How To Overcome The Challenges: Double The Dose?

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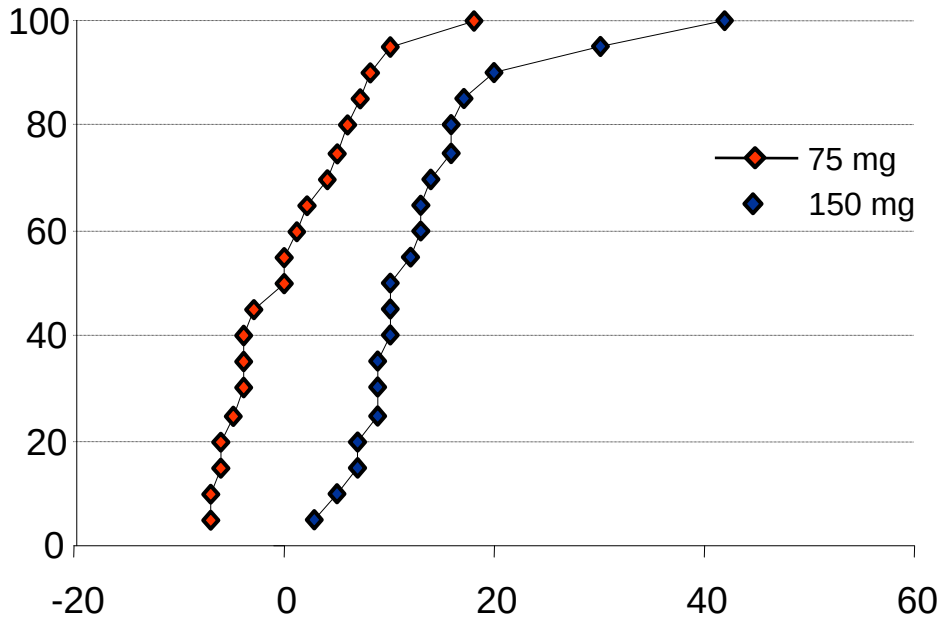
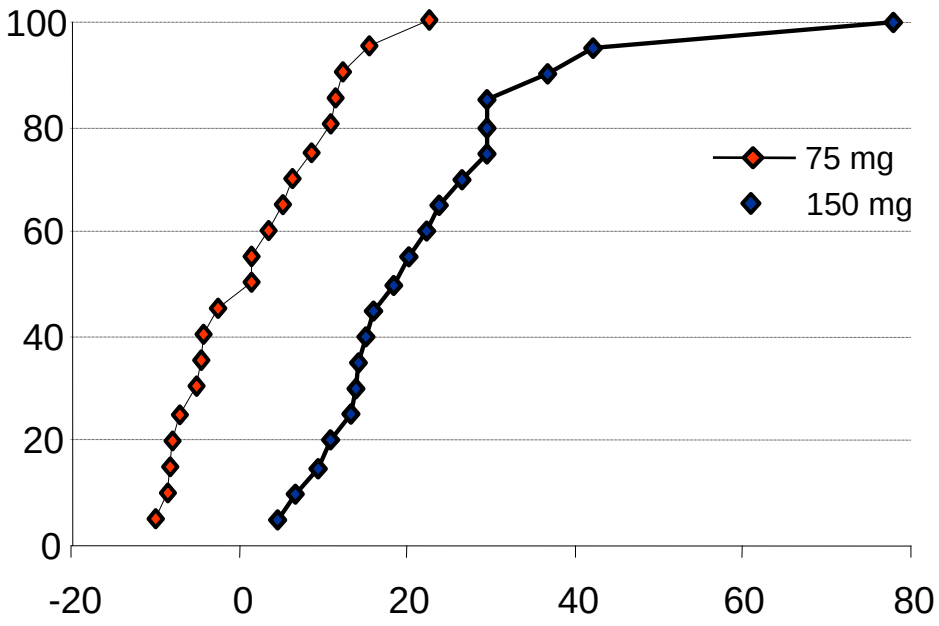
Option 1.

Double The Clopidogrel Dose In Everyone!

OPTIMUS

Cumulative distribution curves of absolute change of maximal platelet aggregation and inhibition of maximal platelet aggregation between baseline (study time point 1) and 30 days (study time point 2)





The absolute change in post treatment platelet reactivity and IPA was >10% in 75% and 85% of patients in the 150mg group, respectively.

Angiolillo DJ et al. *Circulation.* 2007;115:708-16.

