

DEBATE: Antiplatelet Function

Test for all Patients

Not So Fast Data

Are Circumstantial

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Potential Conflicts of Interest

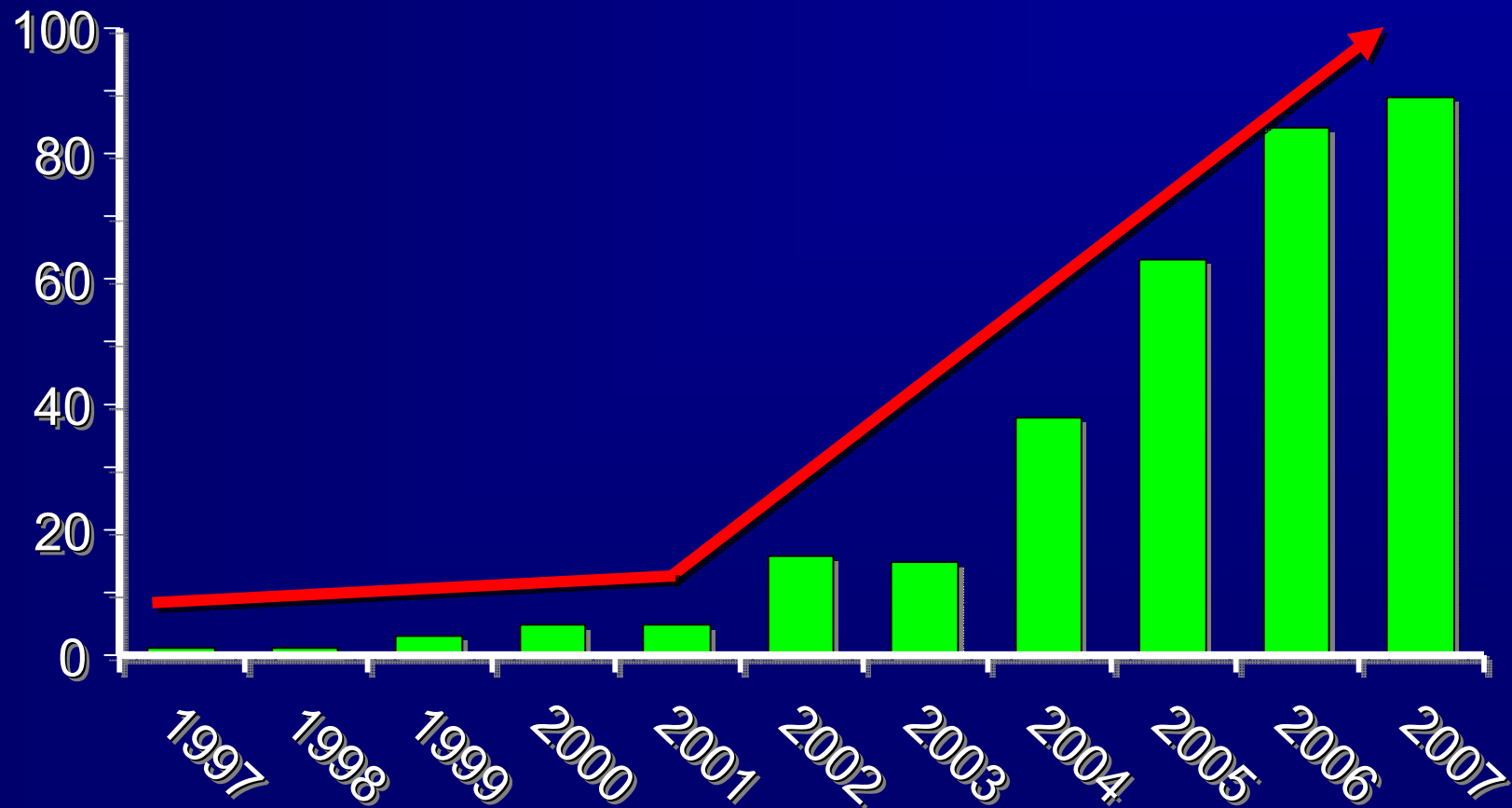
- I have spoken at CME approved scientific symposia supported by BMS, Sanofi-Aventis, the Medicines Company Medtronic, Boston Scientific, Shering Plough, Lilly/Daiichi Sankyo (all for less than \$10,000).
 - I received grants from BMS, Sanofi-Aventis, the Medicines Company Medtronic, Boston Scientific, Shering Plough.
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Issues

- Definitions of “resistance” or hyporesponsiveness
- How to make the diagnosis
- Implications for personalized medicine

Stent thrombosis is multi factorial

Annual Number of Medline Articles with Clopidogrel, Aspirin, or Antiplatelet and Resistance or Responsiveness in the Title 1997-2007



Courtesy of Steve Steinhubl, MD

ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention—Summary Article

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)

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Class IIb: In pts in whom subacute thrombosis may be catastrophic or lethal (unprotected left main, bifurcating left main, or last patent 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)

Level of Evidence C: Consensus opinion of experts, case studies, or standard-of-care.

