The Landscape of Antiplatelet Agents: Which Drug, for Whom, and Why

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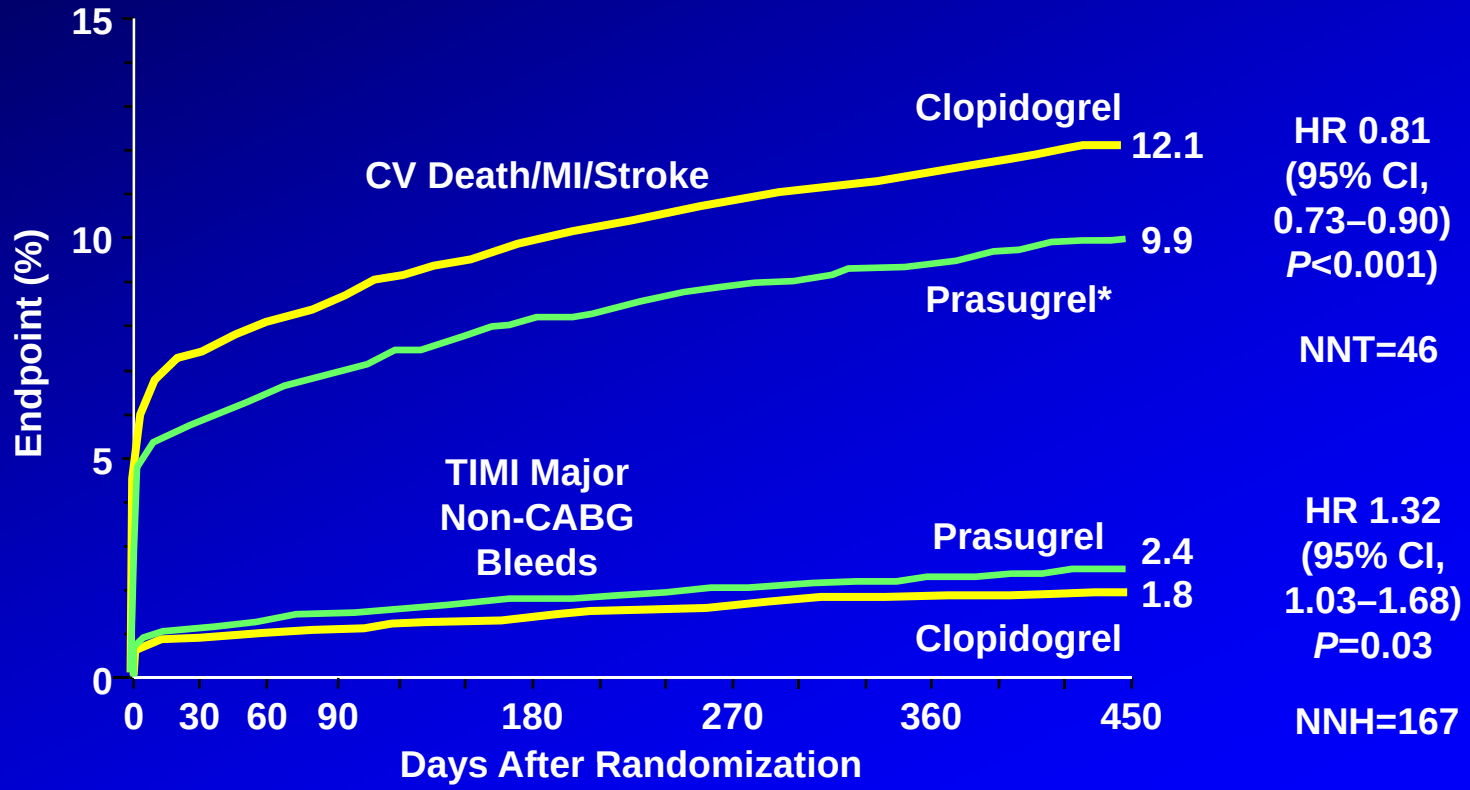
Efficacy of Clopidogrel in Reducing Ischemic Events: *Evident Across Spectrum of CAD*

STEMI	UA/NSTEMI	PCI	Long-term/2° prevention	
CLARITY	CURE	CREDO	CAPRIE	CHARISMA
COMMIT (CCS-2)				
30 Days	*1 Year*	*1 Year*	*1-3 Years*	*Up to 3.5 years*
+ Benefit	+ Benefit	+ Benefit	+ Benefit	+ Benefit in symptomatic pts

Prasugrel *vs* Clopidogrel in ACS Patients Treated With PCI

TRITON-TIMI 38



Wiviott SD et al. *N Engl J Med*. 2007;357(20):2001-2015.

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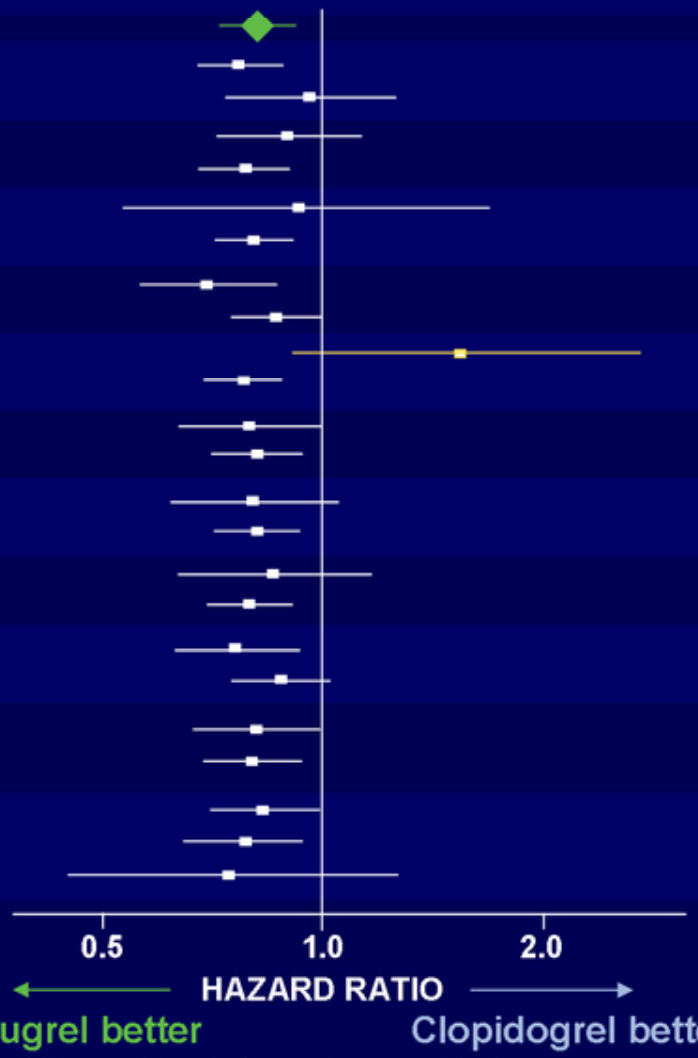
Primary Endpoint Events Across Subpopulations in UA/NSTEMI Patients