CURRENT OASIS-7: Low vs. High-Dose Clopidogrel And Aspirin in ACS Patients Managed Invasively

25,807 ACS patients
Intended PCI ≤ 24 hrs
No restriction on GP IIb/IIIa inhibitors

Clopidogrel 600 mg
150 mg from Day 2 to Day 7
75mg from Day 8 to 30

Clopidogrel 300 mg
75 mg from Day 2 to 30

ASA 300 mg Day 1
75–100 mg
from Day 2 to 30

ASA 300 mg Day 1
300 mg–325 mg
from Day 2 to 30

ASA 300 mg Day 1
75–100 mg
from Day 2 to 30

ASA 300 mg Day 1
300 mg–325 mg
from Day 2 to 30

1º Outcome: Death / MI /stroke, 30 Days; 2º outcome: CURRENT bleeding

Mehta SR et al. N Engl J Med. 2010;363(10):930-942

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Clopidogrel: Double vs Standard Dose Primary Outcome and Components

	Standard	Double	HR	95% CI	P	Intn P
CV Death/MI/Stroke						
PCI (2N=17,232)	4.5	3.9	0.85	0.74-0.99	0.036	0.03
No PCI (2N=7855)	4.3	4.9	1.14	0.95-1.44	0.14	
Overall (2N=25,087)	4.4	4.2	0.95	0.84-1.07	0.370	
MI						
PCI (2N=17,232)	2.6	2.0	0.78	0.64-0.95	0.012	0.025
No PCI (2N=7855)	1.4	1.7	1.25	0.87-1.79	0.23	
Overall (2N=25,087)	2.2	1.9	0.86	0.73-1.03	0.097	
CV Death						
PCI (2N=17,232)	1.9	1.9	0.96	0.77-1.19	0.68	1.0
No PCI (2N=7855)	2.8	2.7	0.96	0.74-1.26	0.77	
Overall (2N=25,087)	2.2	2.1	0.96	0.81-1.14	0.628	
Stroke						
PCI (2N=17,232)	0.4	0.4	0.88	0.55-1.41	0.59	0.50
No PCI (2N=7855)	0.8	0.9	1.11	0.68-1.82	0.67	
Overall (2N=25,087)	0.5	0.5	0.99	0.70-1.39	0.950	

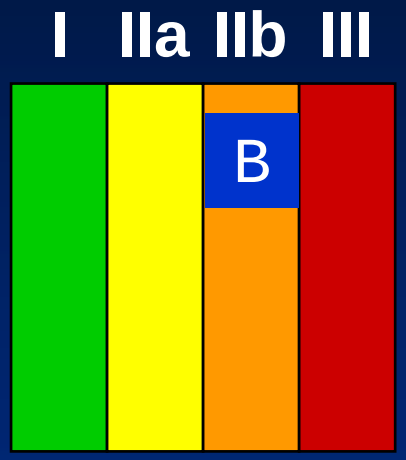
Clopidogrel Double vs Standard Dose Bleeding PCI Population

	Clopidogrel				
	Standard N= 8684	Double N=8548	Hazard Ratio	95% CI	P
TIMI Major[1]	0.5	0.5	1.06	0.70-1.61	0.79
CURRENT Major[2]	1.1	1.6	1.44	1.11-1.86	0.006
CURRENT Severe[3]	0.8	1.1	1.39	1.02-1.90	0.034
Fatal	0.15	0.07	0.47	0.18-1.23	0.125
ICH	0.035	0.046	1.35	0.30-6.04	0.69
RBC transfusion ≥ 2U	0.91	1.35	1.49	1.11-1.98	0.007
CABG-related Major	0.1	0.1	1.69	0.61-4.7	0.31

[1]ICH, Hb drop ≥ 5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal
[2]Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units
[3]Fatal or ↓ Hb ≥ 5 g/dL, sig hypotension + inotropes/surgery, ICH or txn of ≥ 4 units

Recommendations for Antiplatelet Therapy

New Recommendation



In patients with definite UA/NSTEMI undergoing PCI as part of an early invasive strategy, the use of a loading dose of clopidogrel of 600 mg, *followed by a higher maintenance dose of 150 mg daily for 6 days, then 75 mg daily may be reasonable* in patients not considered at high risk for bleeding

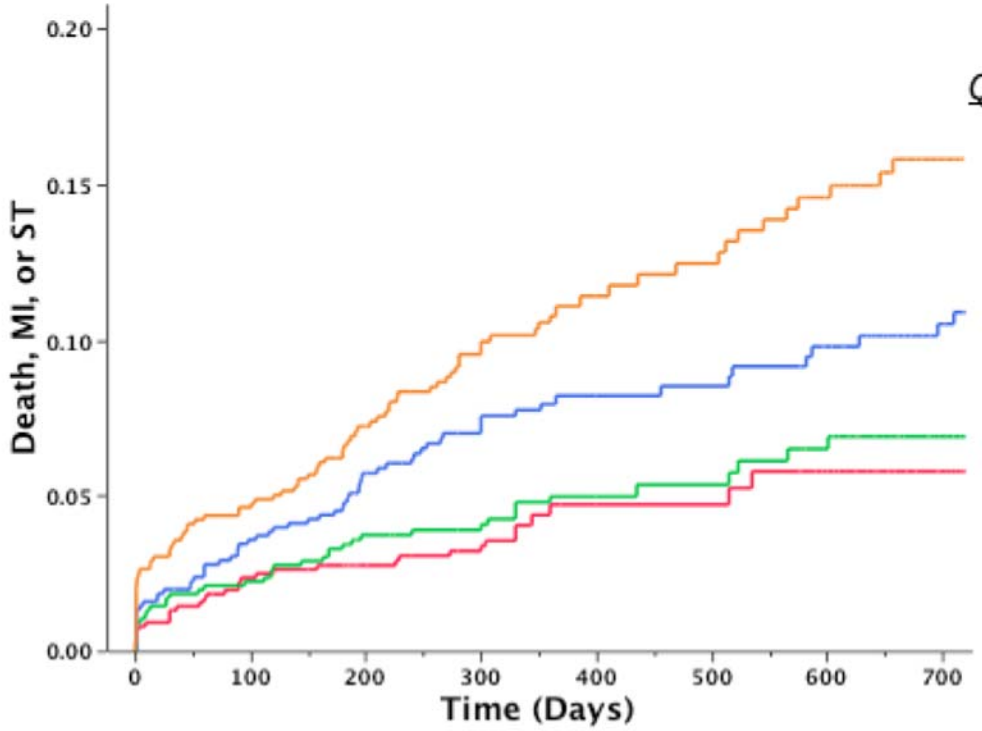
Class IIb: Benefit ≥ Risk; ***Treatment may be considered***
Additional studies with broad objectives needed; additional registry data would be helpful.