Methods to Assess Responsiveness of Antiplatelet Agents

- Light transmission aggregometry (using different agonists, different concentrations of agonists; using either the maximal, final, or slope of aggregation; differing anticoagulants)
 - Flow cytometry (VASP phosphorylation, P selectin, platelet microparticles, leukocyte aggregates, activated IIb/IIIa receptors)
 - VerifyNow
 - Ichor device (Platelet Works)
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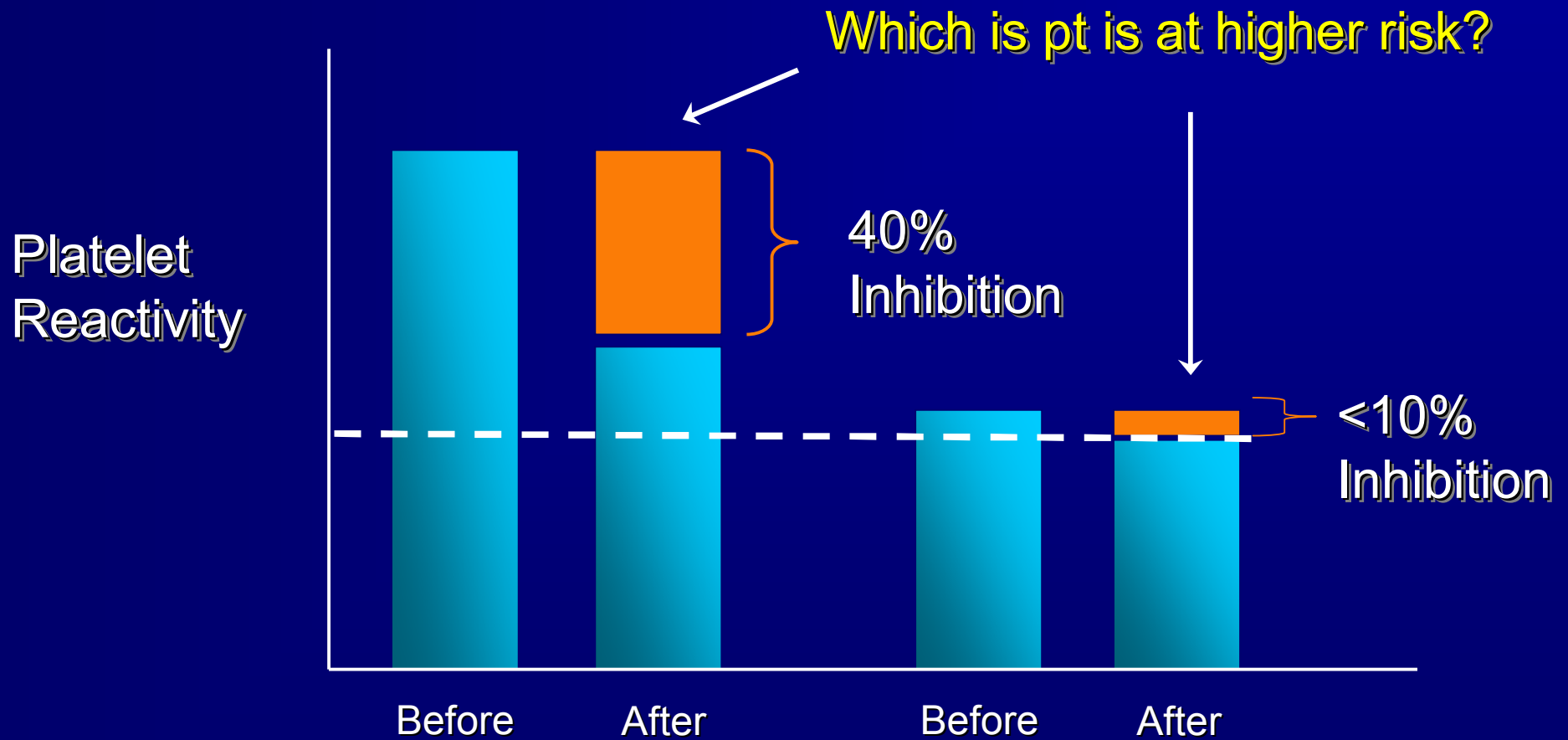
Methods to Assess Responsiveness of Antiplatelet Agents

- PFA 100
- Thromboelastography (TEG) Platelet Mapping
- Urinary thromboxane metabolites
- Serum thromboxane metabolites (not commercially available)
- Thrombovision
- PlaCor device
- Whole blood impedance aggregometry

Definitions of Hyporesponsiveness

- Lower tertile, quartile, quintile of “response”
 - Less than 10% or 20% reduction in responsiveness
 - Bottom 10% or 20% or 50% of residual aggregability
 - >50% the aggregability of platelet poor plasma
 - Many others, using many different methods...
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Responsiveness to Antiplatelet Drugs on Ex Vivo Platelet Function Tests and Clinical Outcome

