Mr B

- 52 years old male
- Smoker
- No prior known CAD
- Presents with 1 hour intermittent crushing retrosternal chest pain
- Transferred by MICU directly to CCU (ASA, Heparin)

On admission

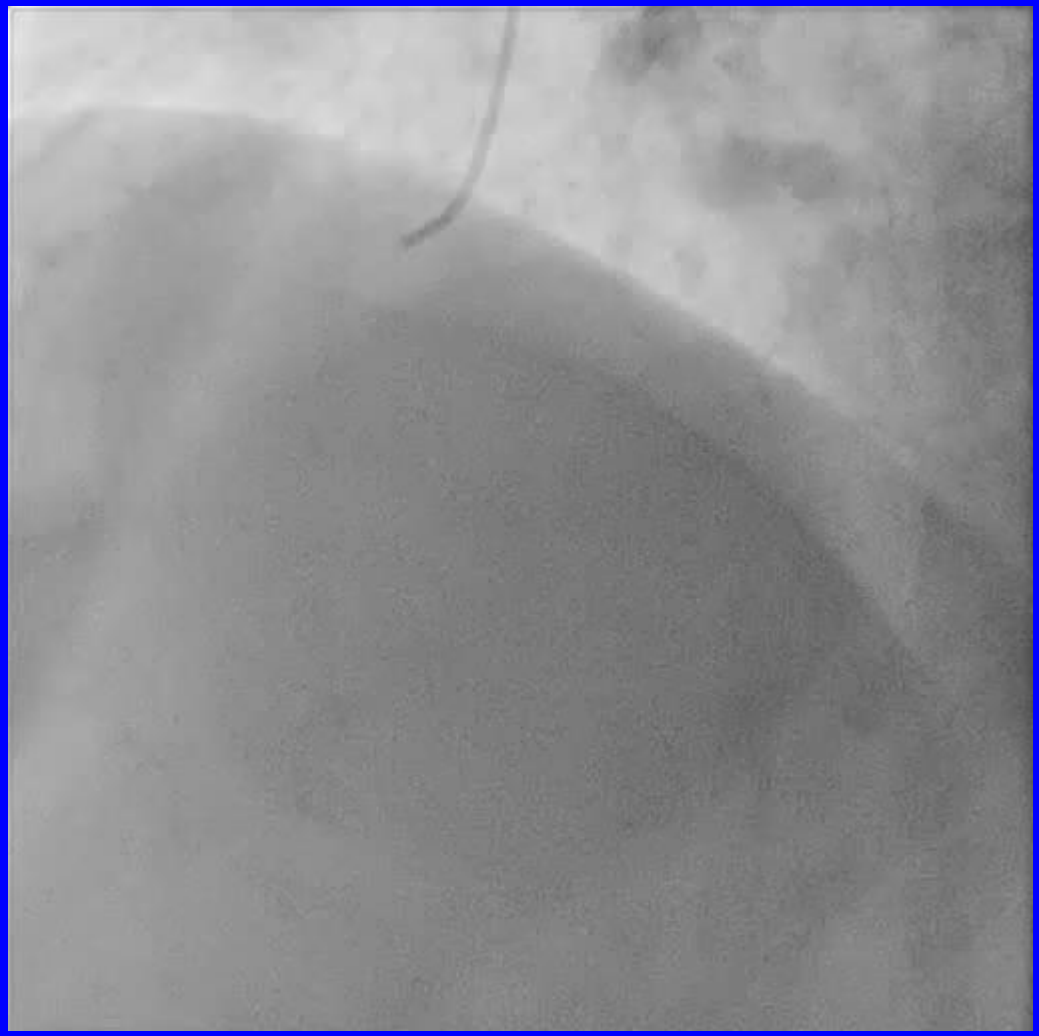
- Intense pain, diaphoretic
- Pulse 90’, BP 140/90
- ECG- ST elevation V1-6, I, aVL
- Dg- **Acute extensive anterior STEMI**
- Referred directly for PPCI
- While on the cath. Lab. the pain abates and ST elevation resolves on monitor.

ECG

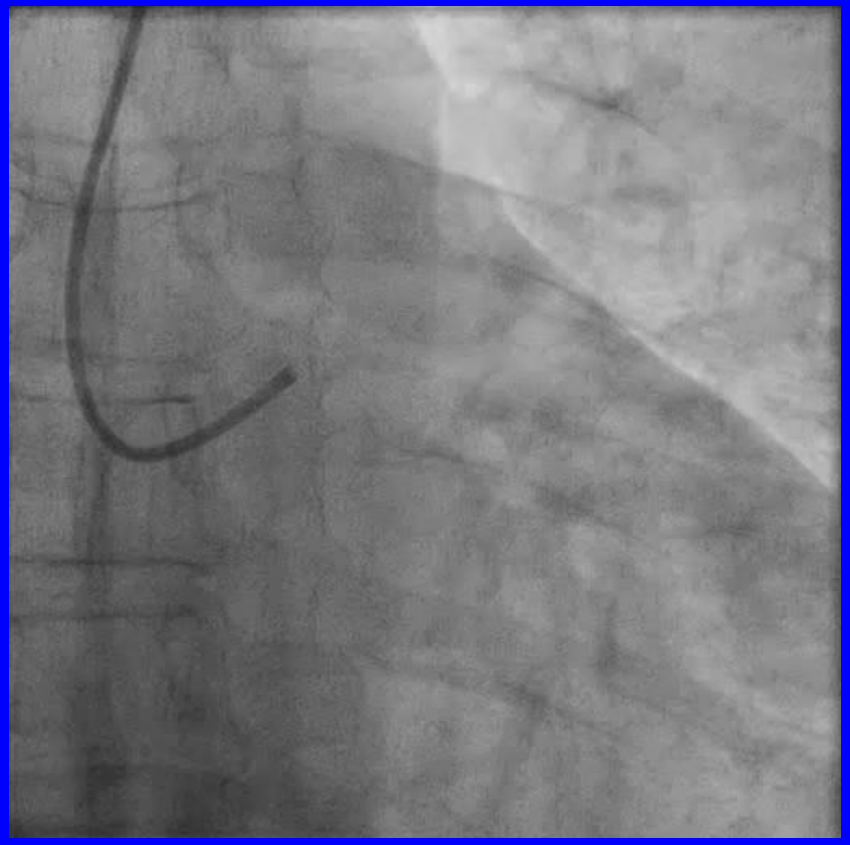
On admission

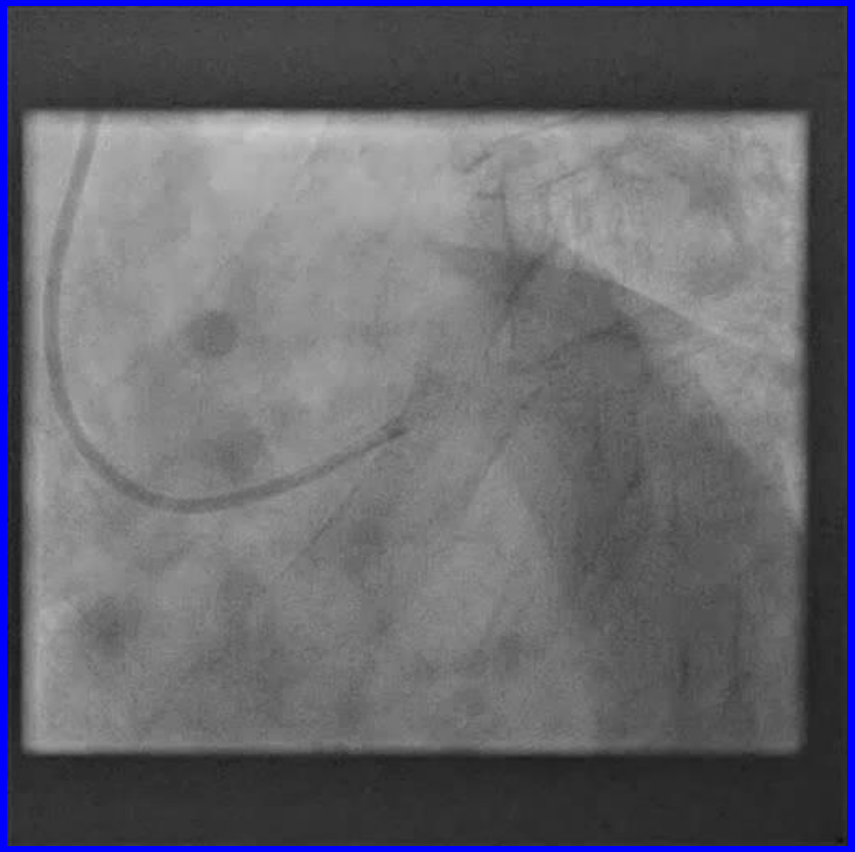
- Intense pain, diaphoretic
- Pulse 90’, BP 140/90
- ECG- ST elevation V1-6, I, aVL
- Dg- **Acute extensive anterior STEMI** (prasugrel)
- Referred directly for PPCI
- While on the cath. Lab. the pain abates and ST elevation resolves on monitor.

Angiogram



Angiogram





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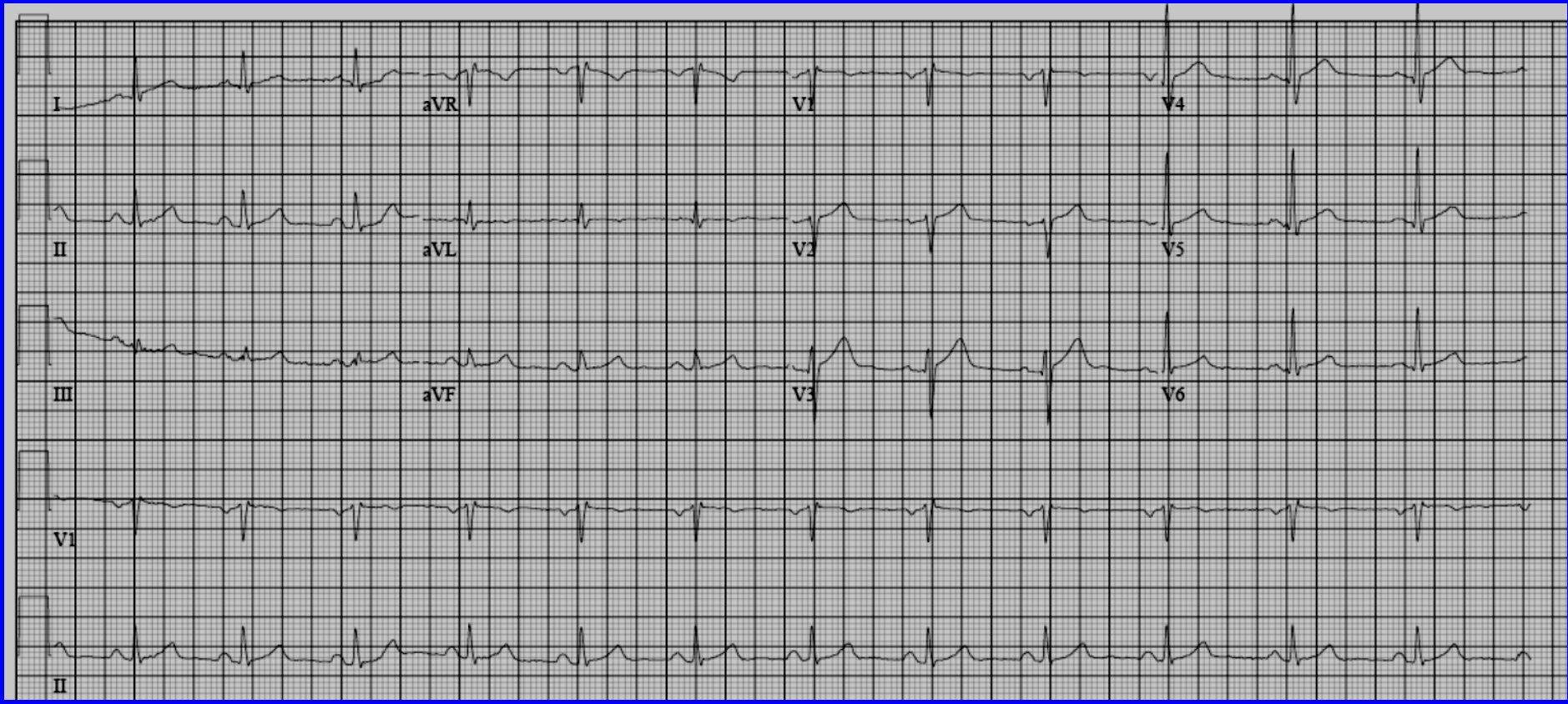
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II

Objectives

- How important is to achieve effective platelet inhibition @ PPCI ?
- Should DAPT be given ASAP in STEMI Pt's undergoing PPCI (FMC) ?
- If yes, What DAPT should be given?
- What should be done if a patient on DAPT required immediate CABG ?
- Non urgent CABG (invasive procedure)?

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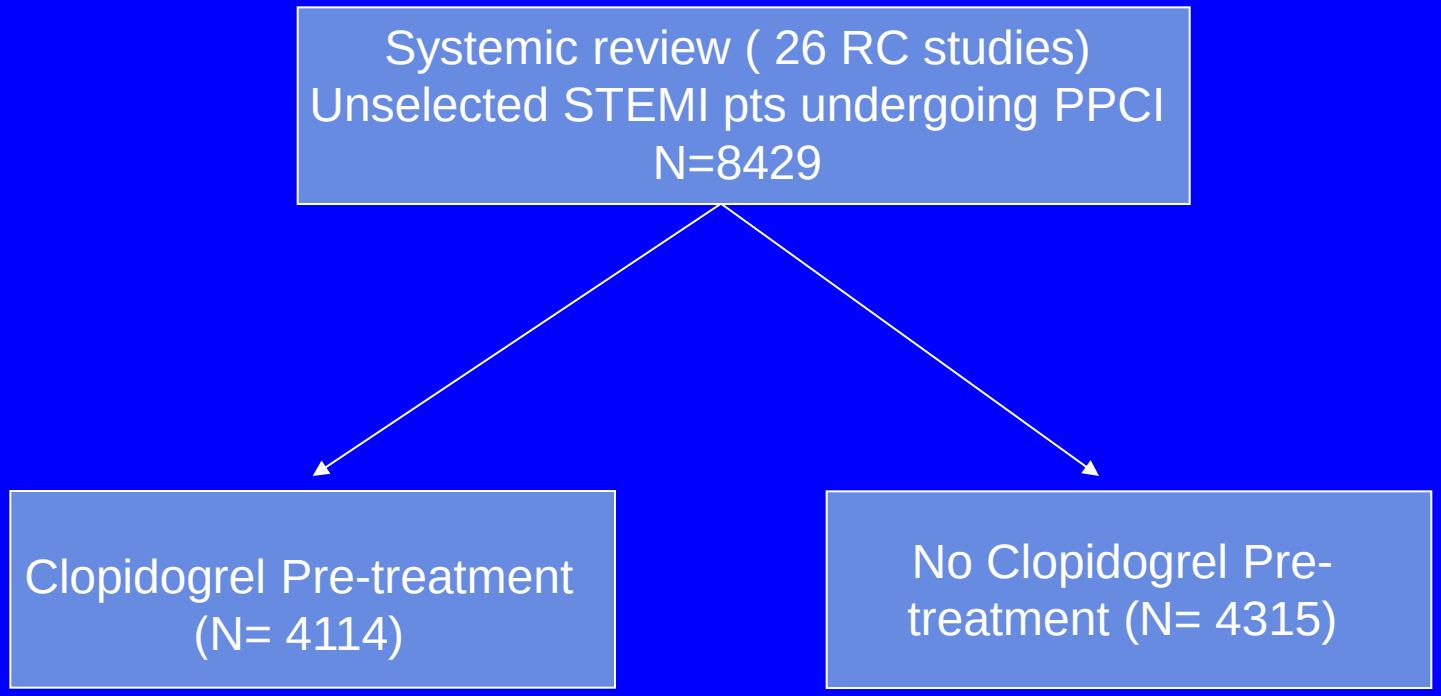
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

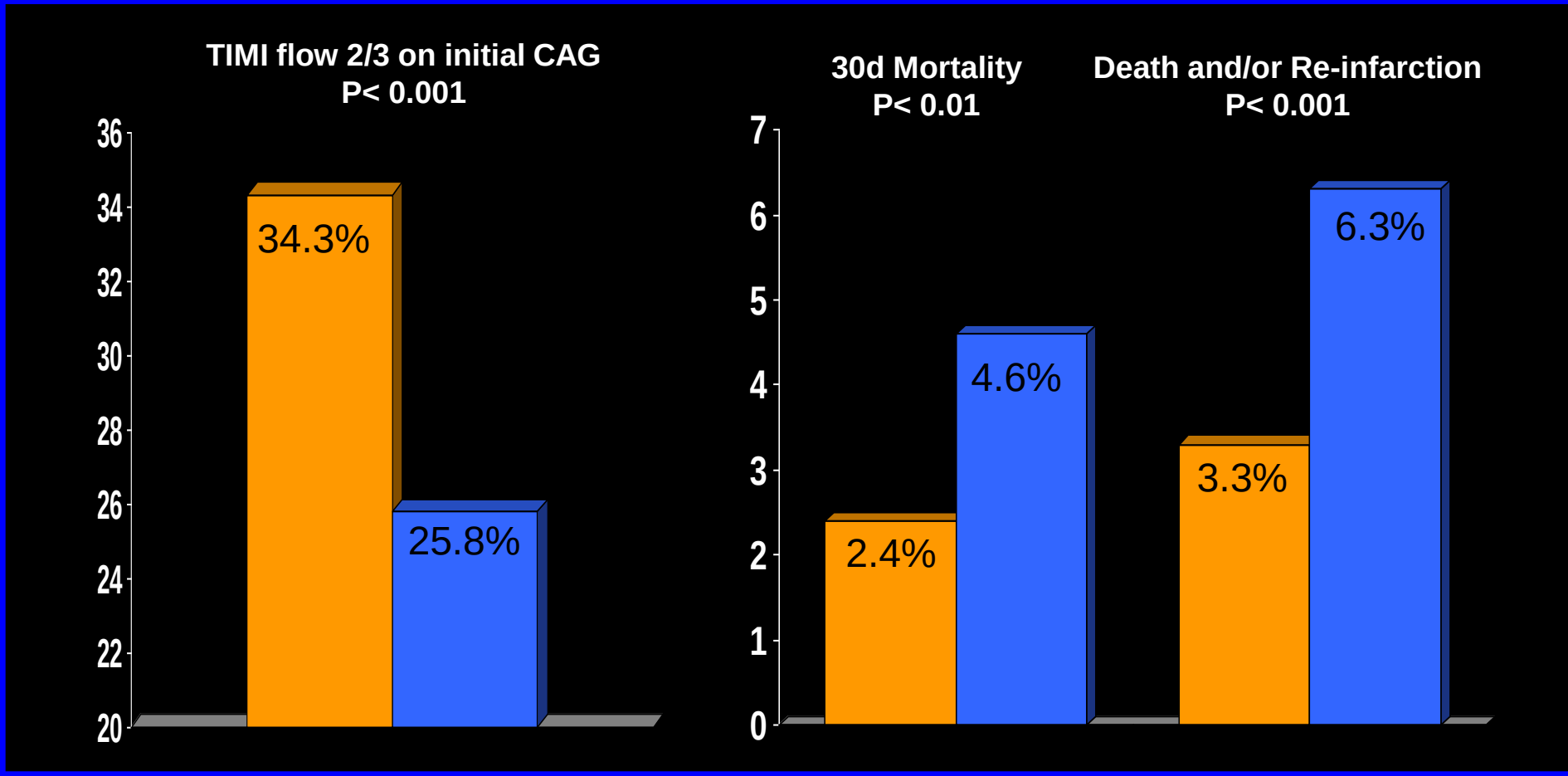
Impact of Pretreatment With Clopidogrel on Initial Patency and Outcome in Patients Treated With Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction : A Systematic Review

Pieter J. Vlaar, Tone Svilaas, Kevin Damman, Bart J.G.L. de Smet, Jan G.P. Tijssen, Hans L. Hillege and Felix Zijlstra



