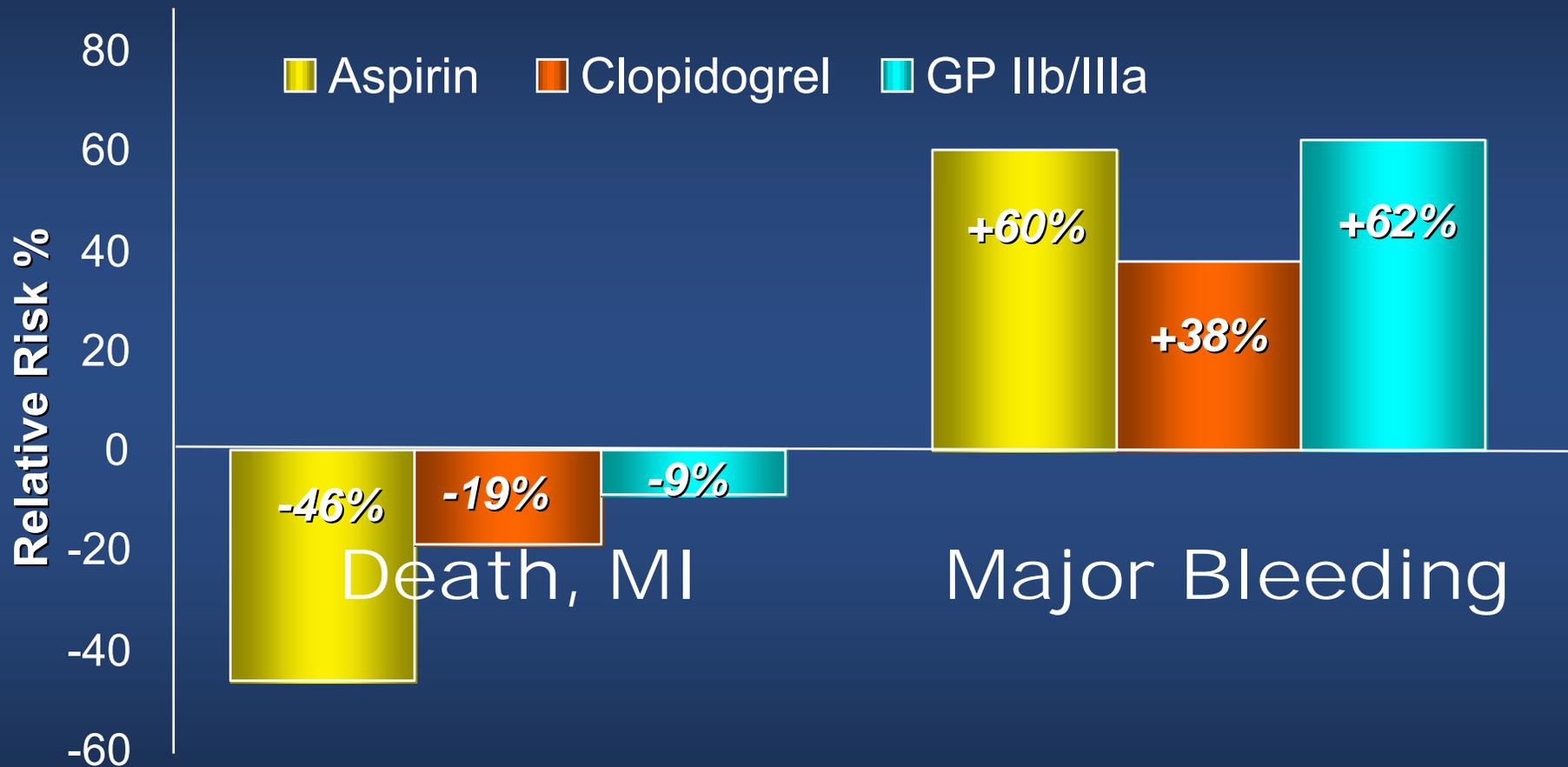


What is the Right Dose, Timing and Duration of Clopidogrel Therapy when Used with Drug Eluting Stents ?