Option 2.

Double The Clopidogrel Dose Based On A Platelet Function Test....

Meta-Analysis of OTR and Ischemic Events Post-PCI: Increasing Risk With Greater Residual Reactivity

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)

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Price MJ, AHA 2010

GRAVITAS Study Design

Elective or Urgent PCI with DES*

VerifyNow P2Y12 Test 12-24 hours post-PCI

N=5429

PRU ≥ 230

R

N = 1109

High-Dose Clopidogrel†
clopidogrel 600-mg, then
clopidogrel 150-mg daily X 6 months

N = 1105

Standard-Dose Clopidogrel†
clopidogrel 75-mg daily X 6 months

Primary Efficacy Endpoint: CV Death, Non-Fatal MI, Stent Thrombosis at 6 mo
Key Safety Endpoint: GUSTO Moderate or Severe Bleeding at 6 mo
Pharmacodynamics: Repeat VerifyNow P2Y12 at 1 and 6 months

*Peri-PCI clopidogrel per protocol-mandated criteria to ensure steady-state at 12-24 hrs

†placebo-controlled All patients received aspirin (81-162mg daily)

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

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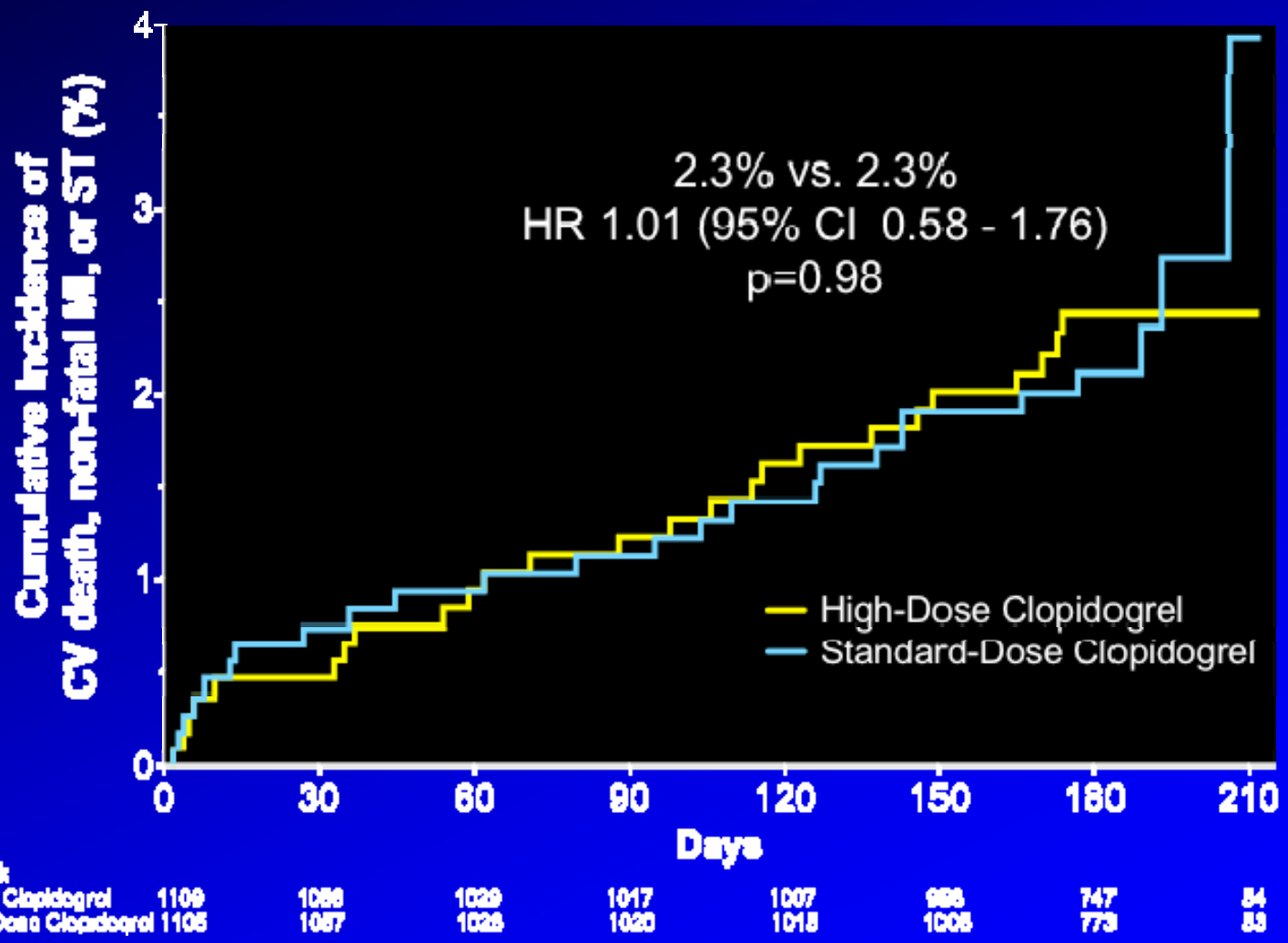
Primary Endpoint: CV Death, MI, Stent Thrombosis