Baseline Characteristics		N	Percent Events	
			Prasugrel	Clopidogrel
OVERALL		**10,074**	**9.9**	**12.1**
Age	<75 years	8672	8.2	10.5
	≥75 years	1402	15.8	16.2
Gender	Female	2724	10.3	11.4
	Male	7350	8.9	11.2
Body weight	<60 kg	503	9.2	9.8
	≥60 kg	9458	9.2	11.1
Diabetes mellitus	Yes	2472	10.8	15.0
	No	7602	8.8	10.0
Previous TIA/stroke	Yes	405	18.3	12.5
	No	9669	8.9	11.2
Previous MI	Yes	2075	12.9	15.8
	No	7999	8.3	10.1
Previous PCI	Yes	1597	12.0	14.8
	No	8477	8.8	10.6
Previous CABG	Yes	957	16.0	18.2
	No	9117	8.6	10.5
Time from symptom onset	≤24 hours	3902	8.3	10.8
	>24 hours	5976	10.1	11.5
GP IIb/IIIa inhibitor use	Yes	5183	9.9	11.9
	No	4891	8.7	10.5
Stent type	DES ≥1	5225	9.2	10.9
	BMS only	4362	9.2	11.6
	None	401	11.7	14.9



Based on Kaplan-Meier estimates.

Effient Full Prescribing Information.

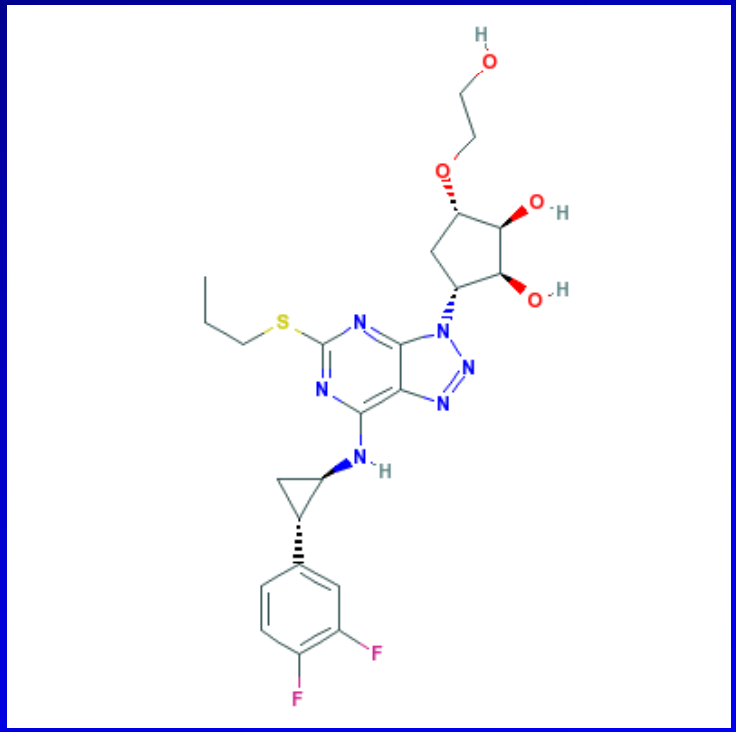
Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

Prasugrel: Summary of Boxed Warning

- *Contraindications:* Clinical hx of Stroke/TIA
- *Generally not recommended* for age ≥ 75 yrs, except in high risk situations (prior MI, DM) where the ischemic benefit appears to be greater
- *Greater risk of bleeding* in patients weighing <60 kg, can consider MD adjustment (5mg)

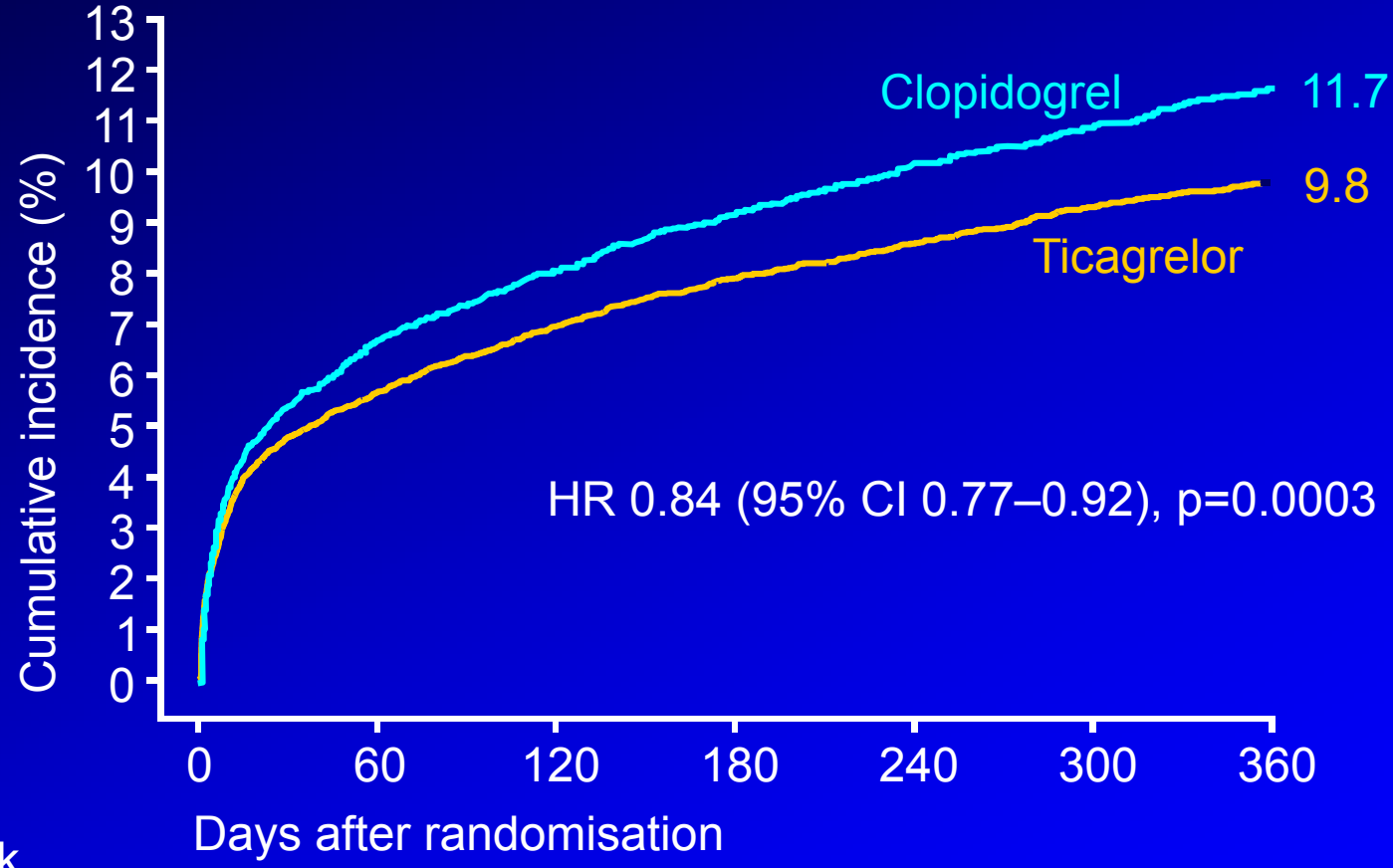
Ticagrelor: Pharmacology

- Class: *Cyclopentyl-triazolo-pyrimidine (CPTP)*
- Mechanism: Direct inhibition of the P2Y12 receptor (no metabolic activation required).
- Onset of action: Rapid, max reached at < 2 hrs
- Administration: Oral
- Plasma $t_{½}$ ≈10-12 hours (bid drug)
- "Off-target" effects: Blocks adenosine reuptake by RBC's



