# Choice Among Antiplatelets – An Review of Antiplatelet Agents

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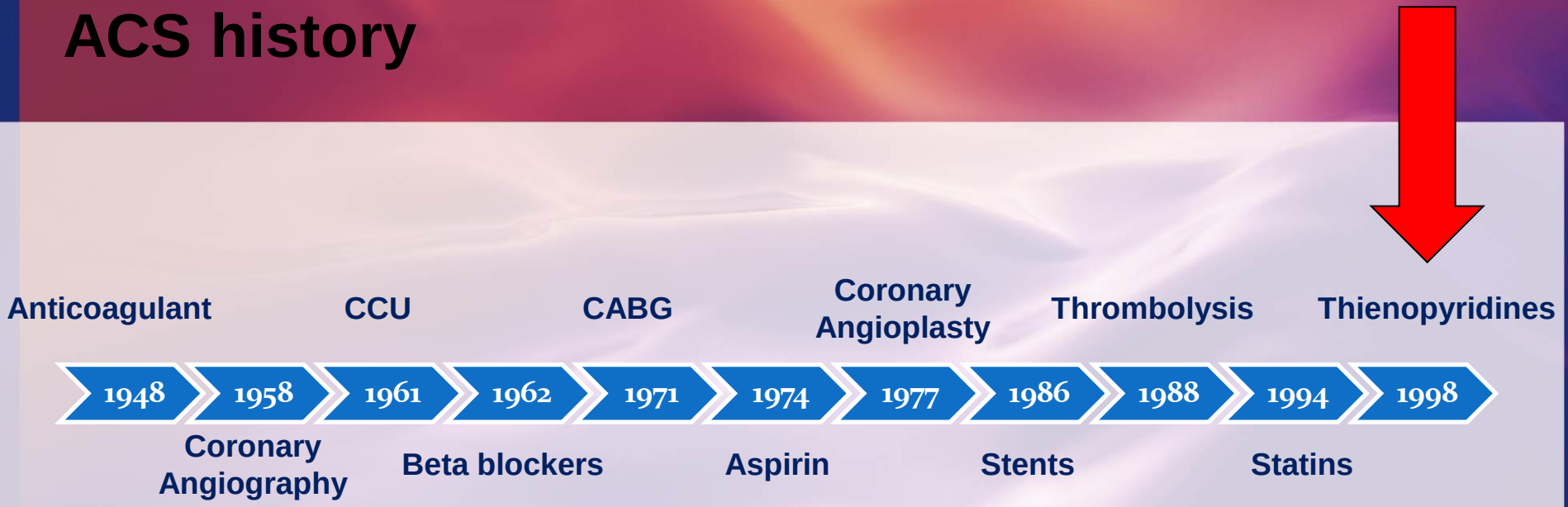
# ACS history




**Since the introduction of new therapies and management strategies in ACS, morbidity and mortality have decreased, but there is room for improvement**

**CCU, coronary care unit; CABG, coronary bypass graft**

*Trans Am Clin Climatol Assoc.* 2006;116:41-53
*Anesth Analg.* 2008;107:552-69
*Lancet.* 1994;344:1383-1389
*N Engl J Med.* 1998;339:1665-1671

# Antiplatelet Agents

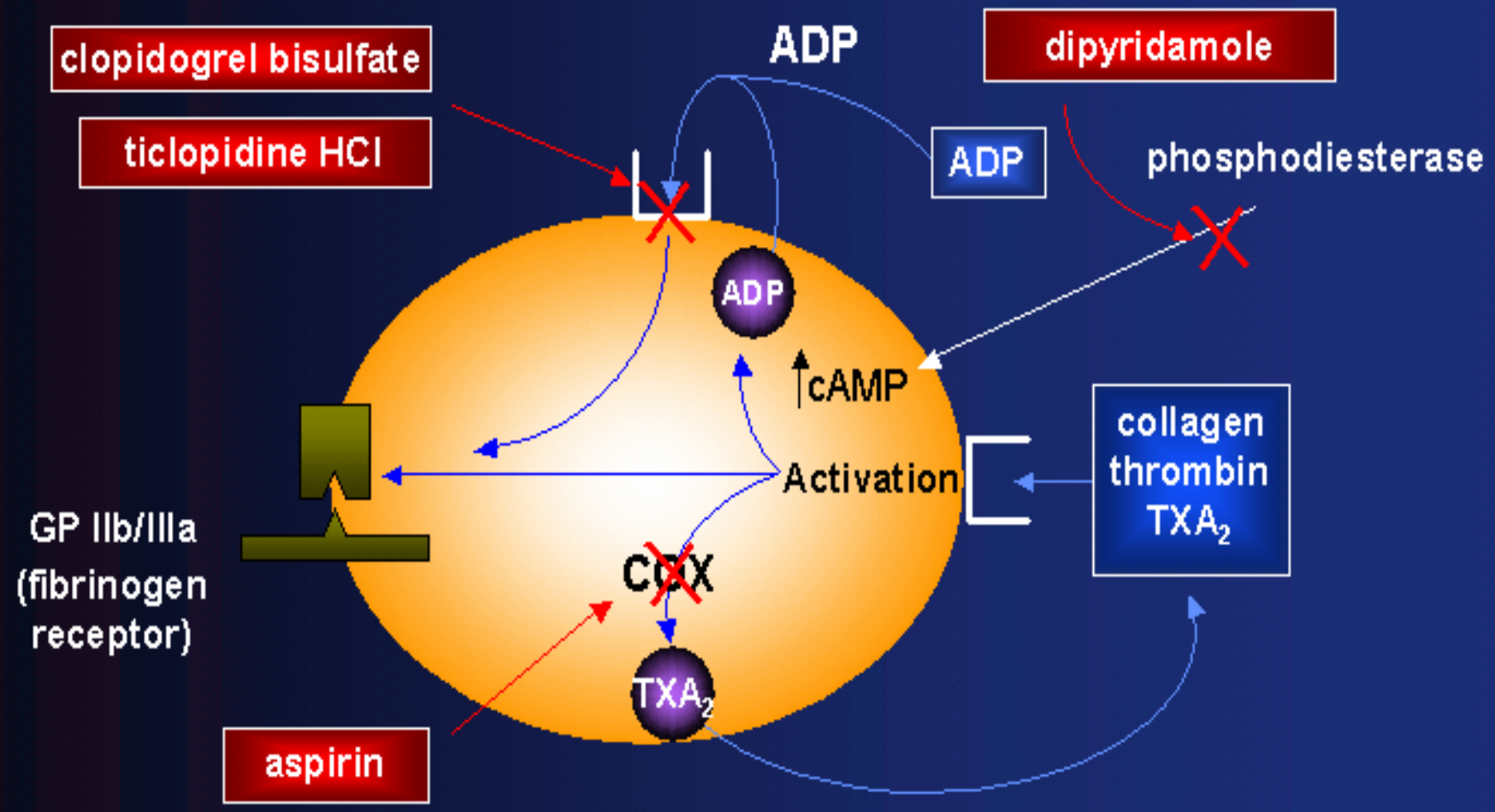
- **Thromboxane A2 inhibitor**
  Acetylsalicylic acid (ASA)

- **Phosphodiesterase inhibitor**
  Dipyridamole, Cilostazol

- **Glycoprotein (GP) IIb/IIIa blockers**
  Parenteral: abciximab, eptifibatide, tirofiban

- **ADP-receptor antagonists**
  Clopidogrel , Prasugrel, Ticagrelor, Ticlopidine

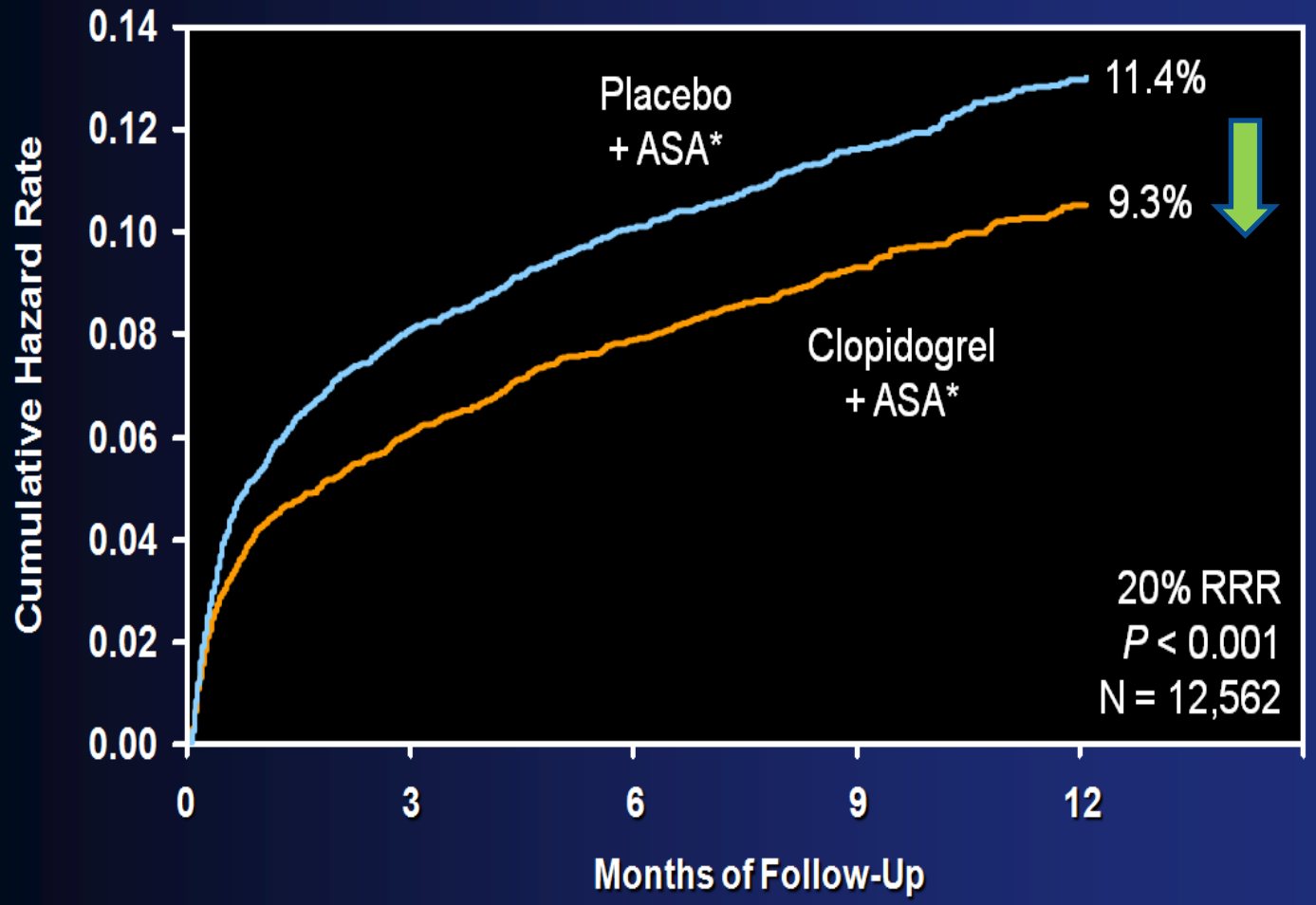
# Mechanisms of Action of Oral Antiplatelet Therapies




ADP = adenosine diphosphate, $TXA_2$ = thromboxane $A_2$, COX = cyclooxygenase.