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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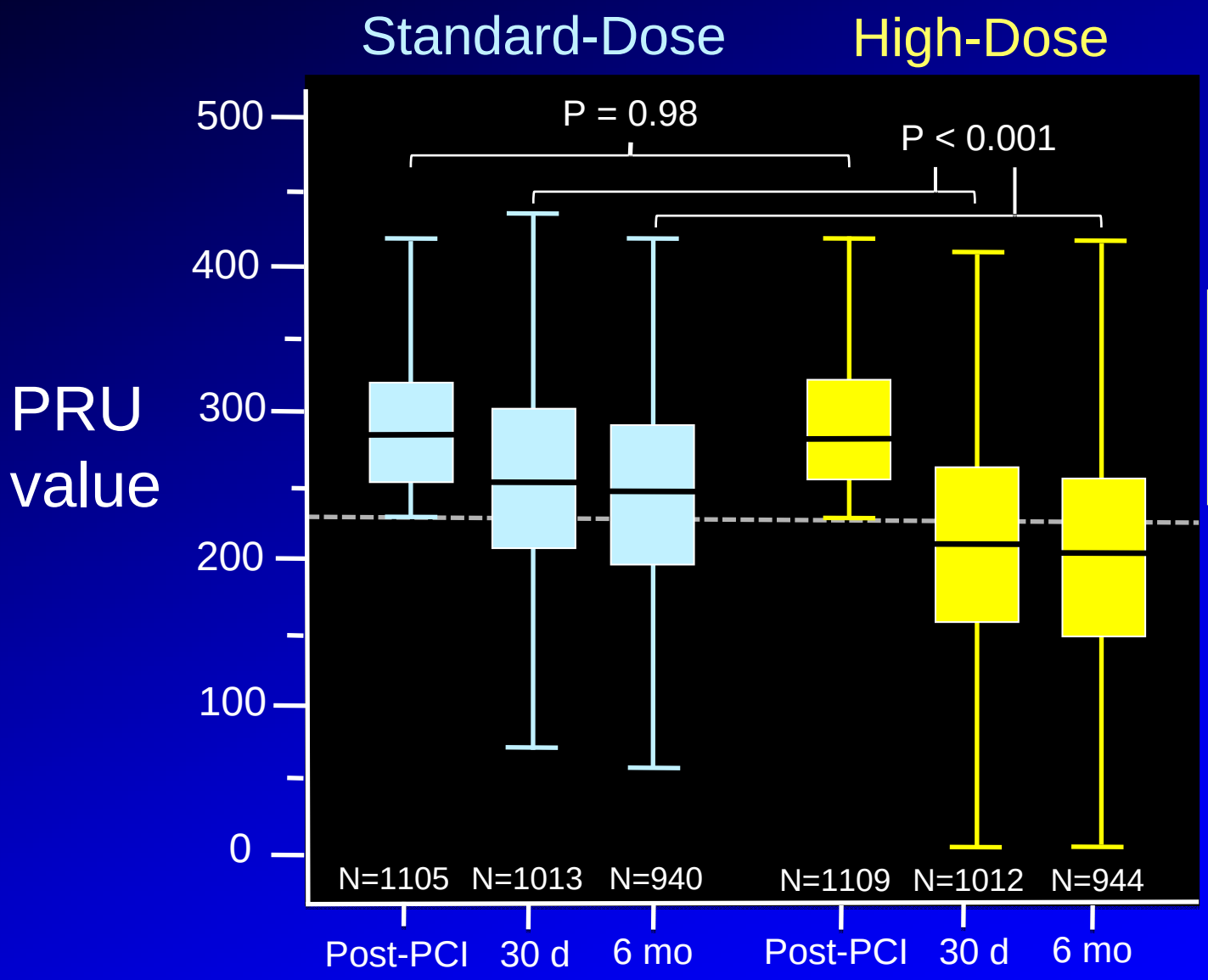
Pharmacodynamics: Effect of SD vs HD Clopidogrel



