

Why I Use Ticagrelor in ACS

Paul A. Gurbel, M.D.

Sinai Center for Thrombosis Research, Baltimore, Maryland, U.S.A.

Professor of Medicine, Johns Hopkins University School of Medicine

Adjunct Professor of Medicine, Duke University School of Medicine

Disclosures

Research Grants/Support

Nanosphere

Haemonetics

Daiichi Sankyo/Lilly

CSL Pharmaceuticals

HCRI

NIH

Honoraria/Consulting

Pozen

AstraZeneca

Daiichi Sankyo/Lilly

Accumetrics

Nanosphere

Boehringer

Merck

Medtronic

CSL

t2 Biosystems

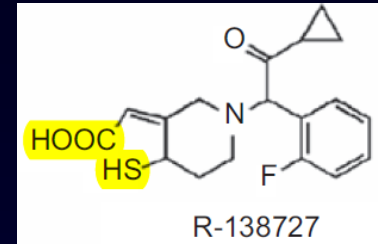
Dr. Gurbel has patents in the field of platelet function testing

5 Reasons:

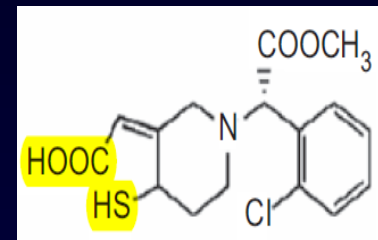
1) Mechanism (s) of Action

Do All P2Y₁₂ Inhibitors Have the Same Basic Effect?

- Molecular structure of clop and pras are ~same
- Equipotent AM
- No known significant off target effects
- At same level of platelet reactivity:
Thrombotic risk should be same

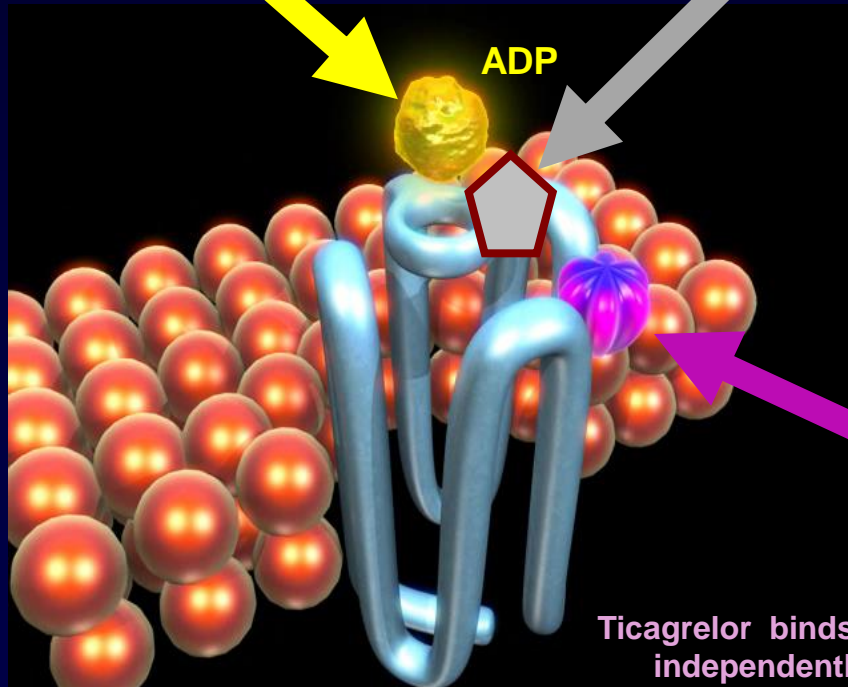


Prasugrel-AM

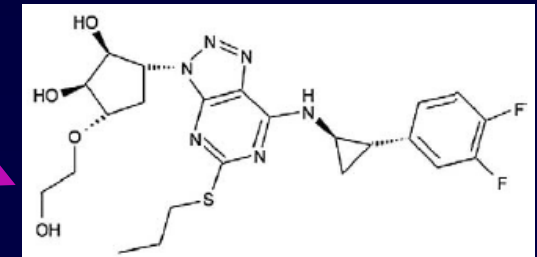


Clopidogrel-AM

ADP binding site



- Ticagrelor is in different class (CPTP)
- ? Important off target effects:
- At same level of platelet reactivity:
thrombotic risk ? less due to off target effect
- Off-target effect can't be measured by PFT



Ticagrelor binds reversibly and independently from ADP
- inhibits conformational change