Robert S. Hillman, PhD
Accumetrics, Inc.
San Diego, CA

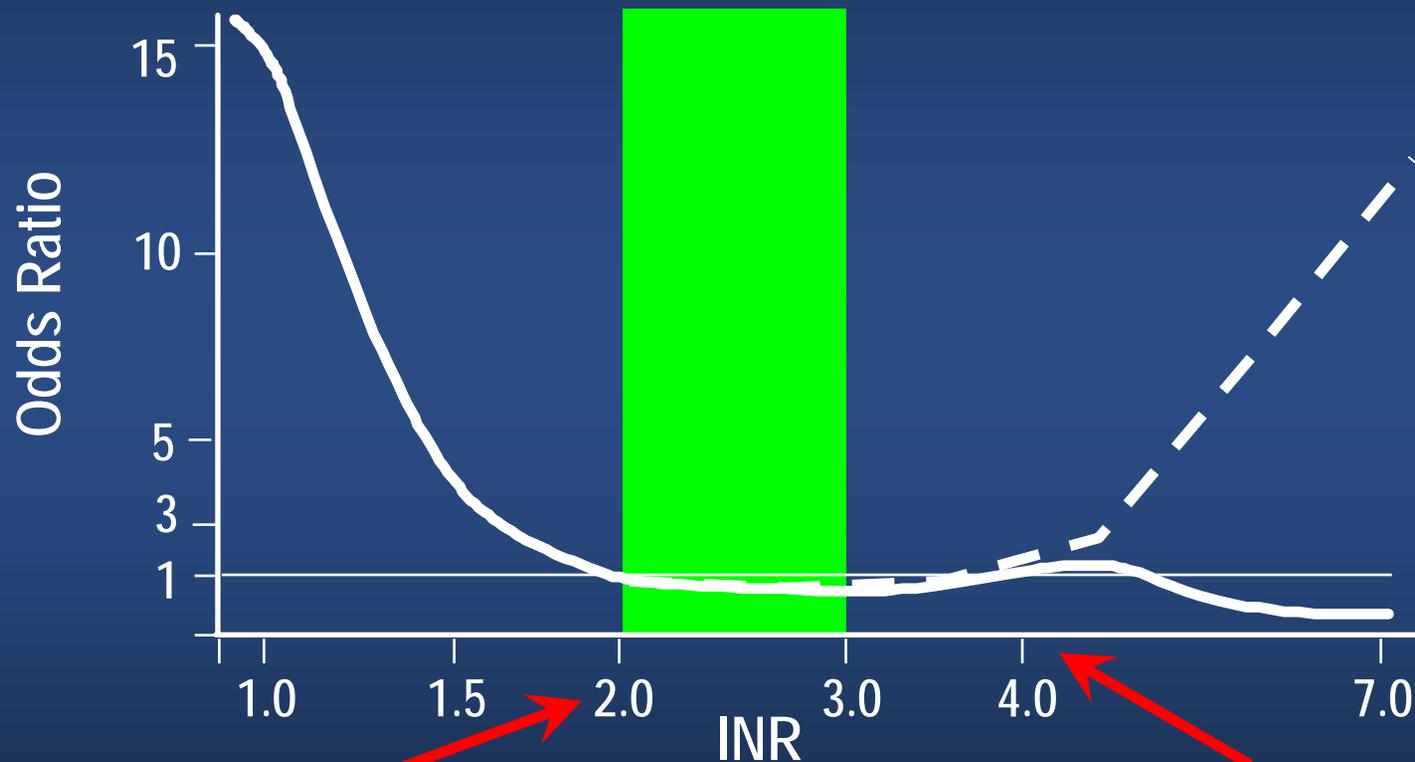
Summary of Efficacy and Safety of Antiplatelet Therapy