Persistently high reactivity @ 30 days: 62% vs 40%, p<0.001

ITT population

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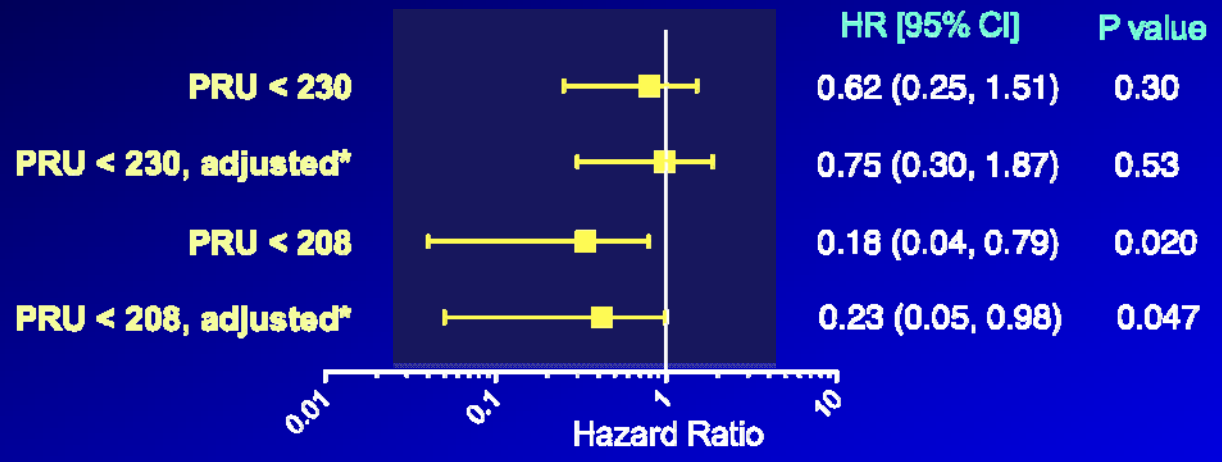
Price MJ et al, JAMA. 2011;305(11):1097-1105

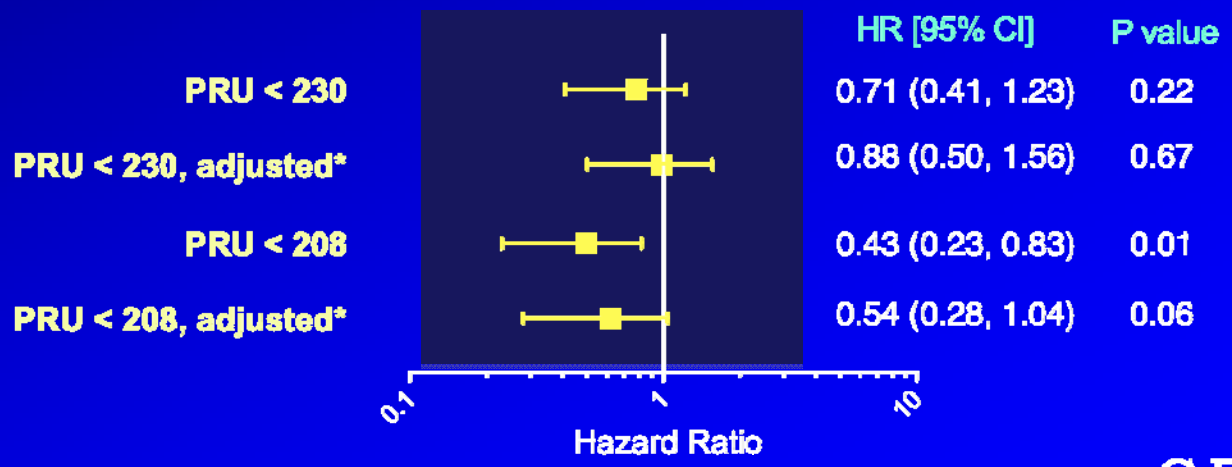
GRAVITAS: Hazard of Primary Endpoint According To *Achieved* OTR (Baseline or 30 days)