O'Donoghue M, Wiviott SD. Circulation. 2006;114:e600-e606;
Angiolillo DJ et al. Am J Cardiov Drugs. 2007; Teng, Eur J Clin Pharmacol 2010;66:487-496

PLATO: Ticagrelor *vs* Clopidogrel - CV death, MI or stroke)

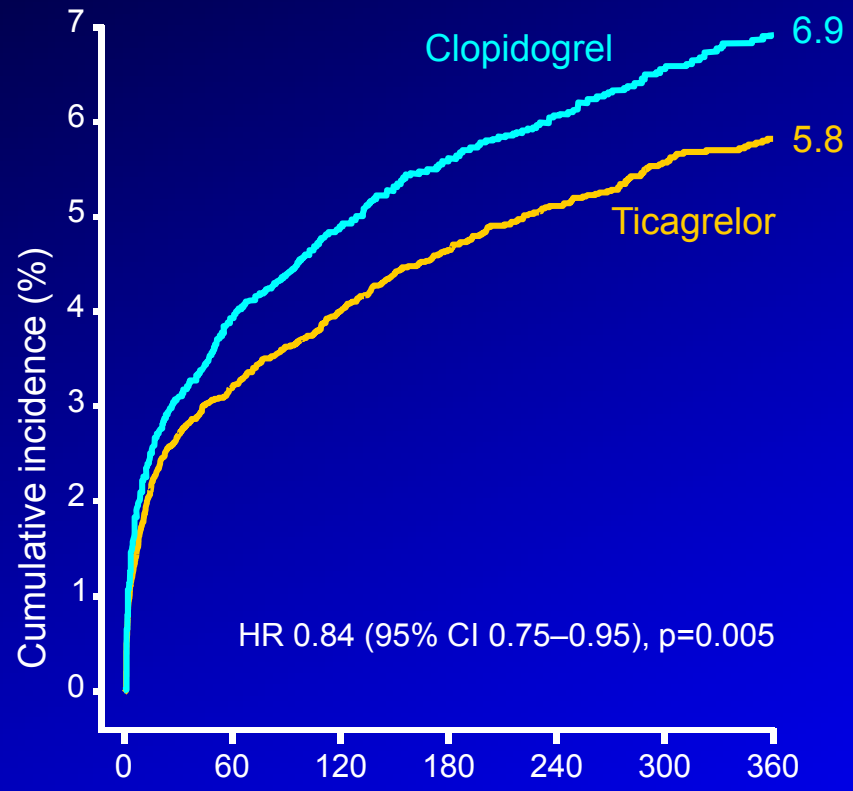


No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

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

PLATO: Secondary Efficacy Endpoints

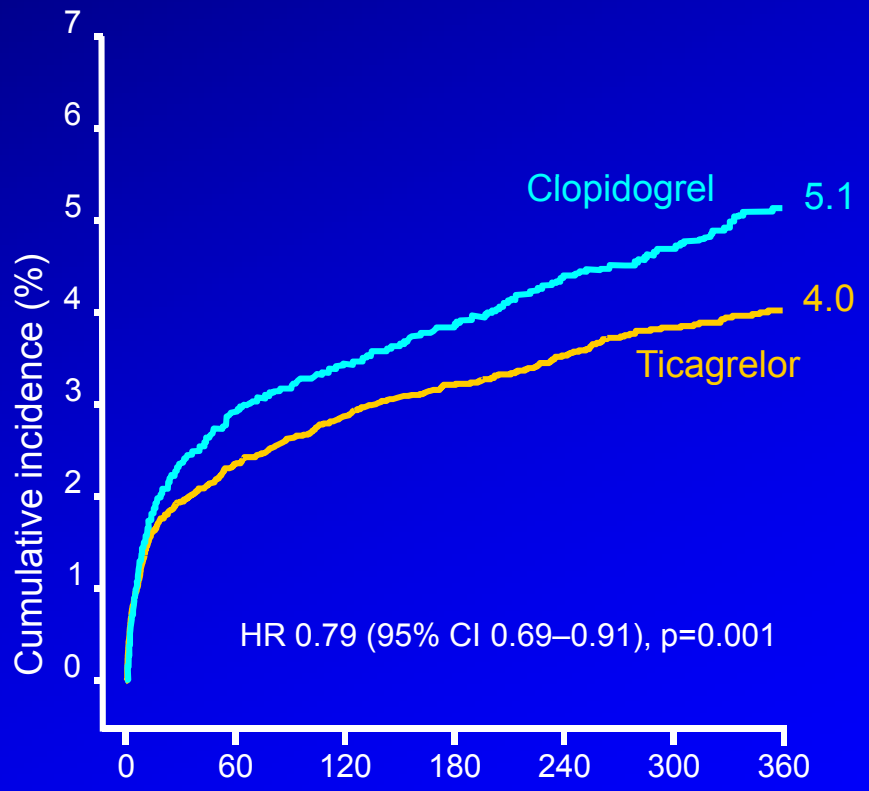
Myocardial infarction



No. at risk

Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

Cardiovascular death



	9,333	8,294	8,822	8,626	7119	5,482	4,419
	9,291	8,865	8,780	8,589	7079	5,441	4,364

