How to Achieve the Best Outcomes with Clopidogrel in Clinical Practice

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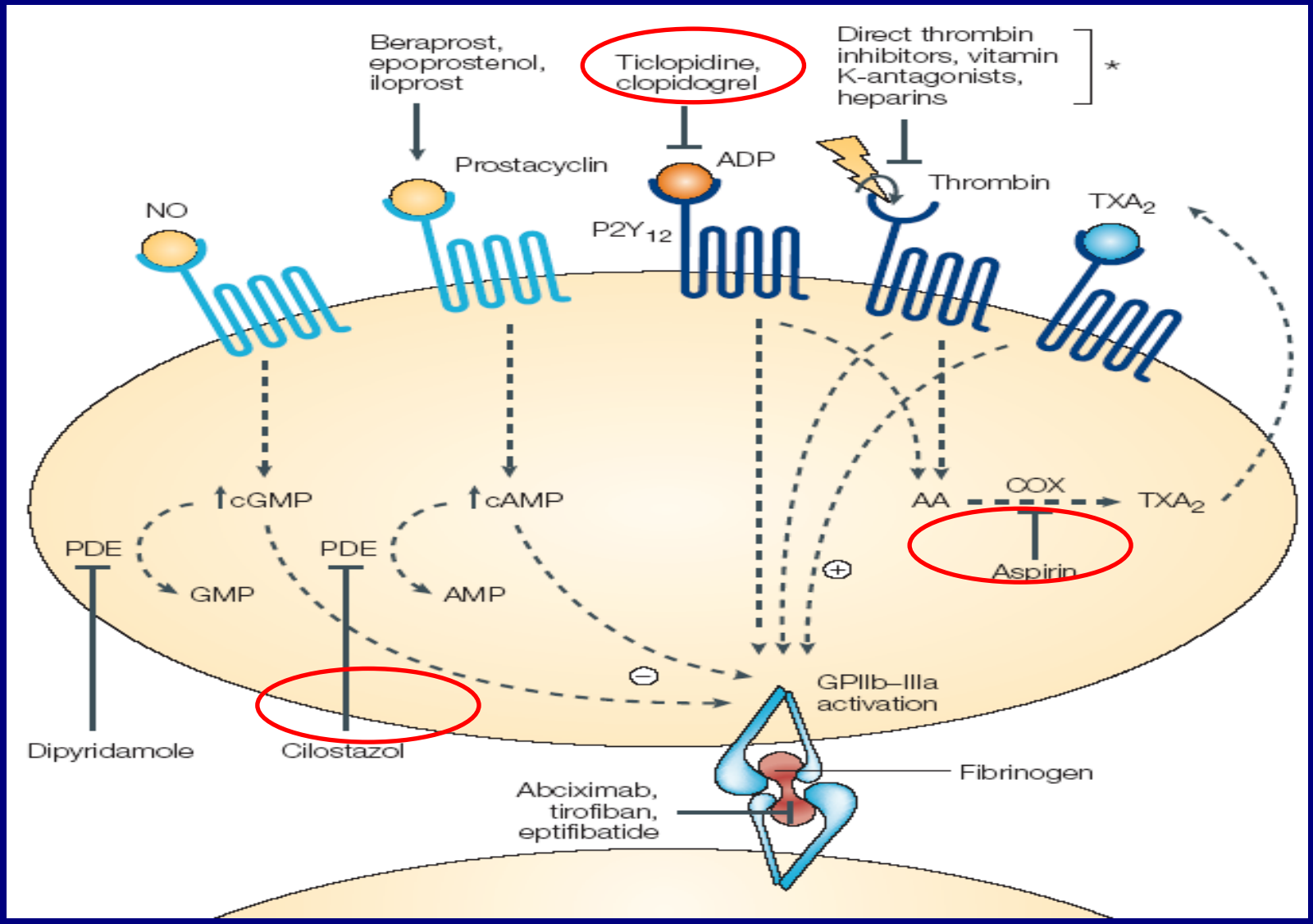
Introduction

Anti-platelet agents



Jackson SP. *Nat Rev Drug Discov 2003;2:775-89*

Overview (1)

1. Aspirin and clopidogrel significantly inhibit platelet aggregation through different pathways, thus combined dual antiplatelet regimen is known to be a standard therapy in patients undergoing percutaneous coronary intervention (PCI)
2. Particularly important in the drug-eluting stent (DES) era due to well-known increased risk of stent thrombosis.

Overview (2)

3. Response variability and non-responsiveness to aspirin and clopidogrel have been known to be associated with higher incidence of clinical ischemic events as compared with well responder.
4. These subjects are clinically important and the majority of practical issues are concentrated on the clopidogrel resistance due to its major contribution in preventing major clinical ischemic events.

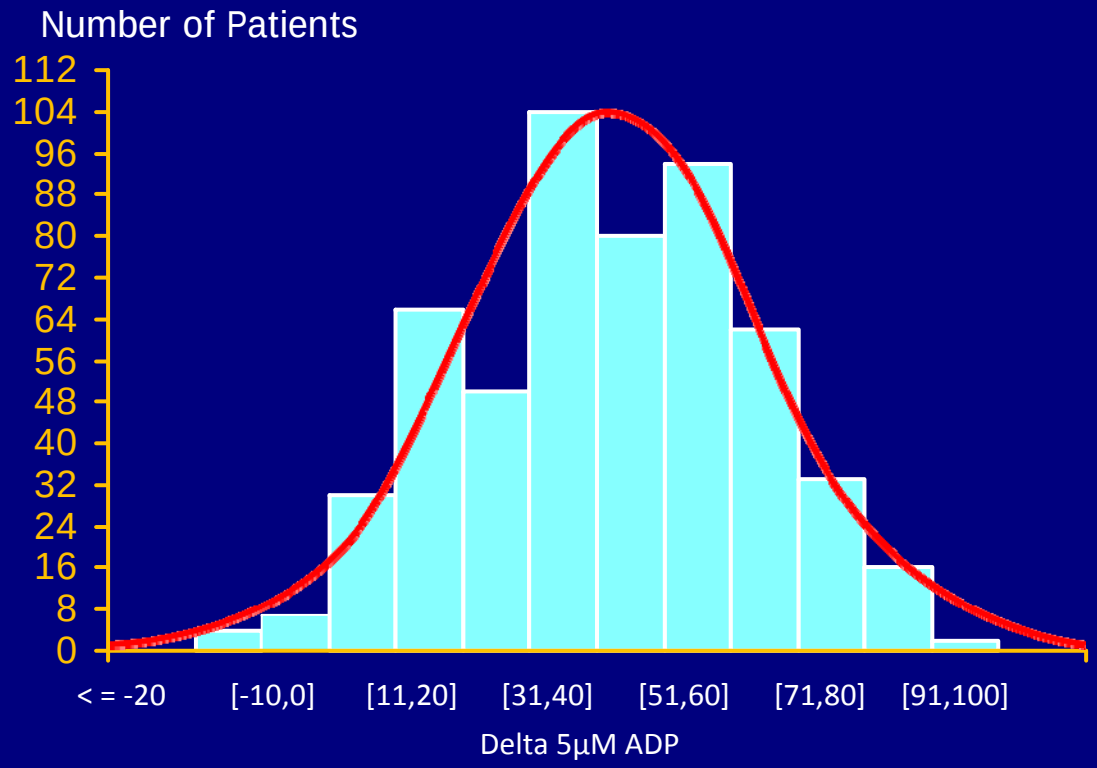
Definition of Clopidogrel Responsiveness

- Standardized & validated definitions for individual responsiveness to clopidogrel are lacking
  - Numerous assays to assess clopidogrel-induced antiplatelet effects
  - Methodological variability within each technique
- Studies have defined clopidogrel responsiveness according to:
  - Absolute differences between pre- and post-treatment platelet reactivity
  - The degree of inhibition of platelet aggregation (IPA), defined as the percent decrease in aggregation at baseline and after treatment
- No matter how studies have defined responsiveness, all have shown clopidogrel-induced antiplatelet effects to be variable. However, the impact of this variability remains to be known

Angiolillo DJ, et al. J Am Coll Cardiol 2007;49:1505-16.

Clopidogrel Response Curve

- Individuals receiving clopidogrel exhibit a wide variability in response that follows a normal distribution curve
- In this study (retrospective analysis of a dataset of different type of patients)
  - Hypo-responsive patients = 4.8%*
  - Hyper-responsive patients = 4.2%*



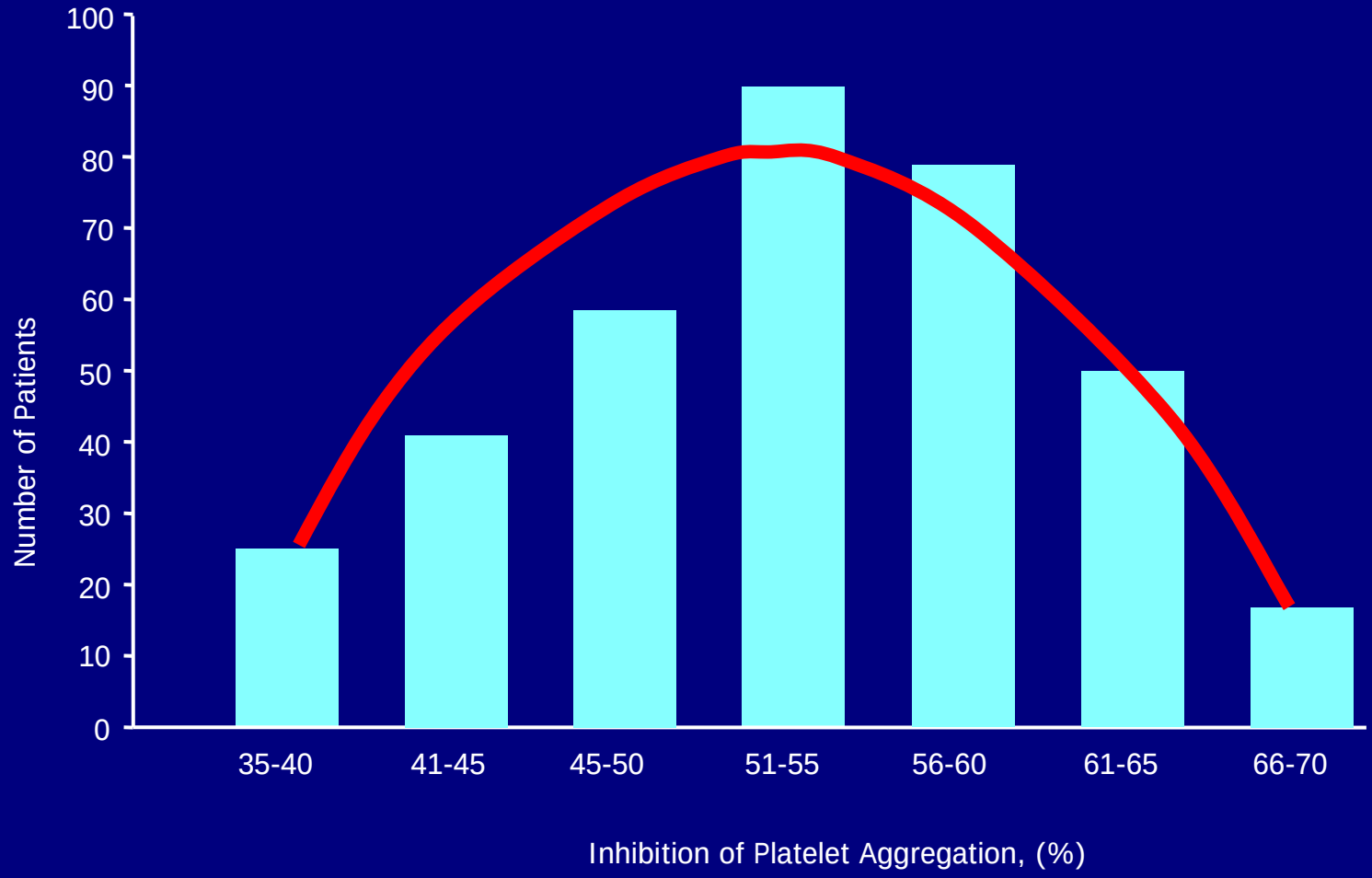
Distribution of the changes in 5 µmol of adenosine diphosphate (ADP)-induced platelet aggregation in 544 patients after receiving clopidogrel therapy. Negative changes in aggregation values represent aggregation values after the administration of clopidogrel that were higher than the baseline readings.

*Defined as to be 2 standard deviation less than and greater than the mean respectively

Serebruany V, et al. J Am Coll Cardiol 2005;45:246-51.

Clopidogrel Responsive Curve in Patients on Chronic Therapy

IPA induced by 5 μmol/L of ADP (n=359)

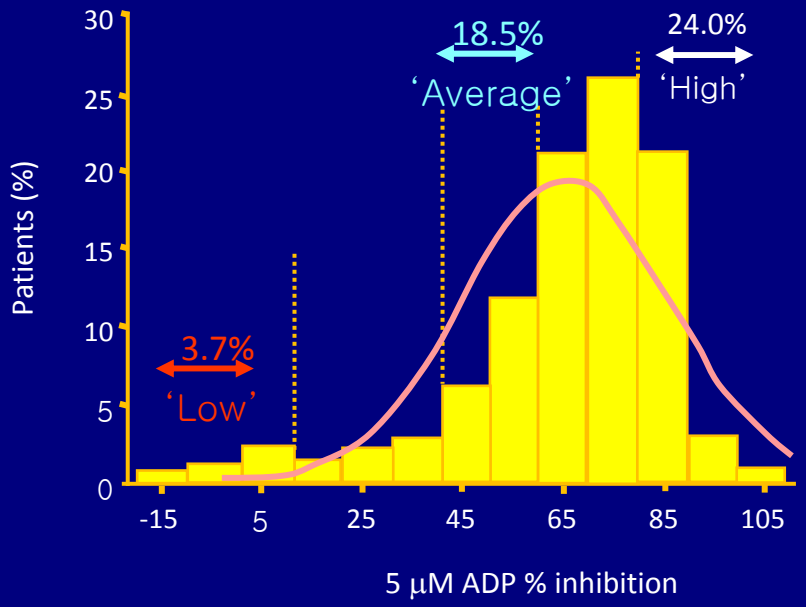


Serebruany V, et al. Am Heart J 2006;153:371-7.

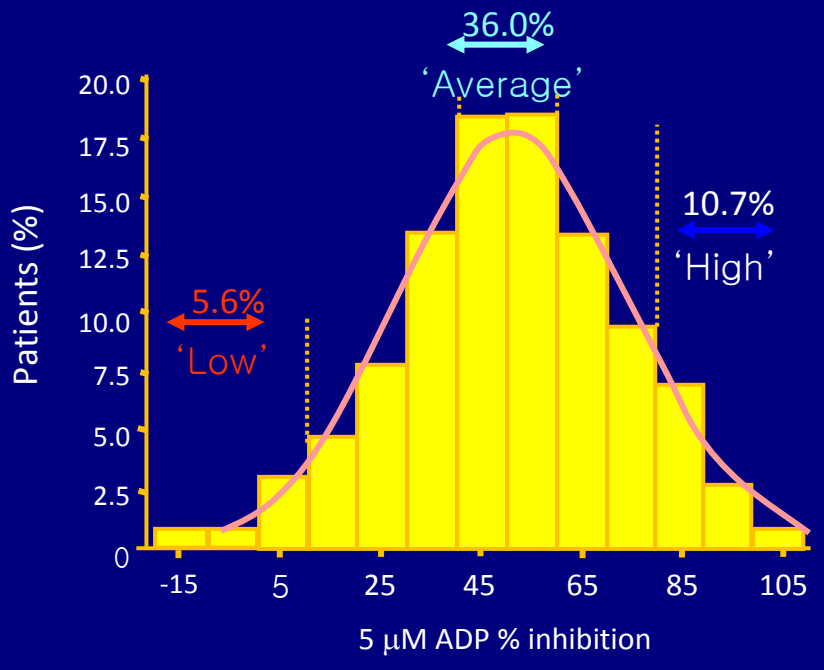
Variability of platelet response to clopidogrel in healthy subjects (POP 5810)

- Incidence of subjects with < 10% inhibition of 5 µM ADP-induced platelet aggregation:
  - 3.7% in the current selected population versus (n=541)
  - 5.6% in in-house database of healthy subjects (n=536)

POP 5810



Meta-analysis



Drouet L, et al. ACC 2007.

Summary

- Variability of response is a common phenomenon with pharmacologic agents
- No standard definition has been validated by scientific studies with regards to variability of response to clopidogrel
- Response to clopidogrel appears to follow a normal “bell-shaped” distribution with a small percentage of hypo- and hyper-responders
- The clinical consequences of hypo- and hyper-responders is unclear. More data are needed

What factors are associated with variable response to clopidogrel?

Possible Causes / Mechanisms of Response Variability With Antiplatelet Agents

Genetic[1]

- Receptors: polymorphisms to $P2Y_{12}$ receptor; H2 haplotype
- Enzymes: COX-1, COX-2, thromboxane A_2 synthetase, etc. (aspirin)

Pharmacokinetic/Bioavailability[1]

- Non-compliance / Premature discontinuation
- Underdosing
- Poor absorption (e.g., enteric coated aspirin)
- Possible drug-drug interactions

Pharmacodynamic[1]

- Incomplete suppression of thromboxane A_2 generation (aspirin)
- Accelerated platelet turnover, with introduction into the blood stream of newly formed, drug-unaffected platelets
- Stress-induced COX-2 in platelets (aspirin)
- Increased platelet sensitivity to ADP and collagen

Environment/Concomitant disease

- Diabetes mellitus[2]
- Coronary artery disease[3]

[1] Michelson A. Circulation 2004;110:e489–93.
[2] Angiolillo DJ et al. Diabetes 2005;54:2430–5.
[3] Michelson A. J Thromb Haemost 2006:5;75–81.

Clopidogrel Resistance

Clopidogrel Resistance
- several meanings -

1. Inter-individual response variability to clopidogrel
2. Clinical failure to clopidogrel therapy
3. Combination thereof

; Regardless of the mechanism or reasons, a low response to clopidogrel is known to be a significant factor of increased risk for ischemic events.

Clopidogrel Resistance
- Genetic Polymorphism-

1. Genetic polymorphism in the cytochrome p450 gene, especially CYP2C19*2 polymorphism is responsible for clopidogrel resistance.
2. A single Korean center study

1) clopidogrel resistance using VerifyNow was in 28.9%
2) CYP2C19*3 single-nucleotide polymorphism was an independent risk factor of clopidogrel resistance in Korean patients with coronary artery disease.

Lee SM et al. Am J Cardiol 2009;104:46–51

Clopidogrel Resistance
- Host Factors-

1. Intrinsic Factors

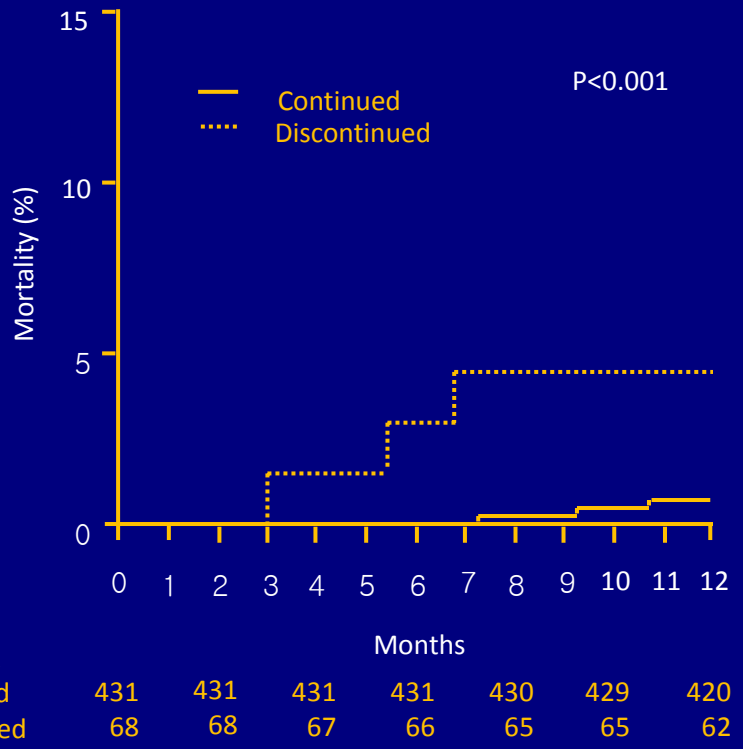
1) variability in P2Y12 receptor number and its affinity for the active metabolite of clopidogrel
2) variability in the internal signaling pathways and glycoprotein IIb/IIIa receptor activation after binding

2. Extrinsic Factors

1) absorption and metabolism variability
2) drug-drug-interactions
3) under-dosing
4) noncompliance

PREMIER Registry and the Effects of Prematurely Stopping Thienopyridine Therapy

- PREMIER Registry – prospectively collected data of MI patients to examine the prevalence & predictors of thienopyridine discontinuation 30 days after receiving a drug-eluting stent (DES)
- Among 500 DES-treated MI patients who were discharged on thienopyridines, 68 (13.6%) stopped therapy within 30 days
- Patients discontinuing use of thienopyridines early were older, less likely to have completed high school or be married, more likely to avoid health care because of cost, & more likely to have pre-existing cardiovascular disease or anemia
- Those who stopped also had a higher 1-year mortality rate compared to those who continued on thienopyridine therapy (7.5% vs. 0.7%, p<0.001)

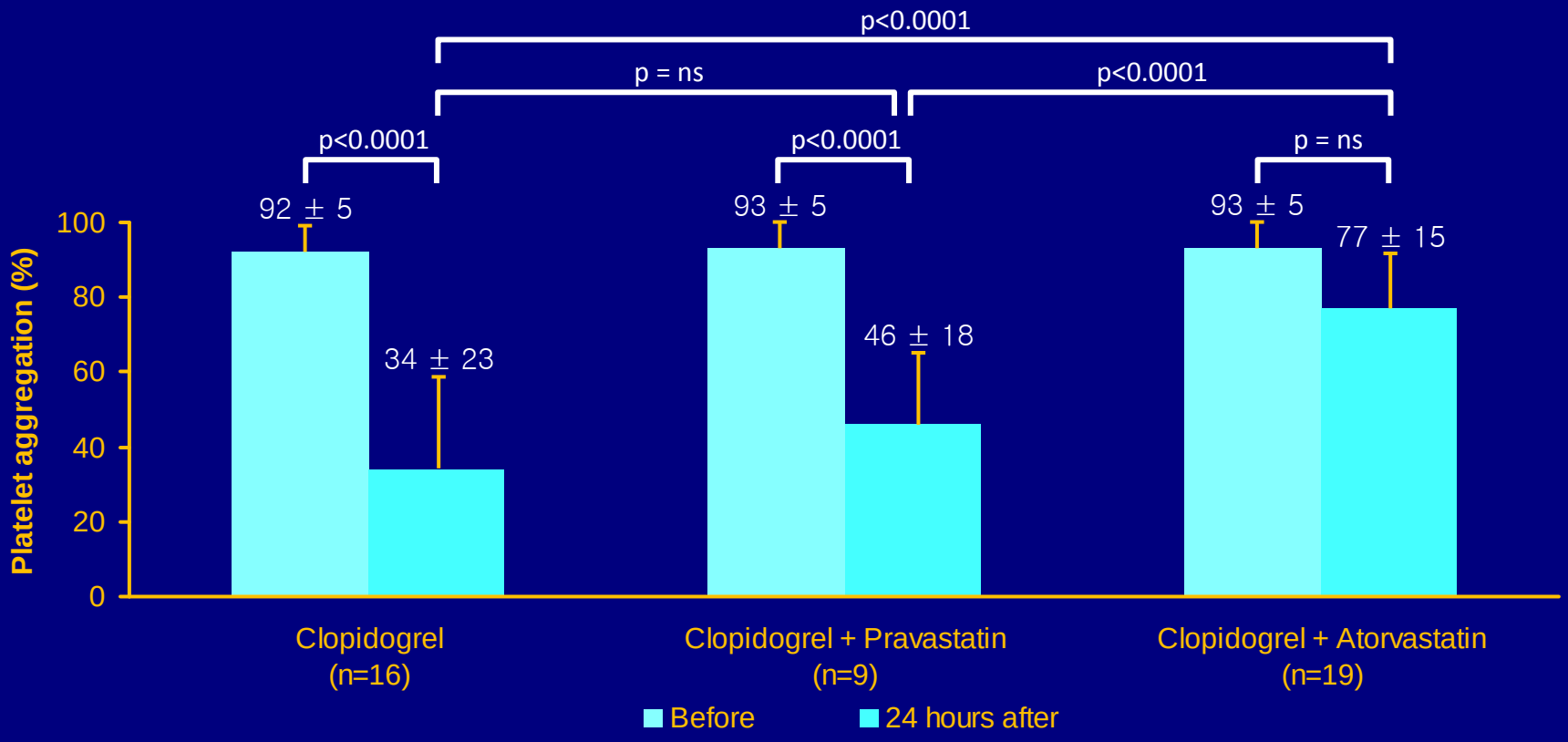


Kaplan-Meier curves of mortality from 1 to 12 months after MI among those who continued and those who discontinued thienopyridine therapy at 1 month after MI.

