Optimal Dosing of Antiplatelet Therapy in ACS

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Optimizing Clopidogrel

- Clopidogrel “resistance”– frequency and clinical outcomes
- Pharmacodynamic studies– can we overcome clopidogrel “resistance” through higher doses?
- Clinical studies– do these changes in platetet inhibition translate into clinical benefit?
- Implications for clinical care

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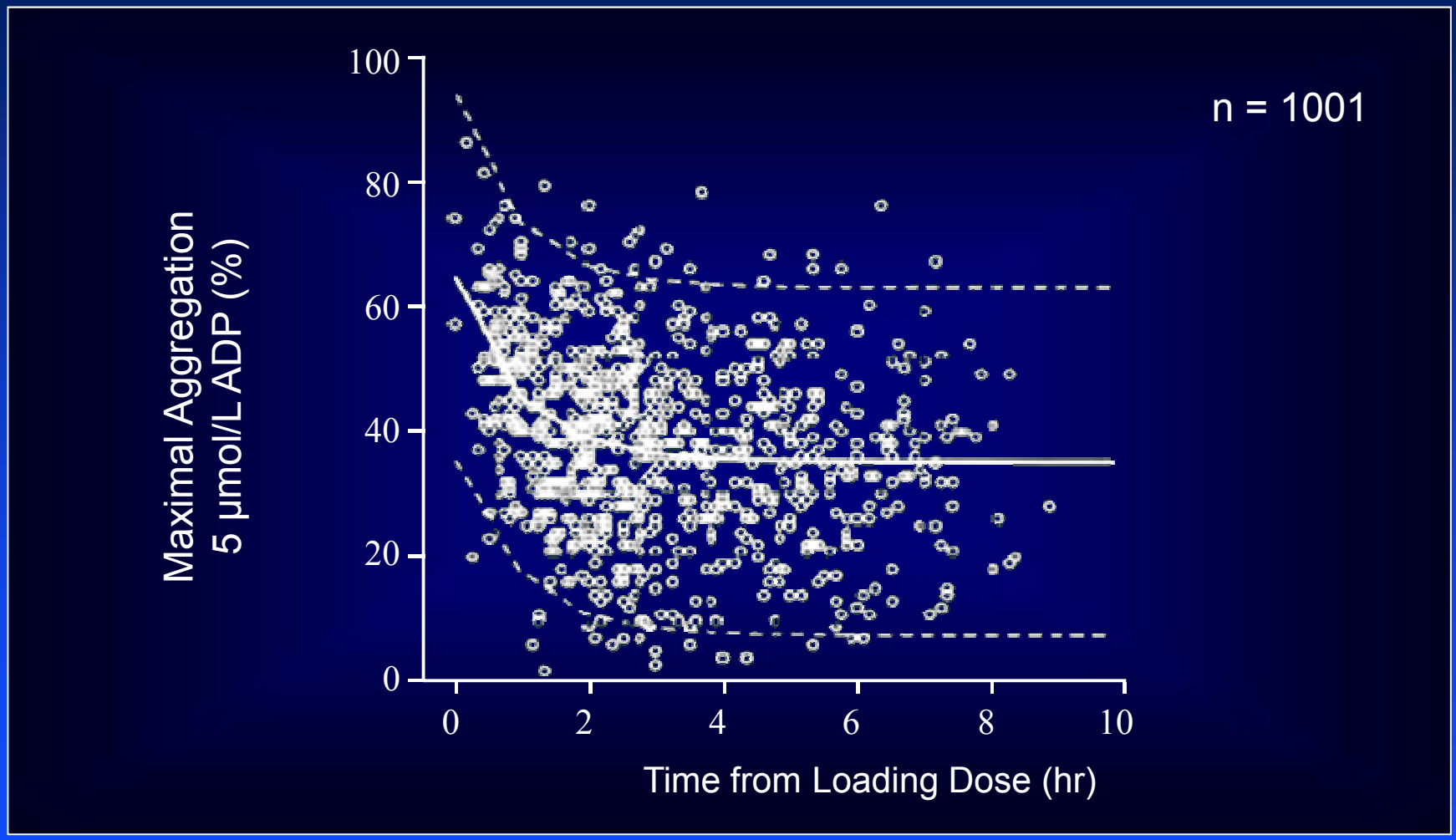
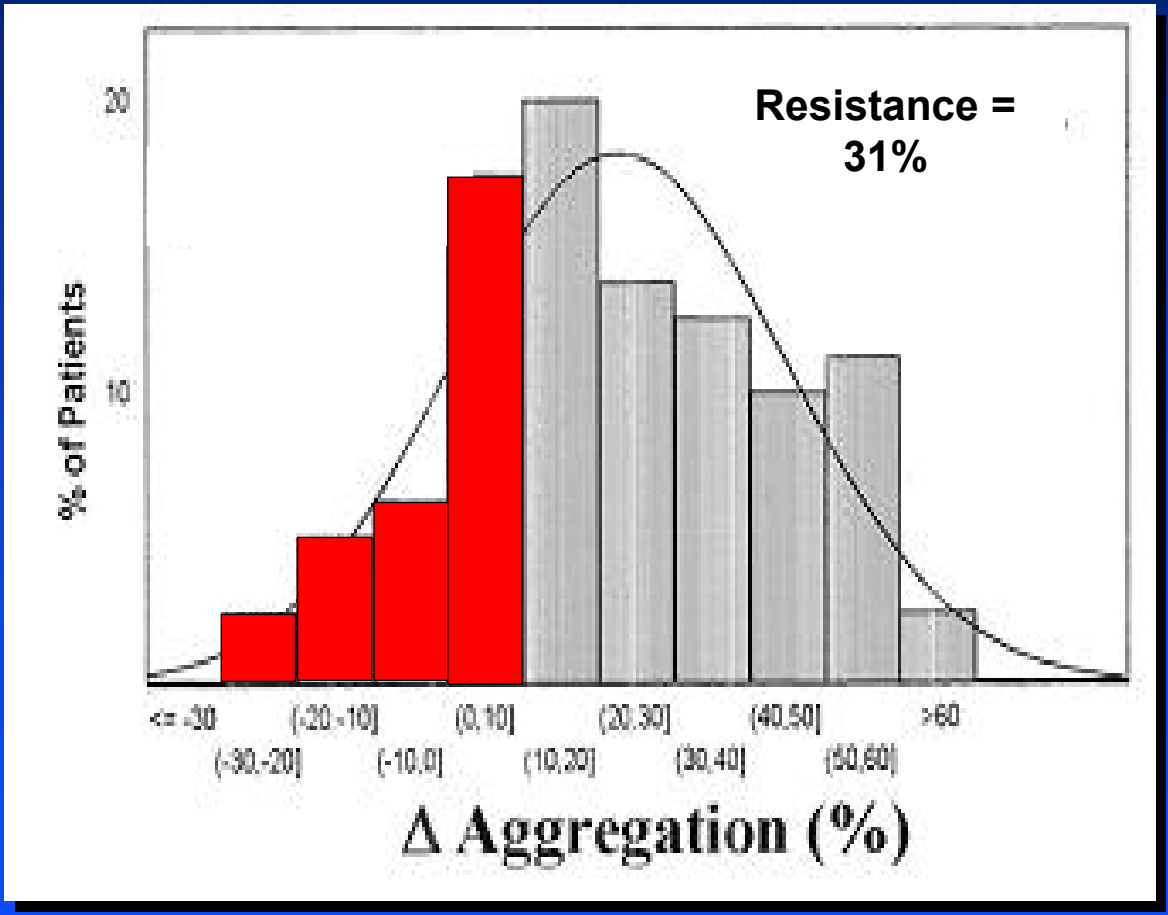
Variability in Platelet Reactivity After Clopidogrel 600 mg



Hochholzer W et al. Circulation. 2005;111:2560-2564.

