

# How Long Should We Prescribe Plavix???

## Resistance and Responders

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## Disclosure

- Consultant and speaker or research grant Support from Medtronic, Boston Scientific, Biotronik, GSK, Sanofi, BMS
- Educational Grant Support for CRT from variety of device and drug companies
- You will find this presentation on

**[WWW.CRTONLINE.ORG](http://WWW.CRTONLINE.ORG)**

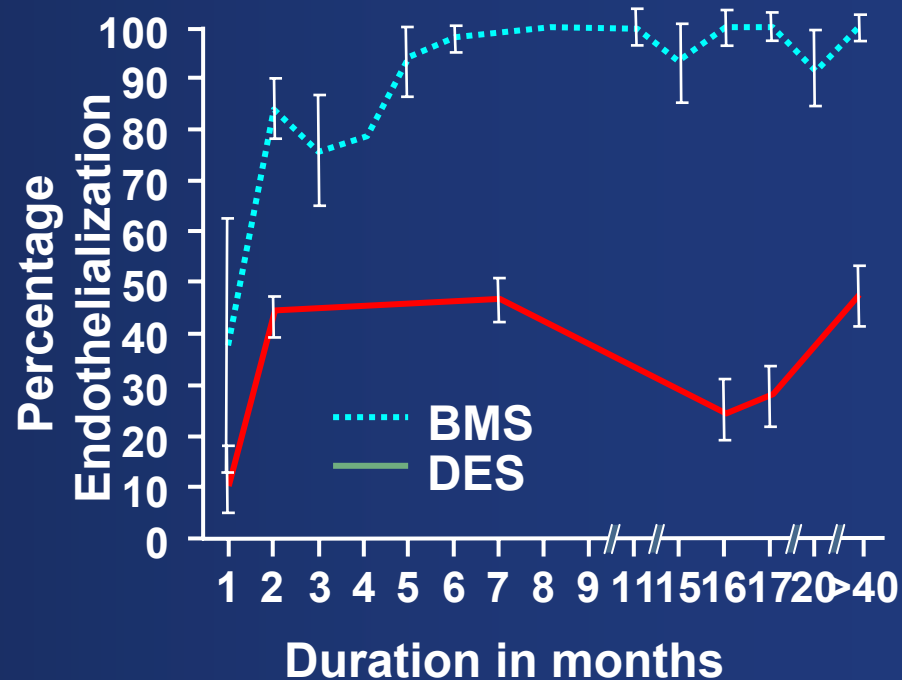
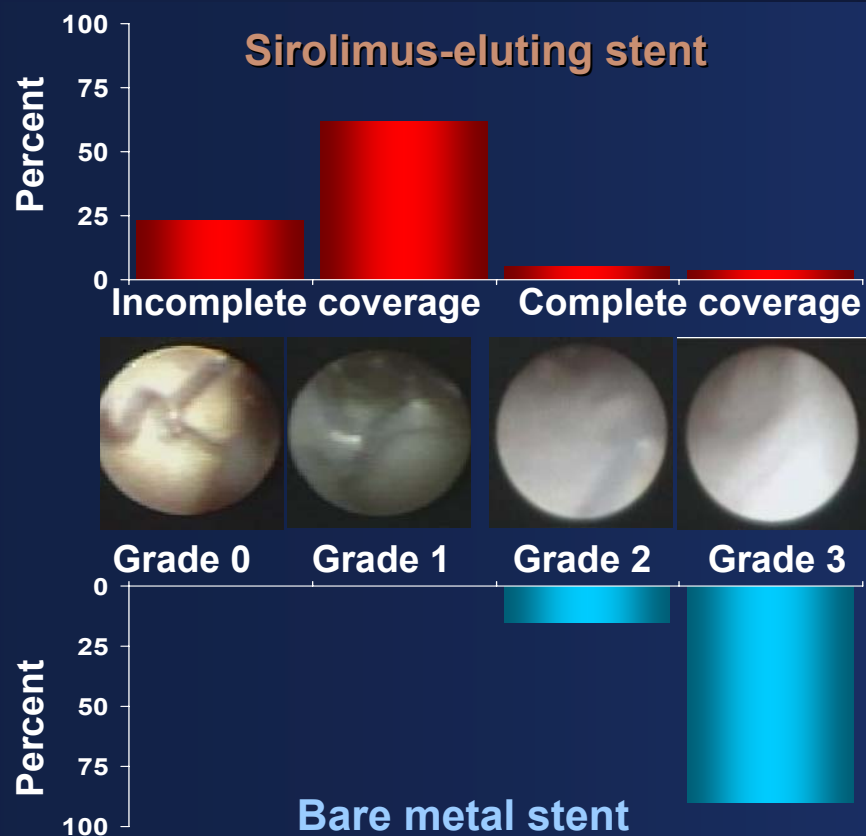
# Antiplatelet Therapy

## Summary of FDA Circulatory Panel Findings

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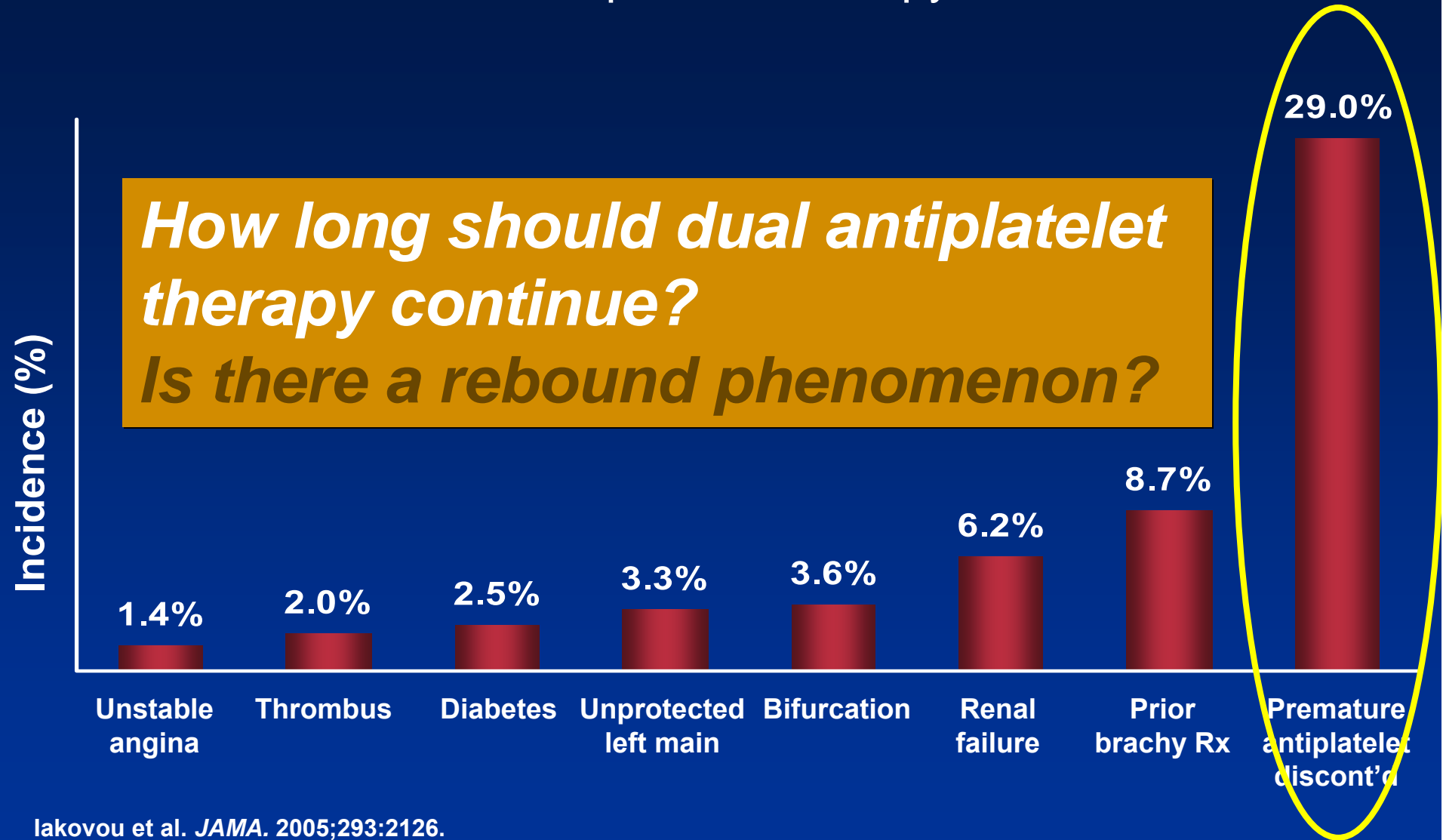
- Premature discontinuation (before labeled duration) of dual anti-platelet therapy is associated with increased risk of ST
- Dual antiplatelet therapy is recommended for at least 12 months post DES implant
- Ideal duration of dual antiplatelet therapy is uncertain
- Cypher and Taxus labels should carry AHA/ACC/SCAI recommendation re: APT 12 months for patients that can tolerate DAP

Despite animal data showing complete coverage at 30 days, DES strut endothelialization is reduced in humans with CAD



➡ **Longer period of anti-platelet therapy is indicated with DES vs. BMS**

## Discontinuation of Anti-platelet Therapy and Risk for ST



# Clopidogrel Cessation: Is it due to lack of antiplatelet therapy or to rebound?

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## ORIGINAL CONTRIBUTION

# Incidence of Death and Acute Myocardial Infarction Associated With Stopping Clopidogrel After Acute Coronary Syndrome

P. Michael Ho, MD, PhD

Eric D. Peterson, MD, MPH

Li Wang, MS

David J. Magid, MD, MPH

Stephan D. Fihn, MD, MPH

Greg C. Larsen, MD

Robert A. Jesse, MD, PhD

John S. Rumsfeld, MD, PhD

**Context** It is unknown whether patients are at increased short-term risk for adverse events following clopidogrel cessation.

**Objective** To assess the rates of adverse events after stopping treatment with clopidogrel in a national sample of patients with acute coronary syndrome (ACS).

**Design, Setting, and Patients** Retrospective cohort study of 3137 patients with ACS discharged from 127 Veterans Affairs hospitals between October 1, 2003, and March 31, 2005, with posthospital treatment with clopidogrel.

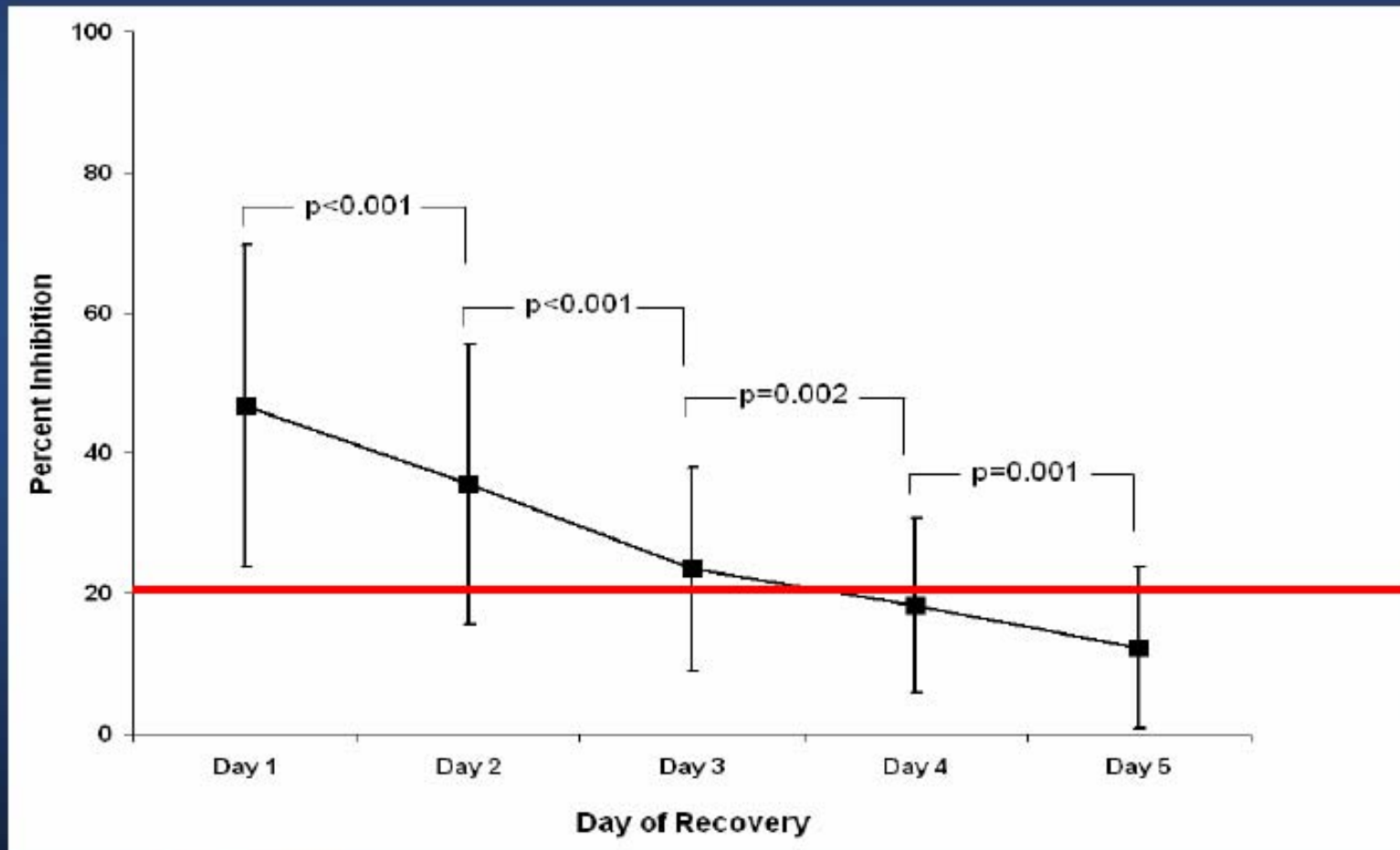
**Main Outcome Measure** Rate of all-cause mortality or acute myocardial infarction (AMI) after stopping treatment with clopidogrel.

# Conclusions

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- First study to evaluate patterns of adverse events after clopidogrel cessation in national cohort of pts w/ ACS
- A clustering of significantly higher risk of death or AMI was found in the initial 90 day period after stopping treatment with clopidogrel compared w/ later follow-up intervals
- These findings were consistent among patients subgroups including those who took shorter versus longer durations of clopidogrel therapy, among patients with and without diabetes, as well as among PCI treated ACS patients.
- In addition the rate of adverse events in the initial 90 days interval after stopping treatment with clopidogrel was higher than the rate of adverse events following hospital discharge while patients still taking clopidogrel.