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

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

Therapeutic Range for Warfarin Therapy

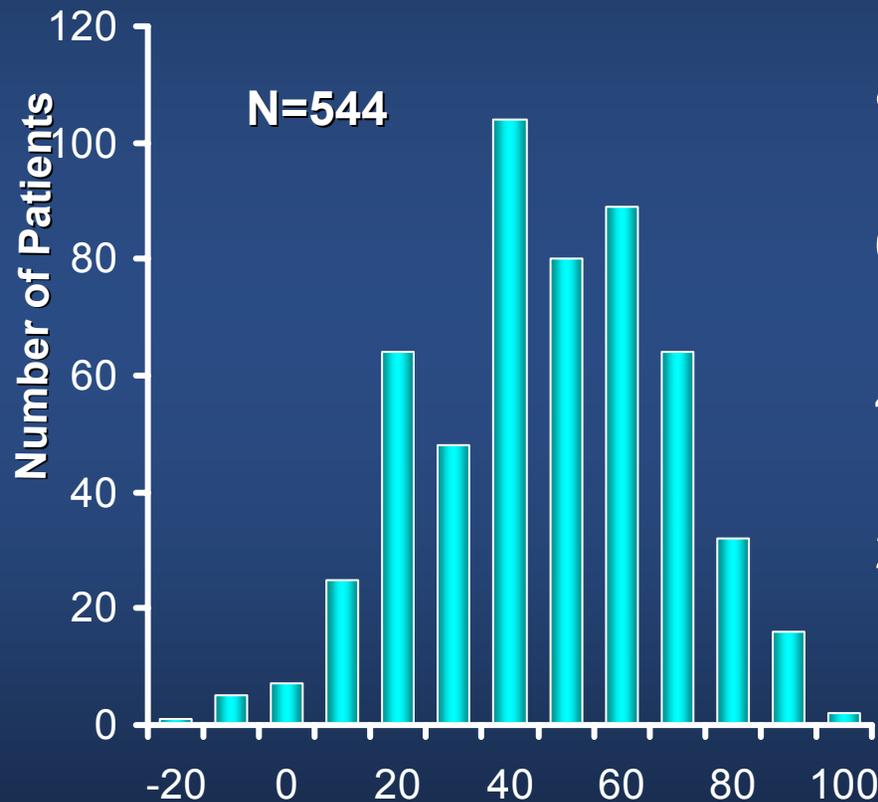


INR below 2.0 results in a higher risk of stroke

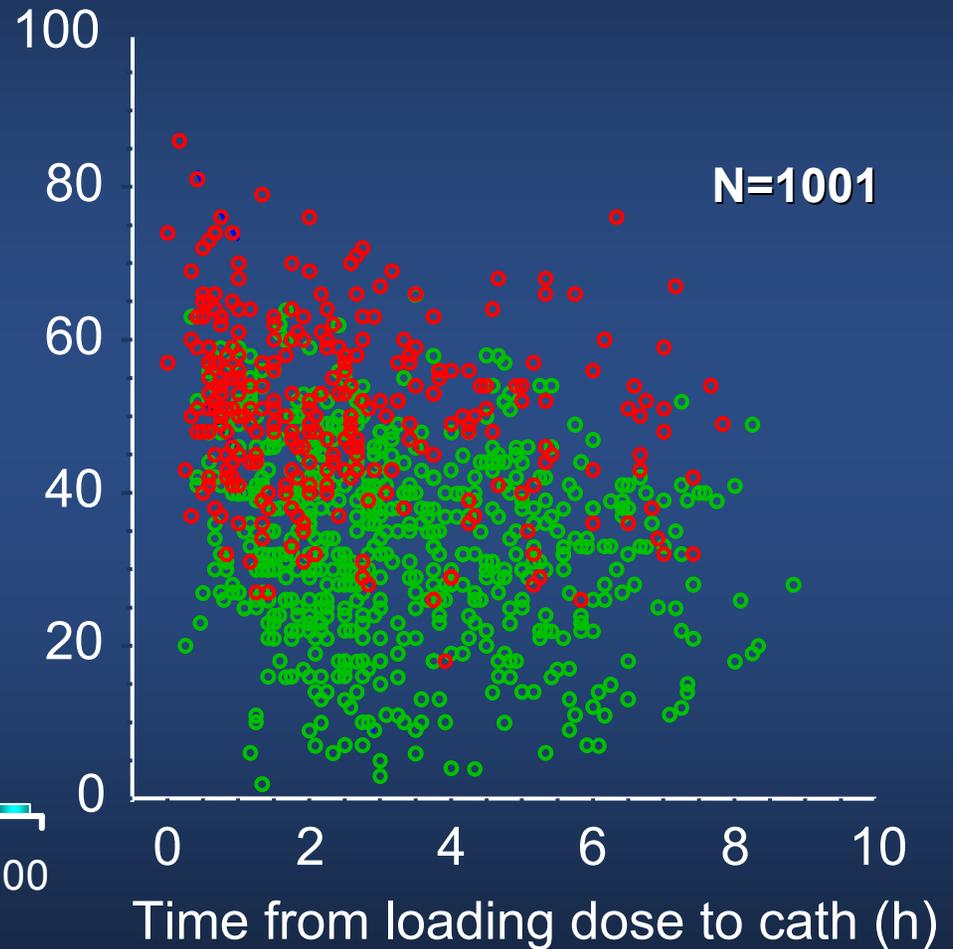
The estimated odds ratio of subdural hemorrhage increased 7 fold as INR increased above 4.0