CURE - Unstable Angina/NSTEMI

# Primary End Point - MI/Stroke/CV Death



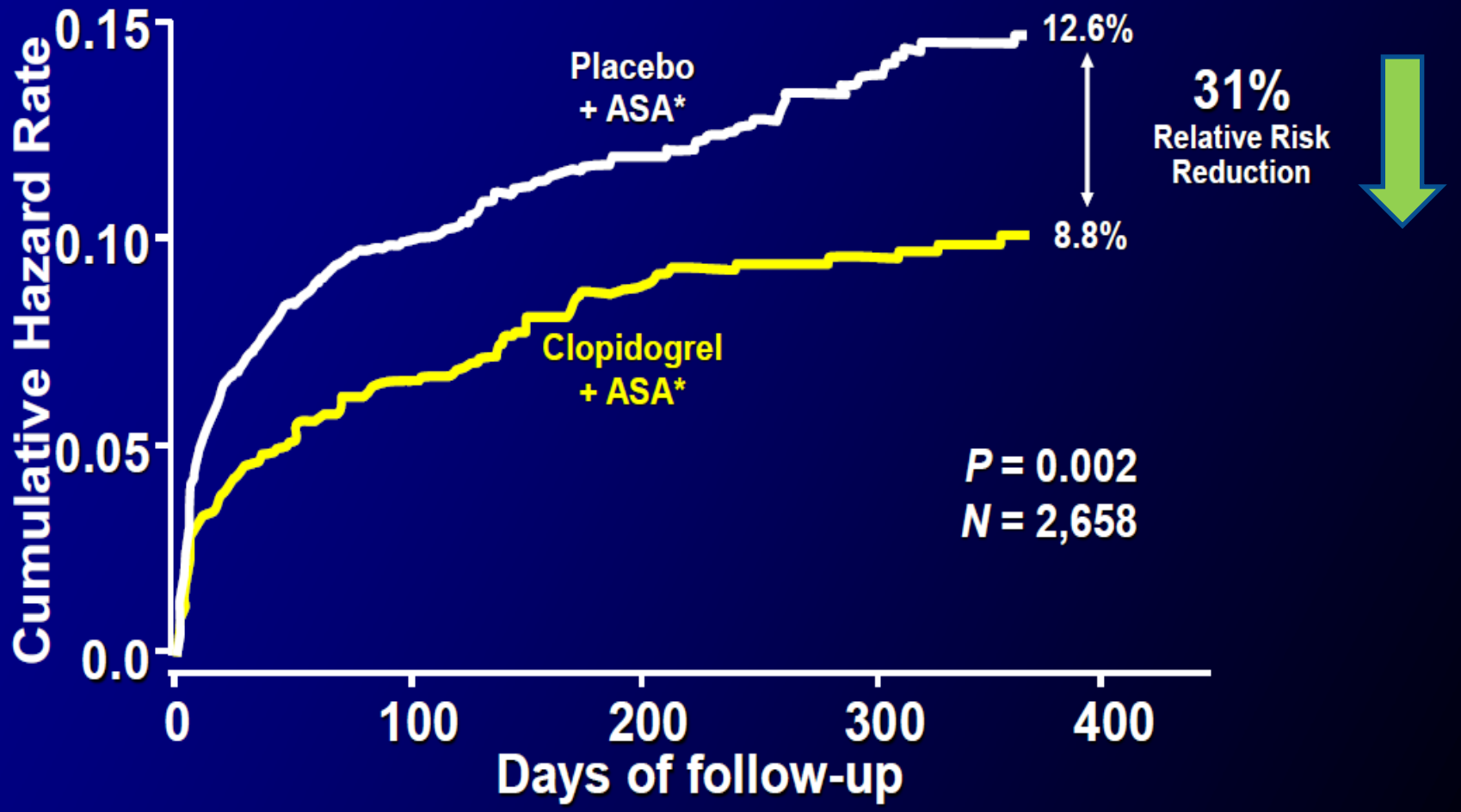

* In combination with standard therapy

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

# Early and Long-term Clopidogrel in PCI Patients with ACS

PCI-CURE

***Composite of MI or cardiovascular death from randomization to end of follow-up***

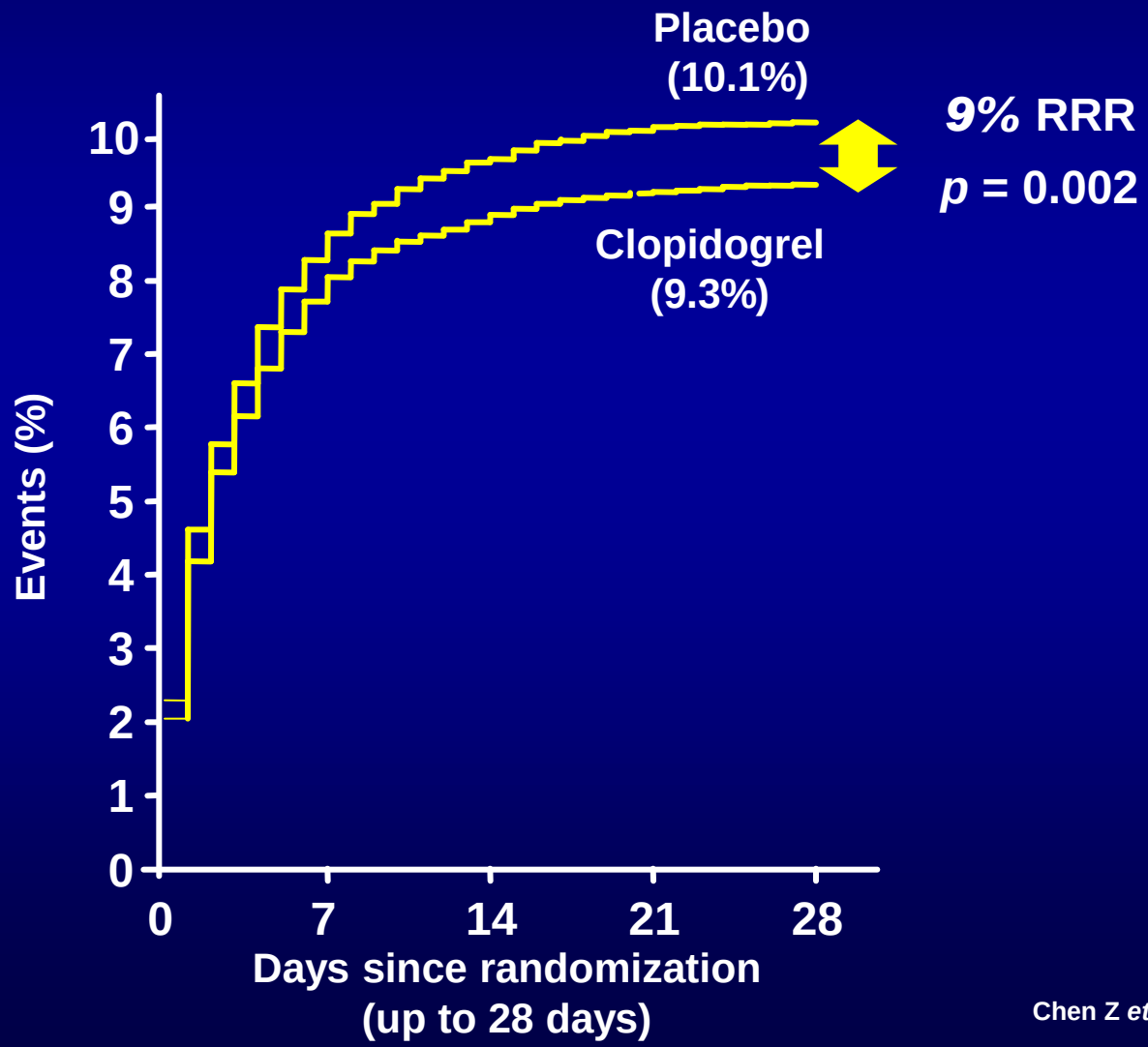



Mehta SR et al. Lancet 2001; 358(9281):527-33.

commit CCS-2

# STEMI

# Clopidogrel reduced the composite of death, MI or stroke by 9%




Chen Z *et al*. *Lancet* 2006;366:1607–1621

# Postprocedural Antiplatelet Therapy


After PCI, aspirin should be continued **indefinitely**.

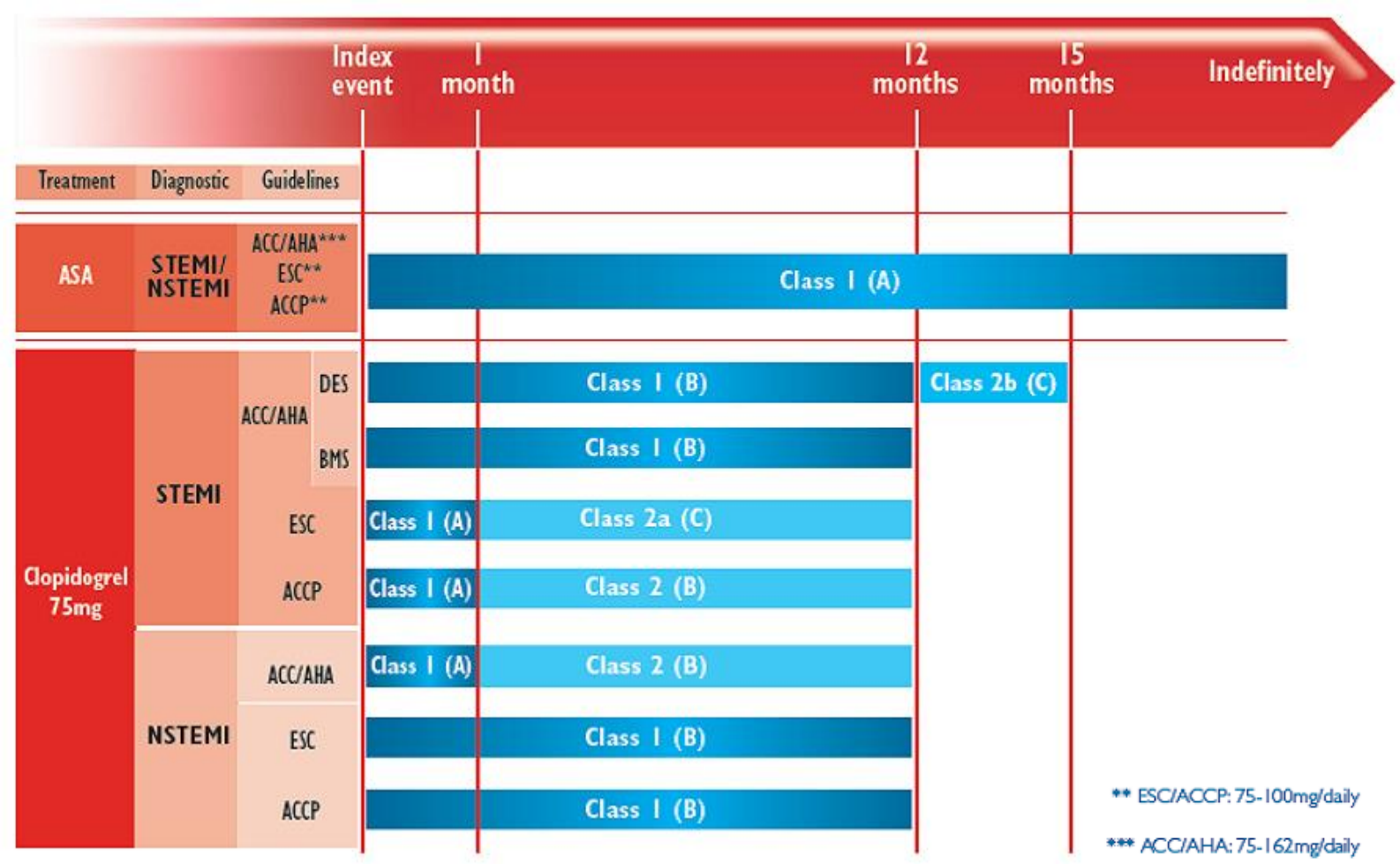

The duration of $P2Y_{12}$ inhibitor therapy after stent implantation should generally be as follows:

a) In patients receiving a stent (BMS or DES) during PCI **for ACS**, $P2Y_{12}$ inhibitor therapy should be given for **at least 12 months (clopidogrel 75 mg daily); prasugrel 10 mg daily; and ticagrelor 90 mg twice daily**.