Vlaar et al. 2008 circulation; 118:1828-1836

Effect of Clopidogrel Pre-treatment on Early Reperfusion and Clinical Outcome

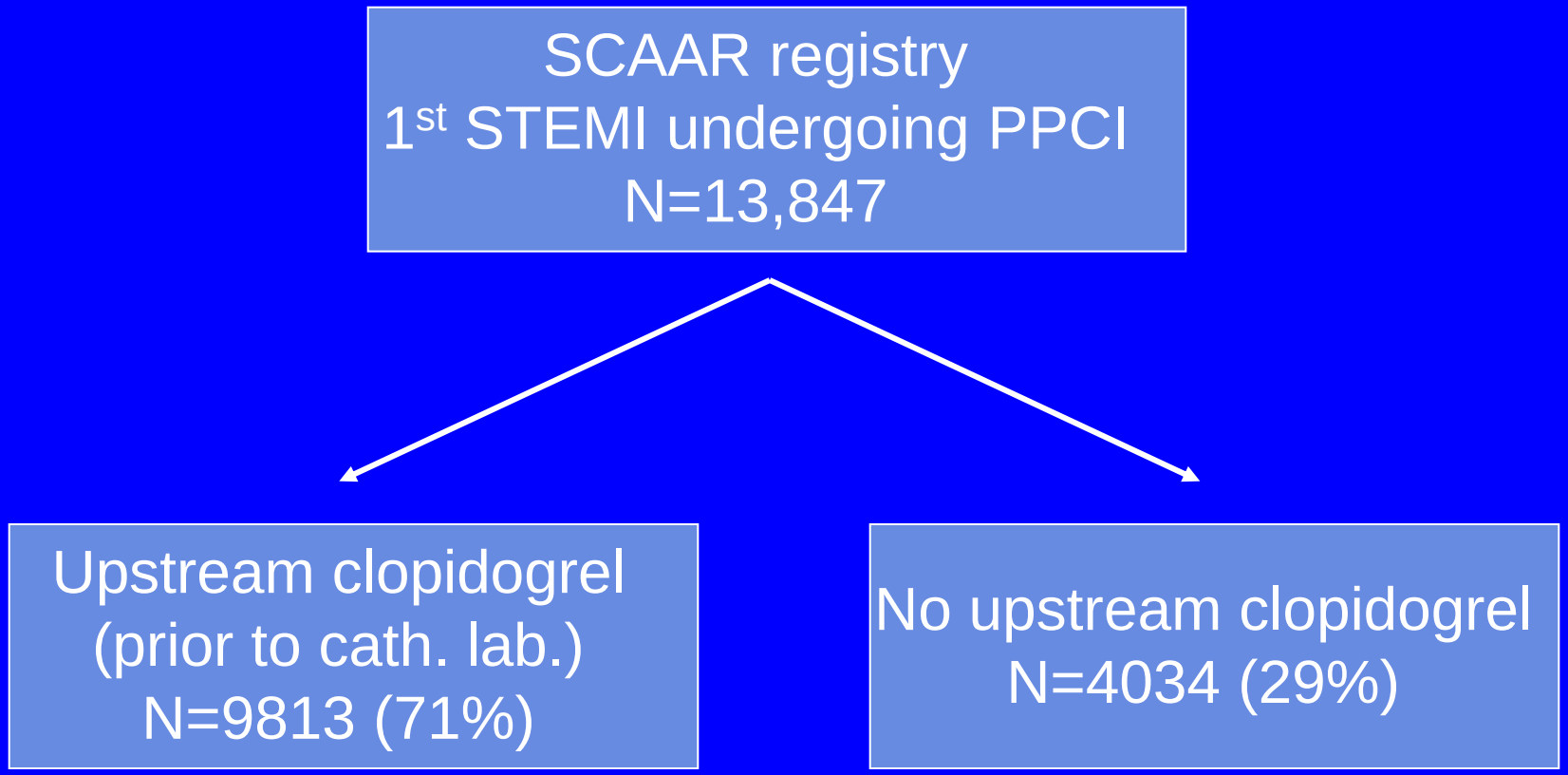


European Heart Journal (2011) **32**, 2989–2997
doi:10.1093/eurheartj/ehr202

CLINICAL RESEARCH

Effect of upstream clopidogrel treatment in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

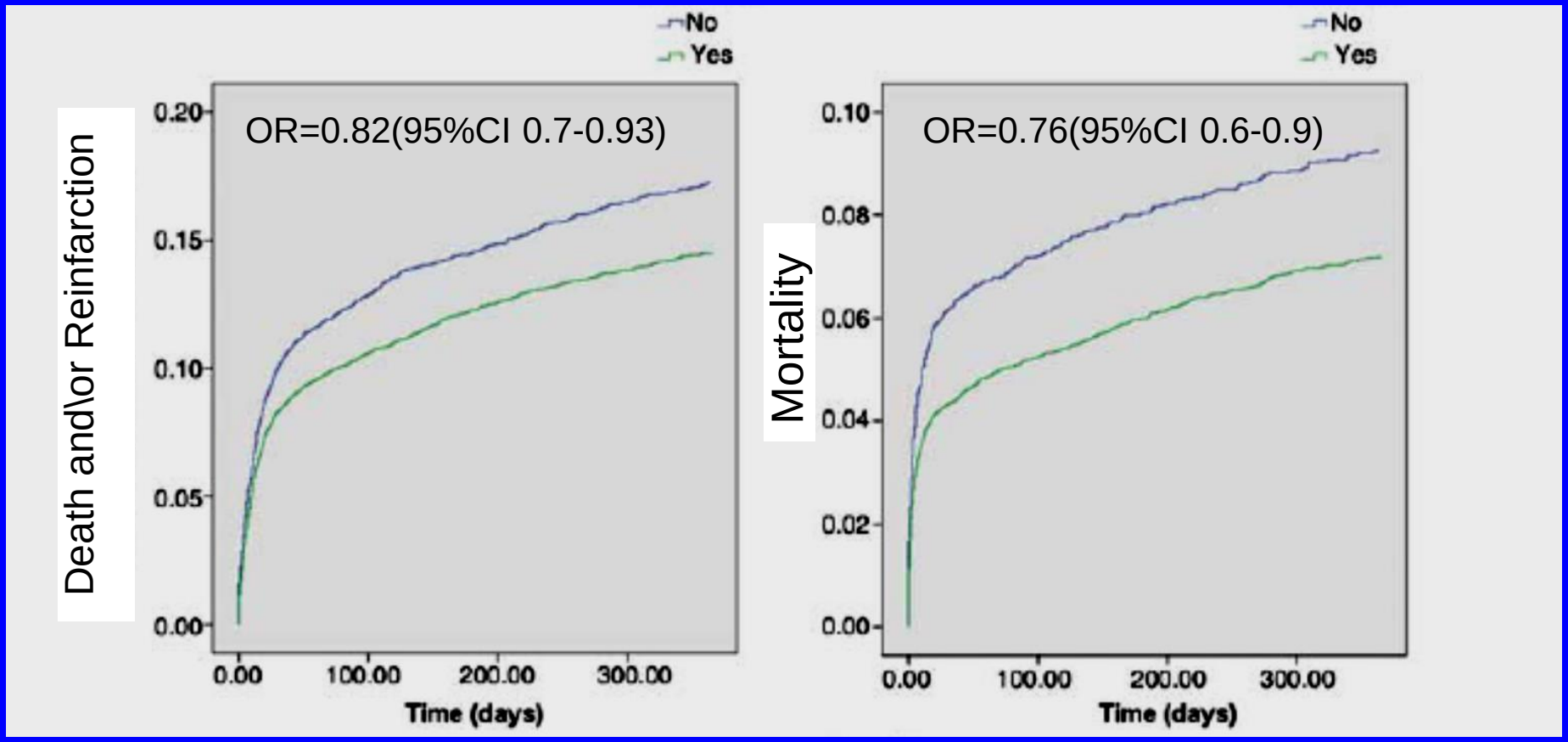
Sasha Koul[1], J. Gustav Smith[1,2], Fredrik Scherstén[1], Stefan James[3], Bo Lagerqvist[3], and David Erlinge[1]*



Koul et al. Eur Heart J 2011; 32: 2989-2997

Effect of Clopidogrel Up-Stream on Mortality and Re-infarction*

* Propensity Score-Adjusted Incidence



Clopidogrel upstream

No clopidogrel Upstream

Koul et al. Eur Heart J 2011; 32: 2989-2997

Objectives

- How important is to achieve effective platelet inhibition @ PPCI ?
- Should DAPT be given ASAP in STEMI Pt's undergoing PPCI (FMC) ?
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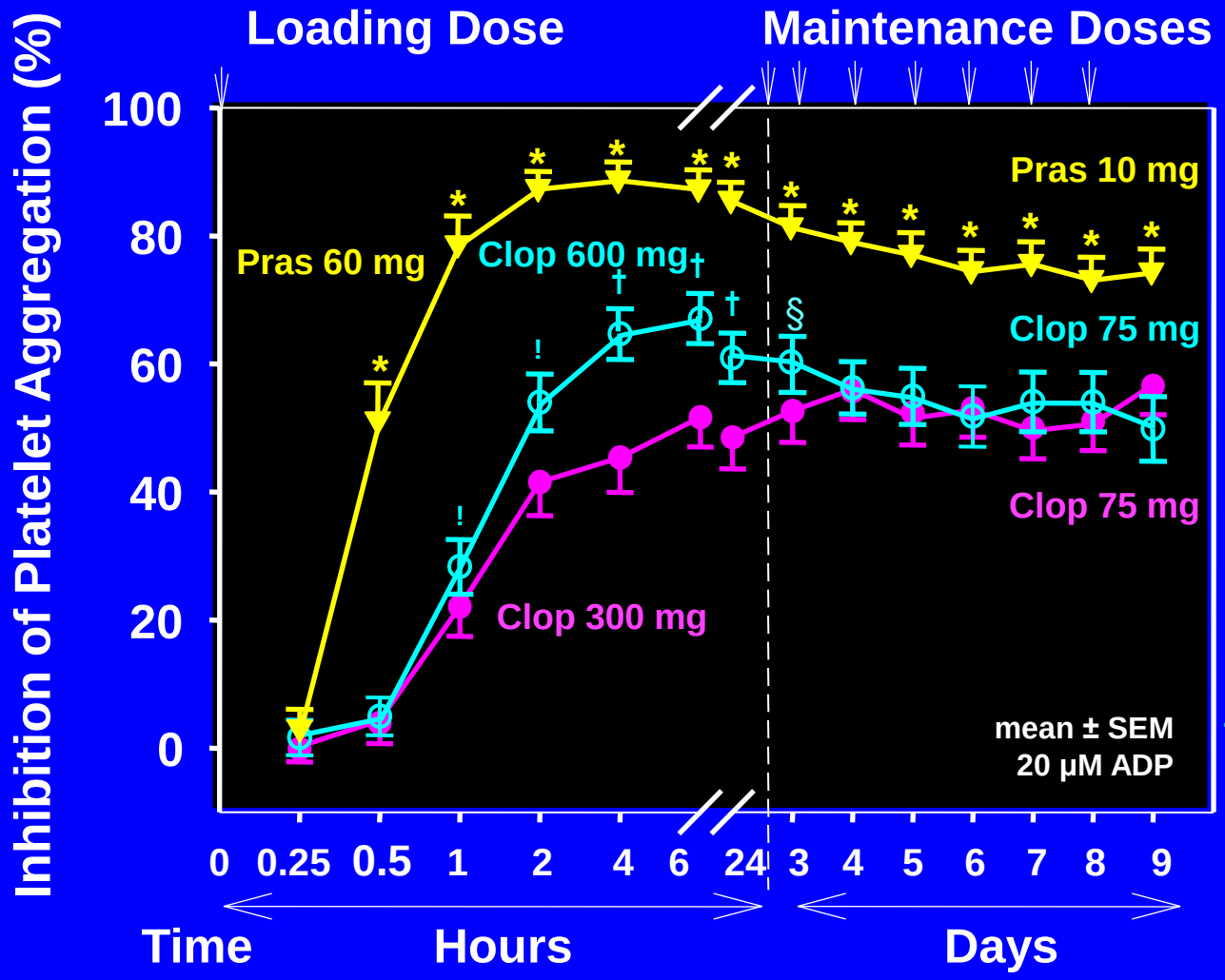
- What should be done if a patient on DAPT required immediate CABG ?
- Non urgent CABG (invasive procedure)?

Prasugrel vs. Clopidogrel Loading Dose: Higher IPA During



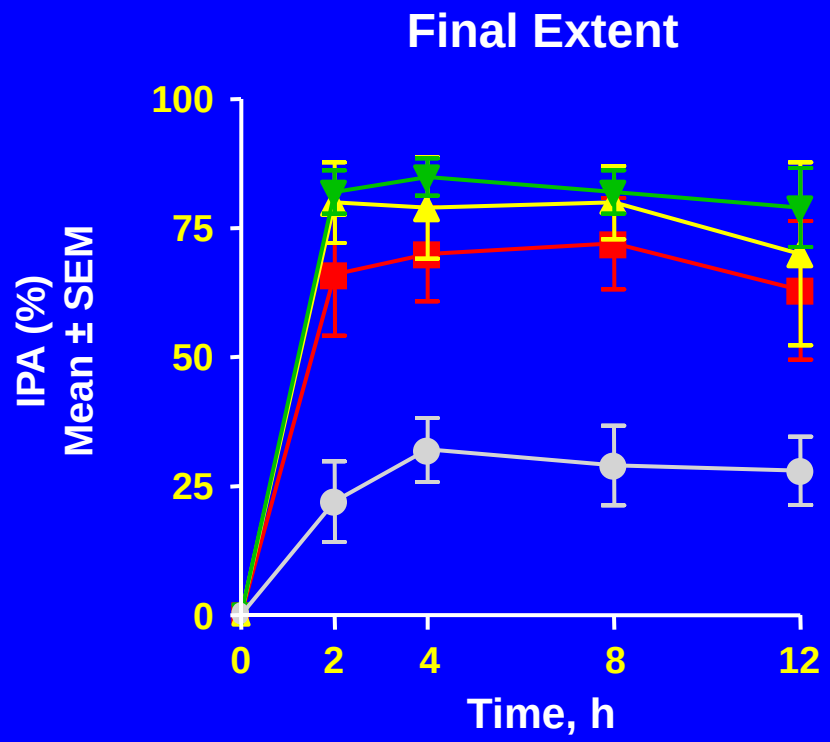
*p<0.001 vs. Clop 300 mg or 600 mg LD

†p<0.001 vs. Clop 300

!p<0.05 vs. Clop 300

§p<0.05 vs Clop 300/75

IPA on Day 1 Clopidogrel Naive Patients

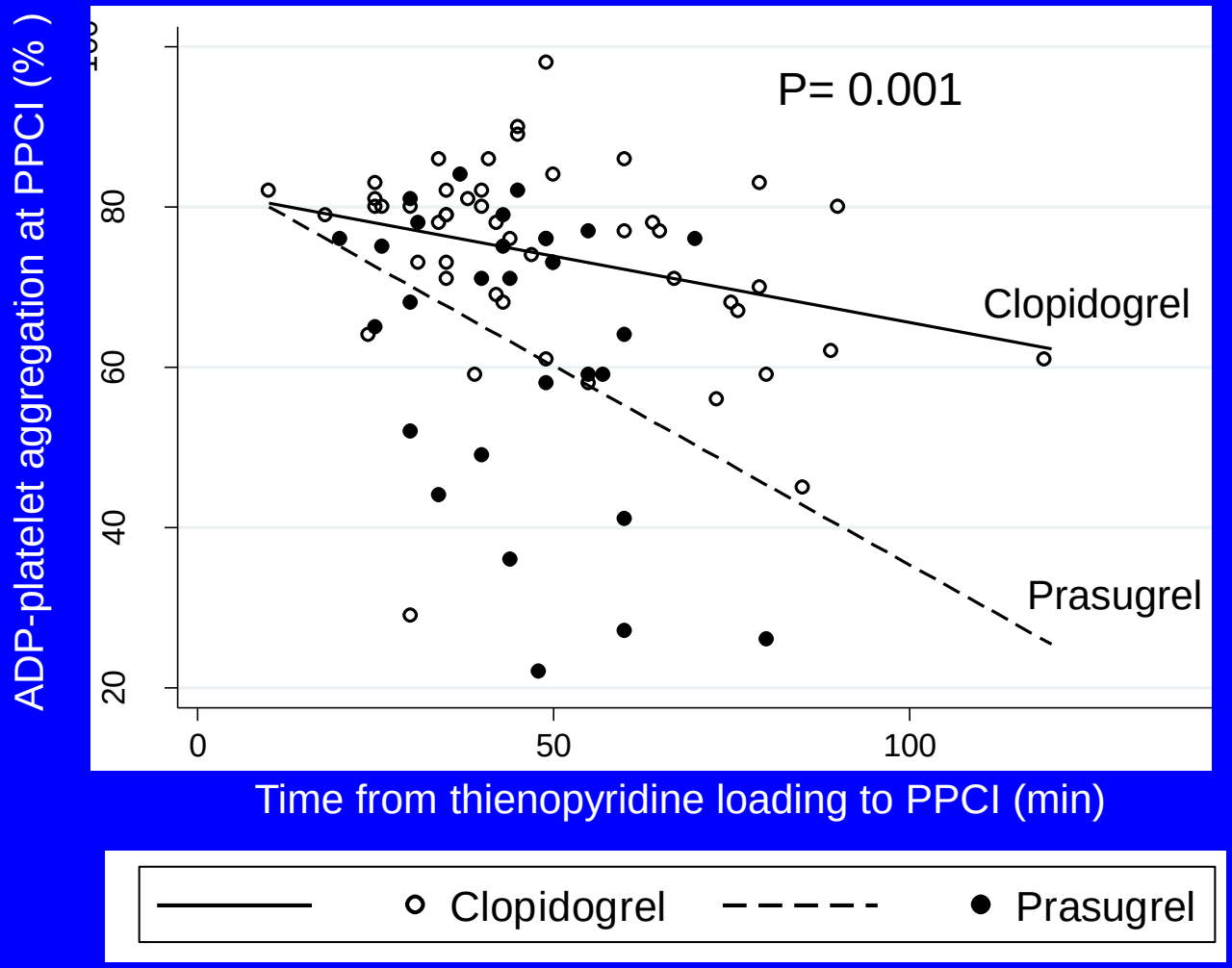


Ticagrelor 90 mg Ticagrelor 180 mg Ticagrelor 270 mg CLOP 300 mg

P<0.0176 for all AZD6140 groups vs clopidogrel at 4 h

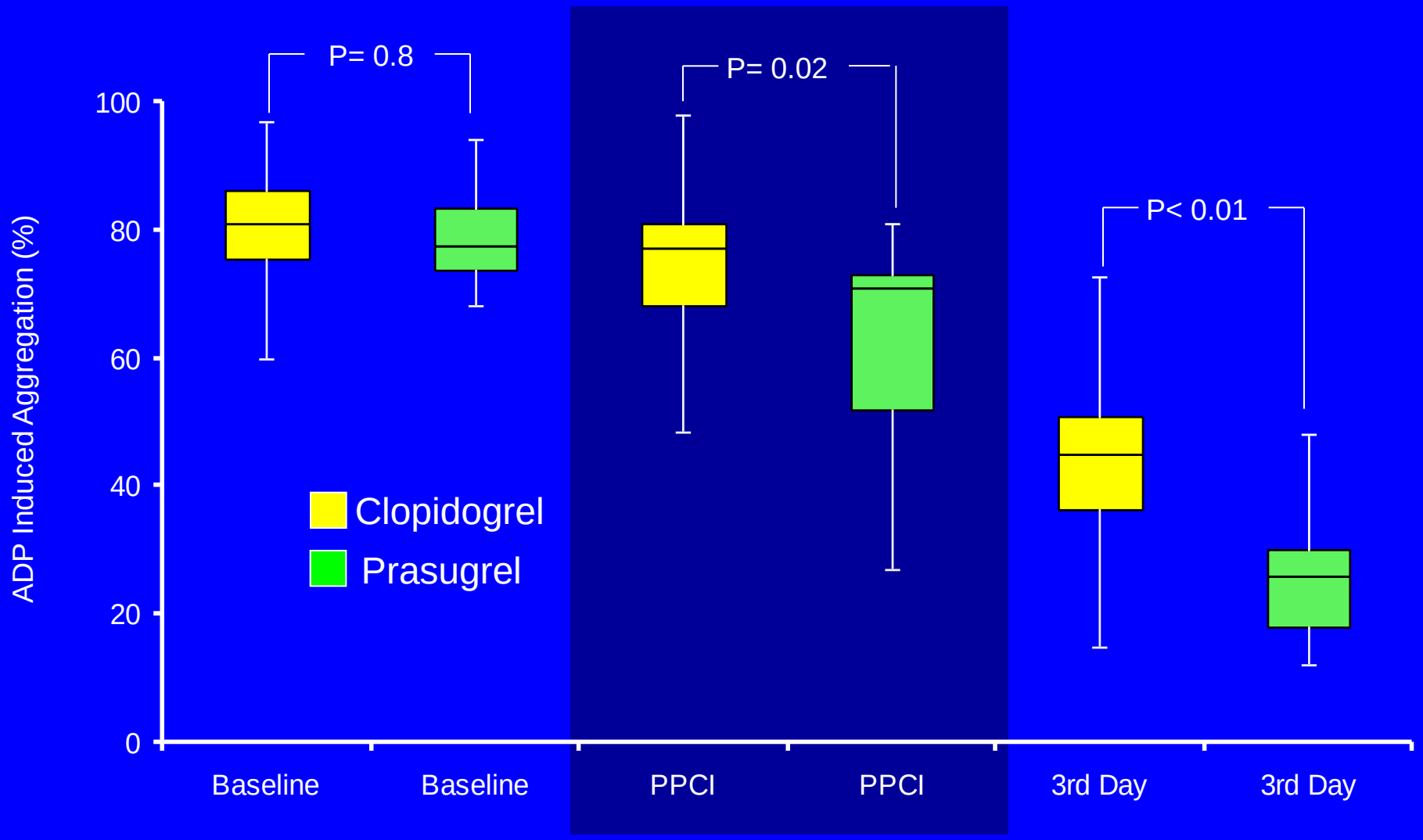
P<0.0002 for all AZD6140 groups vs clopidogrel at 4 h