Variability in Clopidogrel Response

Change in ADP-Induced Platelet Aggregation
75 mg chronic dosing



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

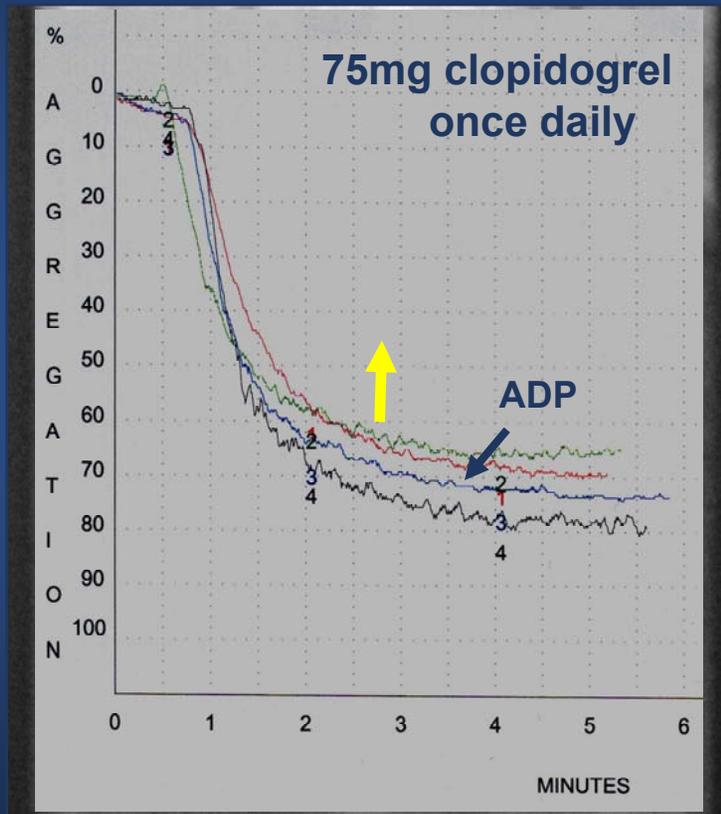


Serebruany. *J Am Coll Cardiol.* 2005;45:246.

Hochholzer W et al., *Circulation* 2005.

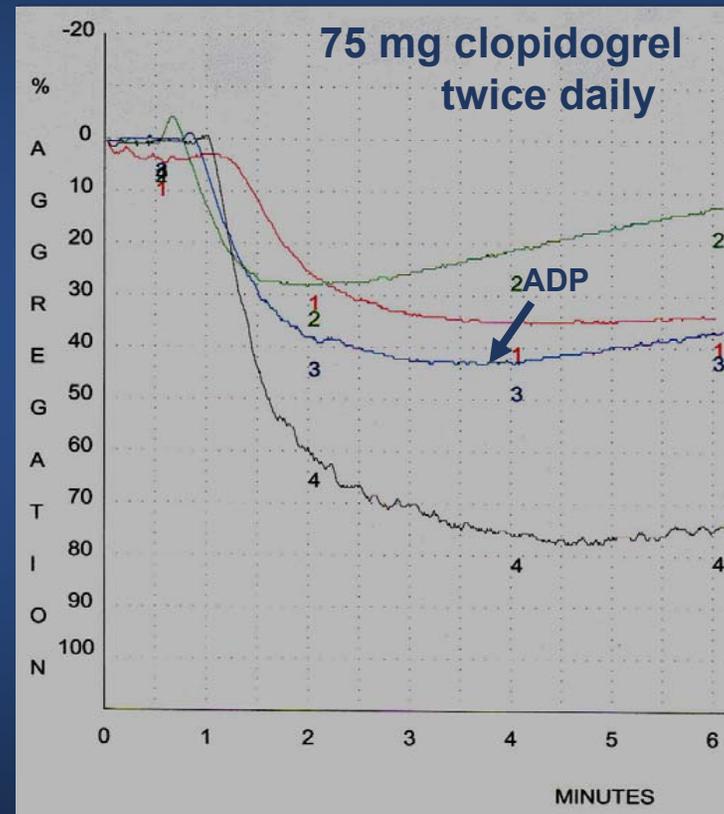
Case Report: Stent Thrombosis

Patient J.V., 64 Years,
Stable Angina, CCS III



26th October, 2004

Patient J.V., Angina at Rest,
Positive Troponin



11th November, 2004

Studies Linking Ex-Vivo Platelet Function to Clinical Events

<u>Study</u>	<u>Results</u>	<u>Clinical Relevance</u>
1. Barragan et al. (Catheter Cardiovasc Interv. 2003;59::295)	↑ P2Y ₁₂ 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 ₁₂ 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