Spertus JA et al. Circulation 2006; 113:2803-09.

Statins Effect on the Ability of Clopidogrel to Inhibit Platelet Aggregation

Platelet Aggregation Before and After Clopidogrel Administration in Patients Treated With or Without Pravastatin (40 mg) and/or Atorvastatin (10-40 mg)



Lau WC, et al. Circulation 2003;107:32-7.

Clopidogrel – Statin Interaction

(CREDO sub-study)

- CREDO enrolled 2116 patients with symptomatic CAD and evidence of ischemia undergoing elective PCI
  - 1172 (55.4%) received statins before randomization
    - 85% received a statin metabolized through CYP3A4 and 15% received a statin not metabolized through CYP3A4
- There was no difference in 28 day (3.4% atorvastatin, 4.6% pravastatin; p=0.63) or 1 year (6.5% atorvastatin, 4.6% pravastatin; p=0.62) event rates for those randomized to clopidogrel
- Author's Conclusion: The sub-study suggests no adverse effects on clinical events when clopidogrel is co-administered with a statin (CYP3A4 or non-CYP3A4)

Saw J, et al. Circulation 2003;108:921–4.

Clopidogrel – Statin Interaction

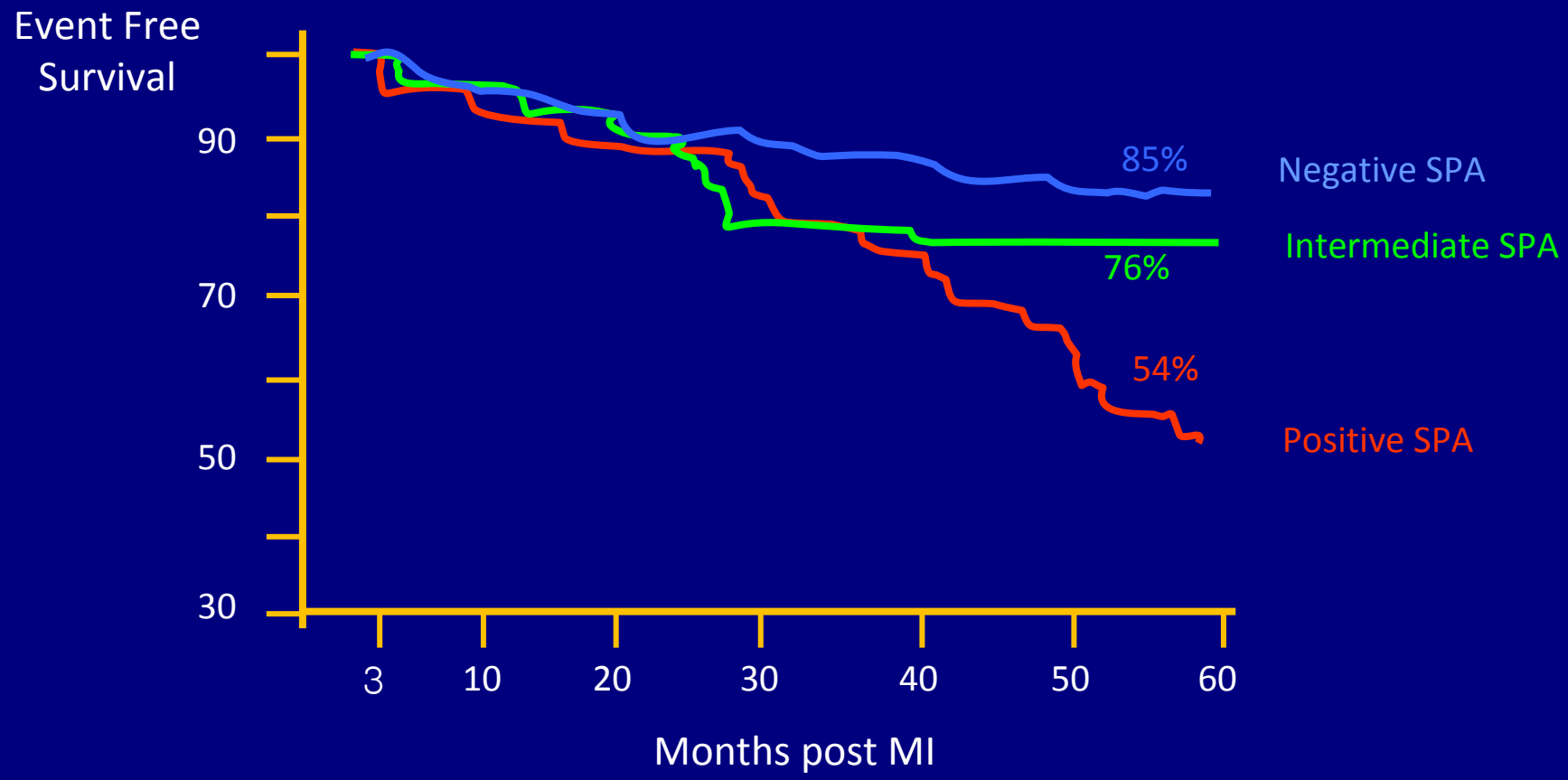
(CHARISMA sub-study)

- CHARISMA enrolled 15,603 patients at high risk for cardiovascular events
  - 10,078 (64.6%) received statins before randomization
    - 82% received a statin metabolized through CYP3A4 and 18% received a statin not metabolized through CYP3A4
- In the overall population, there was no difference in event rates at 28 months (5.7% atorvastatin, 5.1% pravastatin; p=0.54) for those randomized to clopidogrel
  - In the symptomatic subgroup, the interaction between clopidogrel & statins (both CYP3A4 & non-CYP3A4) remained insignificant (p=0.18)
- Author's Conclusion: The sub-study suggests no clinically apparent adverse interaction between long-term administration of clopidogrel & statins (CYP3A4 or non-CYP3A4)

Saw J, et al. JACC 2007;50:291–5.

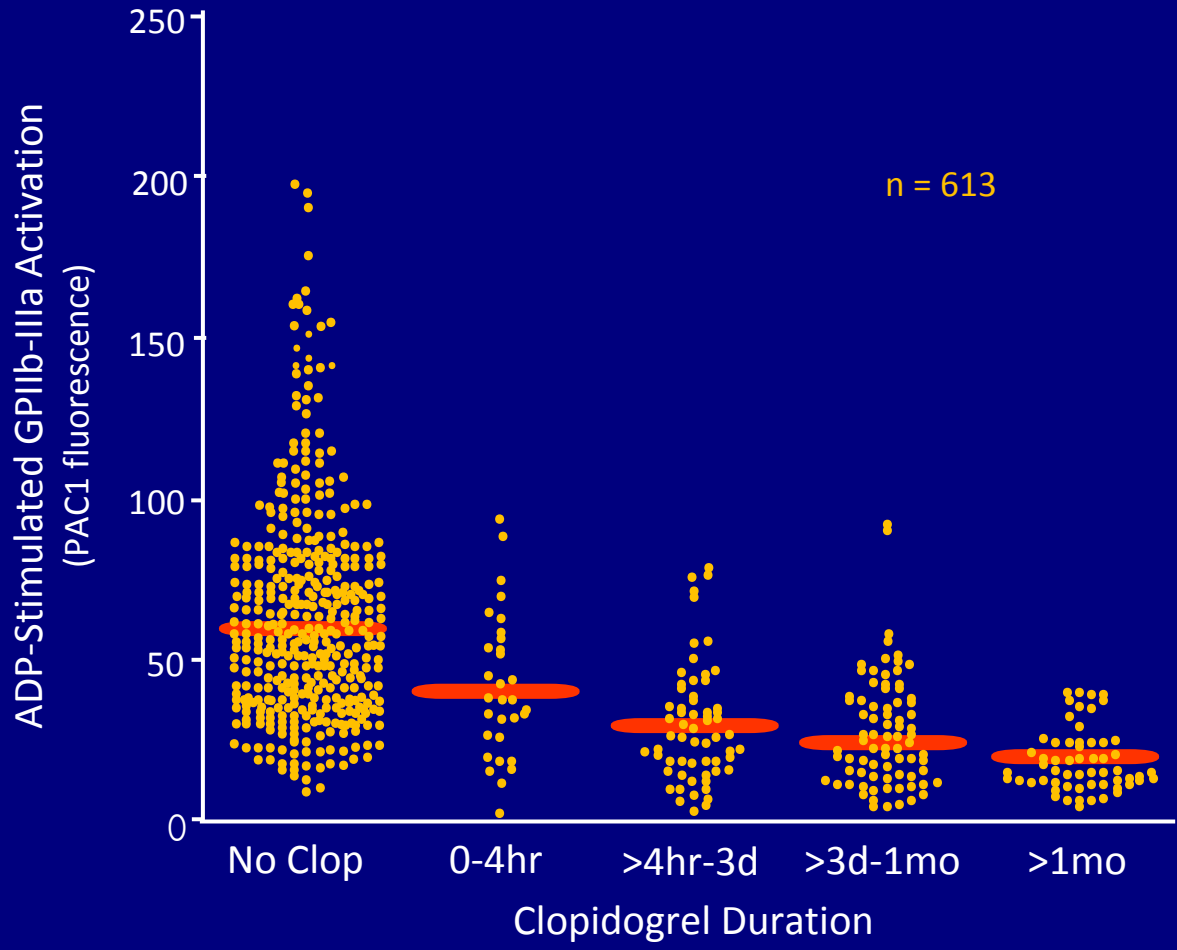
Variability in Platelet Aggregation in Patients Who Are Not Receiving Antiplatelet Therapy

Spontaneous platelet aggregation (SPA), measured in 149 patients 3 months following an MI



Trip MD. New England J Med 1990;322:1549-54.

Pre-existing Variability in Platelet Response

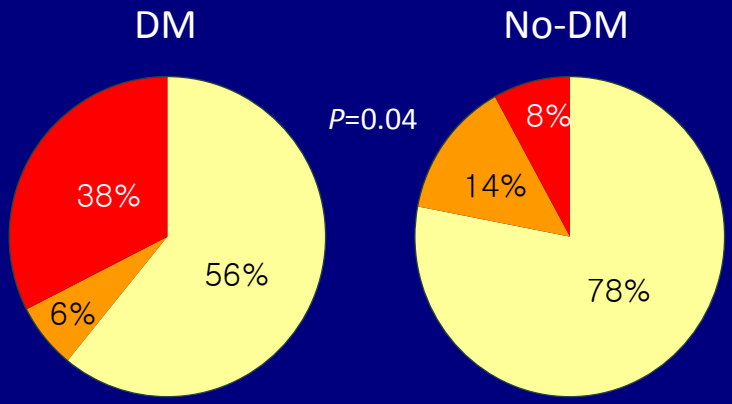


Michelson A. J Thromb Haemost 2006:5;75-81.

Influence of Diabetes Mellitus on Clopidogrel-induced Antiplatelet Effects

Acute phase of treatment[1]

(n=52)

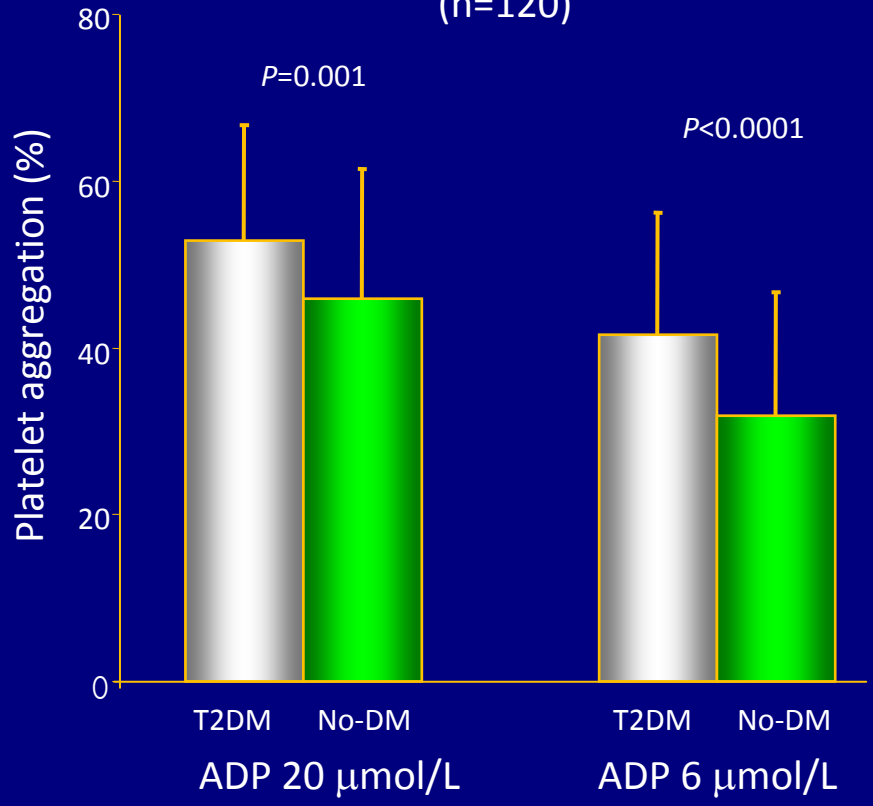


24 hrs post 300 mg LD

- Non-responders (Platelet inhibition <10%)
- Low responders (Platelet inhibition 10-29%)
- Responders (Platelet inhibition >30%)

Long-term phase of treatment[2]

(n=120)



[1]Angiolillo DJ et al. *Diabetes.* 2005;54:2430-5.
[2]Angiolillo DJ et al. *J Am Coll Cardiol* 2006;48:298-304.

Summary

- Variability of response to antiplatelet therapy is a complex issue
- Inter-individual variability is present with or without antiplatelet therapy
- Measured, ex vivo, response to antiplatelet therapy is variable and the reasons are multi-factorial with some being modifiable and some not modifiable
  - Drug-drug interactions
  - Various disease states
  - Poor compliance
- There are limited data correlating variability of response and clinical outcomes. More data are required

Clopidogrel Resistance

-Assessment by VerifyNow-P2Y12 -

1. designed to directly measure the effects of clopidogrel on the P2Y12 receptor
2. more sensitive than ADP-induced platelet aggregometry
3. enhances specificity for the P2Y12 receptor by using prostaglandin E1 to attenuate P2Y1 activation.
4. Results are expressed as

   1) P2Y12 reaction unit (PRU) and

   2) percentage inhibition

   [% inhibition=(1-PRU/estimated baseline)X100].

Clopidogrel Resistance
-Definition-

1. VerifyNow-P2Y12

1) The percent inhibition (%) of <20% indicates the absence of clopidogrel-induced platelet dysfunction and was defined as clopidogrel resistance
2) Prevalence of clopidogrel non-responsiveness has been reported at 5-44%.

2. Light transmittace aggegometry (LTA)

; 5 μmol/l ADP-induced Agg-max>50% have HPPR (High Post-treatment Platelet Reactivity)

Clopidogrel Resistance
-Management-

1. Higher loading dose of clopidogrel
   ; ARMYDA-2, ISAR-CHOICE, ALBION and CURRENT/OASIS 7
2. Higher maintenance dose
   ; OPTIMUS study
3. Addition of other 3rd antiplatelet agent such as cilostazol
   ; ACCEL-RESISTANCE
4. Newer antiplatelet agent; Prasugrel & Ticagrelor
5. Others; Omega-3FA, etc…

How do higher clopidogrel loading doses effect variability of response?

What Is the Relationship of Clopidogrel Dosing on Clinical Outcomes and IPA?

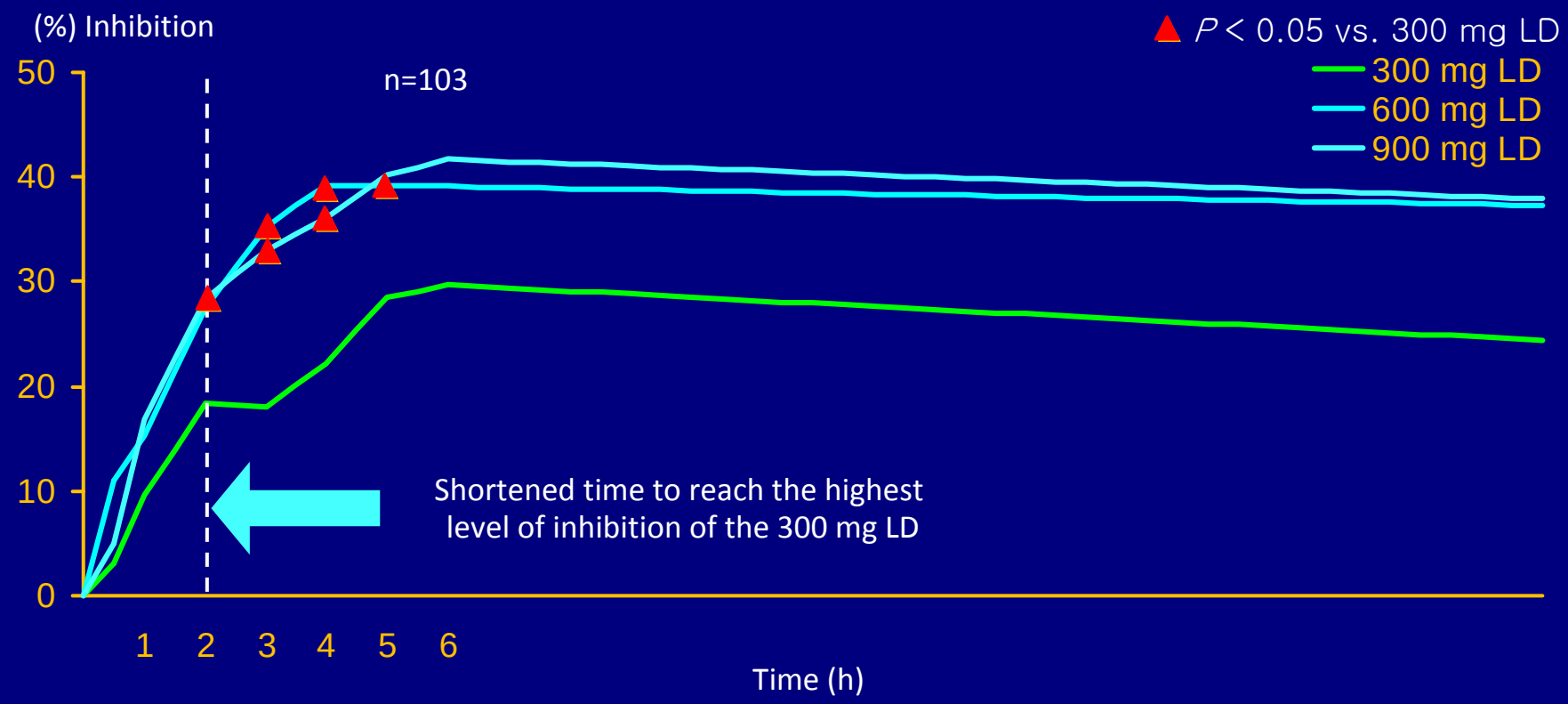
- From a clinical perspective, clopidogrel has been shown to act quickly
  - In COMMIT[1], clinical efficacy seen the first days of treatment with 75mg daily and without any loading dose
  - In CURE[2], clinical efficacy seen within the first hours of treatment with a clopidogrel loading dose of 300mg
  - In CREDO[3], post-hoc analyses shown that the timing for loading patients is also crucial for ensuring a quicker protection
- It has been shown in ISAR-CHOICE[4], ALBION[5], and PREPAIR[6] studies that
  - Higher loading regimen can achieve higher IPA
    - In ISAR-CHOICE and ALBION, there was no significant difference between 600mg* and 900mg*
    - In PREPAIR, there was no significant difference between 300mg and 600mg*
  - Variability of response still exists with higher doses, although to a lesser extent

1.COMMIT collaborative group. Lancet 2005;366:1607-21.
2. Yusuf S et al. Circulation 2003;107:966-72.
3. Steinhubl S et al. J Am Coll Cardiol 2006;47:939-43.
4. von Beckerath N et al. Circulation 2005;112:2946-50.
5. Montalescot G et al. J Am Coll Cardiol 2006;48:931-8.
6. L'Allier et al. JACC 2008;51(11):1066-1072.

*Loading doses greater than 300mg of clopidogrel are outside current labeling

Higher Clopidogrel Doses and IPA (ALBION)

Maximum Inhibition of Platelet Aggregation (5 µM ADP)

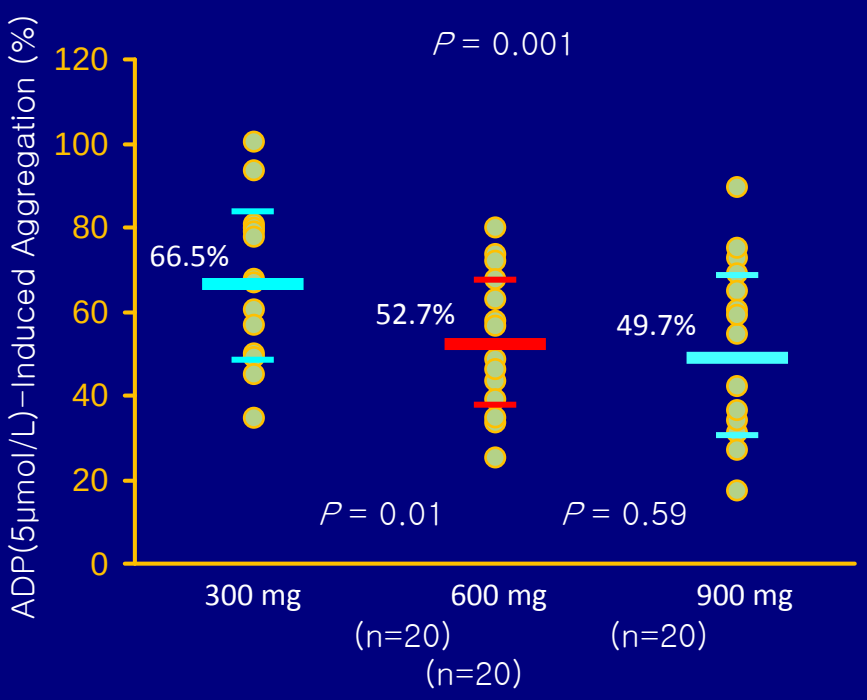


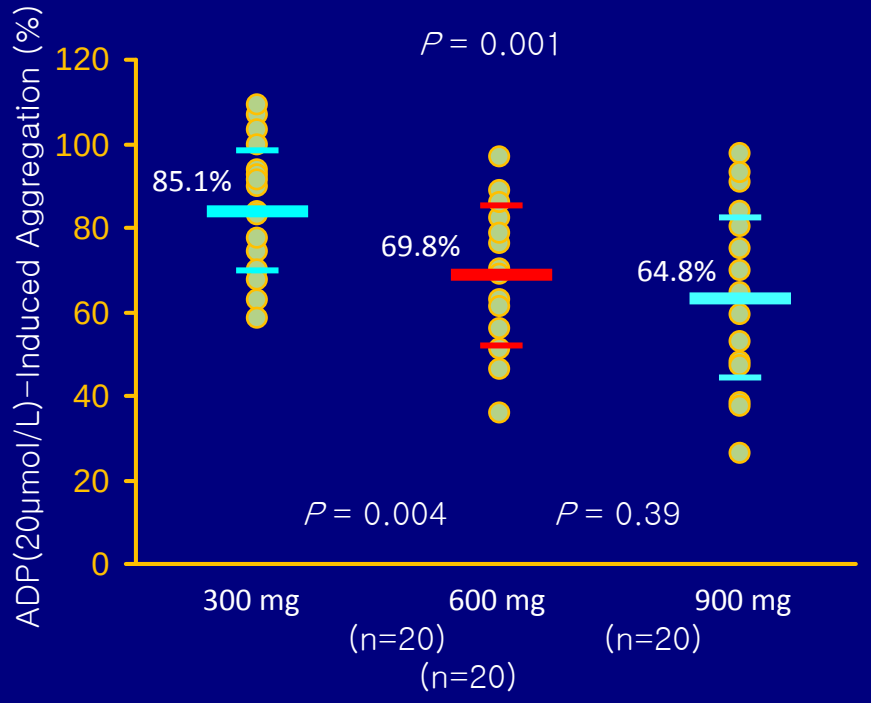
*600mg and 900mg loading doses of clopidogrel are outside current labeling.

Montalescot G, et al. J Am Coll Cardiol 2006;48:931-8.

Higher Clopidogrel Loading Doses and IPA (ISAR-CHOICE)

Greater suppression of ADP–induced (5 and 20μM/L) maximal platelet aggregation with clopidogrel 600mg loading than 300mg loading; no further significant aggregation enhancement with 900 mg LD





*600mg and 900mg loading doses of clopidogrel are outside current labeling

von Beckerath N, et al. Circulation 2005;112:2946-50.