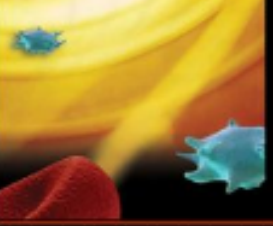
b) In patients receiving a **DES for a non–ACS indication**, clopidogrel 75 mg daily should be given for **at least 12 months** if patients are not at high risk of bleeding.

c) In patients receiving a **BMS for a non-ACS indication**, clopidogrel should be given for a **minimum of 1 month and ideally up to 12 months** (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks).

# Guidelines Recommendations on Antiplatelets




Clopidogrel: unless excessive risk of bleeding
ASA: unless excessive risk of bleeding or allergy



# Personalized Antiplatelet Therapy

## Optimizing Platelet Reactivity

### More of the Same

Increase clopidogrel dose

75 mg/day MD → 150 mg/day

300 mg LD → - 600 mg once
- 2-3 times 600 mg at intervals

### New Drugs

Prasugrel - oral, prodrug, irreversible

- Ticagrelor - oral, direct, reversible
- Elinogrel - oral/IV, direct, reversible X

Add GPIIb/IIIa inhibitors based on risk

IV = intravenous. LD = loading dose. MD = maintenance dose.

# Treatment Strategies for ACS Patients: High-dose Clopidogrel

# Oasis 7- 597 centres/39 countries/25086 pts

Worldwide recruitment – patients with **UA/NSTEMI or STEMI** planned for early invasive strategy, i.e. intent for PCI as early as possible within 72 h

**RANDOMIZE**

**Clopidogrel High Dose Group**
Clopidogrel **600 mg** loading dose Day 1 followed by 150 mg from Day 2 to Day 7; 75 mg from Day 8 to 30

**Clopidogrel Standard Dose Group**
Clopidogrel **300 mg** Day 1 followed by 75 mg from Day 2 to Day 7; 75 mg from Day 8 to 30

**RANDOMIZE**

**Open Label**

**RANDOMIZE**

**ASA low dose group**
At least 300 mg Day 1; 75–100 mg from D2 to D30

**ASA high dose group**
At least 300 mg Day 1; 300–325 mg from D2 to D30

**ASA low dose group**
At least 300 mg Day 1; 75–100 mg from D2 to D30

**ASA high dose group**
At least 300 mg Day 1; 300–325 mg from D2 to D30

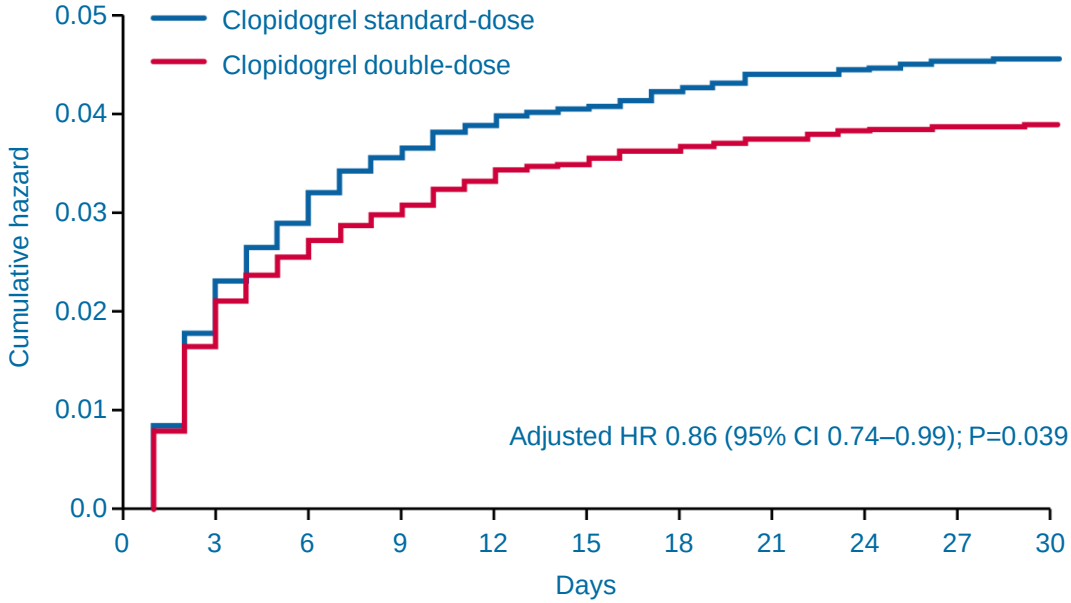
PCI: Percutaneous coronary intervention
UA/NSTEMI: Unstable angina/non-ST-segment elevation myocardial infarction
STEMI: ST-segment elevation myocardial infarction

1. Mehta SR *et al. Am Heart J* 2008;156:1080–1088e1

CURRENT

**7-days double-dose PLAVIX® regimen**

# Clopidogrel dose comparison: cumulative hazards for 1º efficacy outcome at 30 days in PCI cohort[1]




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Clopidogrel standard-dose | 8703 | 8450 | 8364 | 8333 | 8315 | 8303 |
| Clopidogrel double-dose | 8560 | 8341 | 8274 | 8245 | 8228 | 8223 |

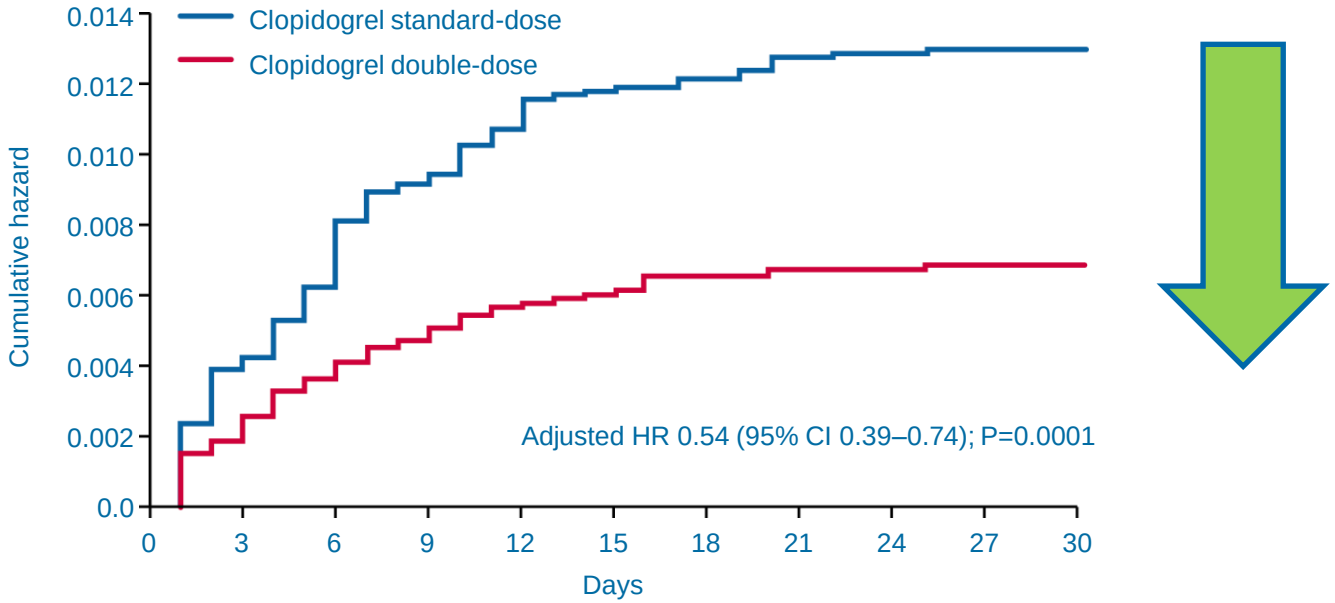
Mehta SR, et al. Lancet 2010;376:1233-43.

1. Mehta SR *et al. Lancet* 2010;376: published online 1 September 2010. DOI: 10.1016/ S0140-6736(10)61088-4

CURRENT

7-days double-dose PLAVIX® regimen

# Clopidogrel dose comparison: definite stent thrombosis in PCI cohort[1]




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Clopidogrel standard-dose | 8703 | 8561 | 8482 | 8455 | 8438 | 8428 |
| Clopidogrel double-dose | 8560 | 8444 | 8390 | 8366 | 8356 | 8347 |

1. Mehta SR *et al. Lancet* 2010;376: published online 1 September 2010. DOI: 10.1016/ S0140-6736(10)61088-4

# Clopidogrel dose comparison: bleeding outcomes in PCI cohort[1]

| Bleeding category | Clopidogrel dose | | Hazard ratio (95% CI) | P value |
|---|---|---|---|---|
| | Double N = 8560, n (%) | Standard N = 8703, n (%) | | |
| CURRENT major | 139 (1.6) | 99 (1.1) | 1.41 (1.09–1.83) | 0.009 |
| CURRENT severe | 96 (1.1) | 72 (0.8) | 1.34 (0.99–1.82) | 0.060 |
| TIMI major | 81 (1.0) | 60 (0.7) | 1.36 (0.97–1.90) | 0.074 |
| Fatal | 6 (0.07) | 13 (0.2) | 0.46 (0.18–1.22) | 0.12 |
| Intracranial | 3 (0.04) | 4 (0.05) | 0.77 (0.17–3.43) | 0.73 |
| Red-cell transfusion ≥ 2 U | 109 (1.3) | 77 (0.9) | 1.42 (1.06–1.91) | **0.019** |
| CABG-related | 10 (0.1) | 6 (0.07) | 1.70 (0.62–4.69) | 0.30 |
| Haemoglobin drop ≥ 50 g/l | 47 (0.6) | 30 (0.3) | 1.60 (1.01–2.53) | **0.045** |
| Minor | 435 (5.1) | 368 (4.3) | 1.23 (1.07–1.41) | **0.004** |

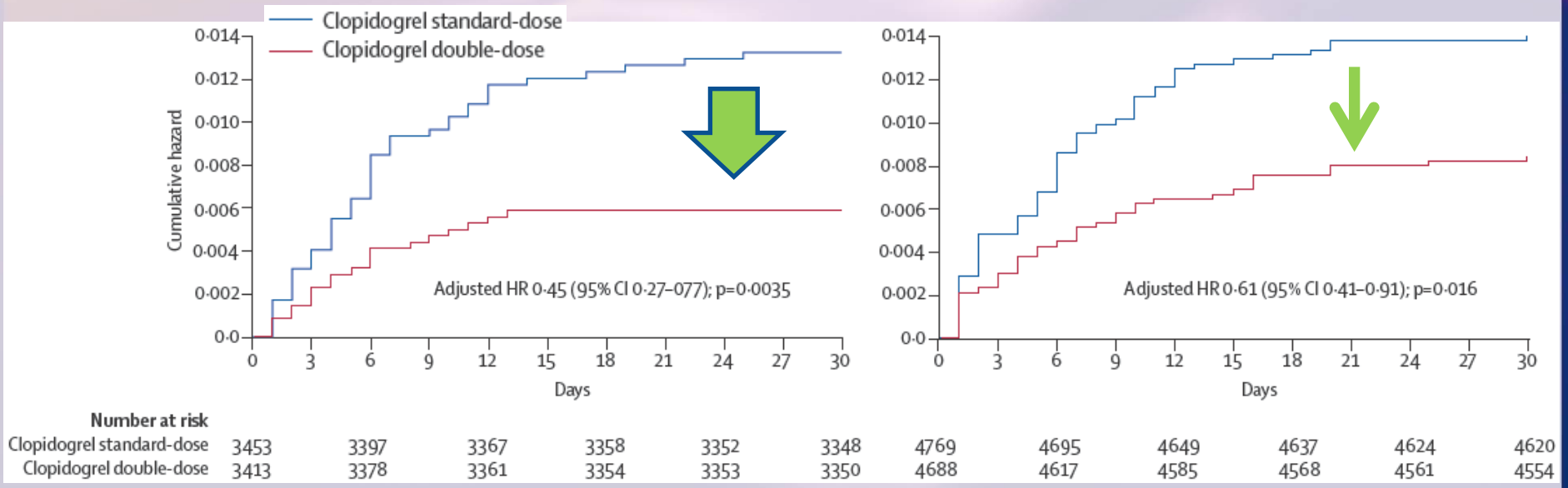
1. Mehta SR *et al. Lancet* 2010;376: published online 1 September 2010. DOI: 10.1016/ S0140-6736(10)61088-4

# High-dose clopidogrel reduced the rate of the stent thrombosis in ACS patients undergoing PCI

## CURRENT-OASIS-7 study

### Definite stent thrombosis in patients receiving a DES

### Definite stent thrombosis in patients receiving a BMS




DES: drug-eluting stent; BMS: bare-metal stent.