Platelet Reactivity @ PPCI According to the Time Elapsed from Thienopyridine Loading to PPCI



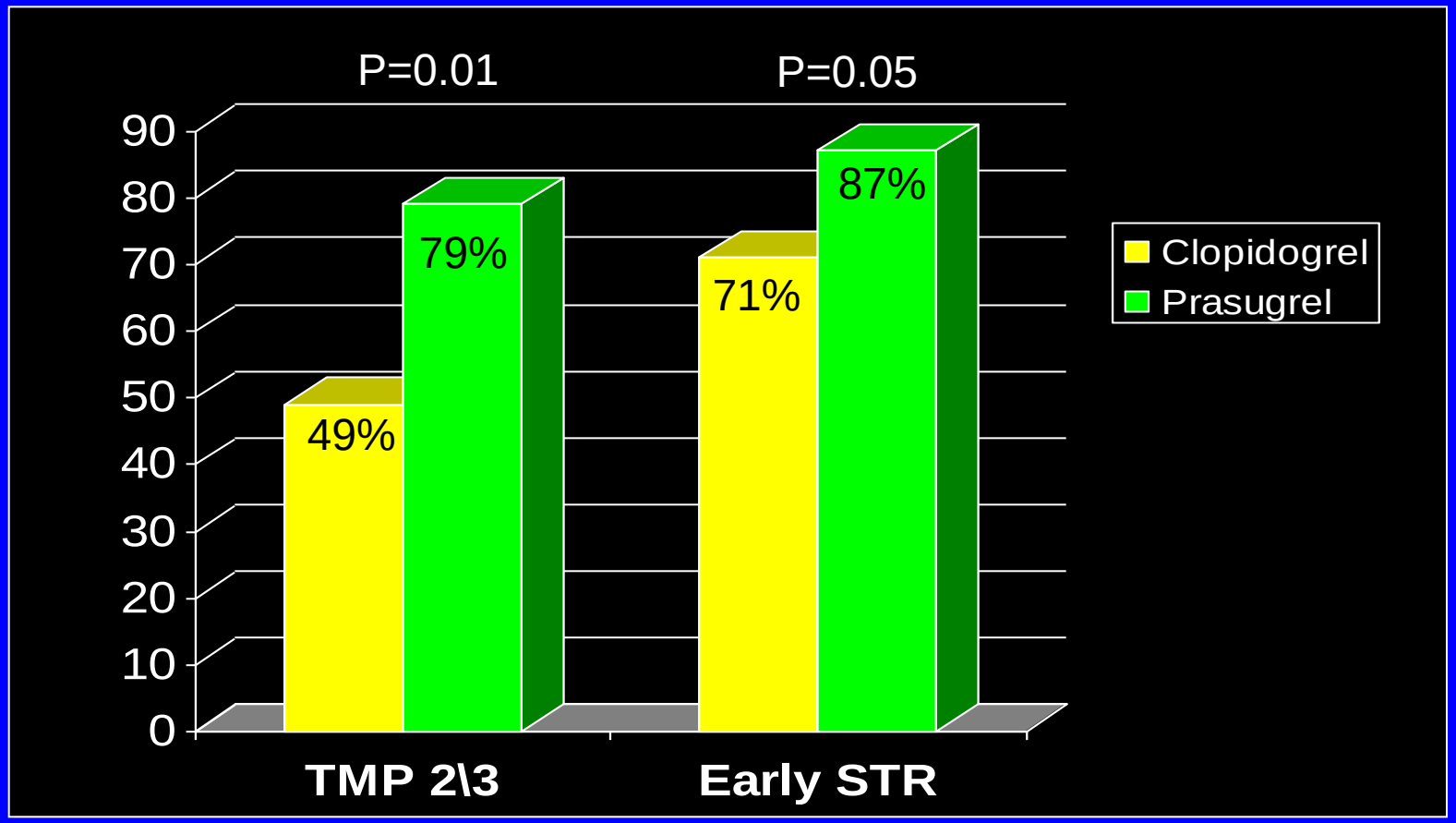
Matetzky et al. ACC 2012

ADP Induced Platelet Aggregation



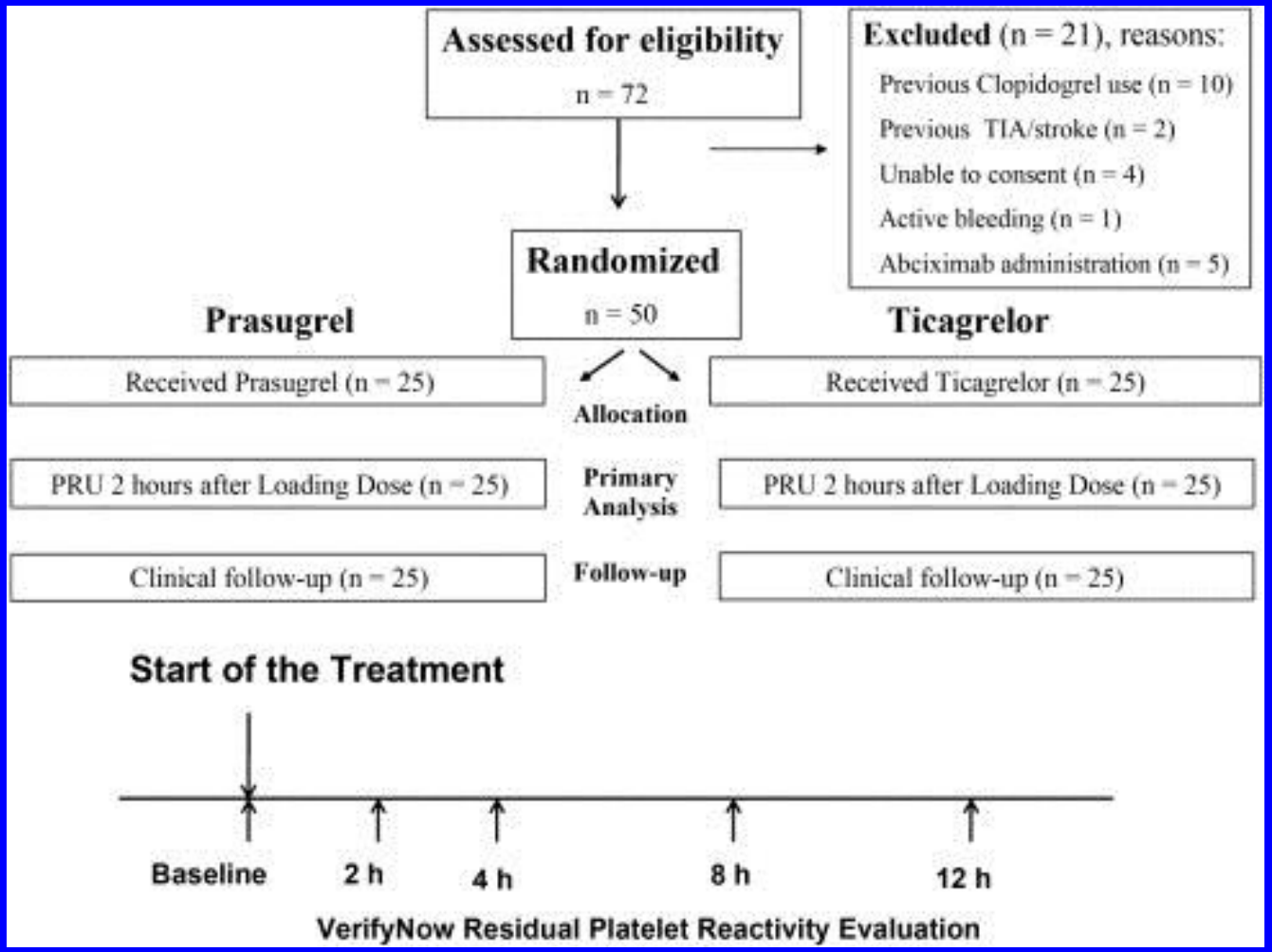
Matetzky et al. ACC 2012

Indices of Myocardial Reperfusion in STEMI Patients Undergoing PPCI



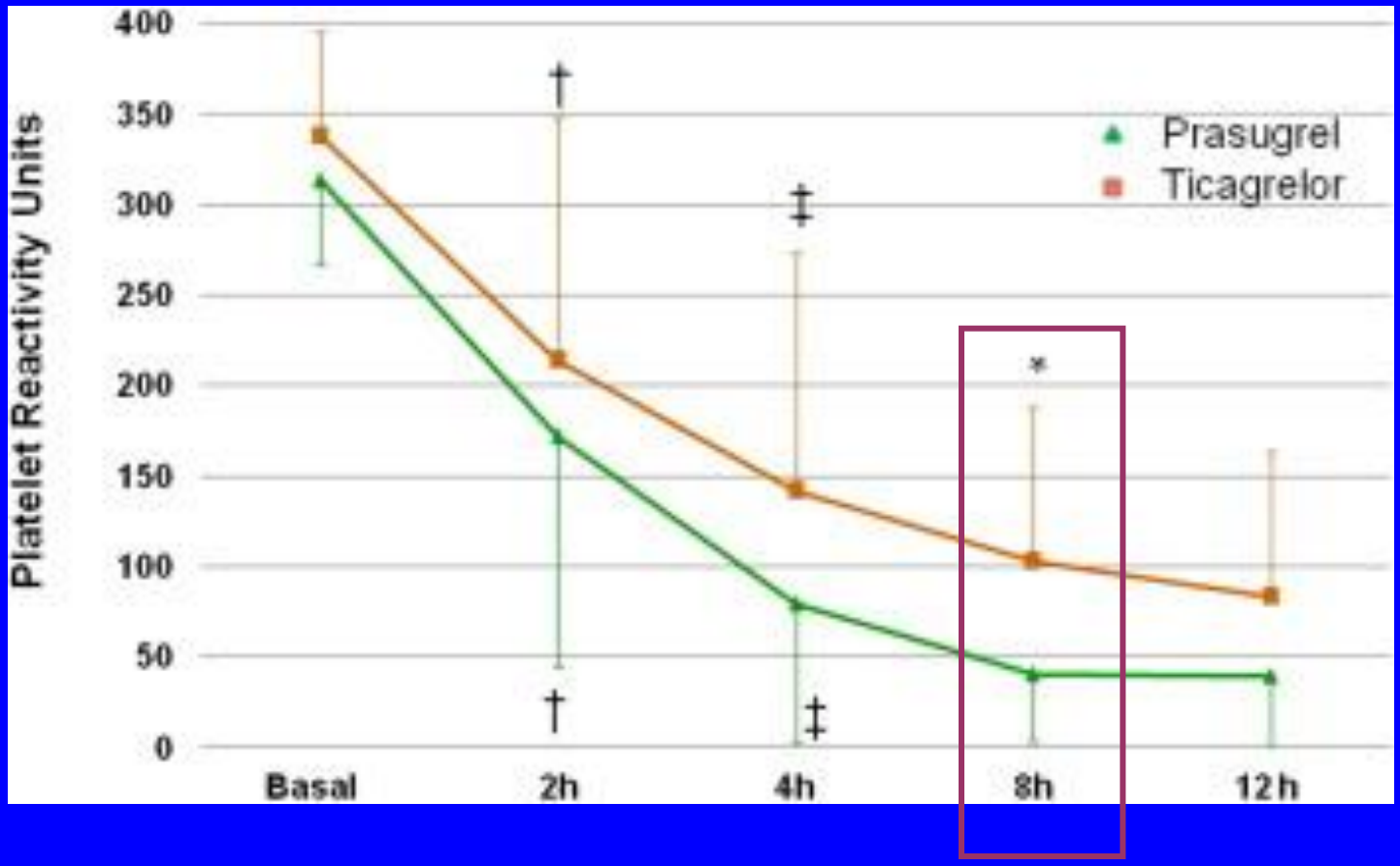
Matetzky et al. ACC 2012

RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study



Parodi G. JACC 2013 (Apr)16 ;61(15):1601-6

Kinetics of Platelet Inhibition Over Time Residual platelet reactivity values assessed by platelet reactivity units VerifyNow at baseline and .2, 4, 8, and 12 h after drug loading

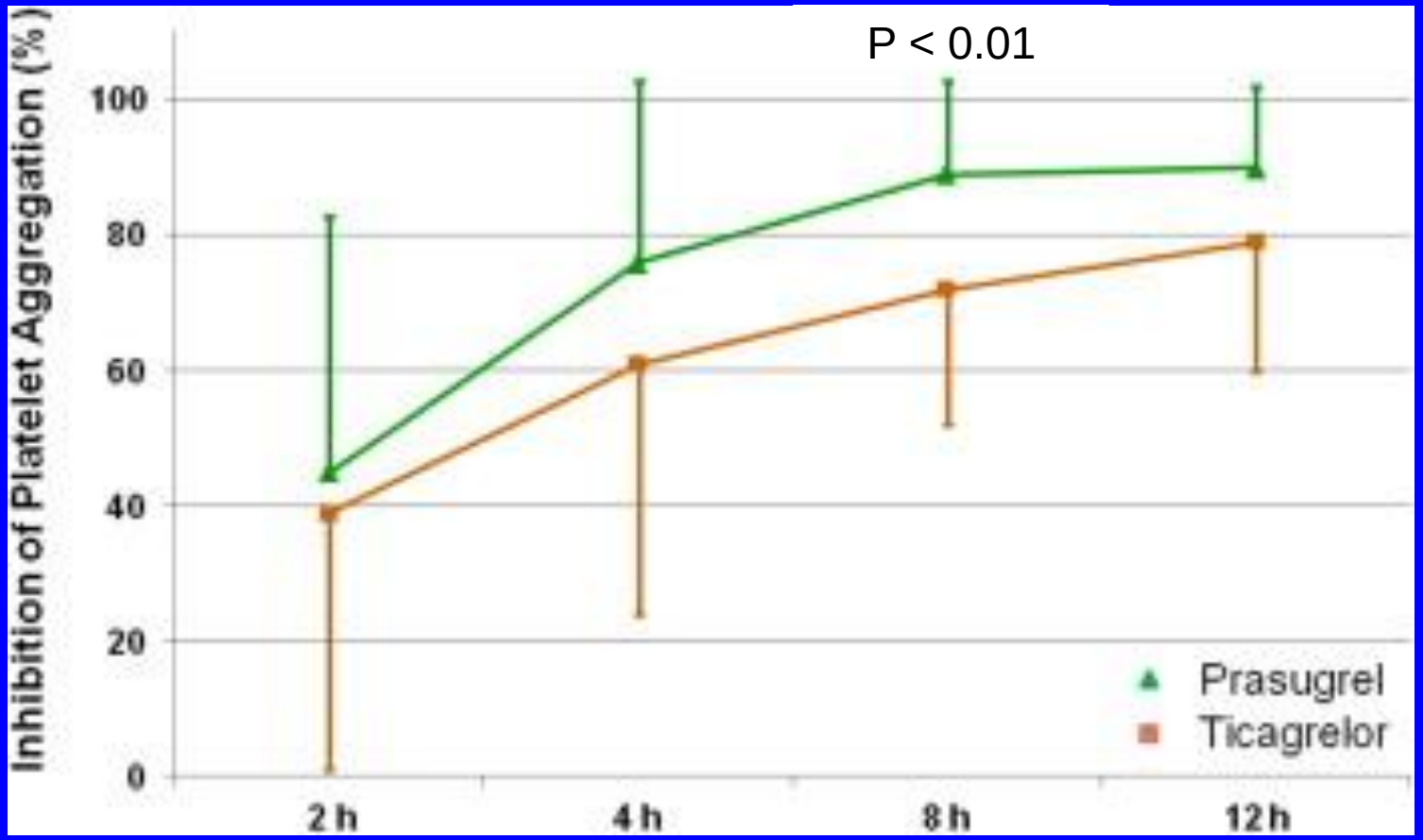


*p < 0.01 versus Ticagrelor.

†p < 0.01 versus baseline, ‡p < 0.01 versus 2 h.