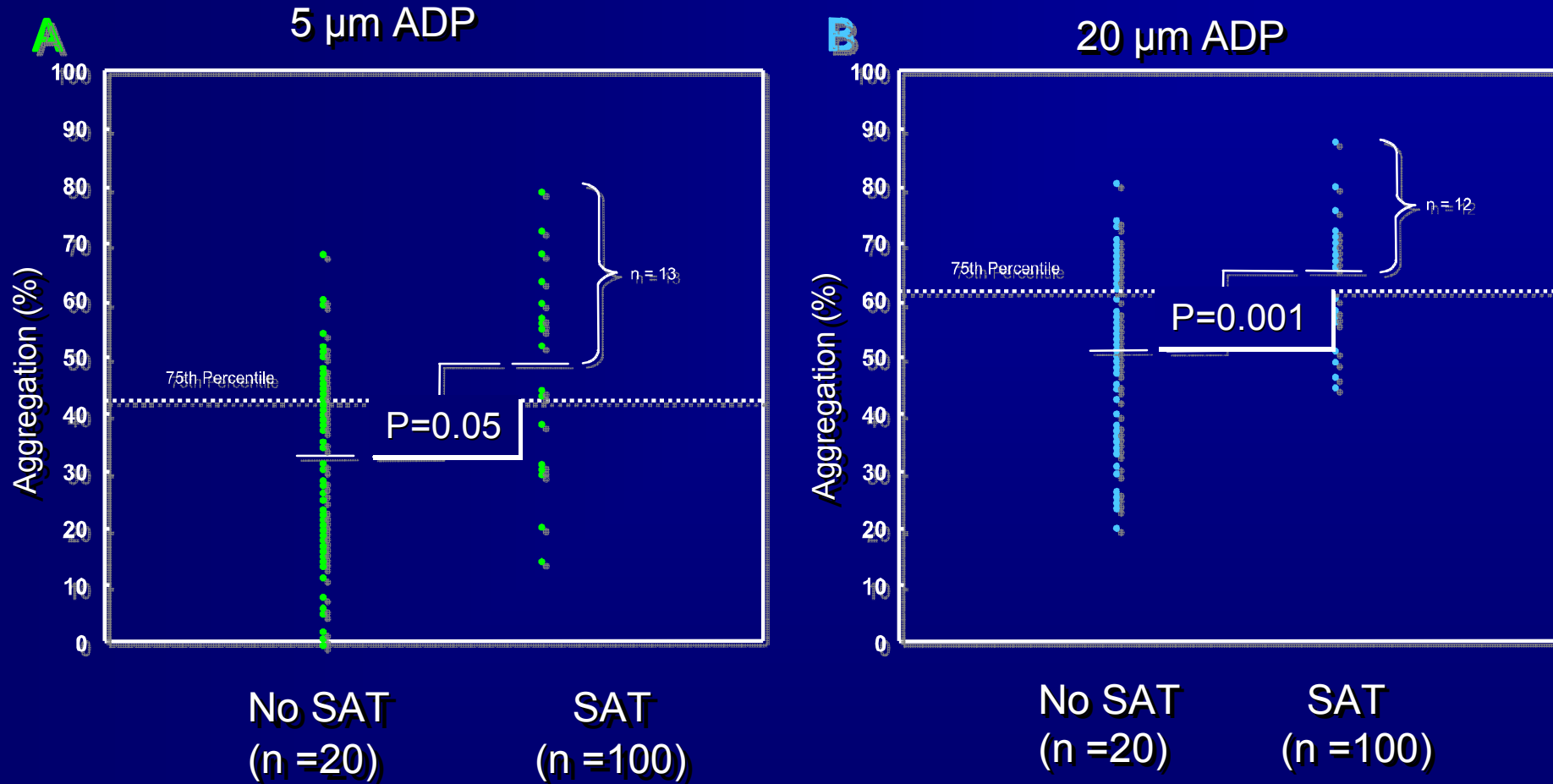


Courtesy of Shamir Mehta

Methods to Assess Responsiveness of Antiplatelet Agents

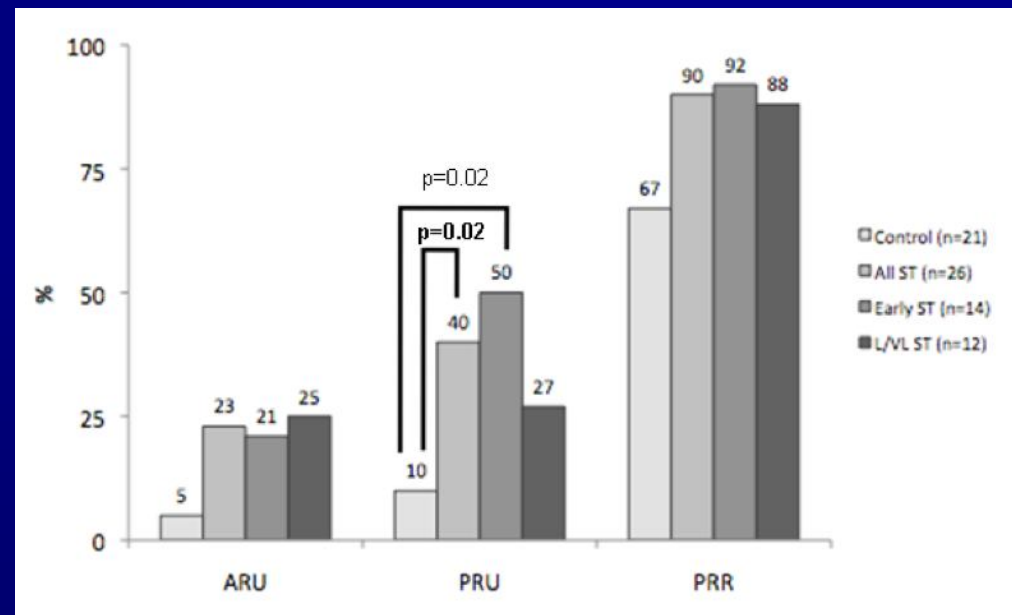
- It is not possible that all the devices are associated with thrombotic events (or bleeding) as they do not correlate with one another
 - Several studies employed more than 1 device and only 1 correlated with outcome
 - Studies have now been performed directly comparing device with one another
- There has been publication bias favoring the positive studies
- Therefore we can not know the true strength of the reported associations