Mehta SR, et al. Lancet 2010;376:1233-43.

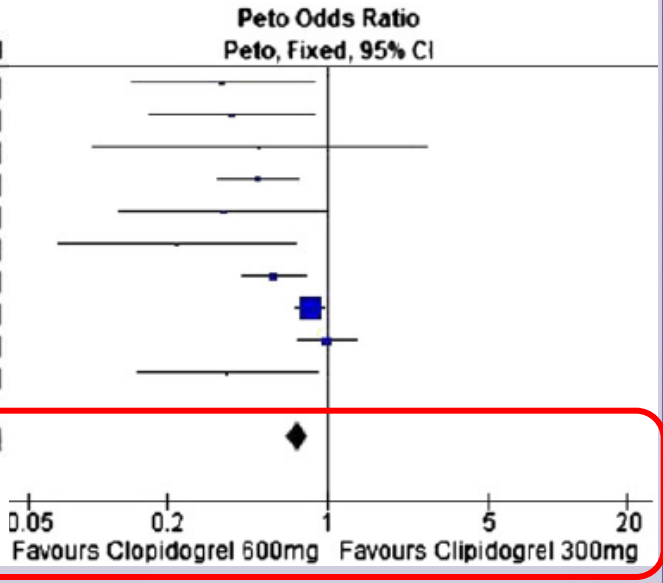
# High-dose clopidogrel reduced the relative risk of MACE

## Meta-analysis

. Major adverse cardiovascular events

| Study or Subgroup | Clopidogrel 600mg LD Events | Total | Clopidogrel 300mg LD Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Patti 2005 | 5 | 126 | 15 | 129 | 1.5% | 0.35 [0.14, 0.87] |
| Cuisset 2006 | 7 | 146 | 18 | 146 | 1.9% | 0.38 [0.17, 0.87] |
| Montalescot 2006 | 2 | 34 | 4 | 35 | 0.5% | 0.50 [0.10, 2.65] |
| Bonello 2008 | 91 | 3146 | 50 | 959 | 8.0% | 0.50 [0.33, 0.74] |
| Abuzahra 2008 | 8 | 77 | 10 | 42 | 1.2% | 0.35 [0.12, 1.01] |
| Jung 2008 | 1 | 73 | 11 | 98 | 0.9% | 0.22 [0.07, 0.73] |
| HORIZONS-AMI | 93 | 2158 | 81 | 1153 | 12.3% | 0.58 [0.42, 0.80] |
| CURRENT-OASIS 7 (PCI) | 330 | 8560 | 392 | 8560 | 56.9% | 0.84 [0.72, 0.97] |
| Choi 2011 | 92 | 1217 | 111 | 1447 | 15.3% | 0.98 [0.74, 1.31] |
| ARMYDA-6MI | 6 | 103 | 15 | 98 | 1.6% | 0.36 [0.15, 0.90] |
| Total (95% CI) | | 15640 | | 12667 | 100.0% | 0.74 [0.66, 0.82] |
| Total events | 635 | | 707 | | | |

Heterogeneity: Chi² = 25.99, df = 9 (P = 0.002); I² = 65%
Test for overall effect: Z = 5.34 (P < 0.00001)




Nijjer SS, et al. Int J Cardiol 2012;158:181-5.

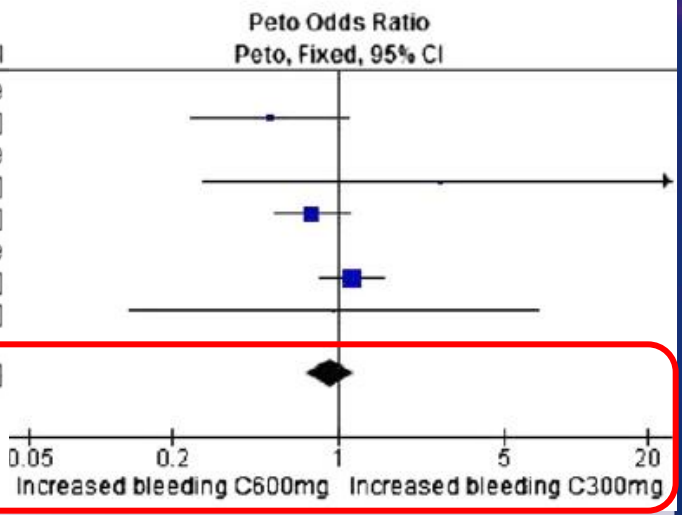
# High-dose clopidogrel did not alter the relative risk of major bleeding

## Systematic review

**. TIMI-defined major bleeding**

| Study or Subgroup | Clopidogrel 600mg LD Events | Total | Clopidogrel 300mg LD Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Patti 2005 | 0 | 126 | 0 | 129 | | Not estimable |
| Bonello 2008 | 24 | 3146 | 13 | 959 | 8.8% | 0.52 [0.24, 1.11] |
| Abuzahra 2008 | 77 | 1 | 42 | 1 | | Not estimable |
| Jung 2008 | 2 | 73 | 1 | 98 | 1.0% | 2.70 [0.27, 26.92] |
| HORIZONS-AMI | 78 | 2158 | 53 | 1153 | 38.2% | 0.77 [0.54, 1.11] |
| Di Sciascio 2010 | 0 | 252 | 0 | 251 | | Not estimable |
| CURRENT-OASIS 7 (PCI) | 81 | 8560 | 72 | 8703 | 50.7% | 1.15 [0.83, 1.57] |
| ARMYDA-6MI | 2 | 103 | 2 | 98 | 1.3% | 0.95 [0.13, 6.85] |
| **Total (95% CI)** | | **14419** | | **11392** | **100.0%** | **0.92 [0.74, 1.16]** |
| Total events | 264 | | 183 | | | |

Heterogeneity: Chi² = 5.74, df = 4 (P = 0.22); I² = 30%
Test for overall effect: Z = 0.69 (P = 0.49)

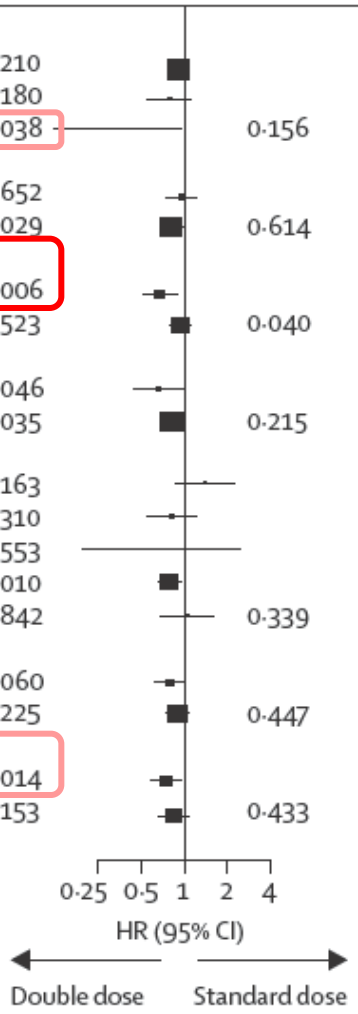



Nijjer SS, et al. Int J Cardiol 2012;158:181-5.

# Current smokers benefit greater in high-dose clopidogrel regimen

**CURRENT-OASIS-7 study**

| | 2N | Event (%) | | HR (95% CI) | Clopidogrel dose comparison | |
|---|---|---|---|---|---|---|
| | | Double dose | Standard dose | | p | p for interaction |
| **Prerandomisation clopidogrel** | | | | | | |
| No | 13769 | 268 (3·9) | 304 (4·4) | 0·90 (0·76–1·06) | 0·210 | |
| <300 | 2886 | 57 (4·0) | 73 (5·1) | 0·79 (0·55–1·12) | 0·180 | |
| ≥300 | 608 | 5 (1·7) | 15 (4·8) | 0·34 (0·12–0·94) | 0·038 | 0·156 |
| **Weight <60 kg or age ≥75 years or previous stroke** | | | | | | |
| Yes | 3766 | 125 (6·7) | 143 (7·5) | 0·95 (0·74–1·21) | 0·652 | |
| No | 13497 | 205 (3·1) | 249 (3·7) | 0·81 (0·67–0·98) | 0·029 | 0·614 |
| **Smoking status** | | | | | | |
| Yes | 6394 | 82 (2·6) | 122 (3·8) | 0·67 (0·51–0·89) | 0·006 | |
| No | 10862 | 245 (4·6) | 269 (4·9) | 0·94 (0·79–1·12) | 0·523 | 0·040 |
| **Prerandomisation proton-pump inhibitor** | | | | | | |
| Yes | 2180 | 39 (3·6) | 62 (5·7) | 0·66 (0·44–0·99) | 0·046 | |
| no | 11085 | 199 (3·6) | 243 (4·3) | 0·82 (0·67–0·99) | 0·035 | 0·215 |
| **Ethnic origin** | | | | | | |
| South Asian | 1570 | 41 (5·3) | 33 (4·1) | 1·40 (0·87–2·25) | 0·163 | |
| East Asian | 2363 | 43 (3·6) | 53 (4·5) | 0·81 (0·54–1·21) | 0·310 | |
| Black African | 121 | 4 (6·9) | 6 (9·5) | 0·68 (0·19–2·43) | 0·553 | |
| European | 10983 | 199 (3·6) | 254 (4·6) | 0·78 (0·65–0·94) | 0·010 | |
| Other | 2226 | 43 (4·0) | 46 (4·0) | 1·04 (0·69–1·59) | 0·842 | 0·339 |
| **Glycoprotein IIb/IIIa inhibitor postrandomisation** | | | | | | |
| Yes | 4932 | 116 (4·7) | 147 (5·9) | 0·79 (0·62–1·01) | 0·060 | |
| No | 12324 | 214 (3·5) | 245 (3·9) | 0·89 (0·74–1·07) | 0·225 | 0·447 |
| **Proton-pump inhibitor postrandomisation** | | | | | | |
| Yes | 5574 | 117 (4·2) | 158 (5·7) | 0·74 (0·58–0·94) | 0·014 | |
| No | 7691 | 121 (3·2) | 147 (3·8) | 0·84 (0·66–1·07) | 0·153 | 0·433 |




Mehta SR, et al. Lancet 2010;376:1233-43.