Parodi G. JACC 2013 (Apr)16 ;61(15):1601-6

Inhibition of Platelet Aggregation by VerifyNow at 2, 4, 8, and 12 h after drug loading dose



Parodi G. JACC 2013 (Apr)16 ;61(15):1601-6

Objectives

- How important is to achieve effective platelet inhibition @ PPCI ?
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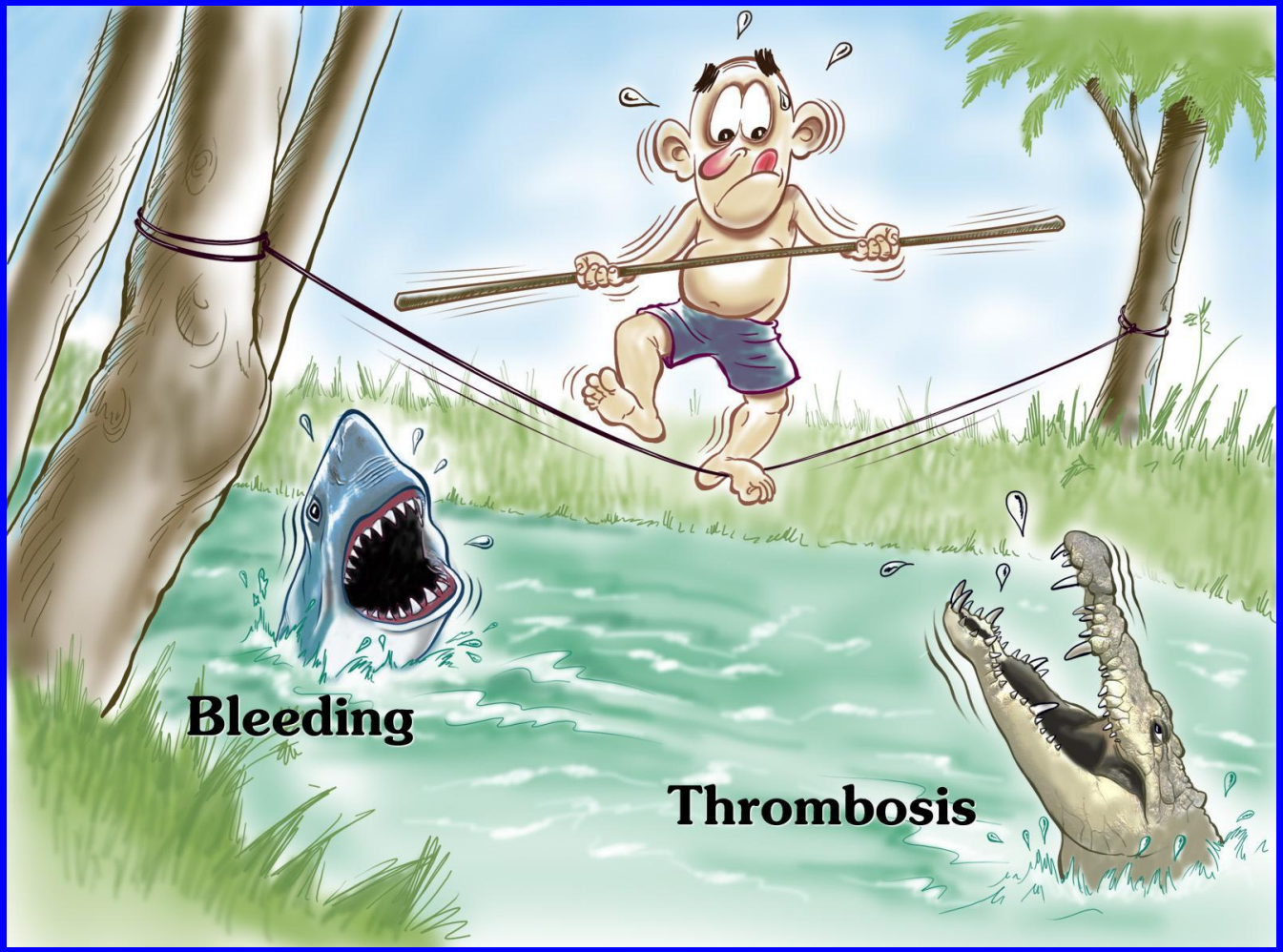
Bleeding
Thrombosis

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Vol. 59, No. 25, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2012.02.042

CME

Recovery of Platelet Function After Discontinuation of Prasugrel or Clopidogrel Maintenance Dosing in Aspirin-Treated Patients With Stable Coronary Disease

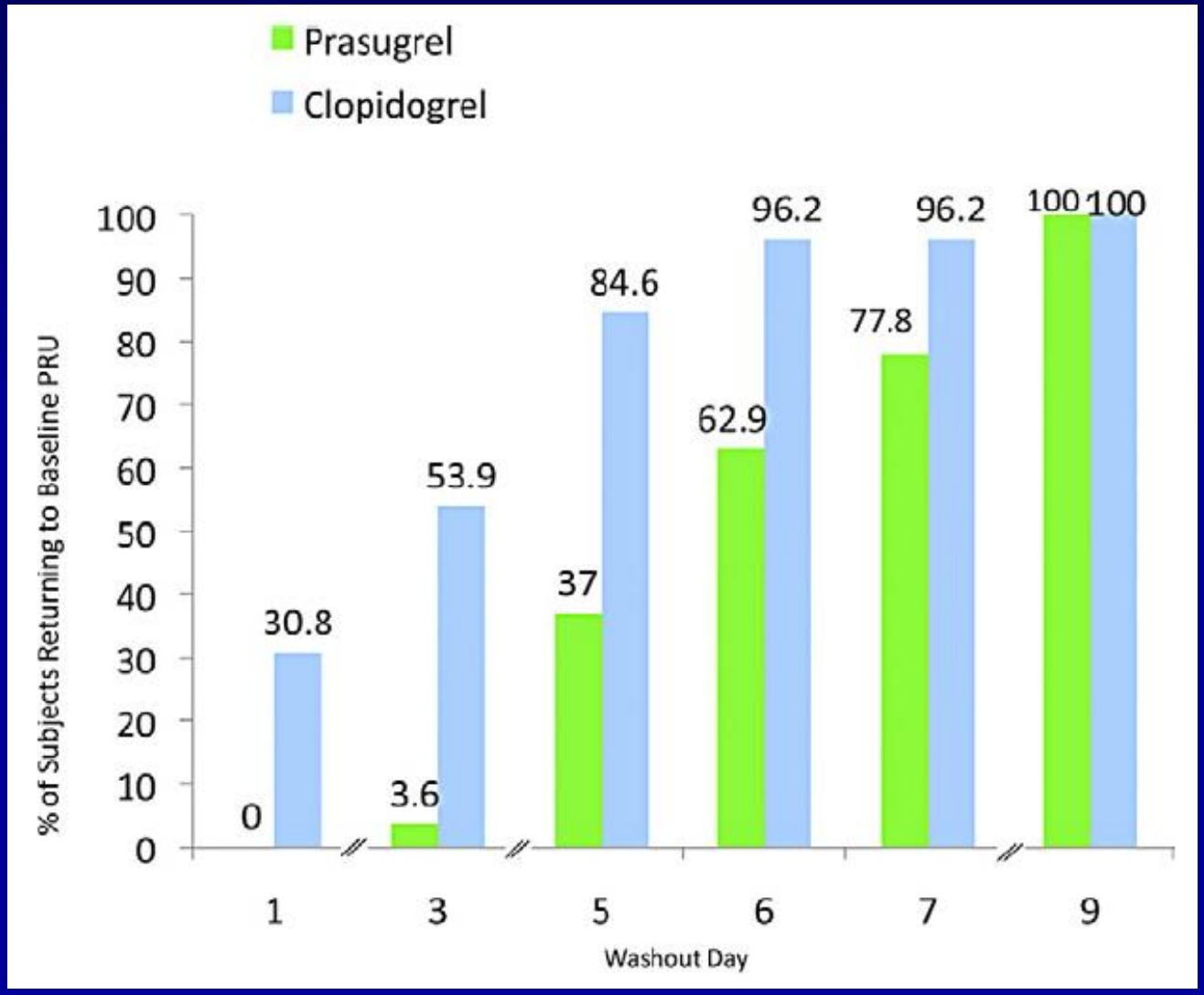
The Recovery Trial

Matthew J. Price, MD,* James S. Walder, MD,† Brian A. Baker, PharmD,‡
Darell E. Heiselman, DO,§ Joseph A. Jakubowski, PhD,§ Douglas K. Logan, MD,‖
Kenneth J. Winters, MD,§ Wei Li, PhD,‡ Dominick J. Angiolillo, MD, PhD¶

La Jolla, California; Rapid City, South Dakota; Parsippany, New Jersey; Indianapolis, Indiana; Cincinnati, Ohio; and Jacksonville, Florida

Price M et al. JACC 2012 June;59 : 2338-43

Proportion of Pts Returning to Baseline Reactivity

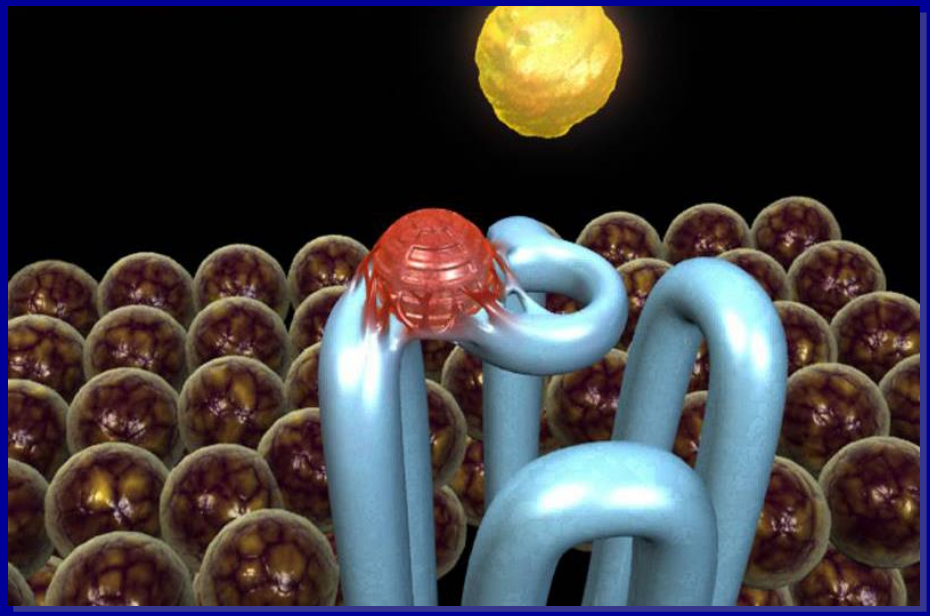


Price M et al. JACC 2012 June;59 : 2338-43

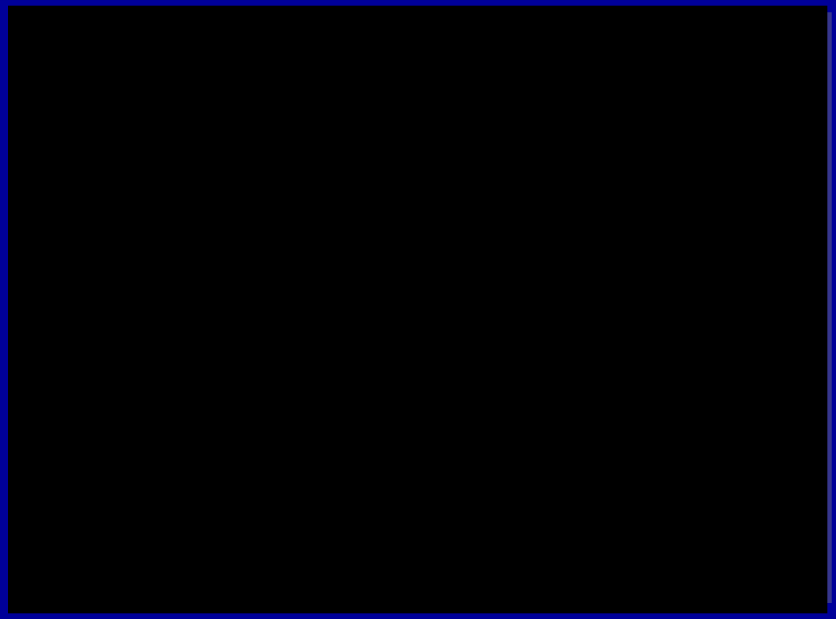
- Thienopyridines bind ***covalently (irreversibly)*** to P2Y12 ADP binding site, rendering the receptors permanently inactivated

- Ticagrelor binds directly to $P2Y_{12}$ receptors and ***reversibly*** interacts with the receptor, to prevent platelet activation and aggregation

Thienopyridines-Irreversible inhibition



Ticagrelor-Reversible inhibition



P Savi, et al. Proc Natl Acad Sci USA 2006; 103:11069-11074.

Journal of Thrombosis and Haemostasis, **5**: 82–90

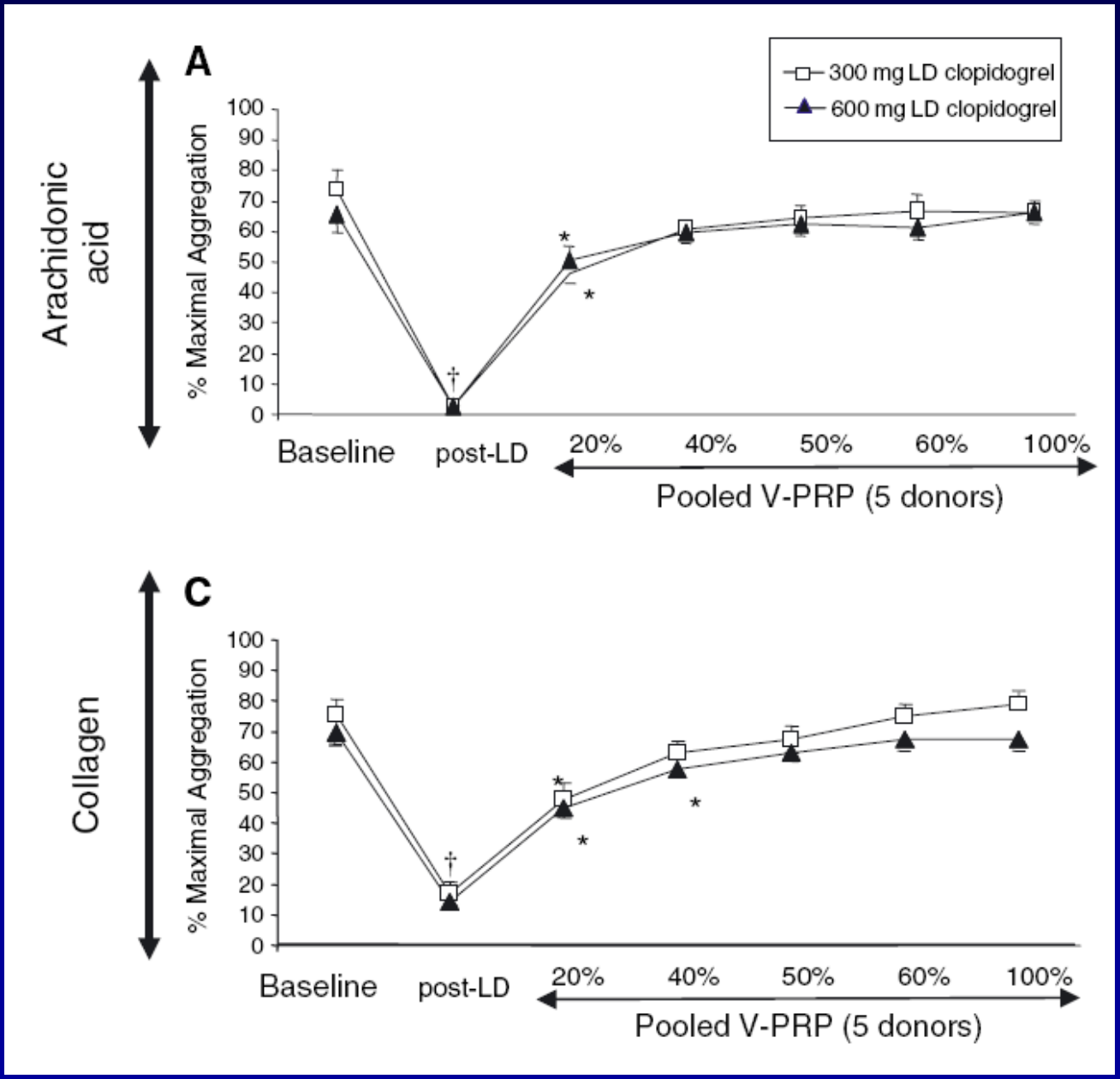
ORIGINAL ARTICLE

Normalization of platelet reactivity in clopidogrel-treated subjects

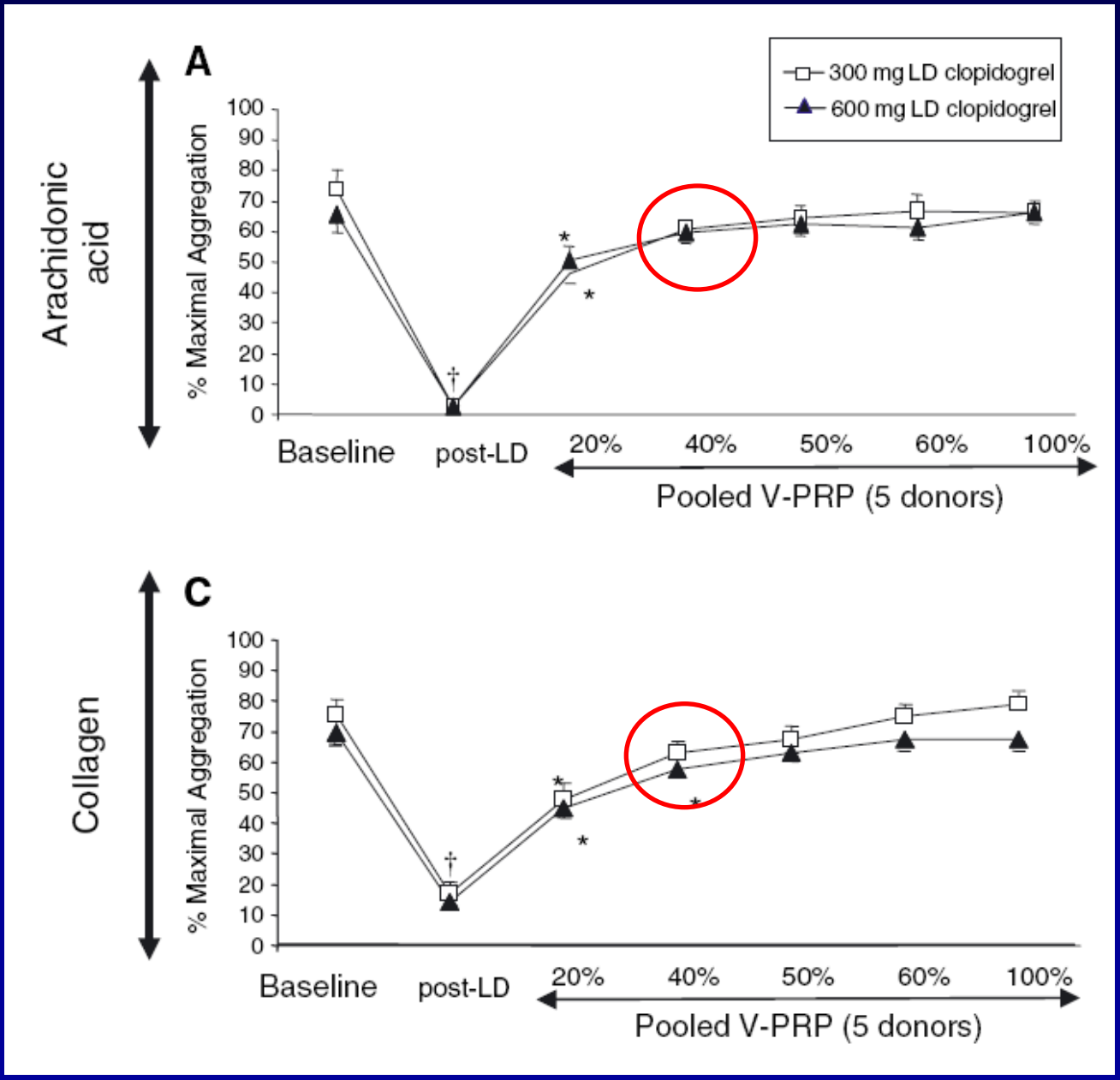
G. VILAHUR,*[1] B. G. CHOI,*†[1] M. U. ZAFAR,* J. F. VILES-GONZALEZ,* D. A. VORCHHEIMER,† V. FUSTER† and J. J. BADIMON*†

**Cardiovascular Biology Research Laboratory; and †Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY, USA*

Vilahur et al J. Thromb. Haemostasis 2007;5:82-90



Vilahur et al J. Thromb. Haemostasis 2007;5:82-90



Vilahur et al J. Thromb. Haemostasis 2007;5:82-90

Mean platelet count ($n = 11$): 250×10^6

% Added pooled V-PRP	Platelet units*	Platelet pools†
20	5	1
40	10	2
50	12.5	2–3
60	15	3

*Platelet units: one platelet unit increases platelet count by 10 000 μL.
†Platelet pools: five platelet units = one platelet pool.

Vilahur et al J. Thromb. Haemostasis 2007;5:82-90

E343
JACC March 27, 2012
Volume 59, Issue 13

Acute Coronary Syndromes

RESTORING PLATELET FUNCTION EX VIVO BY ADDING FRESH PLATELETS WITHIN 24 HOURS OF A PRASUGREL 60 MG LOADING DOSE

ACC Oral Contributions
McCormick Place South, S406b
Saturday, March 24, 2012, 8:39 a.m.-8:52 a.m.

