Invasive							
- Ticagrelor	6732	6439	6375	6241	5141	3951	3233
- Clopidogrel	6676	6376	6331	6209	5114	3917	3164
Non-invasive							
- Ticagrelor	2601	2485	2447	2385	1978	1531	1186
- Clopidogrel	2615	2488	2448	2380	1965	1524	1200

HR 0.75 (0.61-0.93) in the non-invasive cohort and 0.80 (0.61-0.93) in the invasive cohort ***(P_{int}=0.64)***

James SK et al. *BMJ* 2011;342:d3527 doi: 10.1136/bmj.d3527

Substudy: Pts Intended for Medical Rx

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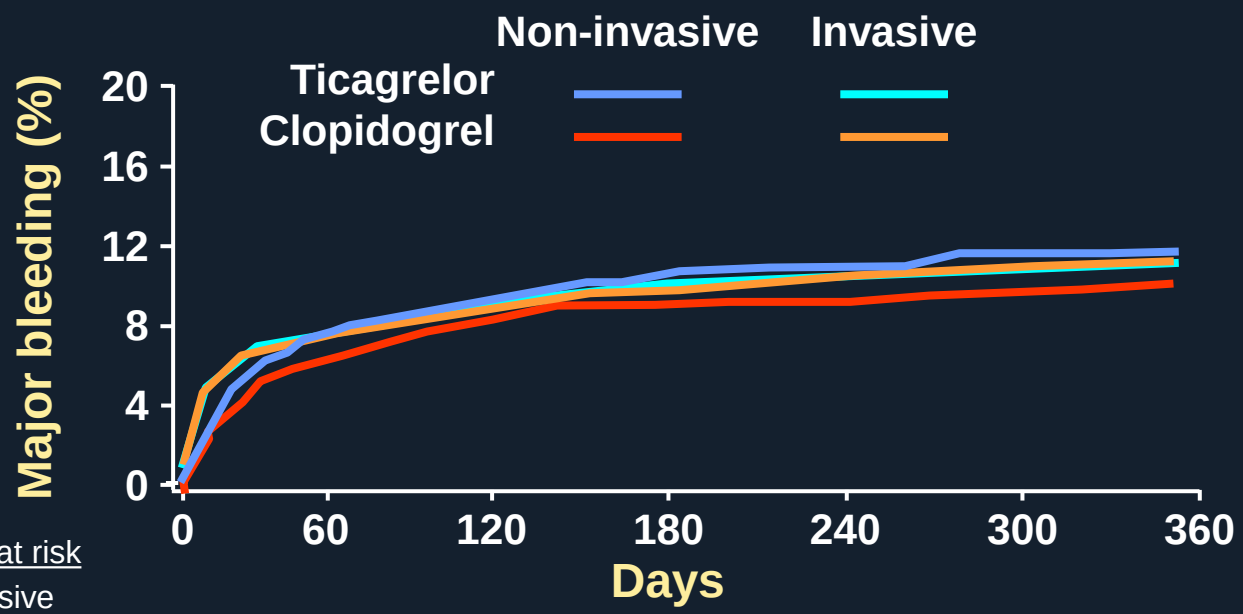
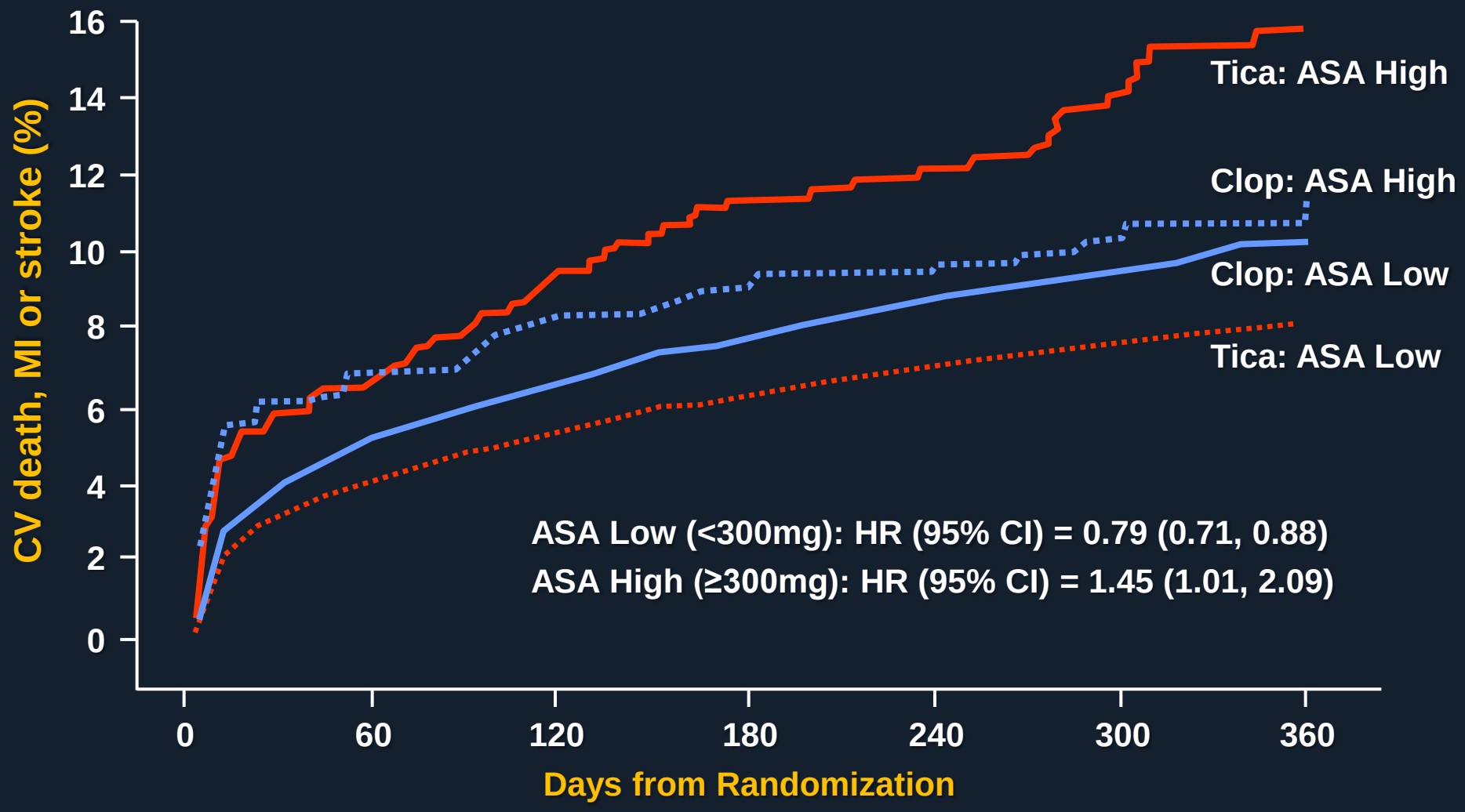
Major Bleeding According to Management