Interpatient Variability in Clopidogrel Response

24 hours after PCI



Platelet Response Study

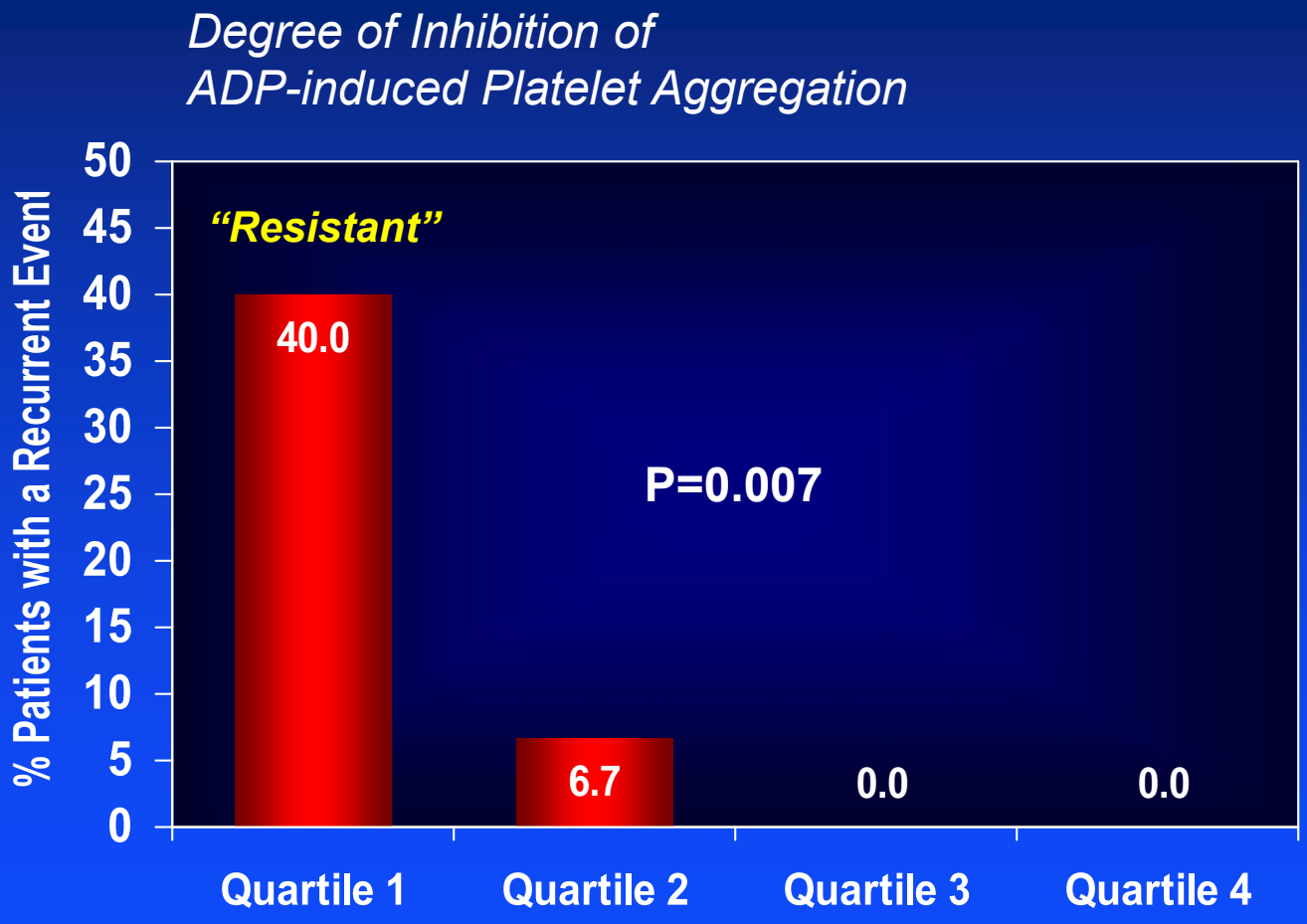
- 100 stent patients treated with clopidogrel 300 mg x 1, then 75 mg QD x 1 month
- Platelet fxn assessed by LTA and p-selectin expression
- Clopidogrel "resistance" defined as <10% reduction in aggregation levels
- Resistance levels
  - 31% at 1 and 5 days
  - 17% at 1 month

Gurbel PA et al. Circulation 2003;107:2908-13

Mechanisms of Variable Response

- Non-compliance
- Differences in underlying platelet reactivity
  - *ACS, smoking, inflammatory state*
- Genetic factors
  - *Cytochrome P450 polymorphisms (e.g. CYP2C19, CYP2C9, CYP2B6) → reduced conversion of clopidogrel to active metabolite*
  - *Differences in absorption (ABCB1 transporter gene)*
- Drug-drug interactions (e.g., PPI)
- Gene-Gene, Gene-Drug interactions….

Relationship Between Clopidogrel Resistance and Post-PCI Ischemic Events



- 60 patients with STEMI treated with Primary PCI (15 patients per quartile)
- Clopidogrel 300 mg load / 75 mg/day x 3 months
- Ischemic events: stent thrombosis, MI, peripheral arterial occlusion

Matetzky et al, Circulation 2004

Poor Outcome and Inadequate Clopidogrel Response:

A strong and consistent association across studies

	N	Clinical Setting	Outcomes
Light Transmittance Aggregometry			
Matetzky et al.	60	STEMI undergoing PCI	Post-primary PCI ischemic events (6 months)
Gurbel et al.	192	Nonemergent PCI	Post-PCI ischemic events (6 months)
Gurbel et al.	120	Elective PCI	Post-PCI myonecrosis/inflammation
Cuisset et al.	106	ACS undergoing PCI	Post-PCI ischemic events (30 days)
Lev et al.	120	Elective PCI	Post-PCI myonecrosis
Geisler et al.	379	Stable and unstable angina undergoing PCI	Post-PCI major cardiovascular events (3 months)
Bliden et al.	100	Chronic clopidogrel undergoing nonemergent PCI	Post-PCI ischemic events (12 months)
Cuisset et al.	190	NSTEACS undergoing PCI	Periprocedural myocardial infarction
Angiolillo et al.	173	Type 2 DM on chronic dual antiplatelet therapy	Ischemic events (24 months)
Marcucci et al.	367	MI undergoing PCI	Post-PCI myonecrosis
Müller et al.	105	Elective PCI	Stent thrombosis
Buonamici et al.	804	PCI with drug eluting stent	Stent thrombosis
VASP-phosphorylation assay			
Bonello et al.	144	Stable angina and low-risk NSTEACS undergoing PCI	Post-PCI major adverse cardiac events (6 months)
Frere et al.	195	NSTEACS undergoing PCI	Post-PCI ischemic events (30 days)
Barragan et al.	46	Subacute stent thrombosis	Stent thrombosis
Gurbel et al.	120	Subacute stent thrombosis	Stent thrombosis
Blindt et al.	99	PCI with high risk for stent thrombosis	Stent thrombosis
VerifyNow $P2Y_{12}$ assay			
Price et al.	380	PCI with drug eluting stents	MACE and stent thrombosis (6 months)
Patti et al.	160	PCI	Major adverse cardiac events (30 days)
Marcucci et al.	683	ACS undergoing PCI	Major adverse cardiac events (12 months)
De Miguel et al.	179	NSTEACS undergoing coronary angiography	Major adverse cardiac events (12 months)
Others			
Sibbing et al.	1608	Elective PCI with drug eluting stent	Stent thrombosis
Ajzenberg et al.	49	Subacute stent thrombosis	Stent thrombosis

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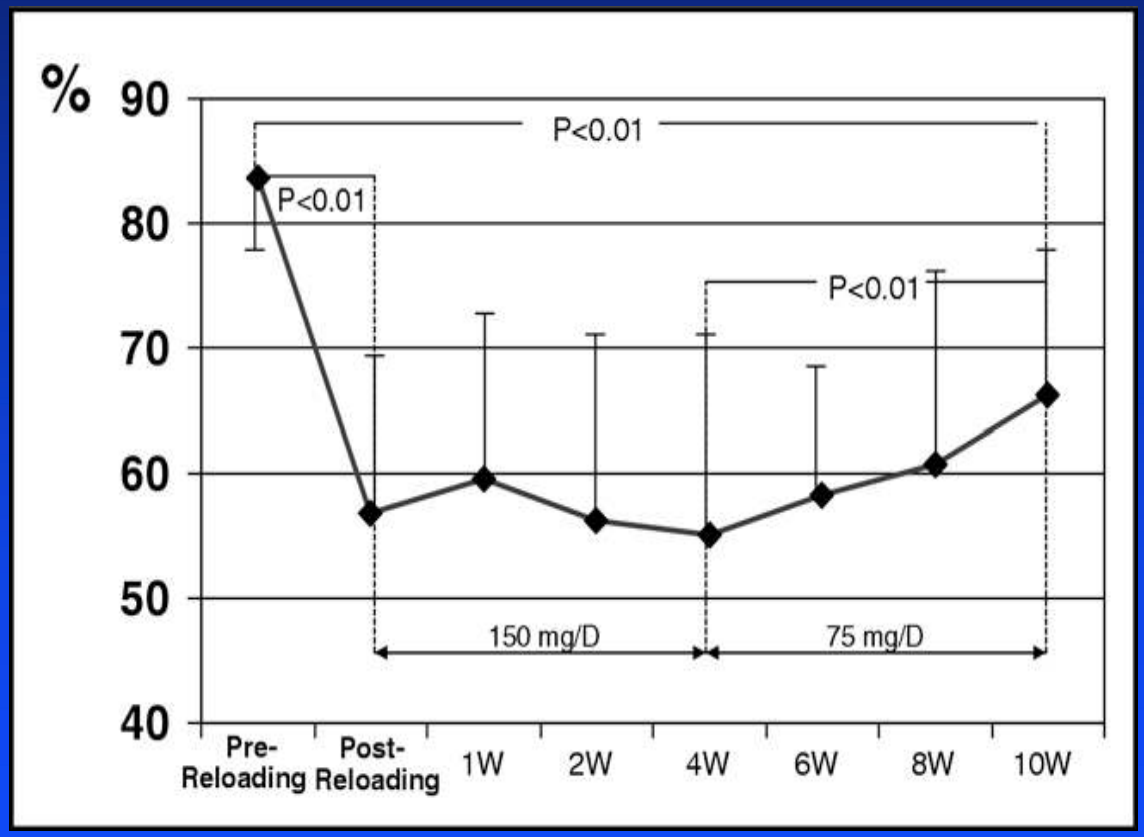
Overcoming Clopidogrel Resistance

20 uM ADP Induced Platelet Aggregation



- 200 pts with AMI and PCI (75% STEMI, 25% NSTEMI)
- Initially received standard-dose clopidogrel (300/75)
- Non-responders (n=30) defined as ADP-induced platelet aggregation >80% on day 4 → all treated with additional 600 mg load and 150 mg/day x 1 month