Clopidogrel and Platelet REactivity in Patients With and Without Stent Thrombosis: CREST

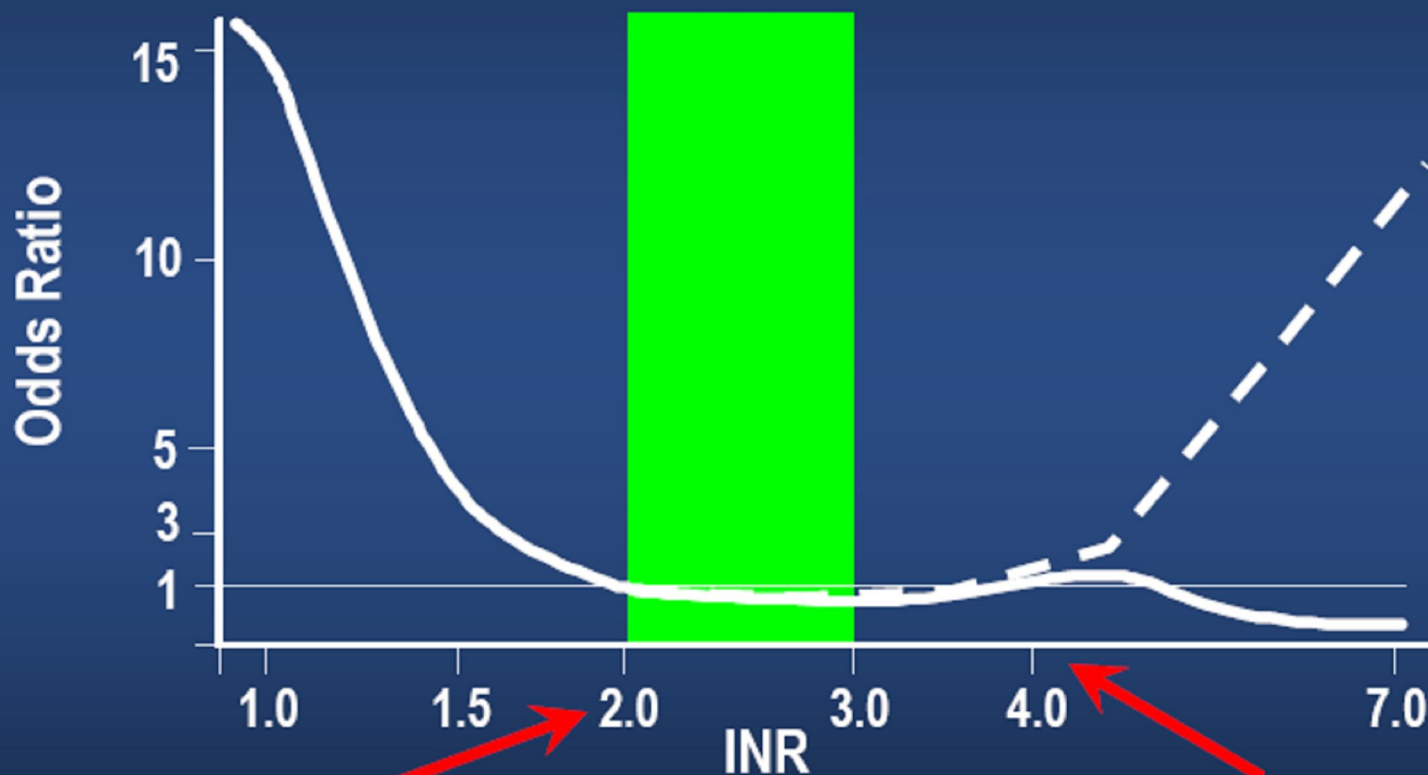
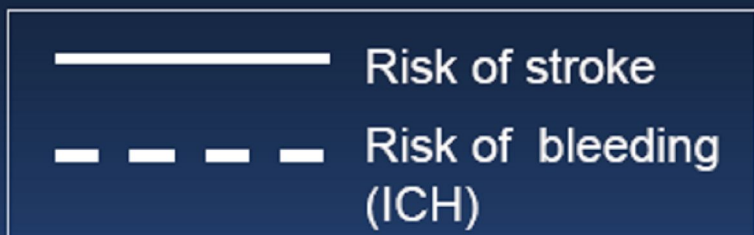


Rates of Aspirin and Clopidogrel Resistance Among Patients With and Without Definite Drug-Eluting Stent Thrombosis

- Patients who experienced ST demonstrated significantly higher rates of clopidogrel resistance by P2Y12 reaction units, **but not** by VASP