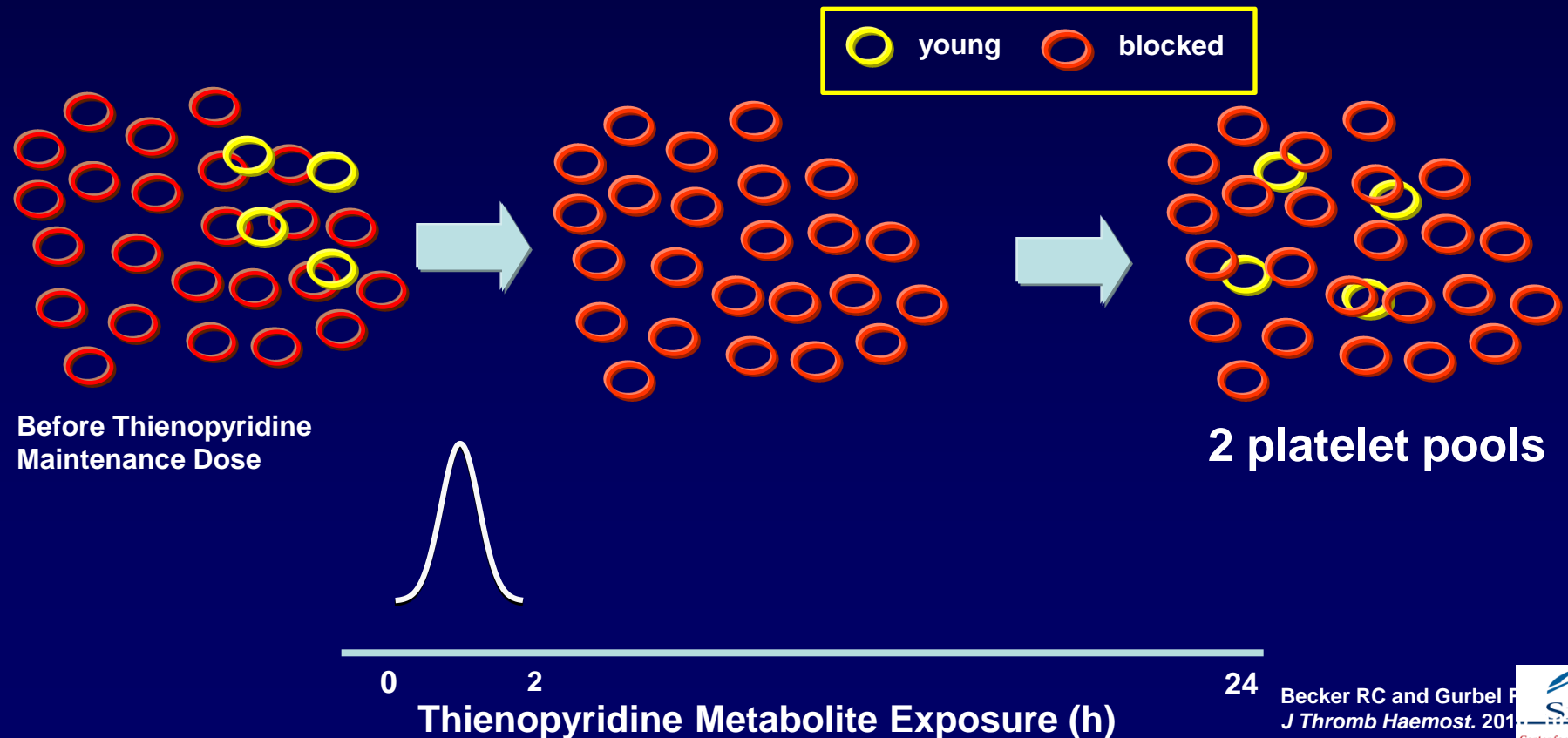
Platelet Turnover and Antiplatelet Drug Response Variability: The 2 Platelet Pools Hypothesis

Explanation for Differences In Antithrombotic Properties of
Thienopyridines Versus Direct Acting P2Y₁₂ Inhibitors

~ 10 % new platelets enter circulation each day

Exposure of circulating platelets to active thienopyridine metabolite is transient

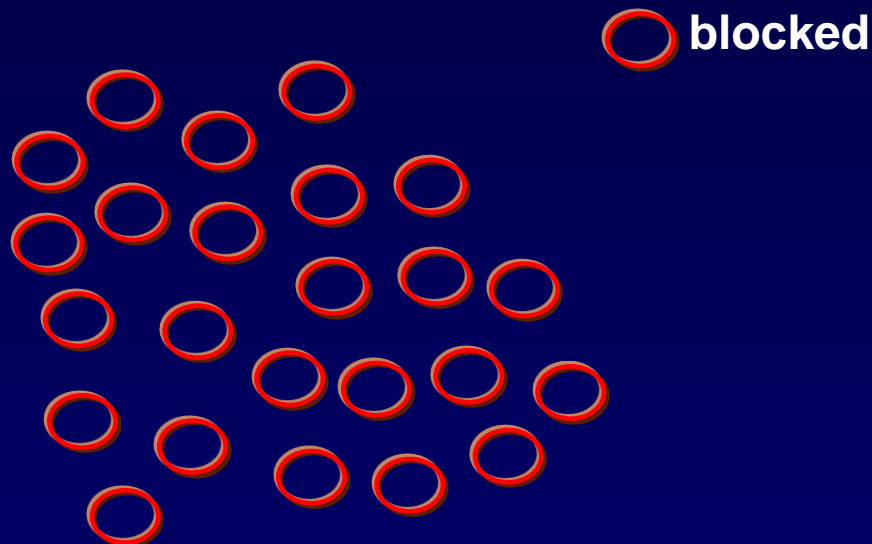
As young platelets enter the circulation in the absence of circulating active thienopyridine metabolite they are not inhibited:



Platelet Turnover and Antiplatelet Drug Response Variability: The 2 Platelet Pools Hypothesis