Higher Clopidogrel Loading Doses and IPA (PREPAIR Study)

- 148 patients with suspected or documented coronary artery disease underwent elective angiography and PCI
- Patients were randomly assigned to one of 3 regimens:
  - Group A: clopidogrel 300mg the day before (≥15h) + 75mg the morning of the interventional procedure
  - Group B: clopidogrel 600mg the morning of the interventional procedure (≥2h before)
  - Group C: clopidogrel 600mg the day before (≥15h) + 600mg the morning of the interventional procedure (≥2h before)
- Primary endpoint: % inhibition of peak aggregation (Agg_{peak}) at the time of angiography
- Efficacy Results: % IPA was consistently better in the *clopidogrel 600mg double bolus* group compared to the other 2 regimens
- Safety Results: There was no death, rehospitalization for MI or TVR up to 30 days. Also, there was no episode of major bleeding during the 30 days. Minor bleeding was low and similar in all 3 groups (p=0.19).

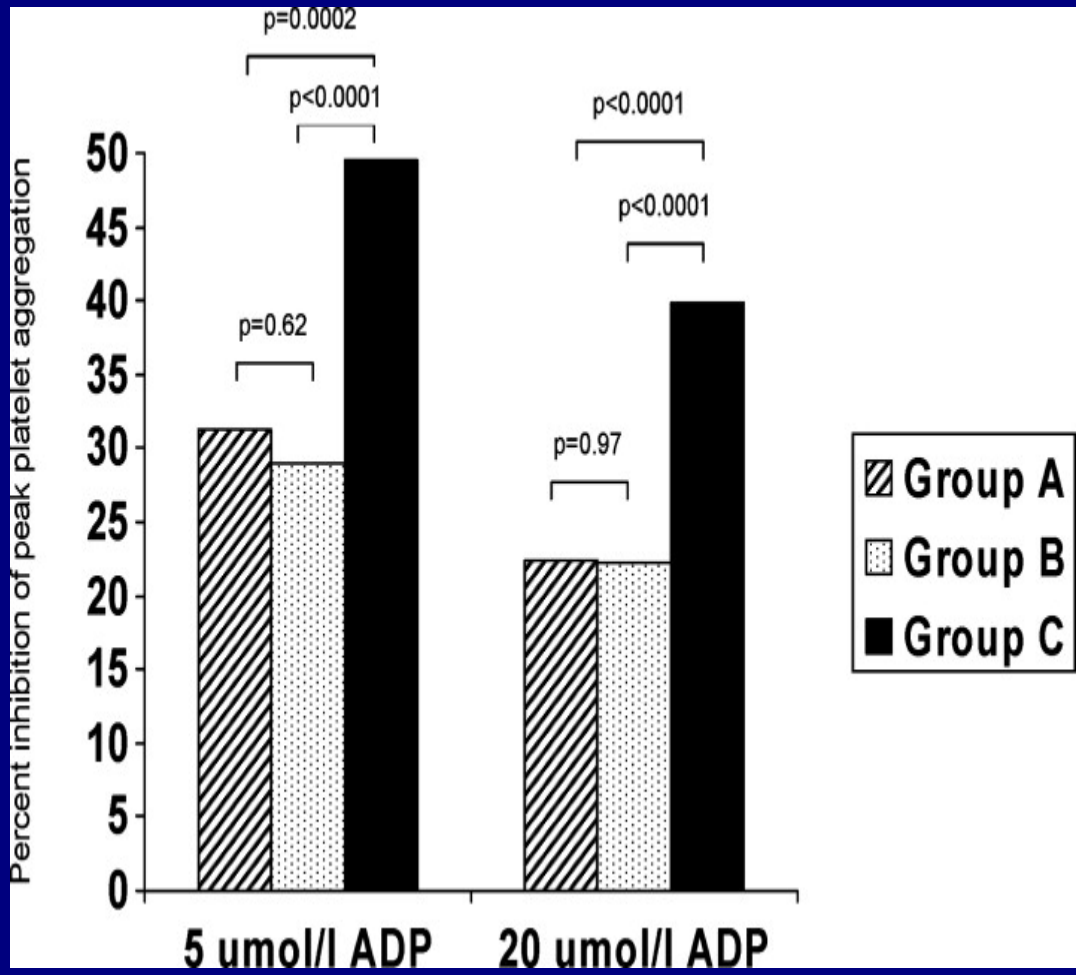
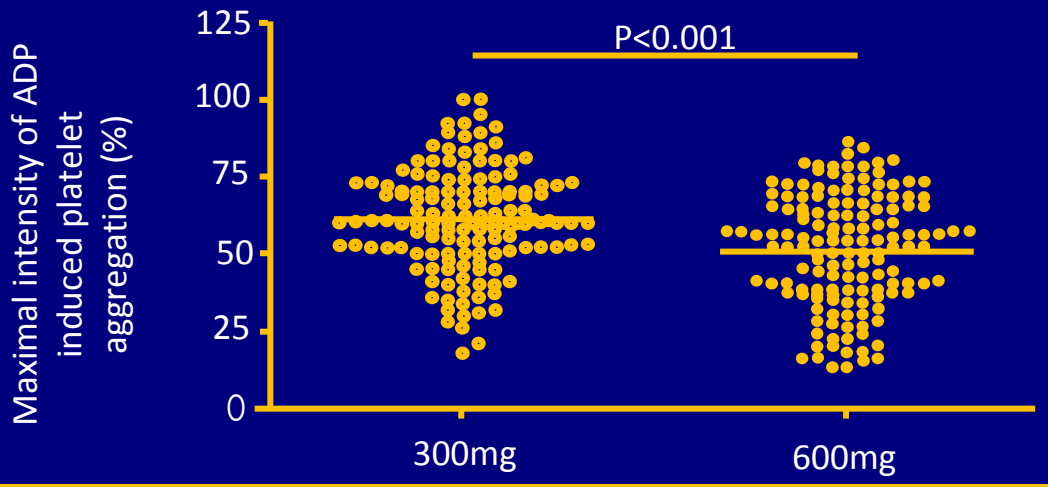


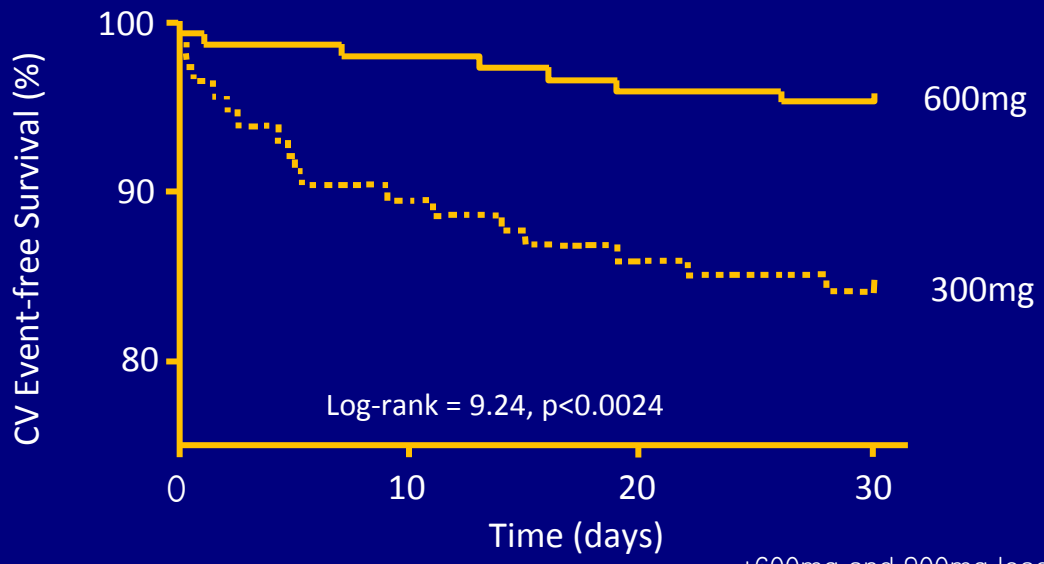
Figure 1. Percent Inhibition of Peak Aggregation
Percent inhibition of peak aggregation was 31.4% (Group A), 29.0% (Group B), and 49.5% (Group C) (p<0.001) when stimulated by 5 µmol/l ADP and 22.4%, 22.3% and 39.8%, respectively, with 20 µmol/l ADP (p<0.0001).
Comparisons between Group C and other groups was significant; and those between Groups A & B were not.

L'Allier et al. JACC 2008;51(11):1066-1072.

Higher Loading Dose and Post-treatment Platelet Reactivity & MACE



n=292

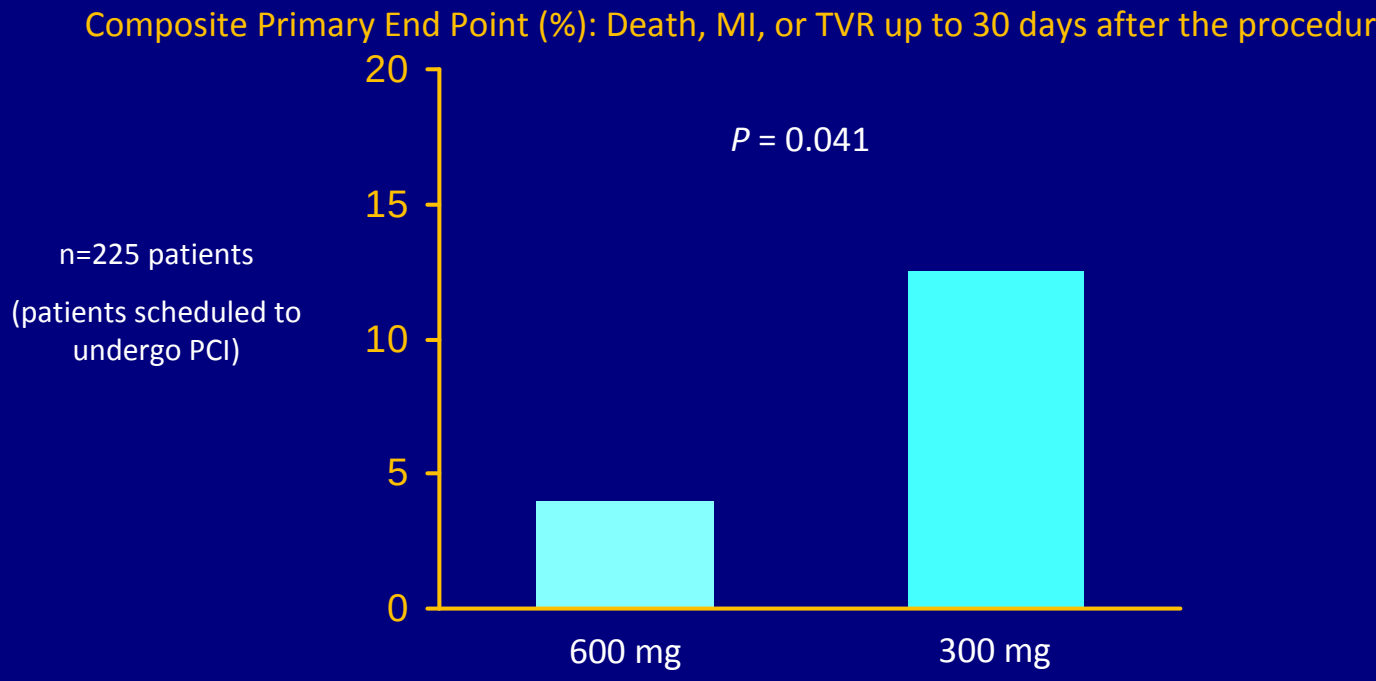


Cuisset T, et al. JACC 2006;48(7):1339-45.

*600mg and 900mg loading doses of clopidogrel are outside current labeling.

Higher Loading Dose and Incidence of MACE in PCI Patients (ARMYDA-2)

- The excess rate of events in the 300 mg group was primarily due to a higher number of MIs
- The incidences of CK-MB, troponin I, and myoglobin elevation were significantly lower in the 600 mg compared with the 300 mg LD group



Patti G, et al. Circulation 2005;111:2099-2106.

*600mg and 900mg loading doses of clopidogrel are outside current labeling.

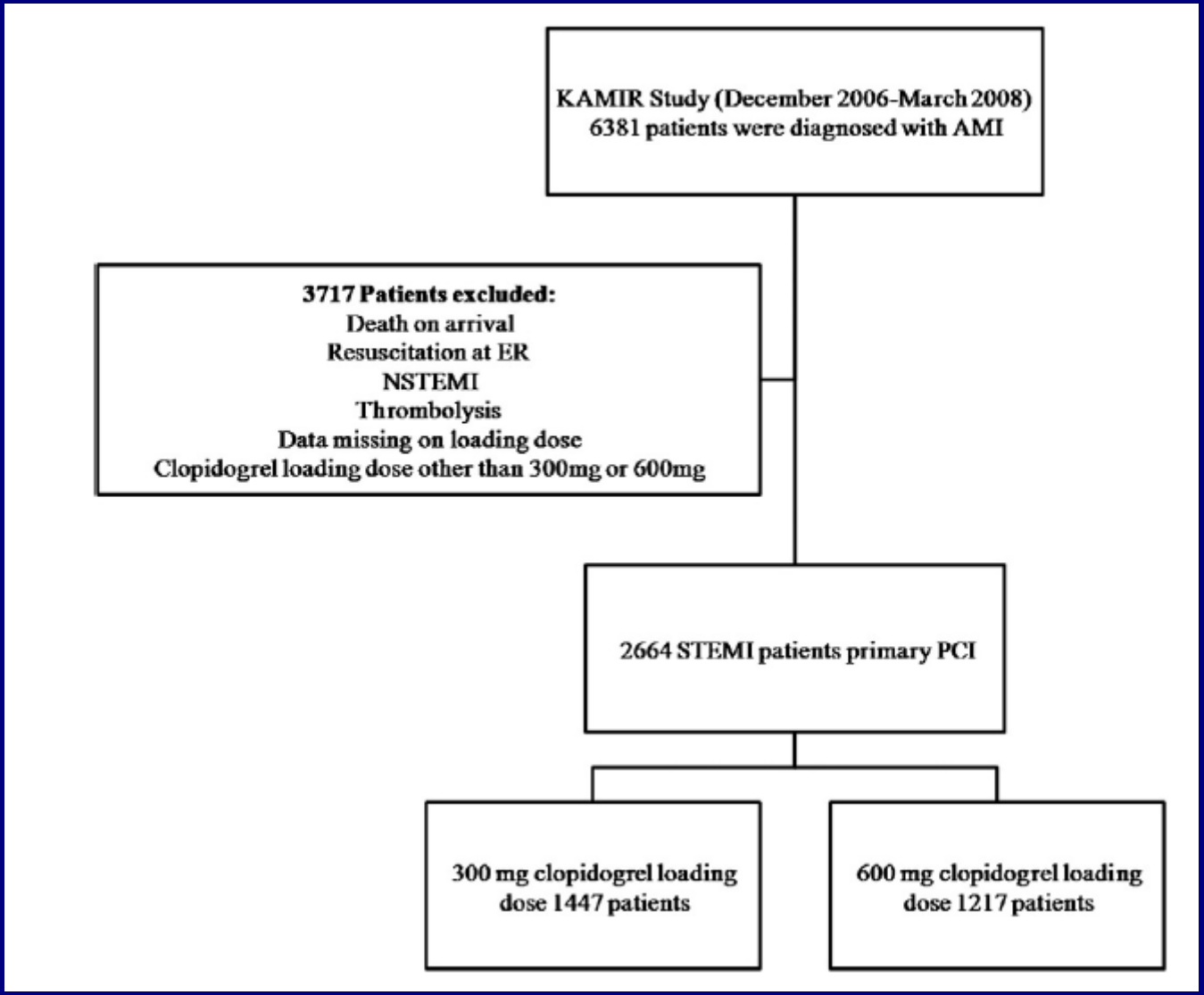
High Loading Dose in Asian?

Standard versus high loading doses of clopidogrel in Asian ST-segment elevation myocardial infarction patients undergoing percutaneous coronary intervention: Insights from the Korea Acute Myocardial Infarction Registry

Cheol Ung Choi, MD,[a] Seung-Woon Rha, MD,[a] Dong Joo Oh, MD,[a] Kanhaiya L. Poddar, MBBS,[a] Jin Oh Na, MD,[a] Jin Won Kim, MD,[a] Hong Euy Lim, MD,[a] Eung Ju Kim, MD,[a] Chang Gyu Park, MD,[a] Hong Seog Seo, MD,[a] Taek Jong Hong, MD,[b,t] Jong-Seon Park, MD,[c,t] Young Jo Kim, MD,[c,t] Seung Ho Hur, MD,[d,t] In Whan Seong, MD,[e,t] Jei Keon Chae, MD,[f,t] Myeong Chan Cho, MD,[g,t] Jang Ho Bae, MD,[h,t] Dong Hoon Choi, MD,[i,t] Yang Soo Jang, MD,[i,t] In Ho Chae, MD,[j,t] Hyo Soo Kim, MD,[k,t] Chong Jin Kim, MD,[l,t] Jung Han Yoon, MD,[m,t] Tae Hoon Ahn, MD,[n,t] Seung-Jea Tahk, MD,[o,t] Wook Sung Chung, MD,[p,t] Ki Bae Seung, MD,[p,t] Shung Chall Chae, MD,[q,t] Seung Jung Park, MD,[r,t] Young Keun Ahn, MD,[s,t] and Myung Ho Jeong, MD[s,t] *Seoul, Pusan, Daegu, Daejeon, Jeonju, Chongju, Bundang, Wonju, and Gwangju, South Korea*

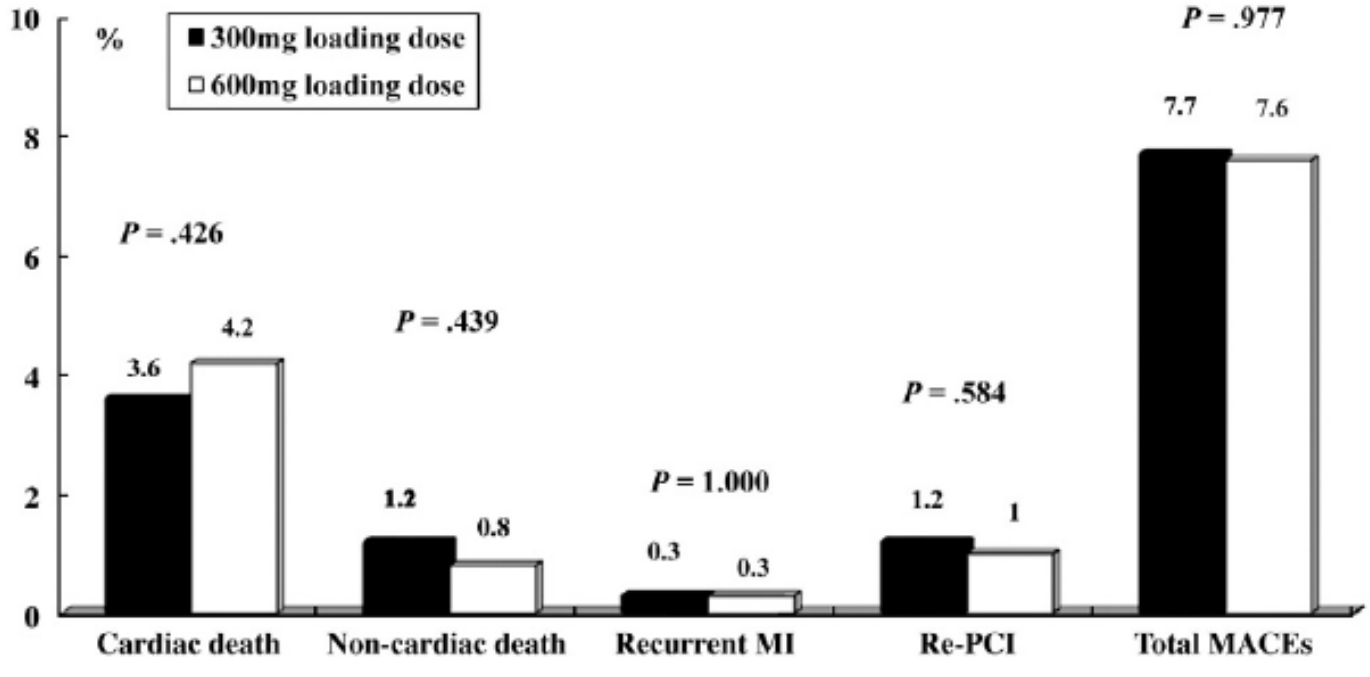
Choi CU, Rha SW, Oh DJ. Am Heart J 2011;161:373-382.e3

Study Flow Chart



In-hospital and 1 month Clinical Outcomes

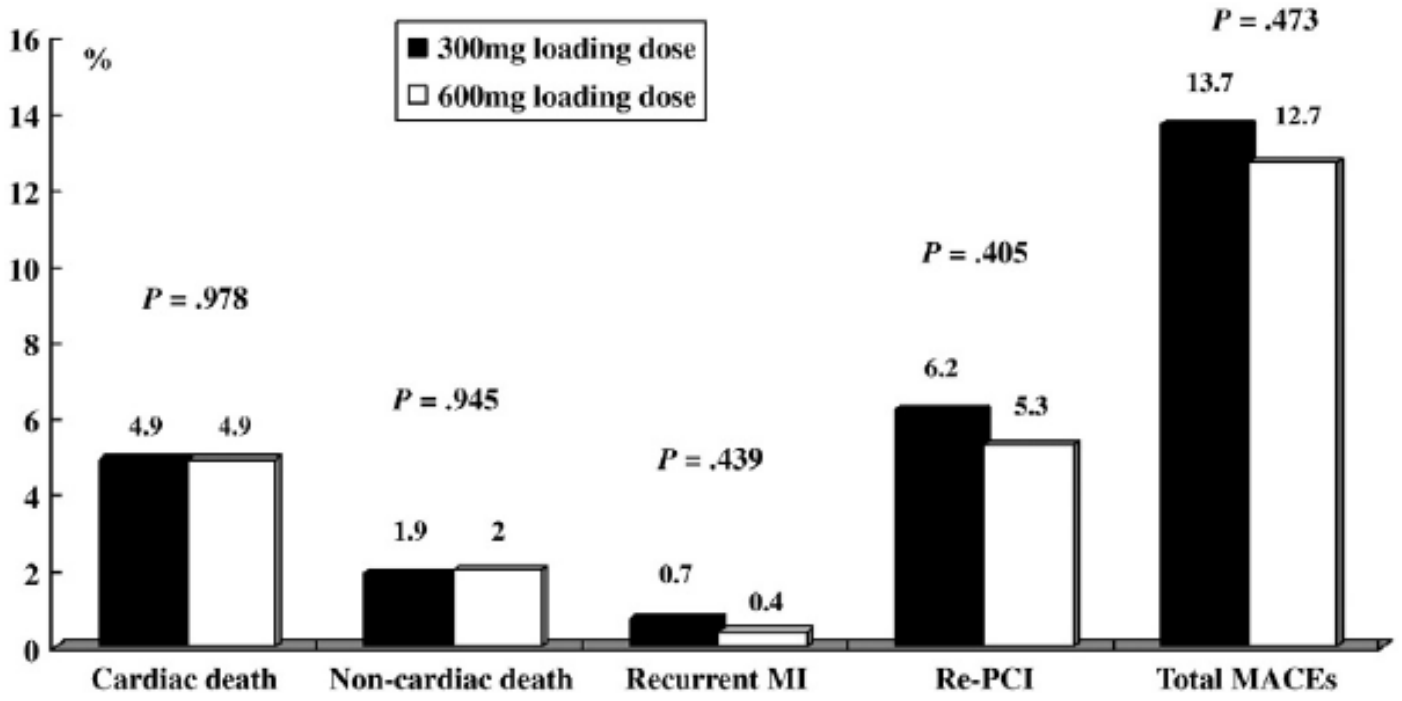
Figure 2



Choi CU, Rha SW, Oh DJ. Am Heart J 2011;161:373-382.e3

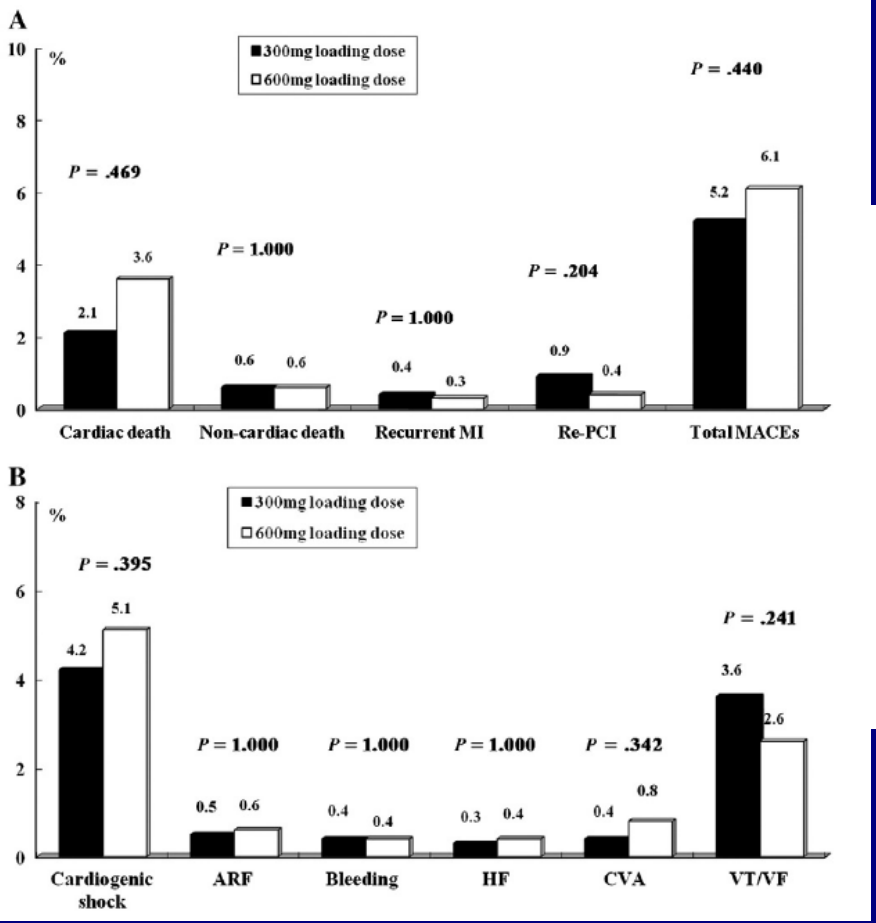
Twelve-month Clinical Outcomes

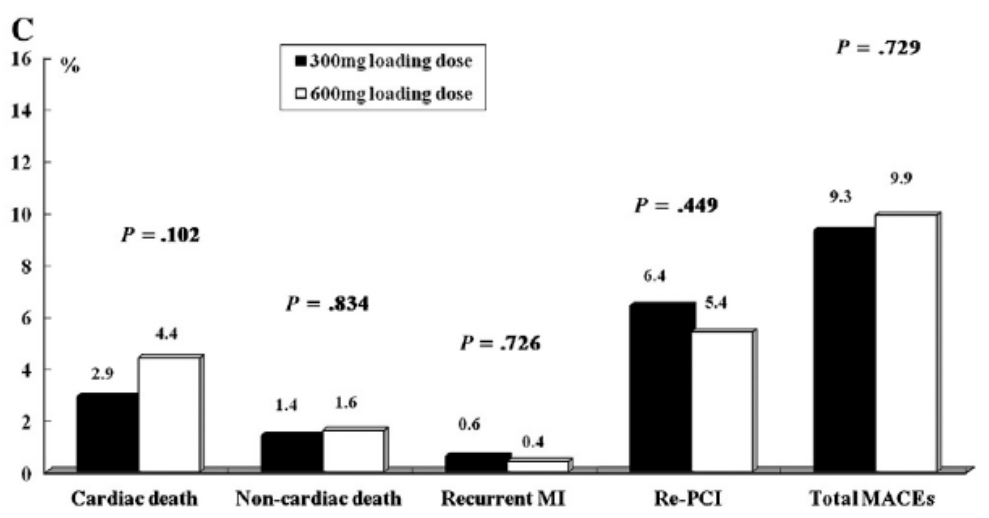
Figure 4



Choi CU, Rha SW, Oh DJ. Am Heart J 2011;161:373-382.e3

Clinical Outcomes after Propensity-Score Matched Analysis





Choi CU, Rha SW, Oh DJ. Am Heart J 2011;161:373-382.e3

Summary & Conclusion

1. There were no difference in 1-and 12-month major clinical outcomes between the two groups in Korean AMI (STEMI) patients.
2. There were no differences in major bleeding complications between the two groups.

