Discovery of Brand New antiplatelet drug, BRILINTA (Ticagrelor)

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- ✓ *Antiplatelet therapy plays a major role in the treatment of acute coronary syndromes.*
- ✓ *Especially, dual antiplatelet therapy including clopidogrel showed an improved short- and long-term benefit.*
- ✓ *However, many limitations still exist in the current antiplatelet therapy.*

Issues in the current antiplatelet therapy

- Prodrug
- Inter-patient variability in inhibition of platelet aggregation (IPA)
- Relatively slow onset & incomplete IPA
- Irreversible $P2Y_{12}$ receptor binding
- High incidence of CV death despite proven current Rx

Issues in the current antiplatelet therapy

- **Prodrug, requiring biotransformation to form an active metabolite**
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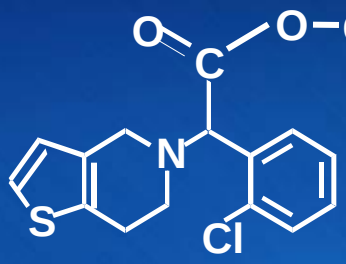
Thienopyridines are prodrug : *Metabolic Elements*



Clopidogrel

Pro-drug

Pre-hepatic metabolism
Esterases in blood (? Small Intestine)

85% Inactive Meta bolites
Esterases in blood

Prasugrel

Concerns on pro-drug

- **Genetic polymorphisms** of genes for CYP450 enzymes involved in active metabolite generation.
- **Drug Interactions** may be important in certain cases. (Ketoconazole, Omeprazole)

Herbert JM, Savi P. *Semin Vasc Med.* 2003;3:113-122.

Issues in the current antiplatelet therapy

- Prodrug
- **Inter-patient variability in inhibition of platelet aggregation (IPA)**
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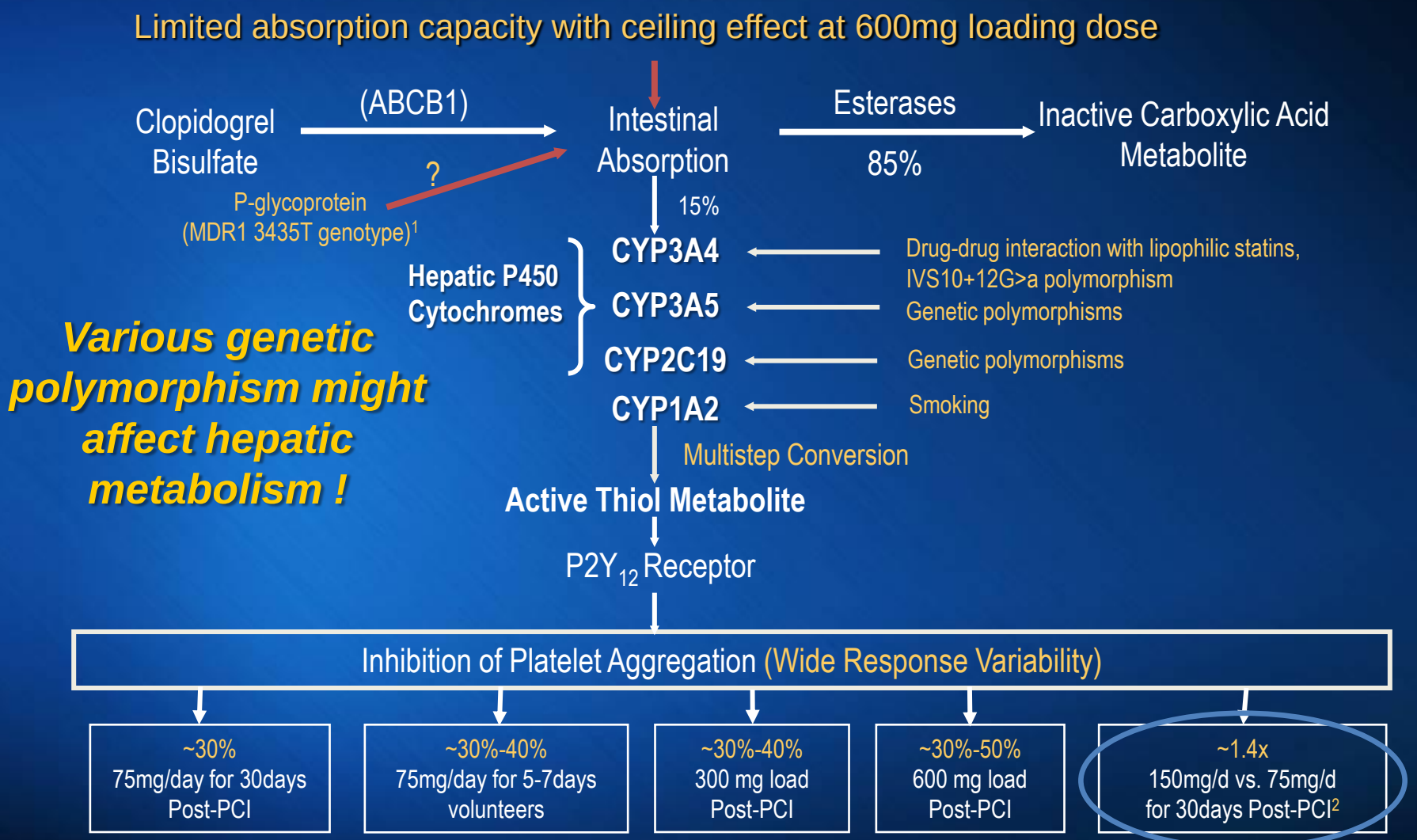
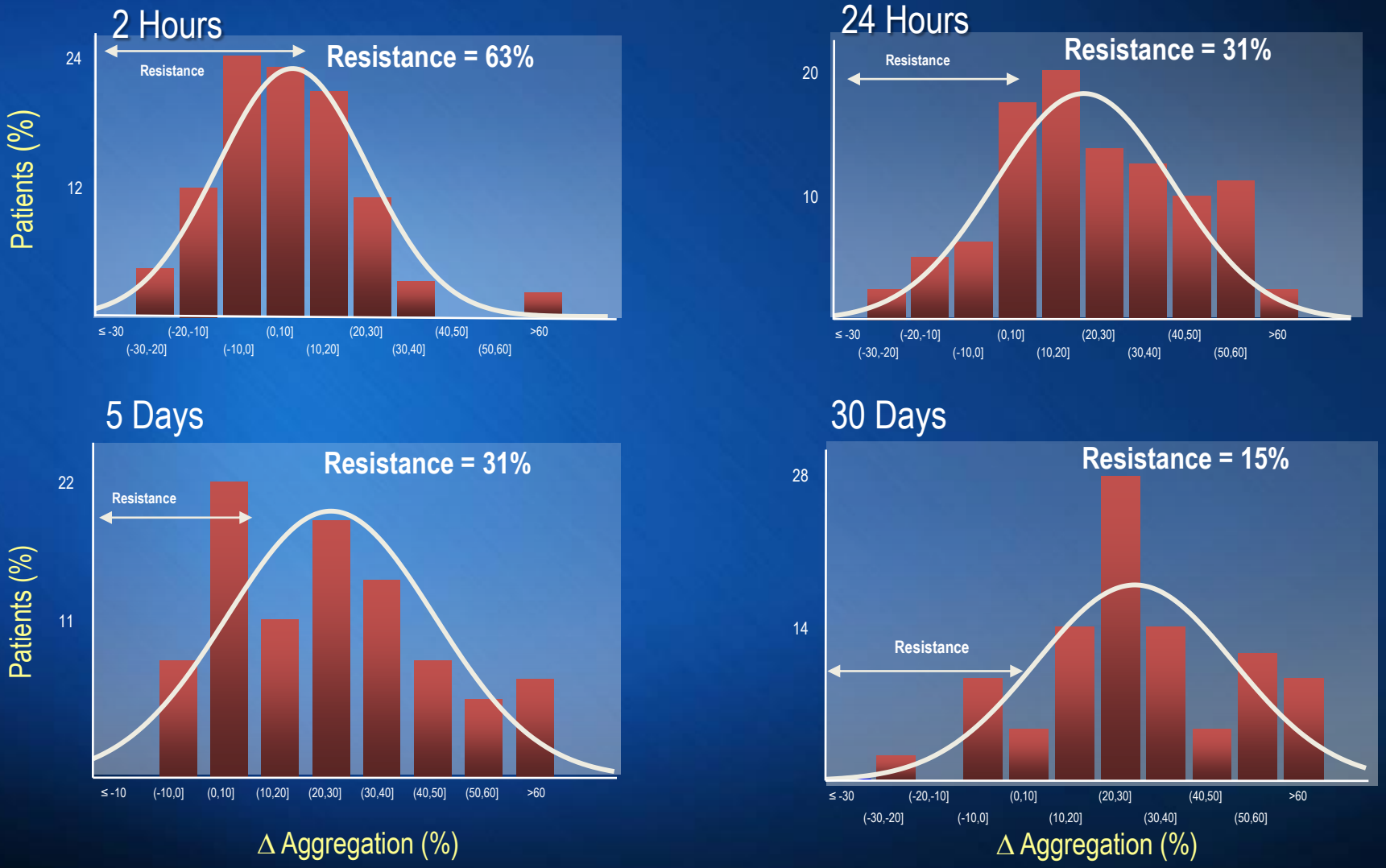
Mechanism of Clopidogrel Response Variability:



Gurbel PA et al. *Thromb Res*. 2006 (Epub).
Taubert et al. *Clin Pharmacol*. 2006.
von Beckerth et al. *Eur Heart J*. 2007 (Epub).

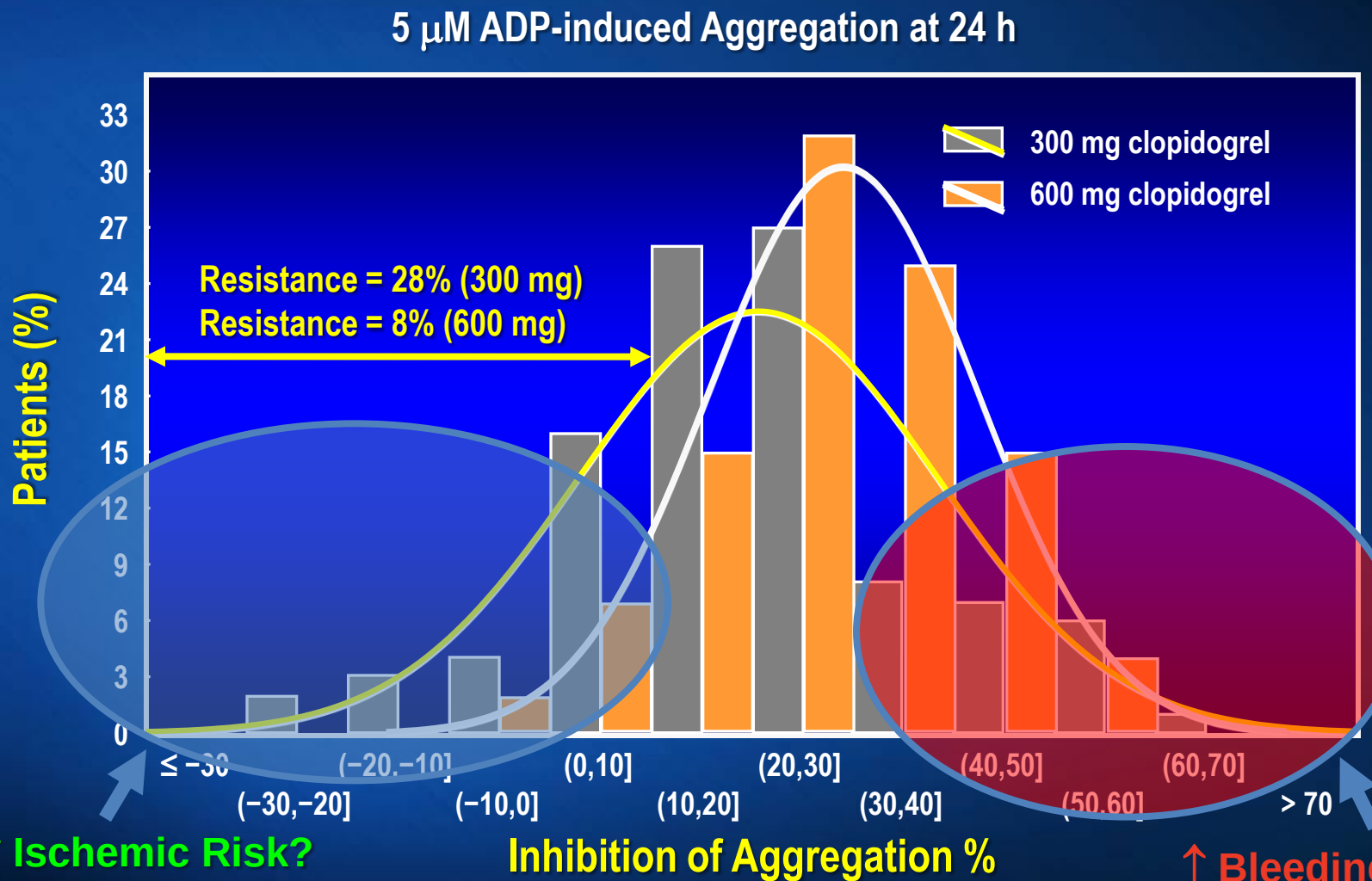
Clopidogrel Responsiveness Study

Platelet aggregation (5 & 20 mol/L ADP) measured in patients undergoing elective PCI with stenting at 2 hours, 24 hours, 5 days, and 30 days after stenting.



Gurbel PA et al. *Circulation.* 2003;107:2908-2913.