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

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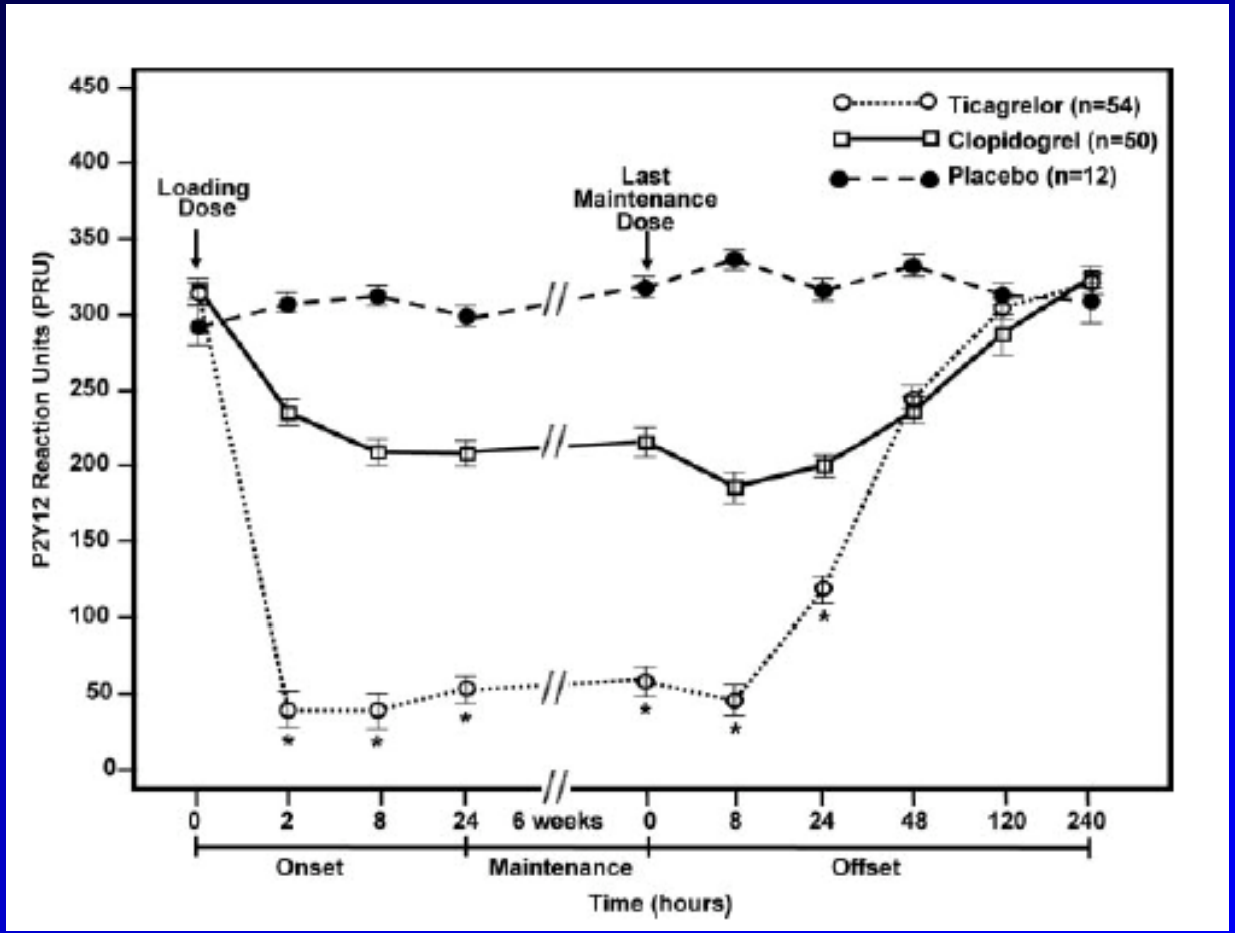
ONSET/OFFSET: Duration Until Complete Recovery After Ticagrelor MD Similar To Clopidogrel MD



"ticagrelor should be discontinued 7 days prior to surgery if a patient is to undergo elective surgery and antiplatelet effect is not desired" – EMEA for ticagrelor

Gurbel P et al, Circulation 2009

Ticagrelor – PLATO results stratified by sex

Ischemic Events

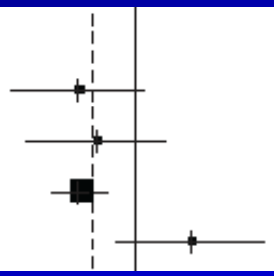
Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Ci.	HR (95% CI)	*P* value (Interaction)
Sex						0.82
Male		13336	9.2	11.1	0.85 (0.76, 0.95)	
Female		5288	11.2	13.2	0.83 (0.71, 0.97)	

Major Bleeding

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Ci.	HR (95% CI)	*P* value (Interaction)
Sex						0.76
Male		13184	11.9	11.4	1.05 (0.94, 1.16)	
Female		5237	10.7	10.5	1.01 (0.85, 1.21)	

Ticagrelor – PLATO results stratified by geographic region

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 CI.	HR (95% CI)	*P* value (Interaction)
Region						0.05
Asia/Australia		1714	11.4	14.8	0.80 (0.61, 1.04)	
Central/South America		1237	15.2	17.9	0.86 (0.65, 1.13)	
Europe/Middle East/Africa		13859	8.8	11.0	0.80 (0.72, 0.90)	
North America		1814	11.9	9.6	1.25 (0.93, 1.67)	



Ticagrelor – PLATO results stratified by clinical presentation

Table 22. Primary Endpoint: Planned Treatment Approach at Randomization *vs.* Index ACS event

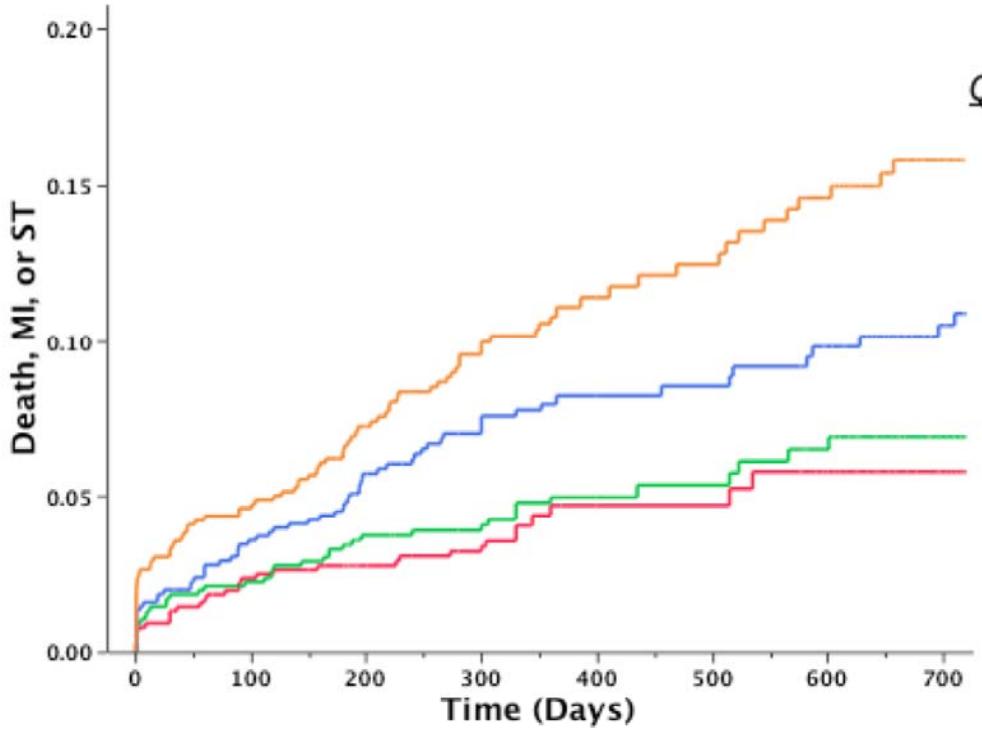
HR (95%CI) events / N	STEMI	NSTEMI	UA
Medical Mgmt	0.73 (0.46, 1.16) 75/451	0.85 (0.70, 1.02) 416/2910	0.97 (0.69, 1.37) 132/1726
Invasive Mgmt	0.86 (0.72, 1.01) 543/6575	0.82 (0.70, 0.97) 526/5045	0.95 (0.67, 1.35) 124/1386

HR from Cox prop. Haz model

More intensive antiplatelet therapy for EVERYONE not beneficial…..