Therapeutic Range for Warfarin Therapy

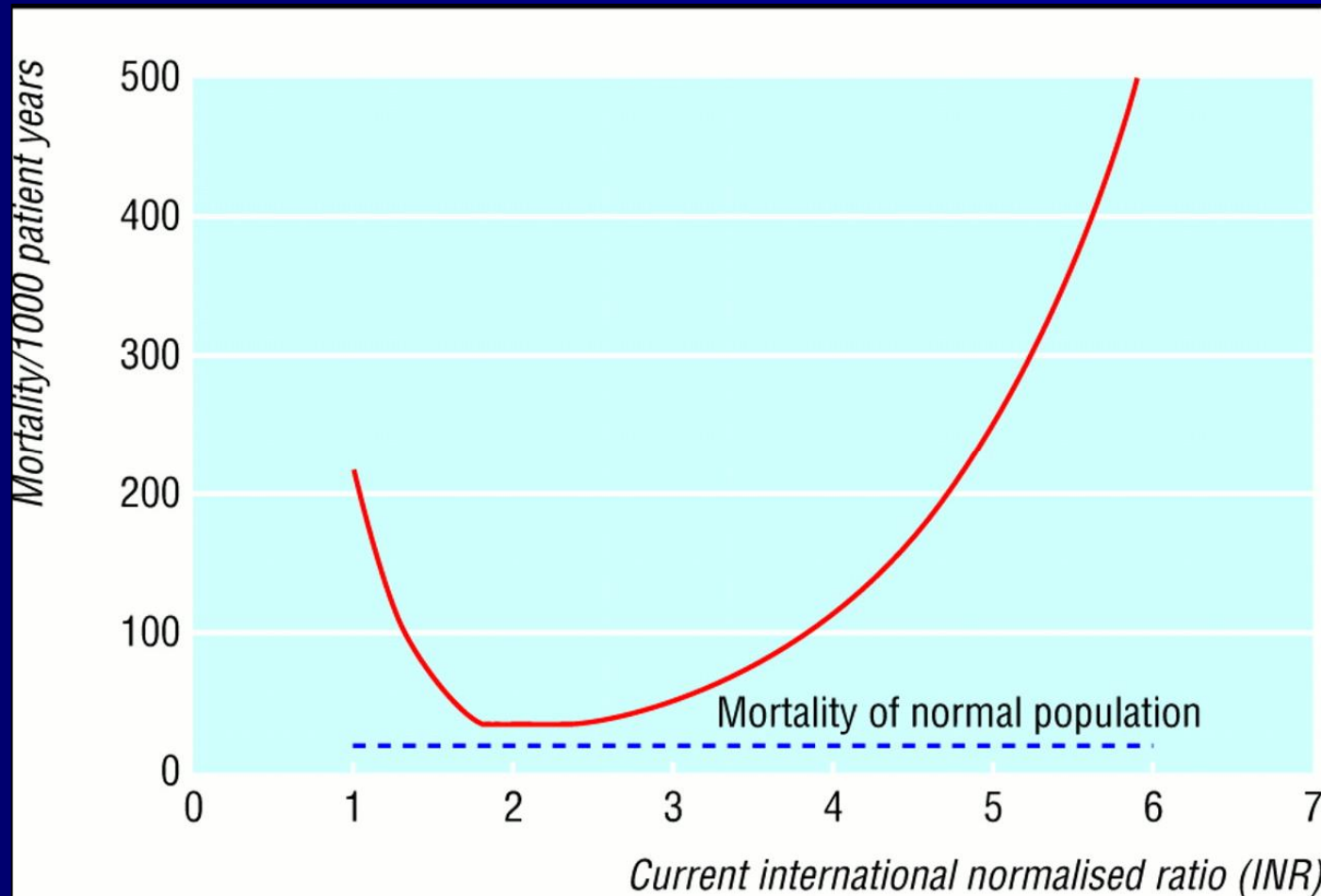


INR below 2.0 results in a higher risk of stroke

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

Warfarin's Narrow Therapeutic Window

Data from 42,451 pts, 3,533 deaths, 1.25 million INRs

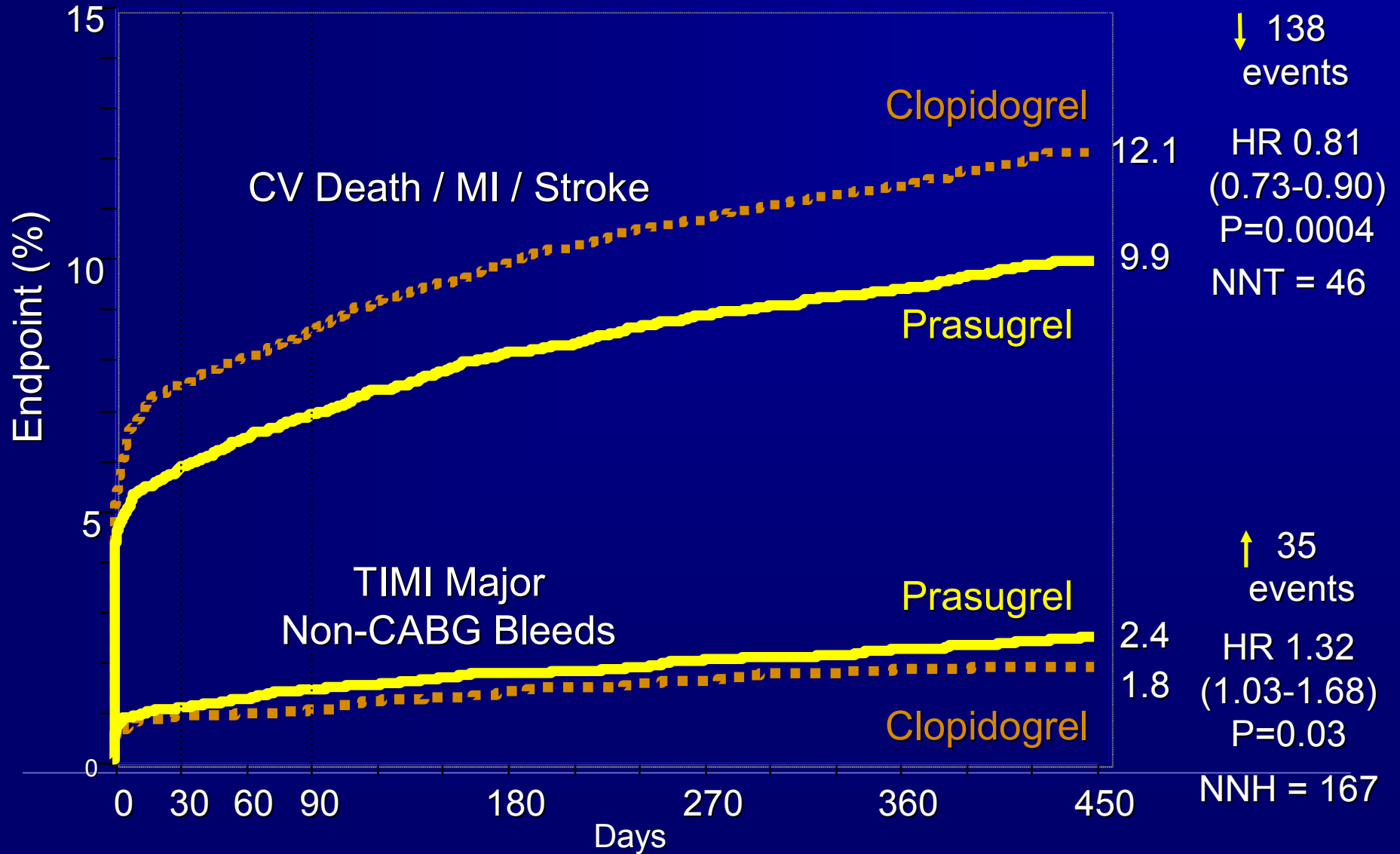


Prasugrel vs. Clopidogrel