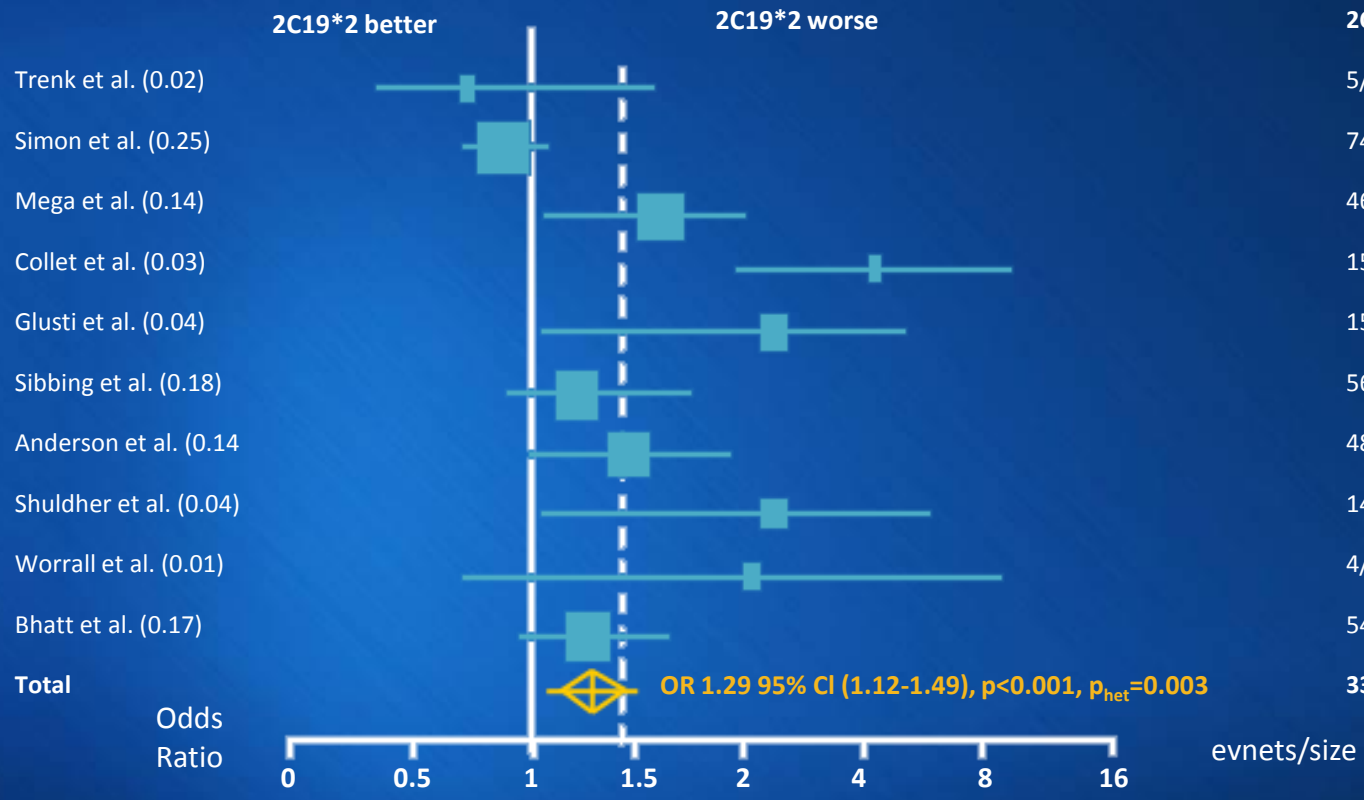
Variability of Response to Clopidogrel



Gurbel et al. *Circulation.* 2003;107:2908-2913.
Gurbel et al. *J Am Coll Cardiol.* 2005;45:1392-1396.

From pooled data (n=11,959), comparing % inhibition of platelet aggregation & CYP2C19 polymorphisms

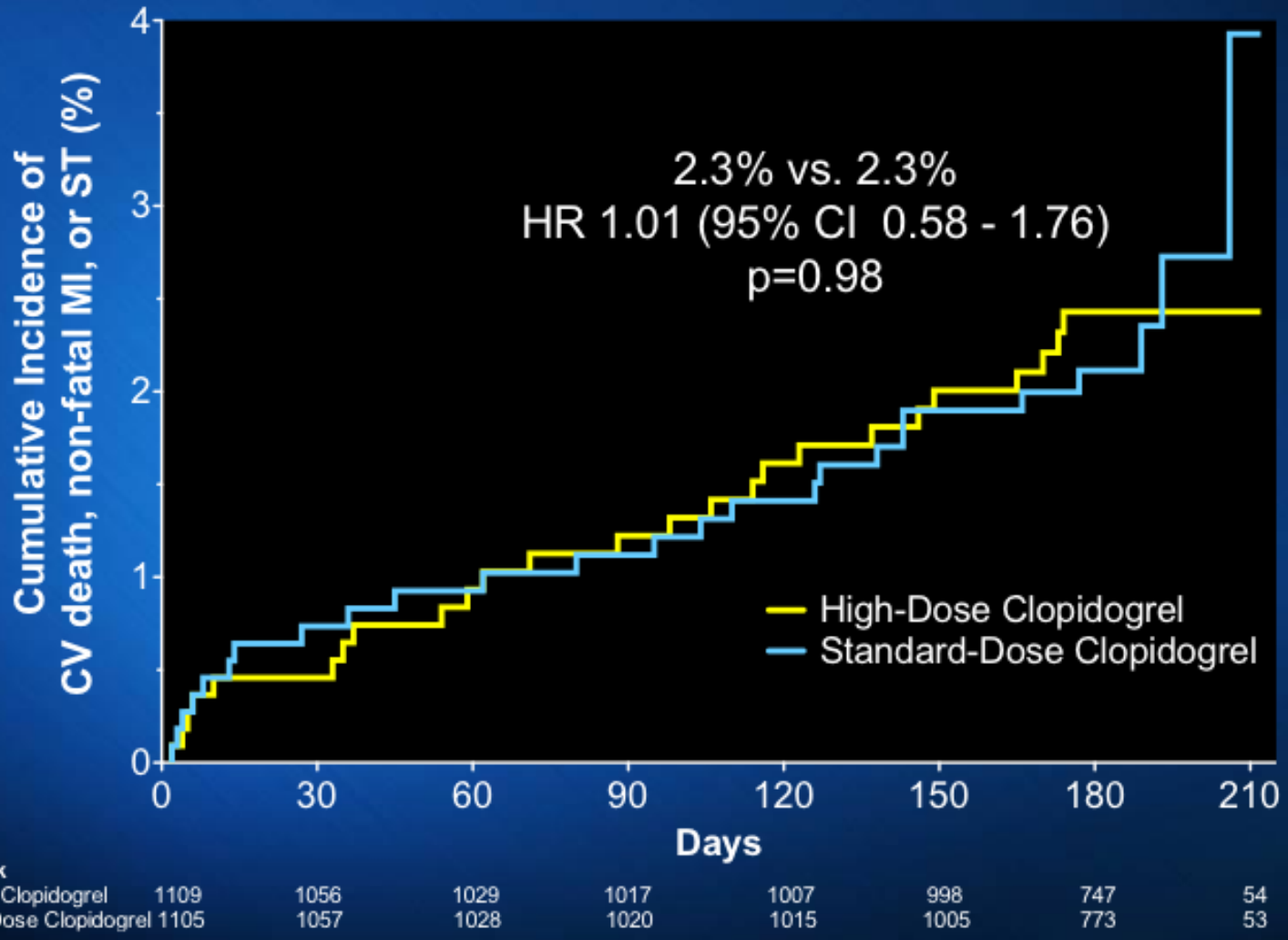
Hulot et al. *J Am Coll Cardiol* 2010;56:134-43



The pooled data showed that carriers of the CYP2C19*2 loss of function allele (28%[n=3,418]) displayed a significant increase in the rate of MACE compared with non-carriers (OR:1.29; 95% CI:1.12 - 1.49; P<0.001)

GRAVITAS

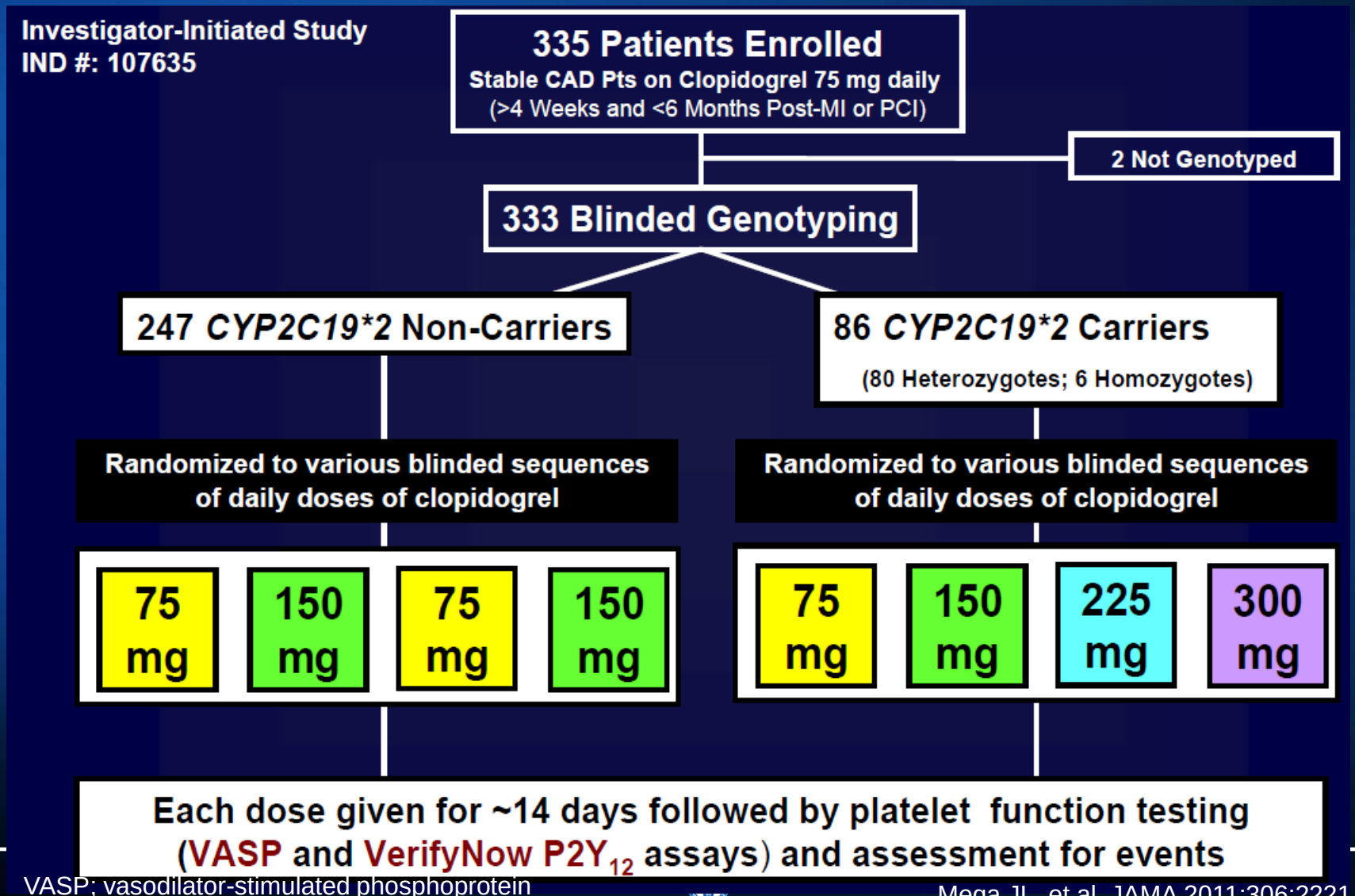
Primary Endpoint (CV Death, MI, Stent Thrombosis)



Observed event rates are listed; P value by log rank test.

ELEVATE TIMI 56

To test whether higher doses of (up to 300 mg daily) improve the response to clopidogrel in the setting of the major loss-of-function *CYP2C19 genotypes*.

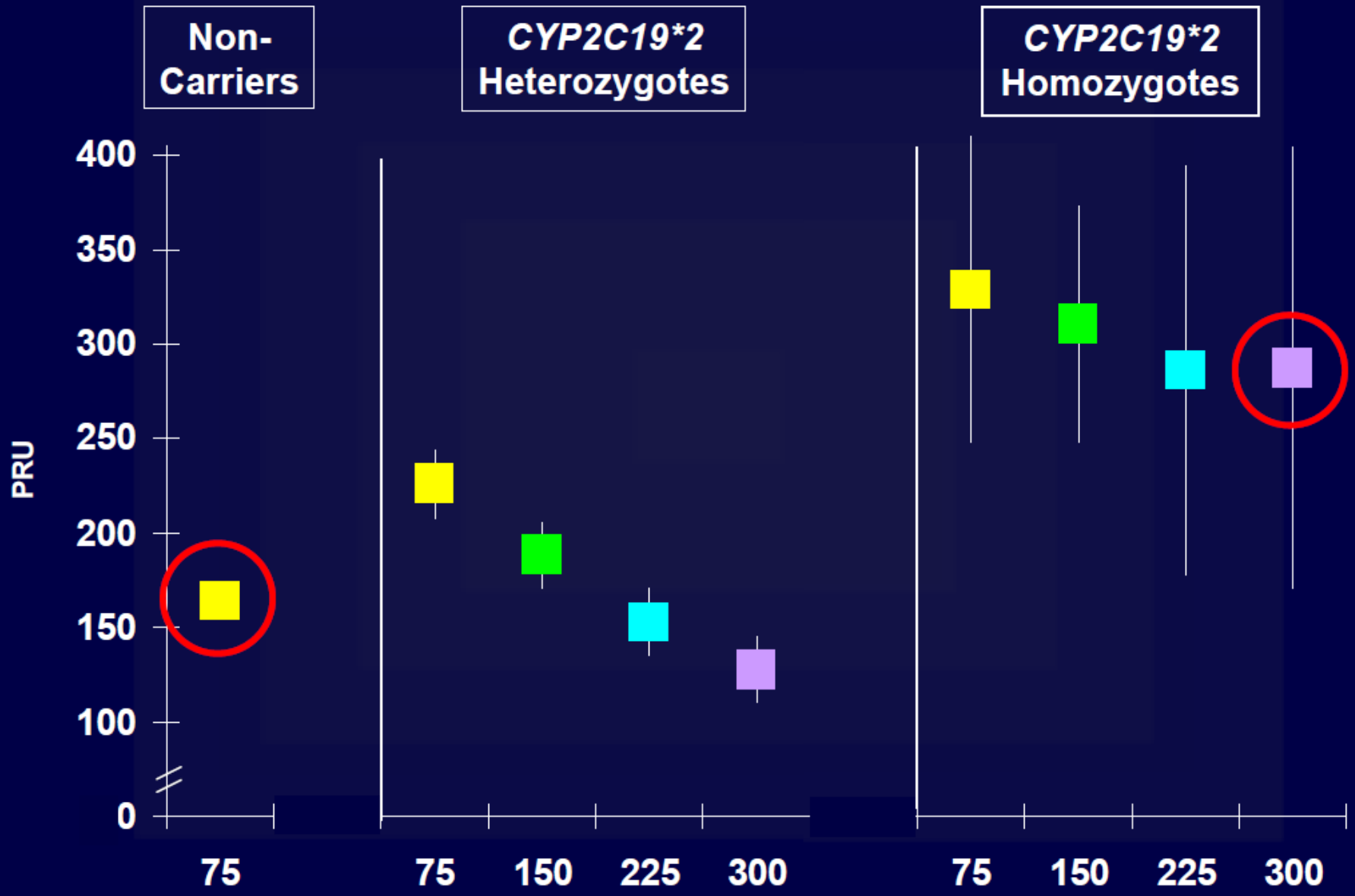


VASP; vasodilator-stimulated phosphoprotein

Mega JL, et al. JAMA 2011;306:2221

ELEVATE
TIMI 56

Platelet Reactivity with ↑ Clopidogrel



Squares represent the means and vertical lines the 95% confidence intervals.