# MADONNA study:
# Stent thrombosis and ACS occurred less in guided-treatment group

Event rates in the guided and control groups during 1-month follow-up.

| Event n (%) | Guided group n = 403 | Non-guided group n = 395 | p |
|---|---|---|---|
| Stent thrombosis (definite and probable) | 1 (0.2) | 7 (1.9) | 0.027 |
| Acute coronary syndrome | 0 (0) | 10 (2.5) | 0.001 |
| Cardiovascular death | 8 (2) | 5 (1.3) | 0.422 |
| TIMI major bleeding | 4 (1) | 1 (0.3) | 0.186 |

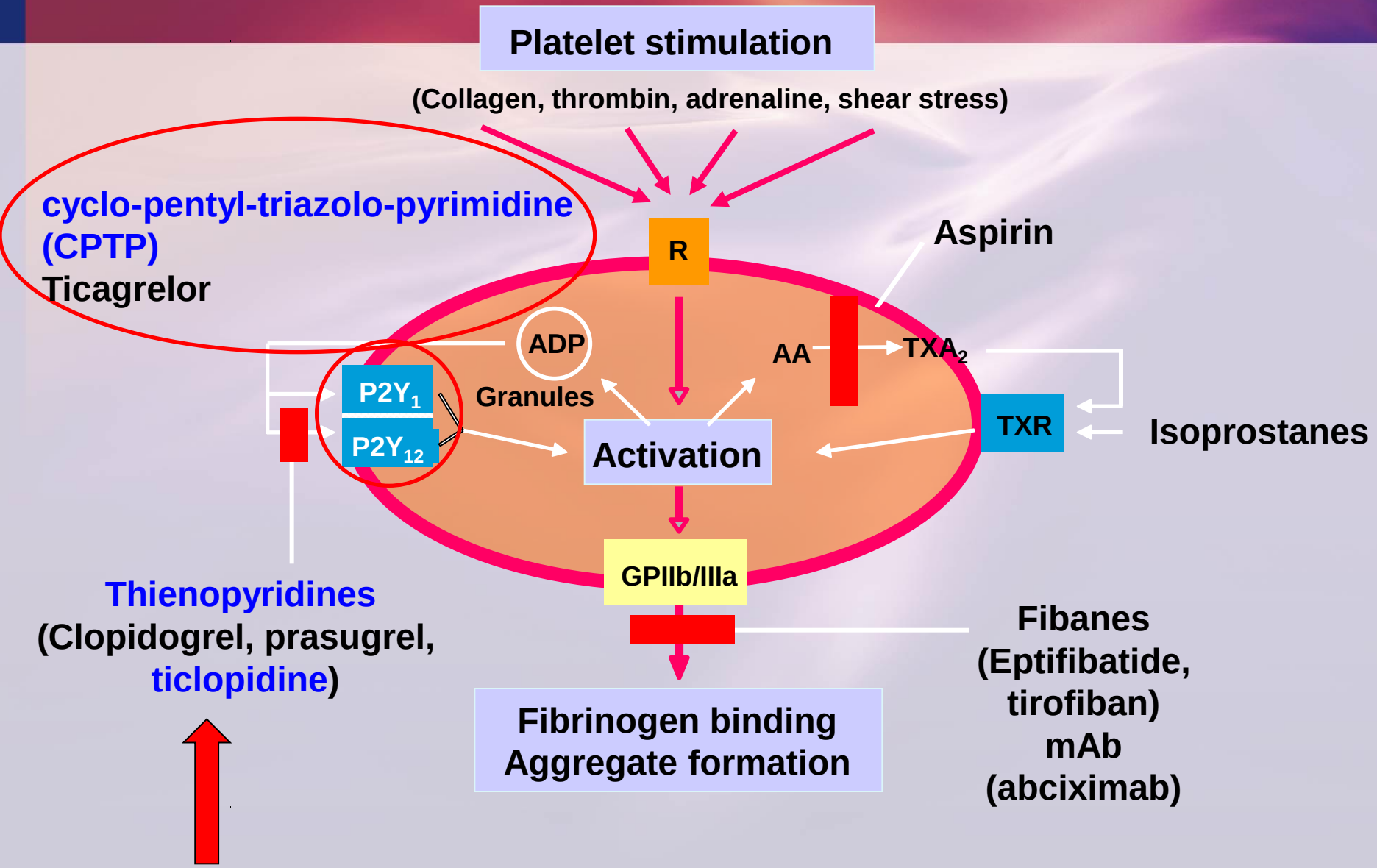
****Guided group: clopidogrel non-responders received repeated loading doses of clopidogrel or prasugrel.**

Non-guided group: clopidogrel non-responders did not undergo any change in treatment.

Siller-Matula JM, et al. Int J Cardiol 2012.

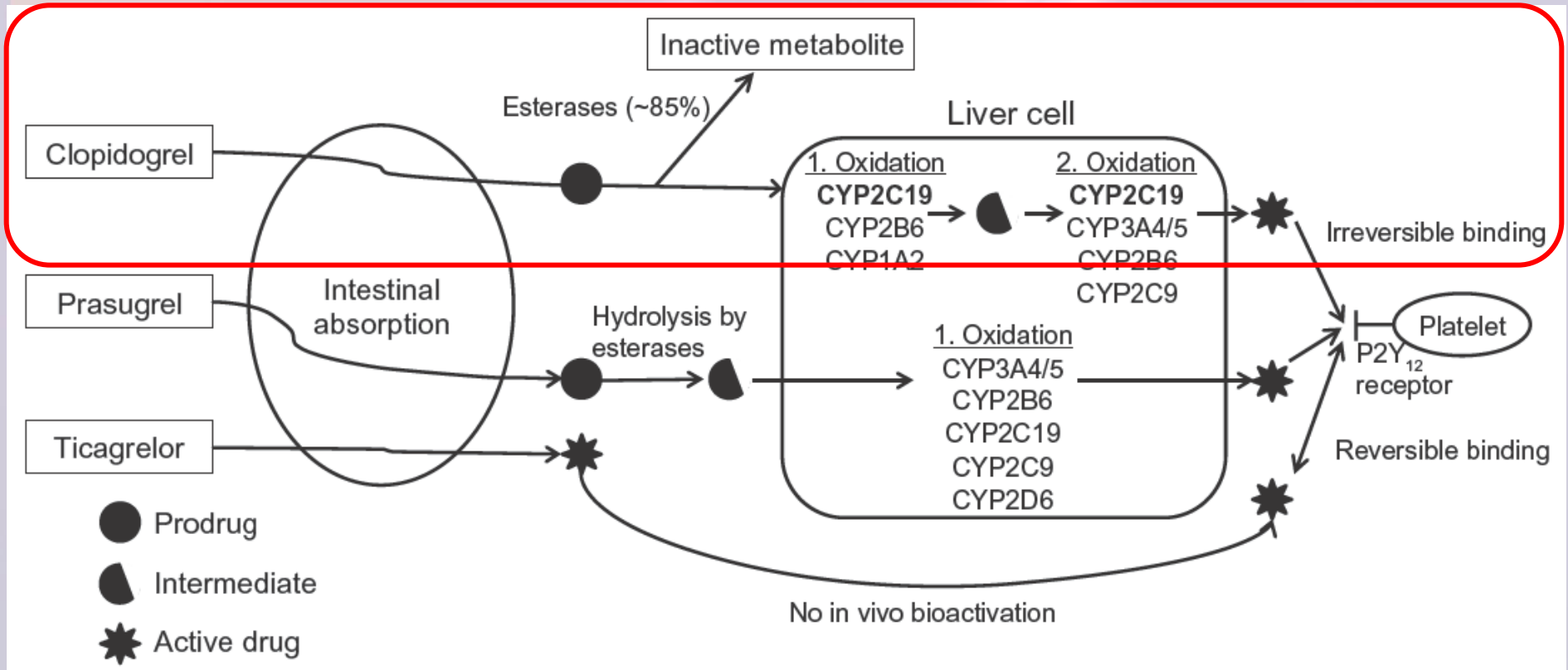
# Characteristics of Current Antiplatelet Drugs

# Sites of action of antiplatelet drugs



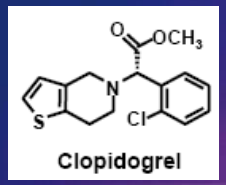
# Characteristics of clopidogrel

- Clopidogrel requires a **two-step bioactivation by liver cell**, which irreversibly binds to P2Y12 receptor, thus inhibiting platelet activation.




Cavallari LH,et al. Pharmgenomics Pers Med 2011;4:123-36.

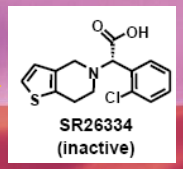
# Genetic polymorphisms may contribute to clopidogrel response variability




Intestinal Absorption

Esterases

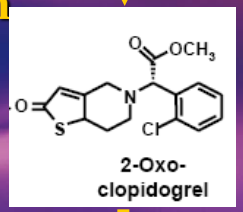
85%




Limited absorption ?

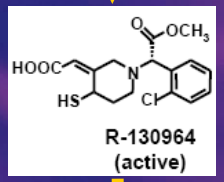
P-glycoprotein
(ABCB1 gene polymorphism)

15%




Hepatic P450 Cytochromes

Two Step Conversion




2C19, 1A2, 2B6

*2,*17

PPI

R-warfarin

Smoking

Genetic polymorphisms and Drug-Drug Interactions

*2,*17

PPI

S-warfarin

Statin, CCB

2C19, 2C9, 3A4, 2B6

Variable Active Metabolite Generation

Wide Pharmacodynamic Response, Nonresponsiveness

Worse Clinical Outcome?

Adapted from Kauzi M, et al. *Drug Metab Dispos*. 2010;38:92–99.
Gurbel PA, et al. *J Inv Cardiol*; 2009:172–175.

# Clopidogrel has major limitation in terms of *CYP2C19* genetic polymorphism

| CYP2C19表現型和基因型頻率 | | |
|---|---|---|
| | **Asian (n= 573)** | Caucasian (n= 1356) |
| Slow meta: CYP2C19*2/*2, *2/*3 or *3/*3 | **14%** | 2% |
| Moderate meta: CYP2C19*1/*2 or *1/*3 | **50%** | 26% |
| Rapid meta: CYP2C19*1/*1 | 38% | 74% |

FDA

## WARNING:
## DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following ACS or PCI than patients with normal CYP2C19 function.
- Consider alternative treatment or treatment strategies in patients as CYP2C19 poor metabolizers.


1. 保栓通衛生署核准仿單
2. Highlights of prescribing information, PLAVIX

# CYP2C19 genotype, clopidogrel metabolism, platelet function, and Cardiovascular events: a systematic review and meta-analysis. Holmes MV, et al. . JAMA 2011;306:2704-14

32 studies/42,016 patients/3545 CVD events/579 stent thromboses/1413 bleeding events. Six studies were randomized trials

In treatment-only analysis, individuals with 1 or more CYP2C19 alleles had
1) lower risk of bleeding (relative risk [RR], 0.84; 95% CI, 0.75-0.94),
2) higher risk of CVD events (RR, 1.18; 95% CI, 1.09-1.28).

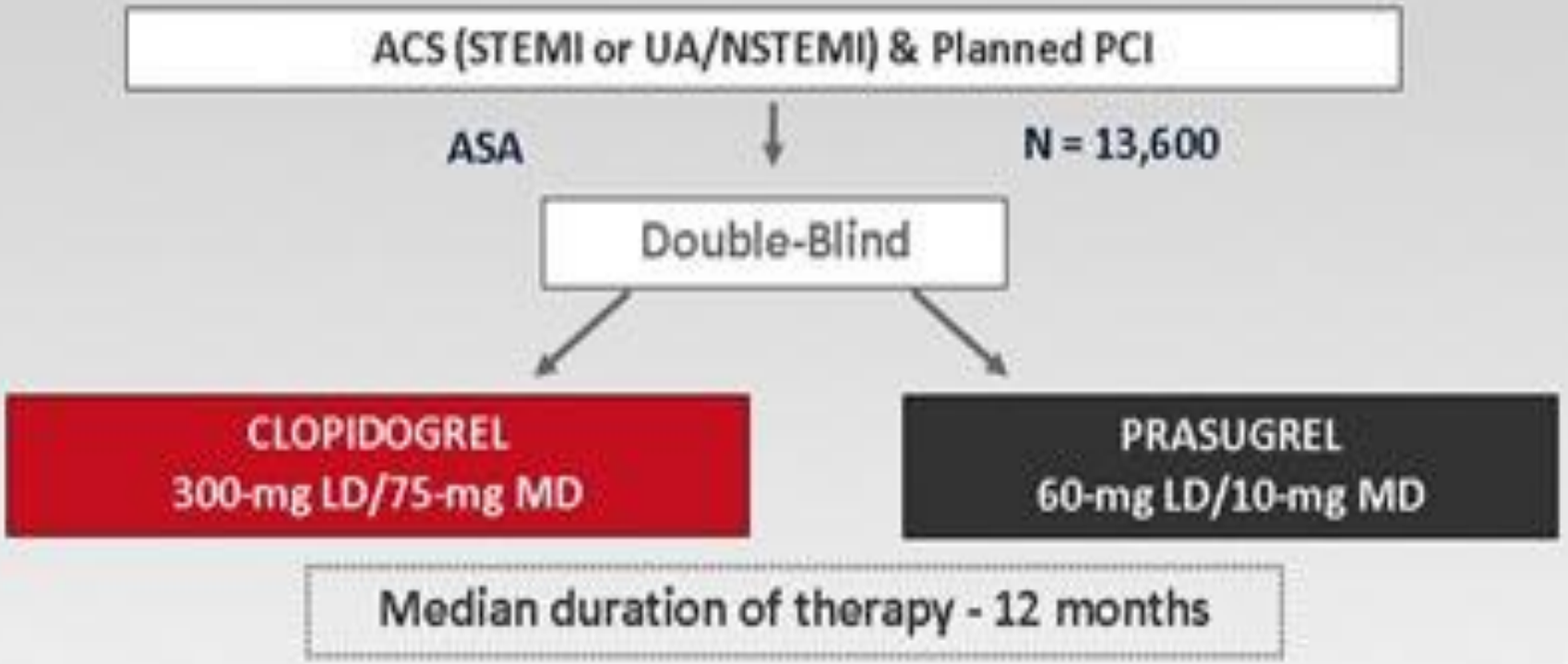
**When analyses were restricted to studies with 200 or more events, the point estimate was insignificant (RR, 0.97; 95% CI, 0.86-1.09).**
**In randomized trials, CYP2C19 genotype was not associated with modification of the effect of clopidogrel on CVD end points or bleeding (P > .05 ).**