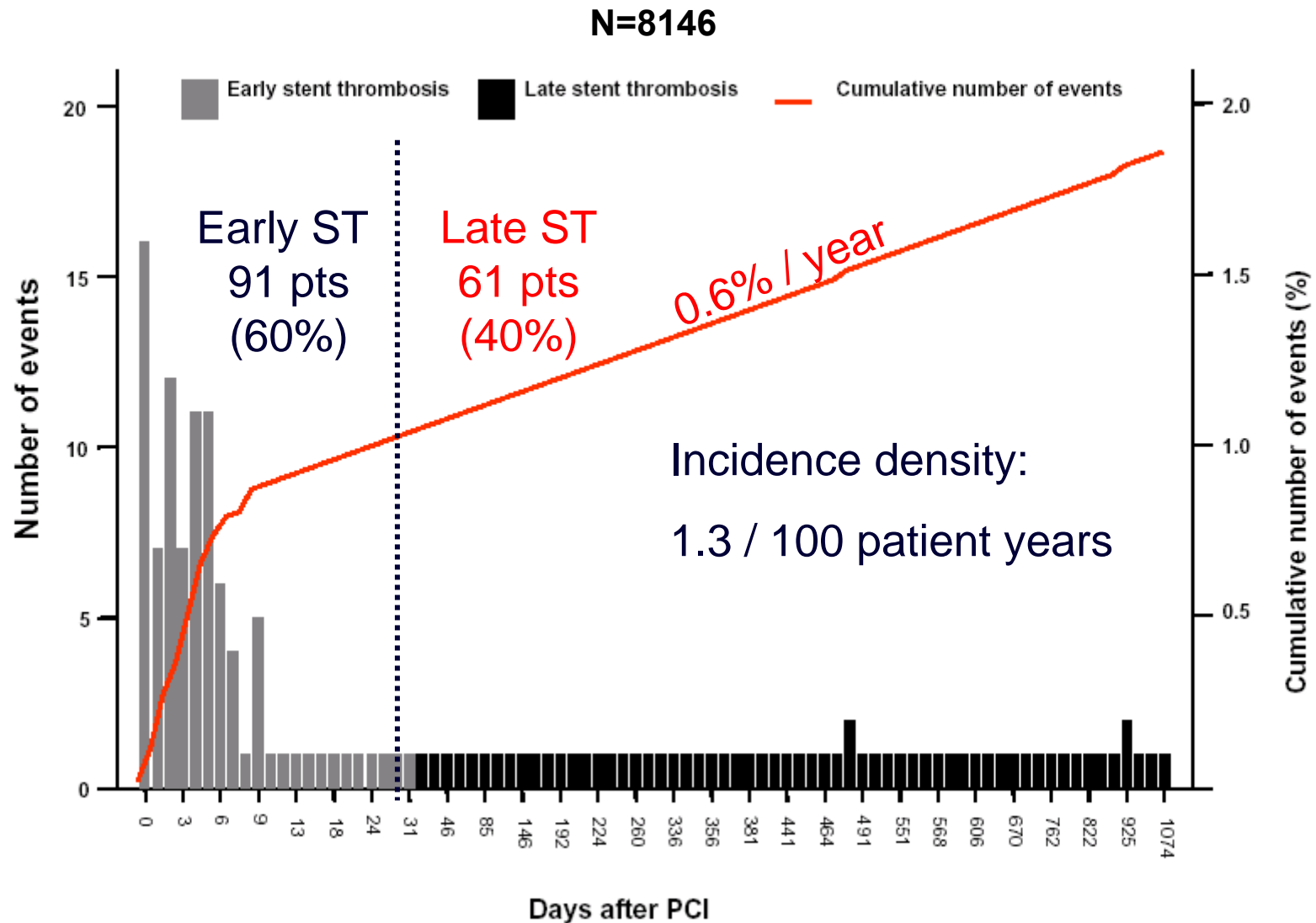
# Offset of Clopidogrel after discontinuation VerifyNow $P_2Y_{12}$ test



Price et al AJC 2006



# Definite Stent Thrombosis With DES: Bern - Rotterdam Cohort Study



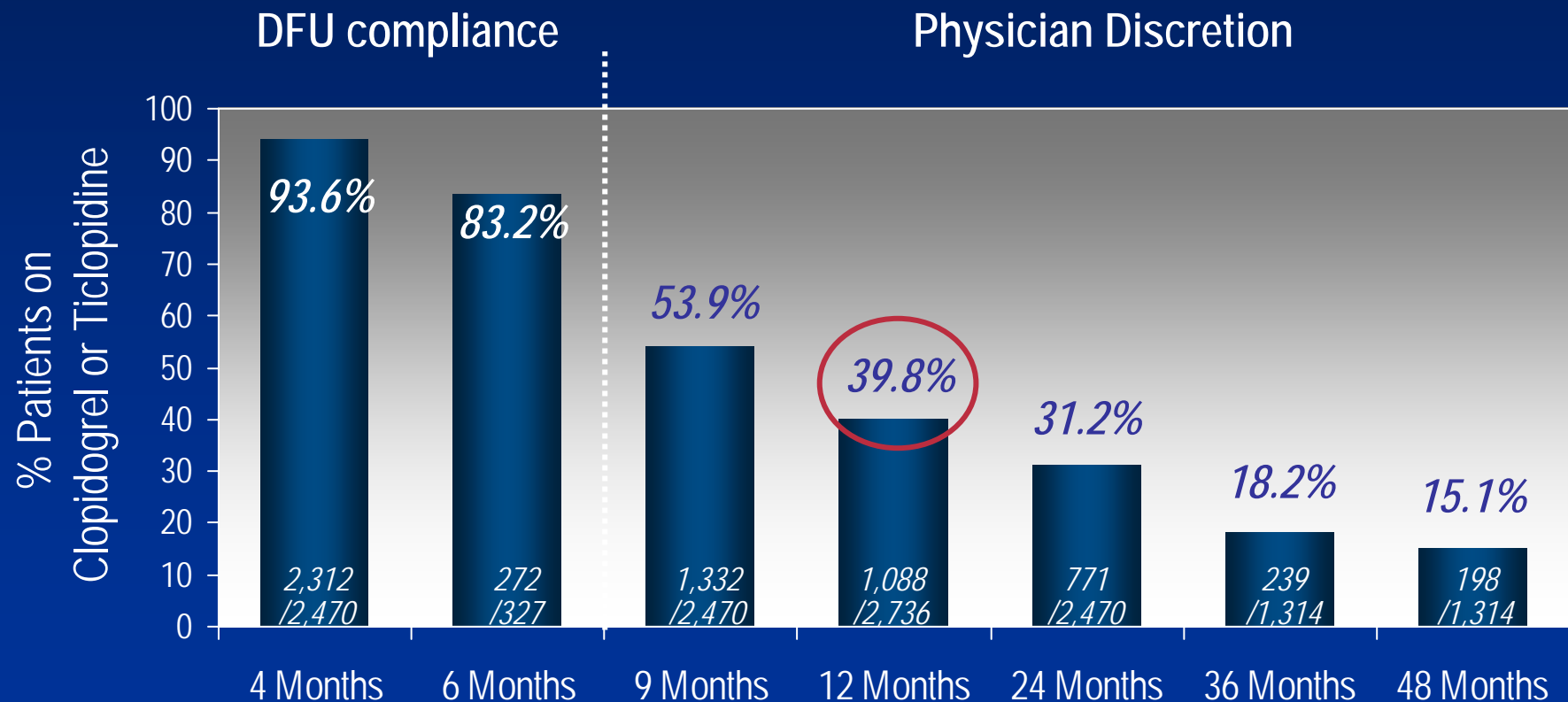
# Long-Term-Thienopyridine Intake in TAXUS Clinical Trial Program

An Earlier time-point (2002) than ARRIVE (2004-5) where 12 month Plavix® use = 70%

## Limitations

No formal medication log

Incomplete data collection between trials at various time points



The safety and effectiveness of the TAXUS® Express® Stent have not been established in patients for longer than 12 months. Clopidogrel was prescribed for a period of 6 months post procedure per TAXUS Clinical series protocol.

# Being on Plavix® at 6 months (which also predicts Plavix to 12 months) Confers the best benefit for DES

The Duke Landmark analysis

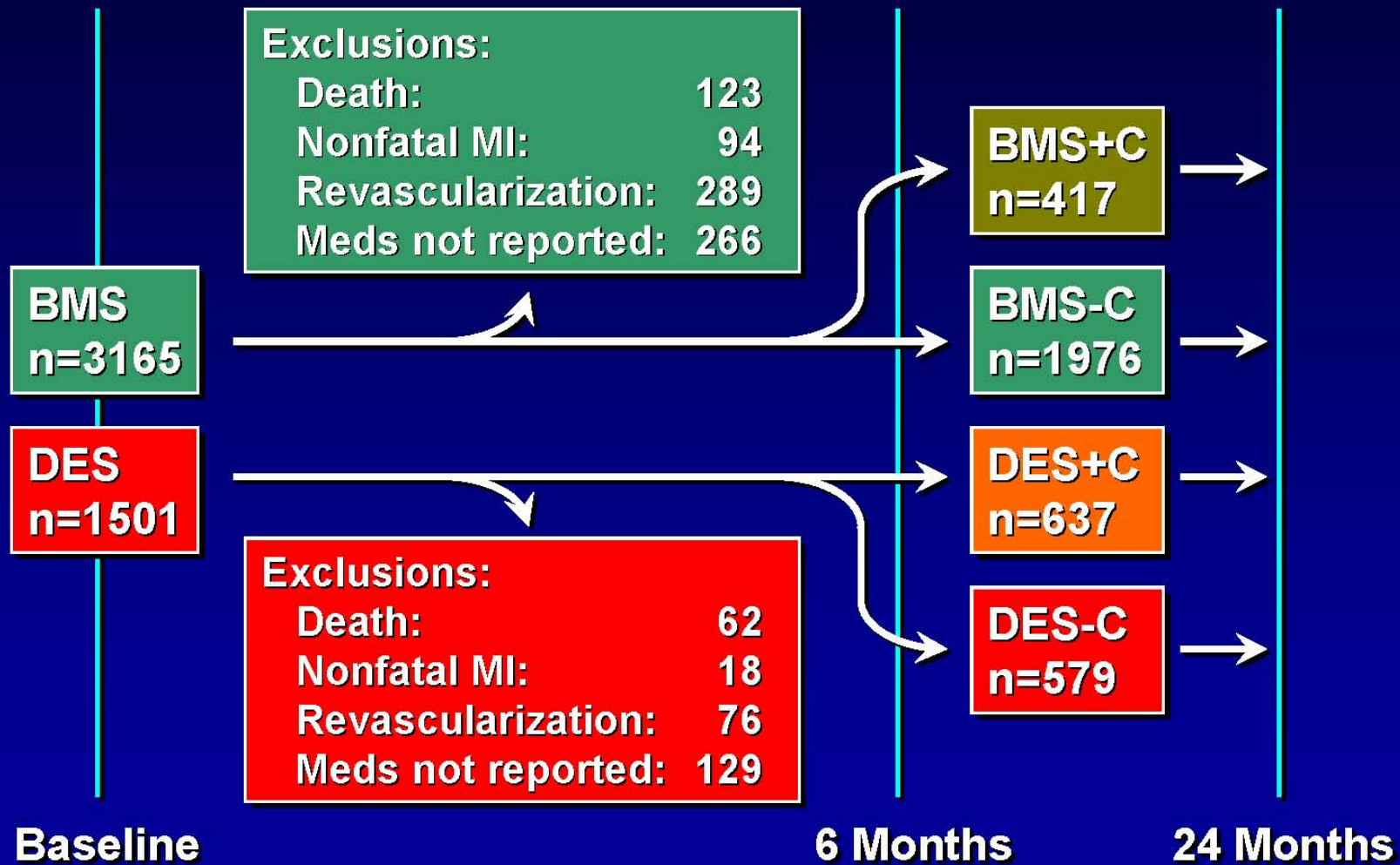
## **Drug-Eluting vs. Bare Metal Stents: Results from a Practice-Based Registry**

Eric L. Eisenstein, DBA; Kevin J. Anstrom, PhD; David F. Kong, MD, AM;  
Linda K. Shaw, MS; Robert H. Tuttle, MSPH; Daniel B. Mark, MD, MPH;  
Judith M. Kramer, MD, MS; Robert A. Harrington, MD;  
David B. Matchar, MD; David E. Kandzari, MD;  
Eric D. Peterson, MD, MPH; Kevin A. Schulman, MD; Robert M. Califf, MD

Clopidogrel Use and Long Term  
Clinical Outcomes After Drug-Eluting  
Stent Implantation

JAMA, Published online December 5, 2006

## 6-Month Landmark View



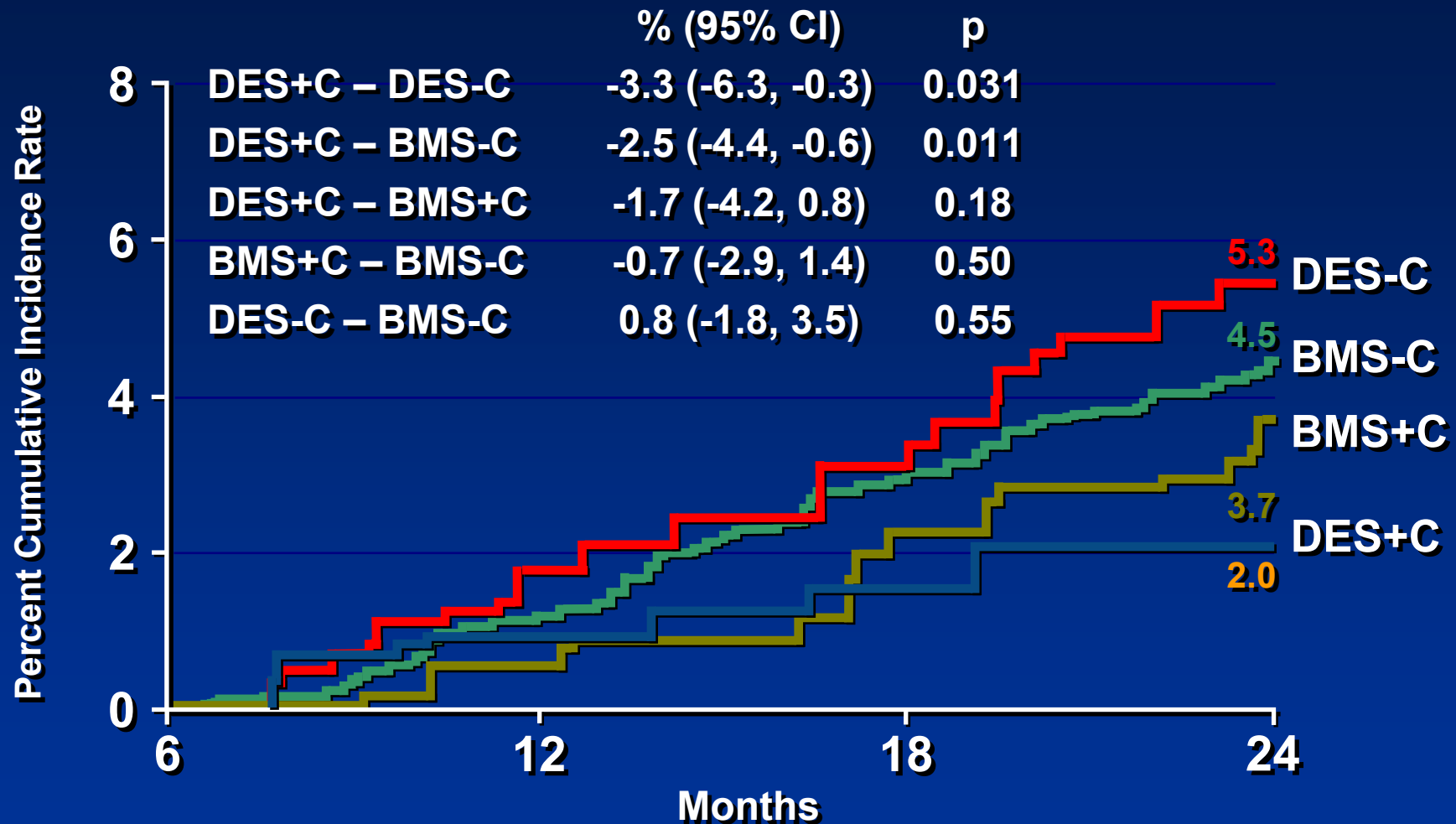
## 6-Month Landmark Patient Characteristics