Targeting Patients To Treat With Other Strategies: *OTR and Ischemic Events Post-PCI*

N=3,041



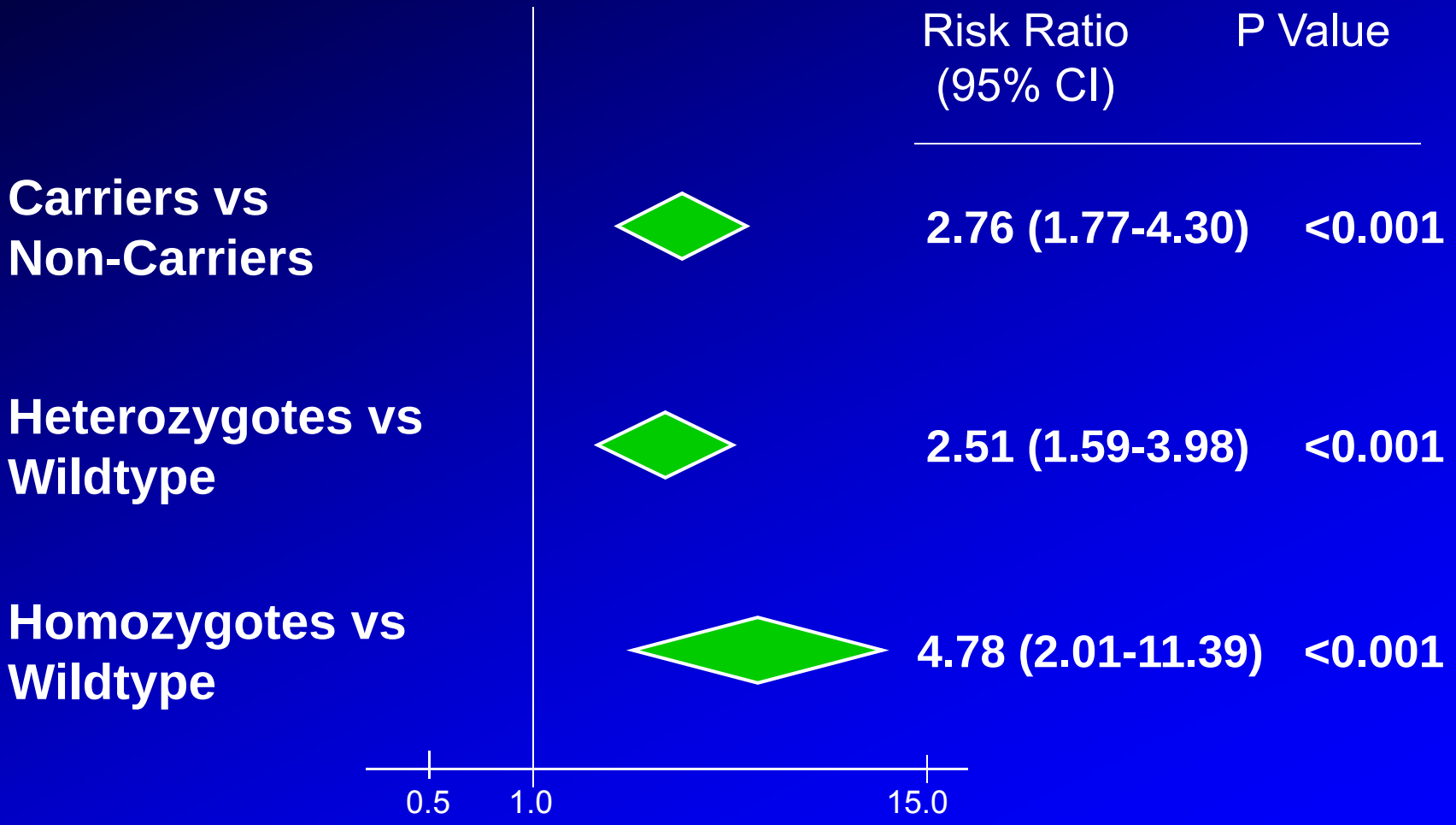
Quartile	Event Rate	P-value*
Q4	15.8%	<0.001
Q3	10.9%	0.02
Q2	6.9%	0.97
Q1	5.8%	–

No. at risk				
Q1	765	639	179	169
Q2	761	611	249	237
Q3	757	595	294	271
Q4	758	588	252	224

P-values adjusted for multiple comparisons

Brar S, ACC 2011 (in press)