Guidelines Suggest Measurement of Platelet Aggregation

ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention)

6.2. Antiplatelet and Antithrombotic Adjunctive Therapies for PCI

6.2.1. Oral Antiplatelet Therapy

Class IIb

In patients in whom subacute thrombosis may be catastrophic or lethal (unprotected left main, bifurcating left main, or last patent coronary vessel), platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg per day if less than 50% inhibition of platelet aggregation is demonstrated. (Level of Evidence: C)

Point of Care Assay Accumetrics VerifyNow



Insert assay device



Add blood sample



Read result in minutes

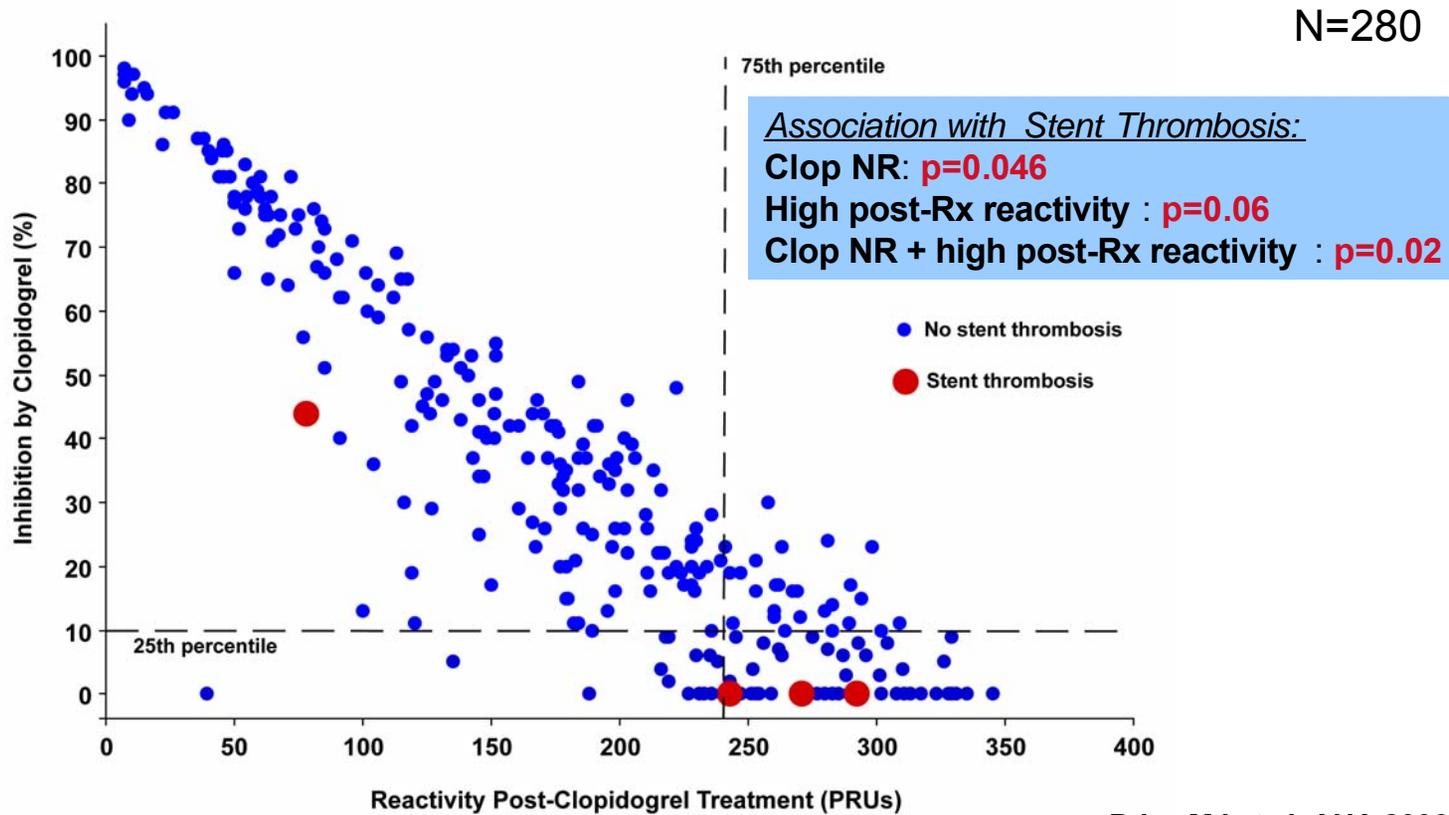