## CONCLUSION:

Although there was an association between the CYP2C19 genotype and clopidogrel responsiveness, **overall there was no significant association of genotype with cardiovascular events.**

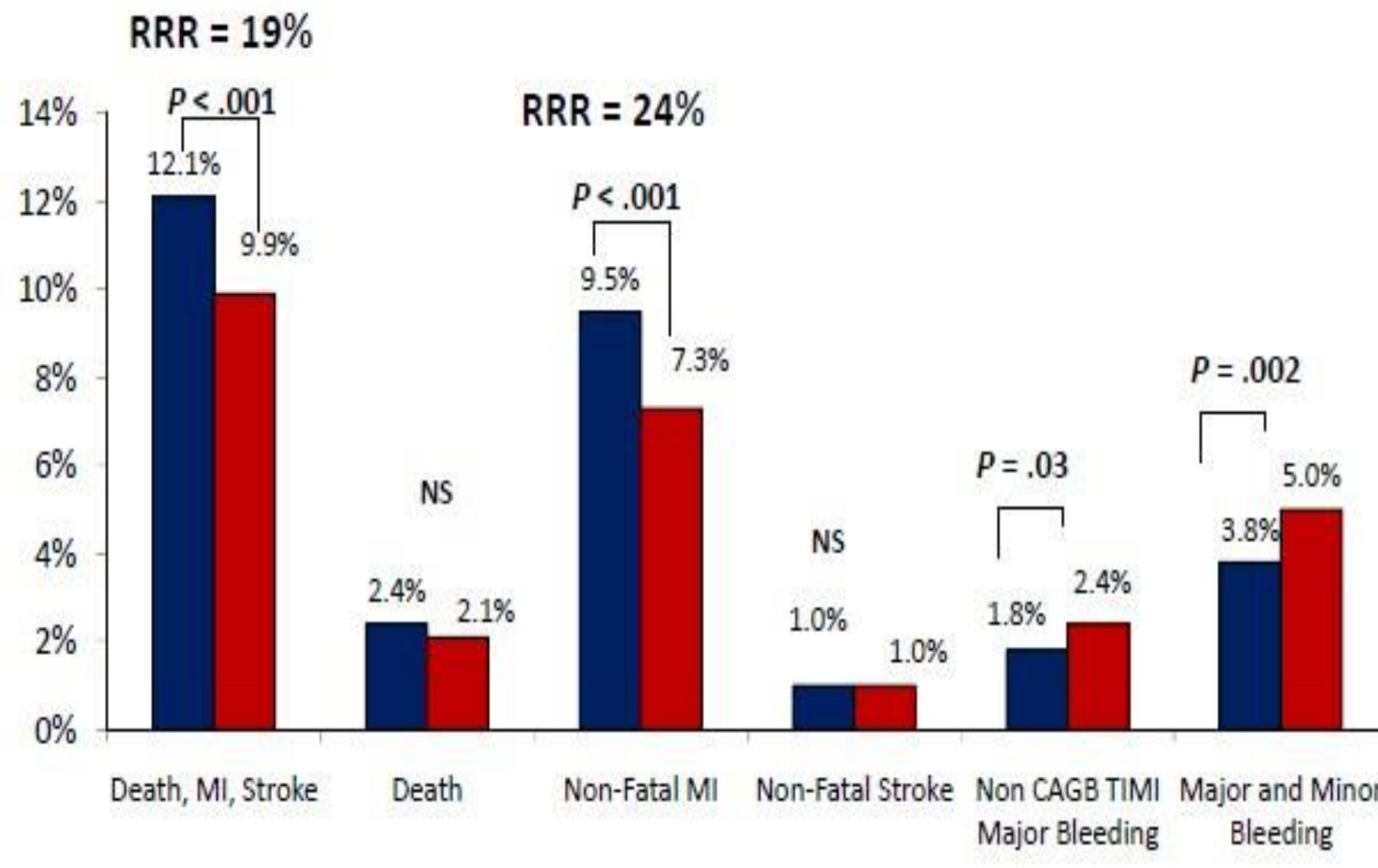
NEJM 2007; 357: 2001-2005

# TRITON Study Design




| | |
|---|---|
| 1° endpoint: | CV death, MI, stroke |
| 2° endpoints: | CV death, nonfatal MI, nonfatal urgent target vessel revascularization |
| Safety endpoints: | TIMI major bleeds, life-threatening bleeds |
| Key substudies: | Pharmacokinetic, genomic |

NEJM 2007; 357: 2001-2005



# TRITON-TIMI 38

NEJM 2007; 357: 2001-2005

**Primary Endpoint**

| Efficacy % | Prasugrel n = 6813 | Clopidogrel n = 6795 | Hazard ratio (95% CI) | *P* value |
|---|---|---|---|---|
| Death from CV causes, nonfatal MI, nonfatal stoke | 9.9 | 12.1 | 0.81 (0.73-0.90) | < .001 |

| Safety % | Prasugrel n = 6741 | Clopidogrel n = 6716 | Hazard ratio (95% CI) | *P* value |
|---|---|---|---|---|
| Non-CABG-related TIMI major bleeding | 2.4 | 1.8 | 1.32 (1.03-1.68) | .03 |

# Higher risks in pts with
# 1) prior CVA or TIA 2) age > 75 y/o 3) BW < 60 kg

NEJM 2007; 357: 2001-2005

## TRITON-TIMI 38
## -safety results-

| Endpoint | Prasugrel(%) | Clopidogrel(%) | P value |
|---|---|---|---|
| Non-CABG-related TIMI major bleed | 2.4 | 1.8 | 0.03 |
| Life-threatening bleed | 1.4 | 0.9 | 0.01 |
| Fatal bleed | 0.4 | 0.1 | 0.002 |
| Major or minor TIMI bleeding | 5.0 | 3.8 | 0.002 |
| Need for blood transfusion | 4.0 | 3.0 | <0.001 |
| CABG-related TIMI major bleed | 13.4 | 3.2 | <0.001 |

# TRILOGY ACS: Results

## Plavix vs. Prasugrel in ACS without PCI -> No reduction in MACE for 12 M

- Primary Outcome Measures:
  Reduction in risk of the composite endpoint of first occurrence of CV death, MI, or stroke

- While prasugrel failed to show a reduction in major cardiovascular events compared with clopidogrel in the first 12 months of study, prasugrel appeared to reduce the risk of events from 12 months onward as the curves began to diverge thereafter.

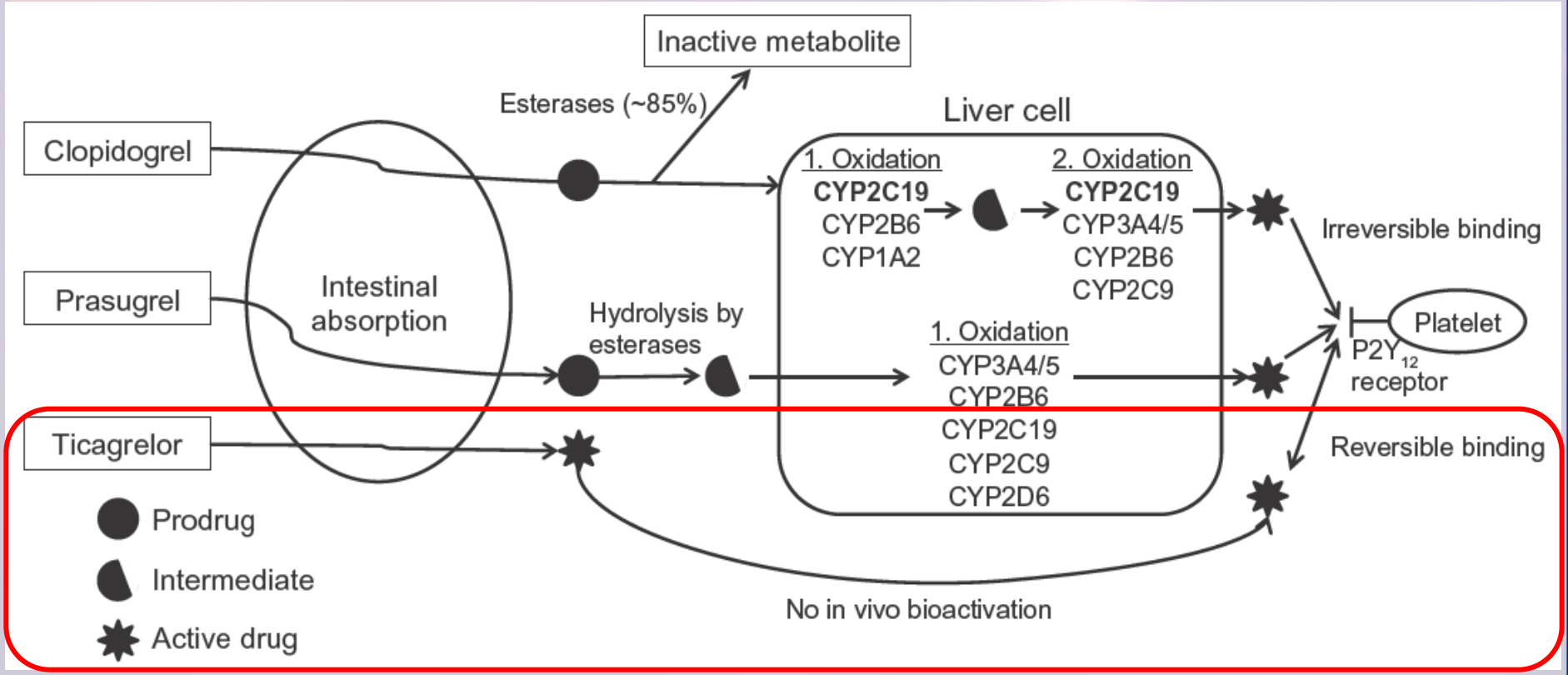
**No difference !**

- Through a median follow-up of 17 month, the primary end point of cardiovascular death, MI, or stroke among those <75 years occurred in 13.9% of patients treated with prasugrel vs 16.0% of patients treated with clopidogrel (HR 0.91; p=0.21). Similar results were observed in the overall population.

- The researchers also performed a prespecified analysis of multiple recurrent ischemic events (all components of the primary end point), which hinted at a lower risk with prasugrel than clopidogrel among those under 75 years (HR 0.85; p=0.044). This suggested a time-dependent treatment effect in favor of prasugrel, with much of the reduction in recurrent events being after one year, which was consistent with the time dependence seen with the primary end point.