Authors: *M. Urooj Zafar, Carlos Santos-Gallego, David Vorchheimer, Juan Viles-Gonzalez, Sammy Elmariah, Chiara Giannarelli, David Small, Joseph Jakubowski, Valentin Fuster, Juan Badimon, Mount Sinai School of Medicine, New York, NY, USA, Eli Lilly and Company, Indianapolis, IN, USA*

Background: ACC/AHA guidelines advise a 5-7 day wait in surgery bound ACS patients to attenuate the effects of antiplatelet therapy. To reduce bleeding risk, platelet infusion may be used in some cases but the resulting recovery of platelet function is unknown. We investigated the degree of platelet function restoration by adding fresh platelets within 24 hours (h) of a prasugrel loading dose.

Methods: Healthy subjects (n=25, 30 ± 5 years, 68% male) on ASA took 60 mg prasugrel after baseline testing with platelet aggregation (PA, ADP 20μM) and VerifyNow P2Y12 assay (VN). Fresh, concentrated platelets from untreated donors were added ex vivo to subject's blood after 2h, 6h, 12h and 24h, in volumes that raised the blood platelet counts by 40%, 60% and 80%. One sample was not supplemented (0%). Platelet function (PA and VN) in supplemented samples were compared to 0% and pretreatment baseline. Prasugrel active metabolite levels were also measured.

Results: Platelet reactivity (PA and VN) was significantly higher ($p<0.05$) in supplemented samples vs. respective 0% at all times (Figure 1, VN data not shown). Reactivity in all samples increased over time, with the sharpest increase seen from 2h to 6h. All results were significantly lower than pretreatment baseline of 65 ± 2.3.

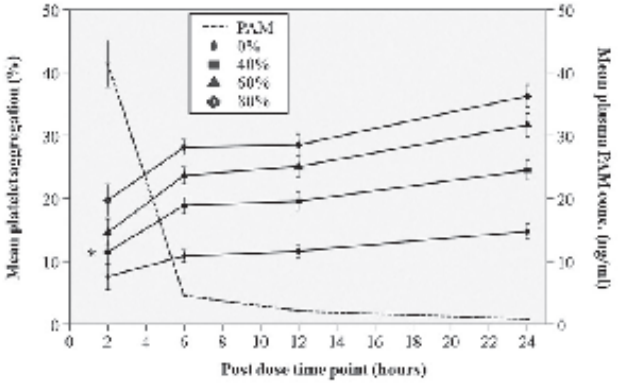
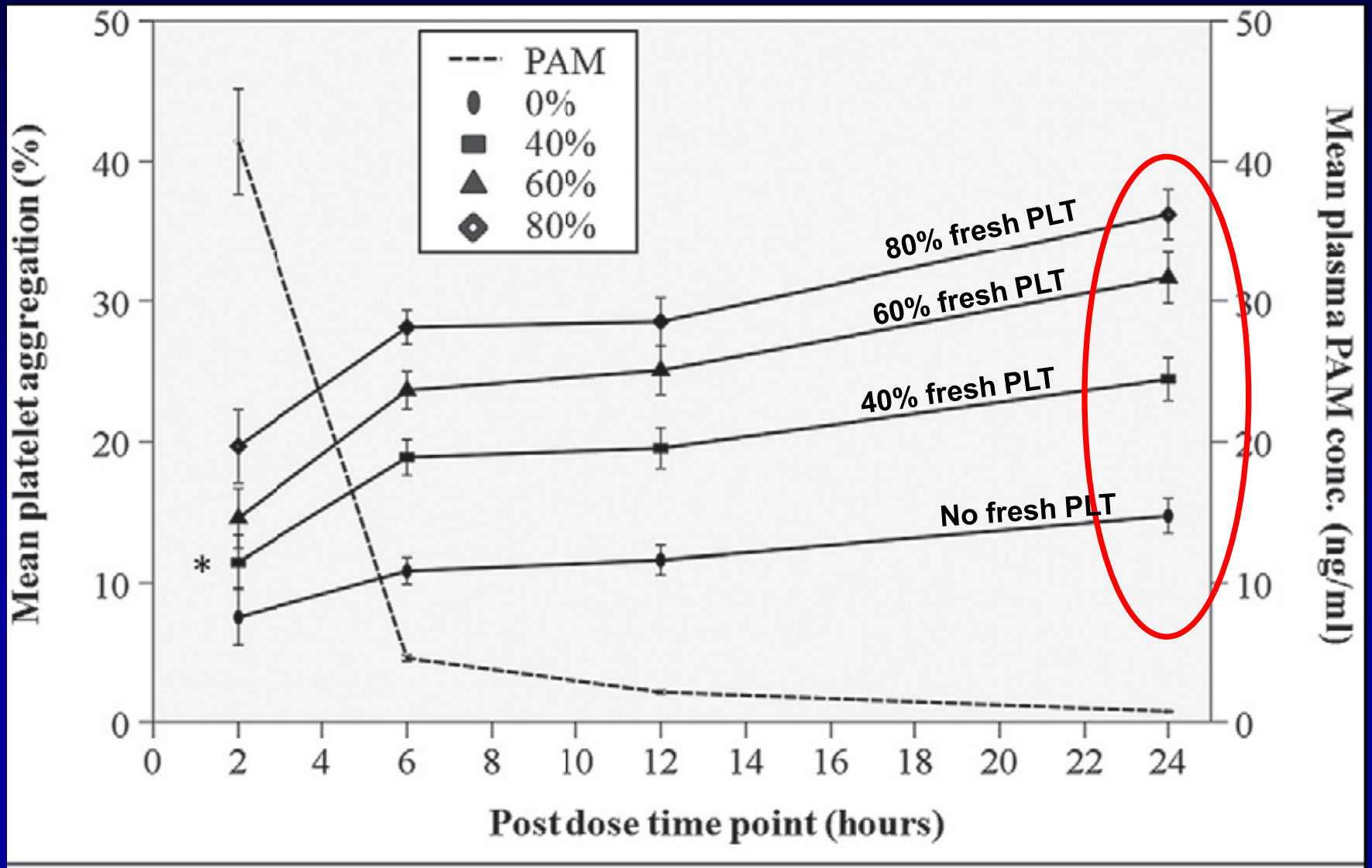


Figure 1: Platelet aggregation (mean + SE) in prasugrel-treated subjects' samples with (40%, 60% and 80%) and without (0%) added fresh platelets over 24 hours. All 40%, 60% and 80% samples are higher than 0% ($p<0.05$) except *. All samples are lower than baseline of 65% ± 2.3% ($p<0.05$). PAM - Prasugrel active metabolite (mean ± SE) shown on the right Y axis

Conclusions: After a prasugrel loading dose, significant functional recovery with platelet transfusion can be achieved by 6 hours. However, full restoration of platelet function is not feasible within 24h even with substantial platelet infusions.



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- Thienopyridines bind ***covalently (irreversibly)*** to P2Y12 ADP binding site, rendering the receptors permanently inactivated
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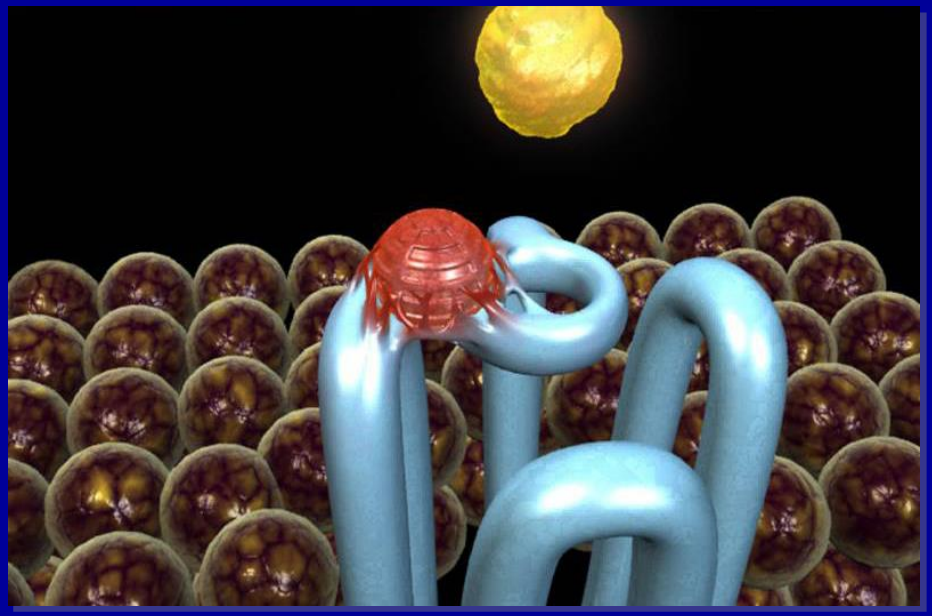
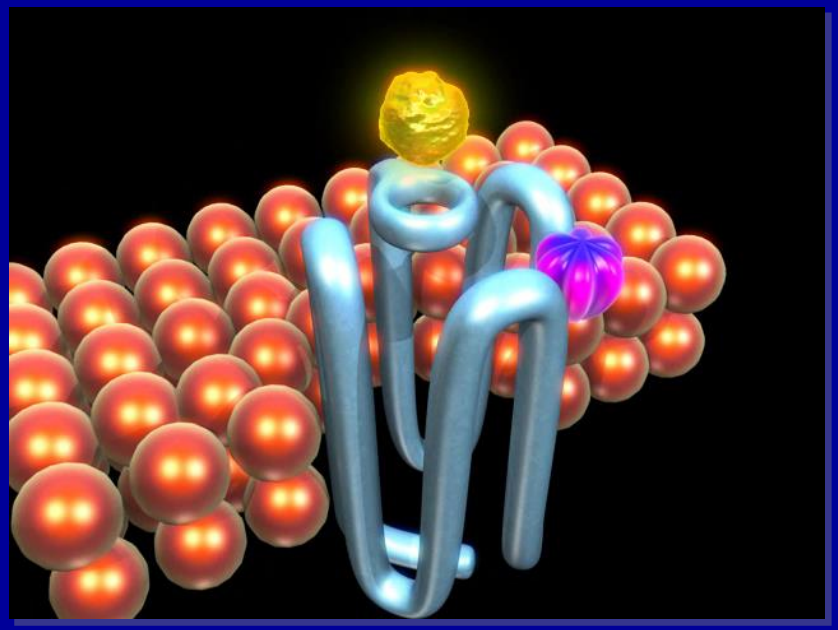


Ticagrelor-Reversible inhibition



P Savi, et al. Proc Natl Acad Sci USA 2006; 103:11069-11074.

ISSN 0009-7322
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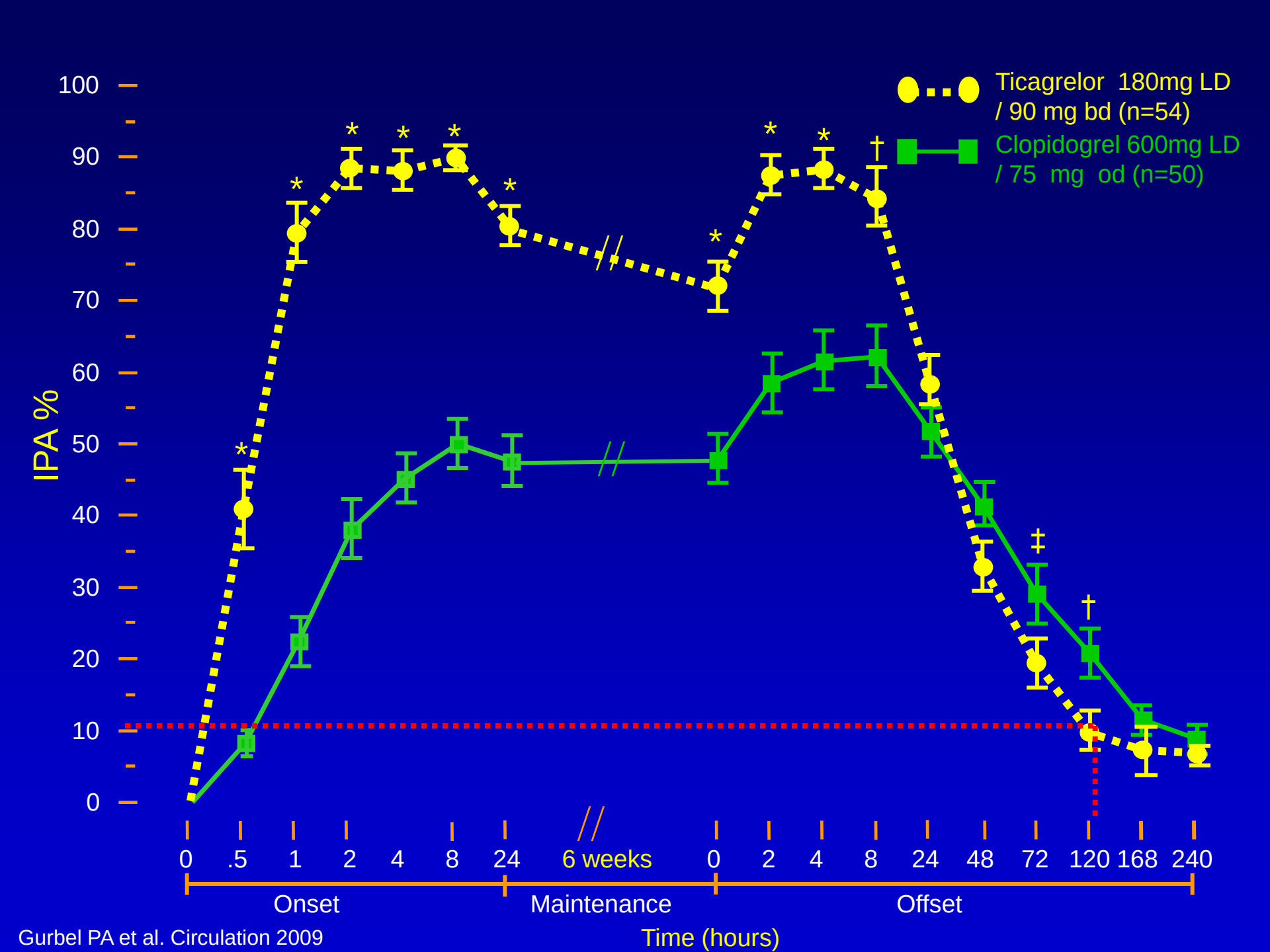
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Randomized Double-Blind Assessment of the Onset and Offset of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients With Stable Coronary Artery Disease

The ONSET/OFFSET Study

Paul A. Gurbel, MD; Kevin P. Bliden, BS; Kathleen Butler, MD; Udaya S. Tantry, PhD; Tania Gesheff, BSN; Cheryl Wei, PhD; Renli Teng, PhD; Mark J. Antonino, BS; Shankar B. Patil, MD; Arun Karunakaran, MD; Dean J. Kereiakes, MD; Cordel Parris; Drew Purdy, MD; Vance Wilson, MD; Gary S. Ledley, MD; Robert F. Storey, MD



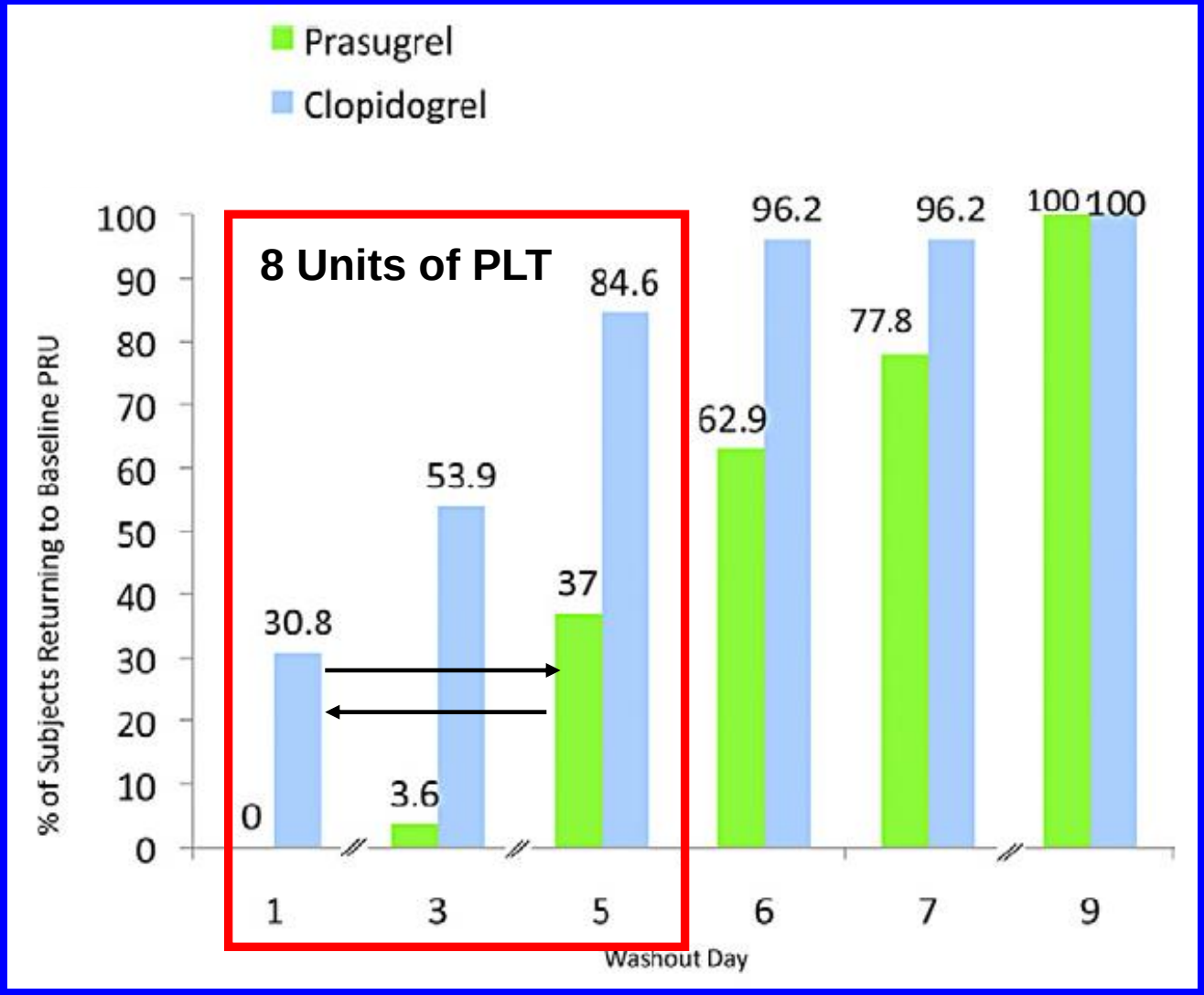
Gurbel PA et al. Circulation 2009

What Can Be Done Within the First 120 hr ?

Objectives

- How important is to achieve effective platelet inhibition @ PPCI ?
- Should DAPT be given ASAP in STEMI Pt's undergoing PPCI (FMC) ?
- If yes, What DAPT should be given?
- What should be done if a patient on DAPT required immediate CABG ?
- Non urgent CABG (invasive procedure)?