Explanation for Differences In Antithrombotic Properties of
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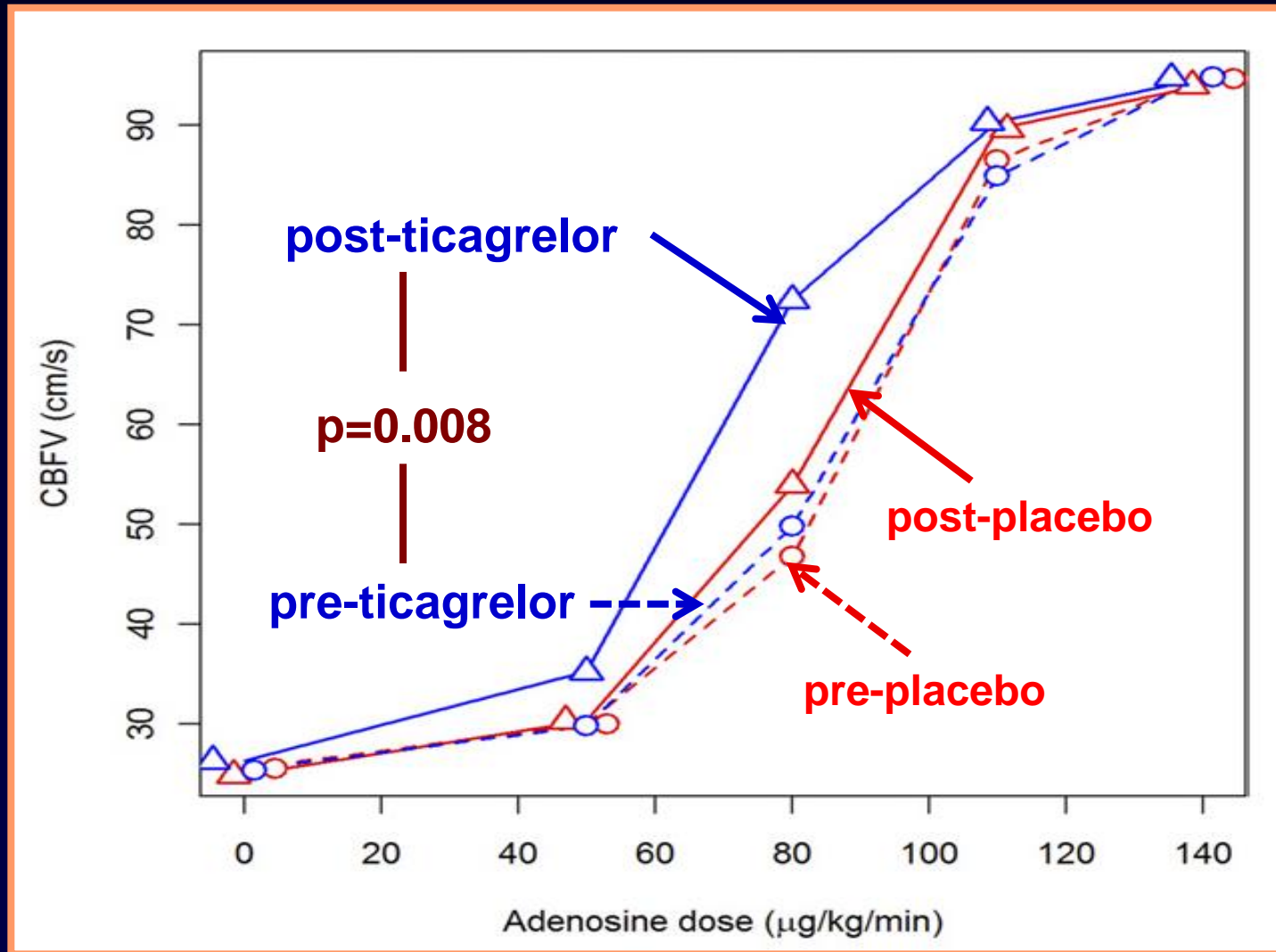
Direct acting P2Y₁₂ inhibitors provide uniform platelet inhibition
dependent on drug plasma concentration:



1 Pool of Uniformly Inhibited Platelets at All Times

Potential Beneficial Off-Target Effects

Influence of Ticagrelor-induced Adenosine Reuptake Inhibition on Coronary Blood Flow Velocity (CBFV)



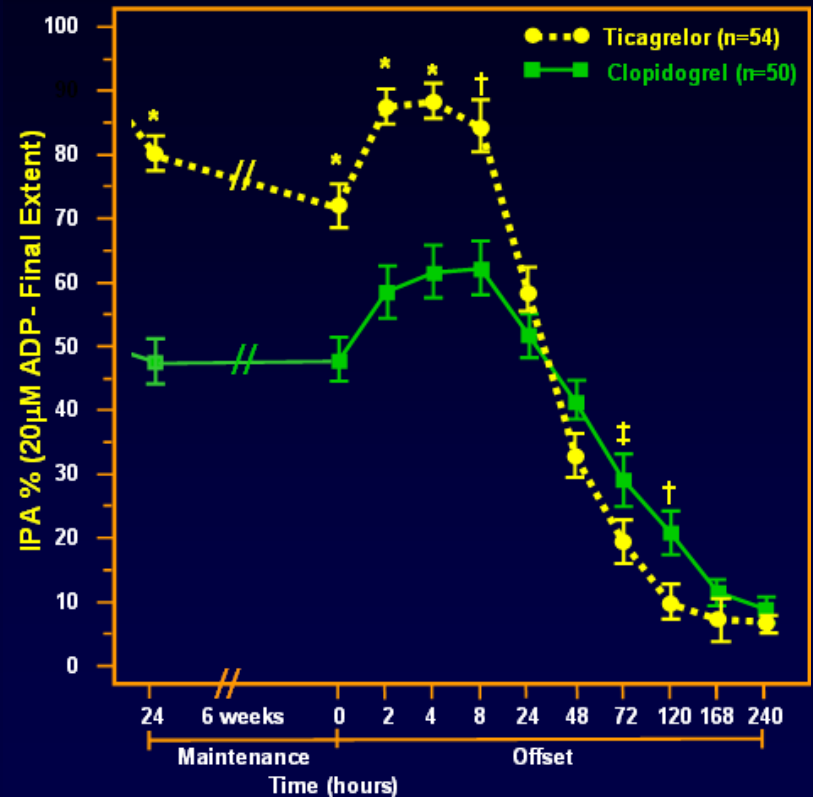
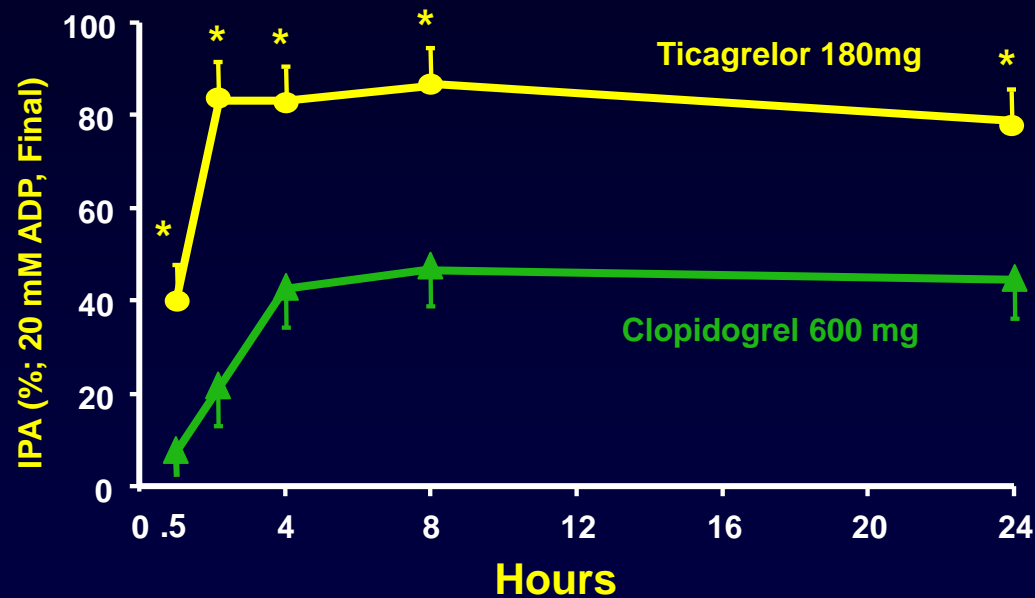
Reason 2. Pharmacology