Mega JL, et al. JAMA 2011;306:2221

FDA Boxed Warning on Clopidogrel

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

- Effectiveness of clopidogrel depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.
- Poor metabolizers treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates following ACS or PCI than patients with normal CYP2C19 function.
- Tests are available to identify a patient's CYP2C19 genotype, and can be used as an aid in determining therapeutic strategy.
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.**

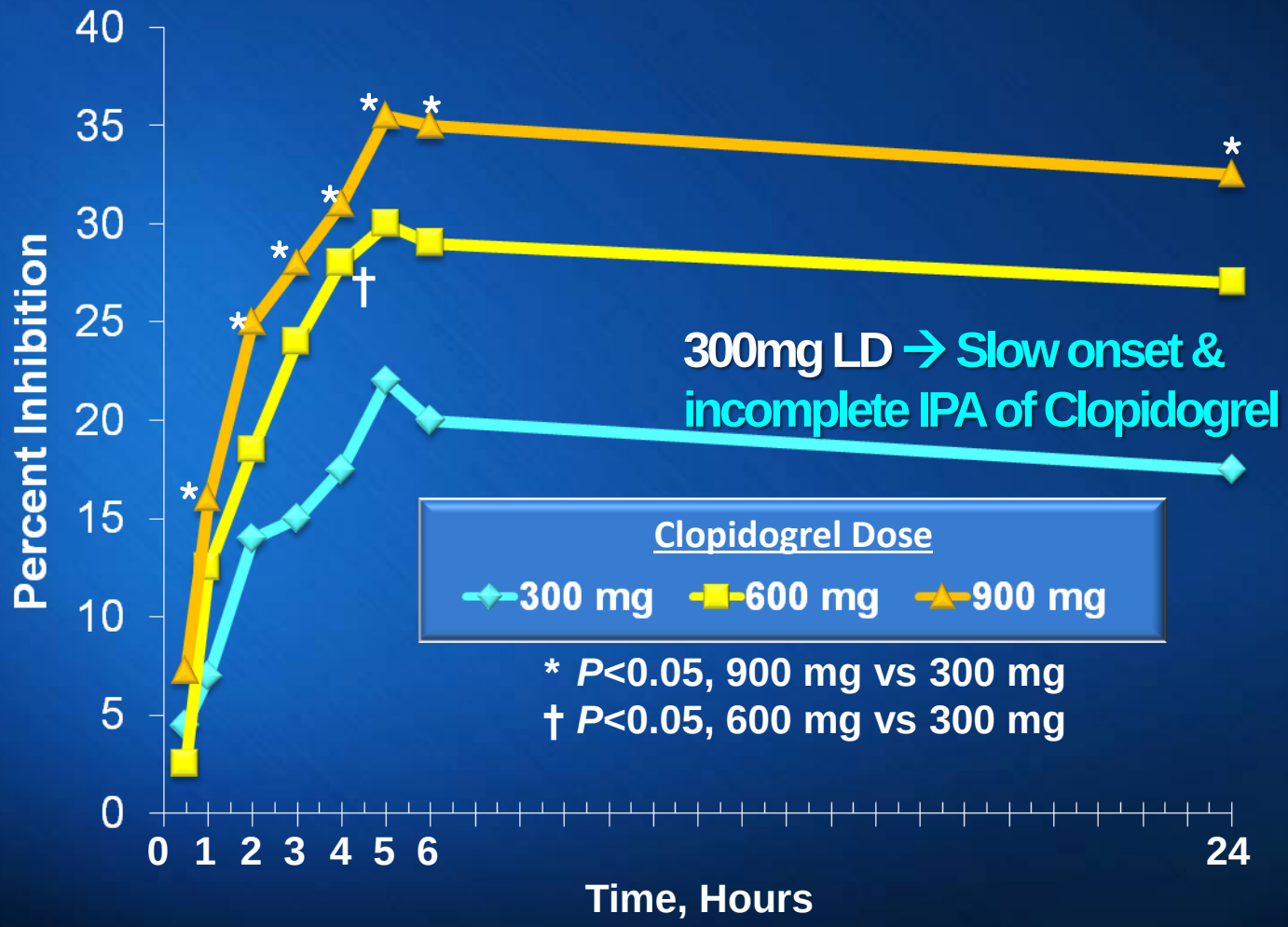
Adapted from clopidogrel package insert.

Issues in the current antiplatelet therapy

- Prodrug requires transformation to active metabolite
- Inter-patient variability in IPA
- **Relatively slow onset & incomplete IPA**
- Irreversible $P2Y_{12}$ receptor binding
- High incidence of CV death despite proven current Rx

From ALBION trial

Patients (n=103) with NSTEMI were randomized to receive a 300-mg, 600-mg, or 900-mg clopidogrel LD → Measure IPA



Montalescot G et al. ALBION Trial Investigators. J Am Coll Cardiol. 2006;48:931-938.

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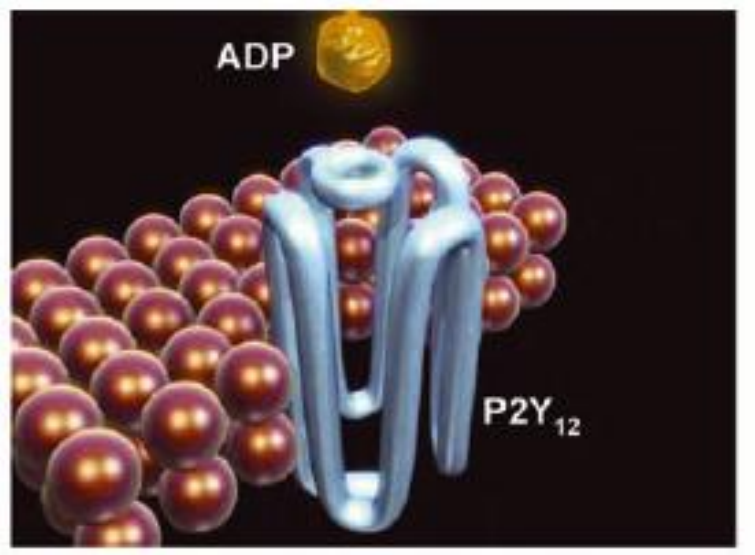
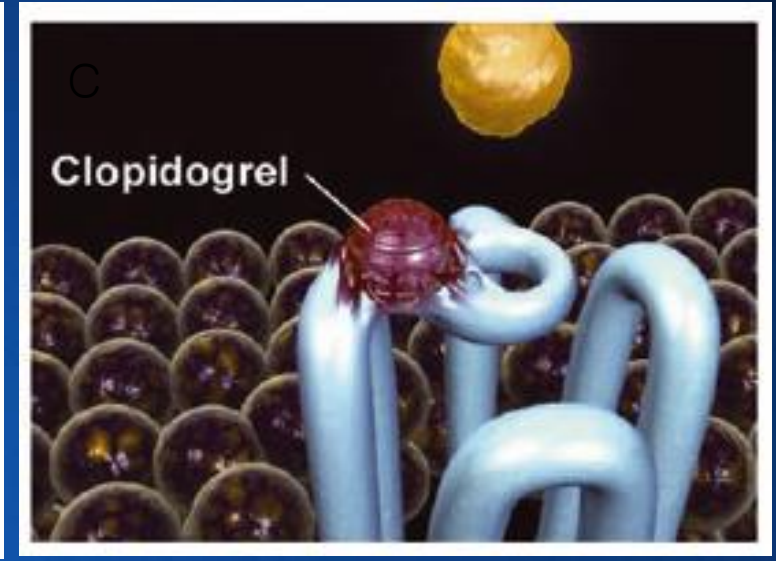
- **Irreversible $P2Y_{12}$ receptor binding**
- High incidence of CV death despite proven current Rx

Irreversible $P2Y_{12}$ receptor binding





- Thienopyridines act by binding covalently to the P2Y12 receptor, causing a structural change, and rendering the receptors **permanently inactivated**
- **Periods of withdrawal before major surgery**

  ; Clopidogrel (5 days) / Prasugrel (7 days)

Husted S, et al. *Cardiovasc Ther.* 2009;27:259–274.

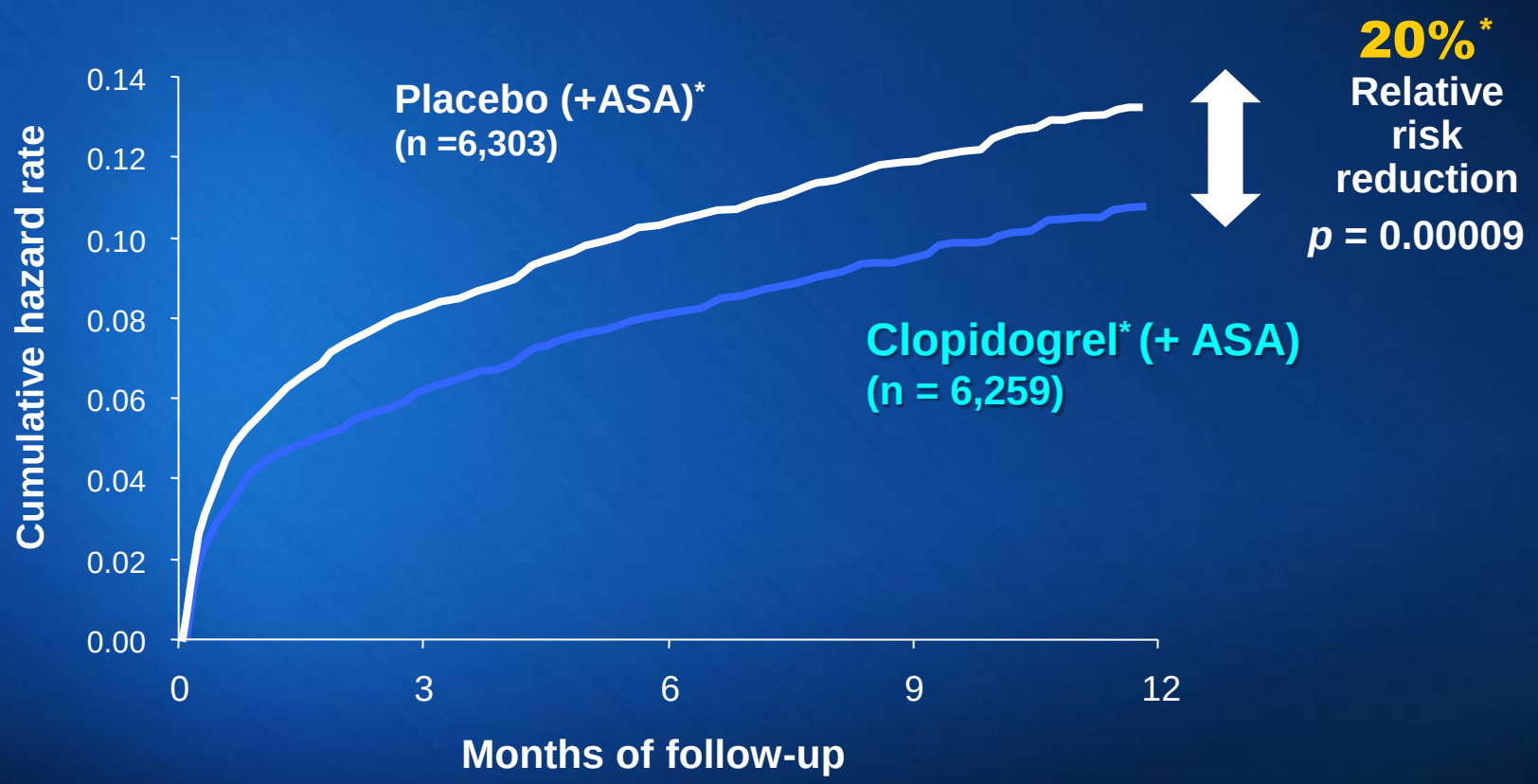
Issues in the current antiplatelet therapy

- Prodrug requires transformation to active metabolite
- Inter-patient variability in IPA
- Relatively slow onset & incomplete IPA
- Irreversible $P2Y_{12}$ receptor binding
- **High incidence of CV death**
  despite proven current therapy

CURE: Early & Long-Term Efficacy of Clopidogrel

Dual (ASA+Clopidogrel) vs. Mono (ASA only) in ACS

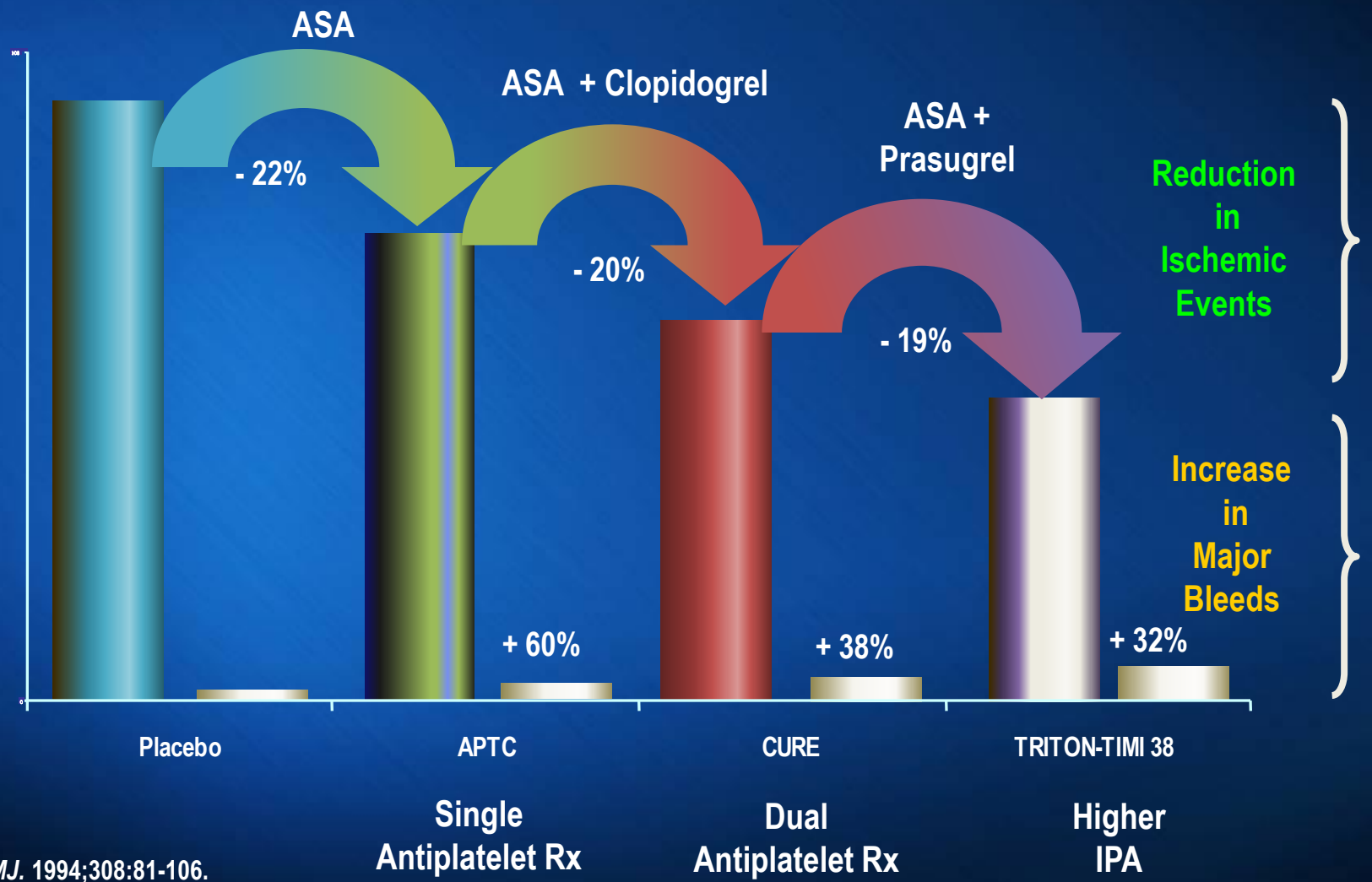
Cumulative events (MI, stroke, or cardiovascular death)