….*Standard loading dose* of clopidogrel may be as safe and similarly effective as the high loading dose *in Asian STEMI patients* undergoing primary PCI.

Choi CU, Rha SW, Oh DJ. Am Heart J 2011;161:373-382.e3

Summary

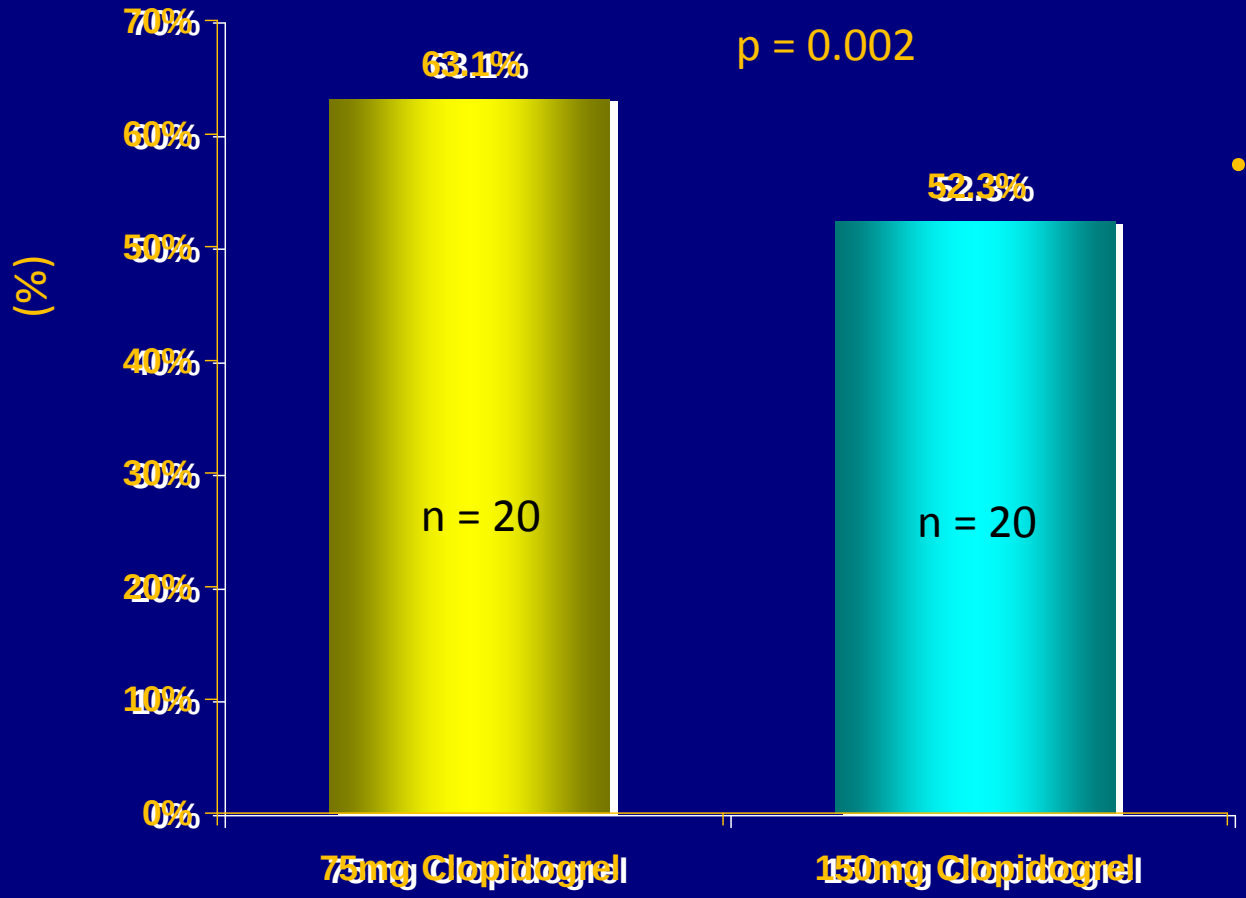
- The rate & extent of IPA are related, at least in part, to the dosing of clopidogrel
- Clopidogrel 600mg increases both the rate & extent of IPA compared to 300mg
- Data from a limited number of small studies suggest a benefit with 600mg versus 300mg in some patients
  Also data from one small randomized study suggests a benefit in IPA with 600mg double bolus of clopidogrel.

*600mg and 900mg loading doses of clopidogrel are outside current labeling.

How do higher clopidogrel maintenance doses effect variability of response?

Higher Maintenance Dose and IPA (OPTIMUS)

Study Time Point 2: Maximal ADP-Induced (20 µmol/L) Platelet Aggregation

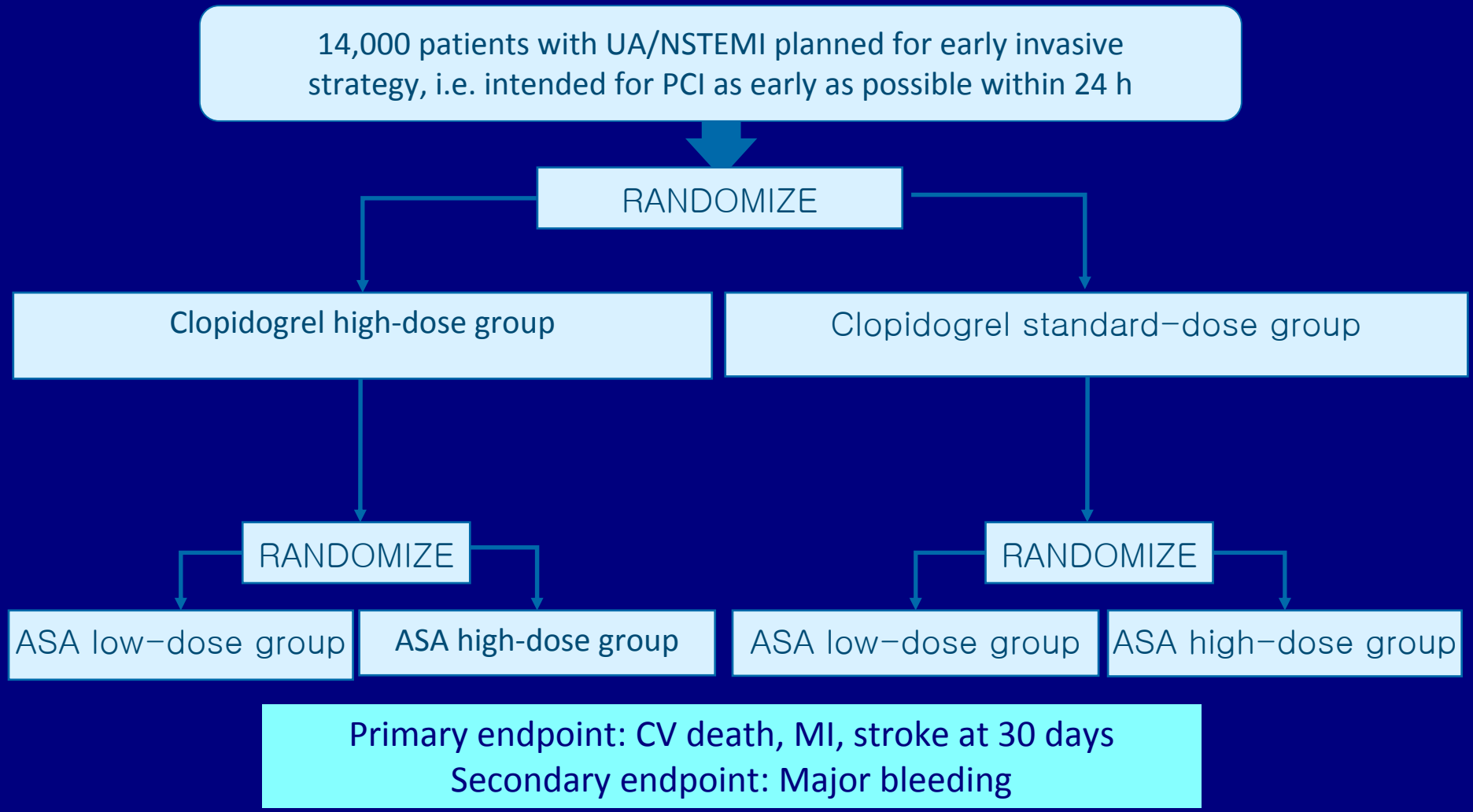


- Platelet aggregation was significantly reduced in the 150mg group compared with the 75mg group (63.1% vs. 52.3%, p=0.002)

*150mg maintenance dose of clopidogrel is outside current labeling

Angiolillo, et al. Circulation 2007;115:708-16.

The CURRENT Study



www.ClinicalTrials.gov

Current Oasis-7

Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial

*Shamir R Mehta, Jean-Francois Tanguay, John W Eikelboom, Sanjit S Jolly, Campbell D Joyner, Christopher B Granger, David P Faxon, Hans-Jurgen Rupprecht, Andrzej Budaj, Alvaro Avezum, Petr Widimsky, Philippe Gabriel Steg, Jean-Pierre Bassand, Gilles Montalescot, Carlos Macaya, Giuseppe Di Pasquale, Kari Niemela, Andrew E Ajani, Harvey D White, Susan Chrolavicius, Peggy Gao, Keith A A Fox, Salim Yusuf, on behalf of the CURRENT-OASIS 7 trial investigators**

Interpretation In patients undergoing PCI for acute coronary syndromes, a 7-day double-dose clopidogrel regimen was associated with a reduction in cardiovascular events and stent thrombosis compared with the standard dose. Efficacy and safety did not differ between high-dose and low-dose aspirin. A double-dose clopidogrel regimen can be considered for all patients with acute coronary syndromes treated with an early invasive strategy and intended early PCI.

Mehta SR et al. Lancet 2010;376;1233–43

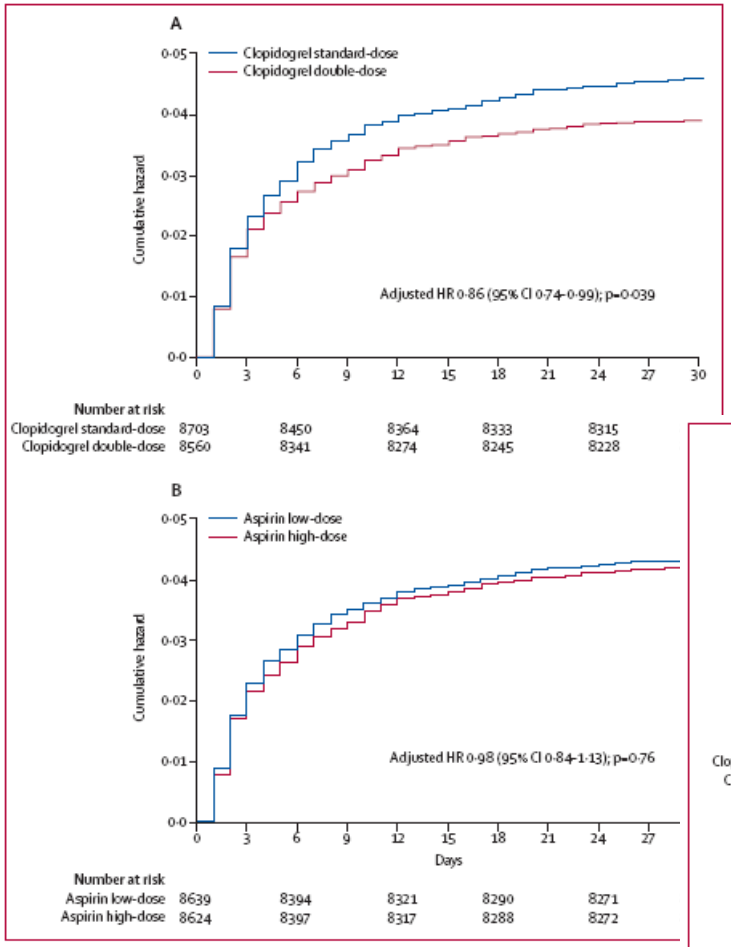


Figure 2: Kaplan-Meier curves for the primary outcome of cardiovascular death, myocardial infarction, stroke, for the clopidogrel dose comparison (A) and the aspirin dose comparison (B)
HR=hazard ratio.

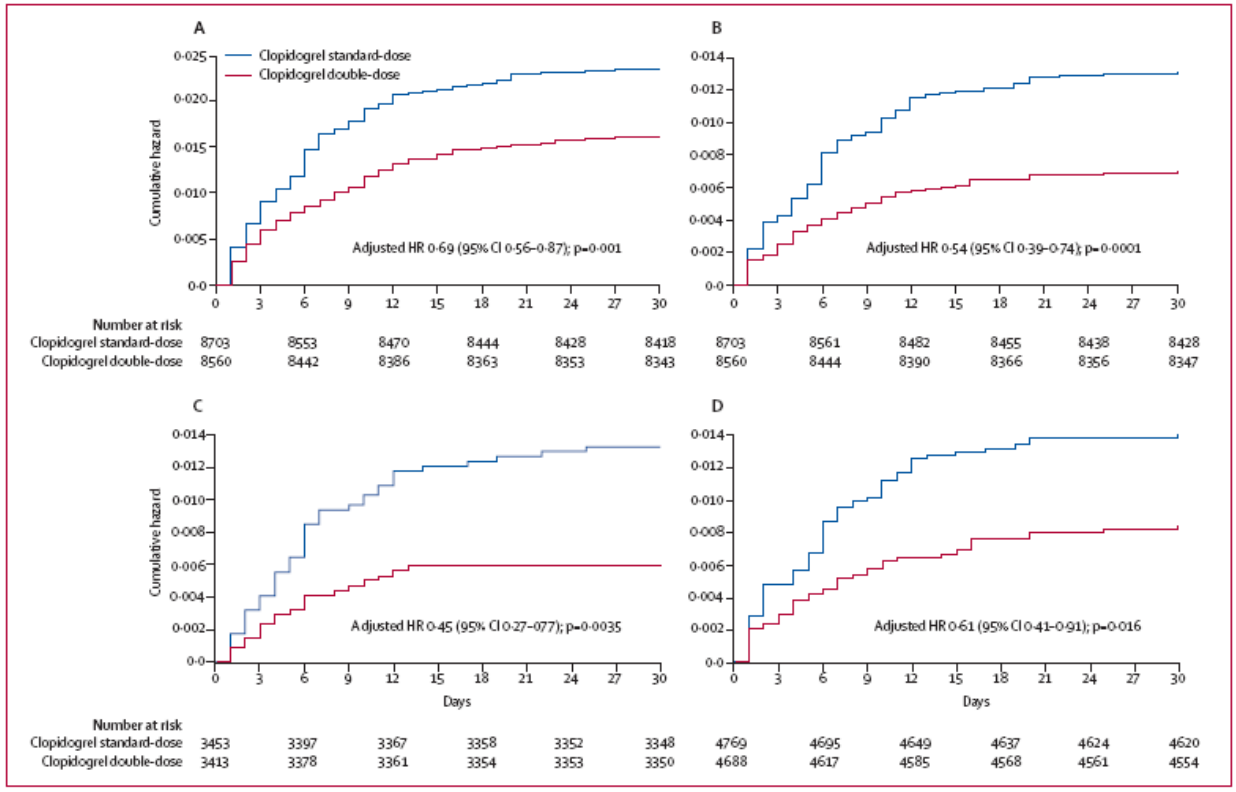


Figure 3: Kaplan-Meier curves for clopidogrel dose comparison for definite or probable stent thrombosis (A), definite stent thrombosis (B), definite stent thrombosis in patients receiving a drug-eluting stent (C), and definite stent thrombosis in patients receiving bare-metal stents (D)
HR=hazard ratio.

Mehta SR et al. Lancet 2010;376;1233–43

Dose Comparisons of Clopidogrel and Aspirin in ACS

ORIGINAL ARTICLE

Dose Comparisons of Clopidogrel and Aspirin in Acute Coronary Syndromes

The CURRENT–OASIS 7 Investigators*

CONCLUSIONS

In patients with an acute coronary syndrome who were referred for an invasive strategy, there was no significant difference between a 7-day, double-dose clopidogrel regimen and the standard-dose regimen, or between higher-dose aspirin and lower-dose aspirin, with respect to the primary outcome of cardiovascular death, myocardial infarction, or stroke. (Funded by Sanofi-Aventis and Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00335452.)

NEJM 2010;363:930–42

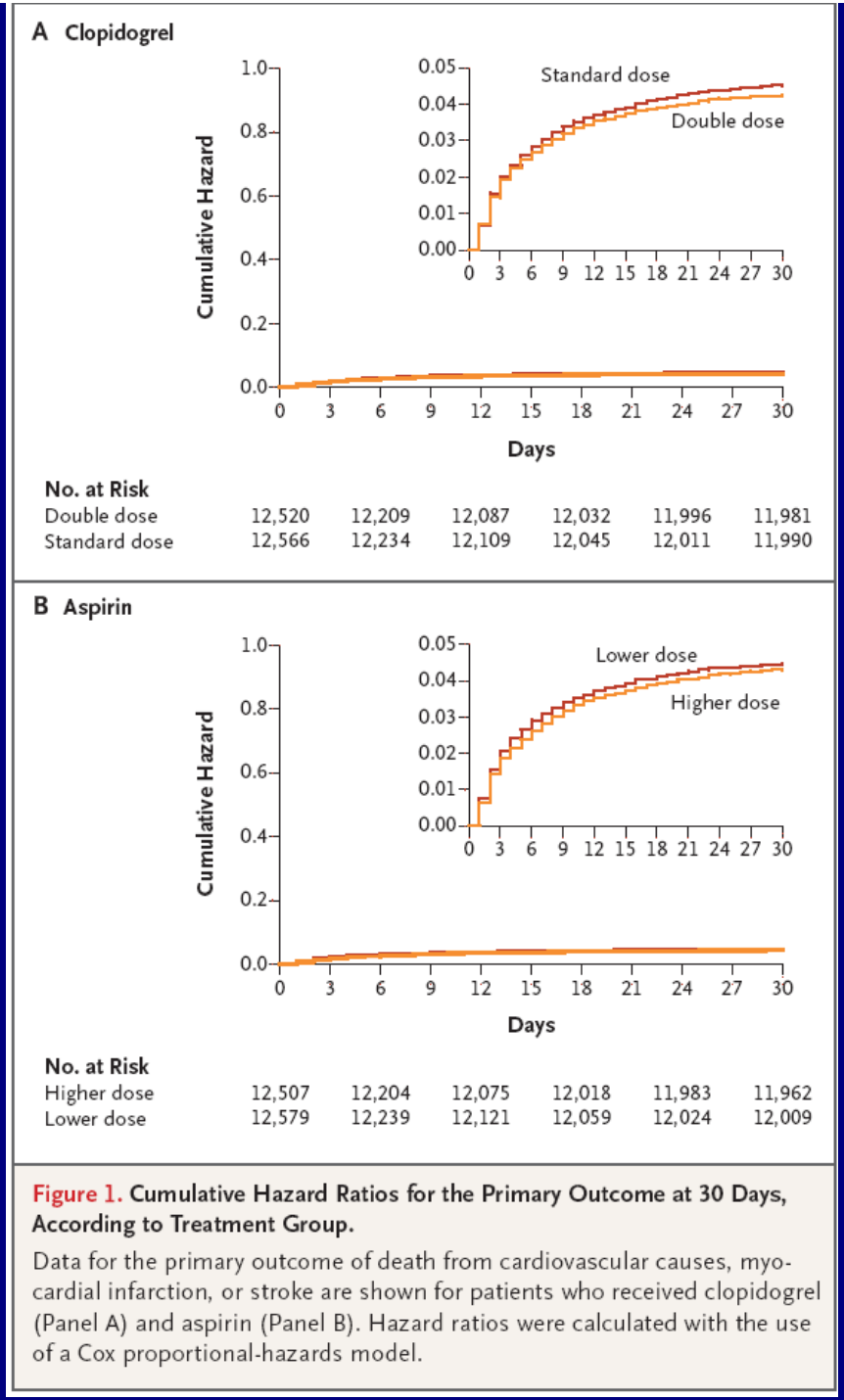


Figure 1. Cumulative Hazard Ratios for the Primary Outcome at 30 Days, According to Treatment Group.

Data for the primary outcome of death from cardiovascular causes, myocardial infarction, or stroke are shown for patients who received clopidogrel (Panel A) and aspirin (Panel B). Hazard ratios were calculated with the use of a Cox proportional-hazards model.