- Prasugrel achieves much greater inhibition of aggregation than clopidogrel with both loading and maintenance doses
 - If TRITON TIMI 38 had not indicated a significant reduction in thrombotic complications and a significant increase in bleeding with prasugrel, it would have been a major blow to a linkage between aggregability (on LTA) and outcome
 - **It did**
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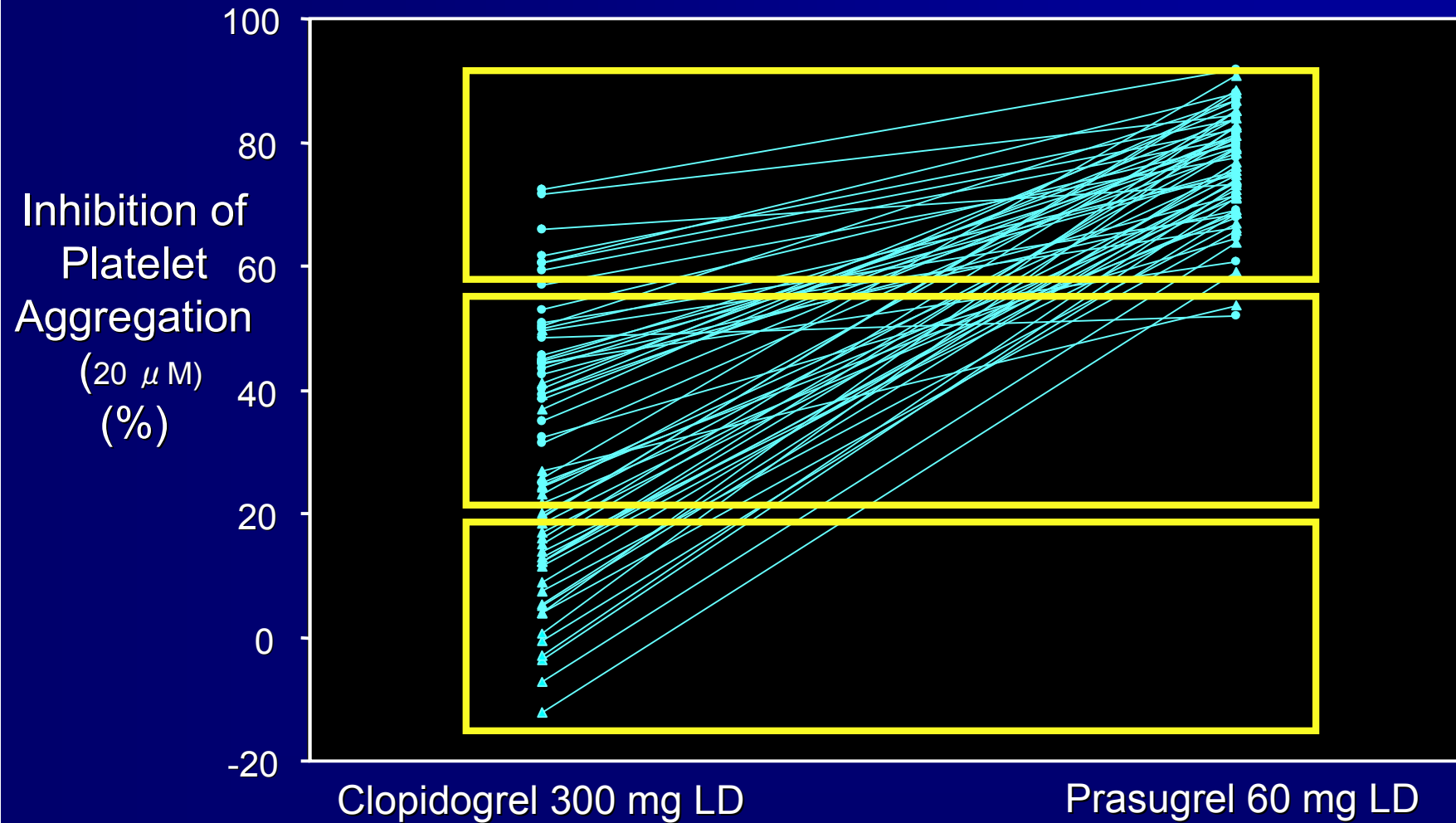
TRITON