*On top of standard therapy (including ASA)

The CURE Trial Investigators. *N Engl J Med* 2001; 345: 494–502

Evolution of Antiplatelet Therapy in ACS

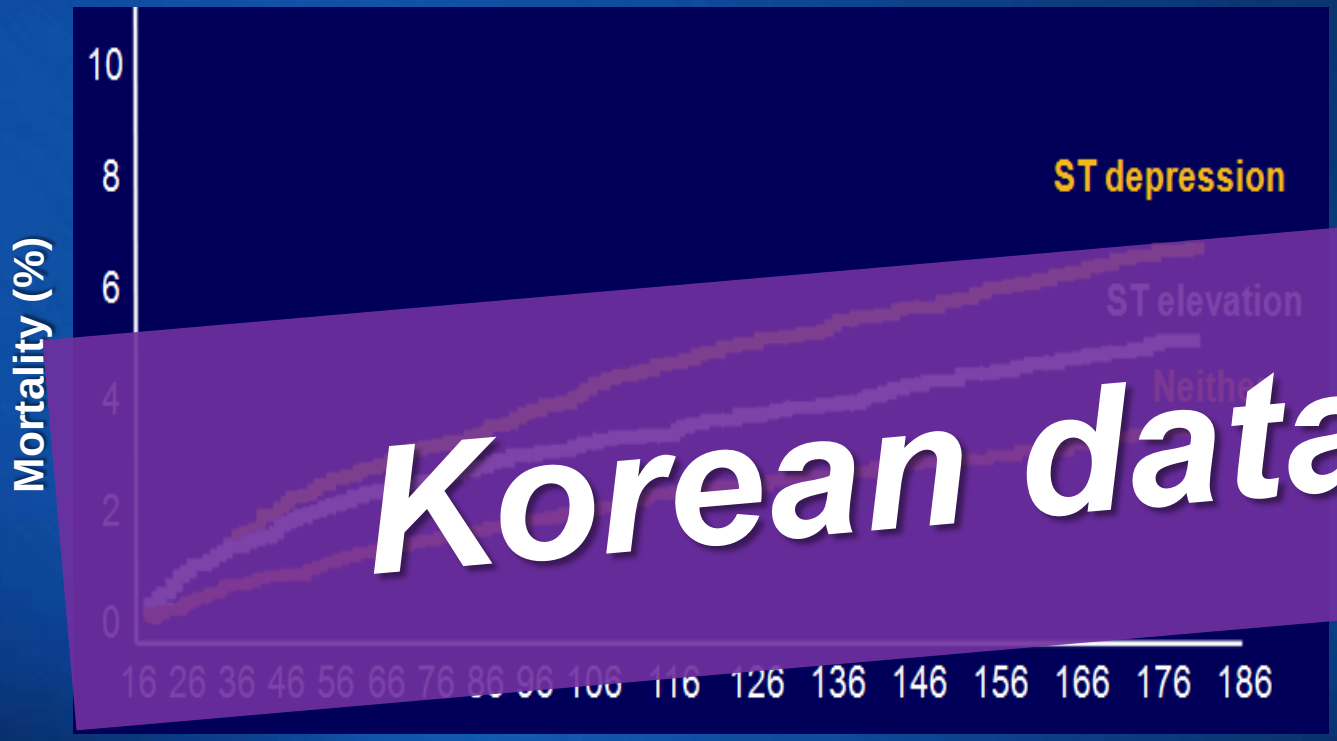


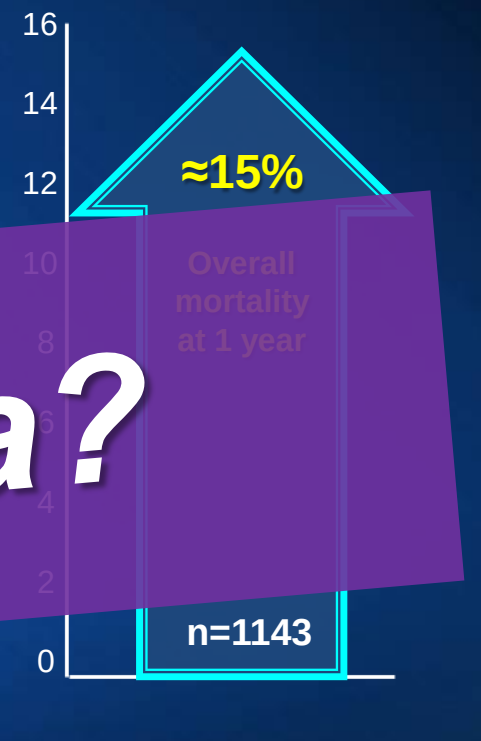
APTC. *BMJ.* 1994;308:81-106.
Mehta SR et al. *Lancet.* 2001;358:527-533.

Form Global Registry of Acute Coronary Events (GRACE) data

Unmet needs of ACS patients

Mortality following discharge by initial ECG presentation[1]





Korean data?

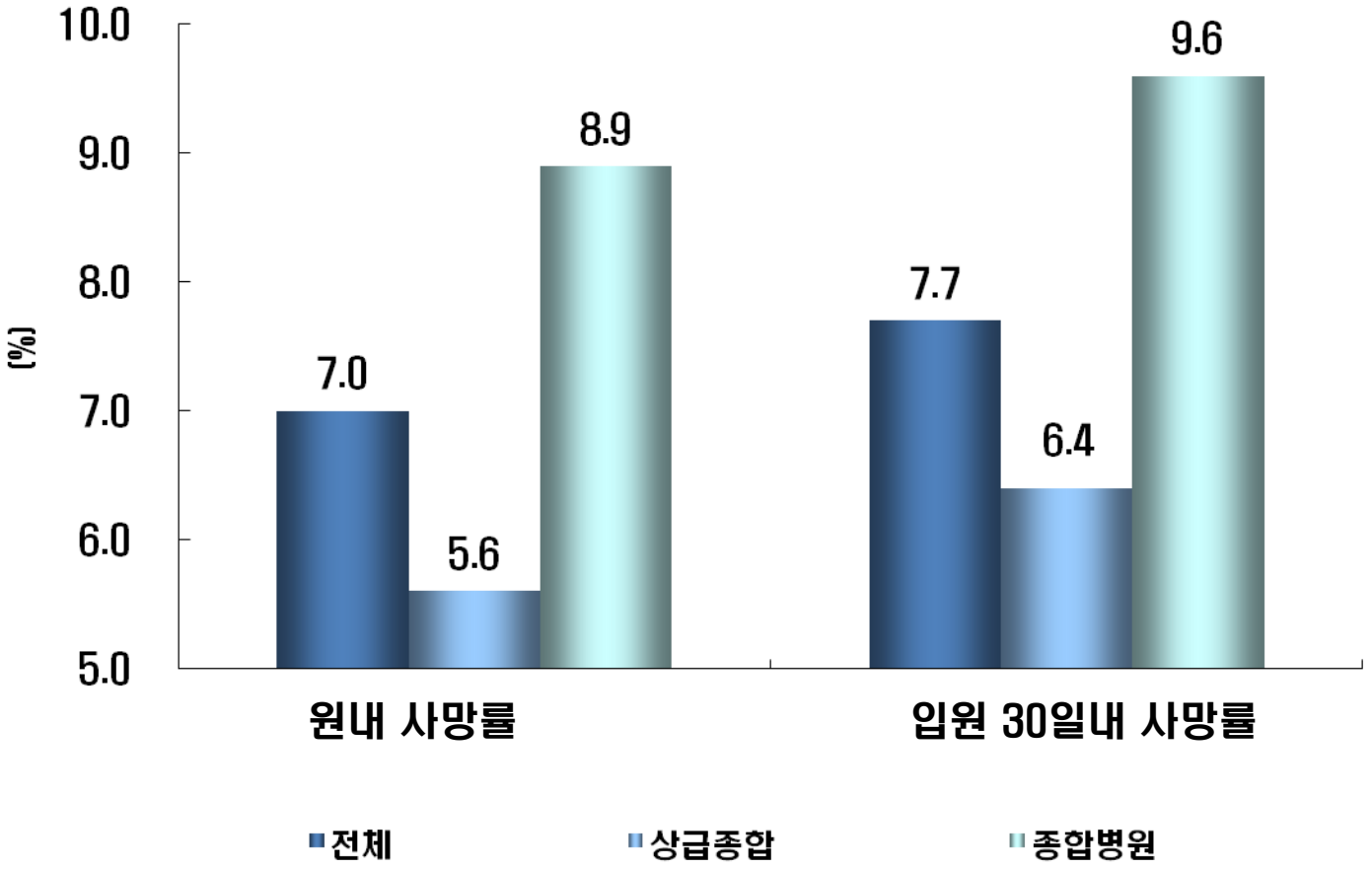
Registry data indicate up to 15% of patients with ACS, may die within 12 months of their initial event.[2]

***Event occurrence based on Global Registry of Acute Coronary Events (GRACE) data.[2]**

1. Fox KA, et al. *Nature Clin Pract Cardiol.* 2008;5:580-589. 2. Tang EW, et al. *Am Heart J*. 2007;153:29-35.

Unmet needs of ACS patients in Korea

급성심근경색증 : 사망률(원내/ 입원 30일내)



- 대상자료
  - 2009.1.1~12.31 진료분 조사표 자료, 종합병원 이상 기관
- 사망률 : 실제 사망률
- 작성기관 : 건강보험심사평가원(2010.11월)

Issues in the current antiplatelet therapy

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- Inter-patient variability in IPA
- Relatively slow onset & incomplete
- Irreversible $P2Y_{12}$ receptor binding
- High incidence of CV death despite proven current Rx

If that, How?

How to overcome?
Use of new antiplatelet agent will be the one of the solutions ?

Strategies to overcome the current issues of antiplatelet

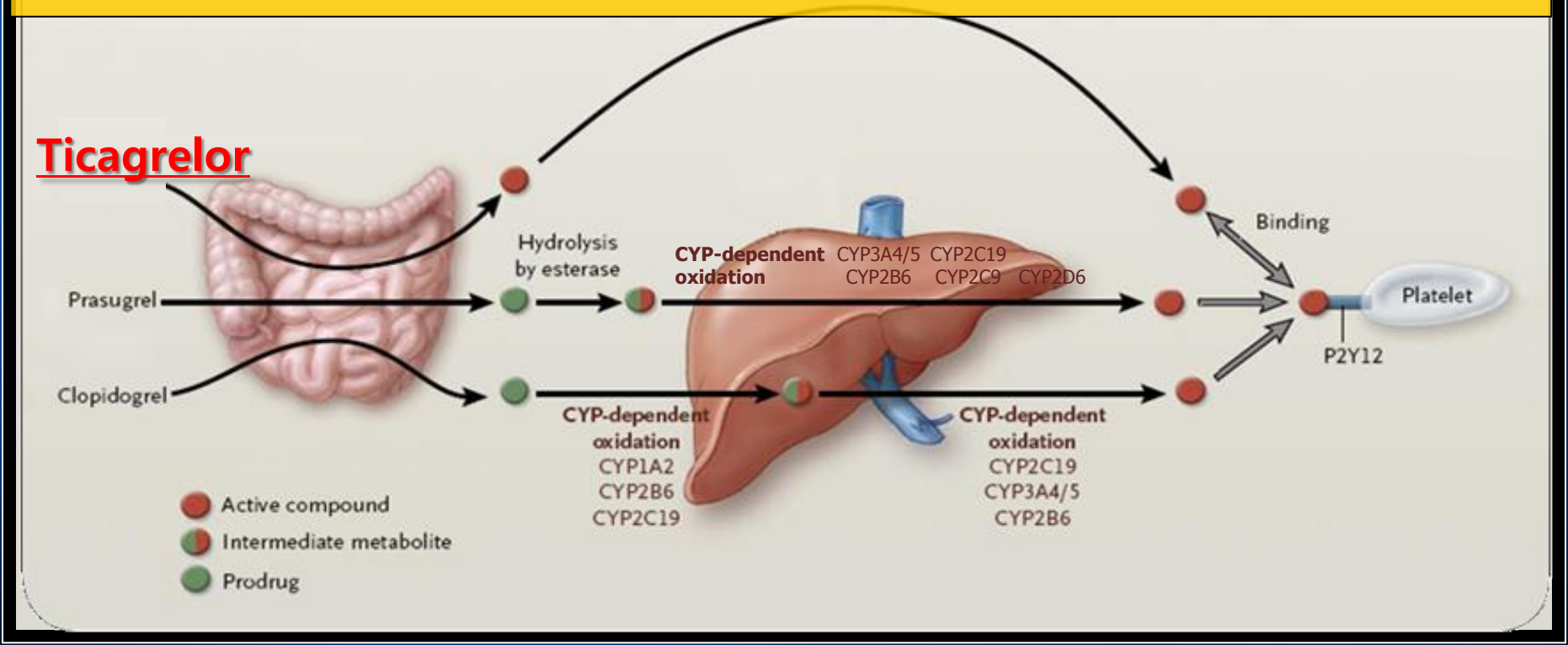
1. **Prodrug, requiring transformation to the active metabolite**

   → Active metabolite itself, not requiring hepatic metabolism.