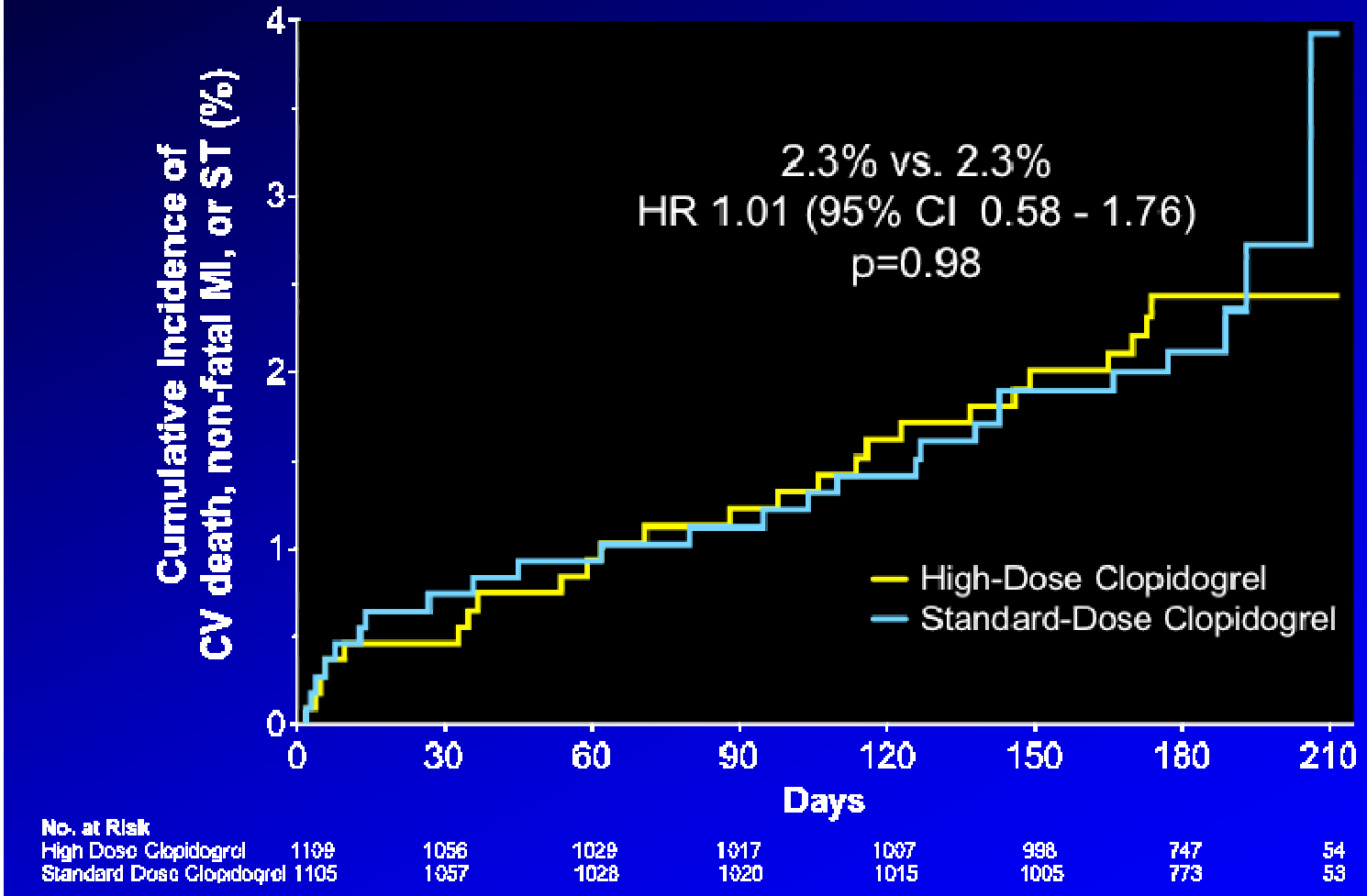
Targeting Patients To Treat With Other Strategies: *CYP2C19* Genotype and Stent Thrombosis



N=5,772

Mega JL et al. JAMA. Oct 27 2010;304(16):1821-1830

GRAVITAS: Standard- *vs* High-Dose Clopidogrel in Patients with High OTR after PCI (≥ 230 PRU)



10% Biomarker +

Observed event rates are listed; P value by log rank test.

Price MJ et al, JAMA 2011;305(11):1097-1105.

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Procedural Characteristics of the Randomized Groups

Characteristic	High-Dose Clopidogrel (N=1109)	Standard-Dose Clopidogrel (N=1105)
Indication for PCI		
Stable angina or ischemia	60%	60%
UA, no ST depression	24%	24%
NSTE-ACS		
UA, ST-dep, biomarker (-)	5%	5%
Cardiac biomarker (+)	10%	10%
ST-elevation MI	0.5%	0.2%
Treated lesions/patient	1.4 ± 0.6	1.4 ± 0.7
Stents/Patient	1.7 ± 1.0	1.6 ± 1.0
Total stented length (mm)	30 ± 23	29 ± 21

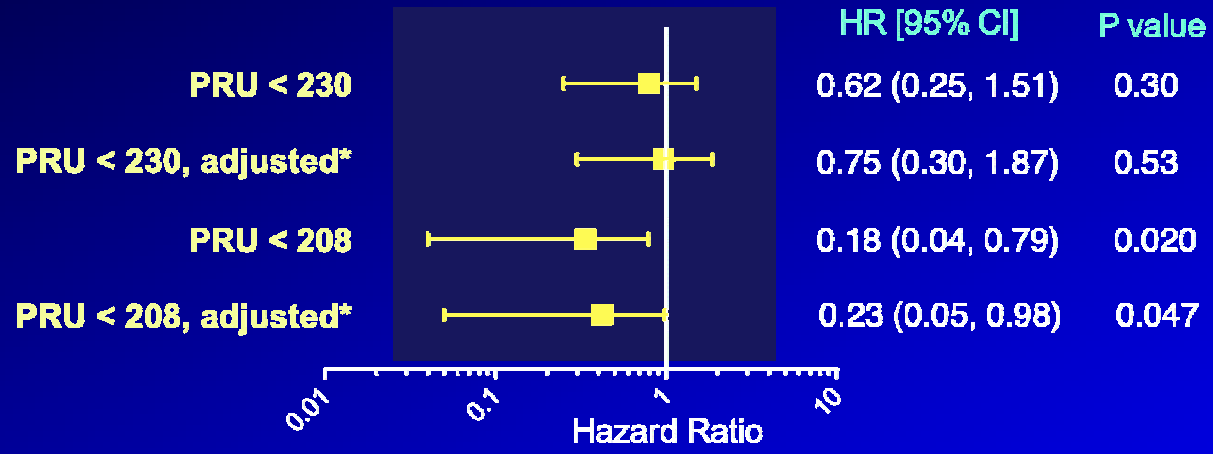
Price MJ, AHA 2010

GRAVITAS

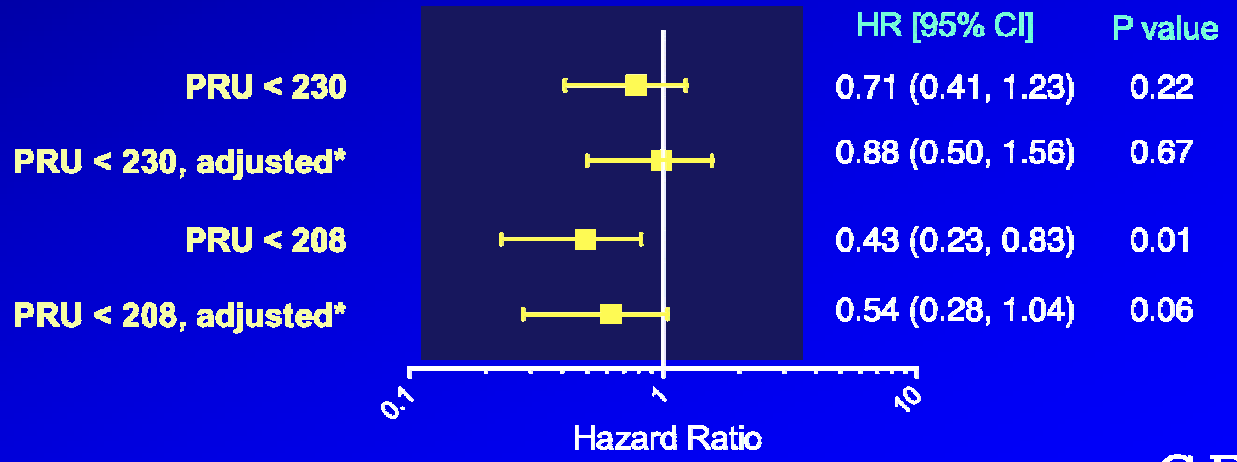
GRAVITAS: Hazard of Primary Endpoint According To *Achieved* OTR (Baseline or 30 days)