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*

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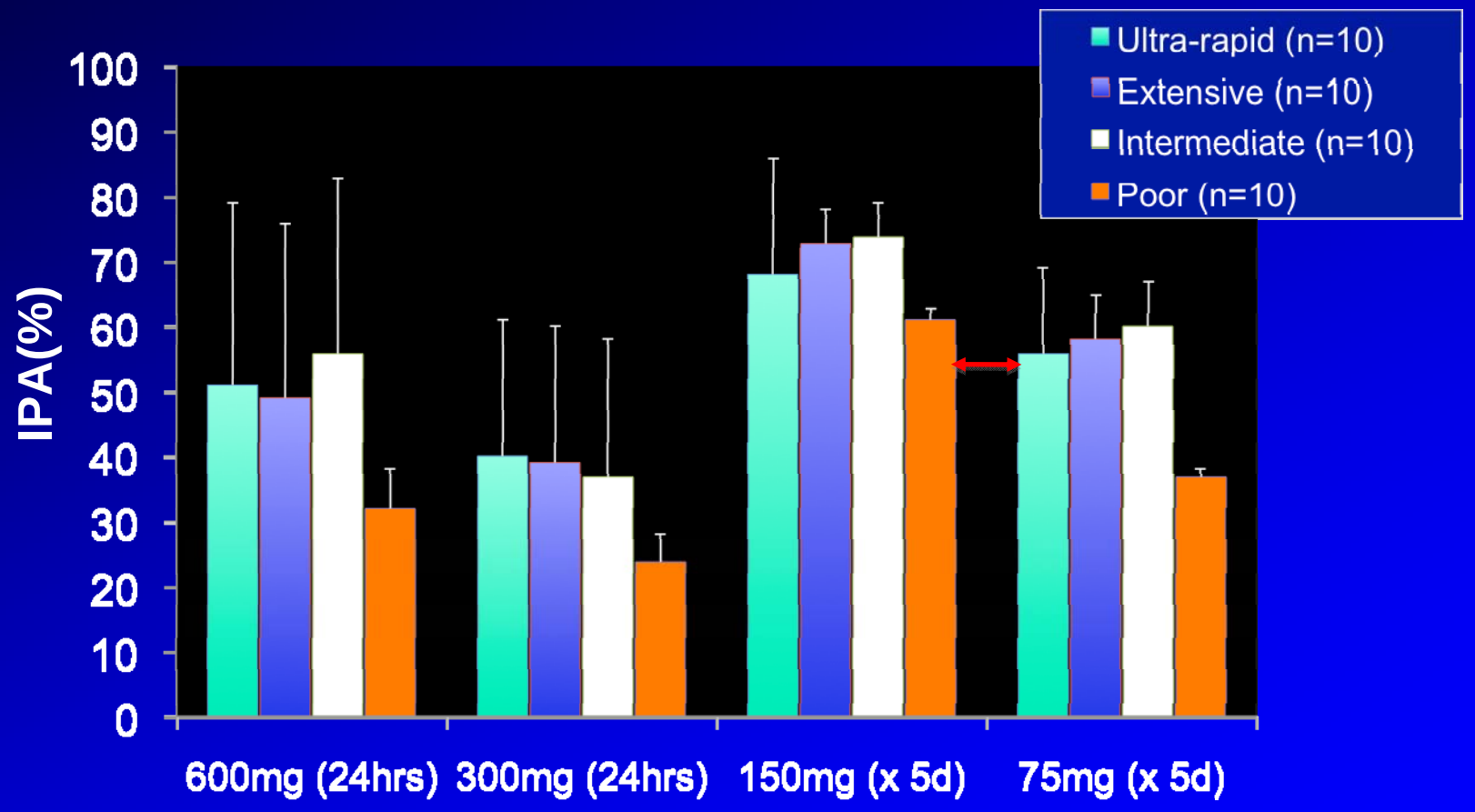
Option 3.

Double The Clopidogrel Dose Based On A CYP2C19 genotype...

High-Dose Clopidogrel Provides Greater Inhibition Than Standard-Dose in Volunteers Regardless of CYP2C19 Metabolic Phenotype: *Light Transmittance Aggregometry*