# Characteristics of ticagrelor

- Ticagrelor is a recently approved reversible P2Y12 antagonist that **does not require hepatic bioactivation.**




**CYP3A4/5**

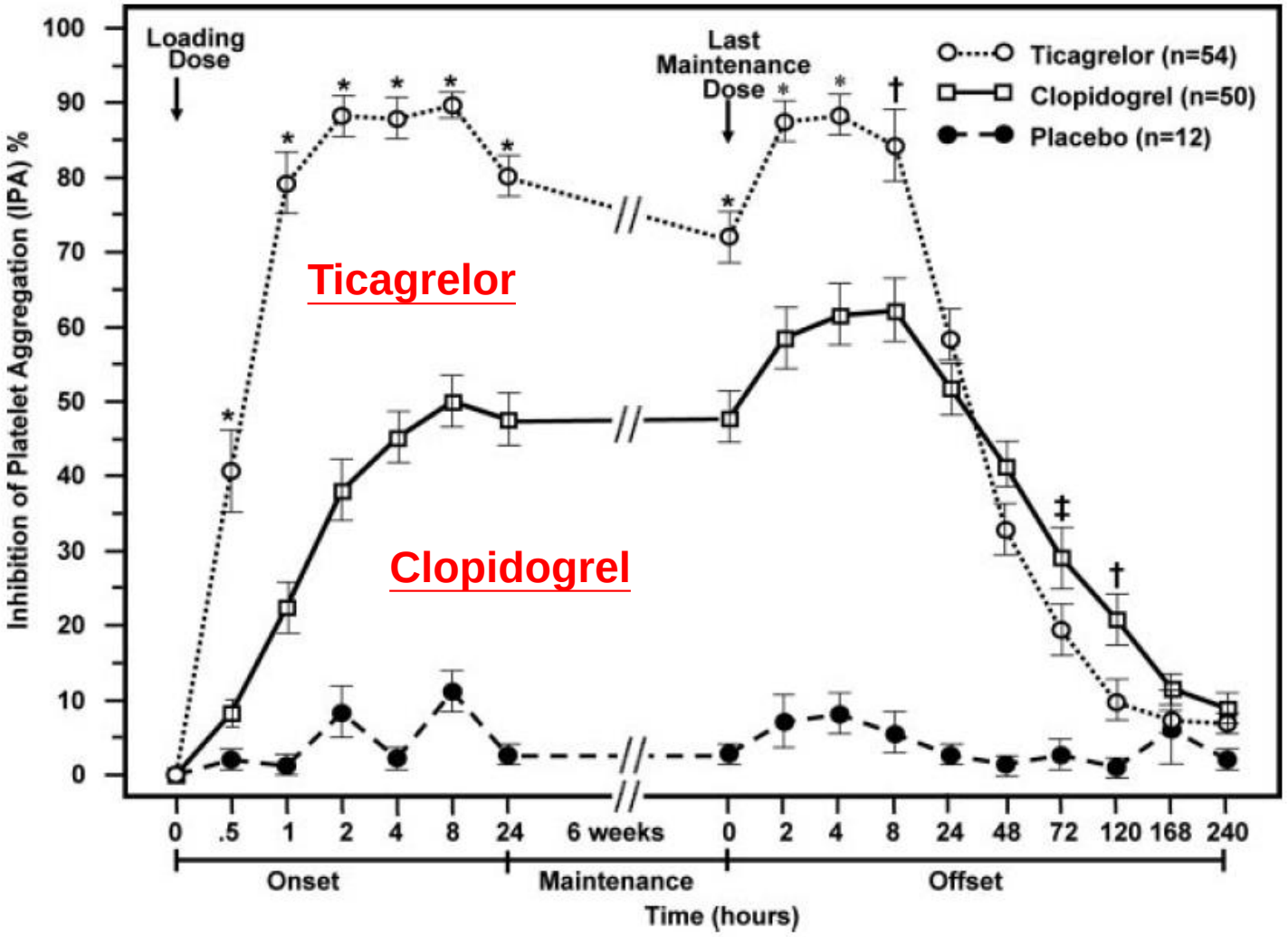
Cavallari LH,et al. Pharmgenomics Pers Med 2011;4:123-36.

# $P2Y_{12}$ inhibitors

| | Plavix® | Prasugrel | Ticagrelor |
|---|---|---|---|
| Class | Thienopyridine | Thienopyridine | **Triazolopyrimidine** |
| Reversibility | Irreversibility | Irreversibility | **Reversibility** |
| Activation | Prodrug | Prodrug | **Active drug** |
| Duration of effect | 3-10 days | 5-10 days | 3-4 days |
| Withdraw before major surgery | 5 days | 7 days | 5 days |

# Results – IPA (Inhibition of Platelet Aggregation %)*

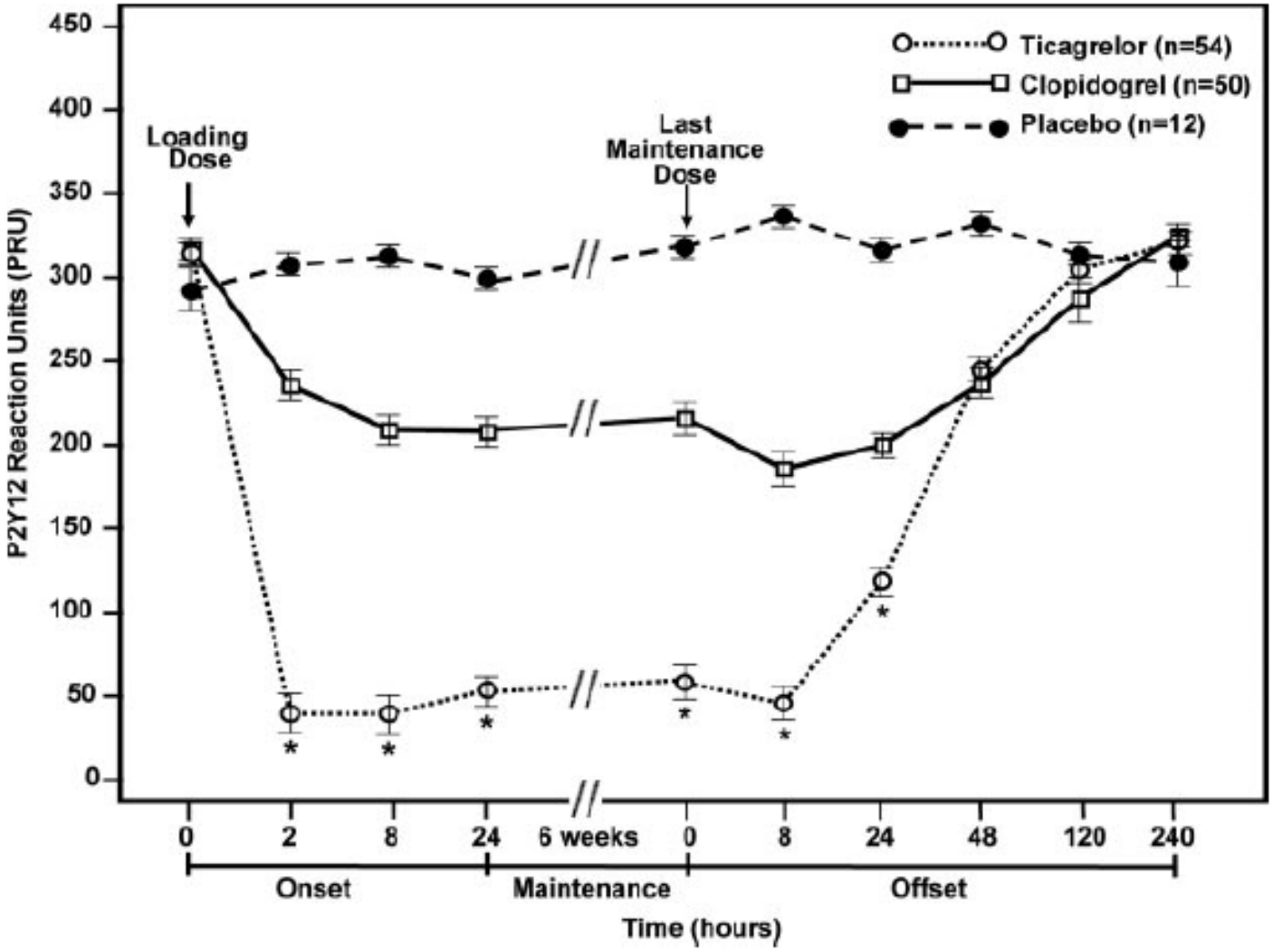
## subject: patients with stable CAD




*IPA measured by LTA.

# Results – PRU (Platelet Reaction Unit) *

## subject: patients with stable CAD



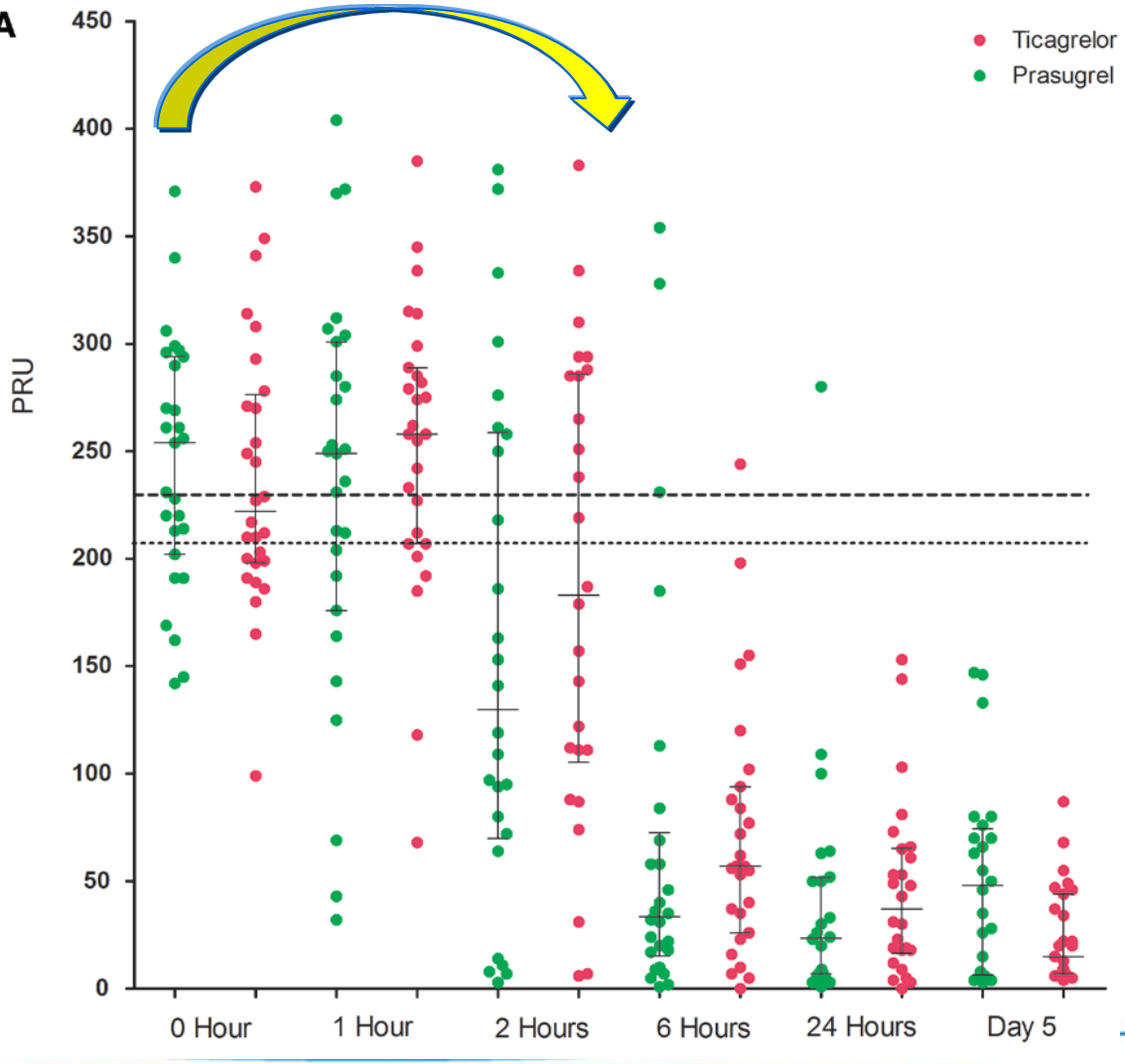

*PRU assessed by VerifyNow.