Proportion of Pts Returning to Baseline Reactivity



Price M et al. JACC 2012 June;59 : 2338-43

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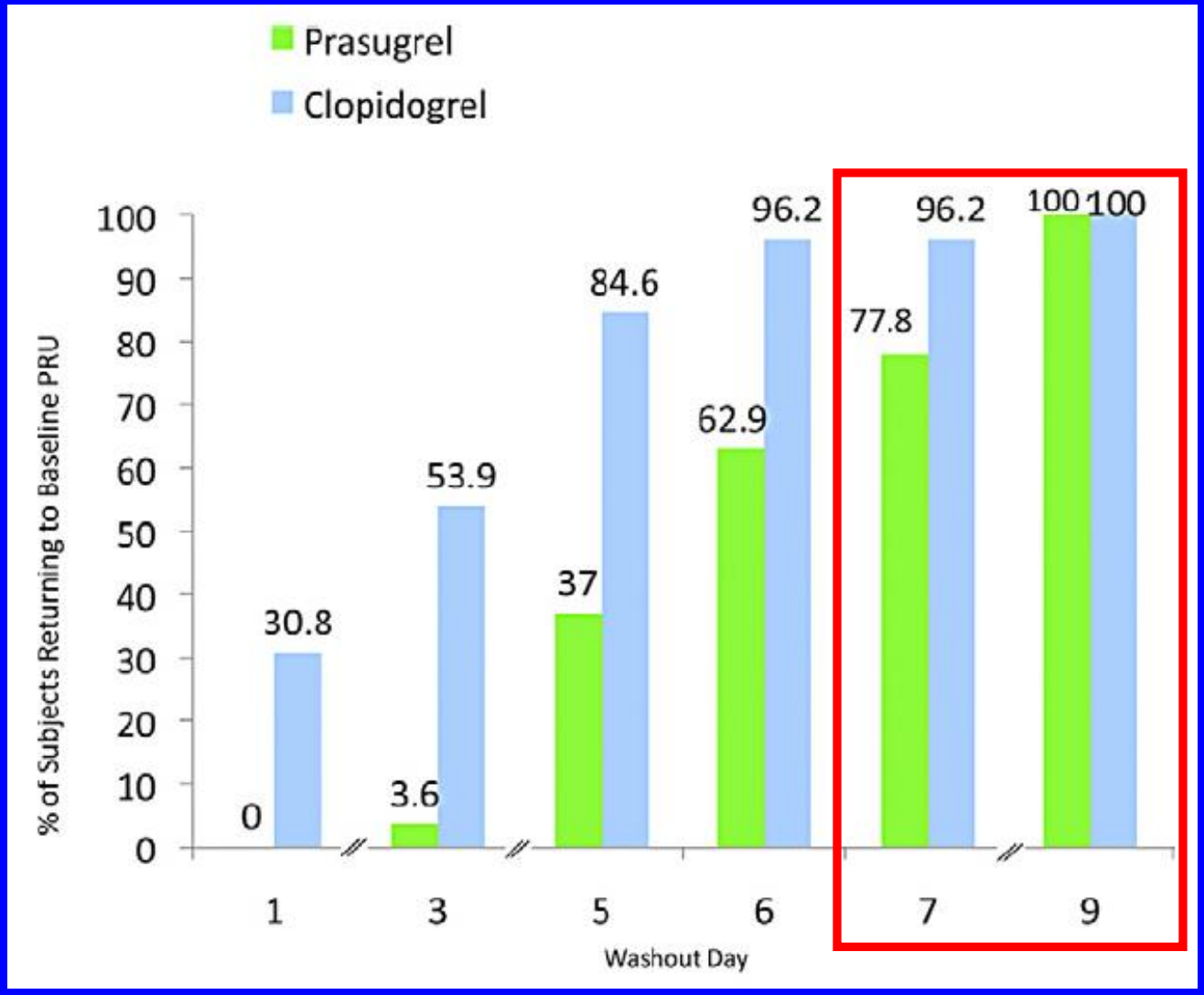

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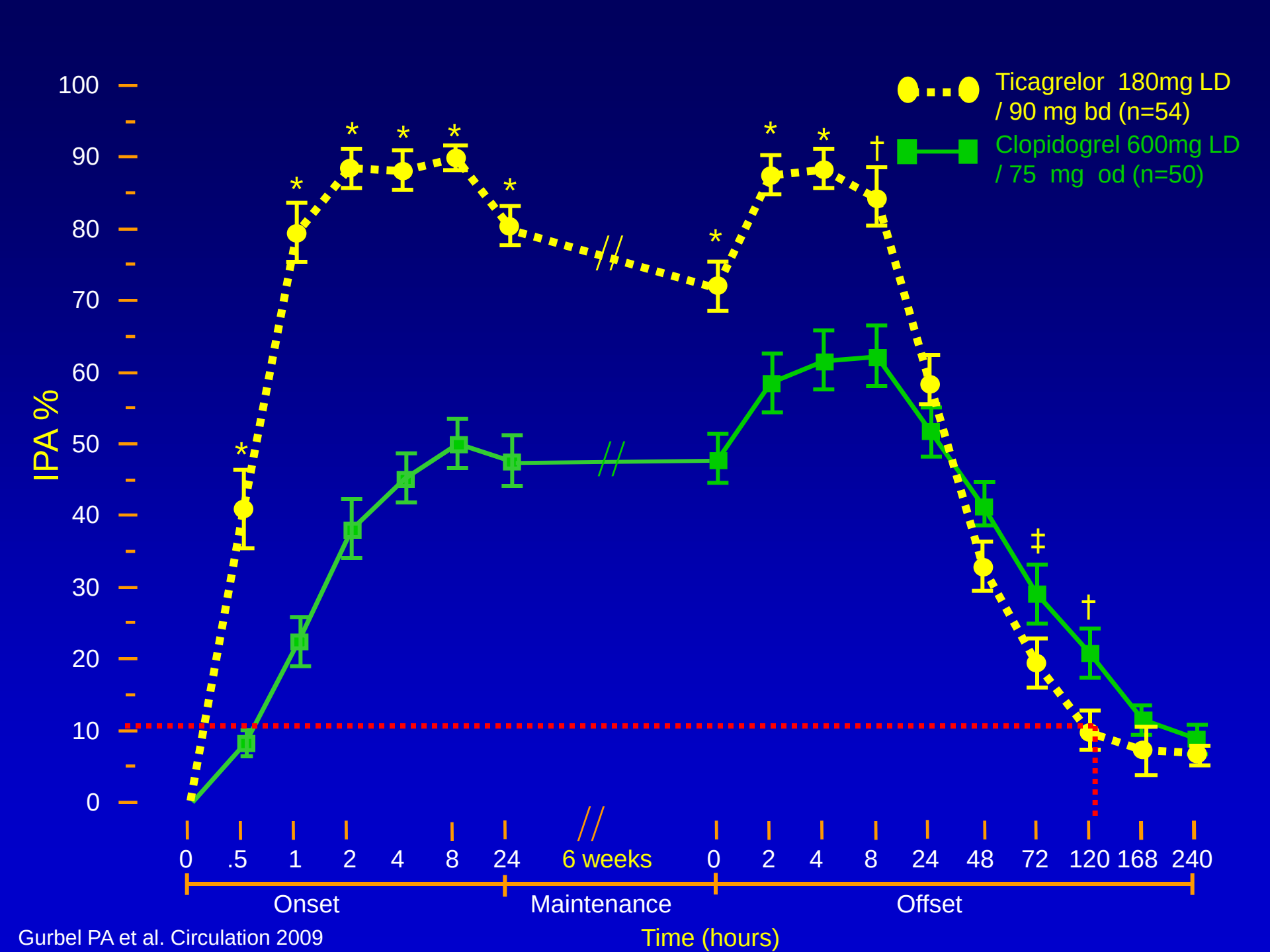
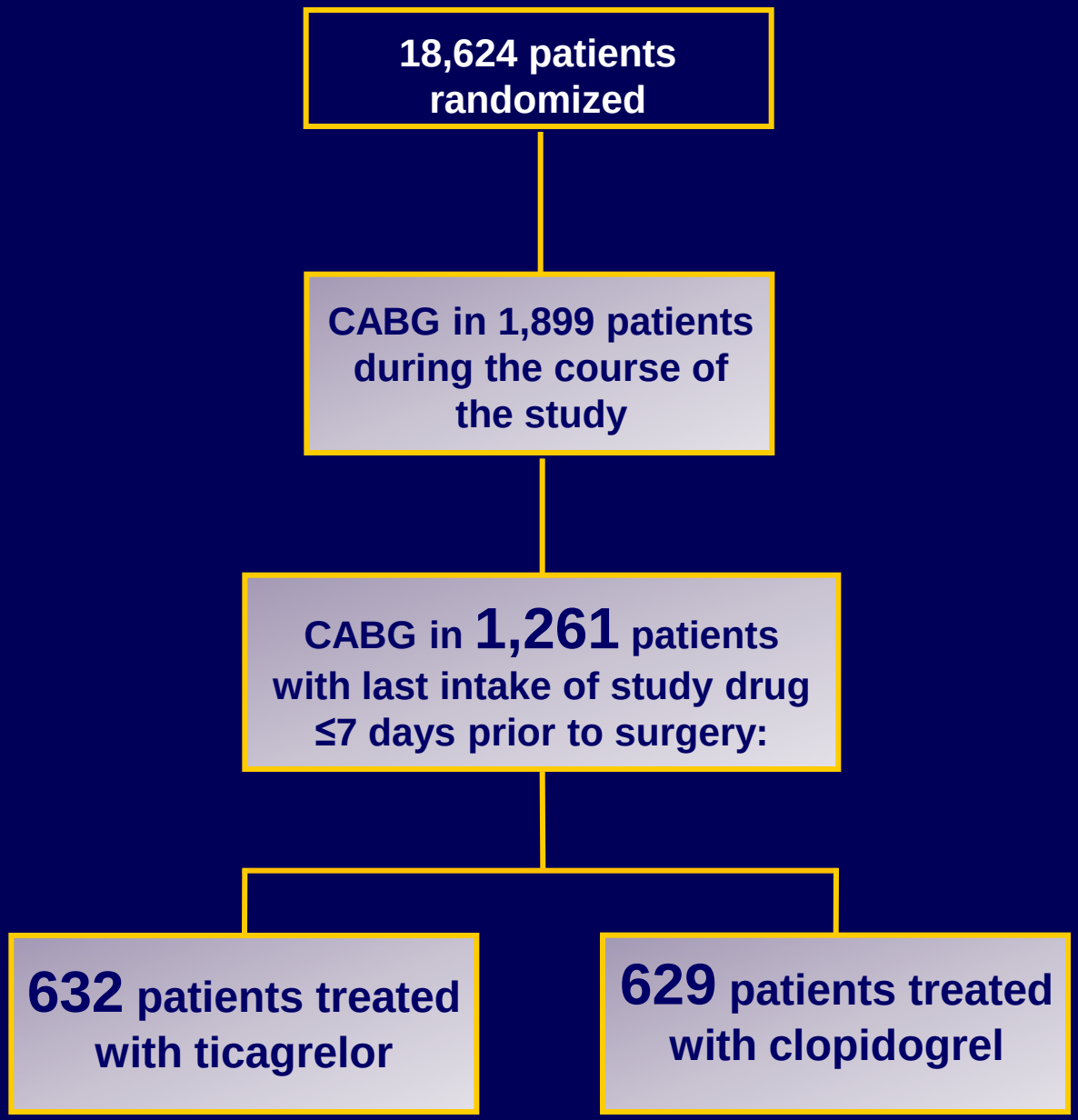


Gurbel PA et al. Circulation 2009

Thank You

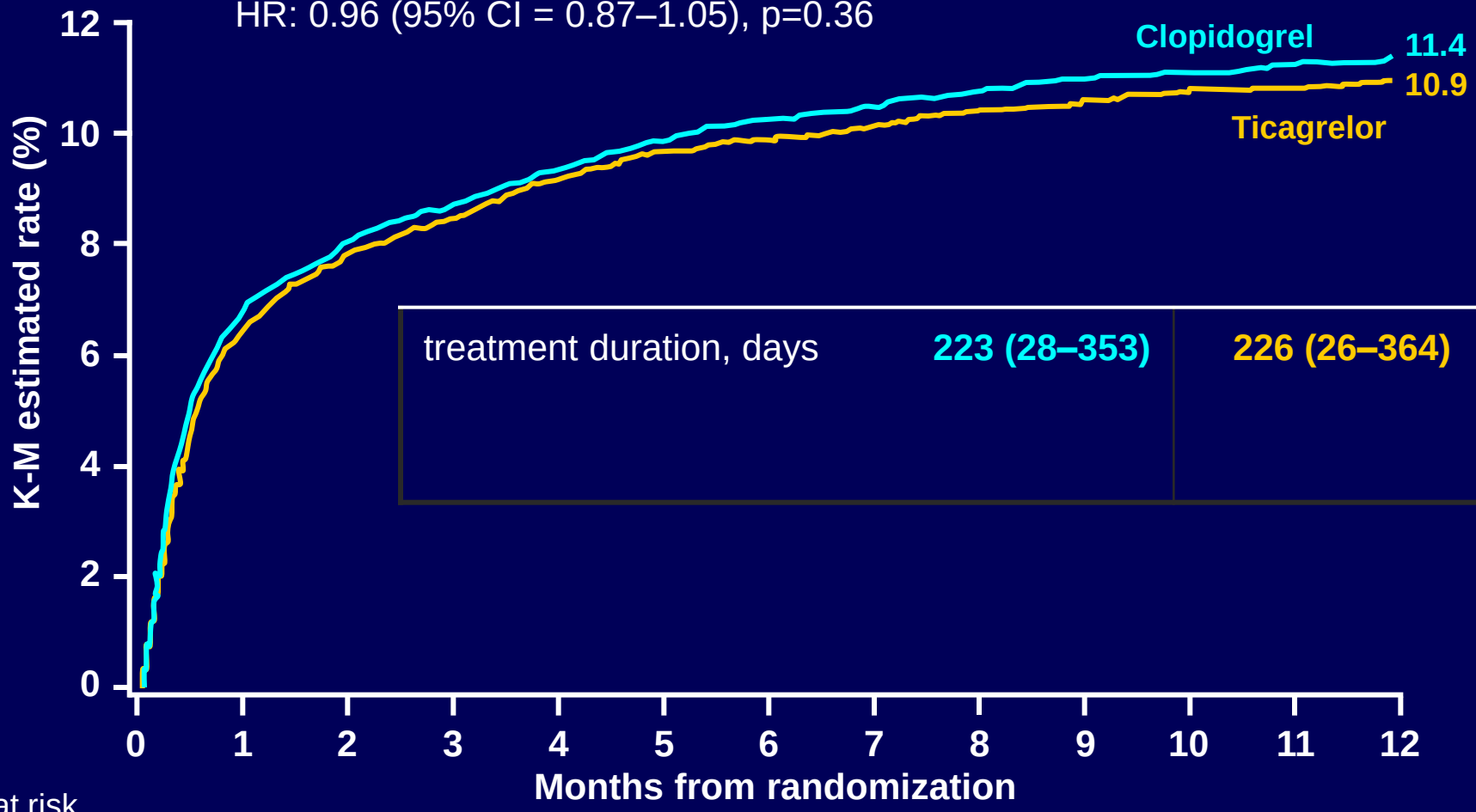
PLATO
CABG



Held et al. JACC 2011; 57(6): 672-84

Time from study entry to first CABG surgery (total PLATO population)

PLATO CABG



No. at risk

Ticagrelor	9,235	7,289	6,862	6,570	5,144	3,775	3,414
Clopidogrel	9,186	7,320	6,936	6,657	5,209	3,843	3,470

Study medication pre- and post-CABG

PLATO CABG

	Ticagrelor (n=632)	Clopidogrel (n=629)
Days study drug stopped before CABG, %		
1 day	**13.3**	**14.0**
2 days	**16.8**	**13.7**
3 days	**18.0**	**11.6**
4 days	**13.3**	**11.0**
5 days	**12.5**	**15.3**
6 days	**14.4**	**17.5**
7 days	**11.7**	**17.0**
Patients not restarted on study drug/unknown	**n=234**	**n=238**
Time study drug restarted after CABG, %	**(n=398)**	**(n=391)**
<7 days	**57.0**	**57.5**
7–14 days	**27.9**	**25.6**
>14 days	**15.1**	**16.9**

Held et al. JACC 2011; 57(6): 672-84

Study medication pre- and post-CABG

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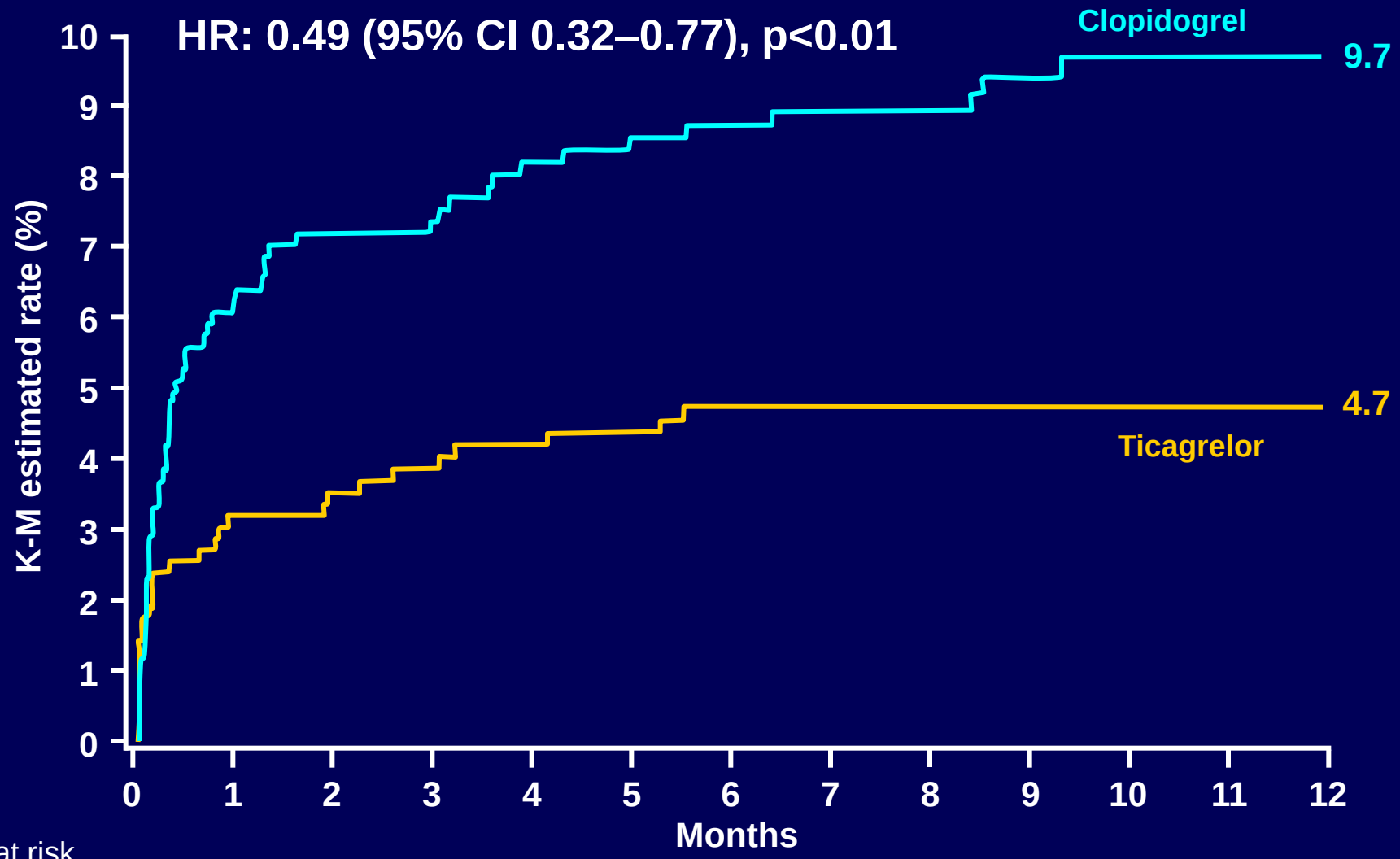
1 day	13.3	14.0
2 days	16.8	13.7
3 days	18.0	11.6
4 days	13.3	11.0
5 days	12.5	15.3
6 days	14.4	17.5
7 days	11.7	17.0
Patients not restarted on study drug/unknown	n=234	n=238
Time study drug restarted after CABG, %	(n=398)	(n=391)
<7 days	57.0	57.5
7–14 days	27.9	25.6
>14 days	15.1	16.9

Held et al. JACC 2011; 57(6): 672-84

Time from CABG to any death

PLATO CABG



No. at risk

Ticagrelor	629	583	557	491	415	291	119
Clopidogrel	629	565	539	472	404	269	130

Held et al. JACC 2011; 57(6): 672-84

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Cardiac Surgery

Mortality Benefit With Prasugrel in the TRITON–TIMI 38 Coronary Artery Bypass Grafting Cohort