Matetzky et al, Am J Cardiol 2008;102 :524-9

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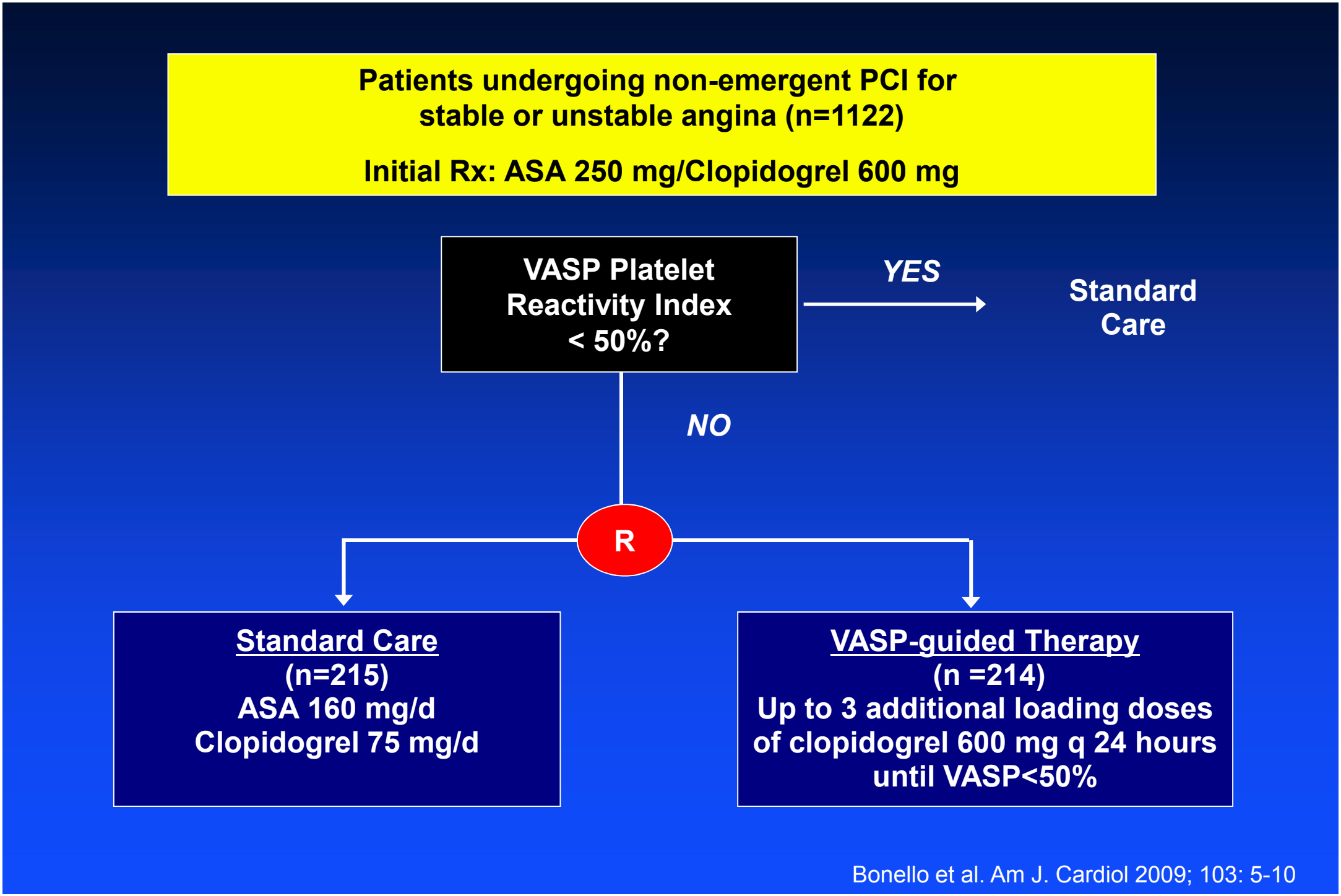
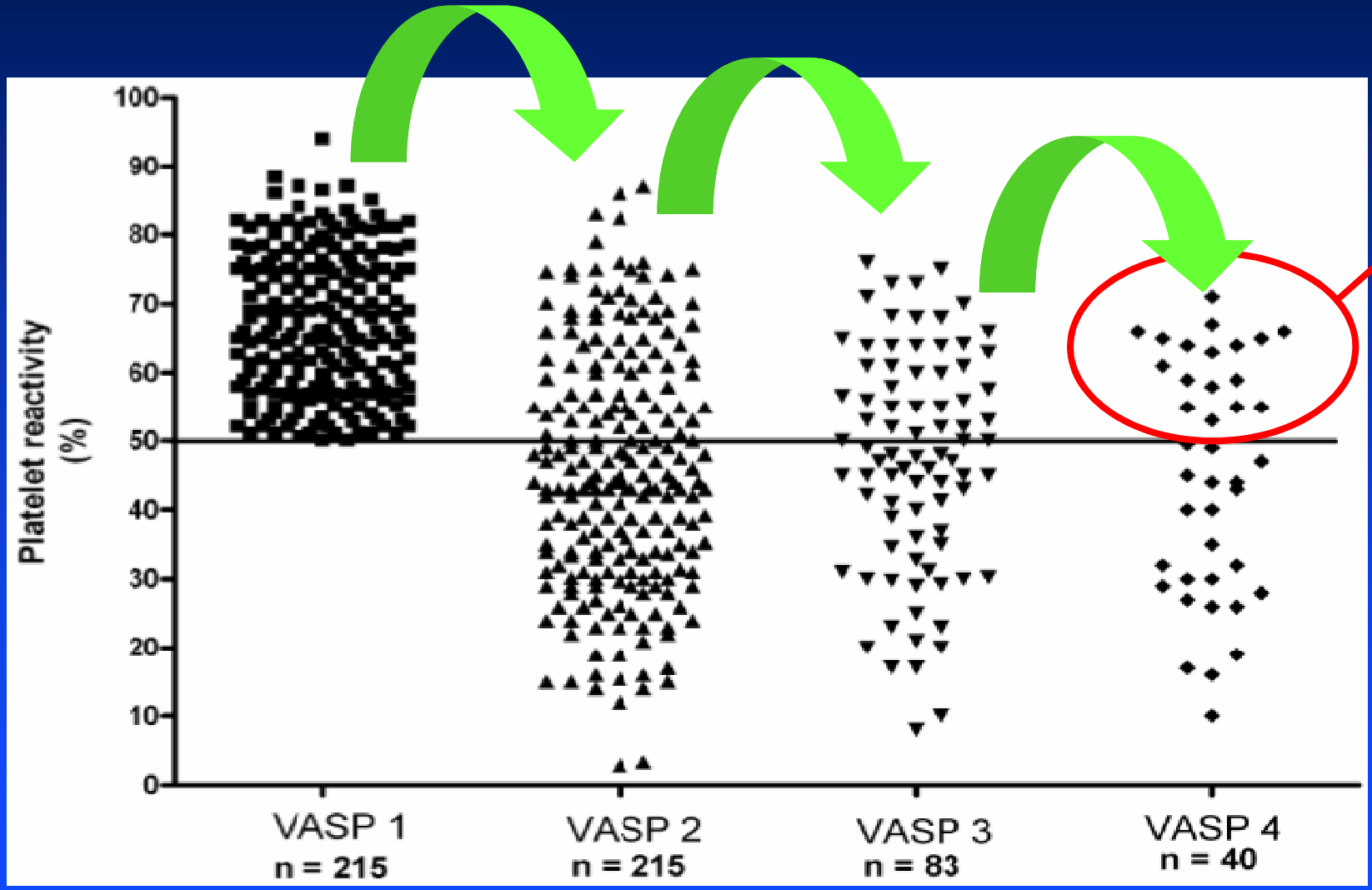