Scripps DES Real World Registry: Platelet Substudy

- **Prospective registry of patients undergoing SES implantation at Scripps Clinic.**
- **Platelet function testing with VerifyNow is performed at baseline (prior to PCI) and again 12 hours post-procedure.**
- **Patients not already on clopidogrel receive a 600-mg load.**
- **Operators are blinded to the results of the platelet function tests (no management decisions are made based on them).**



Stent Thrombosis at 30 day Follow-Up



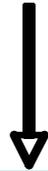
Price MJ et al, AHA 2006



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)**

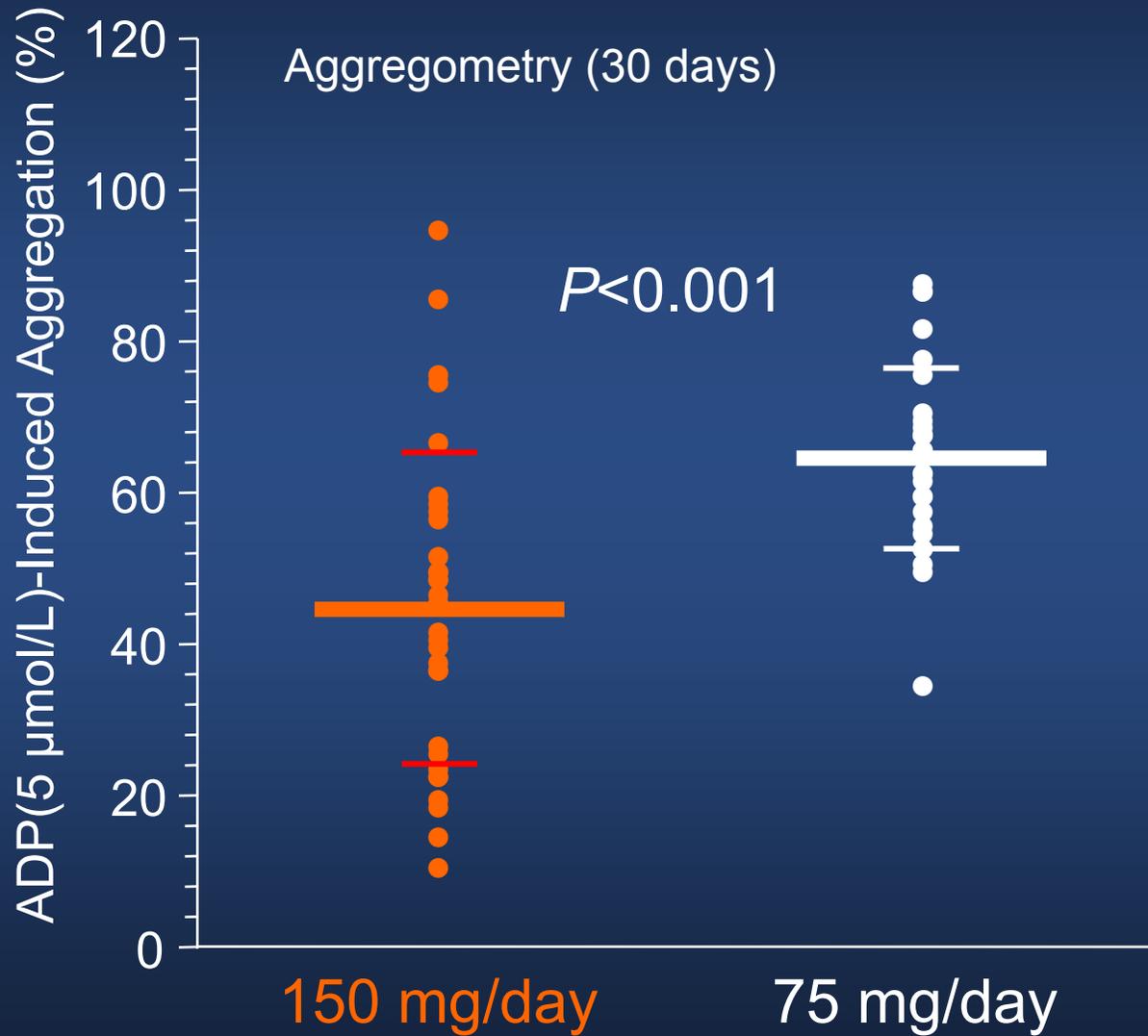


Increase clopidogrel to 75 mg twice daily (± re-load)