ONSET/OFFSET Study

Stable CAD pts

Loading

Maintenance and Offset



*, P<0.0001 ticagrelor vs clopidogrel;
 †, P<0.005 ticagrelor vs clopidogrel;
 ‡, P<0.05, ticagrelor vs clopidogrel

Pharmacokinetics of Ticagrelor

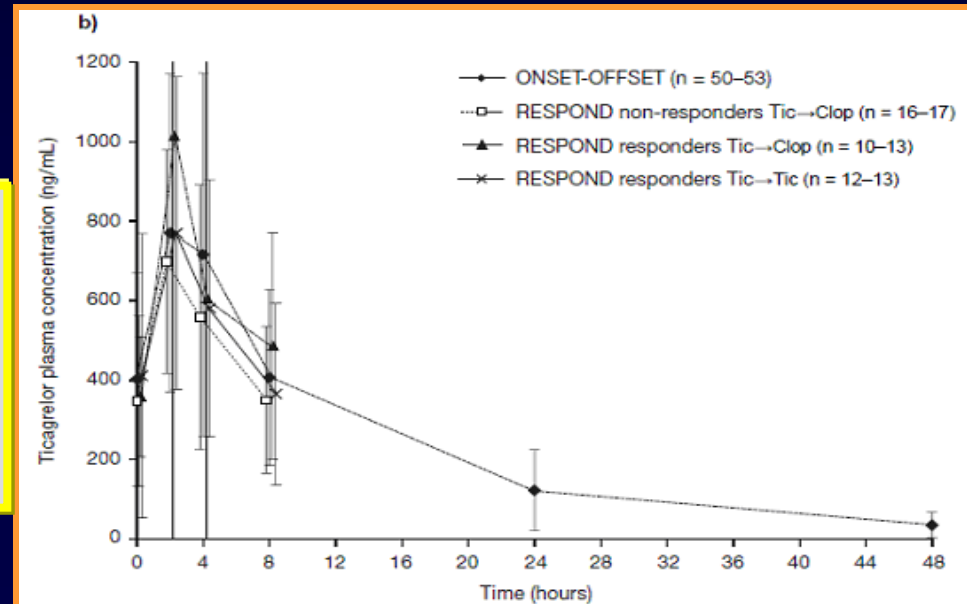
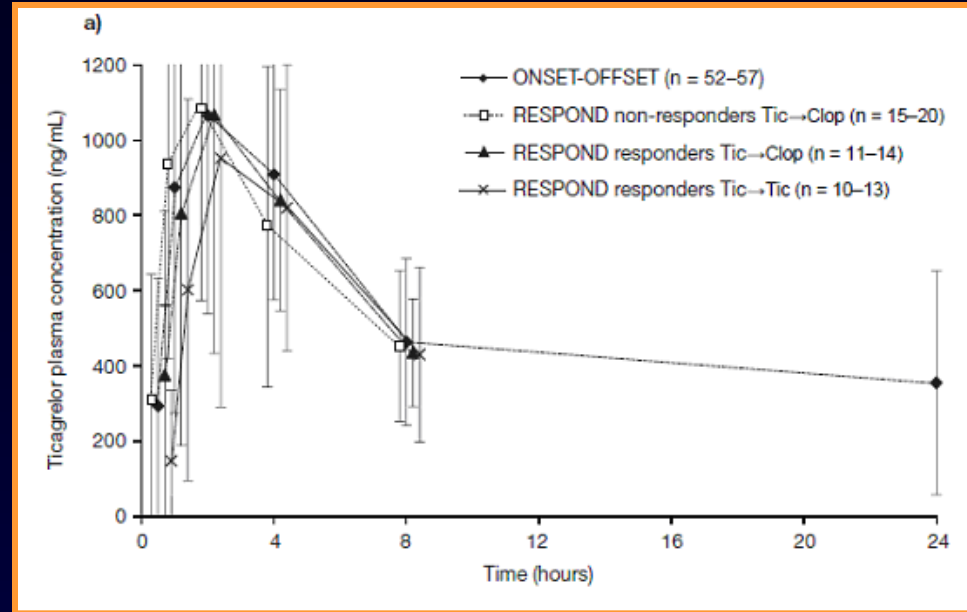
Stable CAD pts