	DES+C (n=637)	DES-C (n=579)	BMS+C (n=417)	BMS-C (n=1976)	p-value
Age, years	61 (53, 71)	60 (53, 70)	61 (53, 70)	61 (52, 71)	0.73
Black race (%)	19	24	20	20	0.18
Male (%)	63	64	64	63	0.93
Hx Diabetes (%)	27	30	29	23	0.001
Hx CHF (%)	10	15	9	11	0.026
Hx MI (%)	39	38	51	46	<0.001
Number of diseased vessels (%)					<0.001
1	58	62	66	67	
2	29	31	26	27	
3	13	8	8	6	



# 6-Month Landmark Analysis

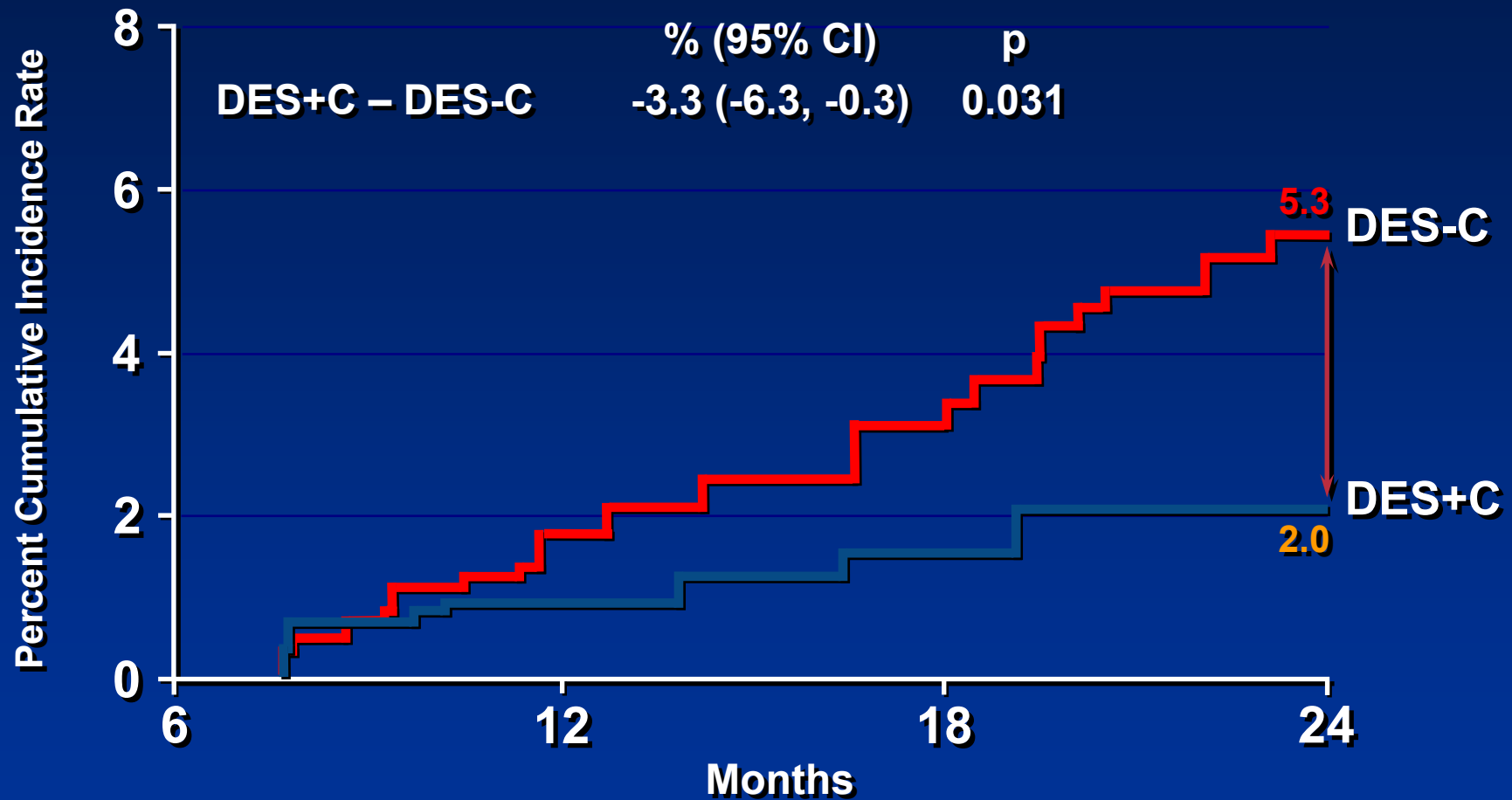
## *Adjusted Cumulative Mortality Rates*



Eisenstein et al. JAMA 2006

# 6-Month Landmark Analysis

## *Adjusted Cumulative Mortality Rates*



Eisenstein et al. JAMA 2006



## Conclusions

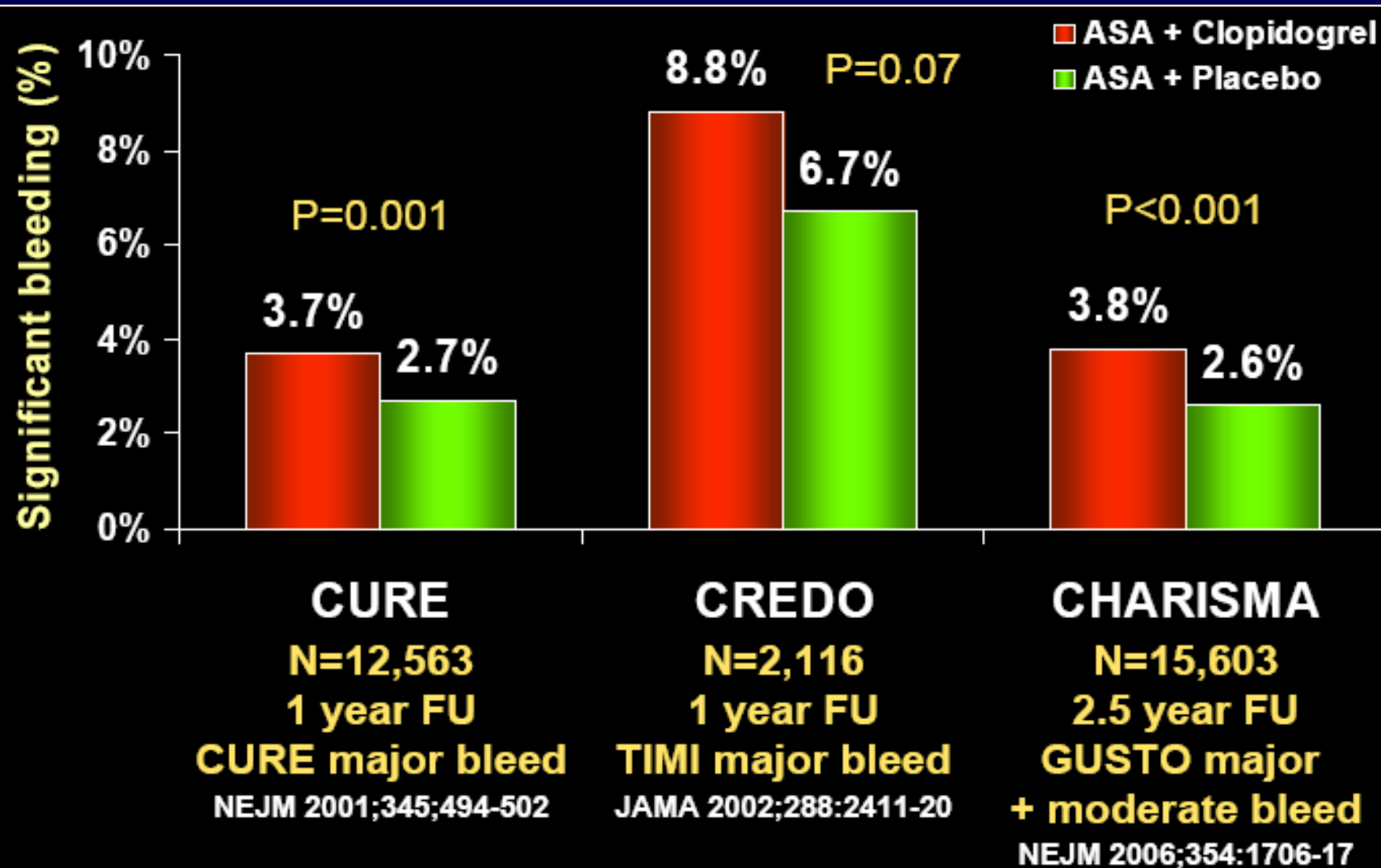
- Compared to BMS, DES is associated with reduced rates of TVR
- Death and MI higher for DES patients stopping clopidogrel therapy at 6 months
- Results consistent with CREDO, BASKET-LATE, and PREMIER
- Need rigorous clinical trials to assess optimal duration of clopidogrel therapy



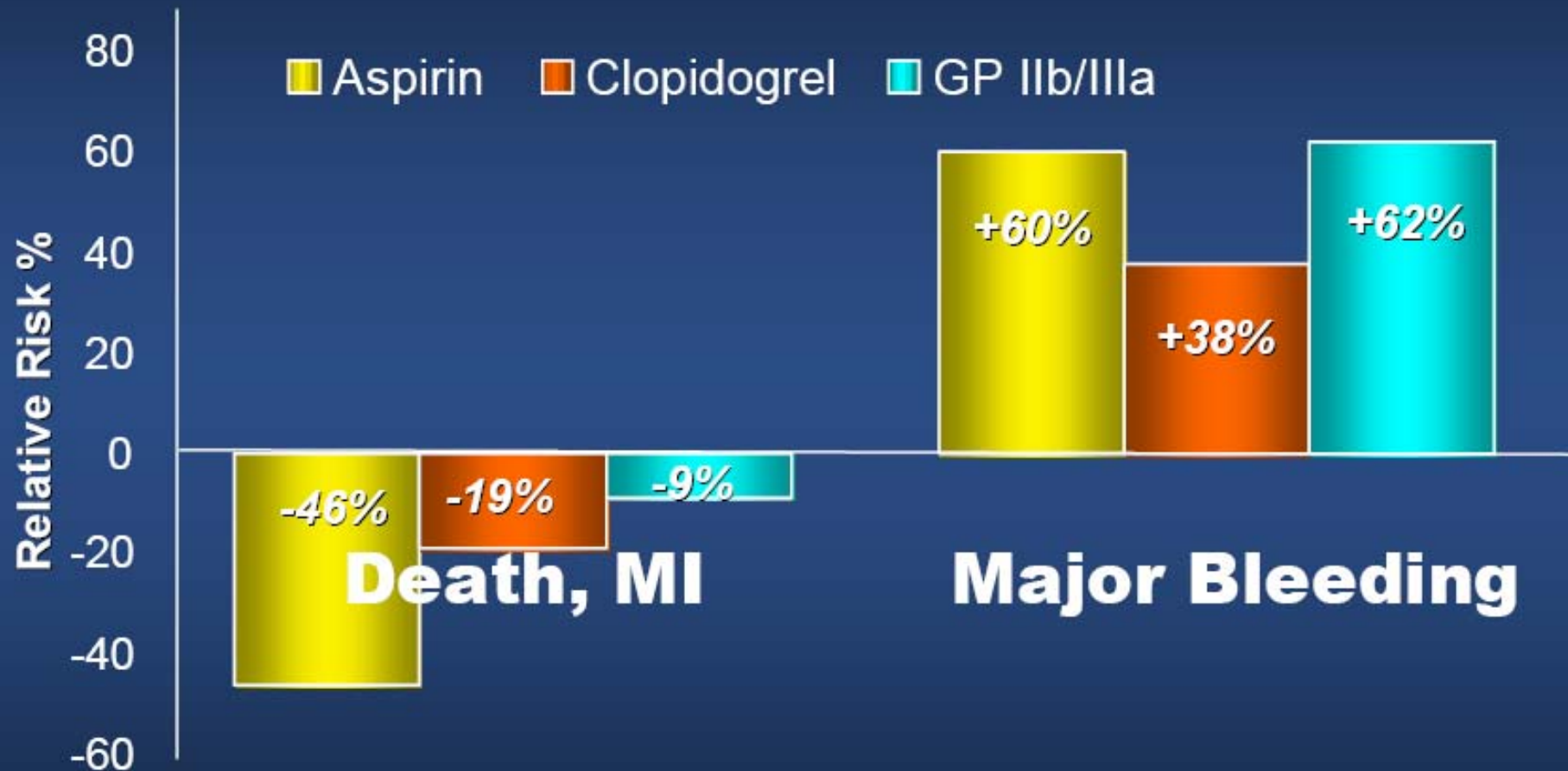


# Safety of Long-Term Clopidogrel

## 3 Placebo Controlled Trials



# Summary of Efficacy and Safety of Antiplatelet Therapy

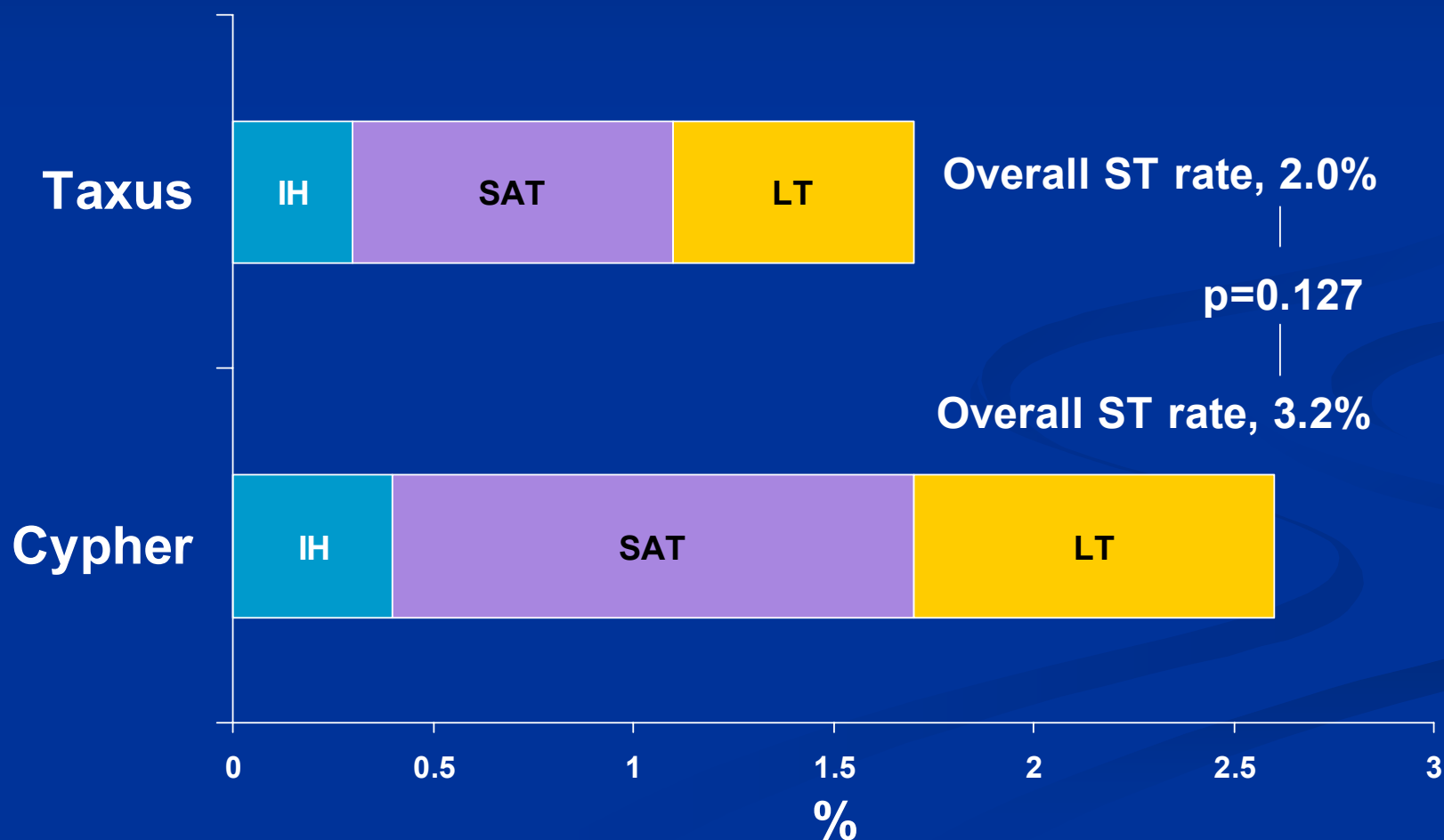


Efficacy-safety endpoint in CURE RR 0.84 (0.78-0.93)  $P=.001$ .