Recheck platelet function in 1 – 2 weeks

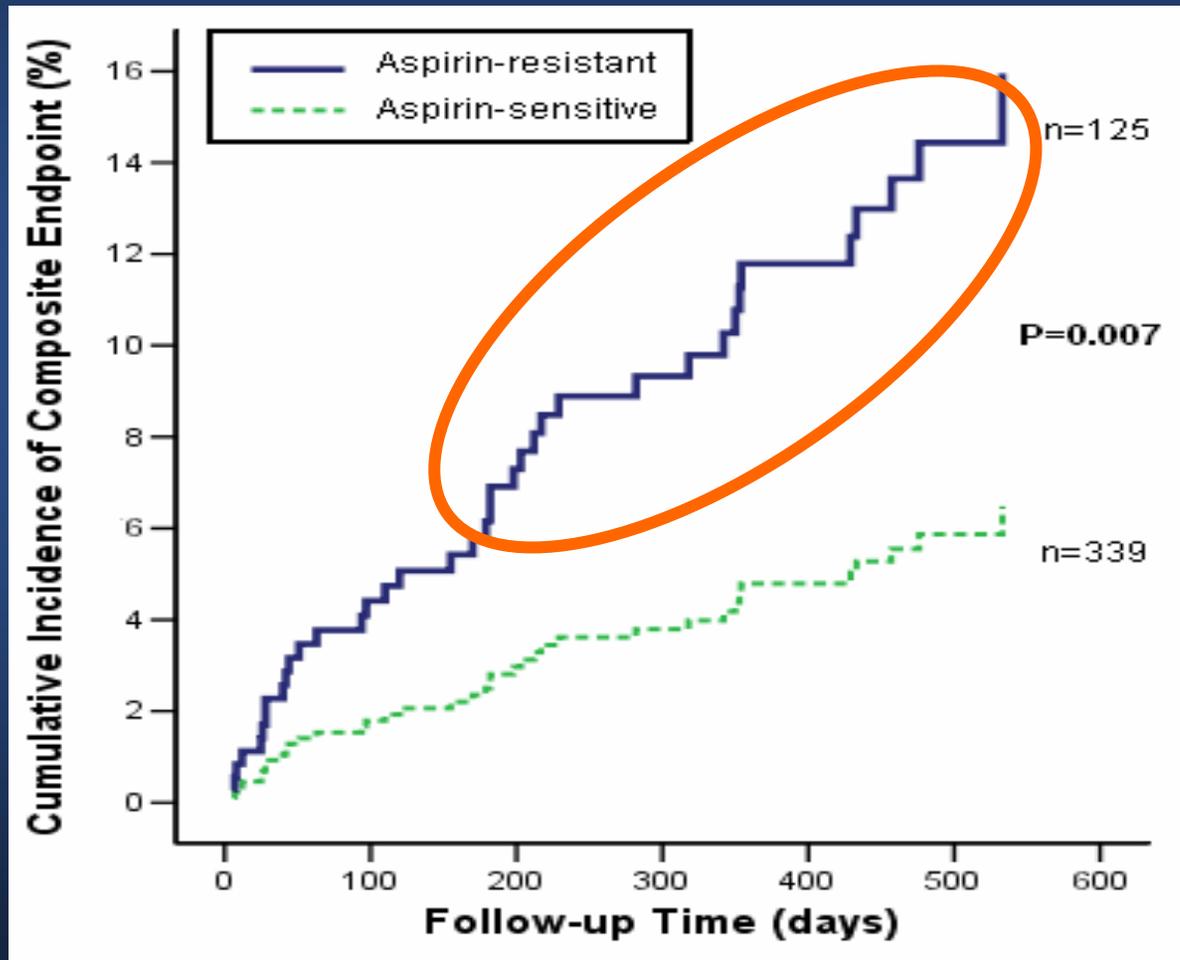
Effect of Increasing Dose on Platelet Inhibition



Aspirin Non-Responsiveness

N=464, 26.9% ASA non-responsive

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



Clinical Significance of Non-Response to ADP-Receptor Antagonists

The level of platelet inhibition at the time of PCI has a clinically relevant impact on outcome.