2. Inter-patient variability in IPA
3. Relatively slow onset & incomplete IPA
4. Irreversible $P2Y_{12}$ receptor binding
5. High incidence of CV death despite proven current Rx

Comparison of metabolism among the antiplatelets

Ticagrelor, orally active and does not require hepatic metabolism for activity.



1. BRILINTA Core Data Sheet, 2010.
2. Husted S, et al. *Cardio Ther*. 2009;27:259-274.
3. Schomig AS. *New Eng J Med* 2009; 361(11): 1108-1111

Strategies to overcome the current issues of antiplatelet

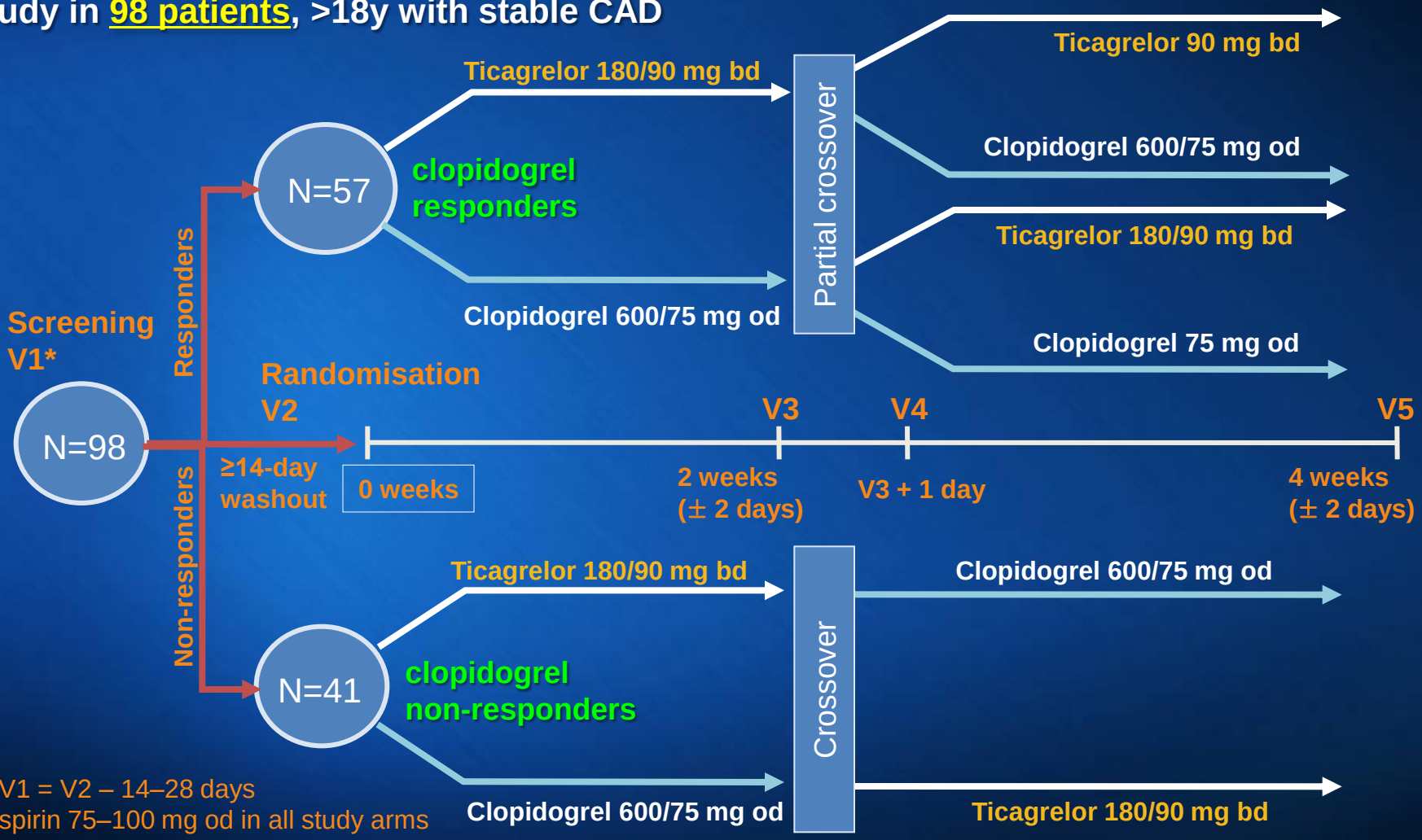
1. Prodrug, requiring transformation to the active metabolite
2. **Inter-patient variability in IPA**

   → *New antiplatelet with a Greater and more Consistent IPA will be needed…*

3. Relatively slow onset & incomplete IPA
4. Irreversible $P2Y_{12}$ receptor binding
5. High incidence of CV death despite proven current Rx

RESPOND study: Design

Randomised, double-blind, double-dummy, crossover study in 98 patients, >18y with stable CAD



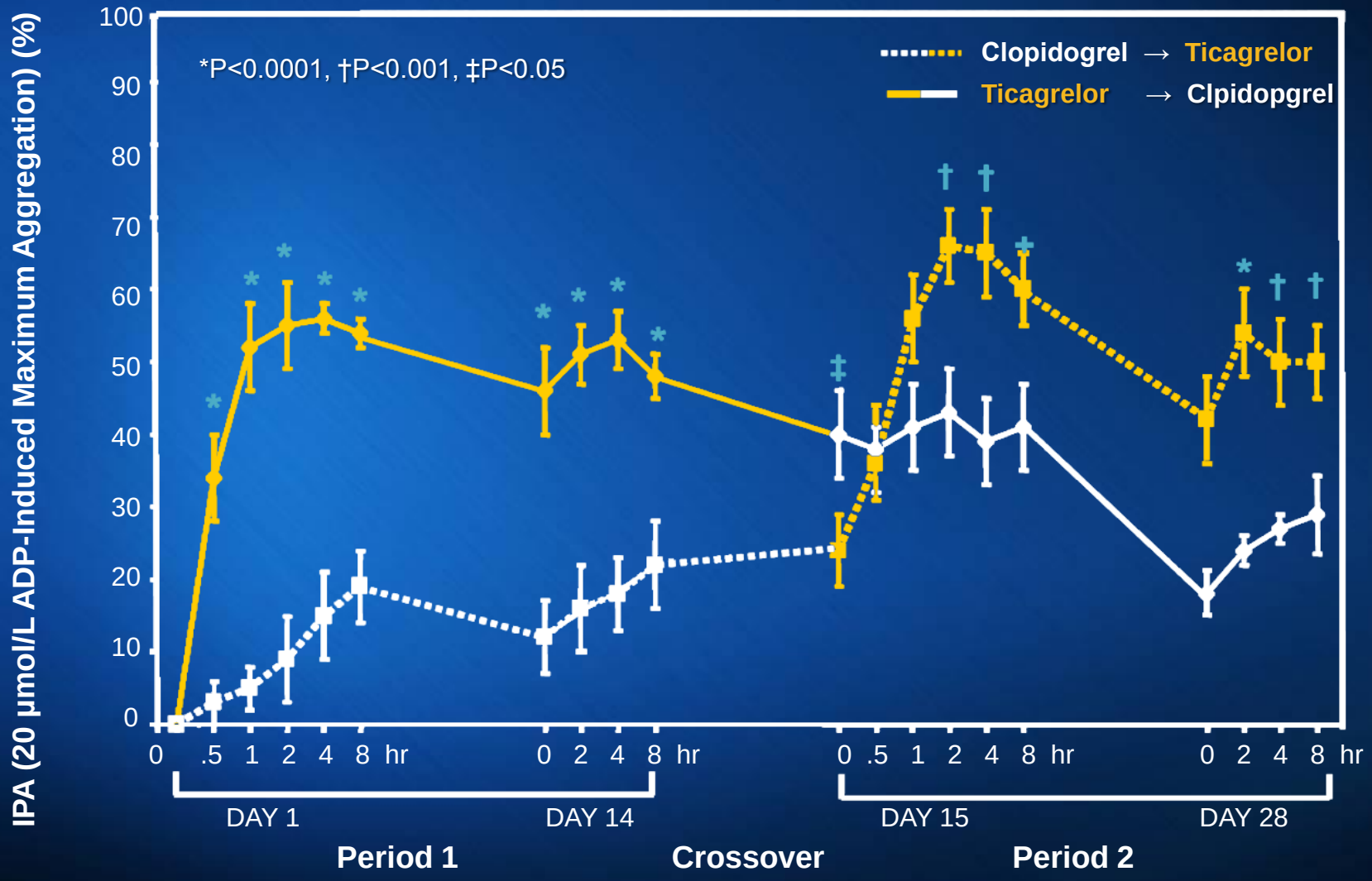
* V1 = V2 – 14–28 days
Aspirin 75–100 mg od in all study arms

Gurbel *et al*. *Circulation* 2010; 121: 1188-1199

Non-responders, identified by light transmittance aggregometry.

RESPOND : Non-responder Cohort

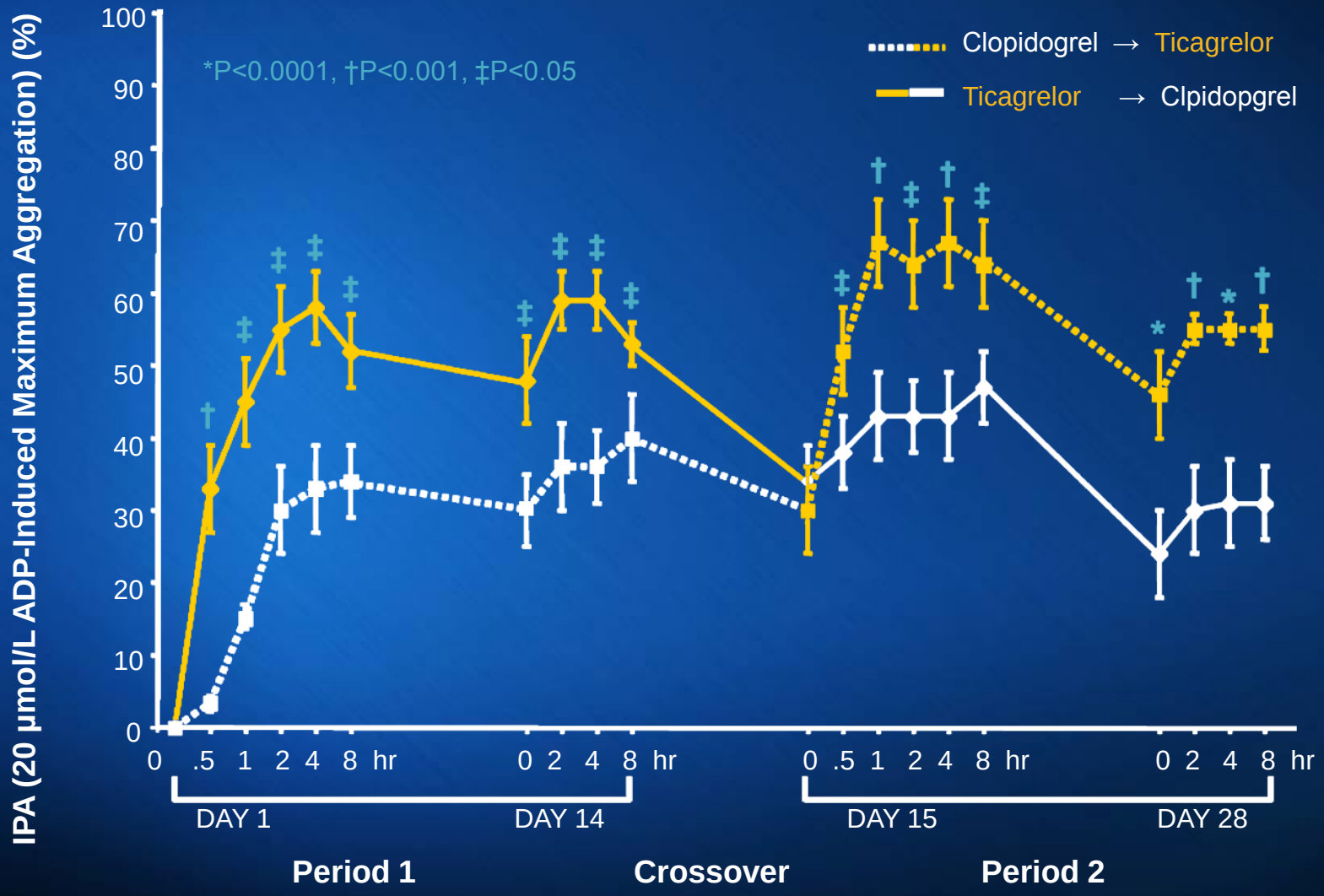
IPA in Response to 20 μmol/L ADP



Gurbel *et al*. *Circulation* 2010; 121: 1188-1199

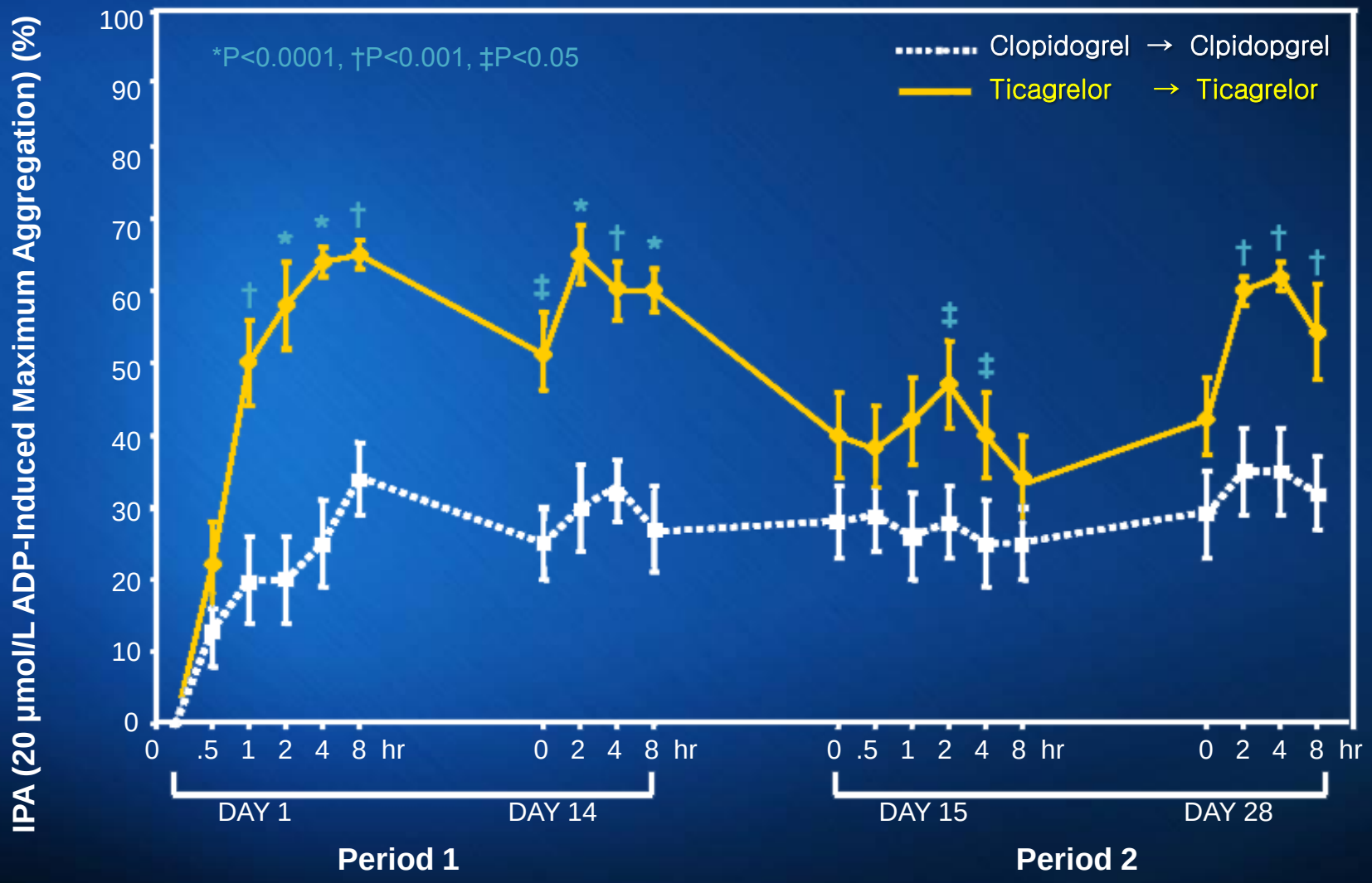
RESPOND : Responder Cohort (Cross-over)