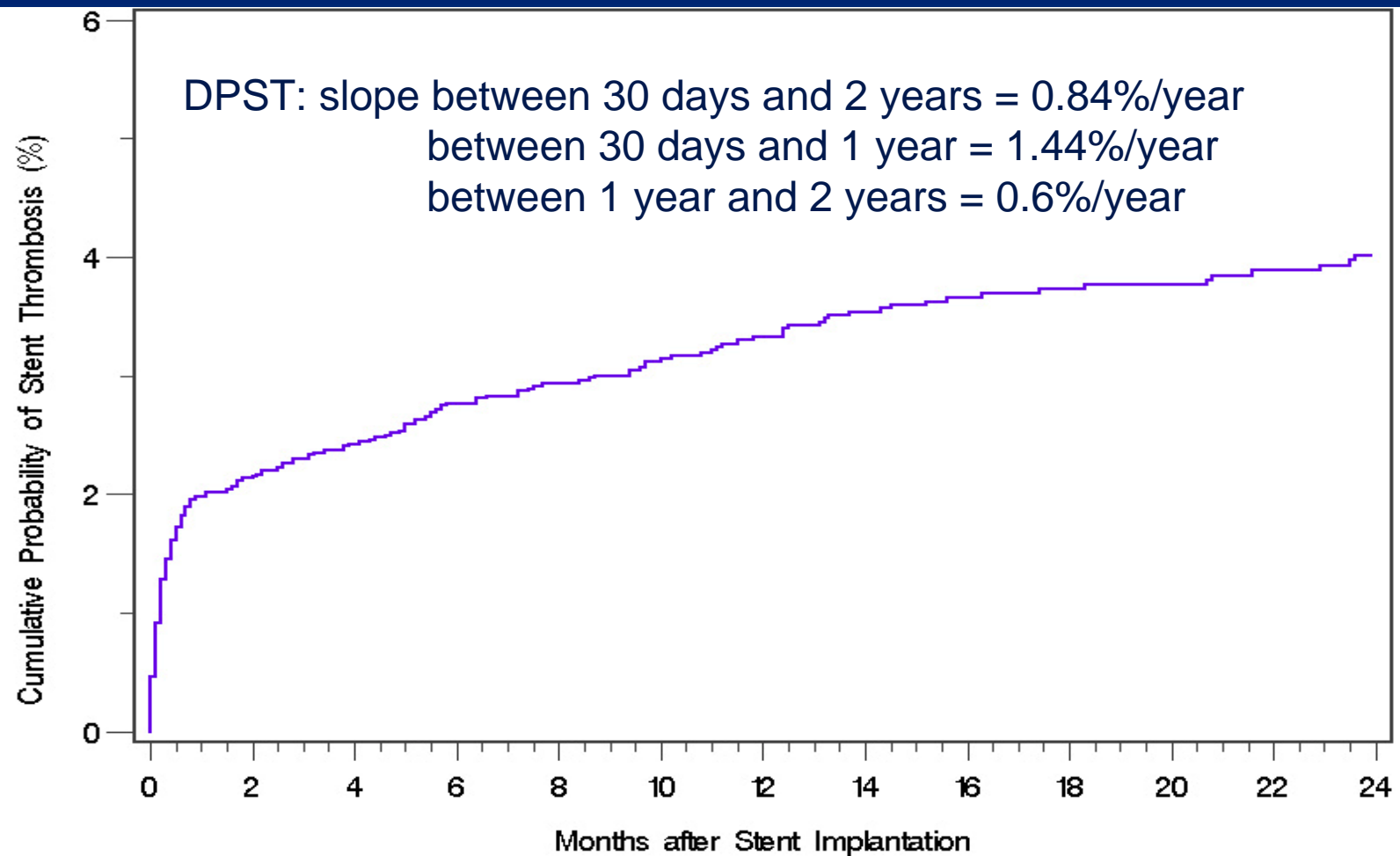
Mehta. *J Am Coll Cardiol*. 2003;41:79S.

## Cumulative Stent Thrombosis – 24 Months

Overall stent thrombosis for both stents at 2 year *2.8%*

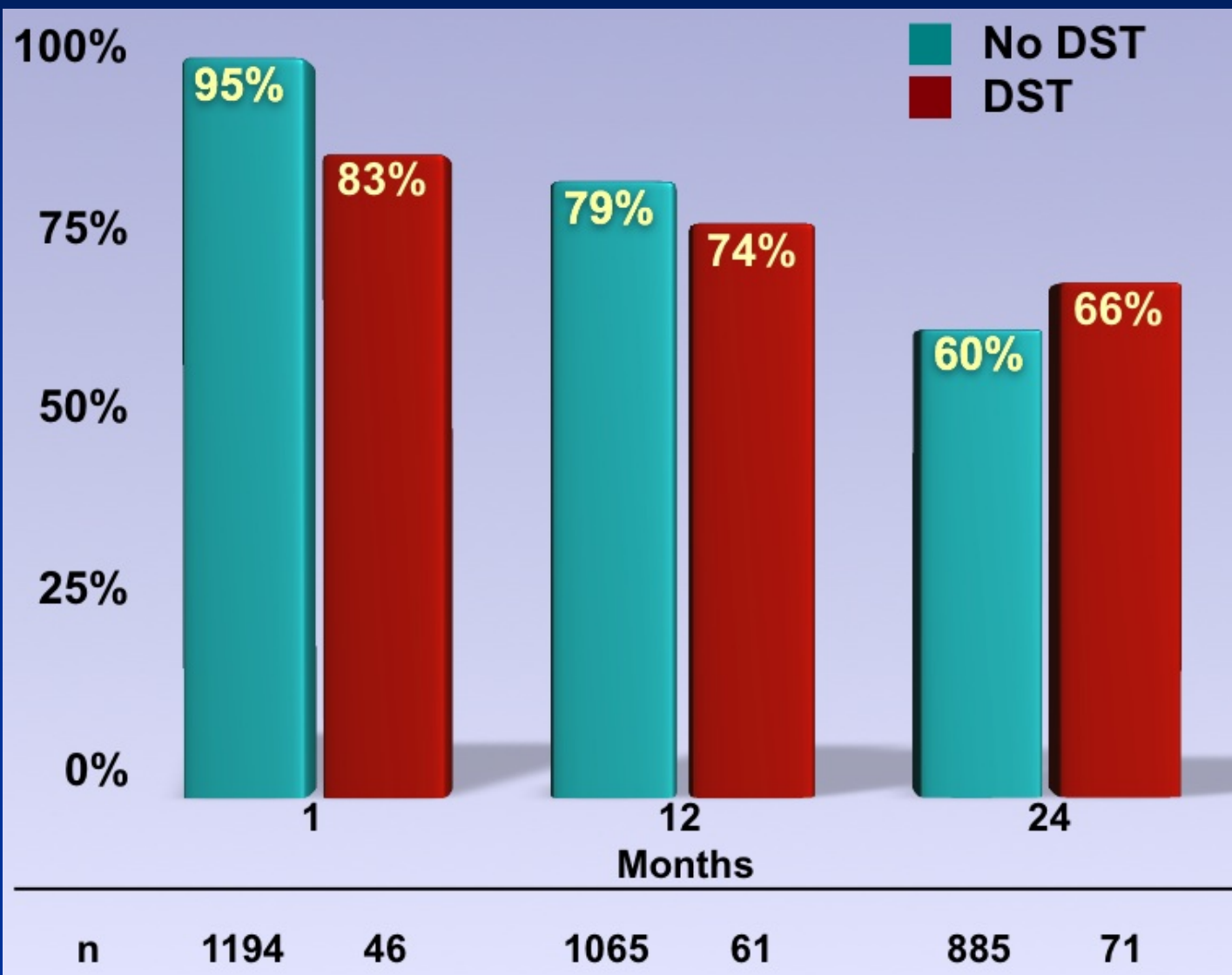


# Definite Probable ST Washington Hospital Center



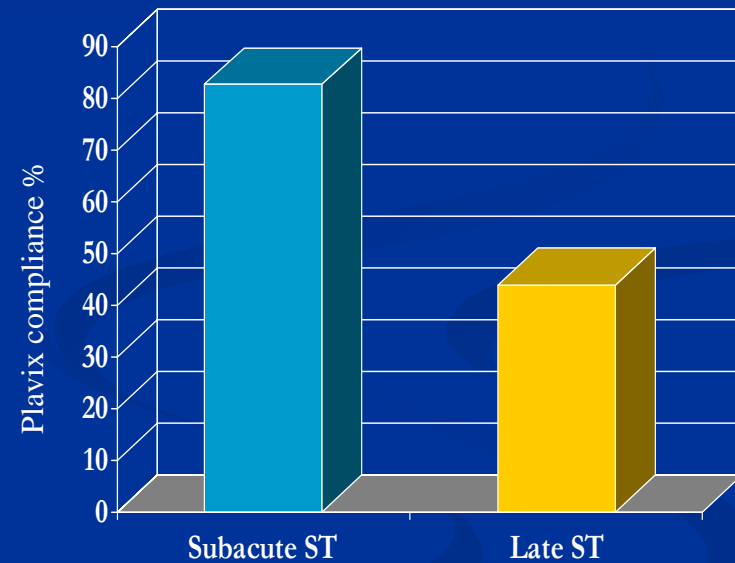
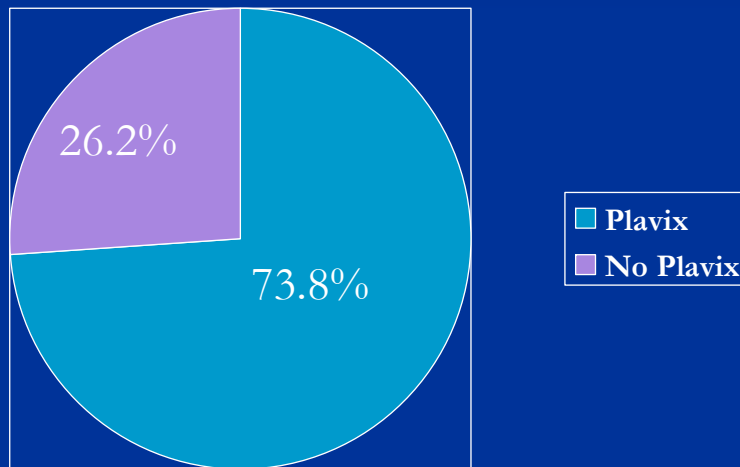
Months after DES Implant	1	12	24
Patients at risk (n)	5730	3821	2150
Cumulative events (n)	119	185	206

# Clopidogrel Compliance



# Clopidogrel Compliance among Patients with Definite Stent Thrombosis

Overall Population N=61

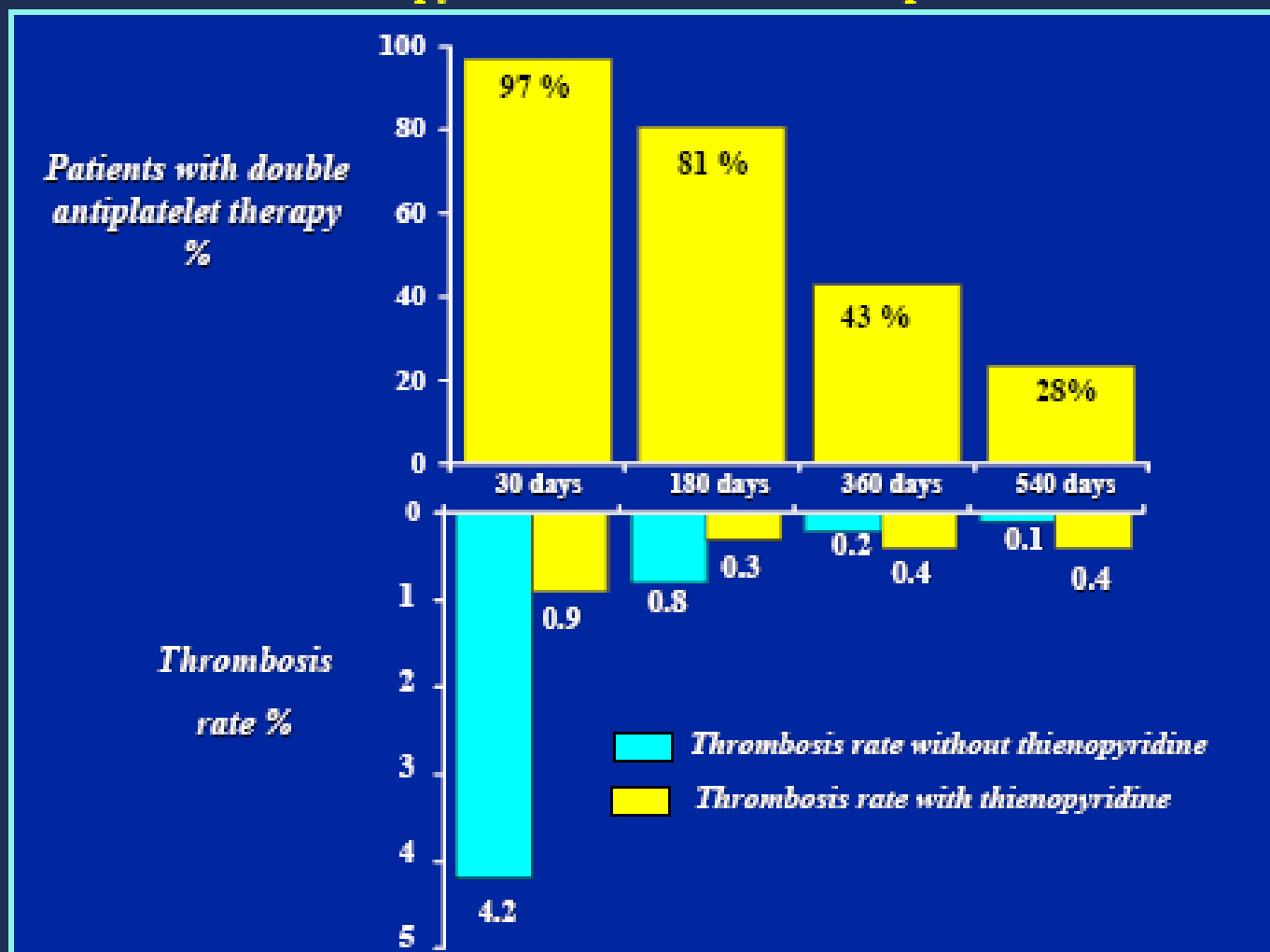


- Clopidogrel compliance defined as that at the time of stent thrombosis.