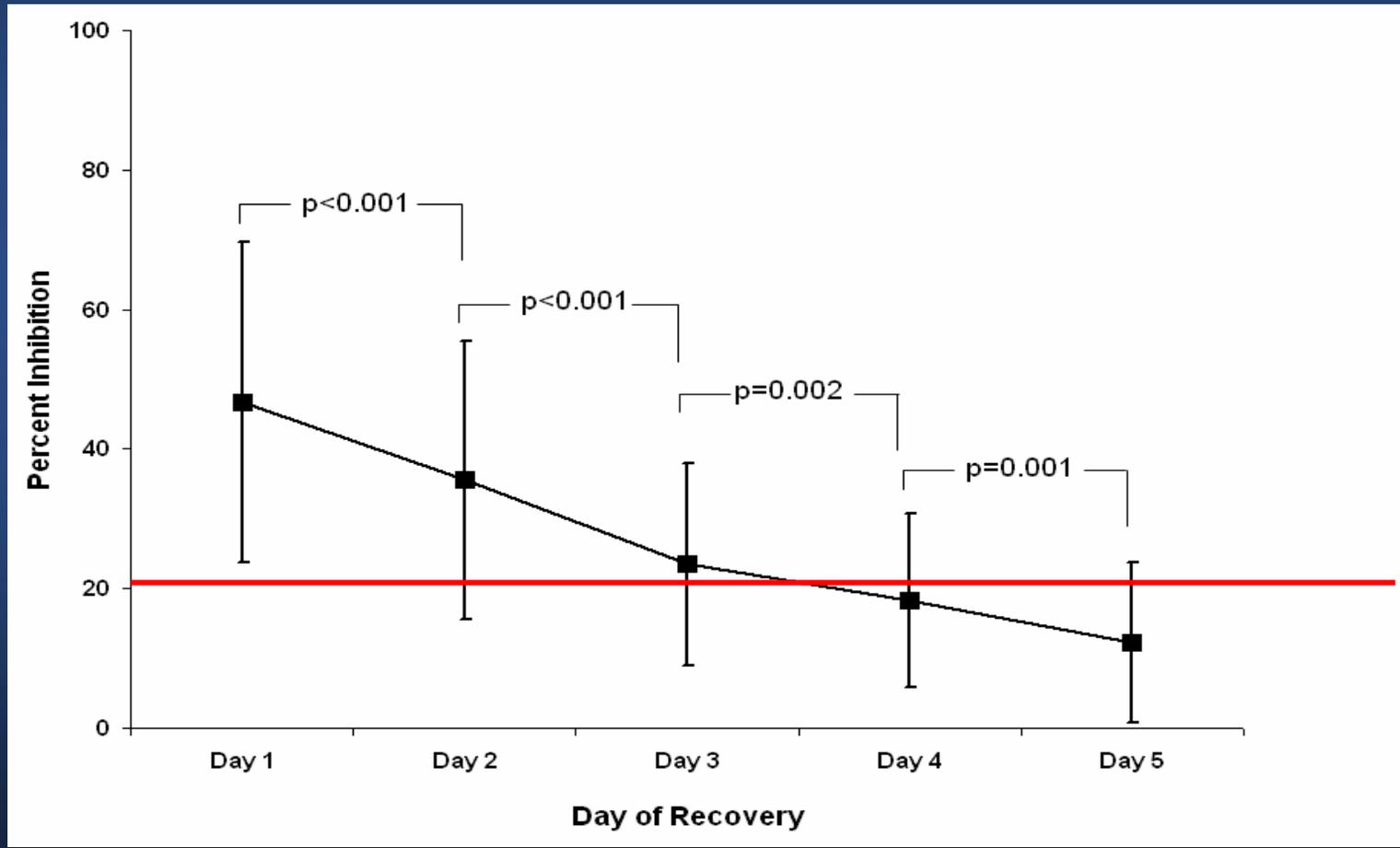
Even after appropriate loading or chronic administration with clopidogrel, platelet inhibition is suboptimal in a large proportion of patients.

Monitoring of platelet inhibition at the bedside is now possible for the first time.

Monitoring will help yield insights into the optimal dose, timing, and duration of antiplatelet therapy in conjunction with drug eluting stents.



Offset of Clopidogrel after discontinuation VerifyNow P₂Y₁₂ test



Price et al AJC 2006

Frequency Distribution of Platelet Inhibition After Cessation of Daily Clopidogrel Therapy