No. at risk							
Invasive							
- Ticagrelor	6651	5238	4948	4766	3730	2748	2521
- Clopidogrel	6585	5220	4985	4798	3756	2760	2507
Non-invasive							
- Ticagrelor	2584	2008	1878	1779	1399	1035	912
- Clopidogrel	2601	2085	1945	1872	1453	1081	972

James SK et al. *BMJ* 2011;342:d3527 doi: 10.1136/bmj.d3527

Interaction Between Treatment Effect and ASA Maintenance Dose



Mahaffey KW et al. Circulation. 2011;124:544-54.

Ticagrelor – FDA Label

"Boxed Warning"

WARNING: BLEEDING RISK

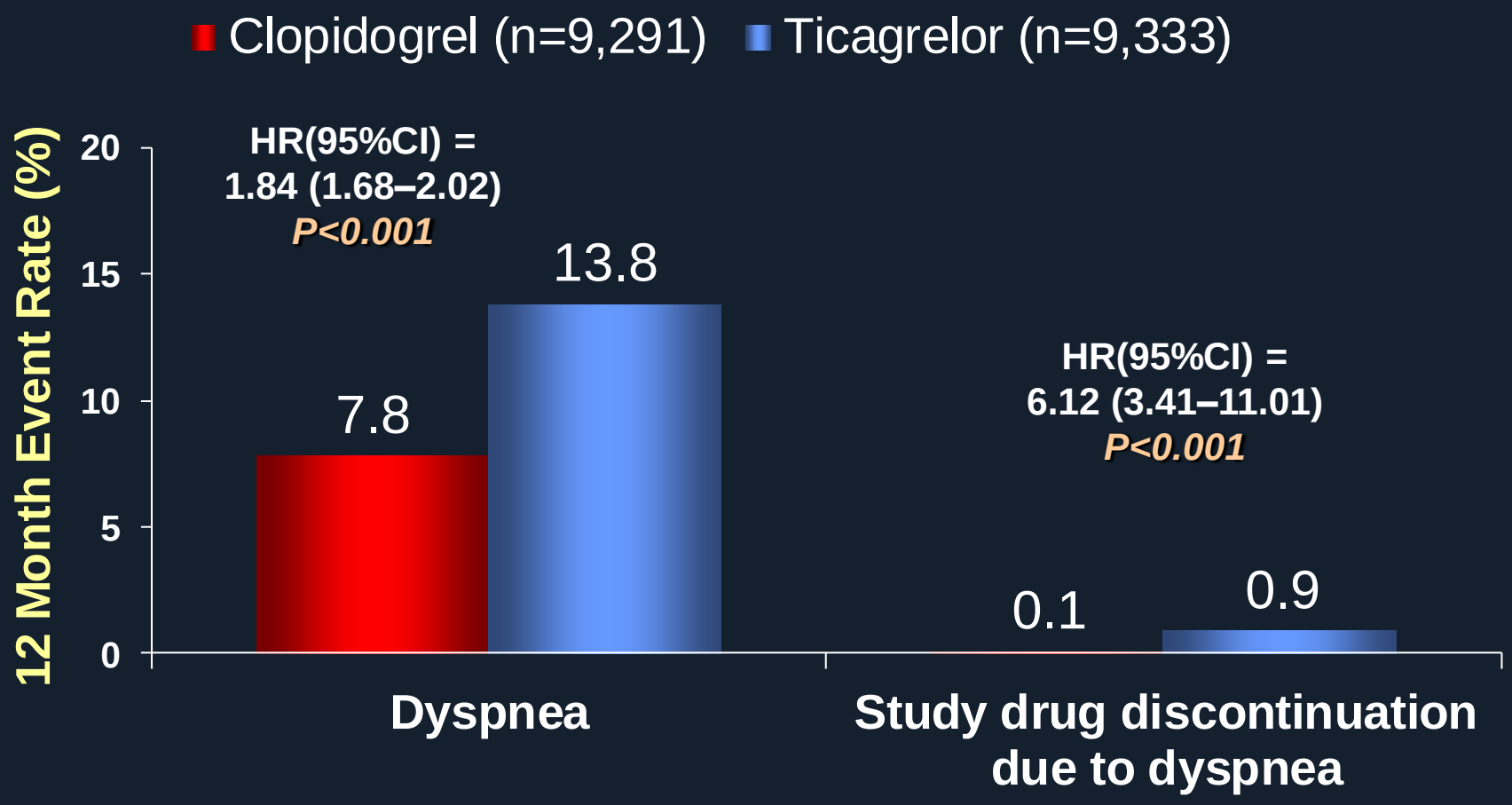
- BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).
- Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).
- Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).
- Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).
- If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).

PLATO: Dyspnea

Ticagrelor blocks rbc re-uptake of adenosine, and thus causes the sensation of dyspnea in some pts



Wallentin L et al. *NEJM* 2009;361:1045-57

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Ticagrelor in ACS: Lessons from PLATO

- In pts with NSTEMI and STEMI undergoing either an early invasive strategy or planned medical management, ticagrelor loading + maintenance for 12 months reduces the composite rate of CV death, MI or stroke compared to clopidogrel
- Ticagrelor also reduces the individual endpoints of MI, stent thrombosis, CV death and all-cause mortality
- Total bleeding, life-threatening bleeding and fatal bleeding are not increased with ticagrelor compared to clopidogrel in ACS, although non-CABG major bleeding is increased
- If CABG is required after ticagrelor, the drug should be discontinued for at least 2-3 days and preferably 5 days before surgery

Ticagrelor in ACS: Lessons from PLATO

- Ticagrelor may be used safely in pts w/advanced age, low body weight, and prior stroke or TIA. However, although total ICH is not increased, fatal ICH is increased with ticagrelor, warranting some caution in pts at risk for ICH
- Other than bleeding, the most common side effect of ticagrelor is dyspnea which is usually mild and self-limited, but occasionally will require drug discontinuation
- Ticagrelor is a bid drug, and should only be administered with a 75-100 mg daily maintenance dose of aspirin
- Currently there is no indication for use of ticagrelor in pts with stable CAD undergoing PCI, and ticagrelor should not be used in patients treated with chronic oral anticoagulation (VKA or NOACs)