# Independent Predictors of Definite Stent Thrombosis at 1, 6 and 12 months

	Hazards ratio	Confidence interval	P
<b>1 month</b>			
Diabetes	2.0	1.1-3.9	0.03
Acute myocardial infarction	3.0	1.6-5.8	<0.01
Clopidogrel cessation	3.5	1.5-8.3	<0.01
<b>6 months</b>			
Acute myocardial infarction	2.4	1.3-4.5	<0.01
Type C lesion	2.1	1.2-3.8	0.02
Number of stents implanted	1.4	1.0-1.8	0.04
Clopidogrel cessation	2.0	1.0-4.2	0.05
<b>12 months</b>			
Acute myocardial infarction	2.2	1.2-3.9	<0.01
Lack of IVUS	1.8	1.0-3.1	<0.01
Number of stents implanted	1.5	1.2-2.0	<0.01

## Occurrence of stent thrombosis in patients assuming thienopyridine in 4 different time periods



While the prevalence of stent thrombosis is higher in patients not taking double antiplatelets in the first 6 months, after 180 days there is an increasing proportion of patients with thrombosis while taking double antiplatelet therapy



# Late Thrombosis with DES after Discontinuation of Antiplatelet Therapy

Late thrombosis	63 yr PCI with TAXUS of LAD Aspirin DC'd prior to bladder polyp resection 5 days after surgery, pt had AMI	343
Late thrombosis	73 yr Aborted out of hospital arrest PCI of PLAD with TAXUS Aspirin DC'd prior to resection of colon CA 7 days after surgery, pt had acute MI	442
Late thrombosis	42 yr VF PCI of LAD (vision), PCI LCX (Cypher) Pt stopped taking aspirin 1 yr later 2 wks later, pt presented with LWMI	375
Late thrombosis	62 yr PCI LAD (Cypher), PCI LCX (Vision) Pt stopped taking ASA/Plavix 11 months later Before colonoscopy and polypectomy 4 days later, pt had AWMI	335

# Why Is There Stent Thrombosis on Clopidogrel: Response Variability

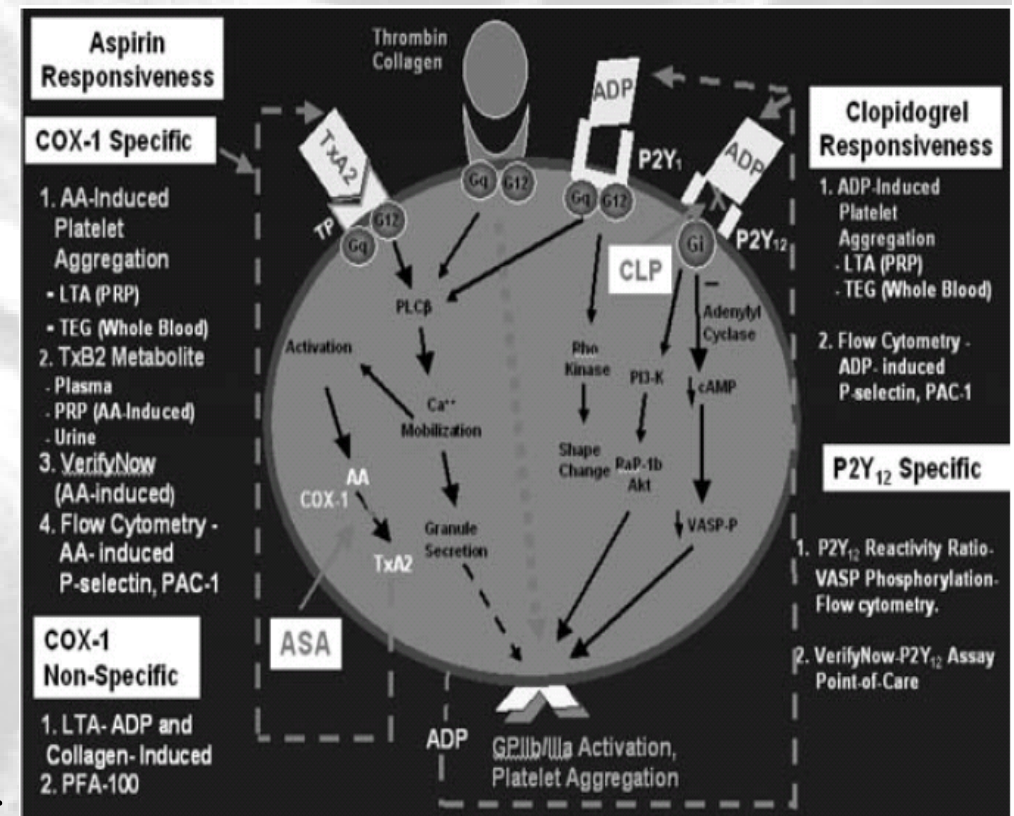
- Poor patient/system compliance
- Intestinal absorption: variable absorption/drug interaction
- Hepatic metabolism: genetic polymorphisms in CYP enzymes; drug-drug interaction
- P2Y<sub>12</sub> receptor: Genetic polymorphisms P2Y<sub>12</sub> receptor; alternate pathways of platelet activation; Increased release of circulating ADP; higher baseline platelet reactivity
- GP IIb/IIIa receptor expression: genetic polymorphism

O'Donoghue and Wiviott Circulation 2006;114:e600

- Should we monitored routinely for antiplatelet responsiveness ???

# What We Need to Know to Optimize Clopidogrel Therapy

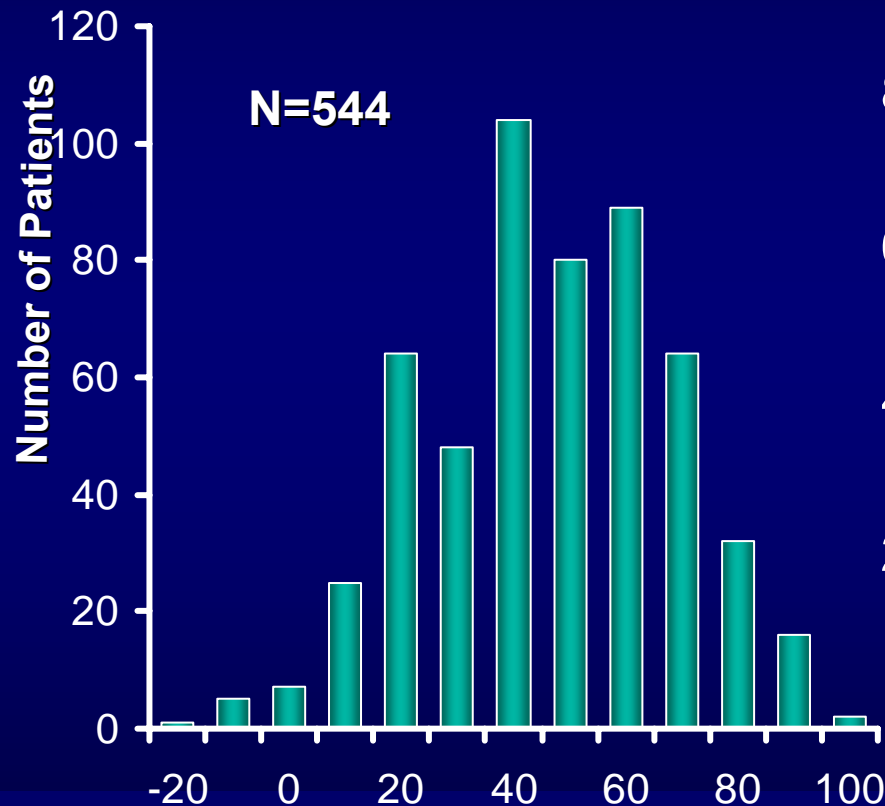
- Proper clopidogrel dosing:  
Load 300, 600, 900  
Maintenance 75; 150; ??
- More about testing for platelet reactivity
  - Who
  - When
  - How
  - How often
- Is there a clopidogrel rebound effect and how can it be avoided?
- What do we do about the need for surgery?
- Is it all about the duration of therapy



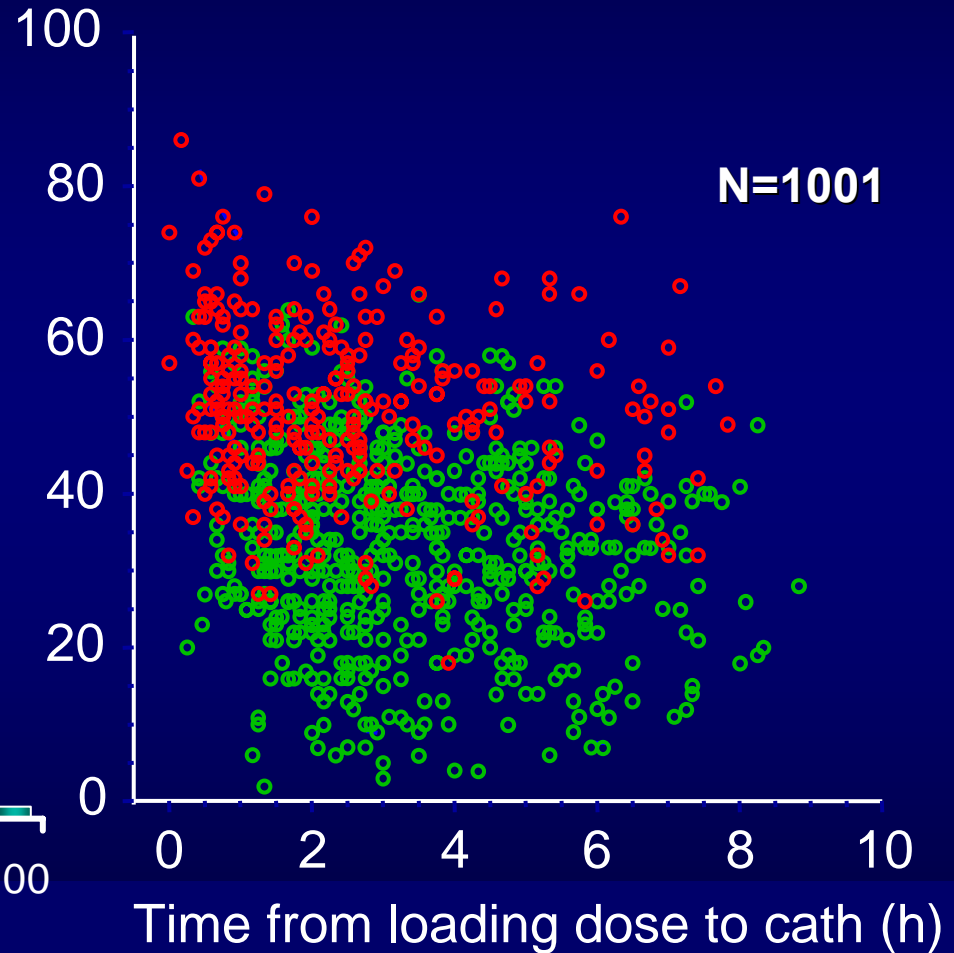
Gurbel and Tantry. J Intervent Cardiol 2006;19:439

# Variability in Clopidogrel Response

Change in ADP-Induced  
Platelet Aggregation  
75 mg chronic dosing



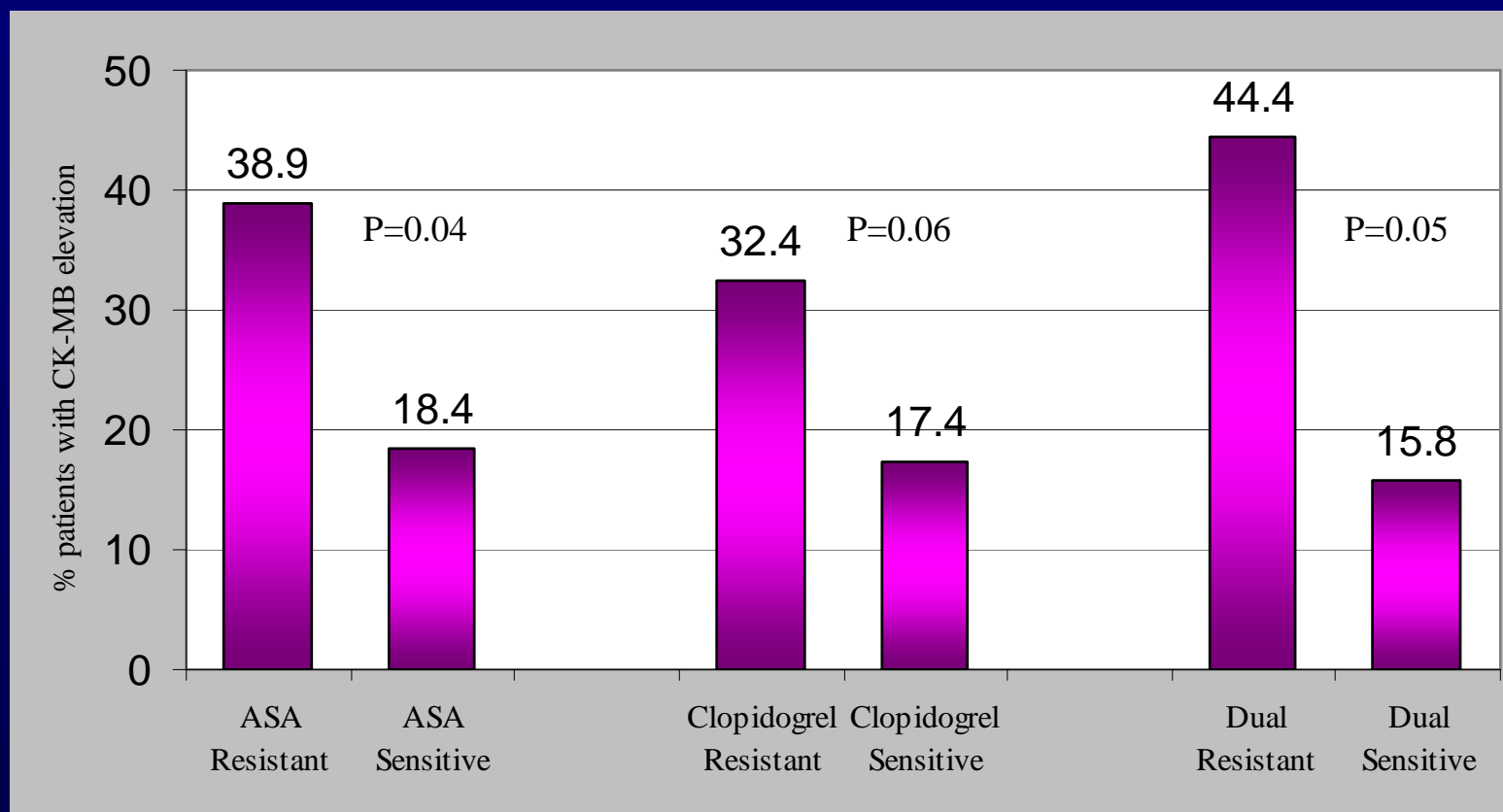
Maximal aggregation 5  $\mu$ mol/L ADP (%)  
following 600 mg loading dose