The higher the IPA, the greater the inhibitory effect of clopidogrel

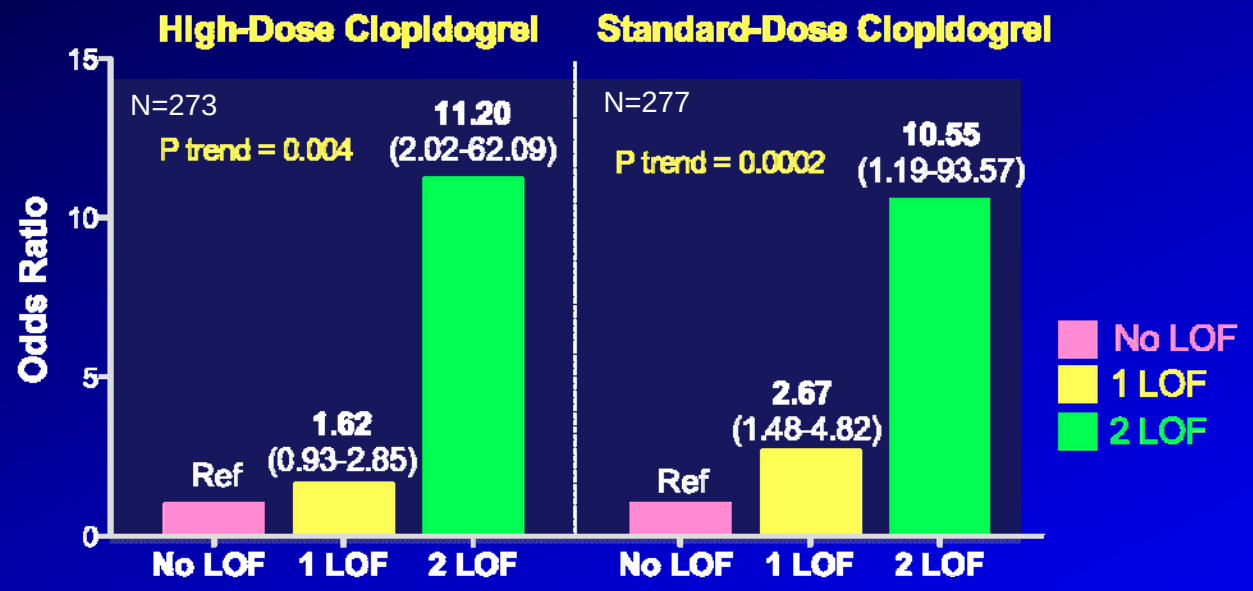
Adapted from Plavix package insert

Price MJ, ACC-i2 2011

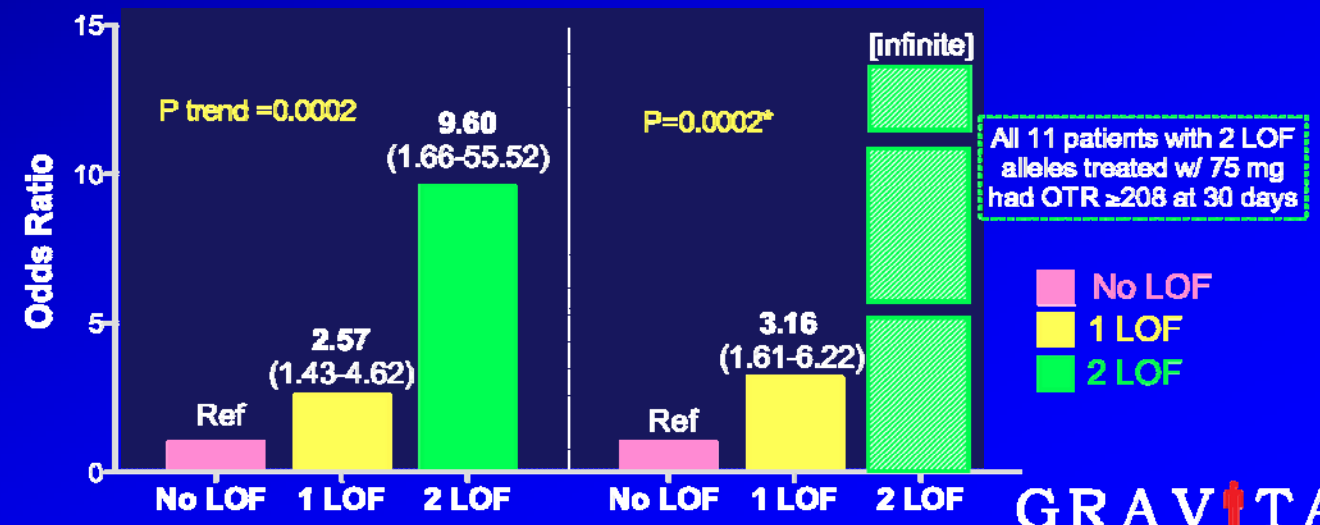
Gift
GENOTYPE INFORMATION & FUNCTIONAL TESTING

CYP2C19 LOF Allele Is Associated With Higher Risk of Persistently High OTR at 30 Days Regardless of Dose

ORs for PRU ≥ 230 at 30 Days



ORs for PRU ≥ 208 at 30 Days



Patients with OTR ≥ 230 PRU at 12-24 hours after PCI. Adjusted ORs.