NEJM 2010;363:930–42

Summary

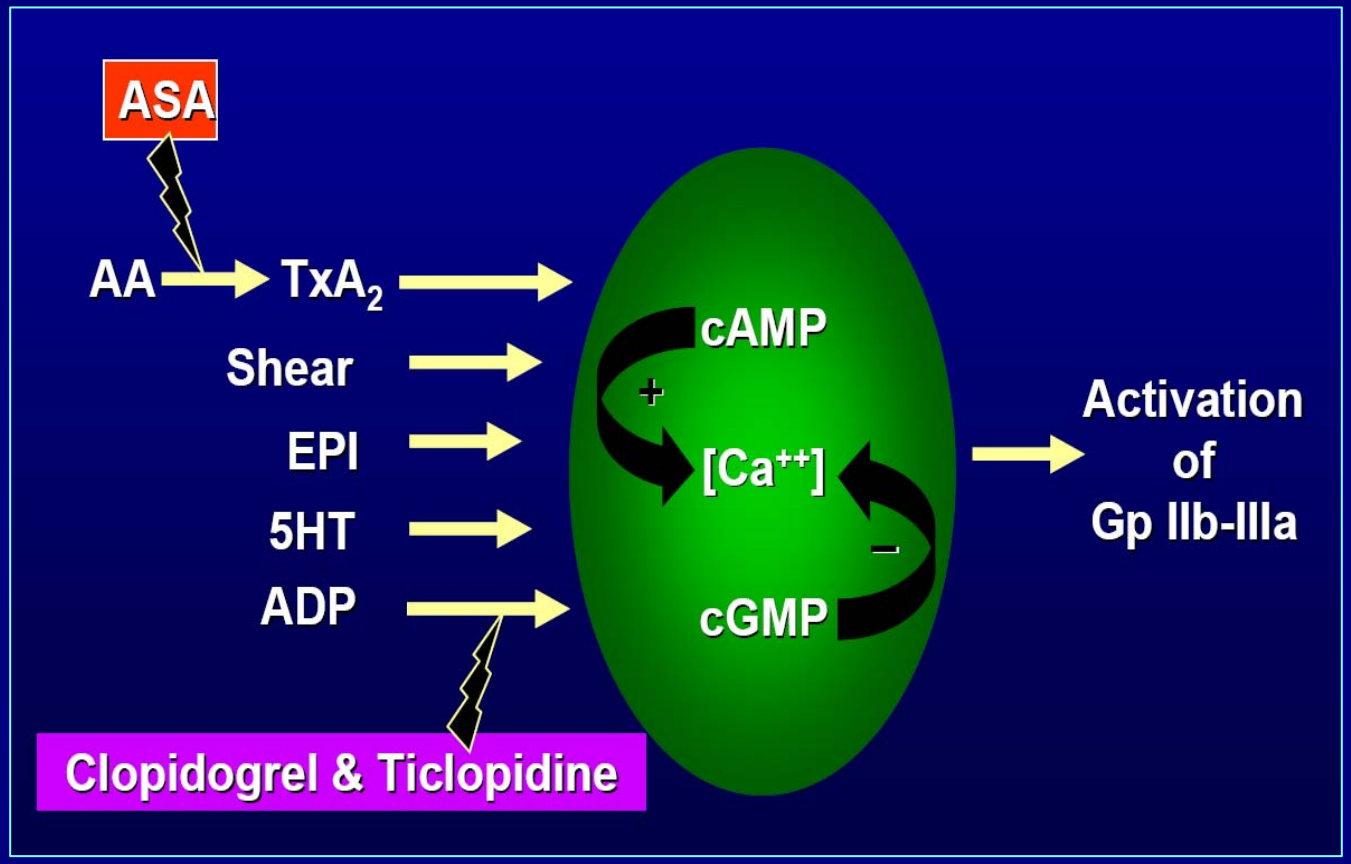
- The rate & extent of IPA are related, at least in part, to the dosing of clopidogrel

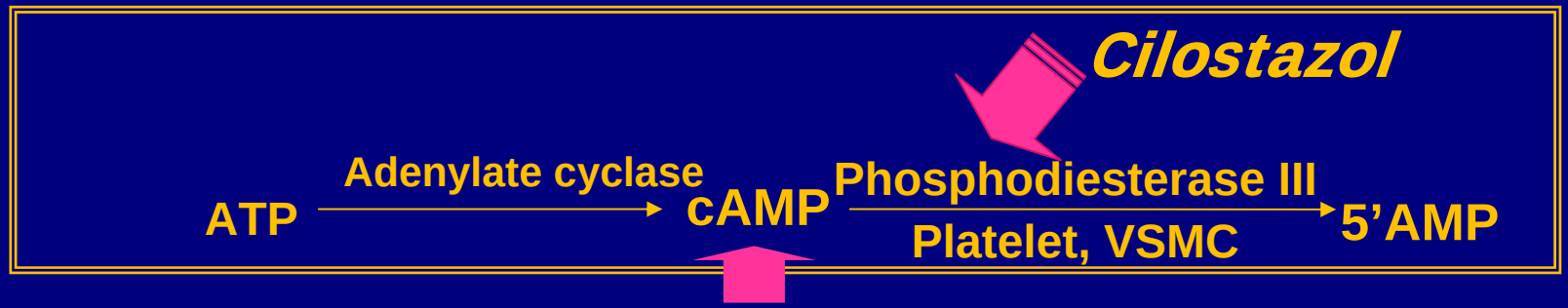
- The 150mg maintenance dose may be beneficial in some patients. Larger studies are needed and underway

*150mg maintenance dose is outside current labeling

Cilostazol in High Risk Subsets

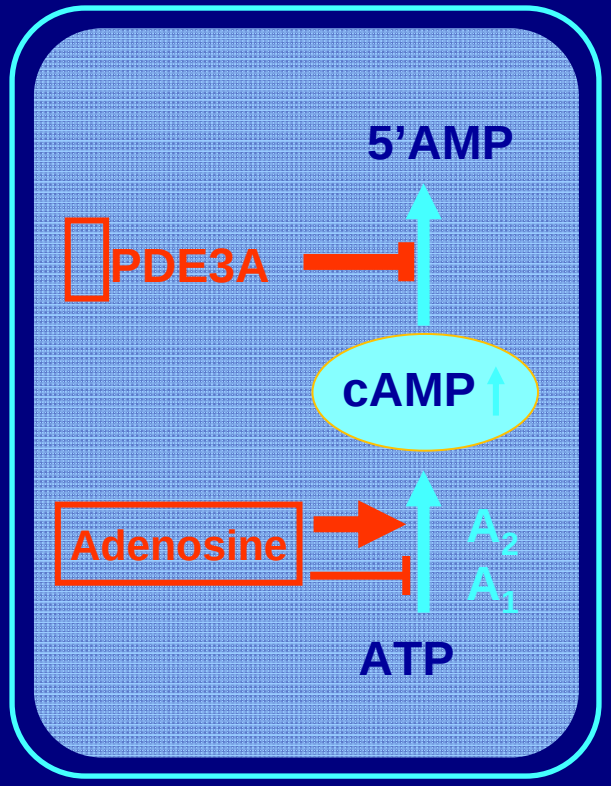
Antiplatelet Agents

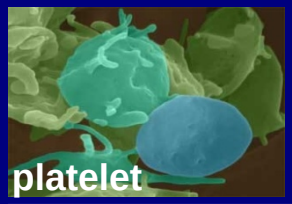
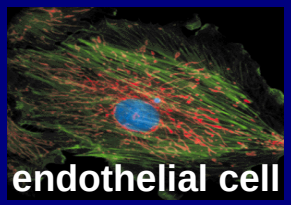




Cilostazol

- Cellular targets



Targets	cAMP actions (selected)
 platelet	Inhibition of aggregation, inhibition of expression of adhesion molecules
 endothelial cell	Inhibition of expression of adhesion molecules, angiogenesis
 smooth muscle cell	Vasodilatory action, inhibition of proliferation, migration and matrix synthesis, headache
 Cardiomyocyte	Palpitation, tachycardia

Pleiotropic Effects of Cilostazol

1. Inhibition of VSMC growth
2. Restoration of Endothelial dysfunction
3. Atherosclerotic plaque stabilization
4. Reduced leukocyte adhesiveness
5. Reduced ischemia-reperfusion injury
6. Enhanced angiogenesis
7. Platelet inhibition and anti-thrombosis

Atherosclerosis suppl 2006;6:1–52

Triple Versus Dual Antiplatelet Therapy in Patients with *Acute ST-Segment Elevation Myocardial Infarction* Undergoing Primary Percutaneous Coronary Intervention

Kang-Yin Chen, *Seung-Woon Rha*, Yong-Jian Li, Kanhaiya L. Poddar, Jae Hyoung Park, Jin Oh Na, *Cheol Ung Choi*, Hong Euy Lim, Jin Won Kim, Eung Ju Kim, Chang Gyu Park, Hong Seog Seo, Dong Joo Oh, Young Keun Ahn*, Myung Ho Jeong*

Korea University Guro Hospital, Seoul, Korea
* Chonnam National University Hospital, Gwangju, Korea

Chen KY, Rha SW. et al. Circulation 2009;119:3207-3214

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

Triple Versus Dual Antiplatelet Therapy in Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

Kang-Yin Chen, Seung-Woon Rha, Yong-Jian Li, Kanhaiya L. Poddar, Zhe Jin, Yoshiyasu Minami, Lin Wang, Eung Ju Kim, Chang Gyu Park, Hong Seog Seo, Dong Joo Oh, Myung Ho Jeong, Young Keun Ahn, Taek Jong Hong, Young Jo Kim, Seung Ho Hur, In Whan Seong, Jei Keon Chae, Myeong Chan Cho, Jang Ho Bae, Dong Hoon Choi, Yang Soo Jang, In Ho Chae, Chong Jin Kim, Jung Han Yoon, Wook Sung Chung, Ki Bae Seung, Seung Jung Park and for the Korea Acute Myocardial Infarction Registry Investigators

Circulation published online Jun 15, 2009;

Background—Whether triple antiplatelet therapy is superior or similar to dual antiplatelet therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention in the era of drug-eluting stents remains unclear.

Methods and Results—A total of 4203 ST-segment elevation myocardial infarction patients who underwent primary percutaneous coronary intervention with drug-eluting stents were analyzed retrospectively in the Korean Acute Myocardial Infarction Registry (KAMIR). They received either dual (aspirin plus clopidogrel; dual group; n=2569) or triple (aspirin plus clopidogrel plus cilostazol; triple group; n=1634) antiplatelet therapy. The triple group received additional cilostazol at least for 1 month. Various major adverse cardiac events at 8 months were compared between these 2 groups. Compared with the dual group, the triple group had a similar incidence of major bleeding events but a significantly lower incidence of in-hospital mortality. Clinical outcomes at 8 months showed that the triple group had significantly lower incidences of cardiac death (adjusted odds ratio, 0.52; 95% confidence interval, 0.32 to 0.84; $P=0.007$), total death (adjusted odds ratio, 0.60; 95% confidence interval, 0.41 to 0.89; $P=0.010$), and total major adverse cardiac events (adjusted odds ratio, 0.74; 95% confidence interval, 0.58 to 0.95; $P=0.019$) than the dual group. Subgroup analysis showed that older (>65 years old), female, and diabetic patients got more benefits from triple antiplatelet therapy than their counterparts who received dual antiplatelet therapy.

Conclusions—Triple antiplatelet therapy seems to be superior to dual antiplatelet therapy in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with drug-eluting stents. These results may provide the rationale for the use of triple antiplatelet therapy in these patients. (*Circulation*. **2009;119:3207-3214.**)

Purpose

; The present study was designed to evaluate the safety and efficacy of additional administration of cilostazol combined with aspirin and clopidogrel in patients with acute STEMI who underwent primary PCI in Korea Acute Myocardial Infarction Registry (KAMIR).

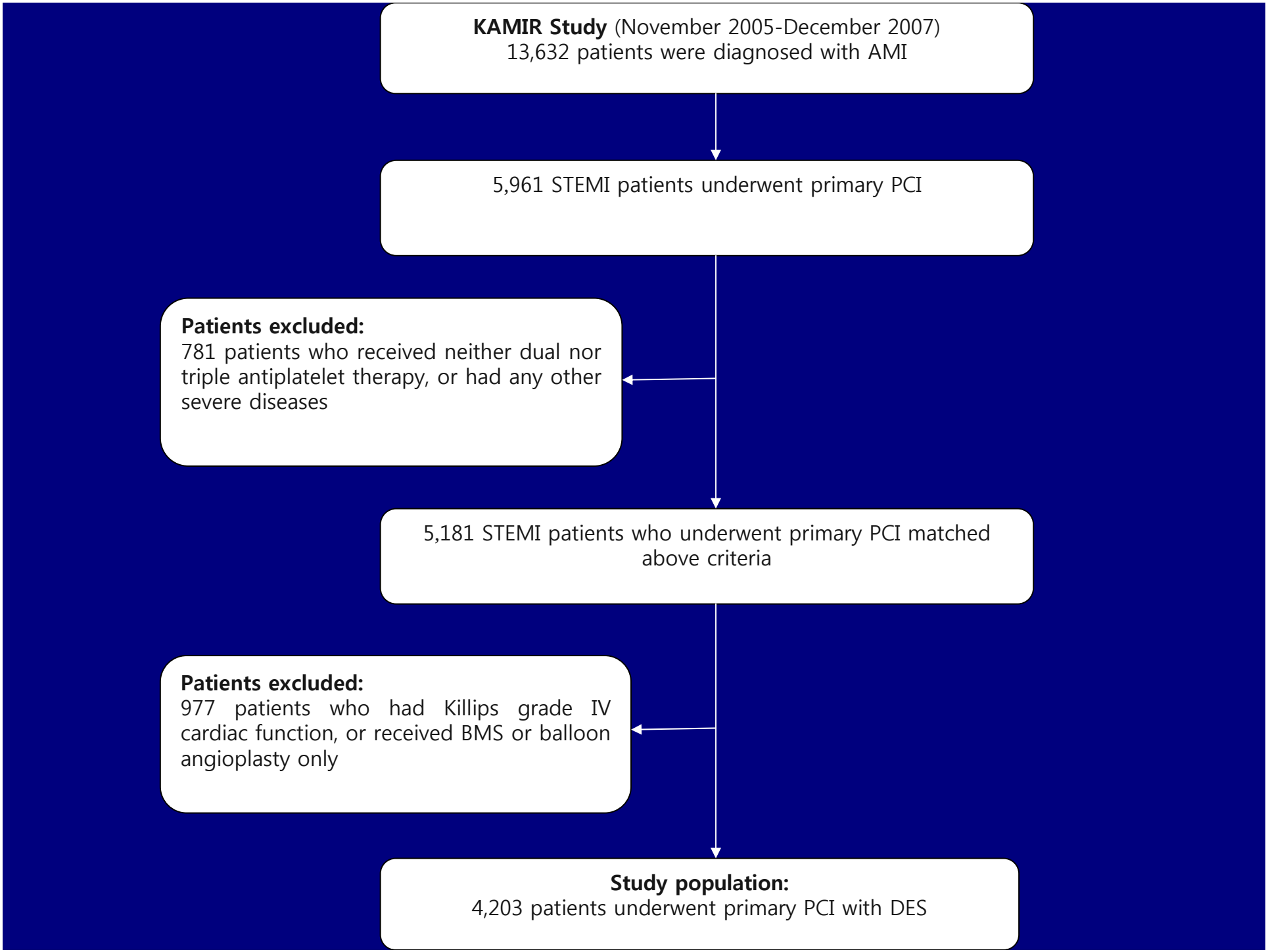
Methods

3. Study Groups

All the pts were assigned to receive one of the following antiplatelet regimens:

1) Dual antiplatelet therapy group (aspirin plus clopidogrel, Dual group, n=2,569 pts);

2) Triple antiplatelet therapy group (aspirin plus clopidogrel plus cilostazol, Triple group, n=1,634 pts).


KAMIR Study (November 2005-December 2007)
13,632 patients were diagnosed with AMI
5,961 STEMI patients underwent primary PCI
Patients excluded:
781 patients who received neither dual nor triple antiplatelet therapy, or had any other severe diseases
5,181 STEMI patients who underwent primary PCI matched above criteria
Patients excluded:
977 patients who had Killips grade IV cardiac function, or received BMS or balloon angioplasty only
Study population:
4,203 patients underwent primary PCI with DES

Methods

4. Antiplatelet Regimen

1) Aspirin; preloaded 200mg, and then 100 mg orally, indefinitely
2) Clopidogrel (Plavix®); preloaded 600 mg before PCI, followed by daily administration of 75 mg and encouraged to continue at least for 1 year.
3) Cilostazol (Pletaal®); preloaded 200 mg before PCI, followed by daily administration of 100 mg bid and encouraged to continue at least for 1 month.
4) In case of suspicious higher risk of stent thrombosis; the glycoprotein IIb/IIIa was administered on physician's discretion.

Methods

6. Study Definition

1) *Revascularization*; both Re-PCI and CABG

2) *All MACE*; included total death, revascularization, and myocardial re-infarction.

7. Study Endpoints

1) The bleeding and vascular complications

2) The clinical outcomes of in-hospital and 8 months between the two groups.

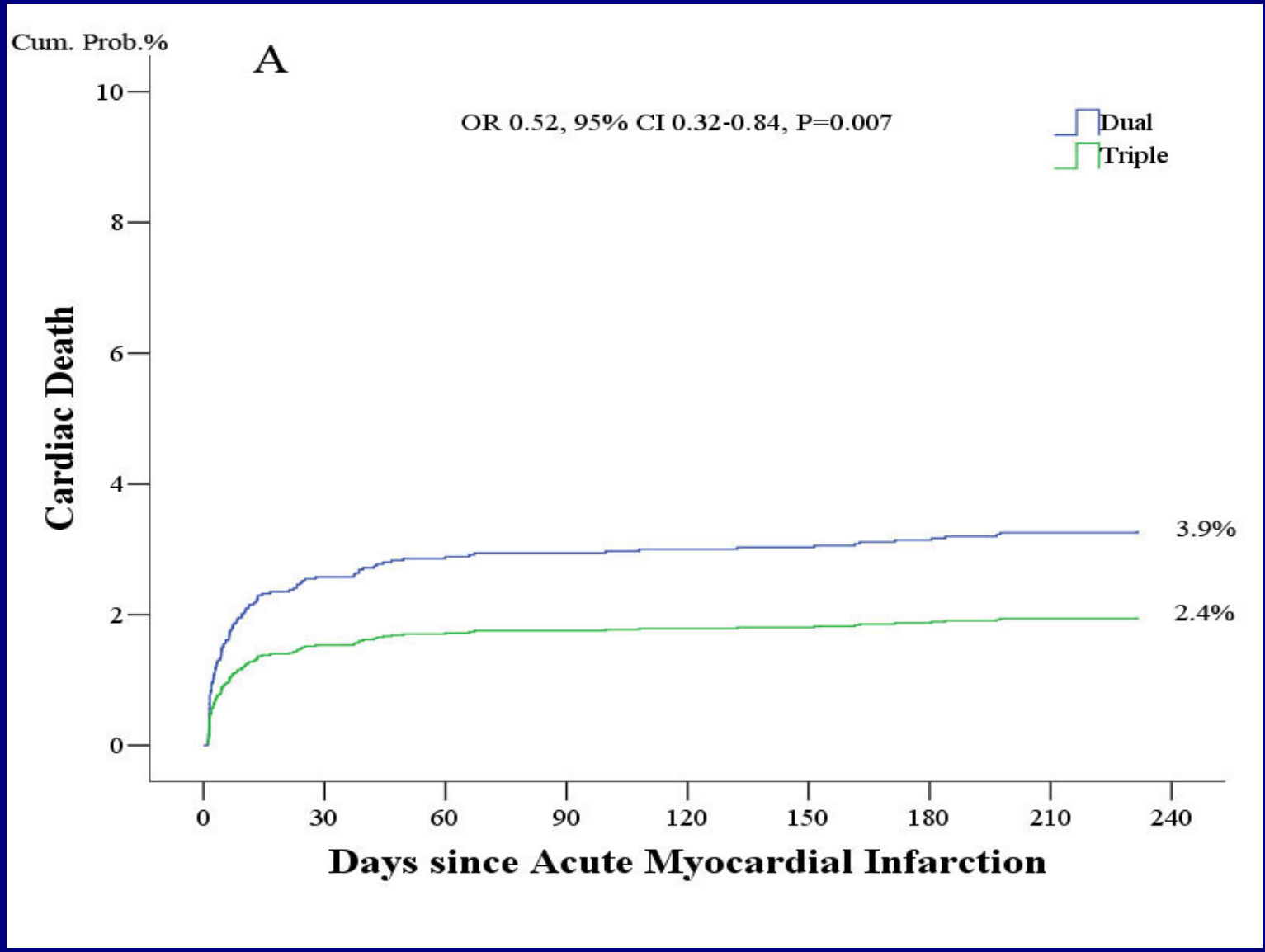
Clinical Outcomes

Variables, n (%)	Dual (n=2,569)	Triple (n=1,634)	*P* value
In-hospital outcomes			
Cardiac death	61 (2.4)	21 (1.3)	0.013
Total death	88 (3.4)	36 (2.2)	0.022
Recurrent MI	6 (0.2)	6 (0.4)	0.429
Major bleeding events	10 (0.4)	3 (0.2)	0.242
Outcomes at 8 months			
Cardiac death	83 (3.2)	33 (2.0)	0.019
Total death	125 (4.9)	51 (3.1)	0.006
Recurrent MI	9 (0.4)	7 (0.4)	0.689
CABG	4 (0.2)	2 (0.1)	1.000
Re-PCI	101 (3.9)	61 (3.7)	0.745
TLR	29 (1.1)	27 (1.7)	0.149
Total MACE	240 (9.3)	124 (7.6)	0.049

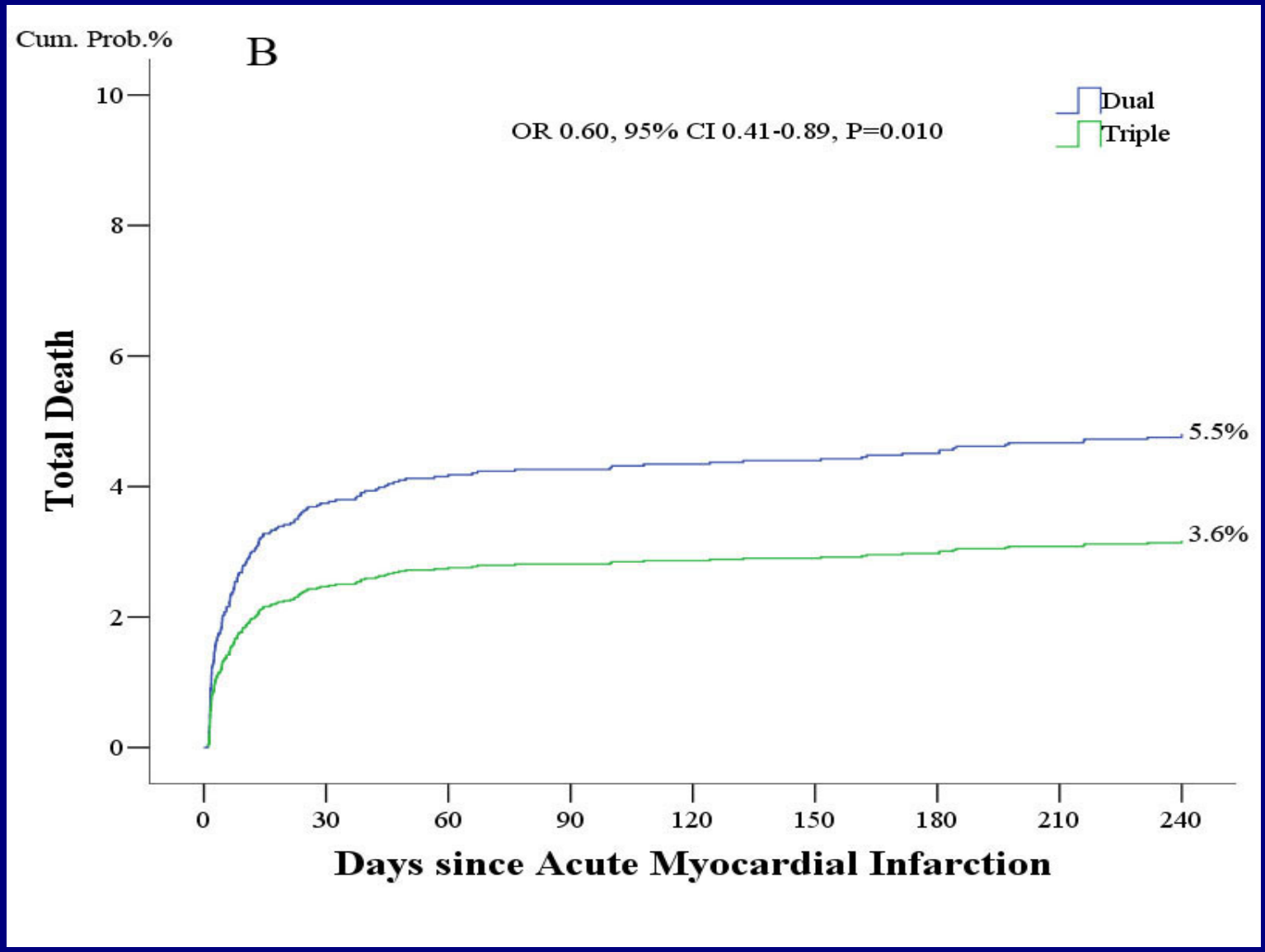
Multivariate Analysis

Variables	Unadjusted OR (95% CI)	*P* value	Adjusted OR * (95% CI)	*P* value
In-hospital outcomes				
Cardiac death	0.53 (0.32-0.88)	0.014	0.44 (0.24-0.80)	0.007
Total death	0.63 (0.43-0.94)	0.024	0.59 (0.36-0.94)	0.026
Recurrent MI	1.57 (0.51-4.89)	0.433	0.96 (0.28-3.35)	0.954
Outcomes at 8 months				
Cardiac death	0.62 (0.41-0.93)	0.021	0.52 (0.32-0.84)	0.007
Total death	0.63 (0.45-0.88)	0.006	0.60 (0.41-0.89)	0.010
Recurrent MI	1.22 (0.45-3.29)	0.689	0.72 (0.24-2.20)	0.565
CABG	0.78 (0.14-4.29)	0.781	0.99 (0.15-6.45)	0.990
Re-PCI	0.95 (0.68-1.31)	0.745	0.83 (0.59-1.18)	0.312
TLR	1.47 (0.87-2.49)	0.151	1.12 (0.63-1.98)	0.694
Total MACE	0.80 (0.64-0.99)	0.049	0.74 (0.58-0.95)	0.019