# Studies Linking Ex-Vivo Platelet Function to Clinical Events

Study	Results	Clinical Relevance
1. Barragan et al. (Catheter Cardiovasc Interv. 2003;59::295)	↑ P2Y <sub>12</sub> reactivity ratio (VASP-P levels)	Stent Thrombosis
2. Ajzenberg et al. (J Am Coll Cardiol. 2005;45:1753)	↑ Shear- Induced platelet aggregation	Stent Thrombosis
3. Gurbel et al. (CREST Study) (J Am Coll Cardiol. 2005;46:1827)	↑ P2Y <sub>12</sub> reactivity ratio ↑ ADP- induced aggregation ↑ Stimulated GPIIb/IIIa expression	Stent Thrombosis
4. Matzesky et al. (Circulation.2005;109:3171)	↑ ADP-Induced platelet aggregation	Recurrent Cardiac Events (4th quartile)
5. Gurbel et al. (CLEAR PLATELETS and CLEAR PLATELETS Ib) (Circulation. 2005;111:1153, J Am Coll Cardiol;2006 (in press)	↑ Periprocedural platelet aggregation	Myonecrosis and Inflammation Marker Release
7. Bliden et al. (J Am Coll Cardiol. 2006; (in press)	↑ Platelet aggregation (pre-PCI) on chronic clopidogrel	1 yr Post -PCI Events
8. Cuisset et al. (J Thromb Haemost. 2006;3:542-9)	↑ Platelet aggregation	30-day Post-PCI events
9. Lev et al. (J Am Coll Cardiol. 2006;47:27)	Clopidogrel/Aspirin resistant patients	Post-PCI Myonecrosis
10. Cuisset e al. (J Am Coll Cardiol. 2006;48:1339-45)	↑ Platelet aggregation	30-day Post-PCI events 600mg- less events
11. Hochholzer et al. (J Am Coll Cardiol 2006;48:1742-50)	↑ Platelet aggregation (Upper quartile)	30 day MACE

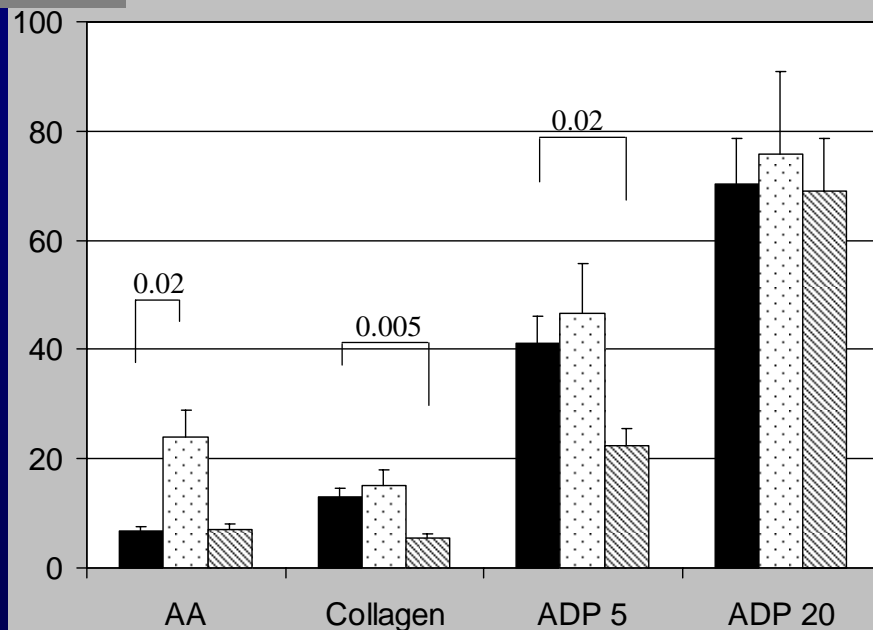
# Response to ASA and Clopidogrel: Association with CK-MB Release after PCI



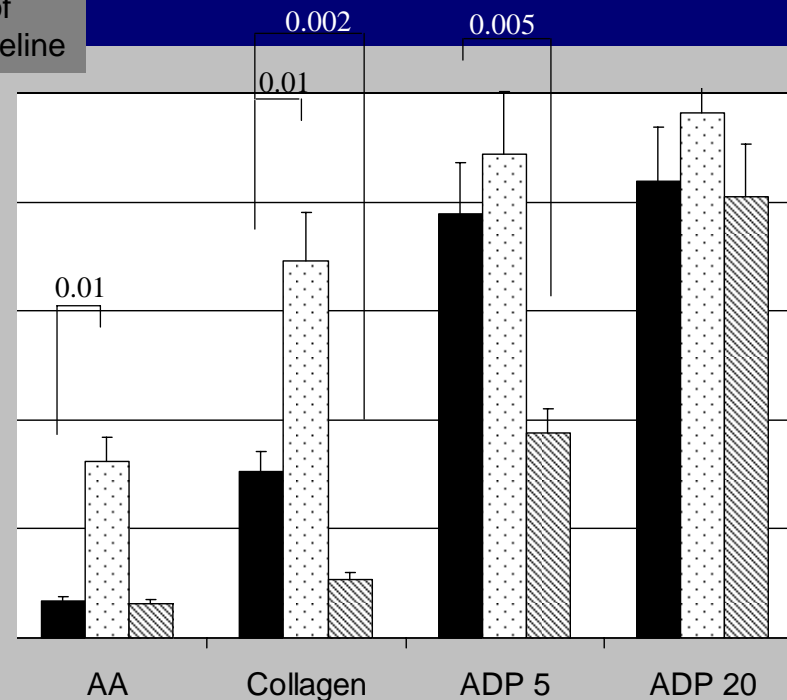
150 pts undergoing elective PCI, treated with Bivairudin

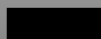
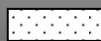

# Interference with the Antiplatelet Effect of Aspirin by Ranitidine


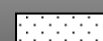

% of  
baseline



% of  
baseline



 Aspirin 53 µmol/L  
 Ranitidine 1.5 mM  
 Combination

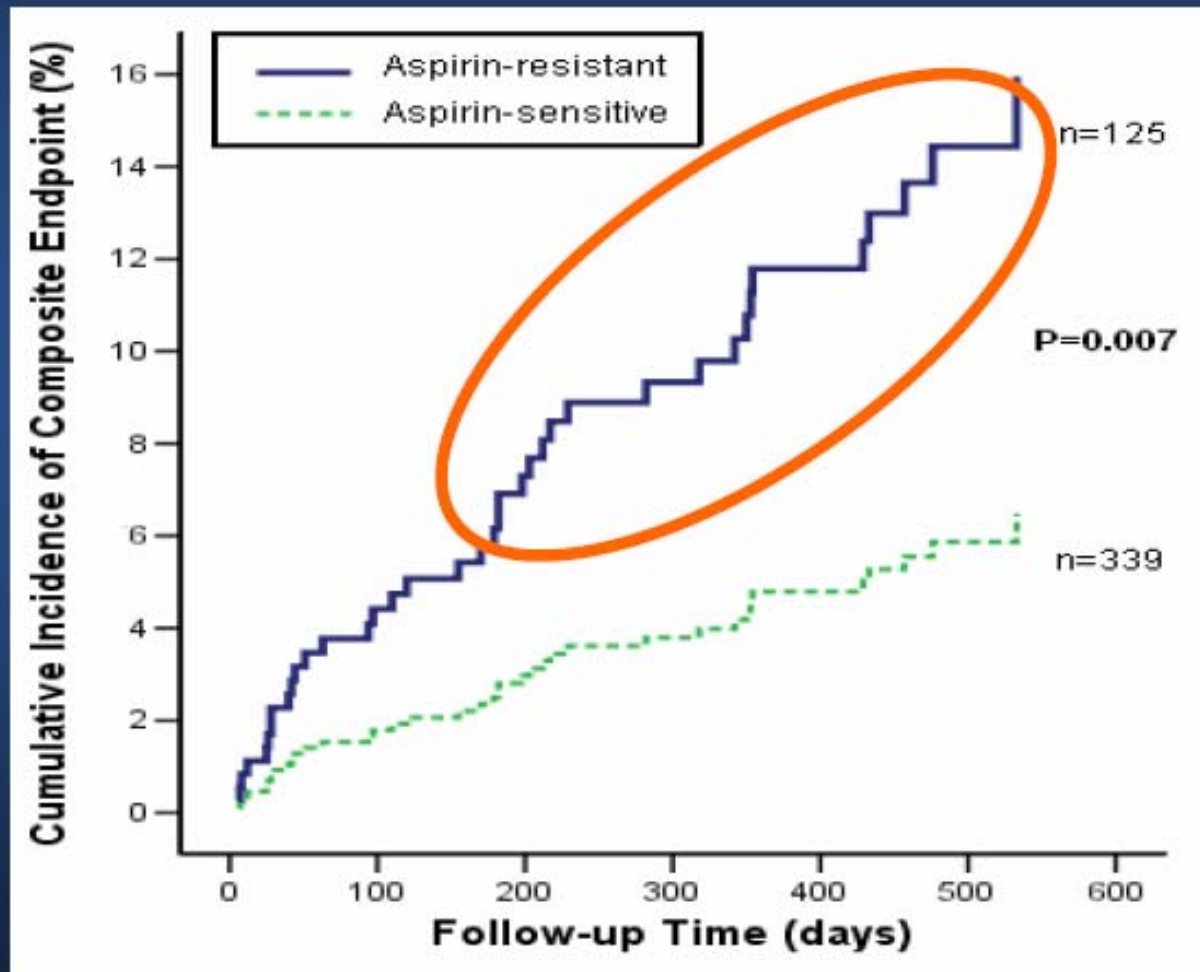
 Aspirin 26.5 µmol/L  
 Ranitidine 0.75 mM  
 Combination