After 180mg LD

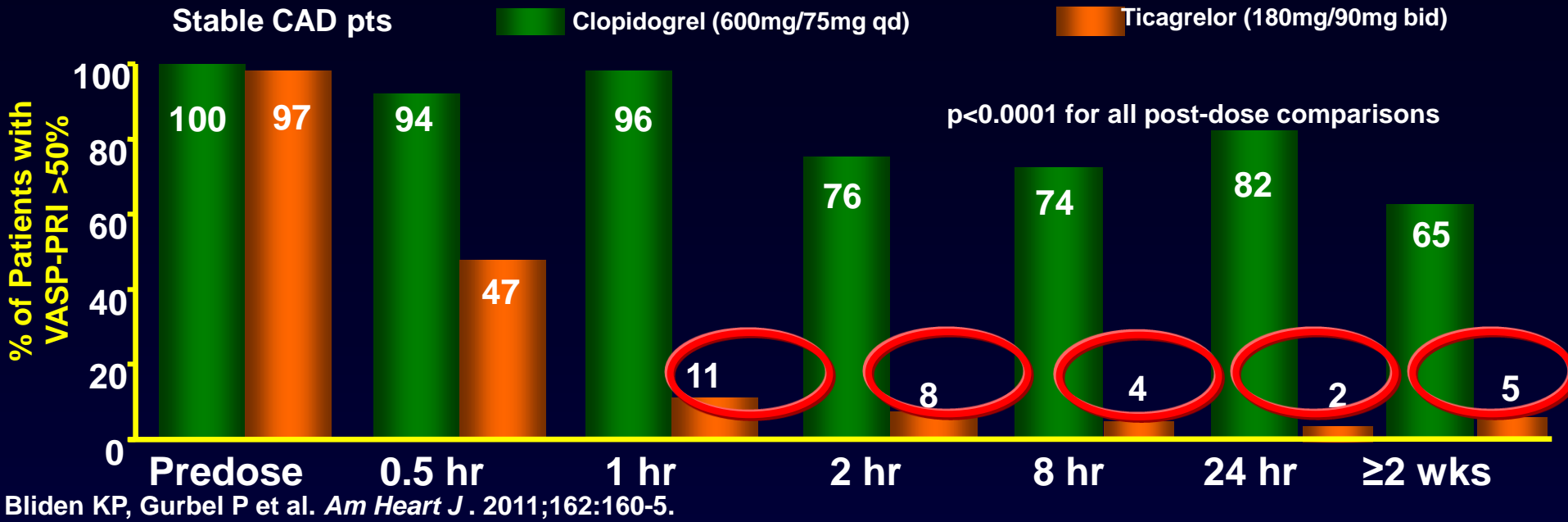
$t_{max} \sim 2$ hrs

At Steady State After
Multiple Ticagrelor 90mg
bid dosing
(4wks-ONSET; 2-4 wks RESPOND)