CV Death, MI or ST at 60 Days

N=2796



CV Death, MI or ST at 6 Months



Cox regression using OTR as a time-varying covariate
Price MJ et al, *in submission*

GRAVITAS

Baseline Characteristics of the Randomized Groups

Characteristic	High-Dose Clopidogrel (N=1109)	Standard-Dose Clopidogrel (N=1105)
Residual platelet reactivity, median (IQR)	282 PRU (255 - 320)	283 PRU (255 - 321)
Age, mean ± SD	64 ± 11	64 ± 11
Male sex	65%	65%
Diabetes Mellitus	44%	47%
Myocardial infarction	30%	29%
PCI	50%	45%
Cr Cl < 60 ml/min	40%	42%
Proton-Pump Inhibitor	30%	30%
Peri-procedural clopidogrel		
Naïve/Clopidogrel 600-mg load	53%	53%
Clopidogrel 75 mg/d > 7d	39%	37%
Clopidogrel Load + 75mg/d < 7d	8%	10%

Price MJ, AHA 2010

Baseline Characteristics: Non-Randomized Comparison

Characteristic	SD – High RPR N=1105	SD – Not High RPR N=586	p
Residual platelet reactivity, median (IQR)	283 PRU (255 - 321)	151 PRU (105 - 191)	<0.001
Age, years	64 ± 11	62 ± 10	<0.001
Male sex	65%	80%	<0.001
Diabetes Mellitus	47%	29%	<0.001
Body mass index (median)	31	29	<0.001
Cr Cl < 60 ml/min	42%	27%	<0.001
Proton pump inhibitor	30%	20%	<0.001
Indication for PCI			0.41
Stable angina or ischemia	60%	56%	
UA, no ST depression	24%	28%	
NSTE-ACS			
UA, ST-dep, biomarker (-)	5%	5%	
Cardiac biomarker (+)	10%	11%	

Gift
GENOTYPE INFORMATION & FUNCTIONAL TESTING

Results: Influence of *PON1*, *CYP2C19*, and *ABCB1* on the Primary Endpoint

P < 0.0013 for statistical significance

On-Treatment Reactivity at Screening (12-24 hrs post-PCI) N=1013

SNP	R^2	
PON1 Q192R	0.2%	P = 0.42
*CYP2C19*2*	6.5%	P = 2.2 x 10^{-15}
*CYP2C19*17*	0.5%	P = 0.08
ABCB1 3435 C→T	0.1%	P = 0.61

Change in On-Treatment Reactivity at 30 days N=714

SNP	R^2	
PON1 Q192R	0%	P = 0.71
*CYP2C19*2*	5.1%	P = 1.4 x 10^{-5}
*CYP2C19*17*	1.2%	P = 0.02
ABCB1 3435 C→T	0%	P = 0.40

GRAVITAS

Co-dominant model, adjusted for tx and characteristics associated with OTR.

GENOTYPE INFORMATION & FUNCTIONAL TESTING

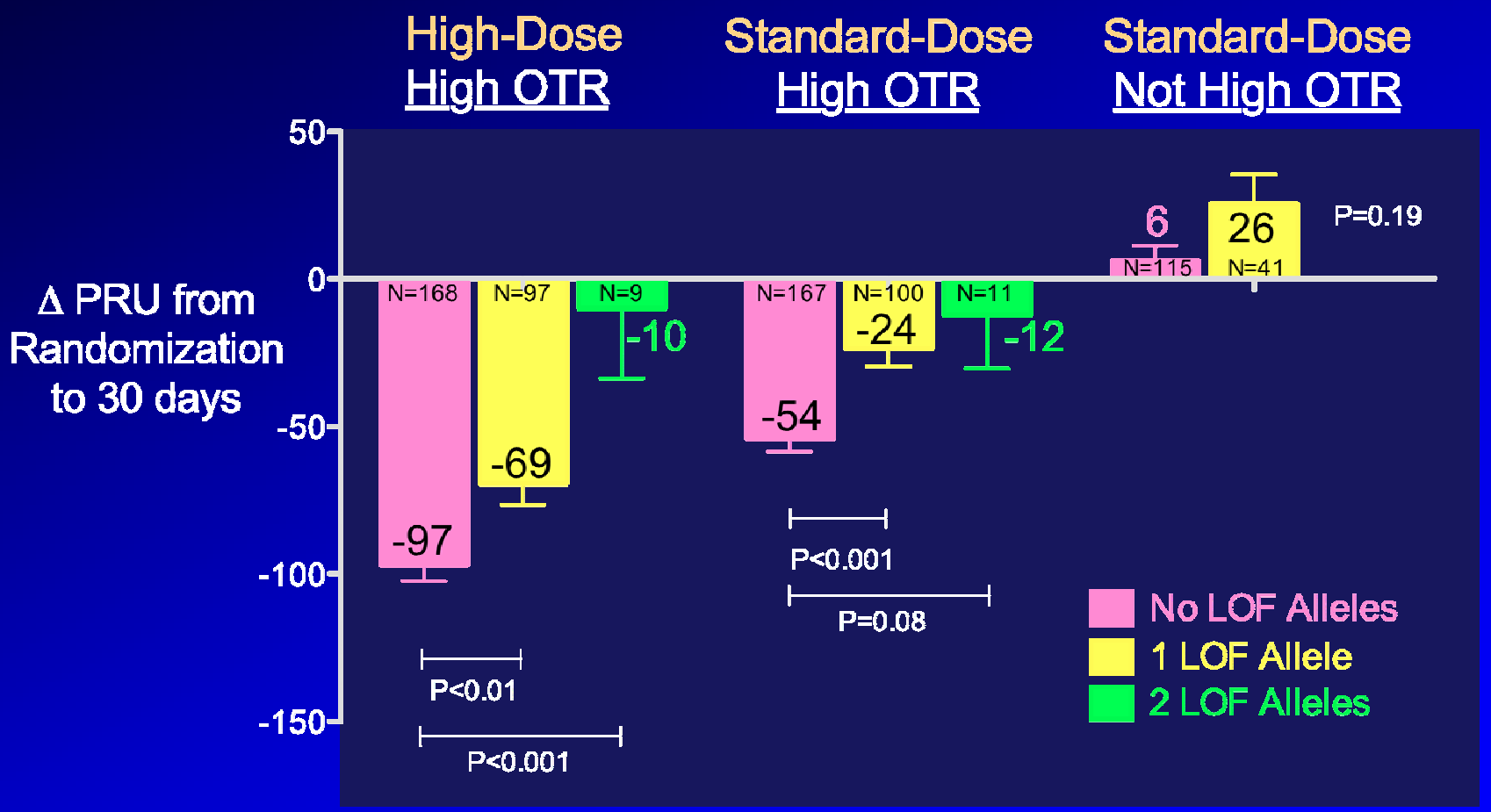
Influence of Sex On Clopidogrel Response Variability