# Aspirin Non-Responsiveness

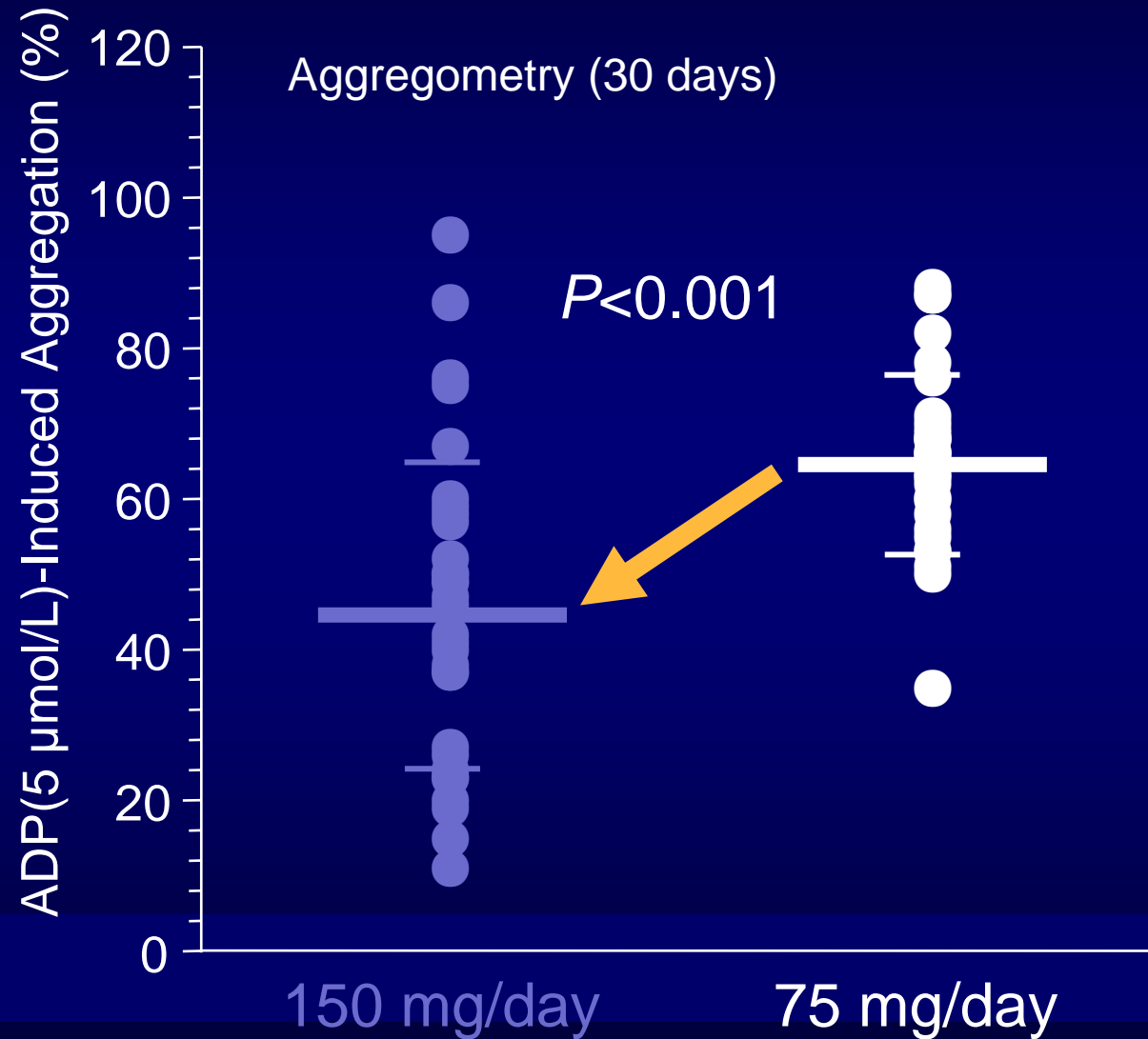
N=464, 26.9% ASA non-responsive

Endpoint= CV Death,MI,CVA/TIA,Hosp UA



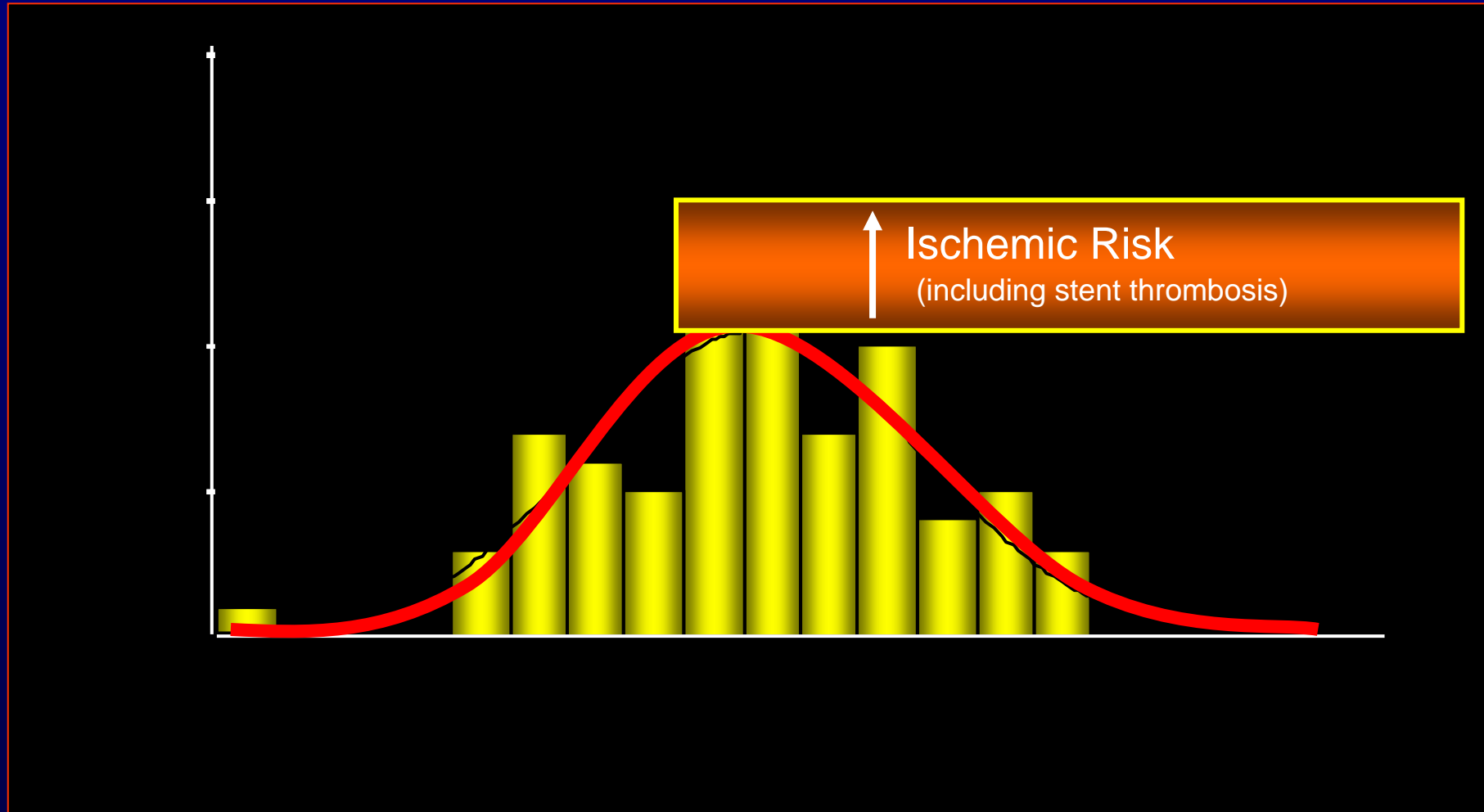


# Increasing Dose decreases Platelet Aggregation



## OPTIMUS-2

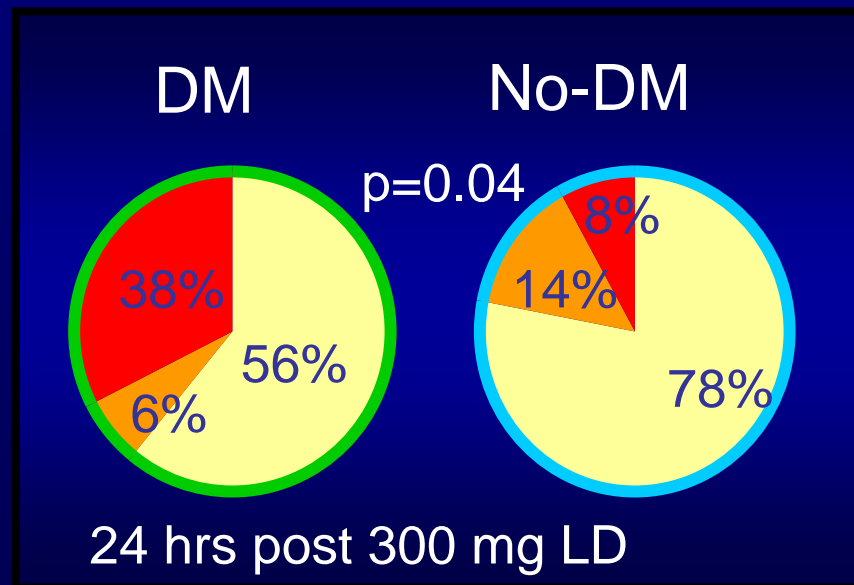
# Individual response variability to dual antiplatelet therapy



# Influence of Diabetes Mellitus on Clopidogrel-induced Antiplatelet Effects

OPTIMUS-2

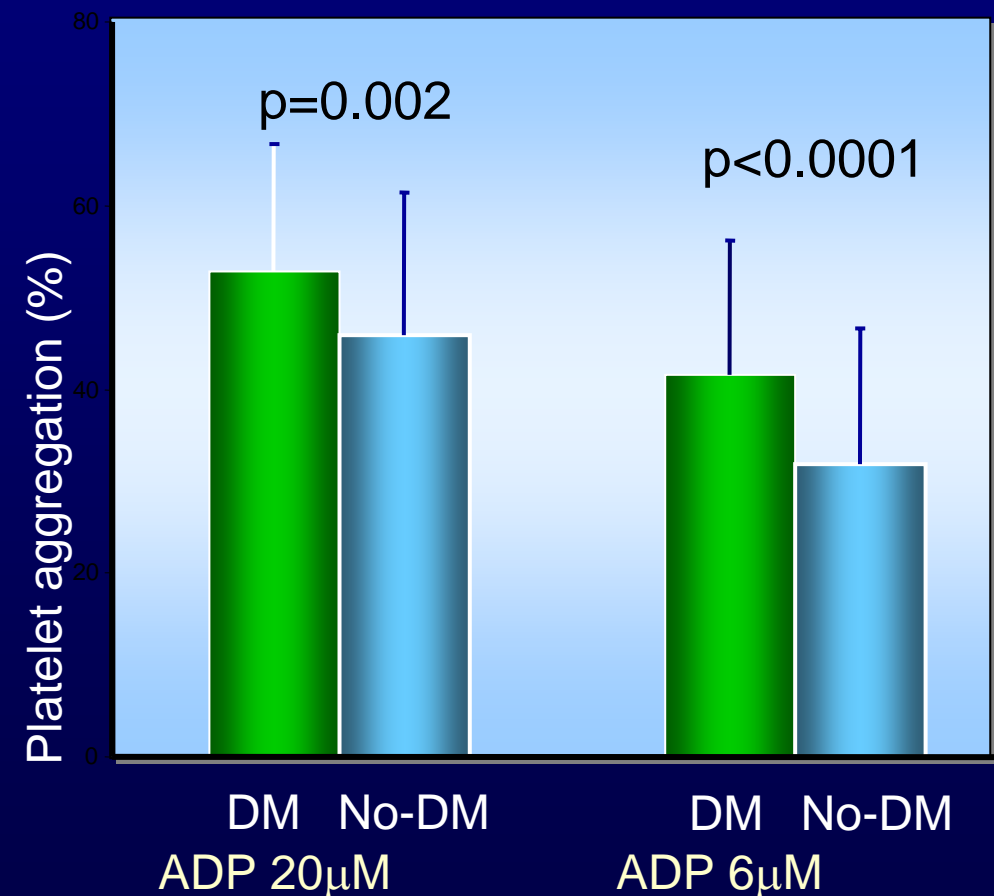
Acute phase of treatment



- Non responders (Platelet inhibition <10%)
- Low responders (Platelet inhibition 10-29%)
- Responders (Platelet inhibition >30%)

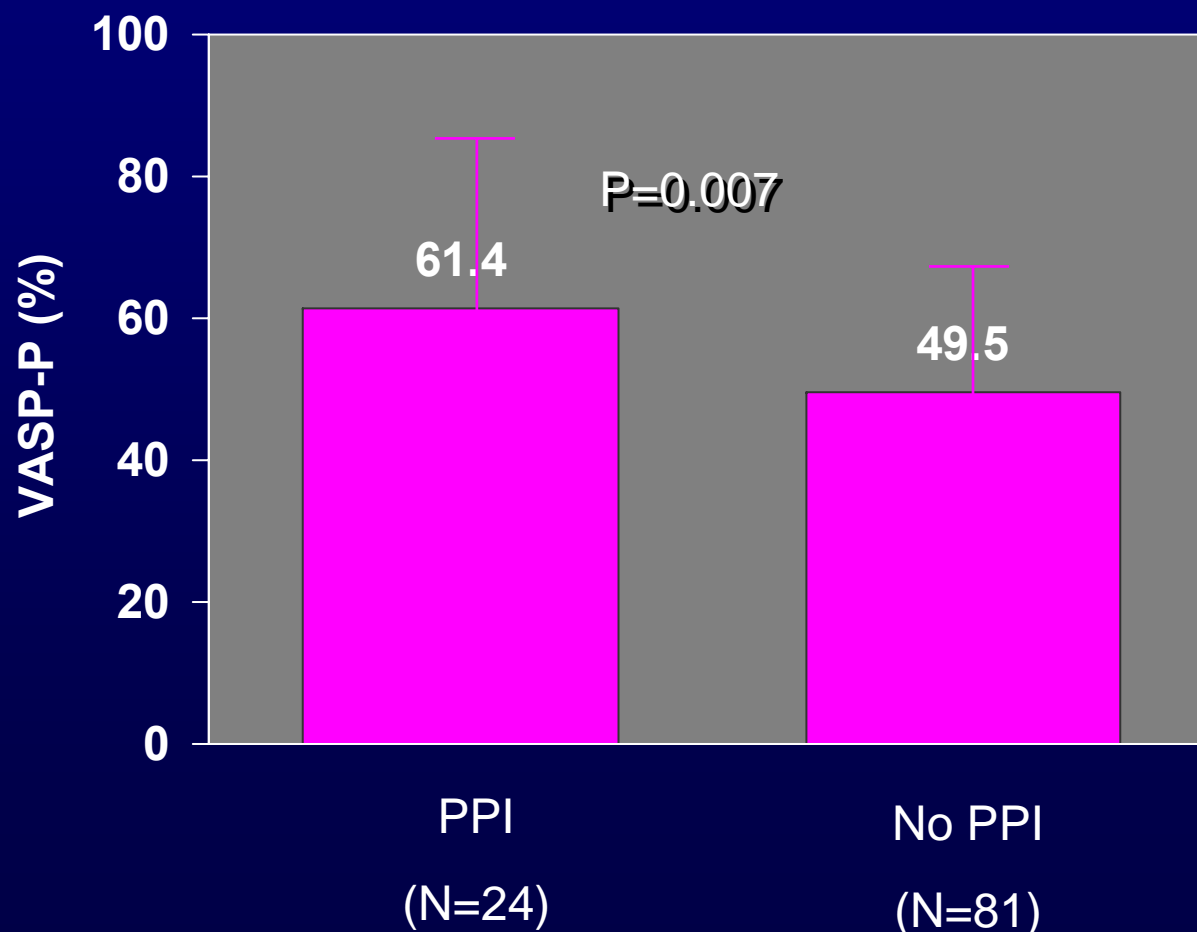
Angiolillo DJ et al. *Diabetes* 2005; 54:2430-5

Long-term phase of treatment



Angiolillo DJ et al. *J Am Coll Cardiol* 2006; 48: 298-304

# Clopidogrel and Proton Pump Inhibitors: Competition at CYP 2C19?

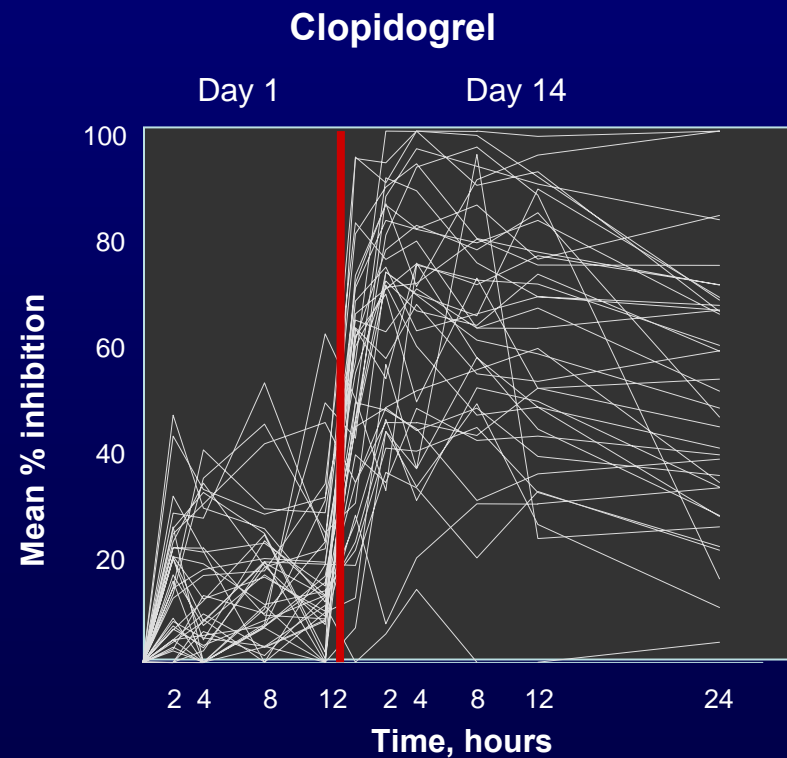
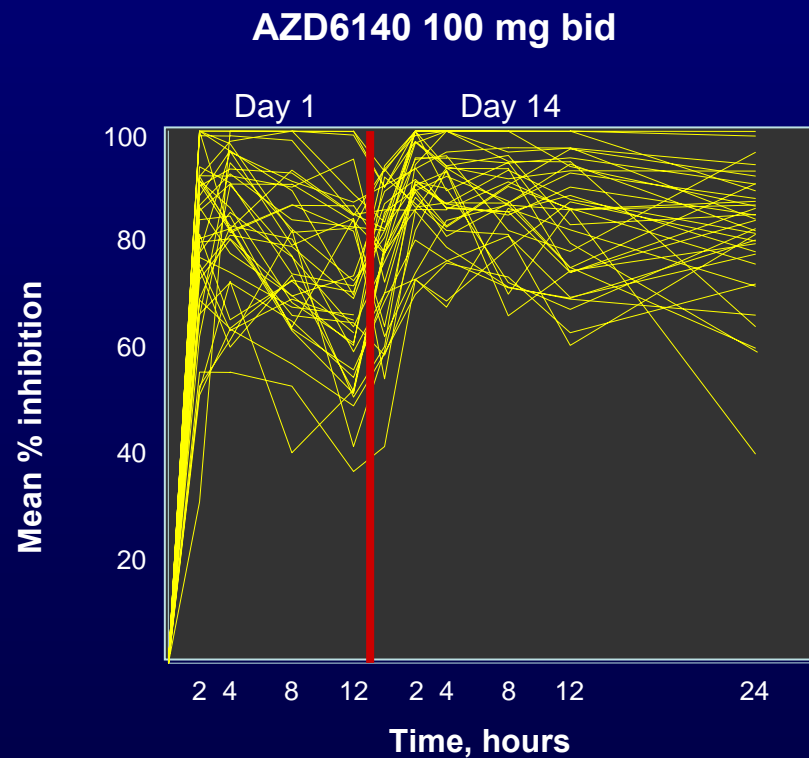