$t_{max} \sim 2$ hrs

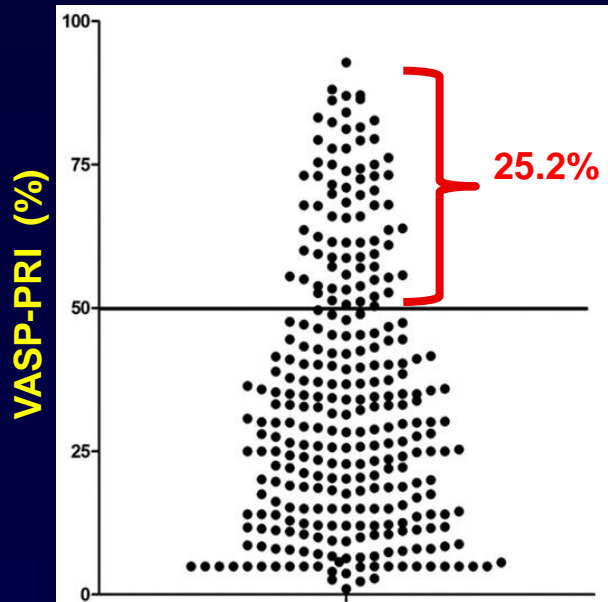


Ticagrelor Pooled Analysis of ONSET-OFFSET and RESPOND Studies

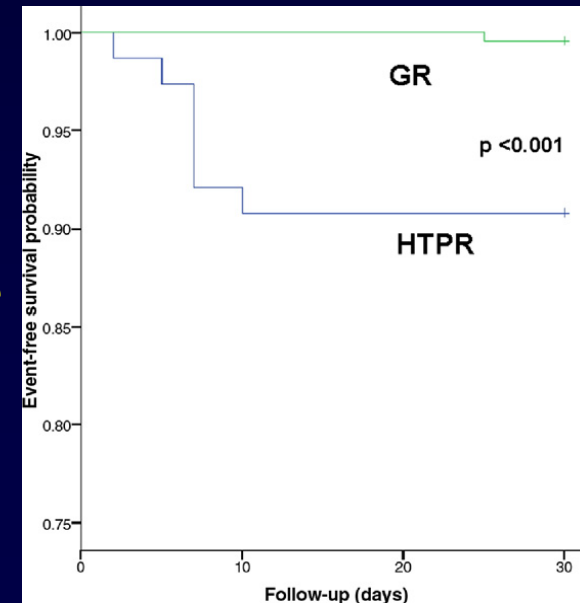


Prasugrel

- 301 ACS pts undergoing PCI
- VASP measured 6 hrs
- 60 mg prasugrel

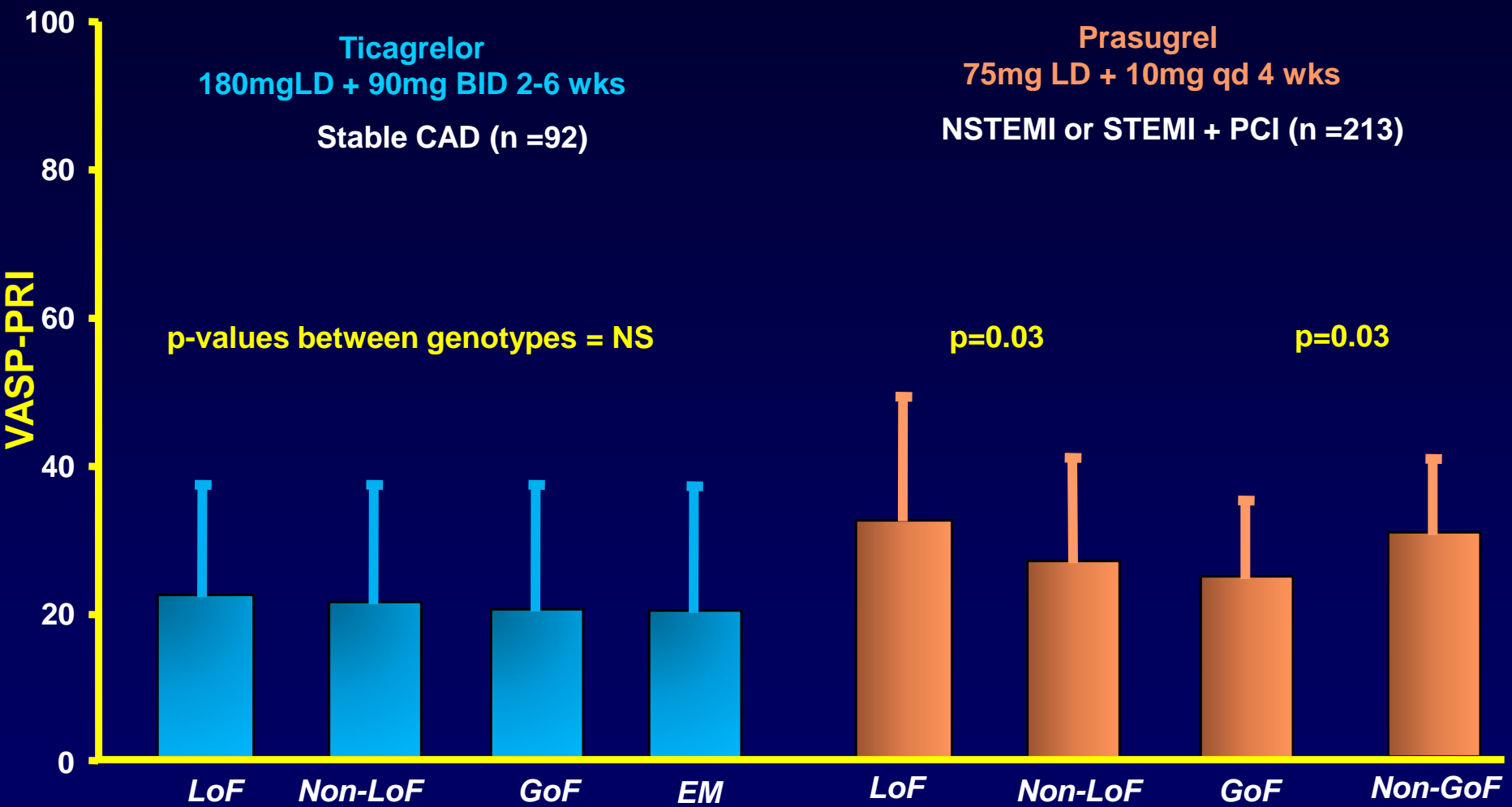


30-day MACE



Bonello L et al.
J AM Coll Cardiol. 2011;58:467-73

No Influence of *CYP2C19* Genotype on Ticagrelor PD



Tantry US et al. *Circ Cardiovasc Genet* 2010;3;556-566

Cuisset T et al. *J AM Coll Cardiol Intv* 2012;5:1280-7

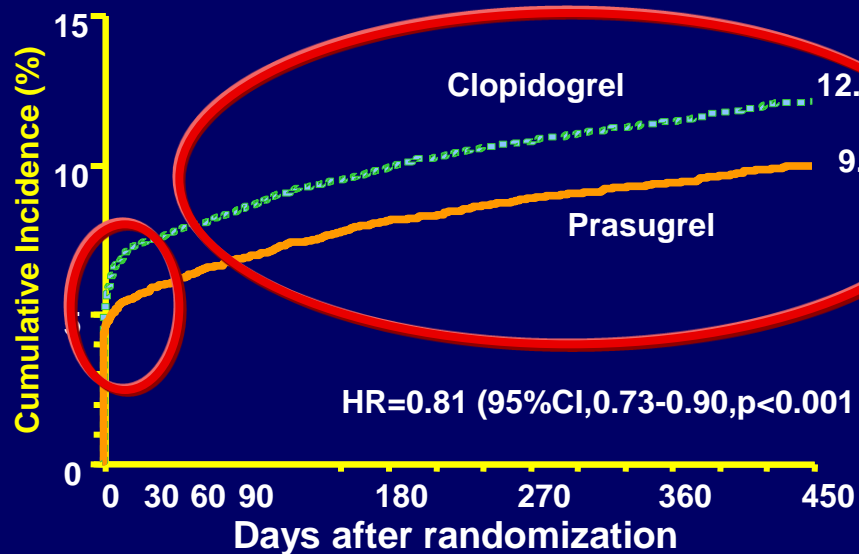