Characteristic	†Partial η^2	P value
CYP2C19 genotype	.067	<.001
Body mass index‡	.036	<.001
Diabetes mellitus	.033	<.001
Age -- years	.013	<.001
Sex	.011	0.001
History of congestive heart failure	.0049	0.027
Creatinine clearance < 60 ml/min	.0020	0.15
History of hyperlipidemia	.0017	0.19
Current smoking	<.001	0.41
History of hypertension	<.001	0.82

GRAVITAS

Gift
GENOTYPE INFORMATION & FUNCTIONAL TESTING

CYP2C19 Genotype is Associated With the PD Effect of Clopidogrel at 30 Days In Patients with High OTR Regardless of Dosing Strategy

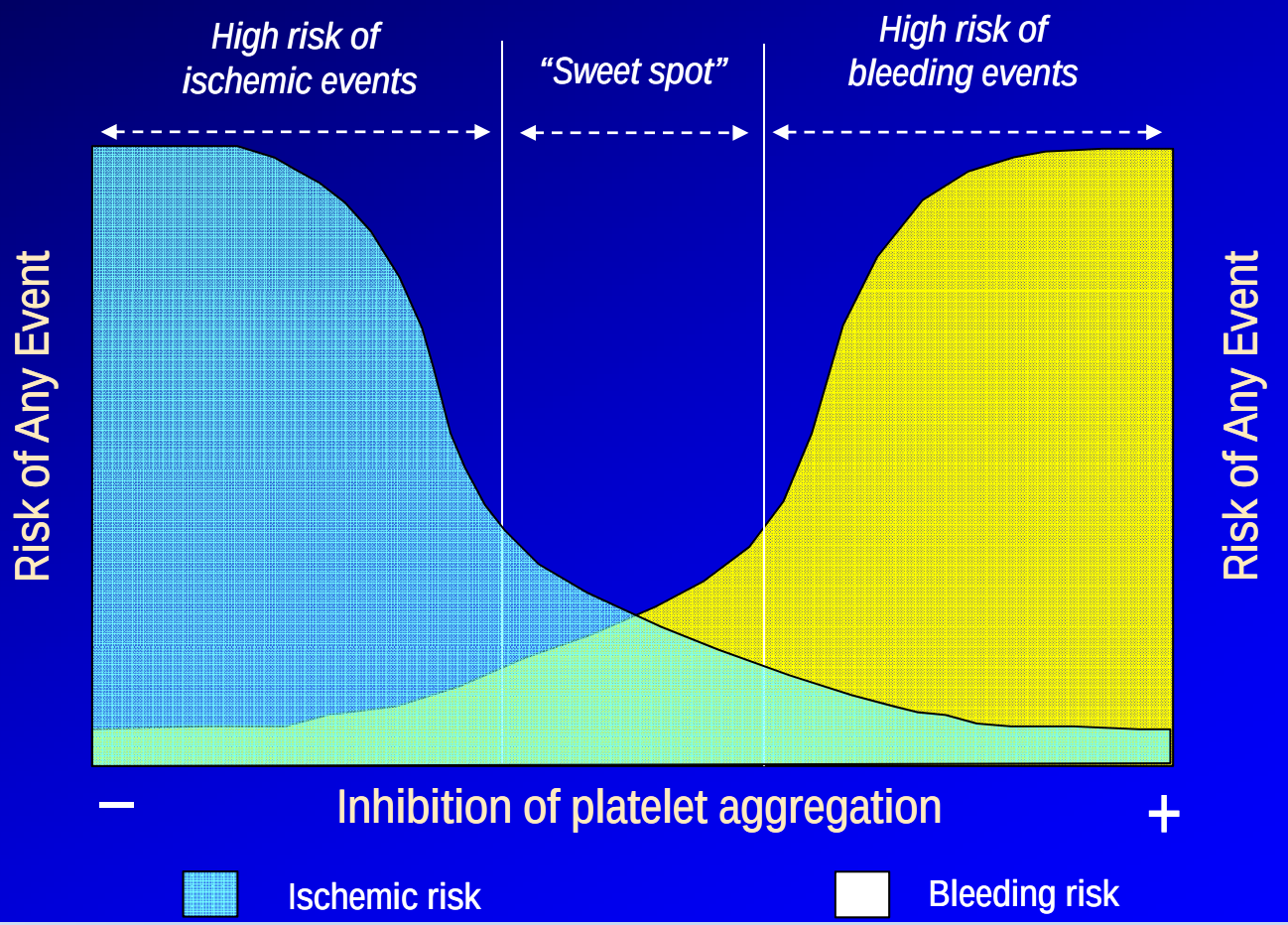


High-dose: clopidogrel 600 re-load then 150 mg/day; Standard-dose: clopidogrel 75 mg/day.
High OTR: ≥ 230 PRU at enrollment (12-24 hrs post-PCI)
P values adjusted for multiple comparisons

GRAVITAS

Implications of GRAVITAS and TRIGGER-PCI: Weigh the Benefits in Low-Risk Patients

Platelet Inhibition Related to the Risk of Ischemic and Bleeding Events



Ferreiro JL et al. Thromb Haemost. 2010;103:1-8.

What are we doing at Scripps Clinic?

- STEMI and 1° PCI – prasugrel reasonable first choice (if no contraindication)
  - If at higher risk for bleed, clopidogrel and if PRU < 208, continue
- NSTE-ACS
  - Quick to lab (< 4 hrs from presentation):
    - Prasugrel if no contraindication
    - Concern for bleeding: clopidogrel, if PRU < 208, continue
  - Later to cath lab
    - Pre-treat, check PRU on table
    - If PRU < 208, continue on clopidogrel
- Elective PCI
  - if complex (multiple stents, DM, bifurcation, etc) and PRU > 208, prasugrel.*

* Consider clopidogrel 150 mg, prasugrel 5 mg, or cilostazol in pts at higher bleeding risk, recheck PRU and FU CYP2C19 genotype in 1 – 2 weeks

Bedside Genotyping Has (Almost) Arrived!
Sample to result turn-around times < 4 hrs

- Nanosphere (3 - 4 hrs), Spartan (1 hr), Quest (1 hr)
- Whole blood/buccal swab
- Includes nucleic acid purification step
- Can run single samples (no need to batch)
- Minimal pipetting – run in cath lab, holding area, or clinical lab

Summary

- Prasugrel superior to clopidogrel in ACS patients treated with PCI.
  - Beware previous CVA/TIA, age ≥ 75 without other risk factors, light body weight.
- Ticagrelor superior to clopidogrel in ACS patients
  - Increased non-fatal non-CABG bleeding
  - Must still wait several days after d/c for surgery
  - No benefit seen in patients with unstable angina, ?North America?

Summary (2)

- Clopidogrel outcomes influenced by response variability and *CYP2C19* genotype.
  - Achieved PRU < 208 predicted improved outcome in GRAVITAS, independent of clinical presentation
- *CYP2C19* genotype predicts reduced PD response to double-dose clopidogrel.
- Although no large RCT trials of individualized APT in ACS patients, the absence of data does not mean the data of absence.