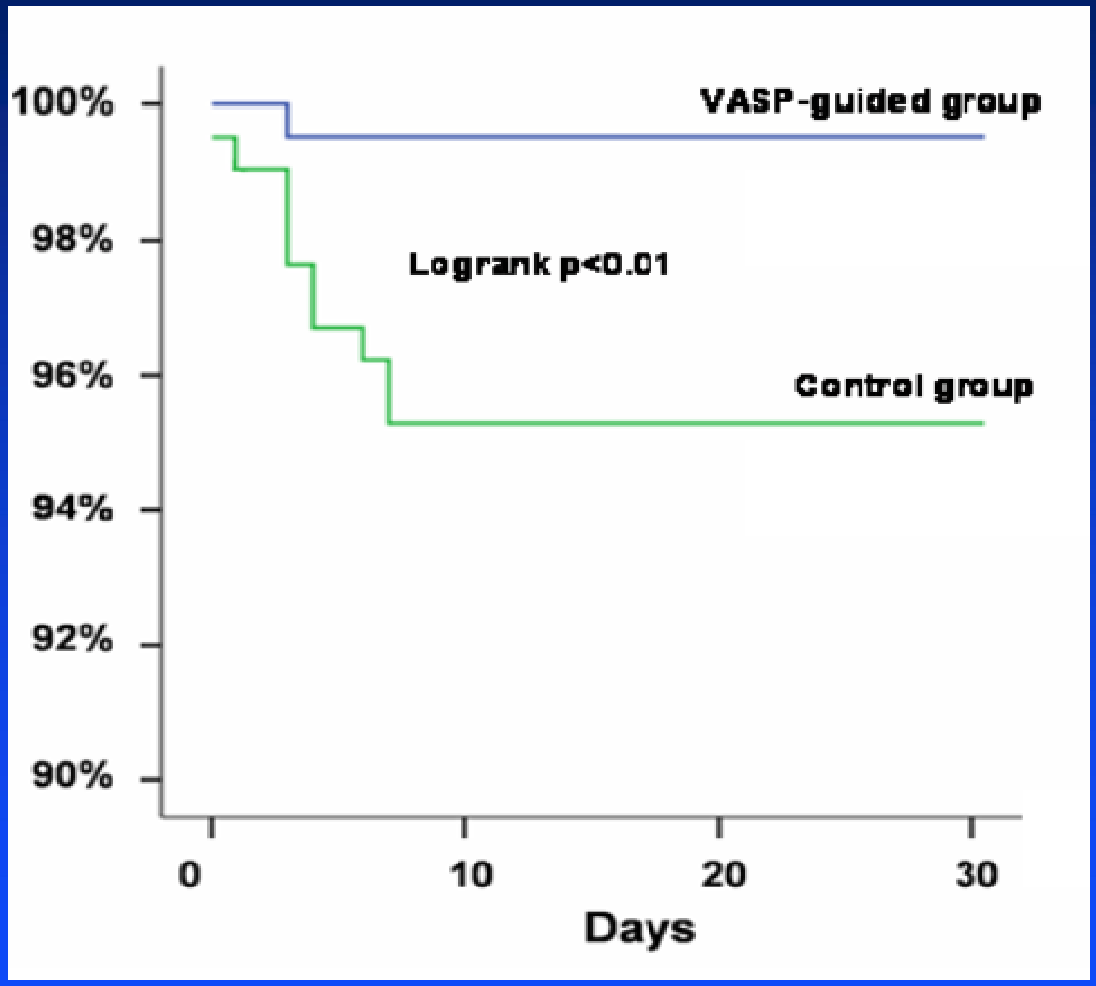
Bonello et al. Am J. Cardiol 2009; 103: 5-10

Tailored Clopidogrel: VASP-PRI



Bonello et al. Am J. Cardiol 2009; 103: 5-10

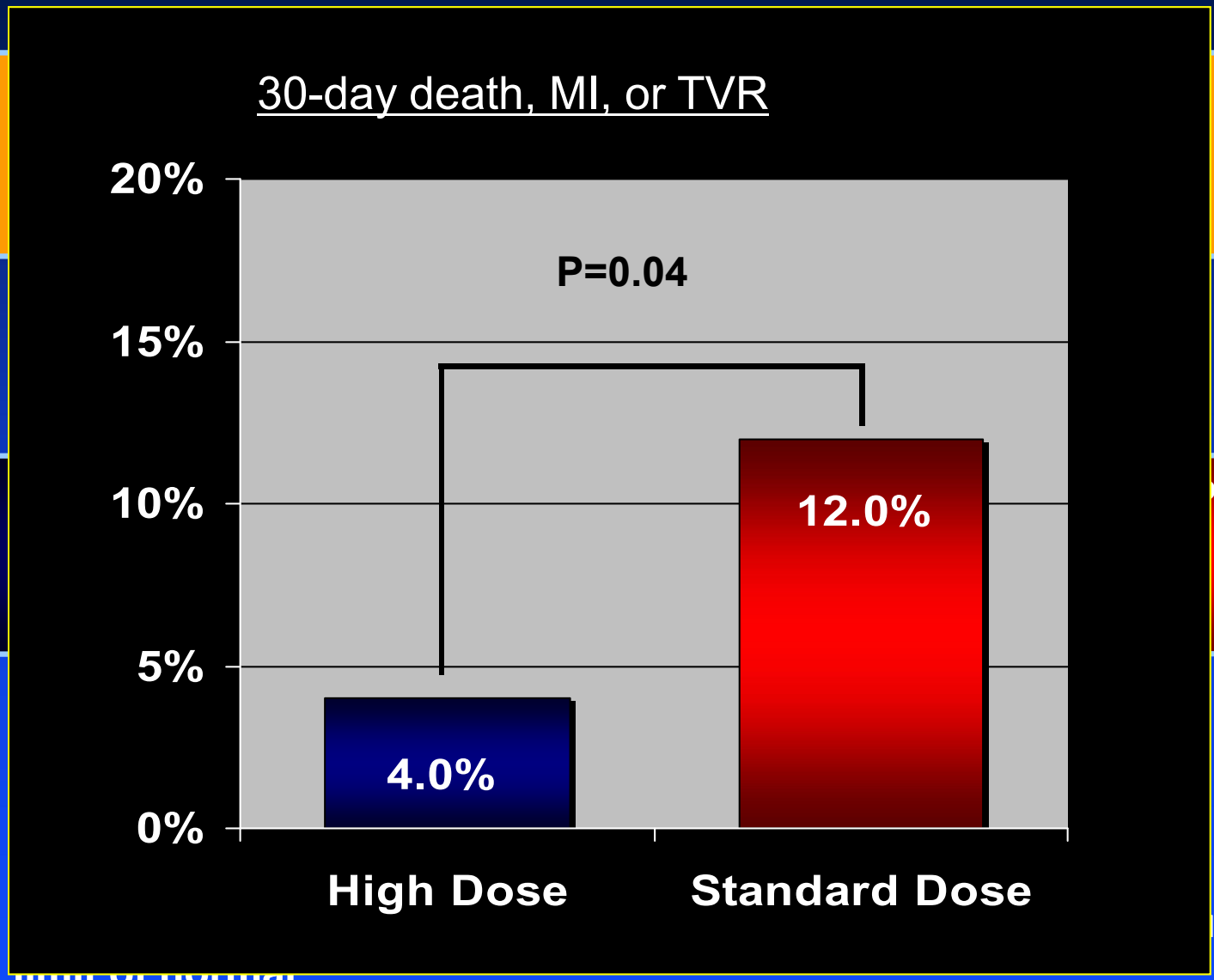
Tailored Clopidogrel: Stent Thrombosis



- Among patients with high residual platelet reactivity, VASP-guided clopidogrel therapy (1200-2400 mg load) reduced SAT from 4.7% to 0.5%
- Relative risk reduction of 90%