Risk-Adjusted Retrospective Data Analysis

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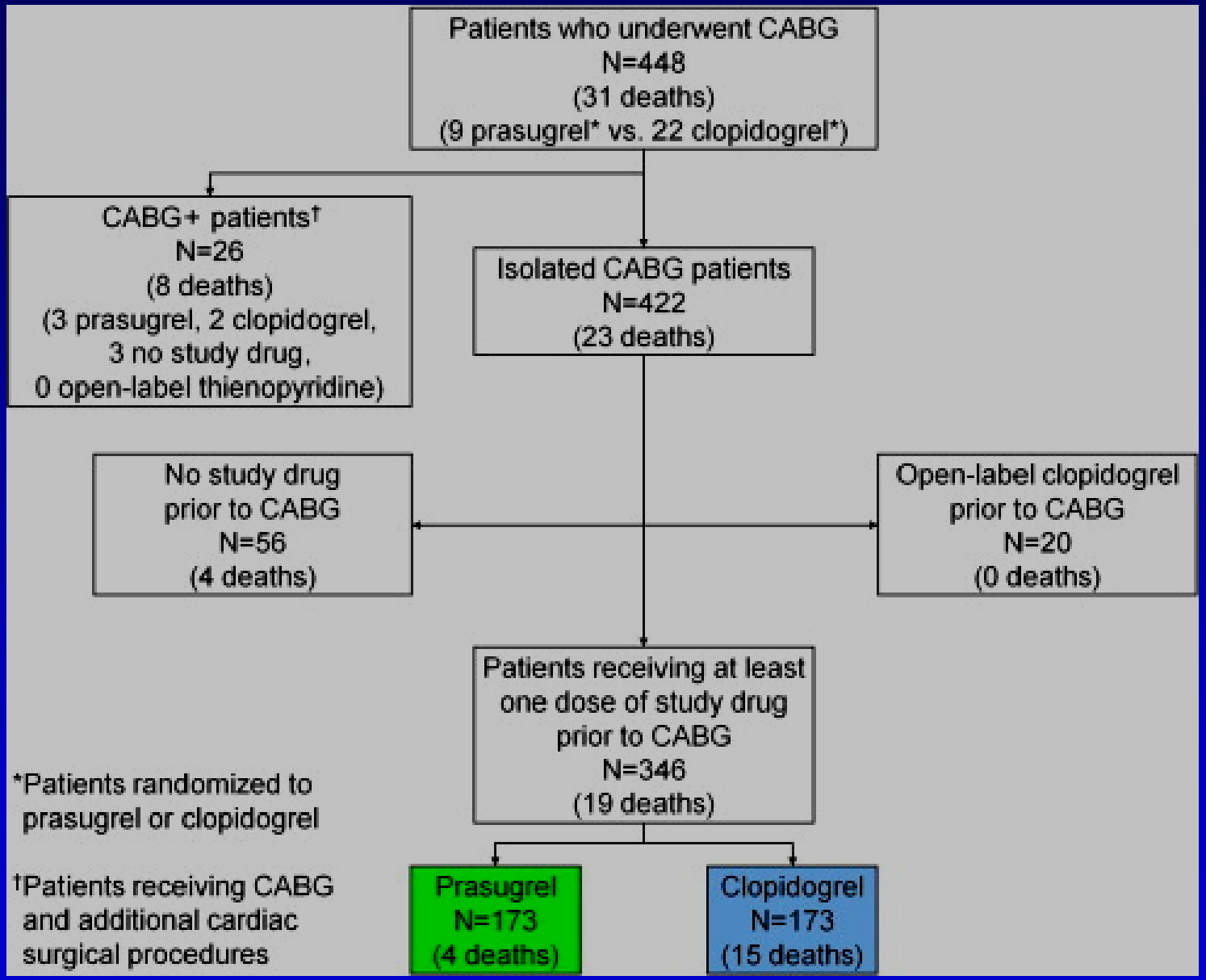
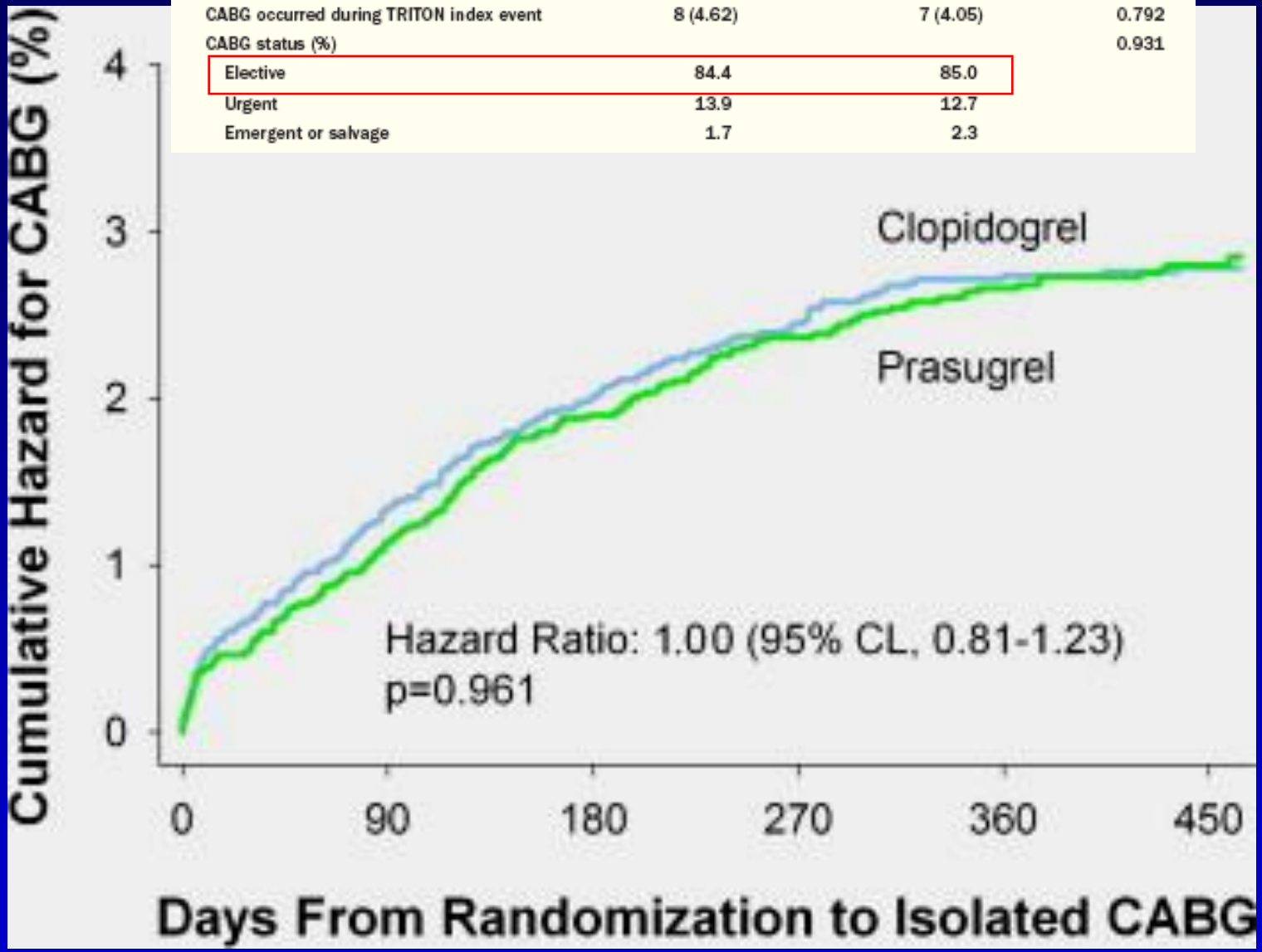
Durham, North Carolina; Stanford, California; Atlanta, Georgia; Tucson, Arizona; and Indianapolis, Indiana



Smith et al. JACC 2012 (July 31);60(5):388-96

Procedural characteristics			
CABG occurred during TRITON index event	8 (4.62)	7 (4.05)	0.792
CABG status (%)			0.931
Elective	84.4	85.0	
Urgent	13.9	12.7	
Emergent or salvage	1.7	2.3	



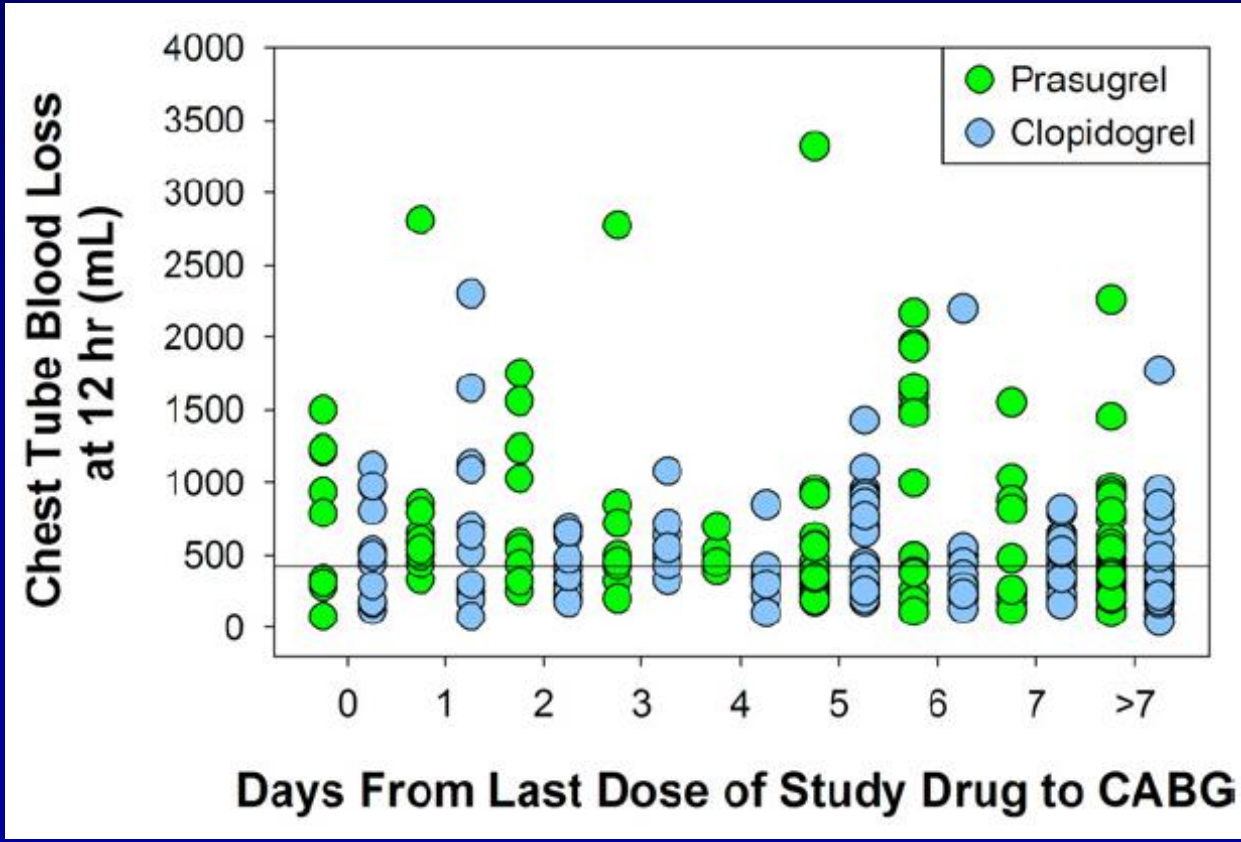
Smith et al. JACC 2012 (July 31);60(5):388-96

Days from last dose to CABG	Prasugrel	Clopidogrel
0	16 (9.2)	14 (8.1)
1	15 (8.7)	13 (7.5)
2	12 (6.9)	17 (9.8)
3	12 (6.9)	10 (5.8)
4	9 (5.2)	11 (6.4)
5	24 (13.9)	34 (19.7)
6	21 (12.1)	16 (9.2)
7	13 (7.5)	25 (14.5)
8–14	36 (20.8)	20 (11.6)
>14	14 (8.1)	12 (6.9)
Unknown or missing	1 (0.6)	1 (0.6)

51%

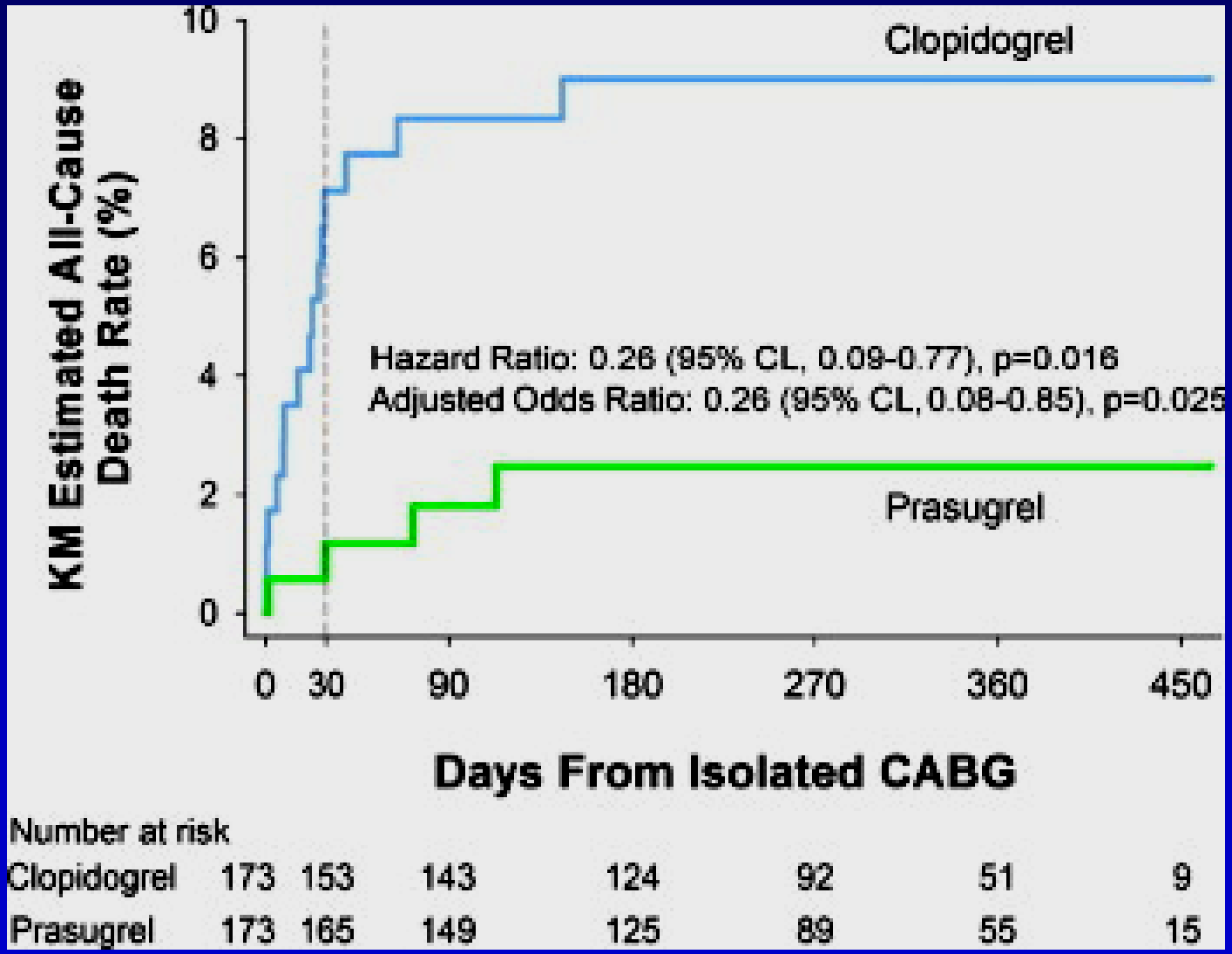
57%

Chest Tube Loss @ 12hr by Days from Last Dose of Study Drug to CABG



	Prasugrel	Clopidogrel
Mean blood loss:	655 ± 580 ml	vs. 503 ± 378 ml (p=0.05)

All Cause Death



Smith et al. JACC 2012 (July 31);60(5):388-96

Factors Contributing to the Lower Mortality With Ticagrelor Compared With Clopidogrel in Patients Undergoing Coronary Artery Bypass Surgery

Christoph Varenhorst, MD, PhD,* Ulrica Alström, MD, PhD,† Benjamin M. Scirica, MD, MPH,‡
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Ph. Gabriel Steg, MD,¶# Jay Horrow, MD,** Kenneth W. Mahaffey, MD,††
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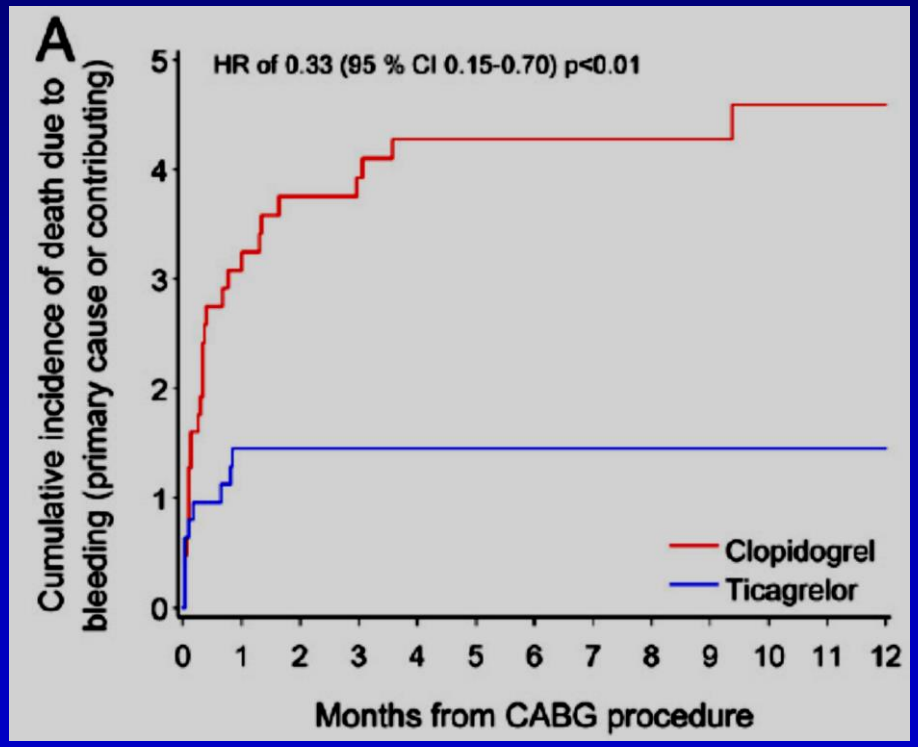
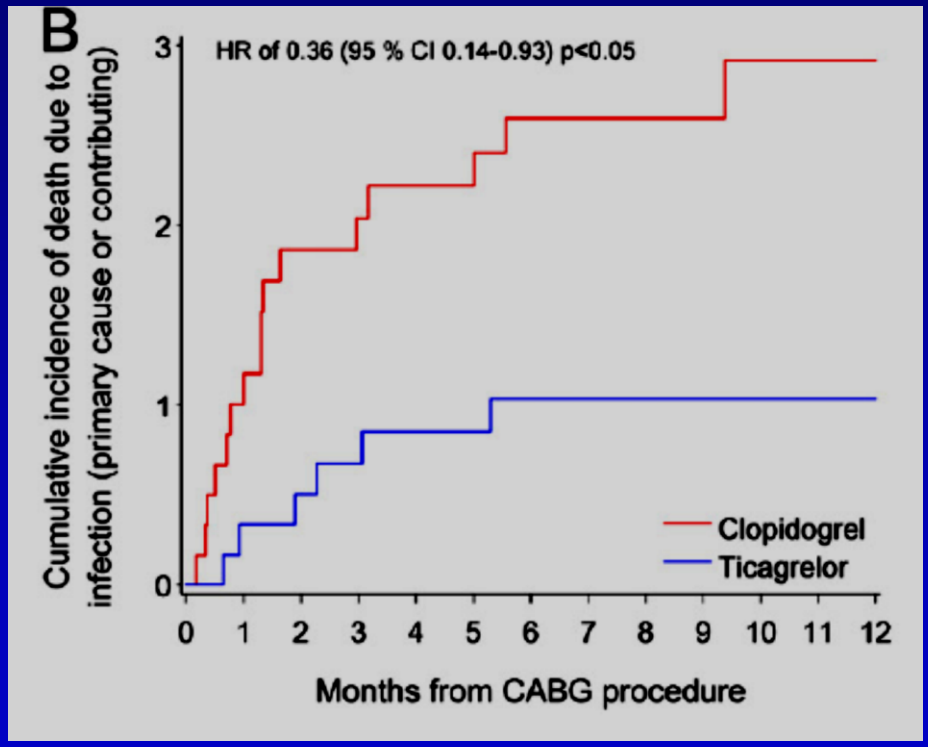
Uppsala and Mölndal, Sweden; Boston, Massachusetts; Baltimore, Maryland; Sheffield, United Kingdom; Paris, France; Wilmington, Delaware; and Durham, North Carolina

Varenhost et al. JACC Oct 2012:1623-30.