IPA in Response to 20 μmol/L ADP



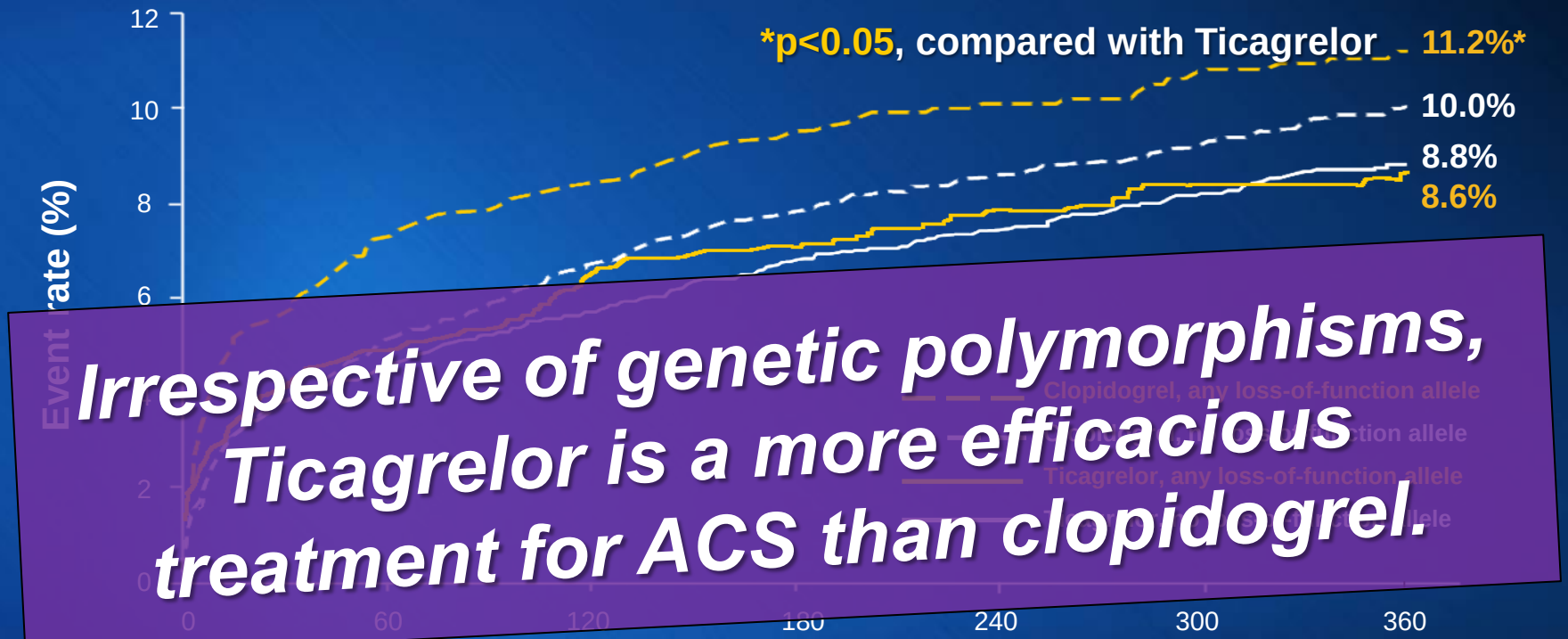
RESPOND : Responder – IPA (Non-crossover)

IPA in Response to 20 μmol/L ADP



Gurbel *et al*. *Circulation* 2010; 121: 1188-1199

From PLATO Genetics sub-study; Kaplan-Meier estimates of the primary efficacy outcomes (Time to First MI, CV Death, Stroke) in relation to the *CYP2C19* genotype



Irrespective of genetic polymorphisms, Ticagrelor is a more efficacious treatment for ACS than clopidogrel.

Number at risk							
Clopidogrel							
Any loss-of-function allele	**1,388**	**1,275**	**1,259**	**1,226**	**1,027**	**801**	**658**
No loss-of-function allele	**3,516**	**3,321**	**3,259**	**3,186**	**2,691**	**2,123**	**1,757**
Ticagrelor							
Any loss-of-function allele	**1,384**	**1,305**	**1,274**	**1,250**	**1,053**	**834**	**683**
No loss-of-function allele	**3,554**	**3,352**	**3,301**	**3,222**	**2,718**	**2,127**	**1,761**

Wallentin *et al. Lancet 2010; 376:1320–28*

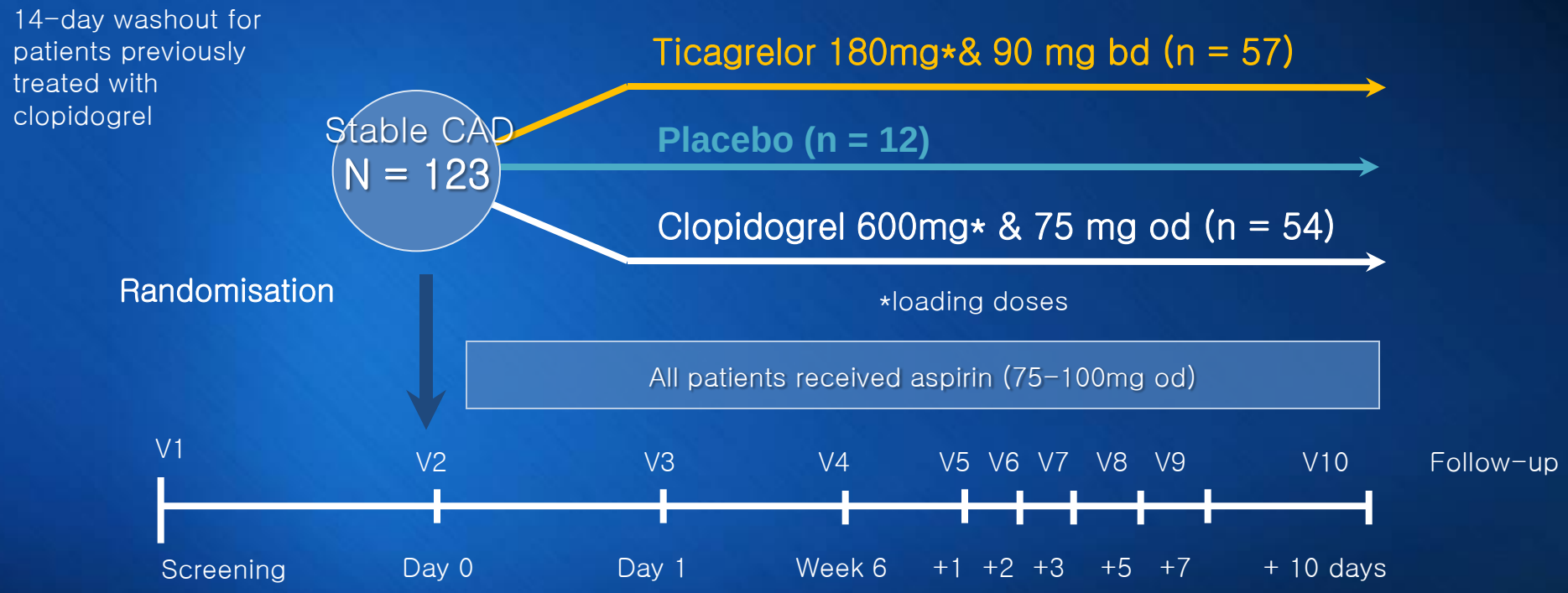
Strategies to overcome the current issues of antiplatelet

1. Prodrug, requiring transformation to the active metabolite
2. Inter-patient variability in IPA
3. **Relatively slow onset & incomplete IPA**