Bonello et al. Am J. Cardiol 2009; 103: 5-10

ARMYDA-2 Trial



CURRENT Study Design, Flow and Compliance

25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)

- ✓ Planned Early (<24 h) Invasive Management with **intended PCI**
- ✓ Ischemic ECG Δ (80.8%) or ↑cardiac biomarker (42%)

Randomized to receive (2 X 2 factorial):

CLOPIDOGREL: Double-dose (600 mg then150 mg/d x 7d then 75 mg/d) **vs Standard dose** (300 mg then 75 mg/d)

ASA: High Dose (300-325 mg/d) **vs Low dose** (75-100 mg/d)

Angio 24,769 (99%)

PCI 17,232 (70%)

No PCI 7,855 (30%)

- **No Sig. CAD 3,616**
- **CABG 1,809**
- **CAD 2,430**

Compliance:

Clop in 1st 7d (median)	7d	7 d	2 d	7d

Efficacy Outcomes:	CV Death, MI or stroke at day 30 Stent Thrombosis at day 30
Safety Outcomes:	Bleeding (CURRENT defined Major/Severe and TIMI Major)
Key Subgroup:	PCI v No PCI

Complete Followup 99.8%

ASA Dose Comparison
Primary Outcome and Bleeding

	ASA 75-100 mg	ASA 300-325 mg	HR	95% CI	P
CV Death/MI/Stroke					
PCI (2N=17,232)	4.2	4.1	0.98	0.84-1.13	0.76
No PCI (2N=7855)	4.7	4.4	0.92	0.75-1.14	0.44
Overall (2N=25,087)	4.4	4.2	0.96	0.85-1.08	0.47
Stent Thrombosis	2.1	1.9	0.91	0.73-1.12	0.37
TIMI Major Bleed	1.03	0.97	0.94	0.73-1.21	0.71
CURRENT Major Bleed	2.3	2.3	0.99	0.84-1.17	0.90
CURRENT Severe Bleed	1.7	1.7	1.00	0.83-1.21	1.00

GI Bleeds: 30 (0.24%) v 47 (0.38%), P=0.051

No other significant differences between ASA dose groups

CURRENT Clopidogrel Dose Comparison

2 Significant Interactions:

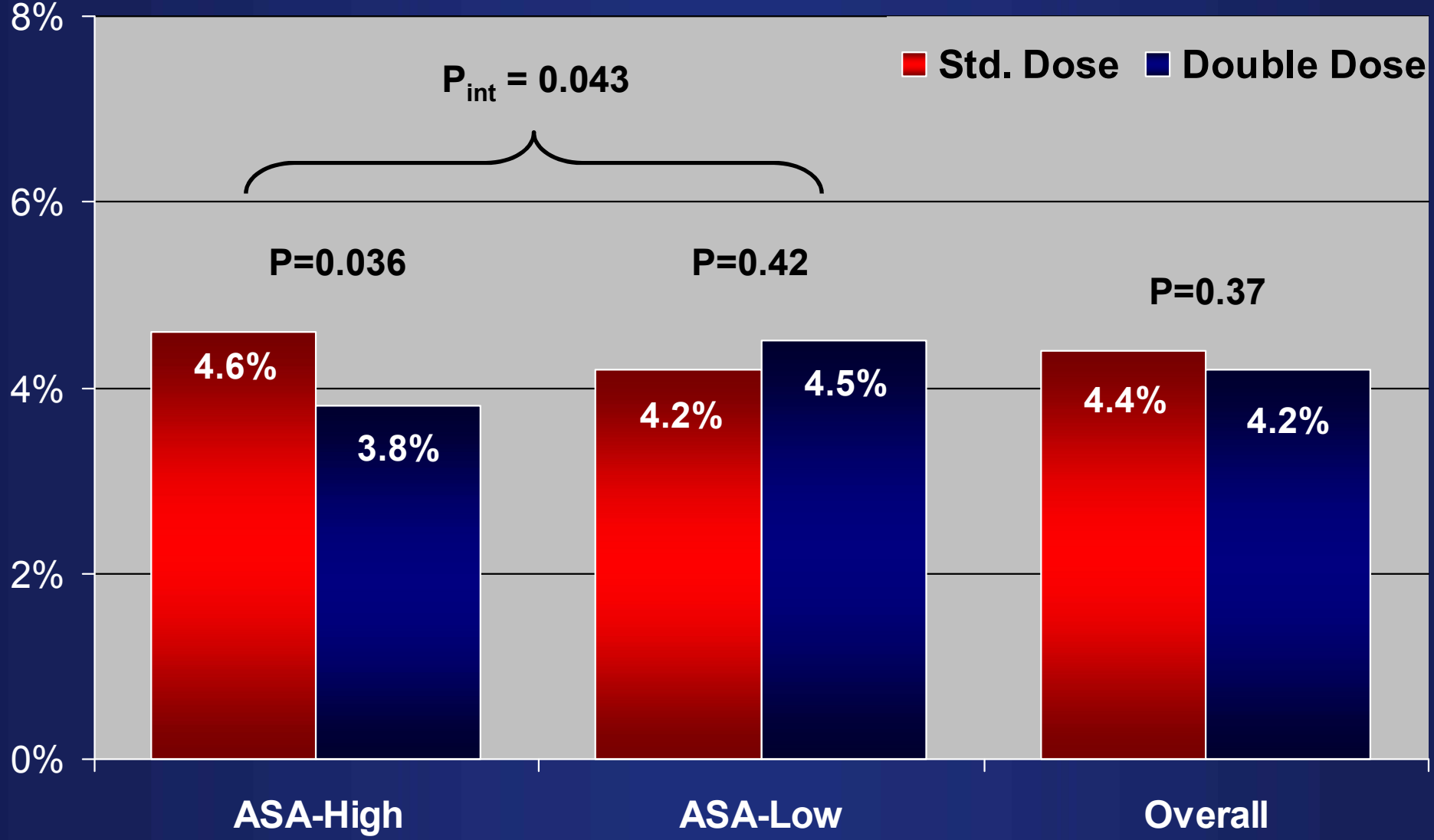
1. PCI v No PCI (P=0.016)
2. ASA dose (P=0.043)

CURRENT

Clopidogrel Dose vs. ASA Dose

CURRENT

Clopidogrel Double-Dose vs. Single-Dose by ASA Factorial



ASA Dose Interaction: Is it real?