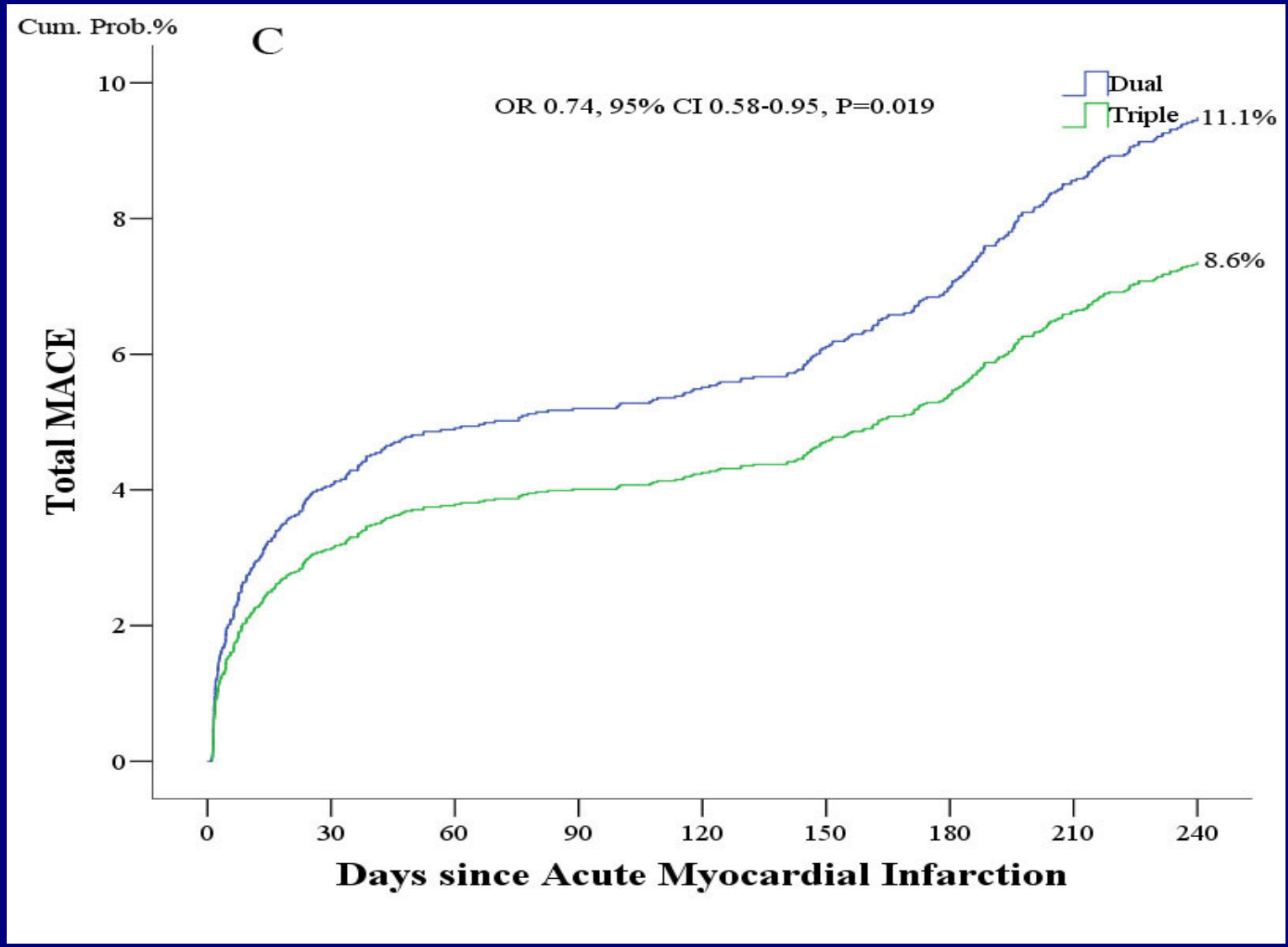
Cardiac Death



Total Death


Cum. Prob.%
B
10
8
6
4
2
0
Total Death
OR 0.60, 95% CI 0.41-0.89, P=0.010
Dual
Triple
5.5%
3.6%
0
30
60
90
120
150
180
210
240
Days since Acute Myocardial Infarction

Total MACE


Cum. Prob.%
C
OR 0.74, 95% CI 0.58-0.95, P=0.019
Dual
Triple
11.1%
8.6%
Total MACE
10
8
6
4
2
0
0
30
60
90
120
150
180
210
240
Days since Acute Myocardial Infarction

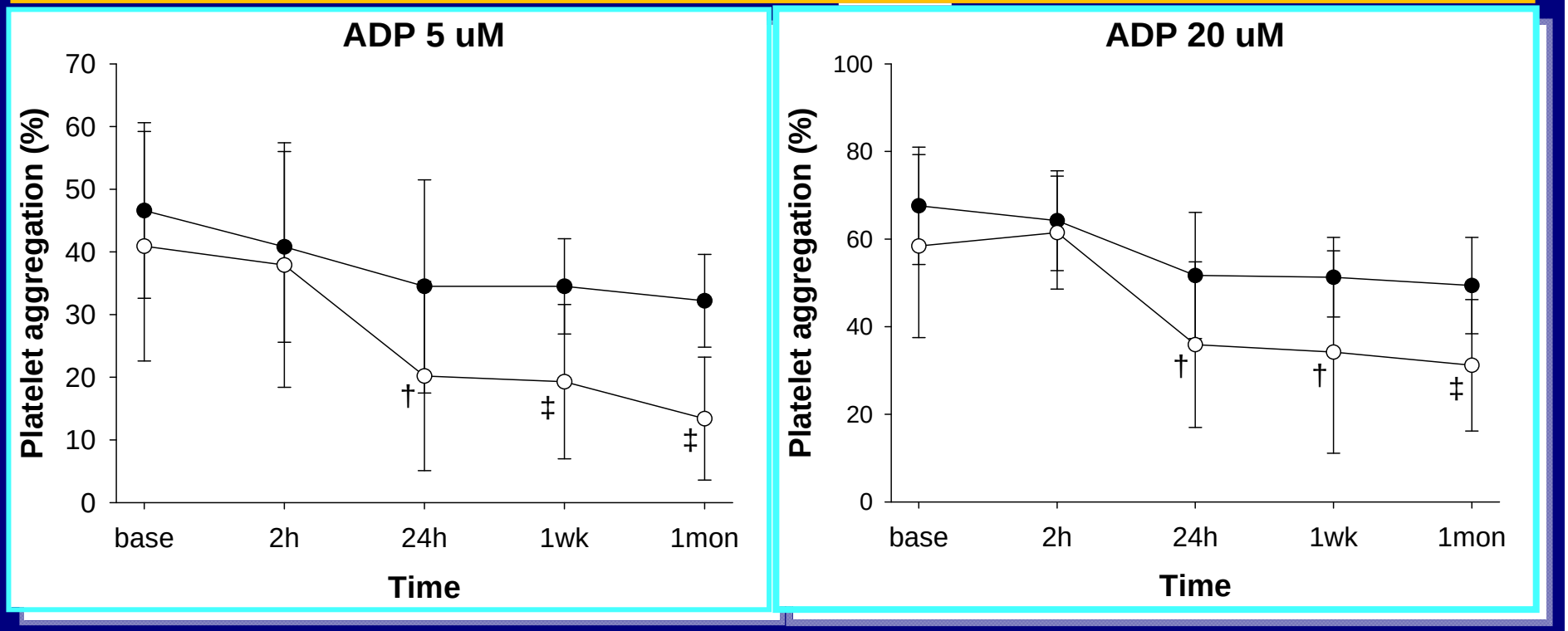
Conclusion

1. Triple antiplatelet regimen including aspirin, clopidogrel and cilostazol at lease for 1 month in patients with acute STEMI undergoing primary PCI with DES not only showed *good safety profiles*, but also *improved mid-term clinical outcomes* compared with those of conventional dual antiplatelet regimen.
2. Notably, *female patients, old patients and diabetic patients* seemed to get more advantages from the triple antiplatelet therapy.
3. These results might provide the rationale for the use of triple antiplatelet strategy in patients with acute STEMI undergoing primary PCI with DES.

Platelet Inhibition and Role of Cilostazol in Clopidogrel Resistance

Platelet aggregation
Triple vs. Dual therapy

Triple therapy (n=10) Dual therapy (n=10)



Results are expressed as the mean value ± SD.

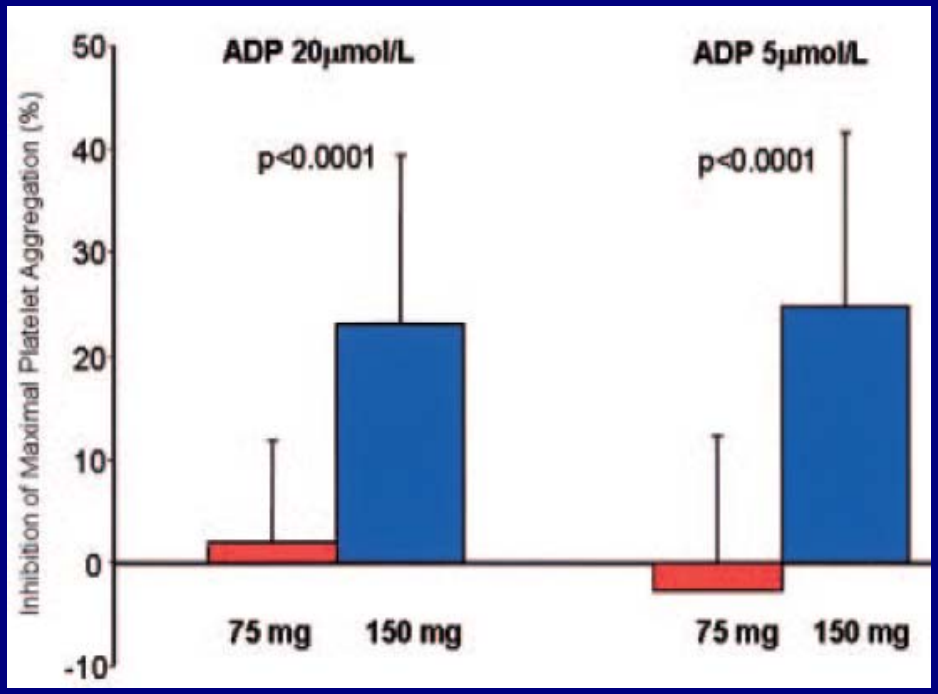
† p<0.05, ‡ p<0.01 between two groups.

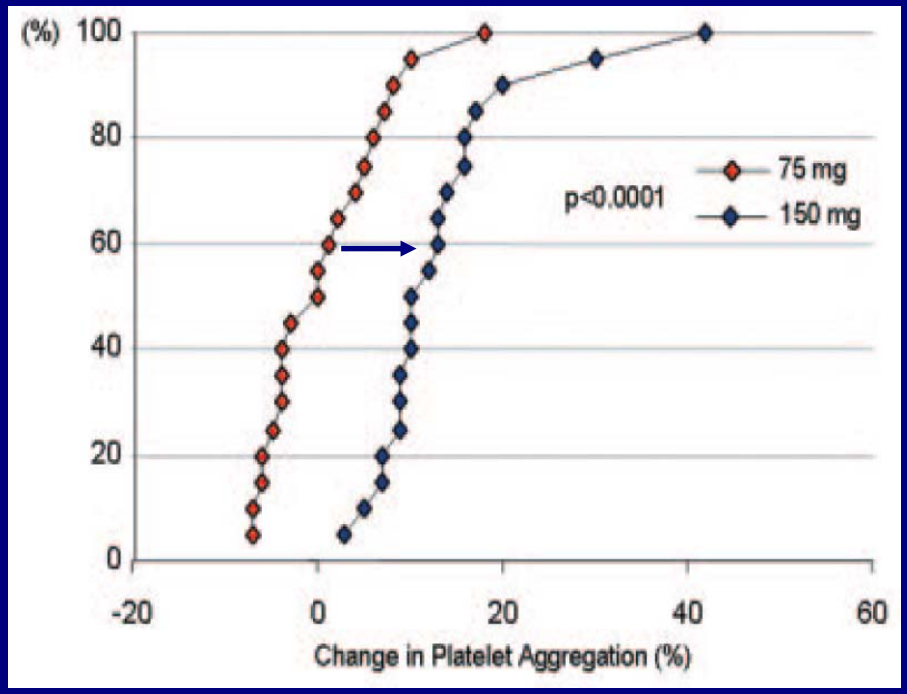
Lee BK, Lee SW, Park SW et al. Am J Cardiol. 2007;100:610.

High MD Clopidogrel in Pts with DM & CAD

OPTIMUS-1 study

40 suboptimal responders (20μmol/L ADP-induced Agg_{max} > 50%) with DM

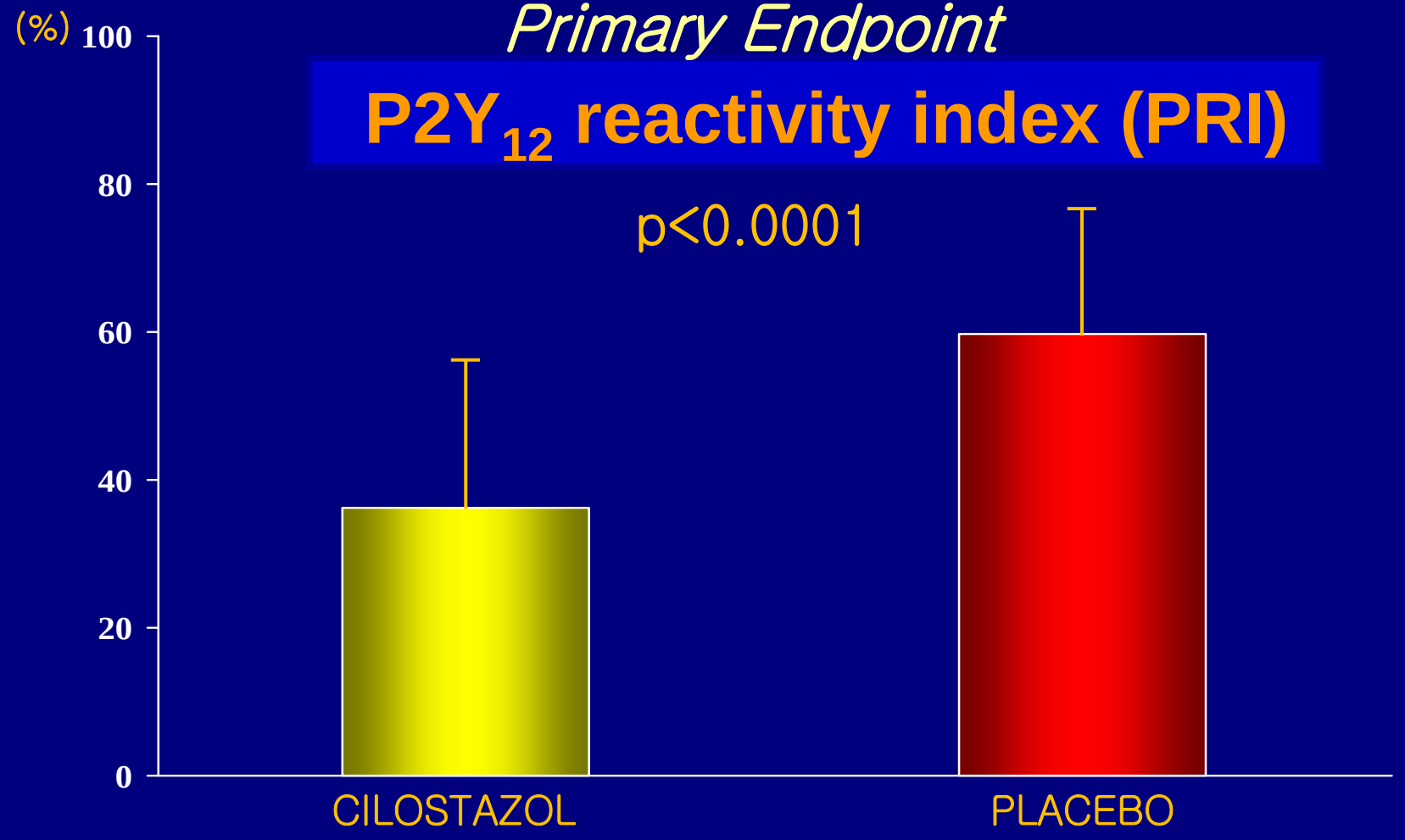




- A 150-mg MD of clopidogrel is associated with enhanced antiplatelet effects compared with 75-mg in high risk T2DM pts.
- Suboptimal clopidogrel response is still present in 60% pts of 150mg regimen.

Angiolillo DJ et al. Circulation 2007;115:708.

OPTIMUS-2: *Impact of adjunctive treatment with cilostazol in Diabetes Mellitus patients on aspirin and clopidogrel*



Angiolillo DJ et al. Eur Heart J 2008; 29:2202.

Randomized Comparison of Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With High Post-Treatment Platelet Reactivity

Results of the ACCEL-RESISTANCE (Adjunctive Cilostazol versus High Maintenance Dose Clopidogrel in Patients With Clopidogrel Resistance) Randomized Study

Young-Hoon Jeong, MD, PHD,* Seung-Whan Lee, MD, PHD,‡ Bong-Ryong Choi, MD,* In-Suk Kim, MD, PHD,† Myung-Ki Seo, MD,* Choong Hwan Kwak, MD, PHD,* Jin-Yong Hwang, MD, PHD,* Seong-Wook Park, MD, PHD‡

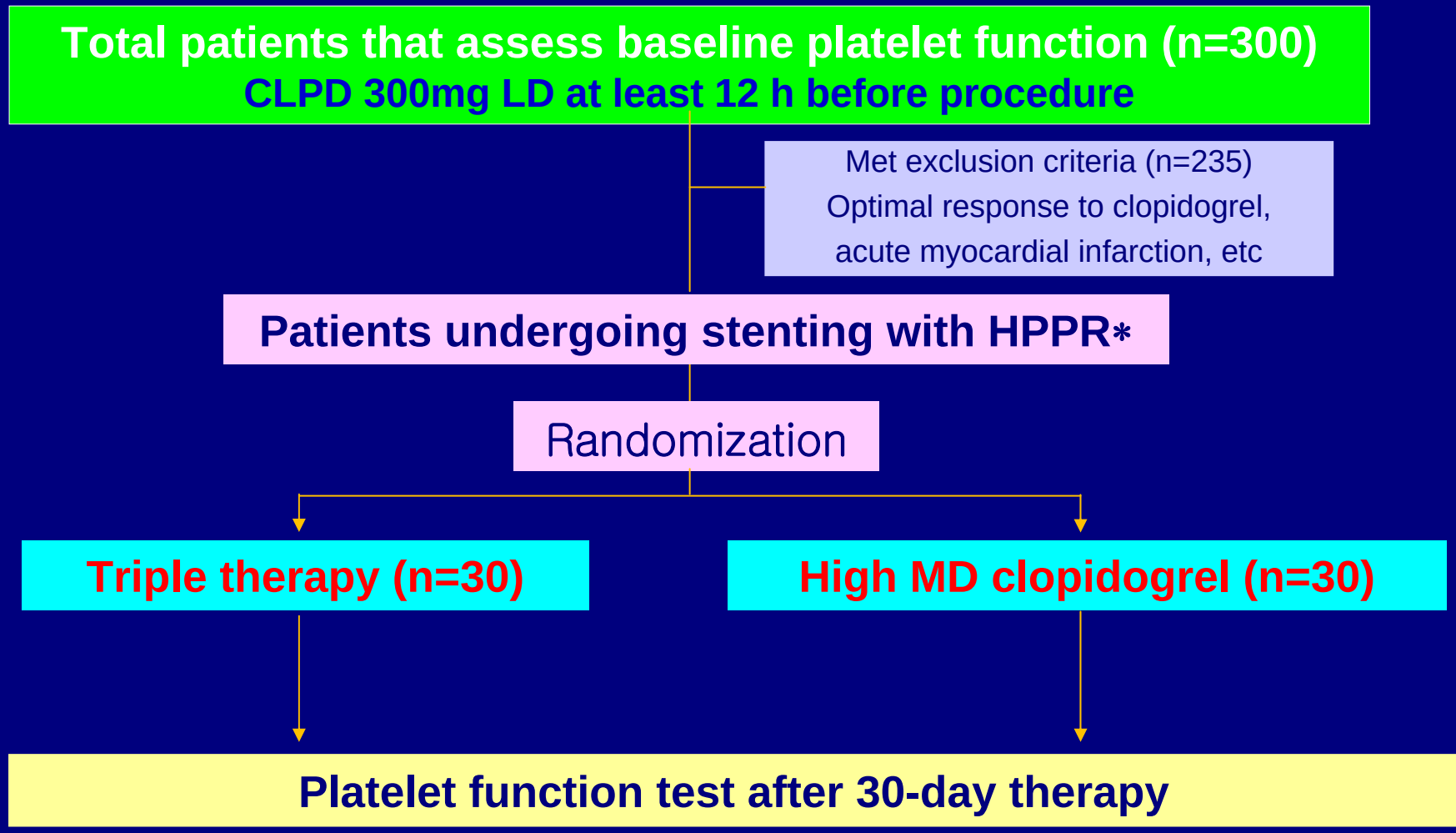
Jinju and Seoul, Korea

Adjunctive Cilostazol reduces the rate of HPPR & intensifies platelet inhibition as compared with a high-MD clopidogrel

Percent inhibitions of 20 μmol/l ADP-induced Agg_{max} and Agg_{late} were consistently greater in the triple versus high-MD group. Percent change of P2Y12 reaction units demonstrated a higher antiplatelet effect in the triple versus high-MD group (39.6 ± 24.1% vs. 23.1 ± 29.9%, p = 0.022).