Reason 3.
Reduced Ischemic Events and Mortality
Despite Clopidogrel PreRx

Influence on Ischemic Outcomes: Prasugrel vs. Ticagrelor



n=13,608



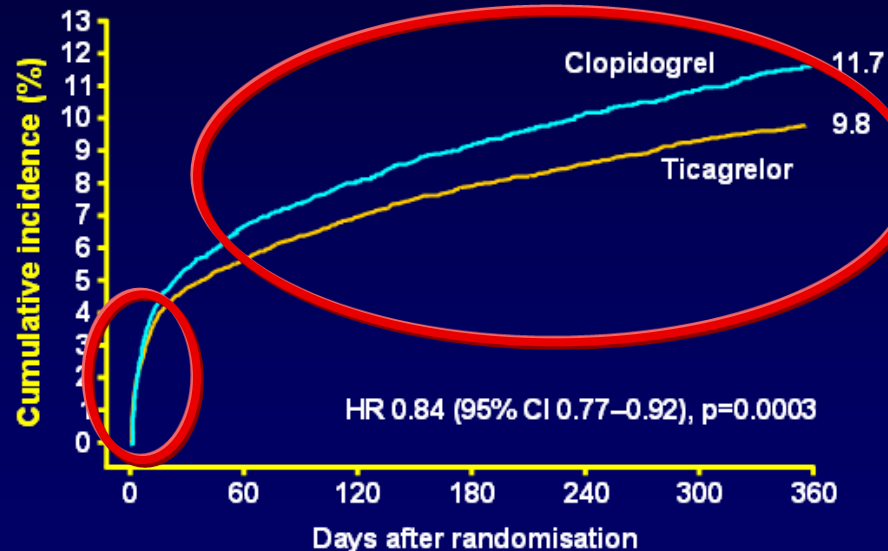
Early Separation

Parallel Curves Post-30D

- In Non-Clopidogrel Pretreated Patient:
- ? Use Prasugrel Early then Switch to Clopidogrel



n=18,624



No early Separation

Diverging Curves Post-30d

- Use Ticagrelor from the Start

Cardiovascular Death

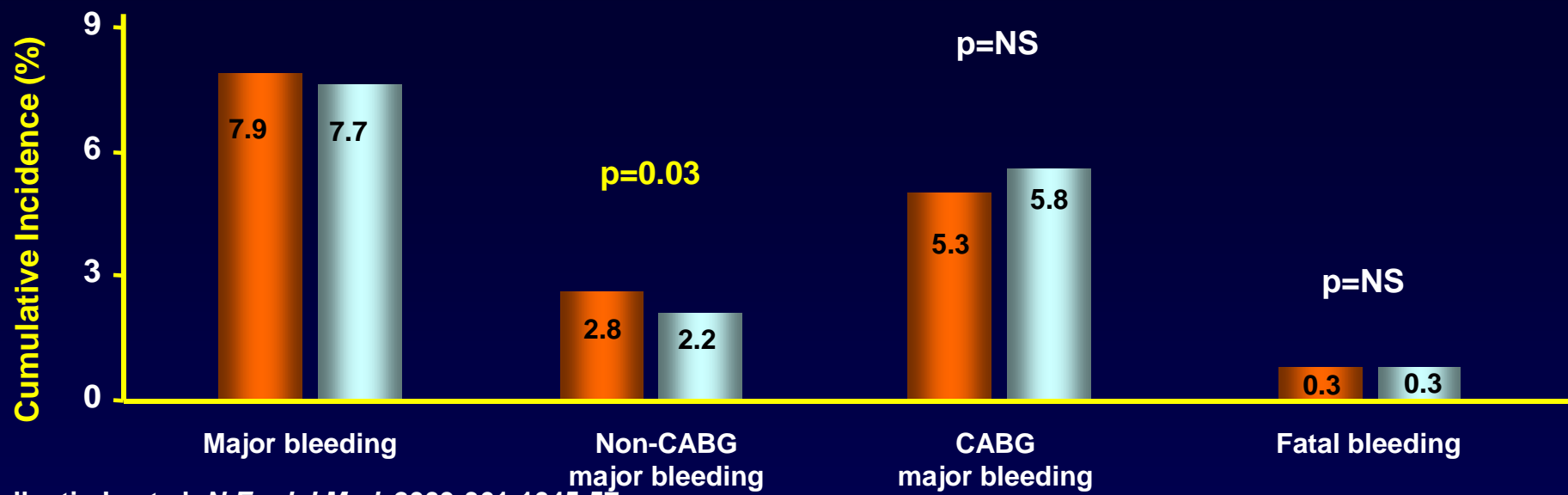
**Is the mortality reduction
the trump card for ticagrelor in ACS?**

Reason 4:

No Difference in Overall TIMI Bleeding

PLATO

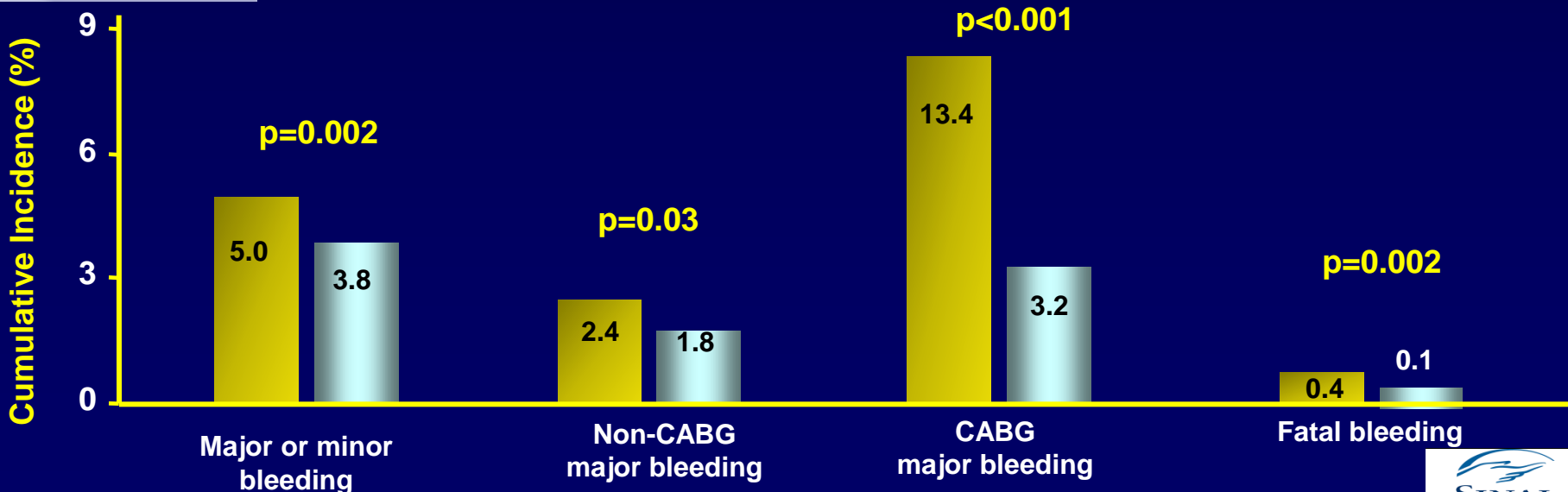
Ticagrelor VS. Clopidogrel



Wallentin L. et al. *N Engl J Med.* 2009;361:1045-57

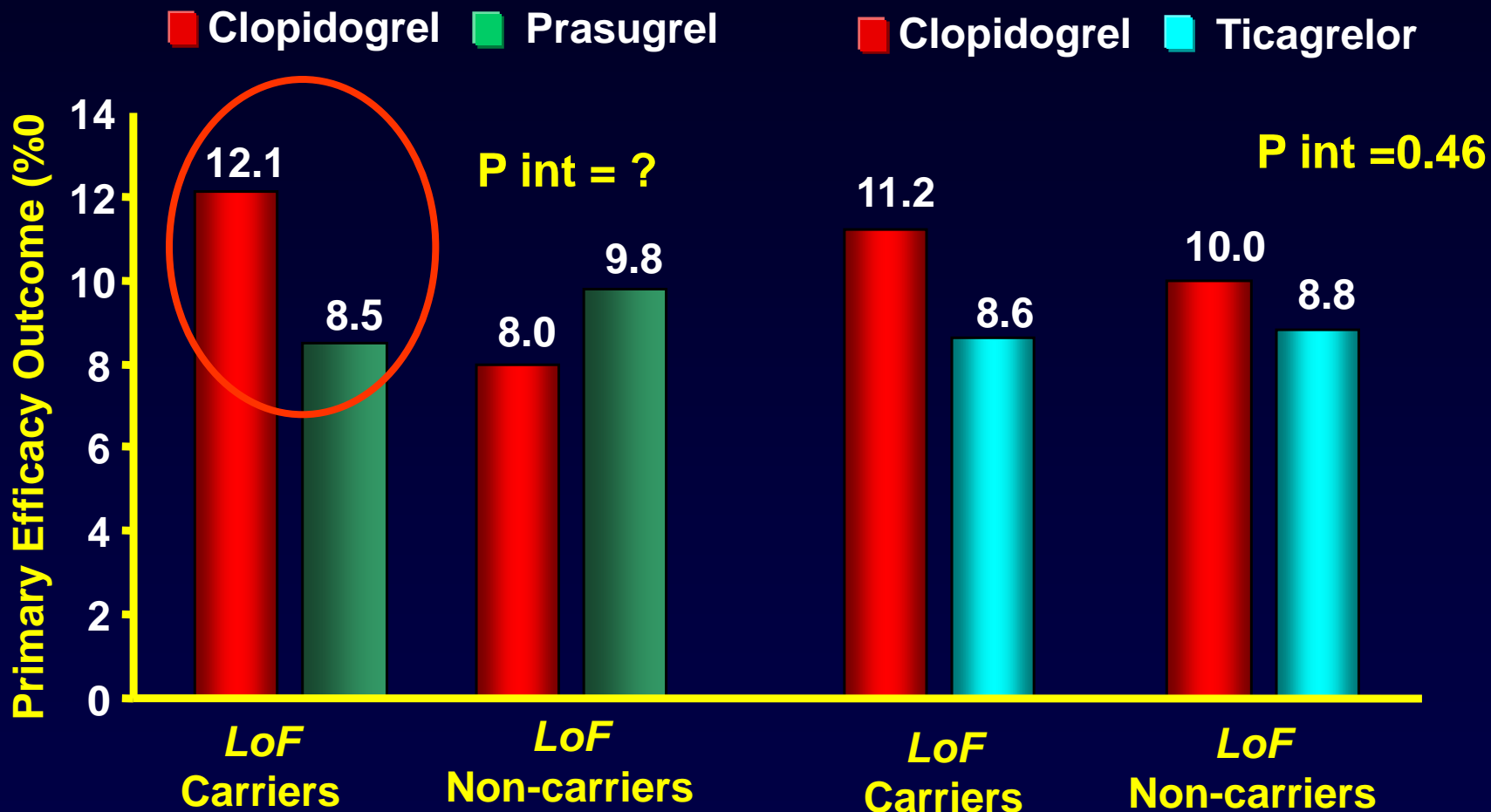
TRITON TIMI-38

Prasugrel VS. Clopidogrel



Wivott SD et al. *N Engl J Med* 2007;357:2001-15.

5. No Influence of Genotype on Clinical Outcomes



Why Do I Use Ticagrelor in ACS?

1) Mechanism of Action and Pharmacologic Properties

- fast onset and faster offset
- elimination of HPR- predictable PD effect
- no influence of genetics
- potential off target beneficial effects
- uniformly inhibited platelets

2) Clinical Outcomes

- no influence of genetics
- benefit on top of clopidogrel preRx
- accruing benefit over time- KM curves continue to separate
- mortality benefit
- no difference in CABG –related bleeding vs clopidogrel