Efficacy and Safety



Prasugrel 60 mg LD vs Clopidogrel 300 mg LD

Is There an Optimal Degree of P2Y₁₂ Inhibition?



From Brandt JT AHJ 153: 66e9,2007

IPA (%) to 20 μM
ADP 24 hr after LD

Prasugrel vs. Clopidogrel

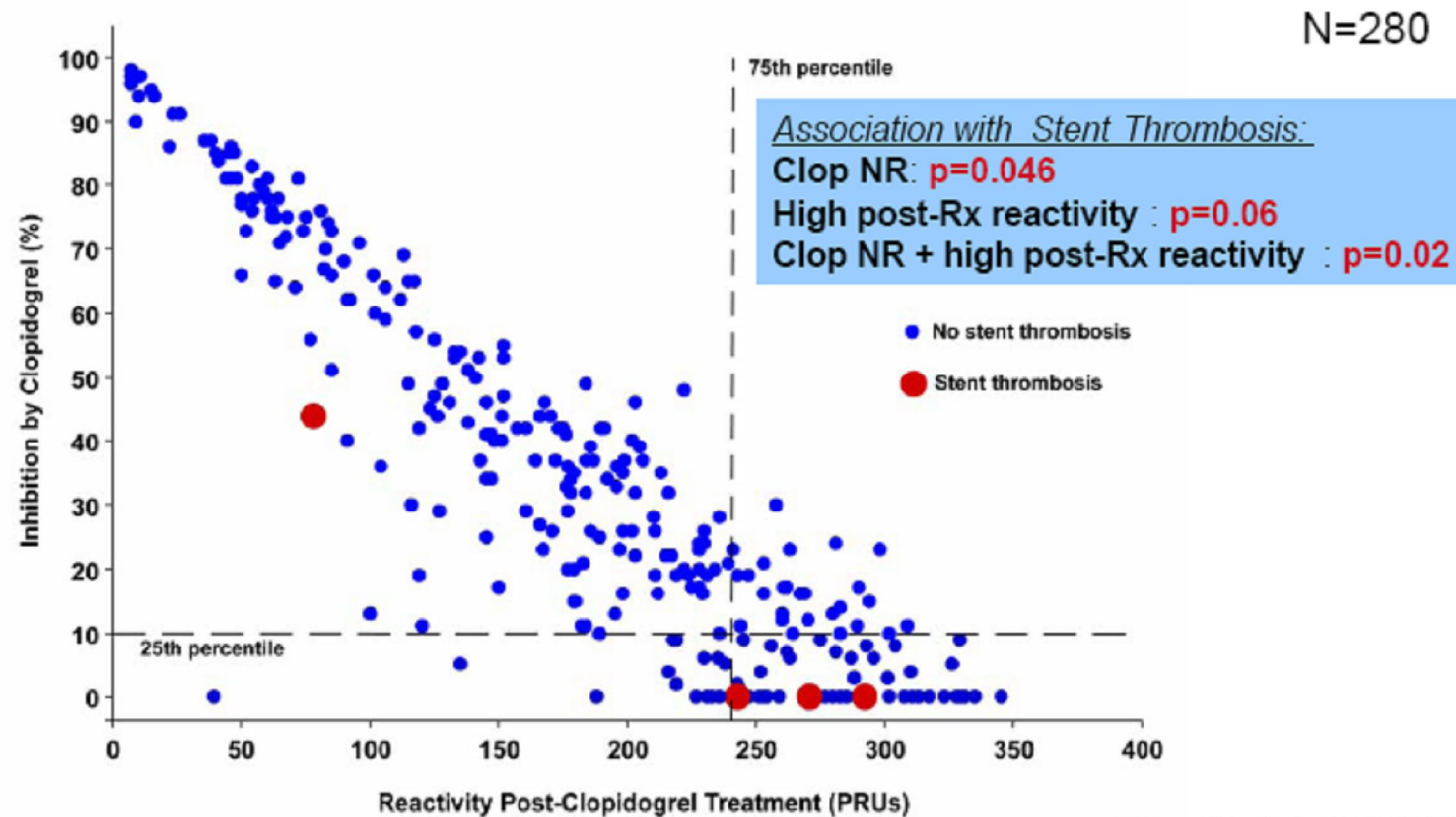
- Suppose a pt had the same residual aggregability after prasugrel and clopidogrel
 - Would their risk of thrombosis and bleeding be the same?
 - If we are going to be able to use one or more measures of aggregability to personalize antiplatelet therapy, the answer has to be yes
 - Requires standardizing definitions, methodology to quantify responsiveness
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Prasugrel vs. Clopidogrel