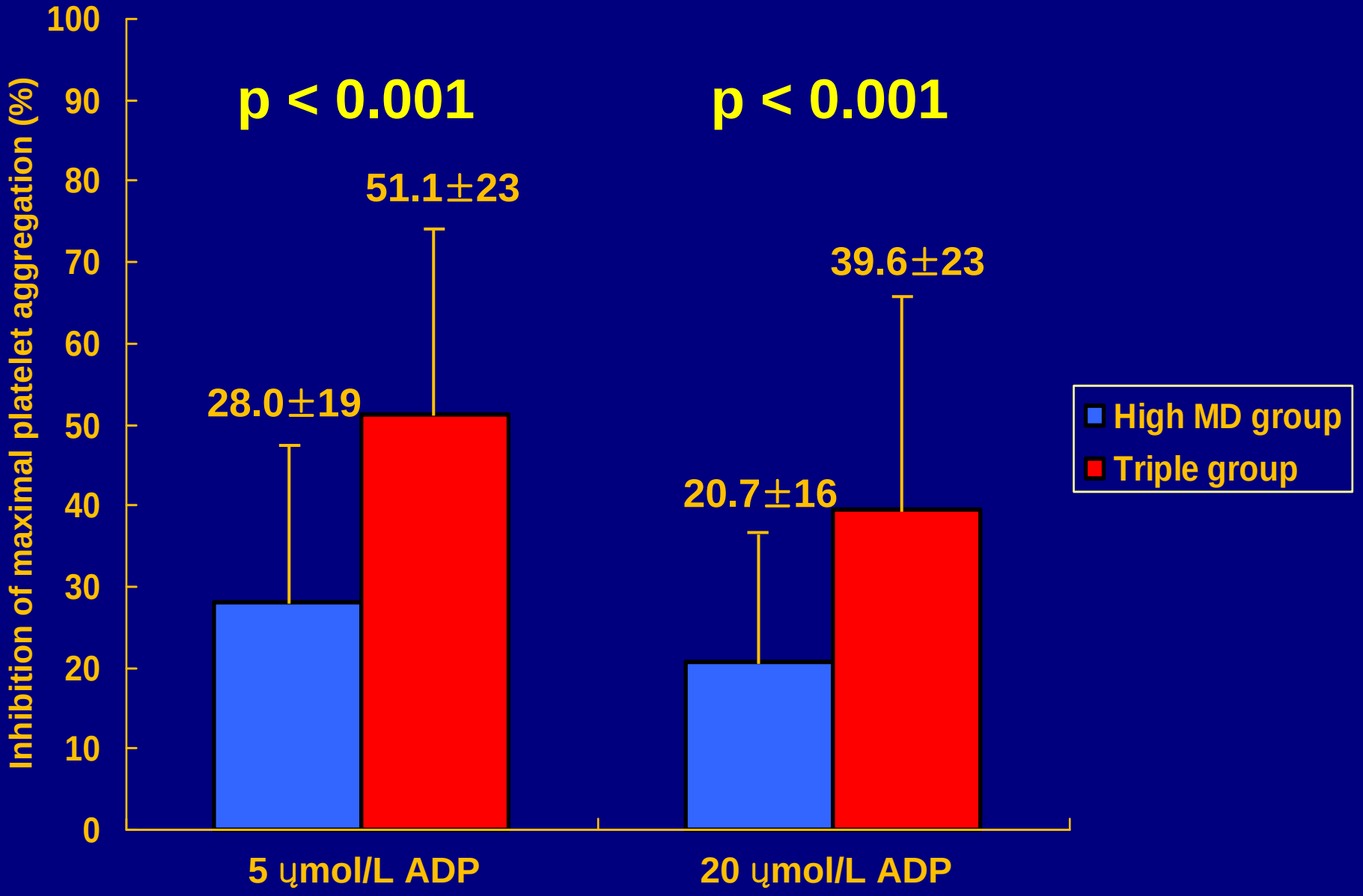
Conclusion Adjunctive cilostazol reduces the rate of HPPR and intensifies platelet inhibition as compared with a high-MD clopidogrel of 150 mg/day. (J Am Coll Cardiol 2009;53:1101–9)

*A*djunctive *C*ilostazol vs. high-MD *C*lopidogr*EL* in HPPR (ACCEL study)



*High Post-CLPD Platelet Reactivity (HPPR) : maximal aggregation > 50% with 5 μM ADP

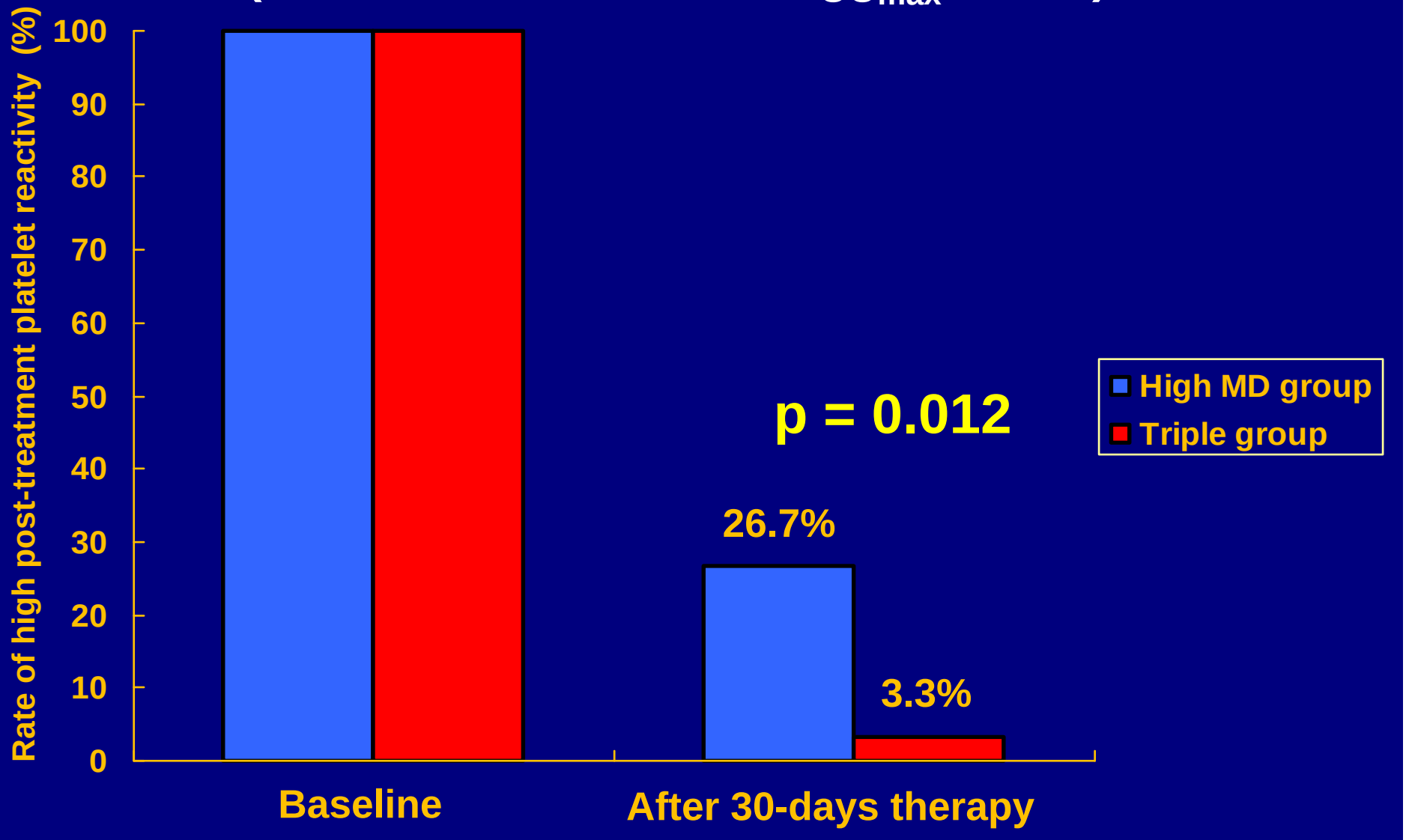
IPA of Agg_{max}



Jeong YH, Park SW et al. JACC 2009;53:1101.

Rate of HPPR

(5 μmol/L ADP-induced Agg_{max} ≥ 50%)



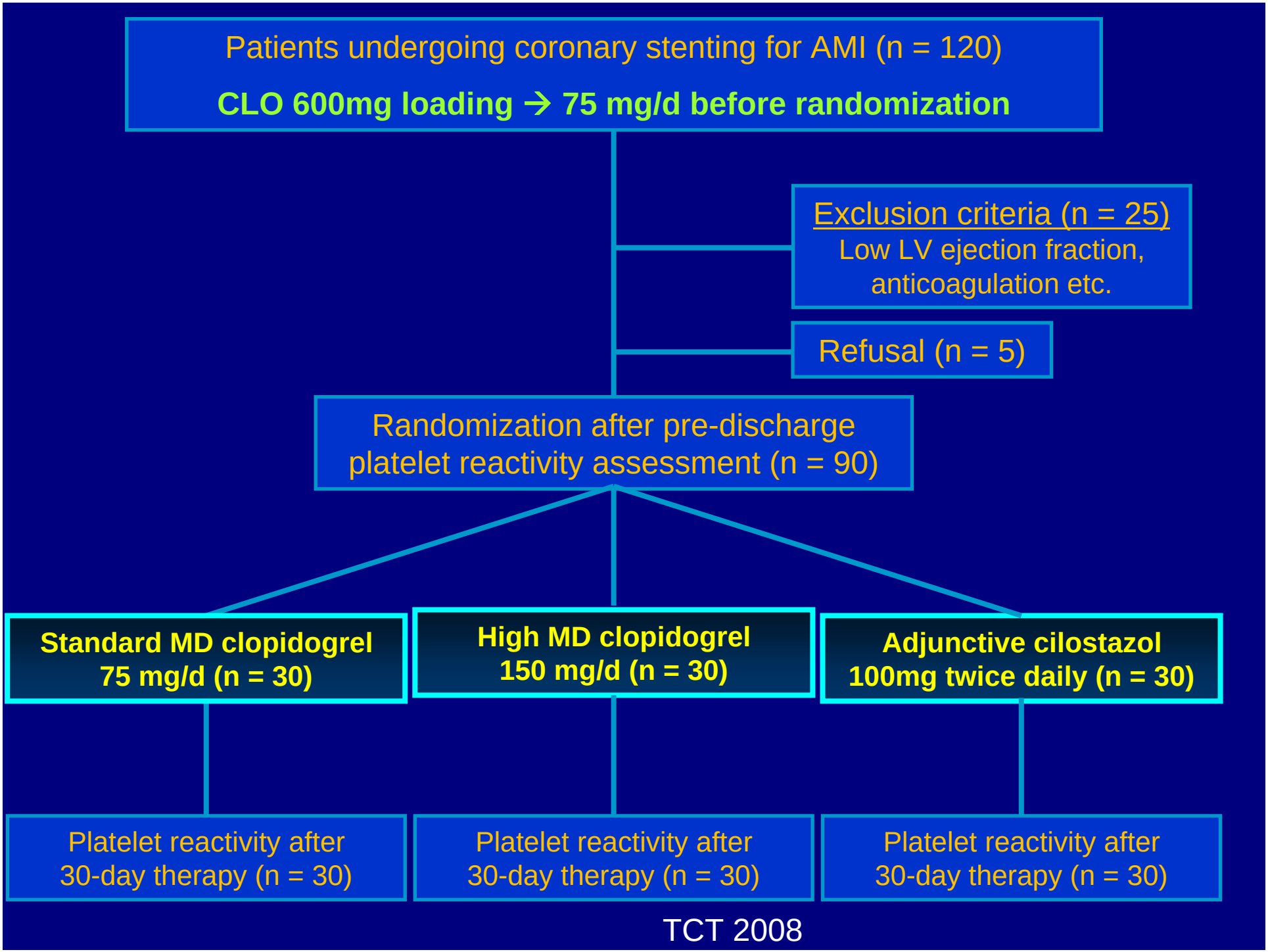
Jeong YH, Park SW et al. JACC 2009;53:1101.

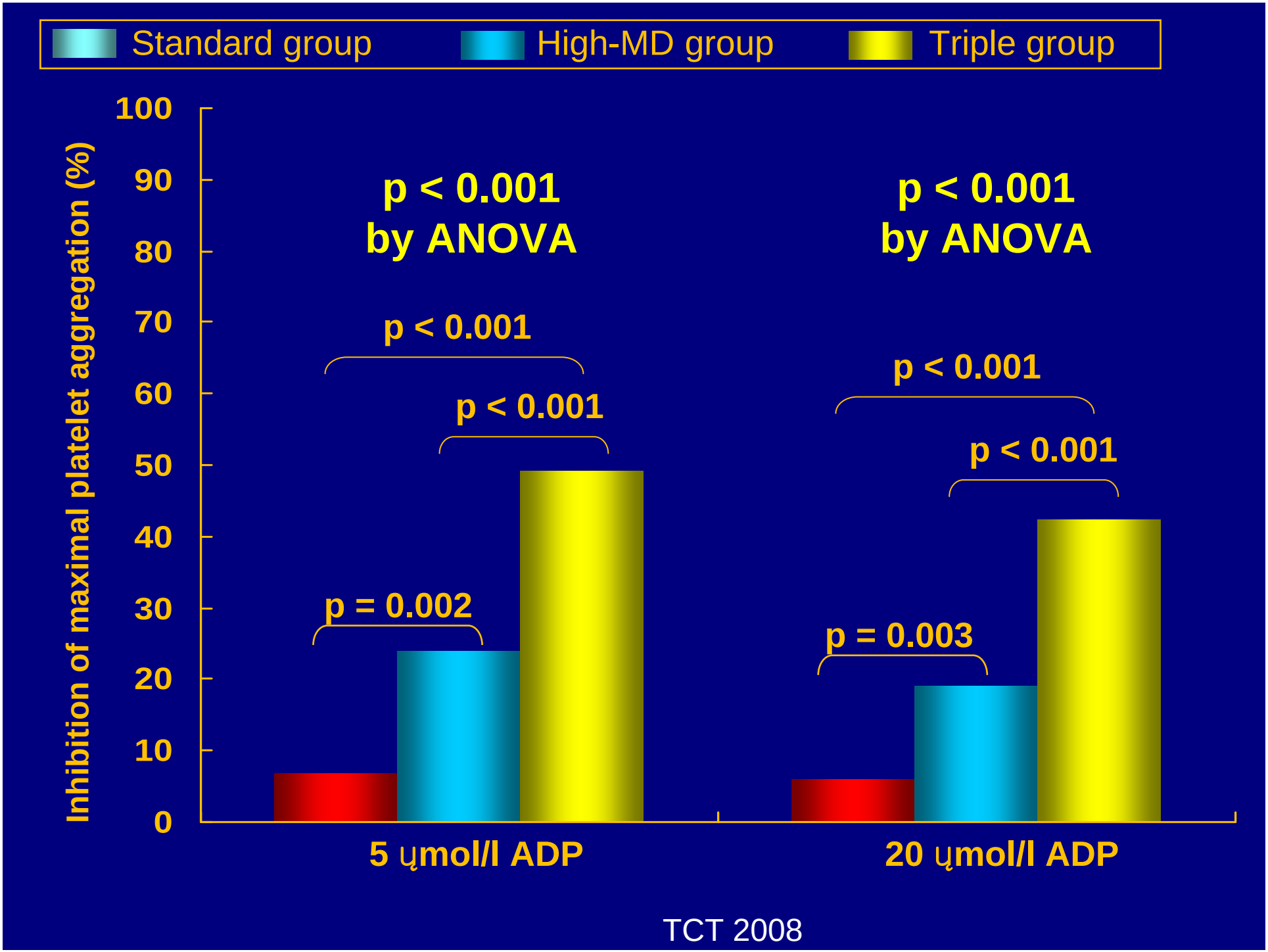
*A*dding Cilostazol to DAPT Achieves Greater Platelet Inhibition than High-MD Clopidogrel in Patients with AMI (*A*djunctive *C*ilostazol versus high MD *C*lopidogr*EL* in patients with AMI)

Young-Hoon Jeong,[1] Jin-Yong Hwang,[1] Younghwi Park,[1] Seok-Jae Hwang,[1] In-Suk Kim,[1] Choong Hwan Kwak,[1] Seung-Whan Lee,[2] Seong-Wook Park,[2] **For the ACCEL-AMI Investigators**

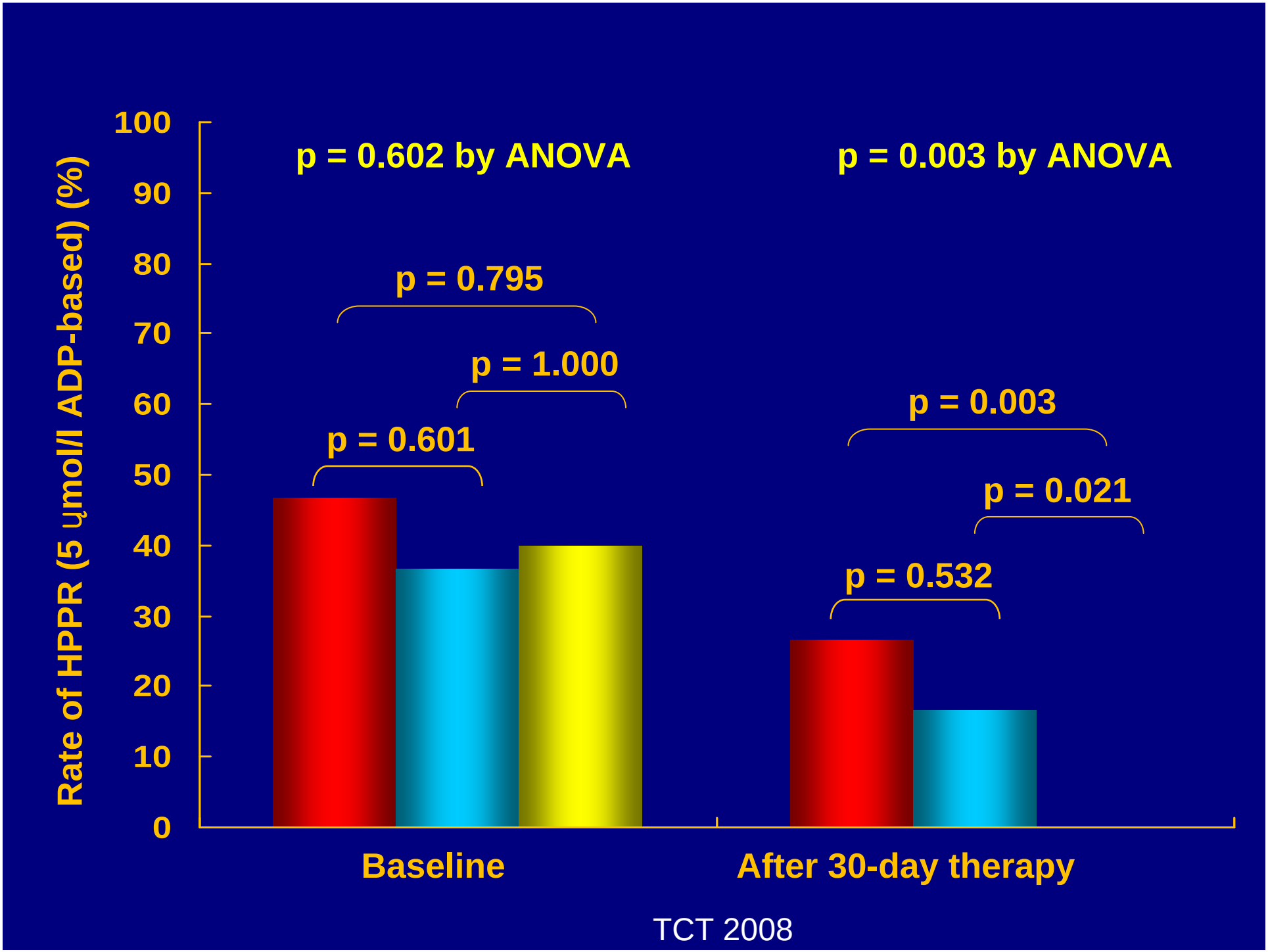
1 Gyeongsang National University Hospital, Jinju, Korea.
2 Asan Medical Center, Seoul, Korea.

Jeong YH, et al. Circ Cardiovasc Interv:in revision: TCT 2008.


Patients undergoing coronary stenting for AMI (n = 120)
CLO 600mg loading → 75 mg/d before randomization
Exclusion criteria (n = 25)
Low LV ejection fraction, anticoagulation etc.
Refusal (n = 5)
Randomization after pre-discharge platelet reactivity assessment (n = 90)
Standard MD clopidogrel 75 mg/d (n = 30)
High MD clopidogrel 150 mg/d (n = 30)
Adjunctive cilostazol 100mg twice daily (n = 30)
Platelet reactivity after 30-day therapy (n = 30)
Platelet reactivity after 30-day therapy (n = 30)
Platelet reactivity after 30-day therapy (n = 30)
TCT 2008


Standard group
High-MD group
Triple group
Inhibition of maximal platelet aggregation (%)
100
90
80
70
60
50
40
30
20
10
0
p < 0.001
by ANOVA
p < 0.001
by ANOVA
p < 0.001
p < 0.001
p = 0.002
p < 0.001
p < 0.001
p = 0.003
5 μmol/l ADP
20 μmol/l ADP

TCT 2008

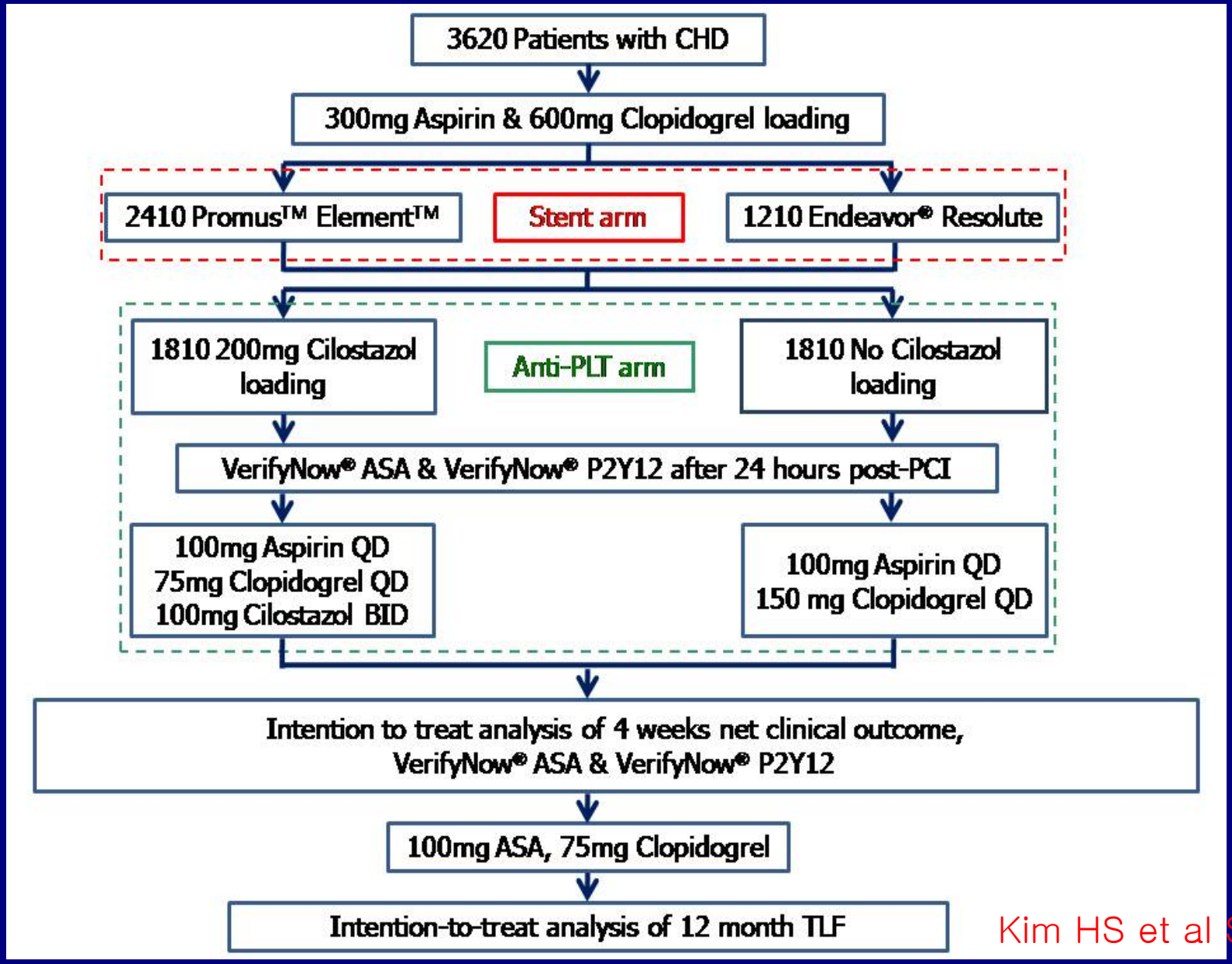

Rate of HPPR (5 μmol/l ADP-based) (%)
100
90
80
70
60
50
40
30
20
10
0
p = 0.602 by ANOVA
p = 0.003 by ANOVA
p = 0.795
p = 1.000
p = 0.601
p = 0.003
p = 0.021
p = 0.532
Baseline
After 30-day therapy
TCT 2008

TAP in Korean Pts in DES Era

1. Triple antiplatelet therapy (TAP) including cilostazol, the prevalence of clopidogrel resistance can be attenuated in patients undergoing PCI with DES.
2. Interestingly, the adjunctive cilostazol was beneficial in reducing clopidogrel resistance but not in aspirin resistance, showing cilostazol may have a specific mechanism in inhibiting DP-P2Y12 mediated platelet inhibition.

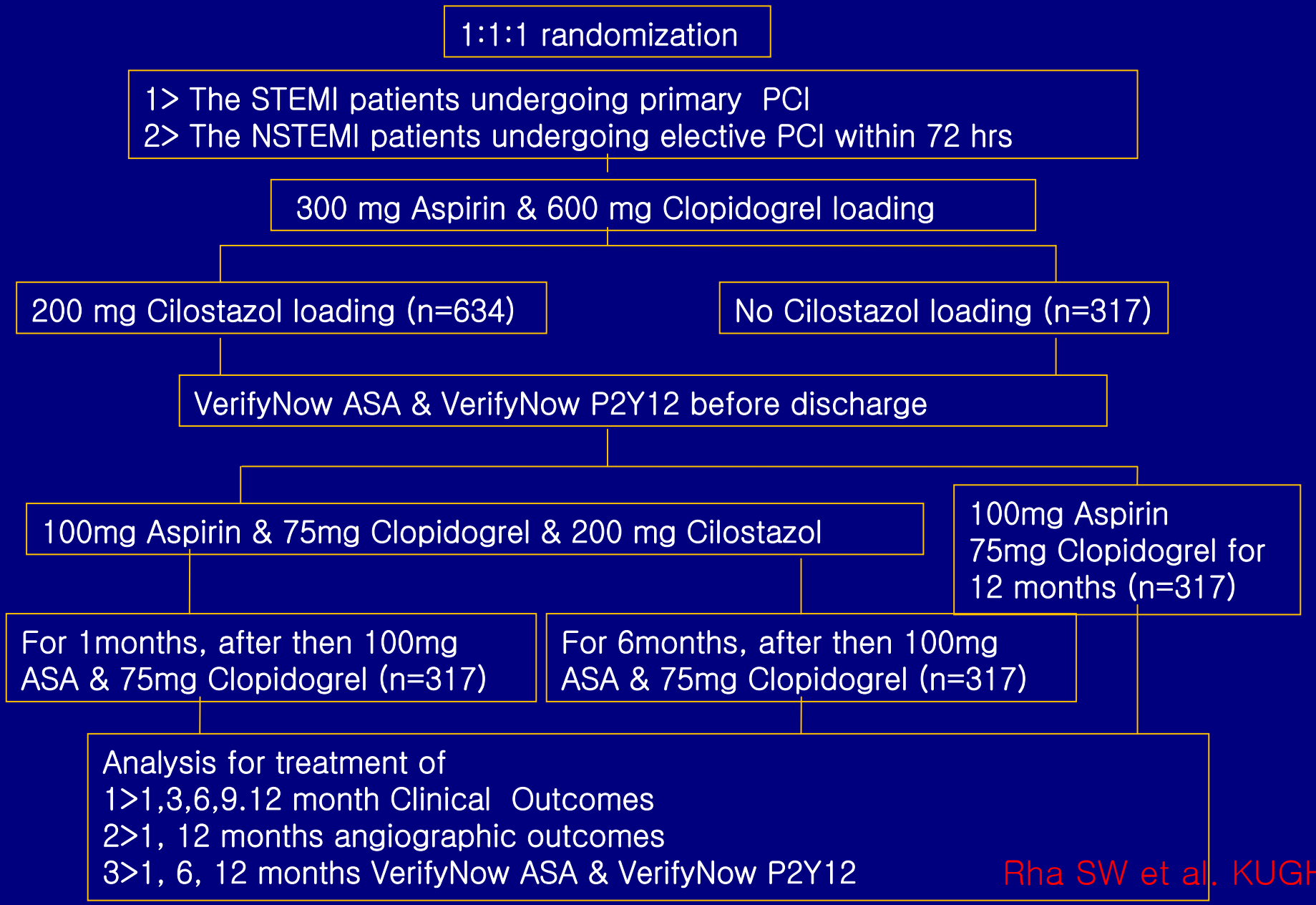
Shim CY et al. Int J Cardiol 2009;134:351–355.