- Interaction statistically borderline (p=0.043)
- No biologic plausibility

Conclusions

- C vs. A interaction unlikely to be real

Implication

- Don't need to analyze clopidogrel dose separately by ASA dose

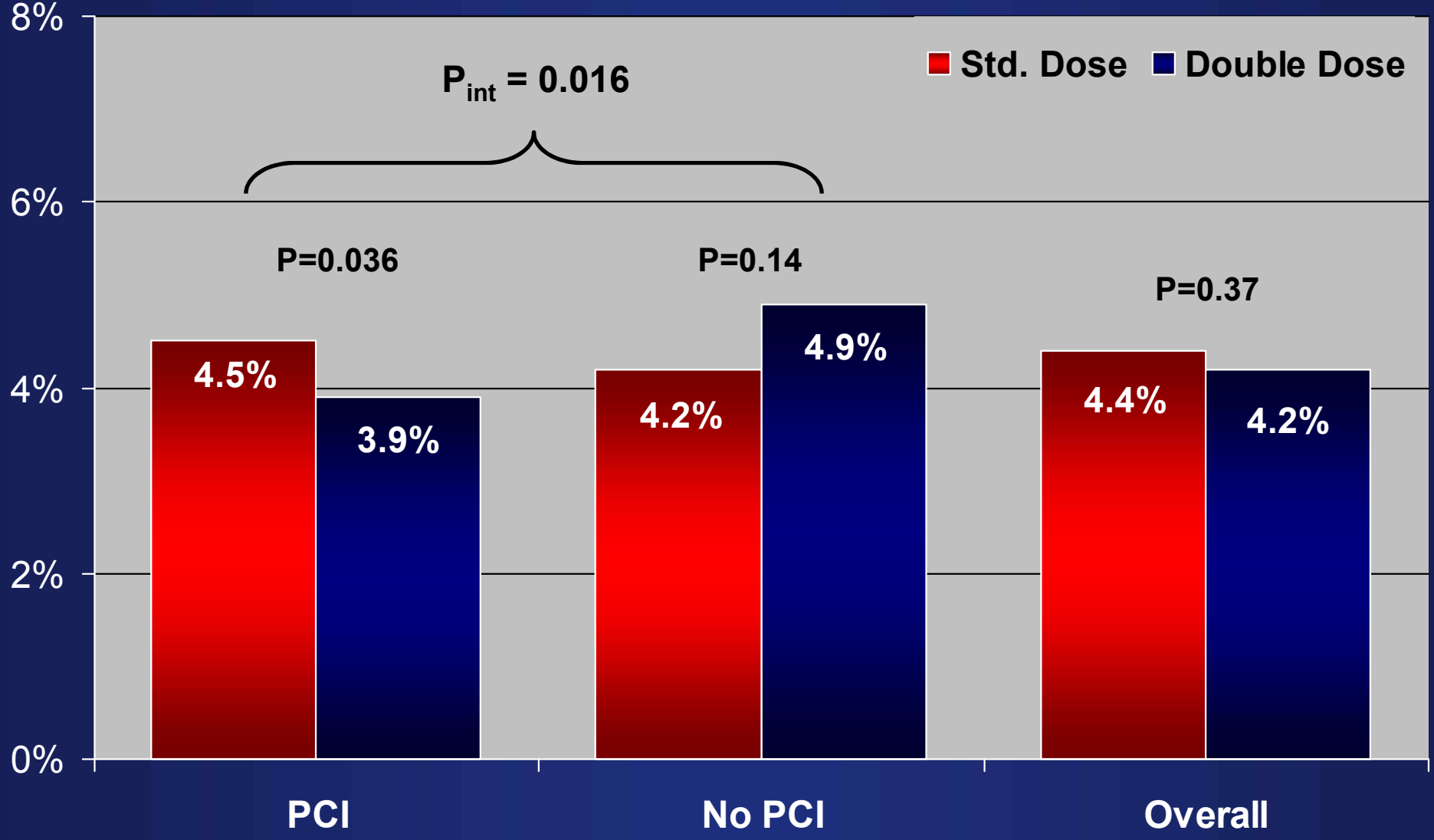
interaction would be accentuated for the most platelet-specific endpoint (stent thrombosis)→ not seen in CURRENT

CURRENT

Clopidogrel Dose vs. PCI Strategy

CURRENT

Clopidogrel Double- vs. Single-Dose by PCI Attempted



PCI-Clodidogrel Dose Interaction: Is it real?

- Statistical interaction fairly strong (p=0.016)
- Previous studies consistently demonstrate greatest

Conclusions

- C vs. PCI interaction is most likely a true effect

Implication

- Need to analyze clopidogrel dose separately by PCI strategy

- Benefits of high-dose vs. low dose clopidogrel on biomarker release previously shown in PCI patients (ARMYDA-2 trial)

CURRENT

PCI Population (N = 17,232)