- Four studies indicate greater inhibition of aggregation with 150 vs 75 mg of clopidogrel
 - Studies of lower doses of prasugrel are planned in certain subgroups; higher doses can also be taken
 - Other P2Y12 inhibitors are being developed
 - There **is** the ability to alter the level of inhibition achieved with most oral antiplatelet agents
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Stent Thrombosis at 30 day Follow-Up

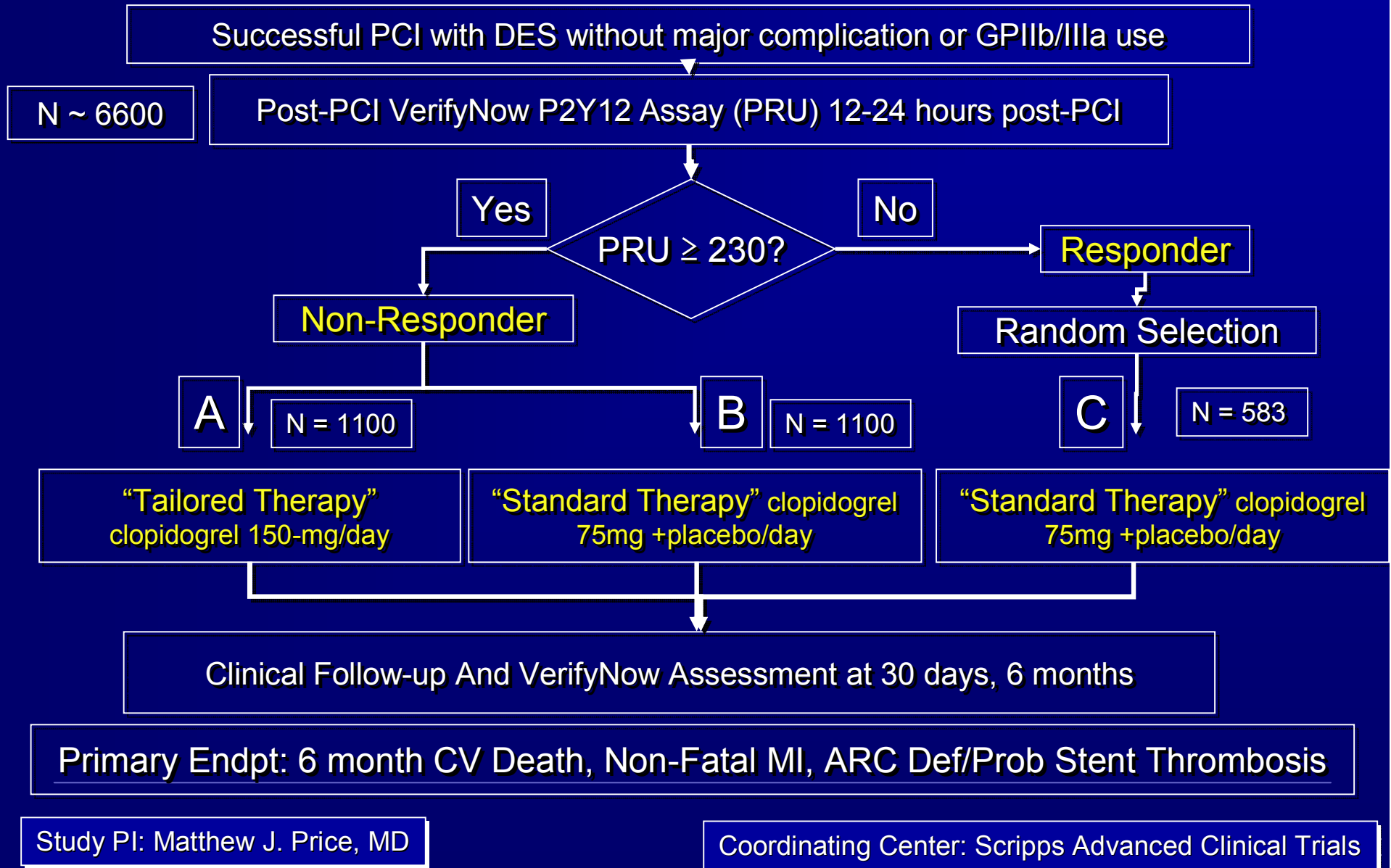


Price MJ et al, AHA 2006

SCRIPPS CLINIC

It is not clear what is the sensitivity and specificity of these tests to detect ST

GRAVITAS



Relationship Between Aggregometry and Outcome

Summary

- Definitions of resistance (hyporesponsiveness) vary
 - Not all methods to assess responsiveness are equal
 - Has been publication bias supporting an association between responsiveness and outcome
 - Has been misinterpretation of data believed to support a relationship between responsiveness and outcome
 - There probably is an association, but much has to be learned before it should be routinely used to make clinical decisions
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The Bottom line

- Antiplatelet Function Test for All ?
- Not ready for Prime time !!!

Thank You