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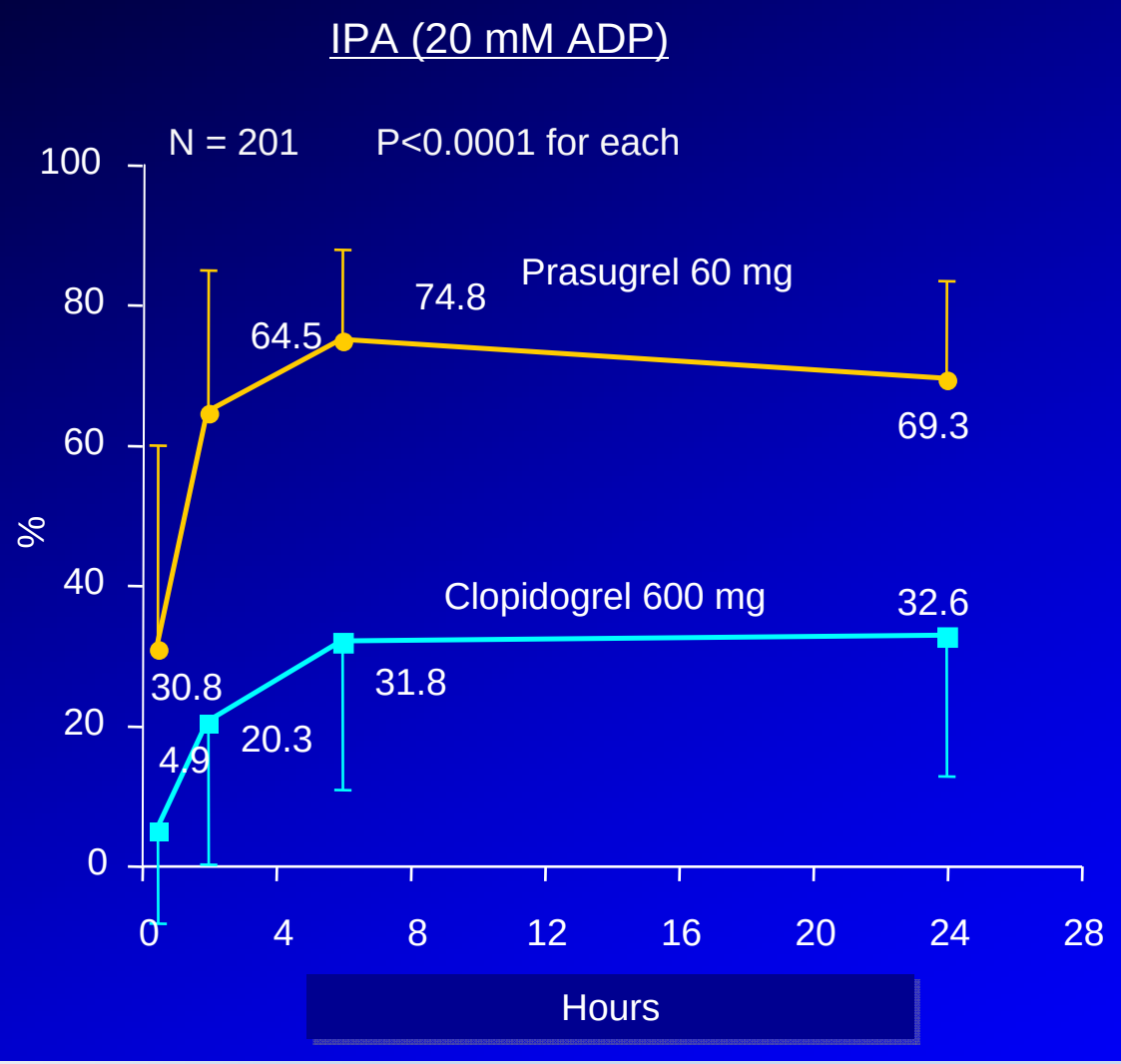
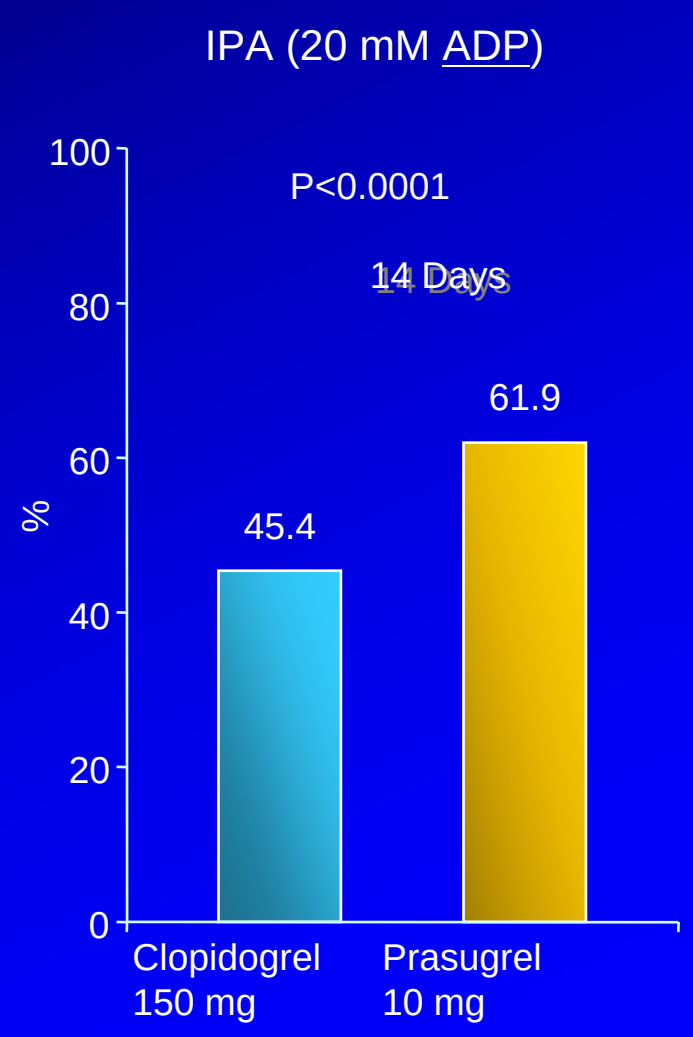
PRINCIPLE TIMI-44: Comparative Pharmacodynamics of Prasugrel and High-Dose Clopidogrel





Wiviott SD et al. Circulation. 2007;116:2923-2932.

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Summary: Clinical evidence supporting double-dose clopidogrel

- In the overall population undergoing PCI, clopidogrel 150 mg daily provides greater inhibition than 75 mg.
  - CYP2C19*2 allele carriage is associated with diminished PD effect
- A uniform approach of 600 mg LD/150 mg x 6 days may reduce ischemic events in ACS patients who end up undergoing PCI, at the cost of increased bleeding.
  - New 2011 ACCF/AHA Class IIB guideline recommendation
- A fixed-dose of clopidogrel 150 mg in non-responders to standard dosing did not reduce ischemic events in GRAVITAS
  - Incremental effect of high-dose was modest and variable
  - Overall, patients with lower reactivity did better (post-hoc)
  - Clinical efficacy of more intensive $P2Y_{12}$ inhibition?