   → *New antiplatelet with rapid onset and complete IPA is needed.*

4. Irreversible $P2Y_{12}$ receptor binding
5. High incidence of CV death despite proven current Rx

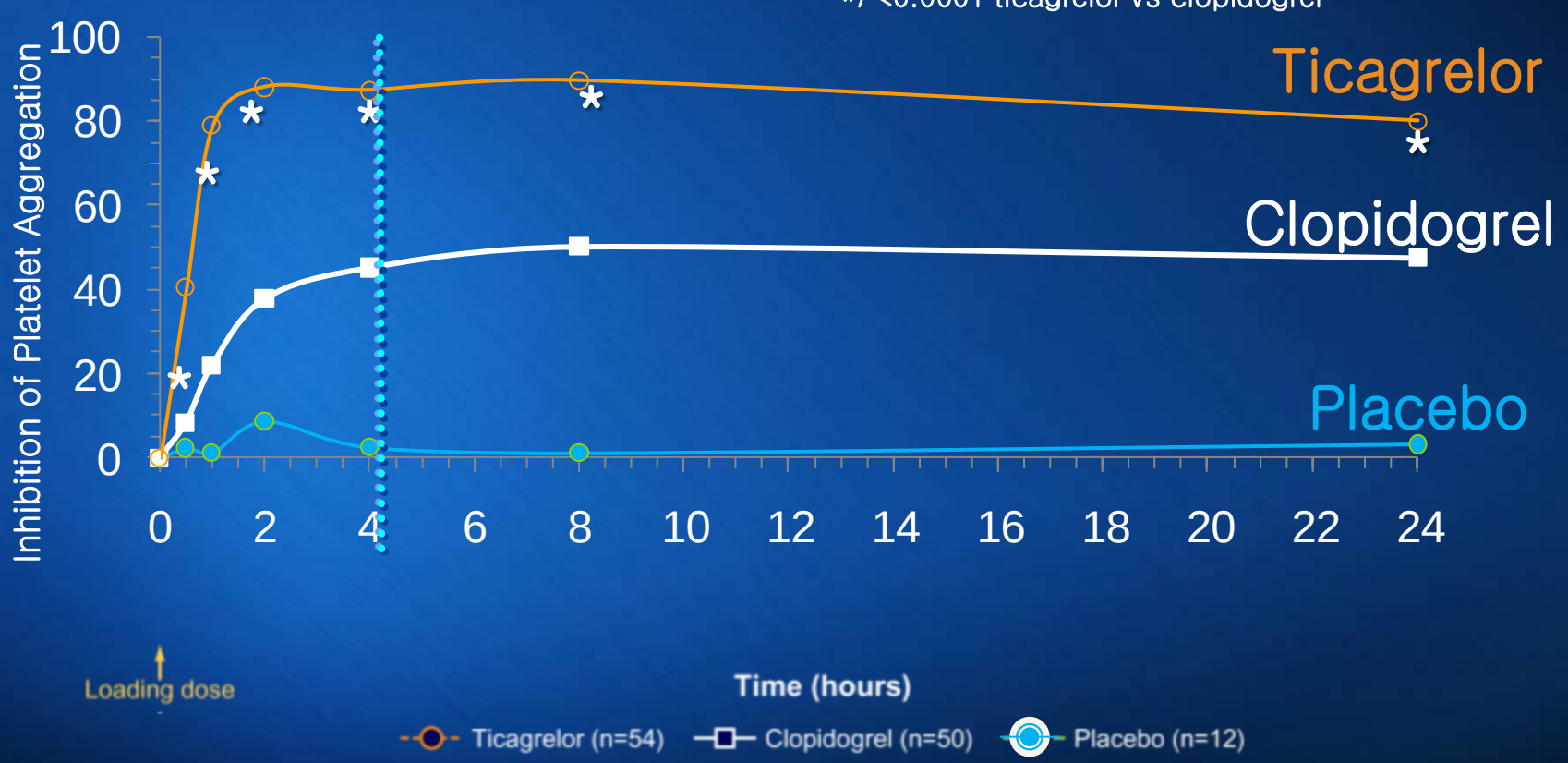
ONSET/OFFSET study: Study Design



Gurbel *et al. Circulation* 2009; 120: 2577-2585

Inhibition of Platelet Aggregation: Onset

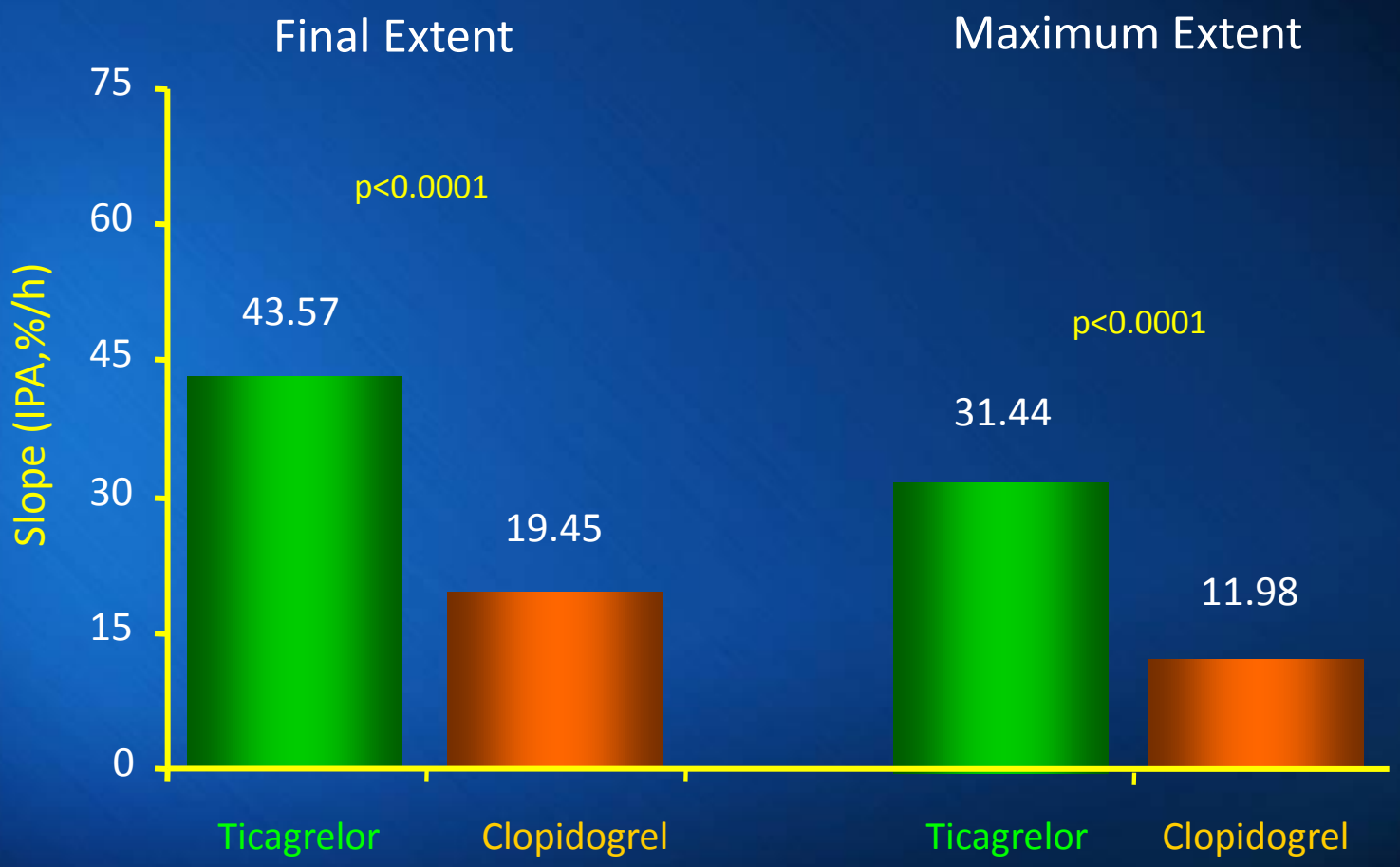
The significantly greater IPA occurred with ticagrelor compared with clopidogrel at 0.5, 1, 2, 4, 8, and 24 hours post loading.



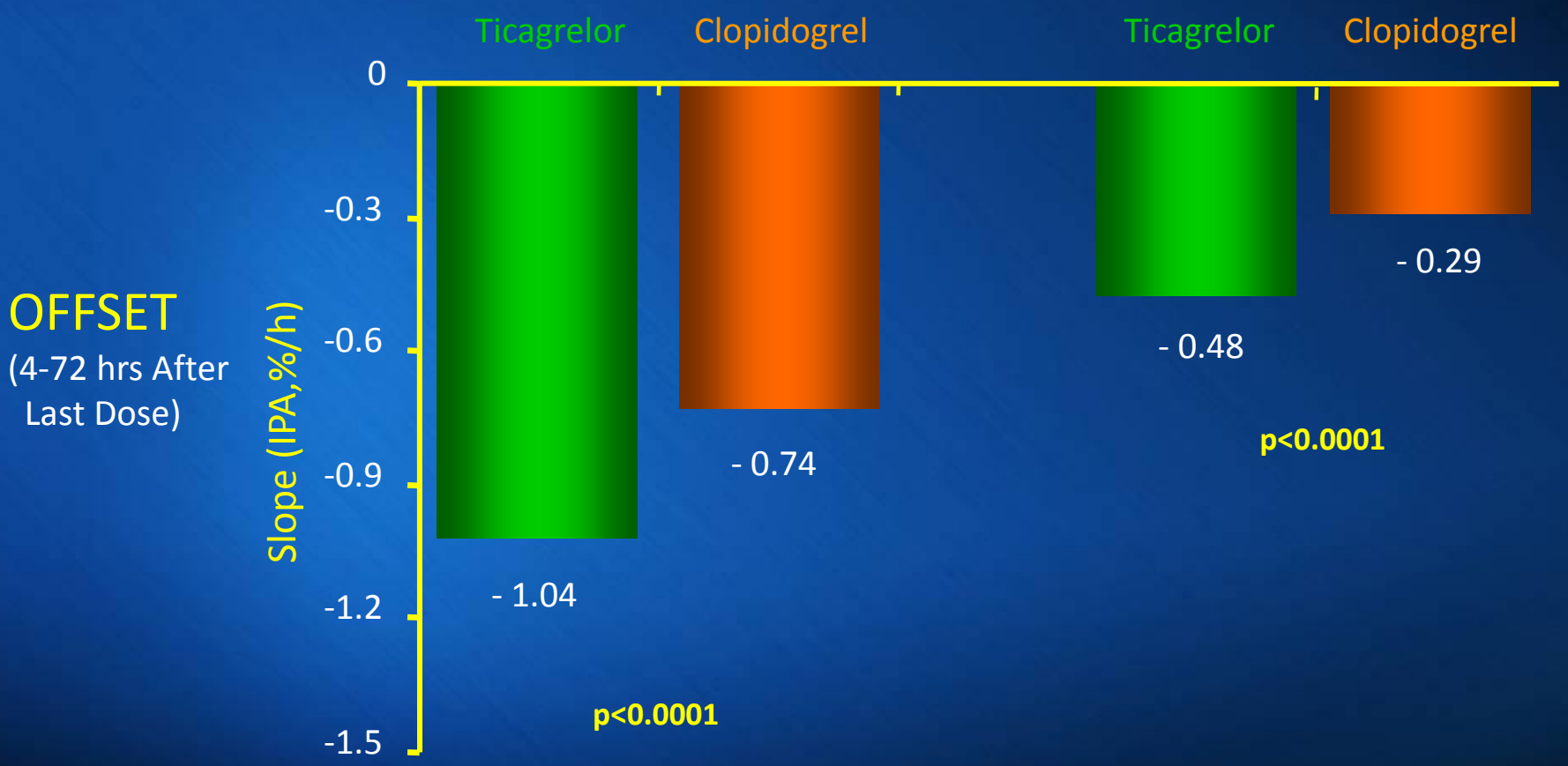
Adapted from Gurbel PA, et al. *Circulation.* 2009;120:2577–2585.

Rate of onset (slope) as assessed by IPA (20 μM ADP)

ONSET
(0-2 hrs After Loading Dose)



Rate of offset (Slope)



ONSET/OFFSET : Onset and Maintenance IPA

Primary end-point for onset; IPA (20 μmol/L ADP) at 2 Hours after loading

	Ticagrelor (n=54)		Clopidogrel (n=50)		*P*	
	IPA, %	PA, %	IPA, %	PA, %	IPA, %	PA, %
Final extent	88±15	7±9	38±33	44±24	<0.0001	<0.0001
Maximum extent	65±17	23±10	25±23	55±18	<0.0001	0.001

Ticagrelor achieved more rapid and greater platelet inhibition than high-loading-dose clopidogrel.

PA indicates platelet aggregation. Values are mean±SD.

MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndromes.

Gurbel *et al*. *Circulation* 2009; 120: 2577-2585

Strategies to overcome the current issues of antiplatelet

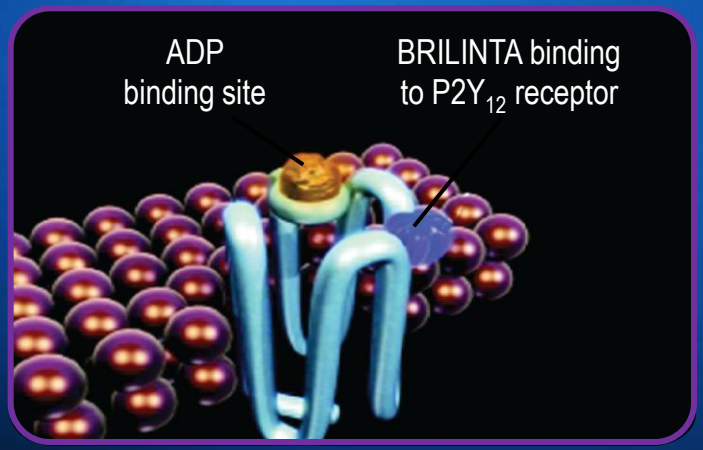
1. Prodrug, requiring transformation to the active metabolite
2. Inter-patient variability in IPA
3. Relatively slow onset & incomplete IPA
4. **Irreversible $P2Y_{12}$ receptor binding**

   → Directly binding to P2Y12 receptors and reversibly inhibition is needed…

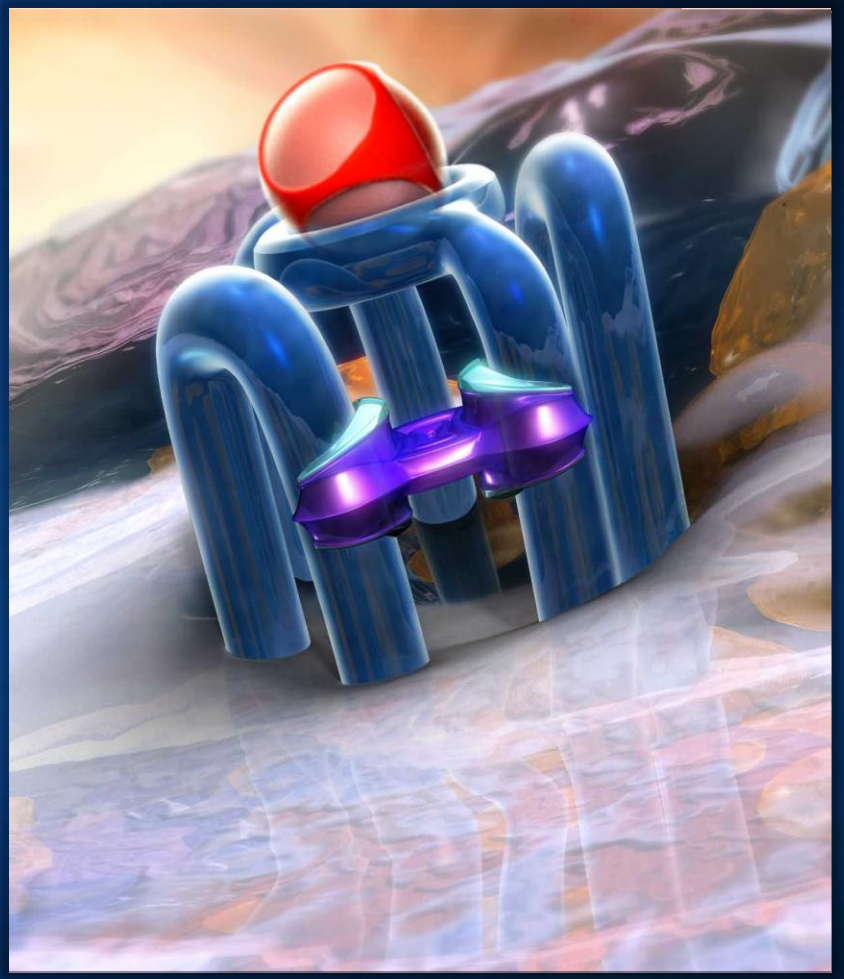
5. High incidence of CV death despite proven current Rx

Ticagrelor $P2Y_{12}$ receptor binding

- BRILINTA binds directly to $P2Y_{12}$ receptors to **reversibly** inhibit platelet activation and aggregation[1]
- Thienopyridines bind covalently to $P2Y_{12}$ ADP binding site for the life of the platelet[2]



Adapted from Husted S, et al, *Cardio Ther*, 2009.[2]



1. BRILINTA Core Data Sheet, 2010. 2. Husted S, et al. *Cardio Ther*. 2009;27:259-274.
2. van Giezen JJJ. *Eur Heart J.* 2008;10 (Suppl D):D23-D29; Husted S, et al. *Eur Heart J*. 2006;27:1038-1047; Gurbel PA, et al. *Circulation.* 2009;120:2577-2585.

Strategies to overcome the current issues of antiplatelet

1. Prodrug, requiring transformation to the active metabolite
2. Inter-patient variability in IPA
3. Relatively slow onset & incomplete IPA
4. Irreversible $P2Y_{12}$ receptor binding
5. **The last remaining issue;**
   High incidence of CV death in ACS

→ PLATO and other studies using new antiplatelet show a better outcome in the patients with ACS.

→ These will be discussed in the next session by Prof Lee.

Conclusion -I

In the ACS management

- In spite of the importance of antiplatelet therapy, the current antiplatelet therapy still shows many limitations as below;
  - Prodrug
  - Inter-patient variable IPA
  - Relatively slow onset & incomplete IPA
  - Irreversible P2Y12 receptor binding

Conclusion -II

In the ACS management

- Therefore, new antiplatelet agent to overcome these limitations are needed.

- Especially, **Ticagrelor**, is expected to improve the clinical outcomes of the patients with ACS as the following potentials;
  - A reversible direct-acting inhibitor of the ADP receptor $P2Y_{12}$
  - A more rapid onset
  - A more pronounced platelet inhibition than clopidogrel
  - A proven improved clinical outcomes

- We should keep watching the further outcomes of “Ticagrelor”.


Thank you for your attention

Back-up

Light-Transmittance Aggregometry

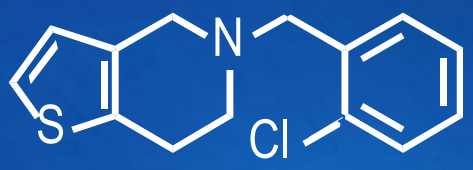
Platelet aggregation induced by ADP (20 and 5 μmol/L), collagen 2 μg/mL, and arachidonic acid 2 mmol/L in platelet-rich plasma was assessed with a Chrono-log Optical Aggregometer (model 490-4D; Chrono-log Corporation, Havertown, Pa) as described previously.[4] The assessment of 2 mmol/L arachidonic acid–induced aggregation was performed to evaluate the effects of aspirin.[15] The final extent of aggregation, measured at 6 minutes after agonist addition, and the maximal extent of aggregation were expressed as the percent change in light transmittance from baseline, with platelet-poor plasma as a reference. IPA was calculated as follows, where PA is platelet aggregation, b is predosing, and t is postdosing:

$$IPA(\%) = 100\% \times \frac{PA_b - PA_t}{PA_b}$$

Conclusion

- Prodrug requires transformation to active metabolite
  - ➢ Direct acting – doesn't require hepatic metabolism for activity
- Inter-patient variability in IPA
  - ➢ Less variability in individual response
- Relatively slow onset & incomplete IPA
  - ➢ Rapid and greater platelet inhibition than clopidogrel
- Irreversible $P2Y_{12}$ receptor binding
  - ➢ Reversibly binds to the $P2Y_{12}$ receptor
- High incidence of CV death despite proven current Rx
  - ➢ ?