Time to Death due to Bleeding and Infection (primary cause or contributing)

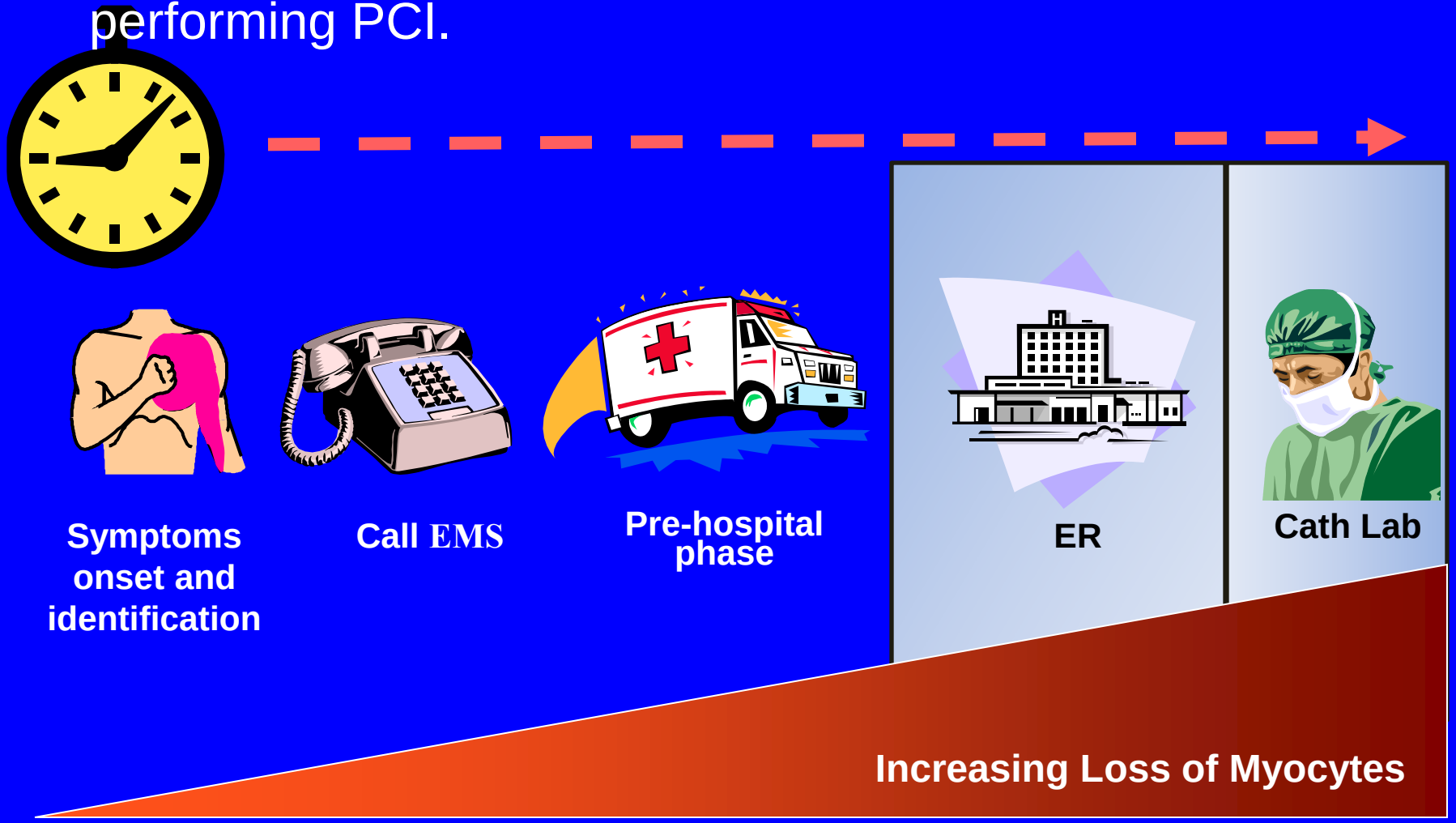




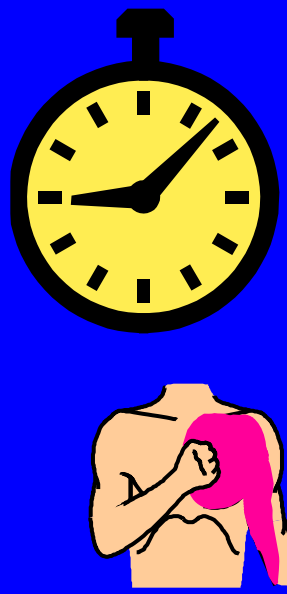
Varenhost et al. JACC Oct 2012:1623-30.

Conclusion

Based on the existing date and current guidelines it is recommended to initiate DAPT ASAP especially before performing PCI.



The question whether further benefit can be achieved by earlier initiation of DAPT at 1st medical contact is currently under examination by a number of prospective trials



Symptoms onset and identification

Call EMS

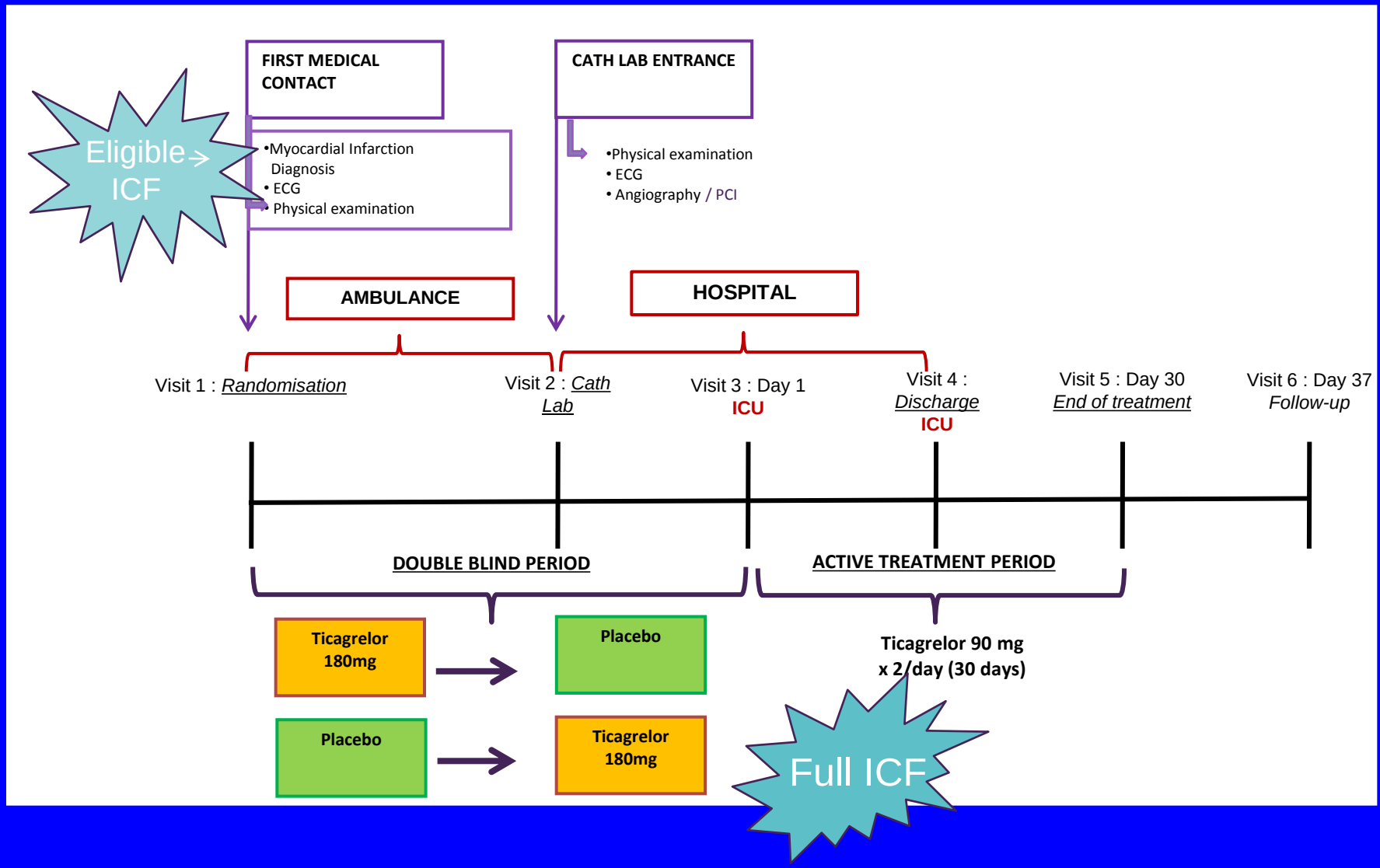
Pre-hospital phase

ER

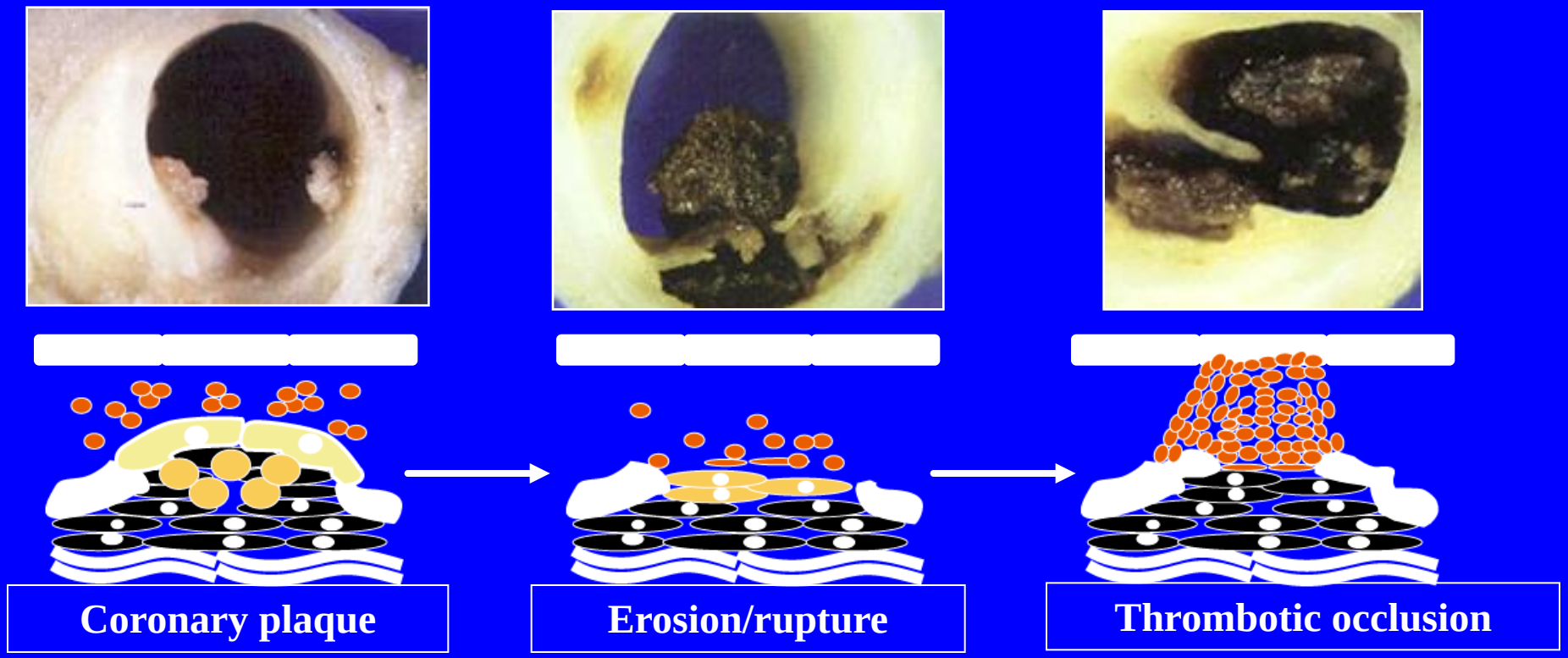
Cath Lab

Increasing Loss of Myocytes

ATLANTIC: Study Design

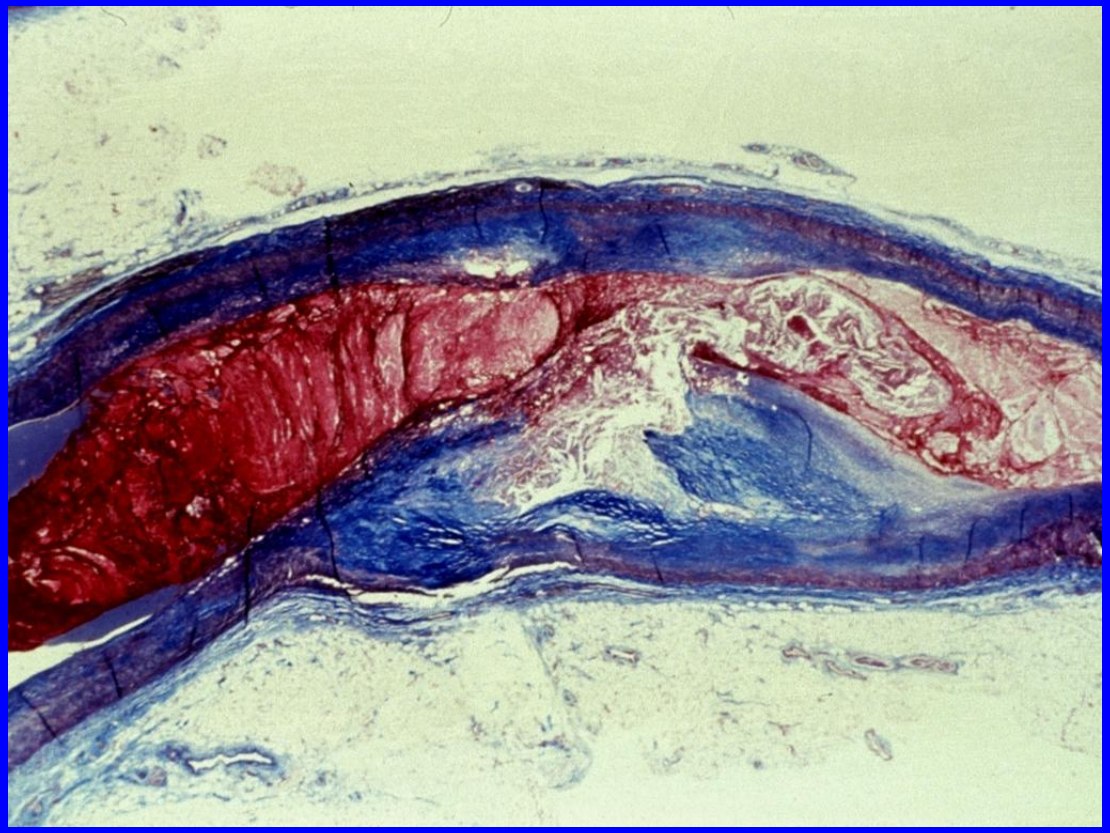


Platelet activation plays a major role in thrombus formation and pathogenesis of ACS



DAPT became a cornerstone of the treatment for ACS

Davies MJ. Am J Cardiol. 2001 Aug 16;88(4A):2F-9F

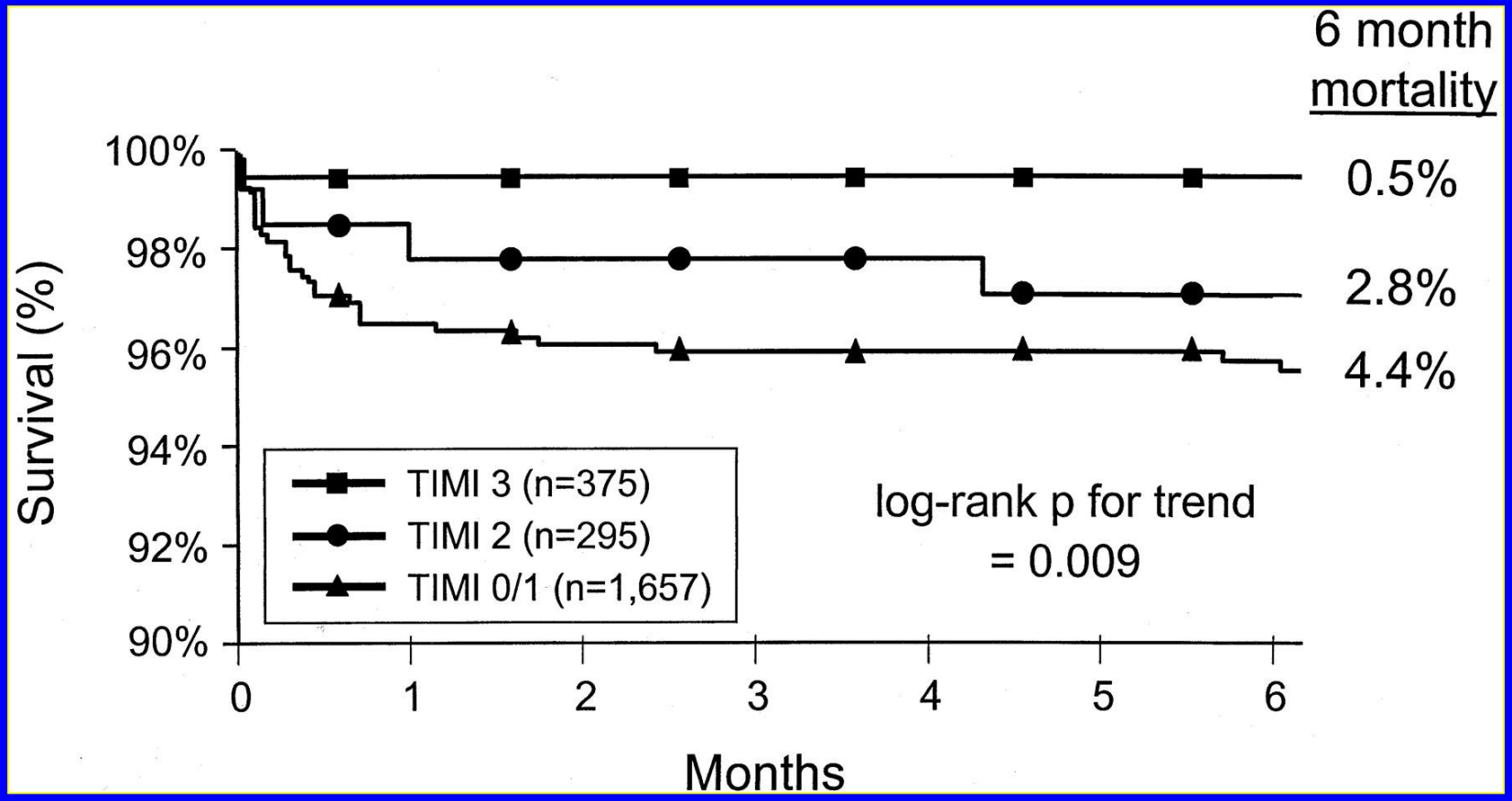


Should DAPT be given ASAP (@ 1st medical contact) ?

How important is to achieve effective/optimal platelet inhibition before PCI ?

TIMI-3 Flow Before PPCI for STEMI Is an Independent Determinant of Survival

PAMI Trials



Gregg W. Stone Circulation 2001;104:636

Can We do Better ?