HOST ASSURE study



Kim HS et al SNUH

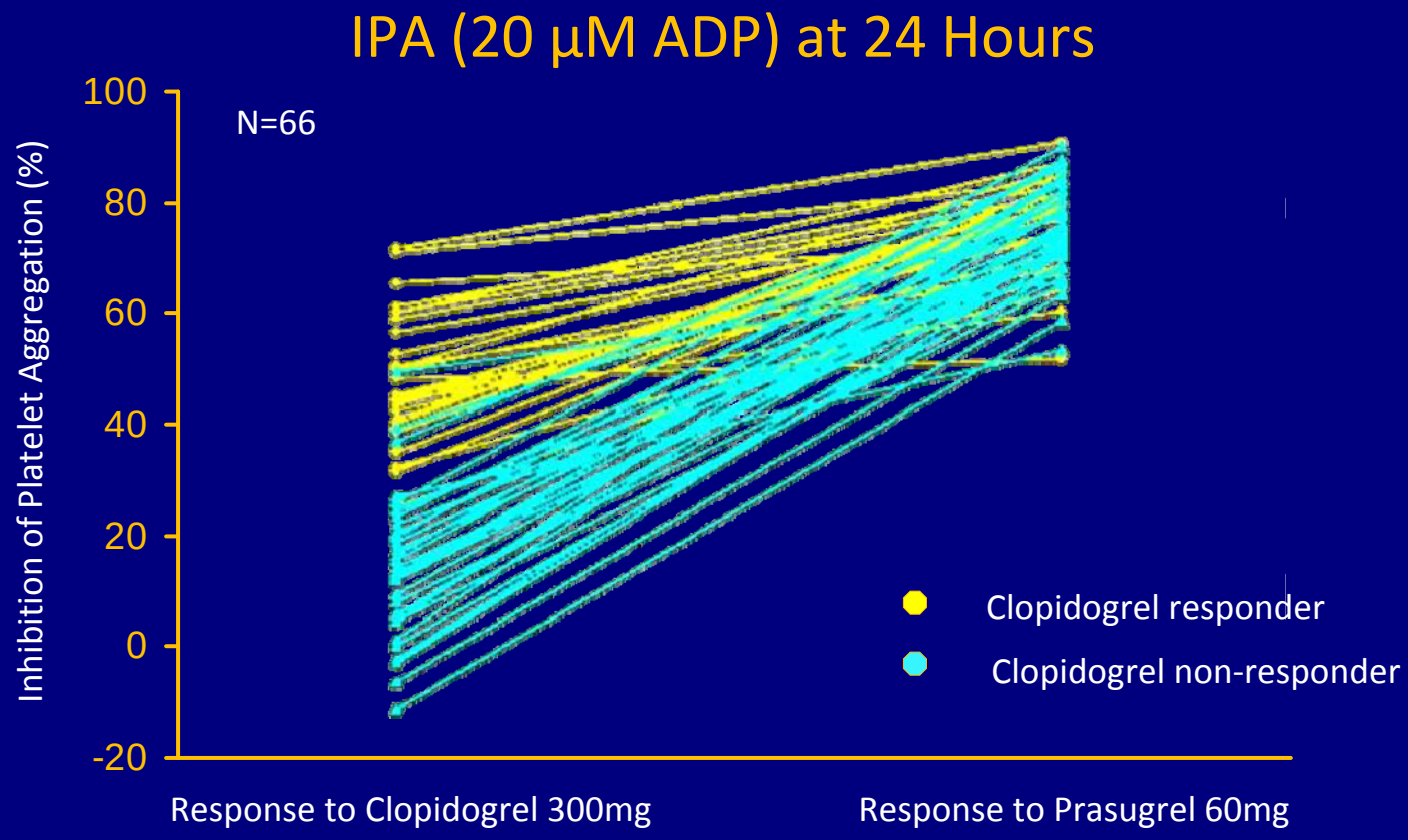
SILOAM Trial



What data are there comparing platelet response and clinical outcomes of clopidogrel and prasugrel?

Inhibition of Platelet Aggregation with Clopidogrel and Prasugrel

Healthy Volunteer Crossover Study - Comparison With Prasugrel

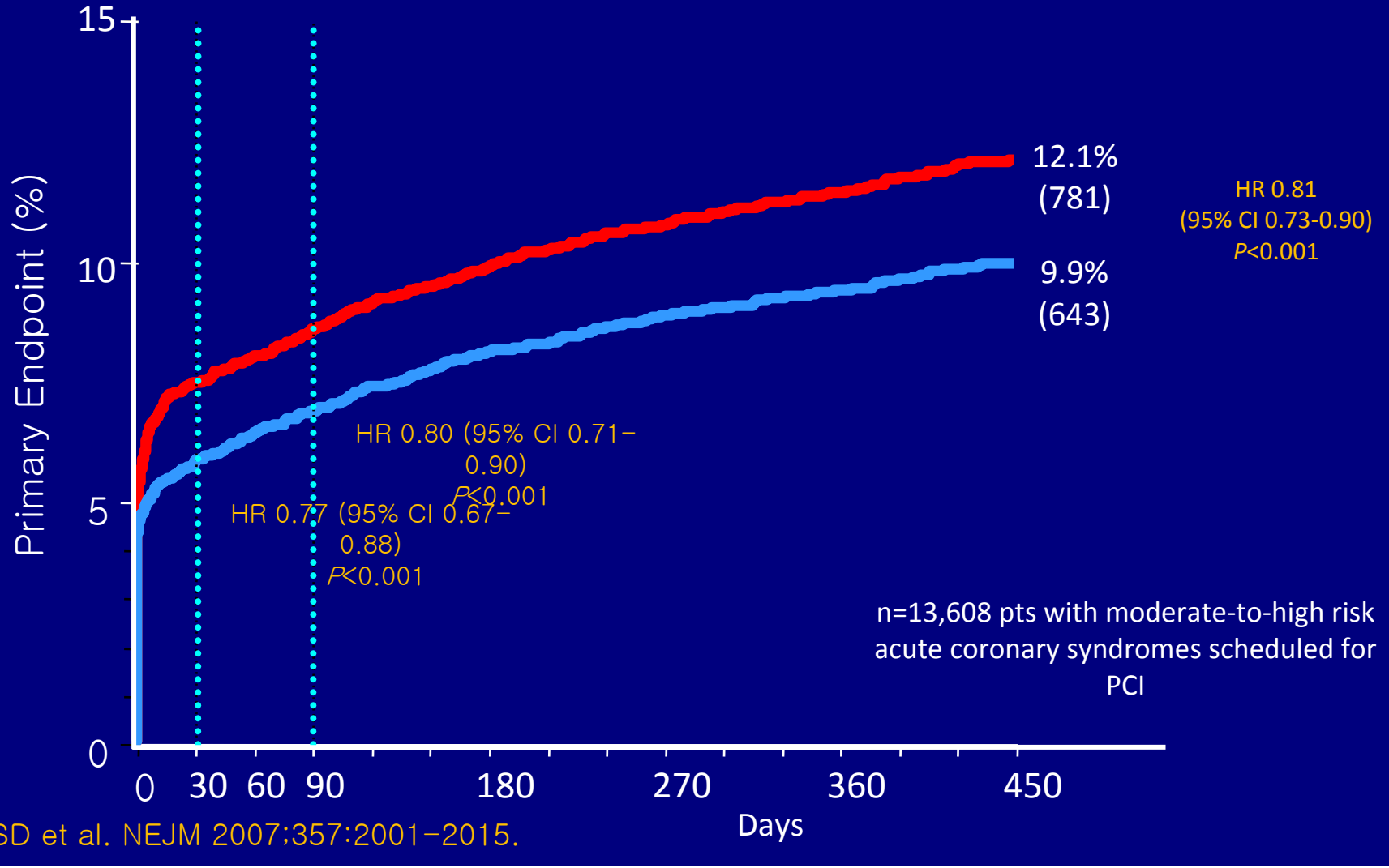


Responder ≥ 25% IPA at 4 and 24 hours

Brandt JT et al. Am Heart J. 2007 Jan;153(1):66.e9-16.

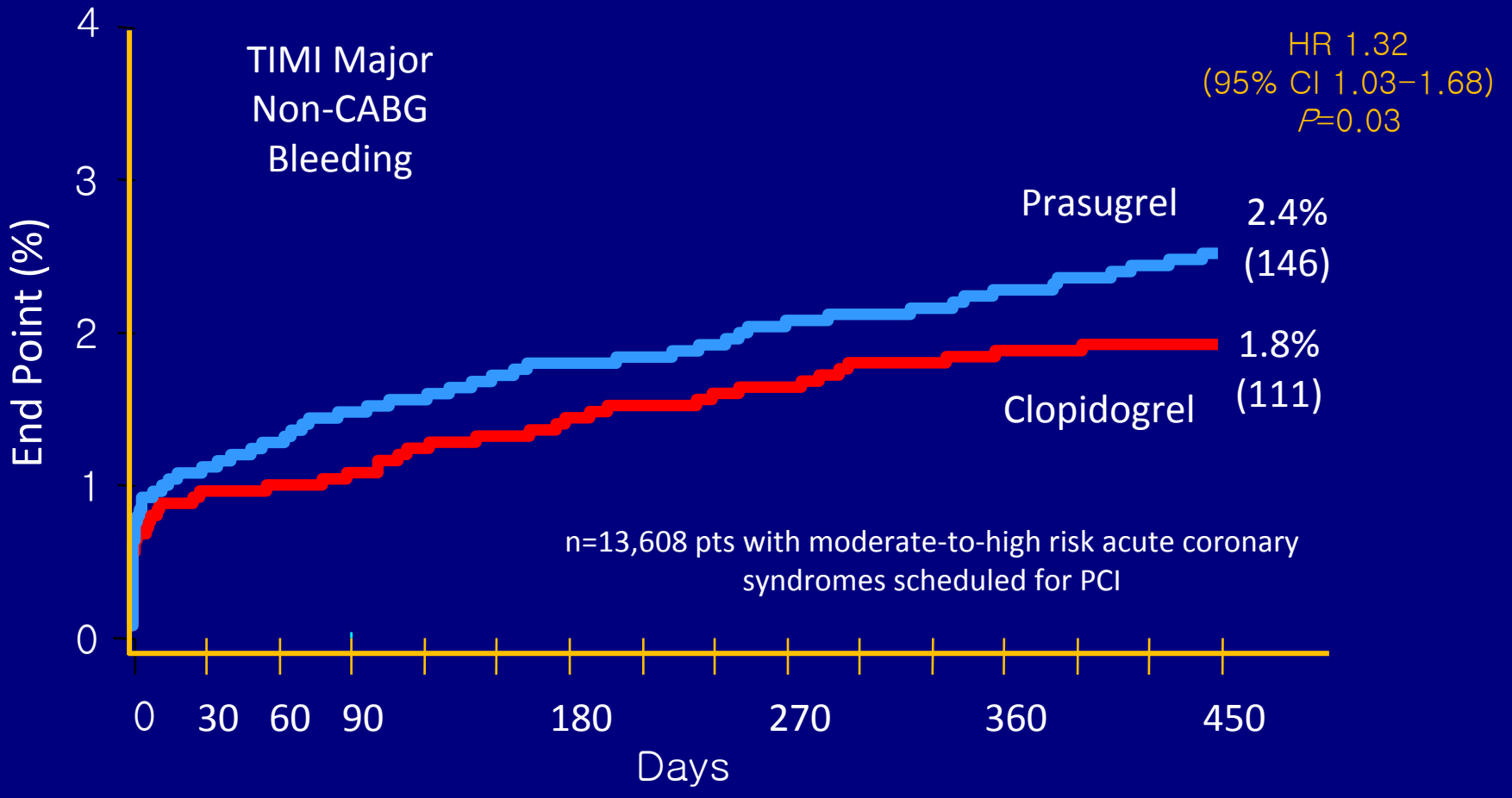
Efficacy of Clopidogrel and Prasugrel (TRITON-TIMI 38)

Primary efficacy endpoint (composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke)



Wiviott SD et al. NEJM 2007;357:2001–2015.

Primary Safety Endpoint of Clopidogrel and Prasugrel (TRITON-TIMI 38)



Wiviott SD et al. NEJM 2007;357:2001–2015.

Summary

- Limited comparative data between prasugrel and clopidogrel are from phase I & II studies. Phase III comparative studies are underway
- Comparative IPA trials have used inconsistent doses of clopidogrel and prasugrel
  - Phase I data indicates an equipotency of 10:1 (clopidogrel: prasugrel)
  - Phase II & III data have used or are using a 5:1 ratio (300mg clopidogrel vs. 60mg prasugrel)
  - More data are needed
- Data from TRITON supports the hypothesis that higher IPA correlates to more effective prevention of ischemic events; however, the benefit seen with prasugrel in terms of efficacy was coupled with a significant increase in major bleeding, including life-threatening and fatal bleeding events

OMEGA-3 Fatty Acids

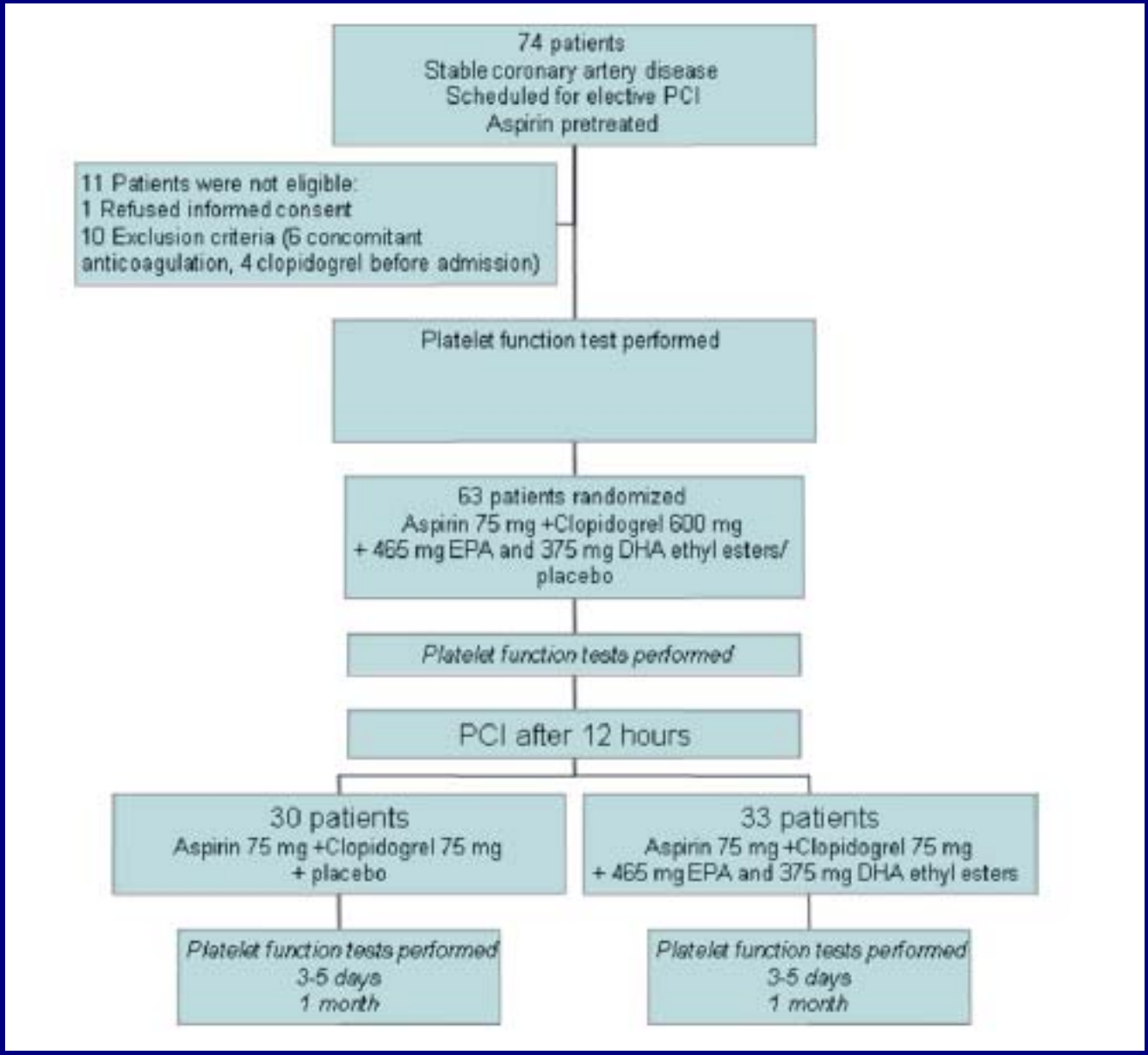
Effects of Polyunsaturated Omega-3 Fatty Acids on Responsiveness to Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention

The OMEGA-PCI (OMEGA-3 Fatty Acids After PCI to Modify Responsiveness to Dual Antiplatelet Therapy) Study

Grzegorz Gajos, MD, PHD,* Pawel Rostoff, MD,* Anetta Undas, MD, PHD,†
Wiesława Piwowarska, MD, PHD*†

Cracow, Poland

Gajos G et al. J Am Coll Cardiol 2010;55:1671–8


74 patients
Stable coronary artery disease
Scheduled for elective PCI
Aspirin pretreated
11 Patients were not eligible:
1 Refused informed consent
10 Exclusion criteria (6 concomitant anticoagulation, 4 clopidogrel before admission)
Platelet function test performed
63 patients randomized
Aspirin 75 mg +Clopidogrel 600 mg
+ 465 mg EPA and 375 mg DHA ethyl esters/
placebo
Platelet function tests performed
PCI after 12 hours
30 patients
Aspirin 75 mg +Clopidogrel 75 mg
+ placebo
33 patients
Aspirin 75 mg +Clopidogrel 75 mg
+ 465 mg EPA and 375 mg DHA ethyl esters
Platelet function tests performed
3-5 days
1 month
Platelet function tests performed
3-5 days
1 month

Benefit of Omega-3 PUFAs

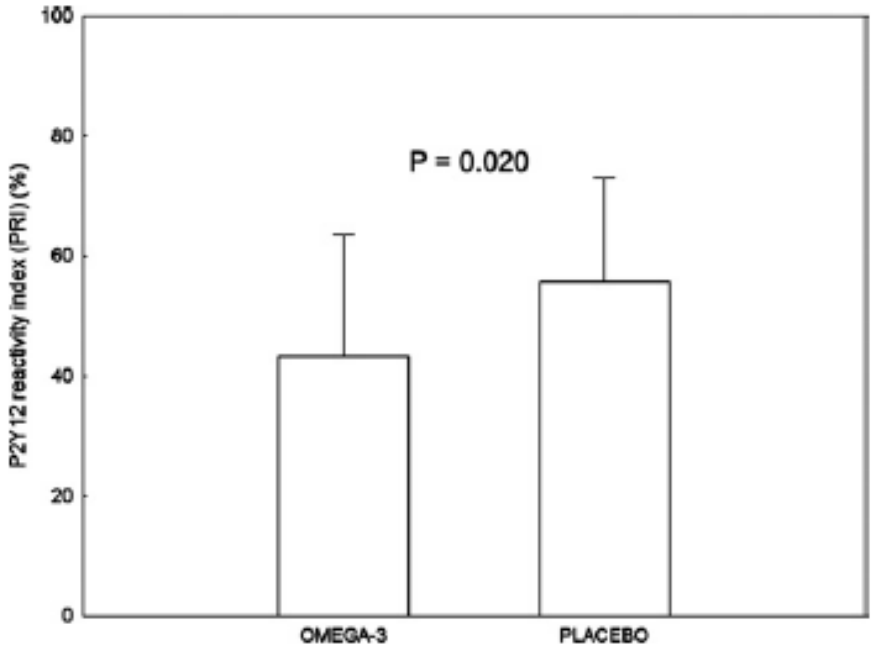


Figure 2 **Benefit of Omega-3 PUFAs on the Primary End Point of the OMEGA-PCI Study**

Patients in whom omega-3 polyunsaturated fatty acids (PUFAs) were added to standard therapy with aspirin and clopidogrel had greater platelet inhibition when assessed by the $P2Y_{12}$ reactivity index (PRI) compared with placebo after 1 month of treatment. **Error bars** indicate SDs of the mean.

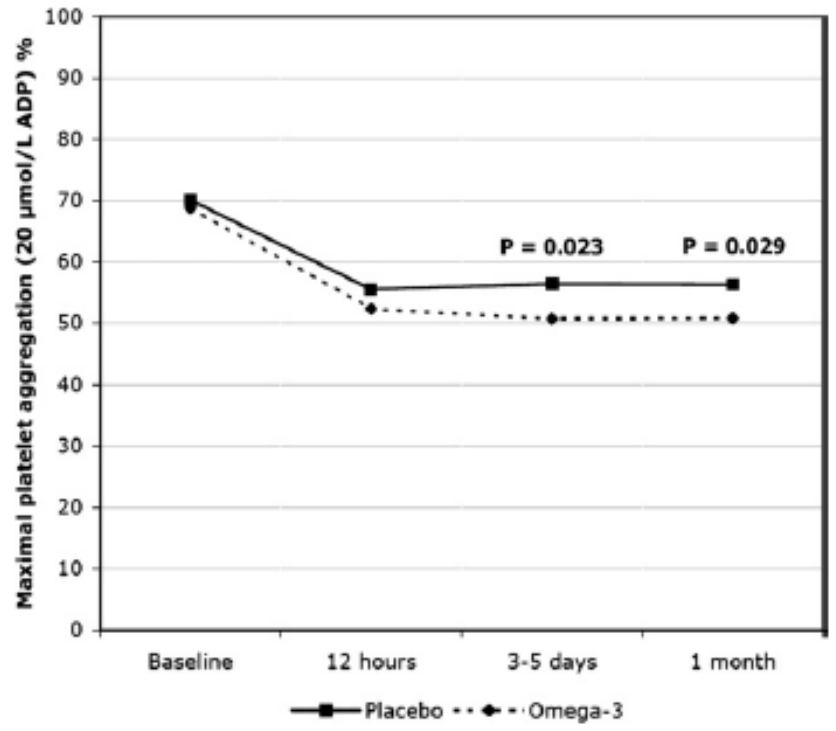


Figure 3 **Maximal Platelet Aggregation Induced by 20 µmol/l ADP Over Time in the Placebo and Omega-3 Groups**

Potentiated platelet response to clopidogrel after percutaneous coronary intervention was demonstrated in patients receiving triple therapy with aspirin, clopidogrel, and omega-3 polyunsaturated fatty acids compared with standard dual antiplatelet therapy. Statistically significant maximal platelet aggregation between placebo and omega-3 groups at each time point is indicated. ADP = adenosine diphosphate.

Gajos G et al. J Am Coll Cardiol 2010;55:1671–8

Omega-3 FA & Clopidogrel

- The addition of omega-3 ethyl esters to the combination of aspirin and clopidogrel significantly potentiates platelet response to clopidogrel after PCI.

- Mechnism; multifactorial & unclear…

  It has its own antiplatelet activity and so on…

Summary

1. Introduction
2. Clopidogrel Responsiveness and Resistance
3. Optimal Clopidogrel dosage in Asian Population
4. How to overcome clopidogrel resistance

1) Higher MD
2) Triple antiplatelets
3) Newer antiplatelets
4) Others; Omega-3 FAs

Conclusion

1. Aspirin and clopidogrel resistance is a clinically important issue in preventing future ischemic cardiovascular events, especially in patients undergoing PCI with DES.

2. VerifyNow provides a easy and quick measurement of platelet function and this result can be directly applied to individual patient management.