*Gilard, J Thromb Hem.*  
2006; 4: 2508

# Future Directions (I): Clopidogrel Resistance

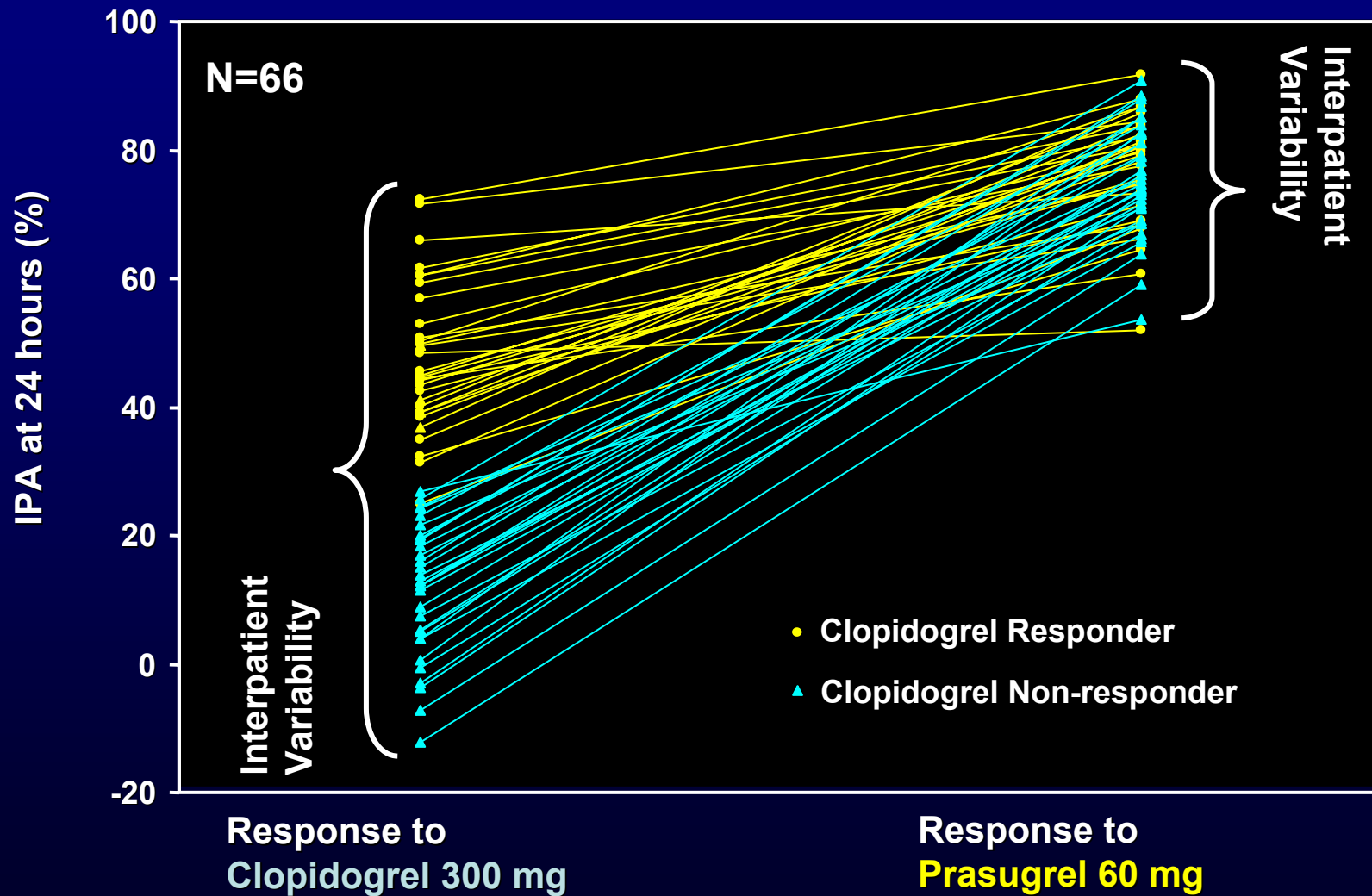
- New Drugs
  - Prasugrel
  - AZD 6140
  - Cangrelor
  - PRT 128

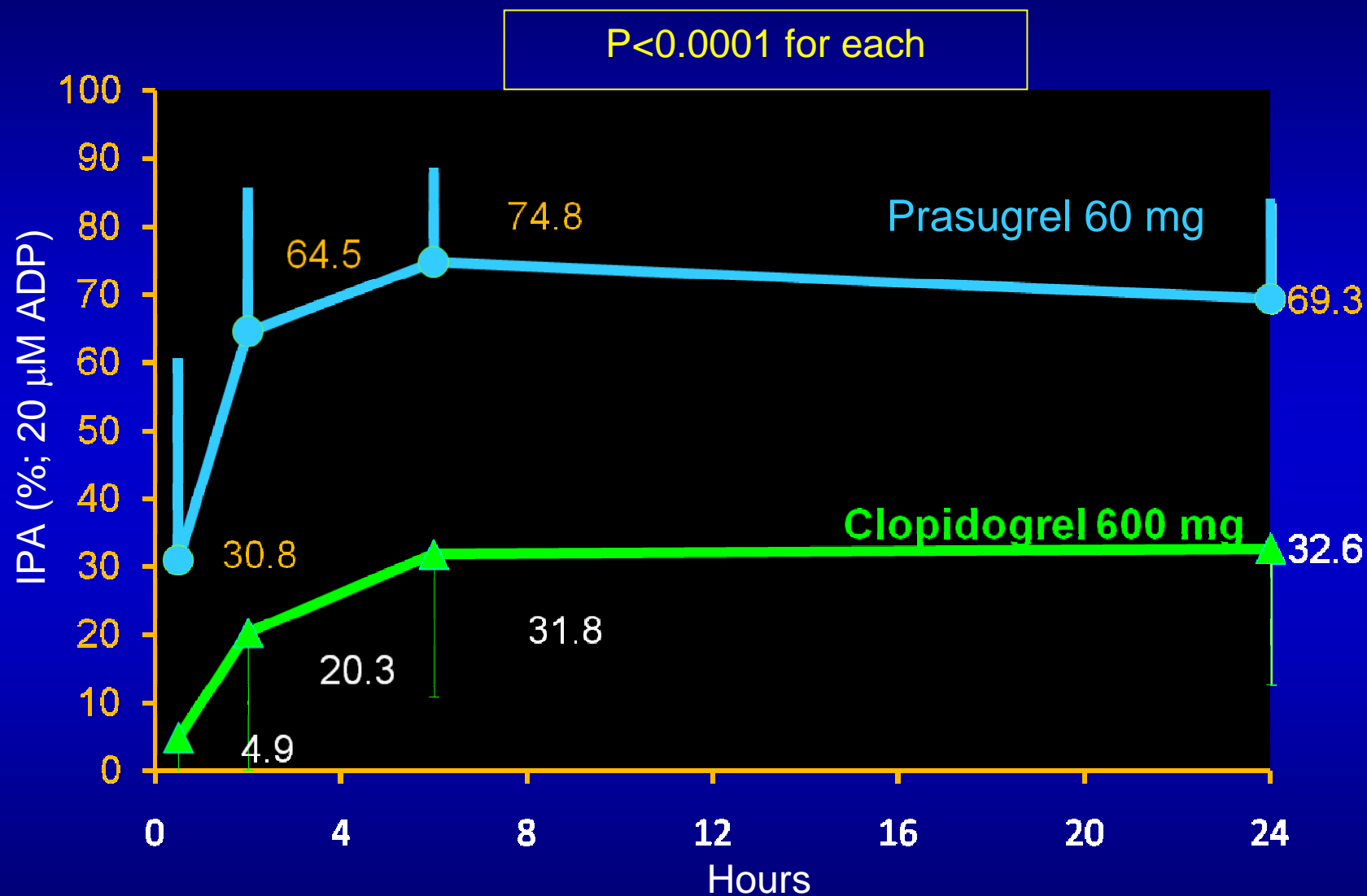
# Greater and More Consistent IPA with AZD6140 than Clopidogrel: Final Extent





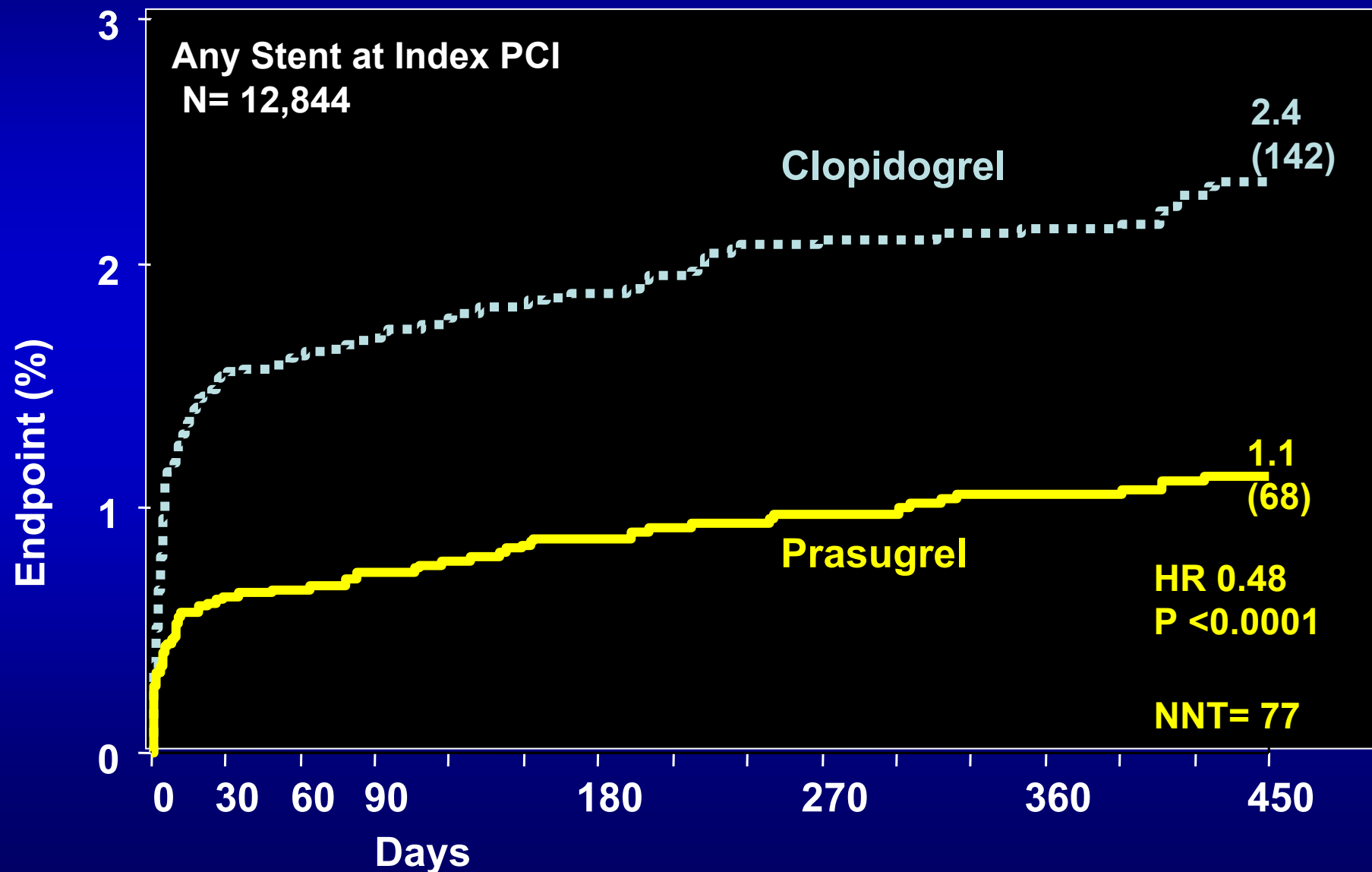
# Healthy Volunteer Crossover Study



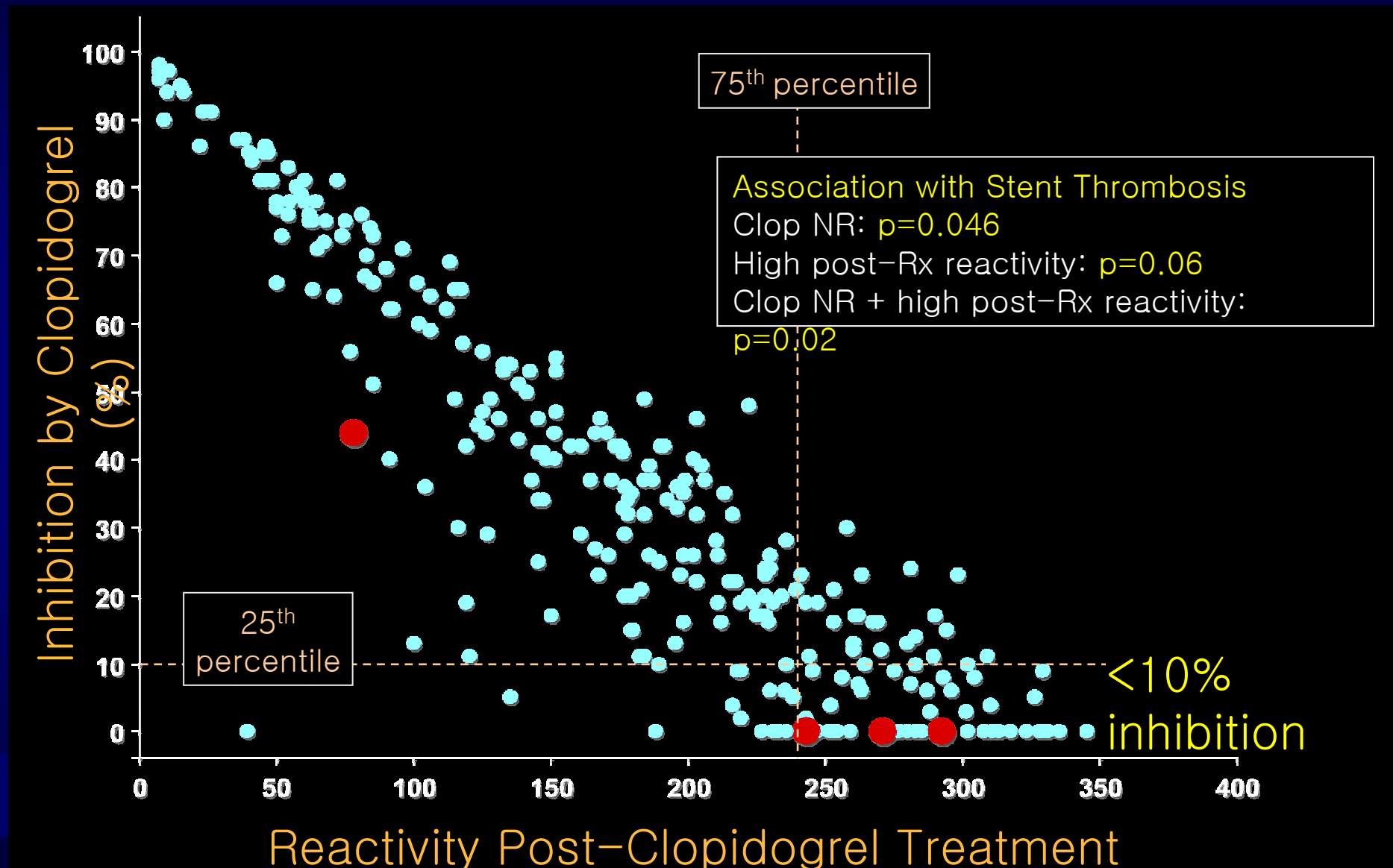


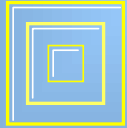


# Stent Thrombosis (ARC Definite + Probable)



# Clopidogrel Responsiveness at the Time of PCI and Stent Thrombosis After Cypher w/i 30 Days: N=280





## Potential Approach to Platelet Function Screening **Post-PCI**

**AT RISK PATIENT:** overweight (> 100 kg), MI, DM, CHF

**Clopidogrel Non-Responder/High Absolute Reactivity**  
(% inhibition < 10-15%, PRU > 240)



Increase clopidogrel to 75 mg twice daily ( $\pm$  re-load)



Recheck platelet function in 1 – 2 weeks

## Final Comments and Recommendations

- **SCAI AHA ACC Guidelines are 12 months of dual antiplatelet therapy if patients do not experience side effects or bleeding complications**
- *Dual antiplatelet therapy beyond 6 months is recommended but not proven to be prohibitive of late stent thrombosis*
- *Do not Stop Aspirin and consider higher dose with cessation of Plavix*
- **DES should be contraindicated for patients with poor compliance or allergic to Plavix or Aspirin.**
- **New antiplatelet therapy (prasugrel or cangrelor ) may be more effective to prevent late thrombosis**

**Thank You**