The Thienopyridine Family

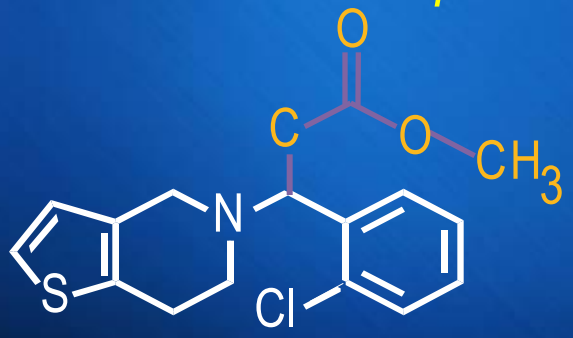


Ticlopidine

(1st generation)

- $P2Y_{12}$ ADP receptor antagonism: antithrombotic treatment of choice for coronary stenting
- Side effects: neutropenia, thrombocytopenia, rash, diarrhea, etc.
- Delayed time frame to achieve full antiplatelet effects

Solution to these problems:



Clopidogrel

(2nd generation)

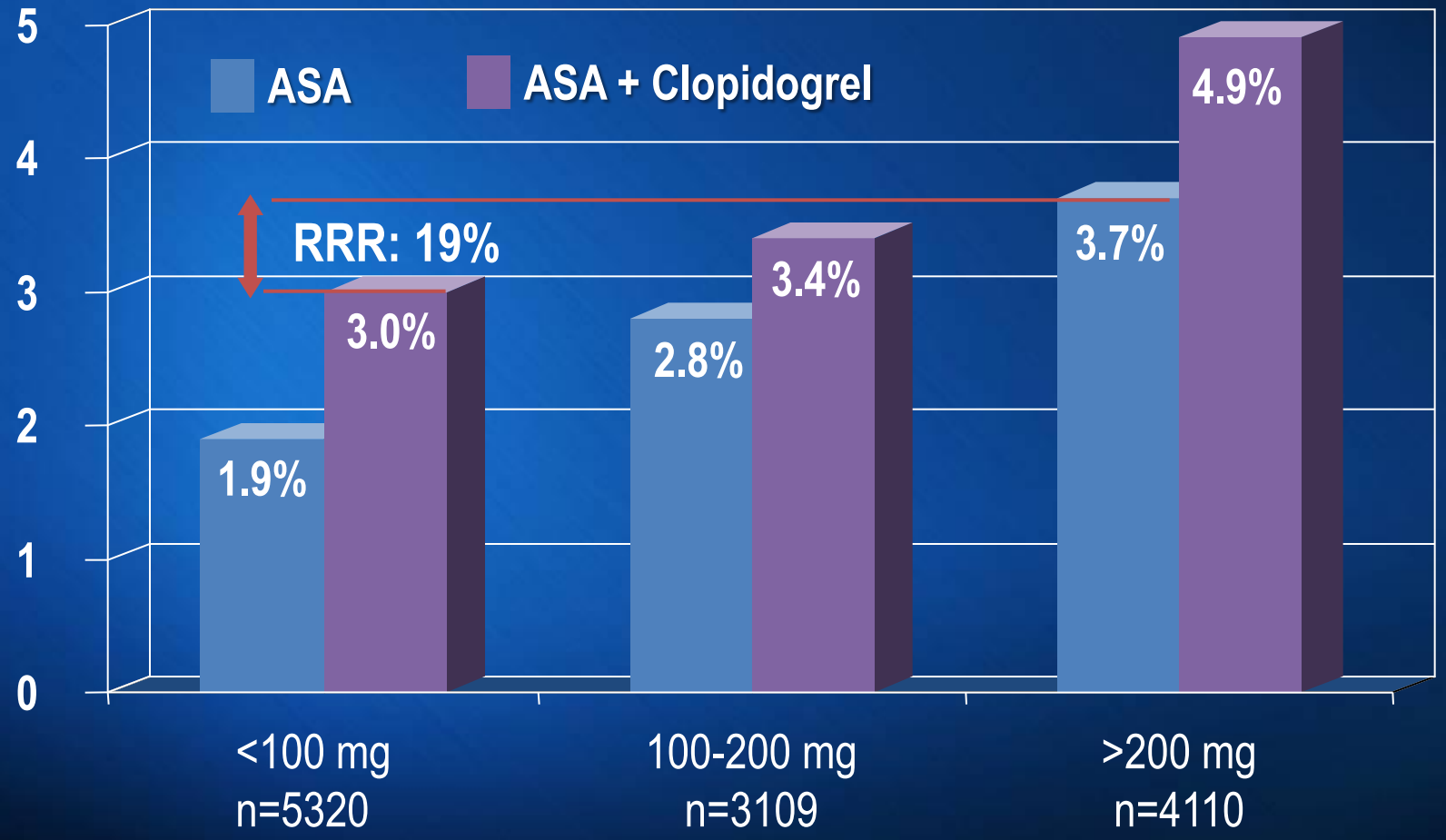
- Better Safety profile - Fewer side effects
  (CLASSICS trial. Bertrand NE et al. *Circulation.* 2000;102:624-629.)
- Rapid onset of action with a loading dose
  (Cadroy Y et al. *Circulation*. 2000;101:2823-2828.)
- Better clinical outcomes
  (Bhatt DL *et al. J Am Coll Cardiol.* 2002;39:9-14.)

Clopidogrel - a "game changer"

- Gradual but ultimately wide uptake
- Major impact on clinical practice
  - Simple regimen with few adverse effects
  - Prompt and reliable stabilization
  - Fewer recurrent and refractory episodes
  - Reduced need for GP IIb/IIIa antagonists
  - Safe and easy transition to cath lab and to PCI
  - Compatible with a variety of anti-coagulants

Aspirin Dose and Incidence of Major Bleedings

Insights from CURE



Peters RJ et al. *Circulation.* 2003;108:1682-1687.

Limitations of clopidogrel

- Despite clinical benefits achieved with clopidogrel, patients continue to have CV events, which may be due to limitations with clopidogrel
  - Prodrug requiring metabolic activation [Angiolillo 2008:A]
  - Slow time to peak of antiplatelet activity (TIPAmax=8 hours) [Gurbel 2009:A]
  - Variable individual patient response [Angiolillo 2007:A]
  - Irreversibly binds to the P2Y12 receptor [Angiolillo 2008:B]
  - Restoration of platelet function requires the production of new platelets [Angiolillo 2008:B]

$TIPA_{max}$, time to maximum inhibition of platelet aggregation

Angiolillo DF, et al. *Am Heart J*. 2008;156:S3-S9; Gurbel PA, et al. *Circulation.* 2009;120:2577-2585.

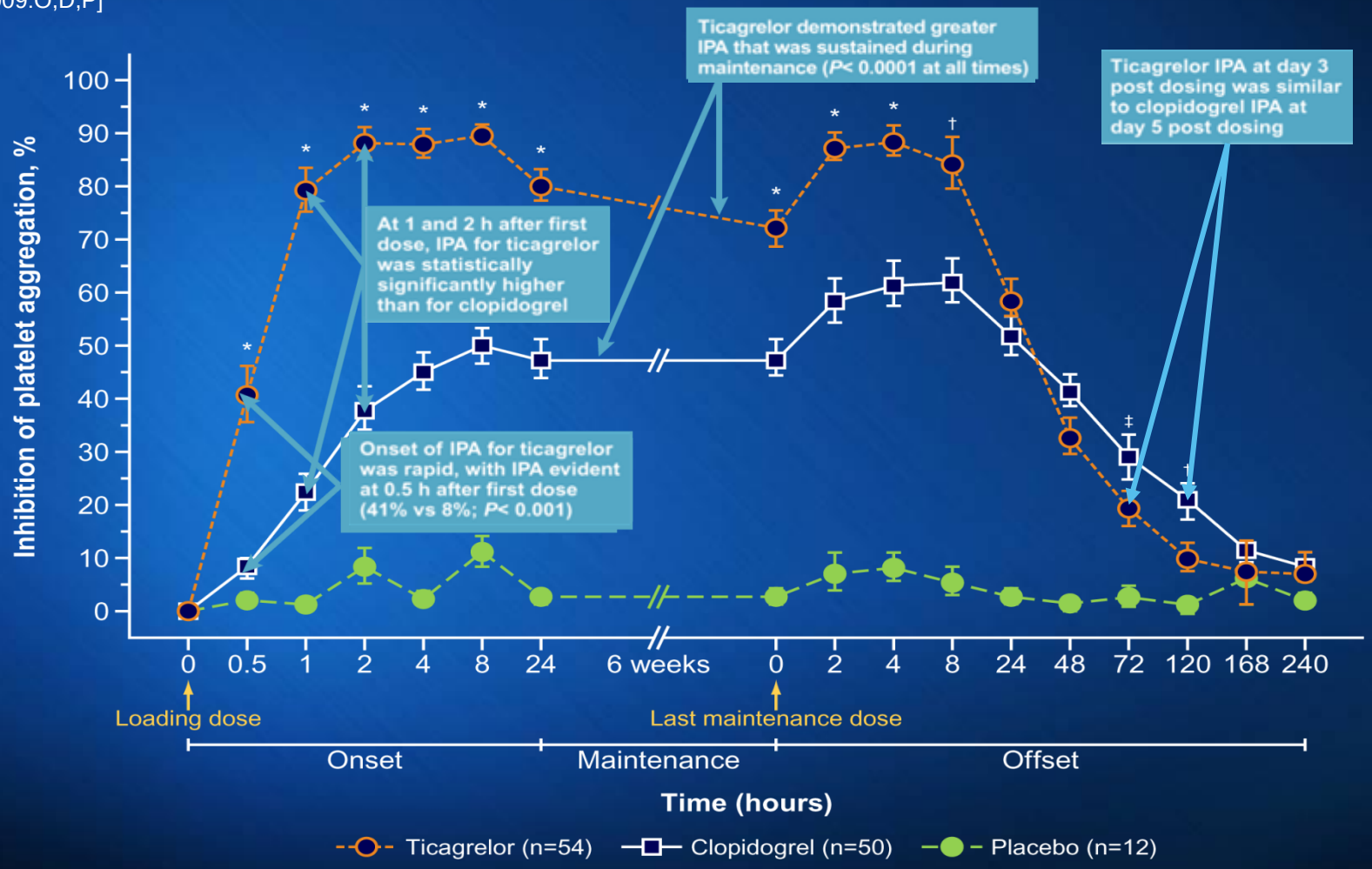
Clinical Pharmacology: Ticagrelor and Clopidogrel

	Ticagrelor	Clopidogrel
Chemical class	CPTP	Thienopyridine
Reversible Inhibition of P2Y12 receptor	Yes	No
PD variability with CYP2C19 genotype	No	Yes
Dosing	Twice daily (bid)	Once daily (qd)
Mean inhibition of platelet aggregation (IPA) at 30 minutes	41%	8%
Mean IPA at 2 hours	89%	38%

Gurbel PA, et al. *Circulation.* 2009;120:2577–2585.
BRILINTA Summary of Product Characteristics 2010.
PLAVIX® [package insert]. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; 2010.

ONSET/OFFSET: inhibition of platelet aggregation

[Gurbel 2009:O,D,P]



Gurbel *et al*. *Circulation* 2009; 120: 2577-2585

PLATO Genetic Substudy

Effect of *CYP2C19 and ABCB1* single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial

PLATO Genetics : Objective and Methods

- **Objective**
  - → To investigate the role of *CYP2C19* and *ABCB1* polymorphisms on efficacy and safety outcomes both between and within the ticagrelor and clopidogrel

- A blood sample was obtained from every participant as close to randomisation as possible
- 10,285 patients consented to give a blood sample for genetic analysis

- The alleles genotyped in the total PLATO genetics population were:
  - *CYP2C19 loss-of-function alleles *2, *3,**4, *5, *6, *7, and *8
  - *CYP2C19 gain-of-function allele* *17
  - *ABCB1 single nucleotide polymorphism 3435Cycosine→Thymine (rs1045642)*

Wallentin *et al*. *Lancet* 2010; 376: 1320–28

PLATO Genetics : Results

Primary Efficacy& Safety Endpoints

	Ticagrelor (n=5,137)	Clopidogrel (n=5,148)	HR for (95% CI)	P	p*
MI / CV Death / Stroke, n (K-M %)					
Any CYP2C19 loss of function allele (n=1384)	**115 (8.6)**	**149 (11.2)**	0.77 (0.60–0.99)	0.038	0.46
No CYP2C19 loss of function allele (n=3554)	**296 (8.8)**	**332 (10.0)**	0.86 (0.74-1.01)	0.061	
Low Expression of ABCB1 3435C→T SNP (n=1349)	**122 (9.5)**	**137 (10.5)**	0.90 (0.70-1.15)	0.40	0.39
Med Expression of ABCB1 3435C→T SNP (n=2570)	**208 (8.5)**	**233 (9.8)**	0.86 (0.71-1.03)	0.11	
High Expression of ABCB1 3435C→T SNP (n=1167)	**98 (8.8)**	**138 (11.9)**	0.71 (0.55-0.92)	0.01	
Major Bleed, n (K-M %)					
Any CYP2C19 loss of function allele (n=1384)	**149 (11.8)**	**143 (11.3)**	1.04 (0.82-1.30)	0.77	0.60
No CYP2C19 loss of function allele (n=3554)	**331 (10.3)**	**340 (10.6)**	0.96 (0.83-1.12)	0.61	
Low Expression of ABCB1 3435C→T SNP (n=1349)	**132 (10.9)**	**137 (10.9)**	0.97 (0.76-1.23)	0.77	0.80
Med Expression of ABCB1 3435C→T SNP (n=2570)	**240 (10.3)**	**245 (10.6)**	0.96 (0.80-1.15)	0.66	
High Expression of ABCB1 3435C→T SNP (n=1167)	**121 (11.5)**	**116 (10.8)**	1.06 (0.83-1.37)	0.63	

Wallentin *et al*. *Lancet* 2010; 376: 1320–28