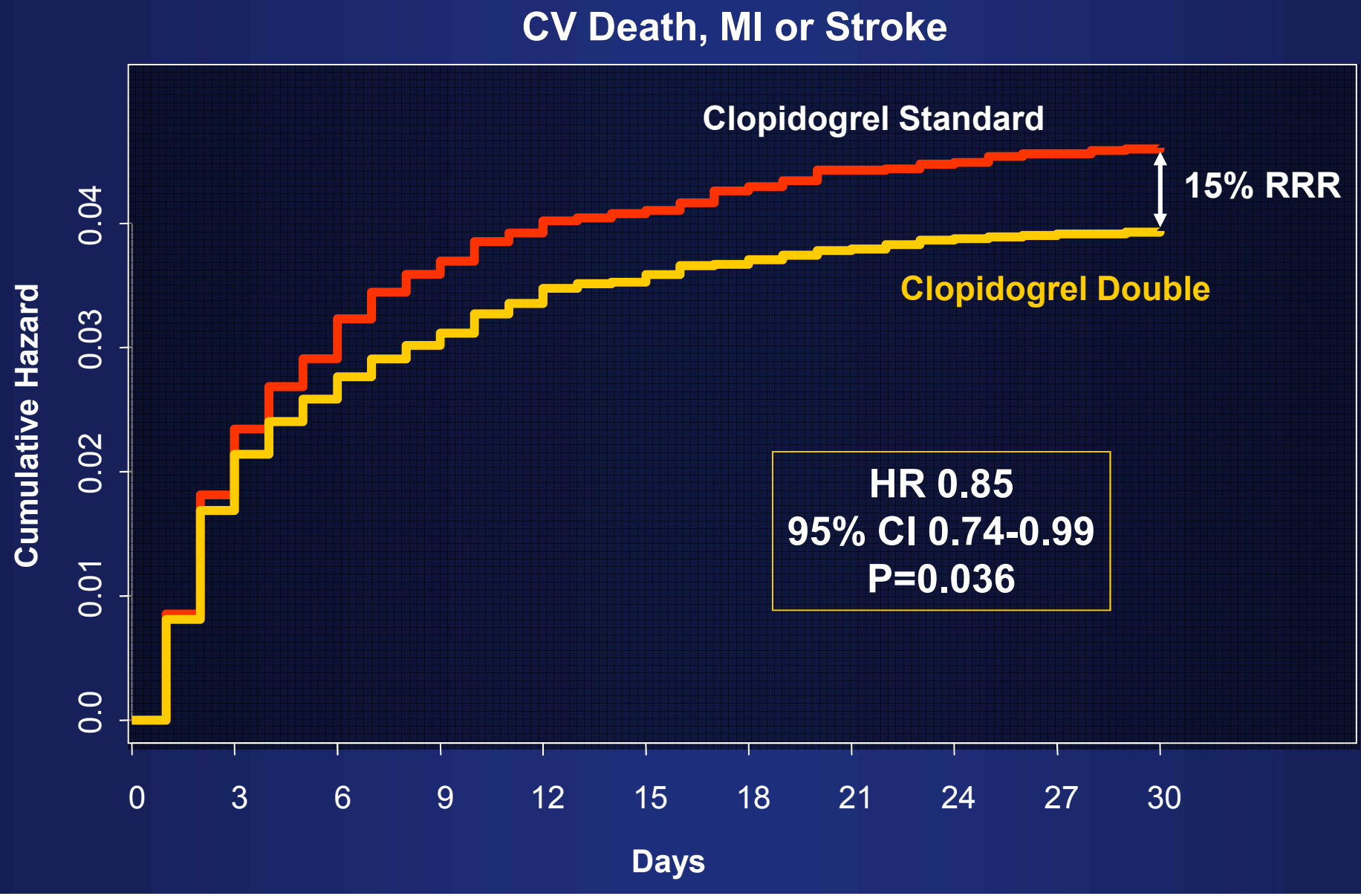
CURRENT

Clopidogrel: Double vs Standard Dose Major Efficacy Outcomes in PCI Patients

Day 30	Clopidogrel				
	Standard N=8684 %	Double N=8548 %	Hazard Ratio	95% CI	P value
Stent Thrombosis	2.3	1.6	0.71	0.57-0.89	0.002
Definite	1.2	0.7	0.58	0.42-0.79	0.001
MI	2.6	2.0	0.78	0.64-0.95	0.012
MI or stent thrombosis	3.7	3.0	0.80	0.68-0.94	0.008
CV Death	1.9	1.9	0.96	0.77-1.19	0.68
Stroke	0.4	0.4	0.88	0.55-1.41	0.59
CV Death/MI/Stroke	4.5	3.9	0.85	0.74-0.99	0.036

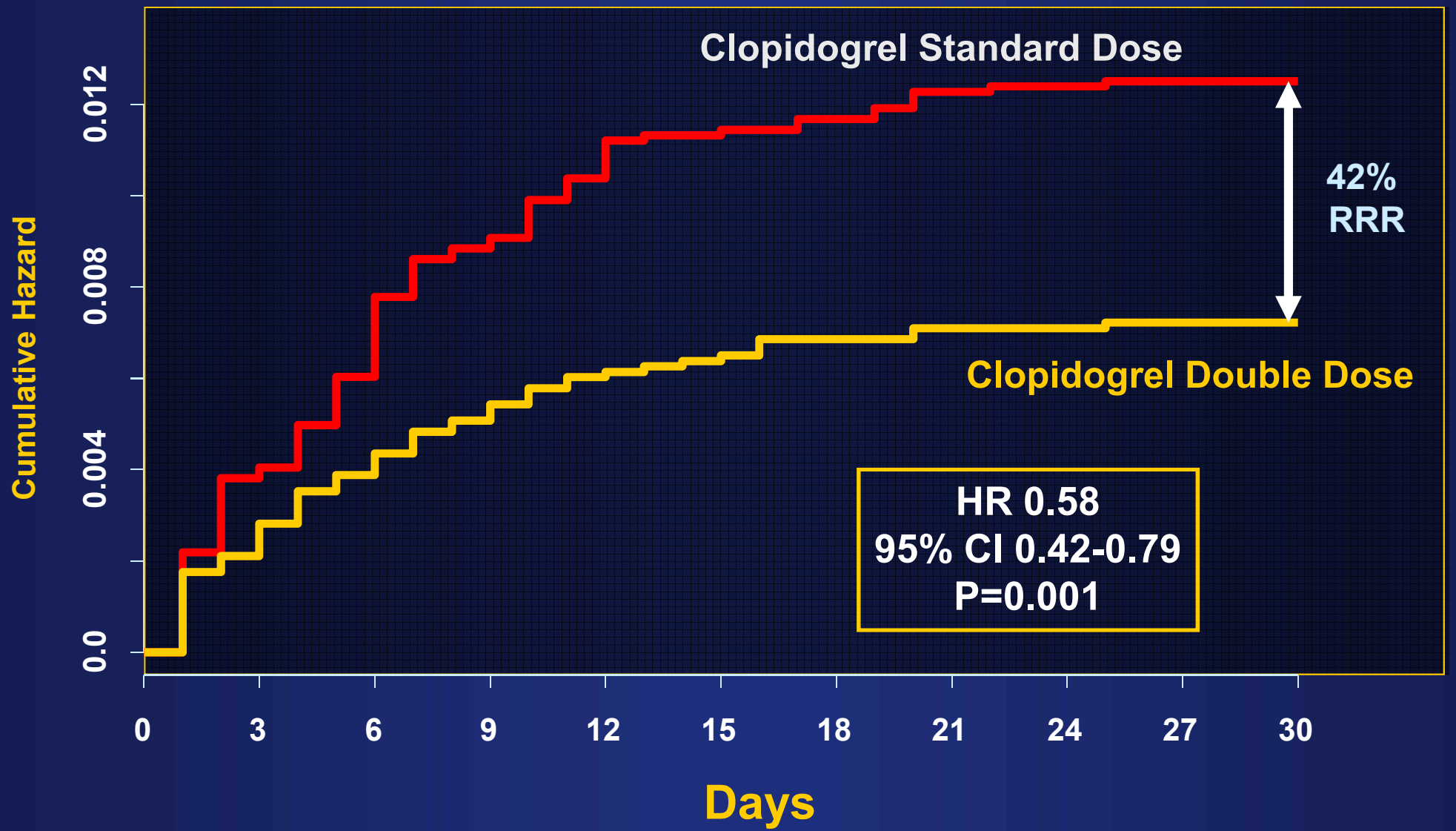
CURRENT

Clopidogrel: Double vs Standard Dose
Primary Outcome: PCI Patients



CURRENT

Clopidogrel: Double vs Standard Dose
Definite Stent Thrombosis



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

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CURRENT

Clinical Implications

1. Based on the CURRENT/OASIS-7 results, double-dose clopidogrel should be considered optimal for patients with ACS undergoing an early invasive management strategy
2. For patients who undergo PCI, double-dose clopidogrel should be continued for at least 1 week to assure maximal benefit
3. For patients who do not undergo PCI, the dose can be reduced once coronary anatomy has been defined
4. ASA dose probably doesn't matter for either efficacy or bleeding– at least in the short run