# Results – PRU*

## subject: patients with STEMI

**Red: Ticagrelor**

**Green: Prasugrel**

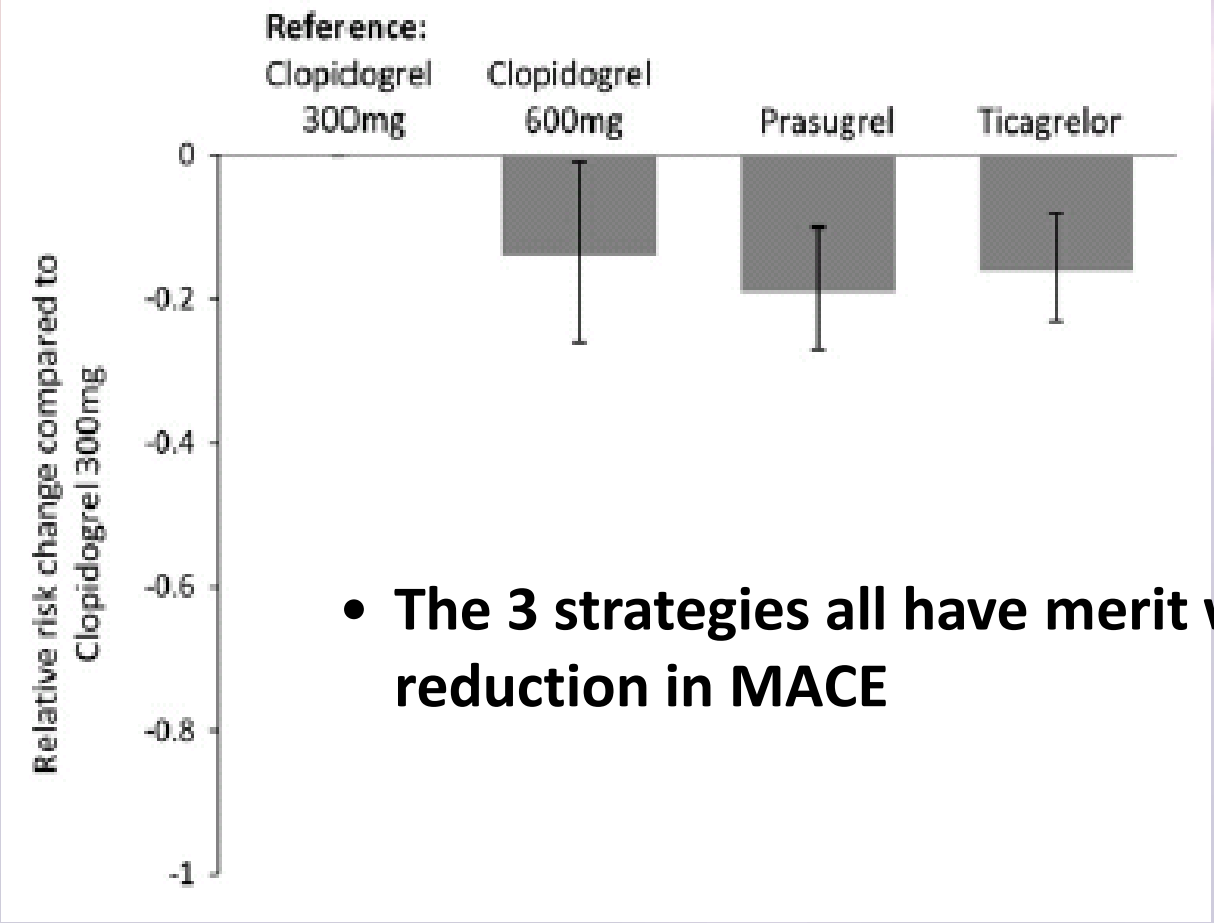



- Both ticagrelor and prasugrel exhibit an initial delay in the onset of antiplatelet effects in STEMI.
- Platelet reactivity does not differ among patients treated with either ticagrelor or prasugrel during the first 24 hours of STEMI.

*PRU assessed by VerifyNow.

**Randomized Assessment of Ticagrelor vs Prasugrel Antiplatelet Effects in Patients with STEMI.** Circ Cardiovasc Interv. 2012;5:797-804.

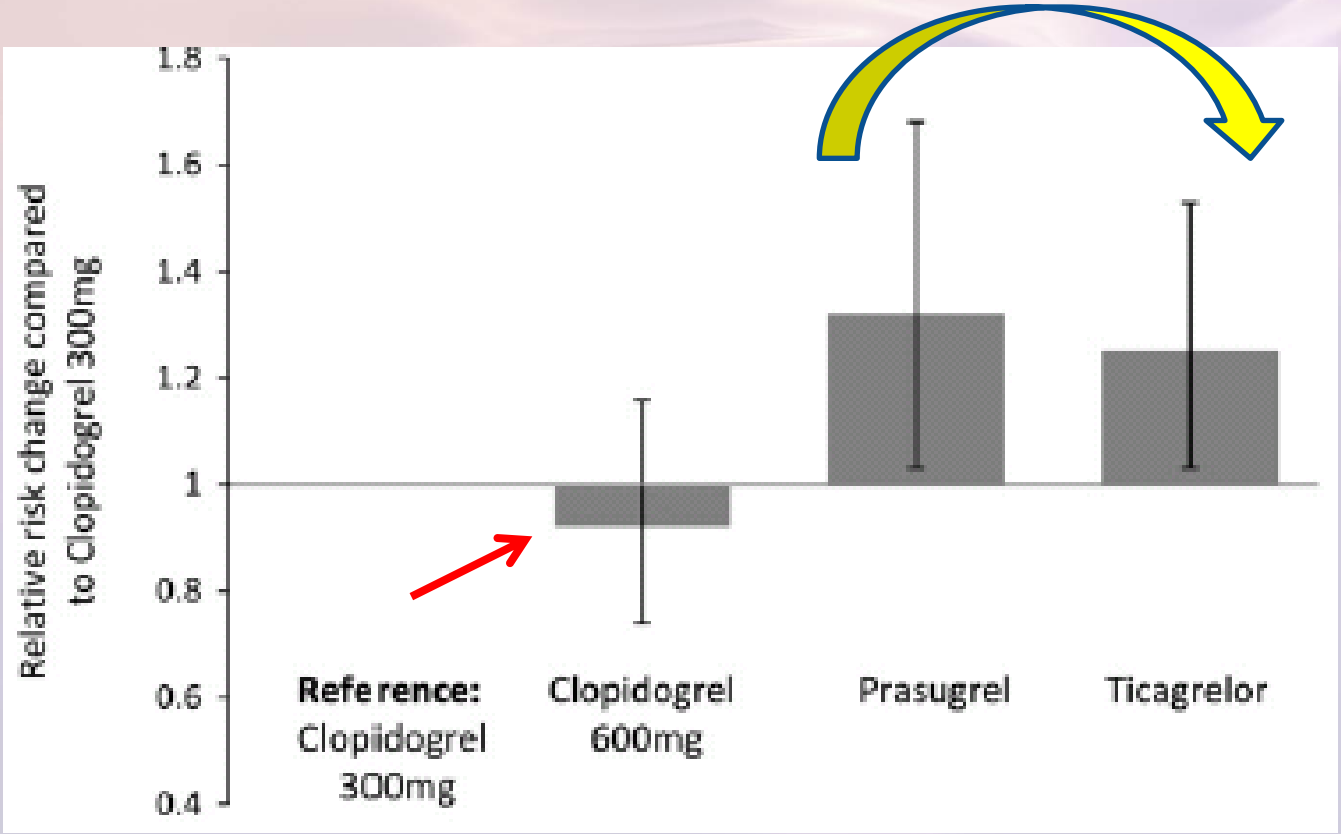
# Reduction in MACE are similar in the 3 strategies




- **The 3 strategies all have merit with reduction in MACE**

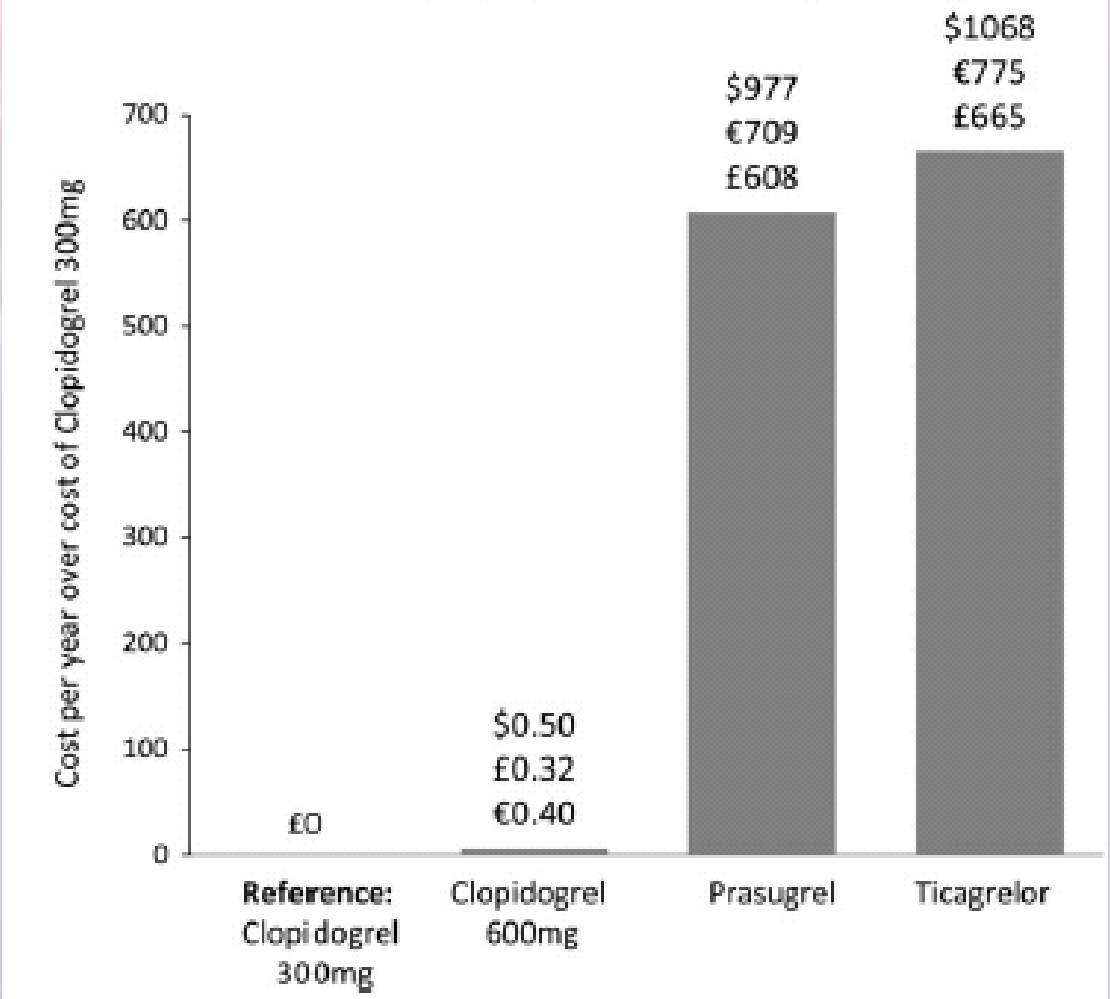
International Journal of Cardiology 158 (2012) 181–185

# Bleeding is significantly increased with both prasugrel and ticagrelor



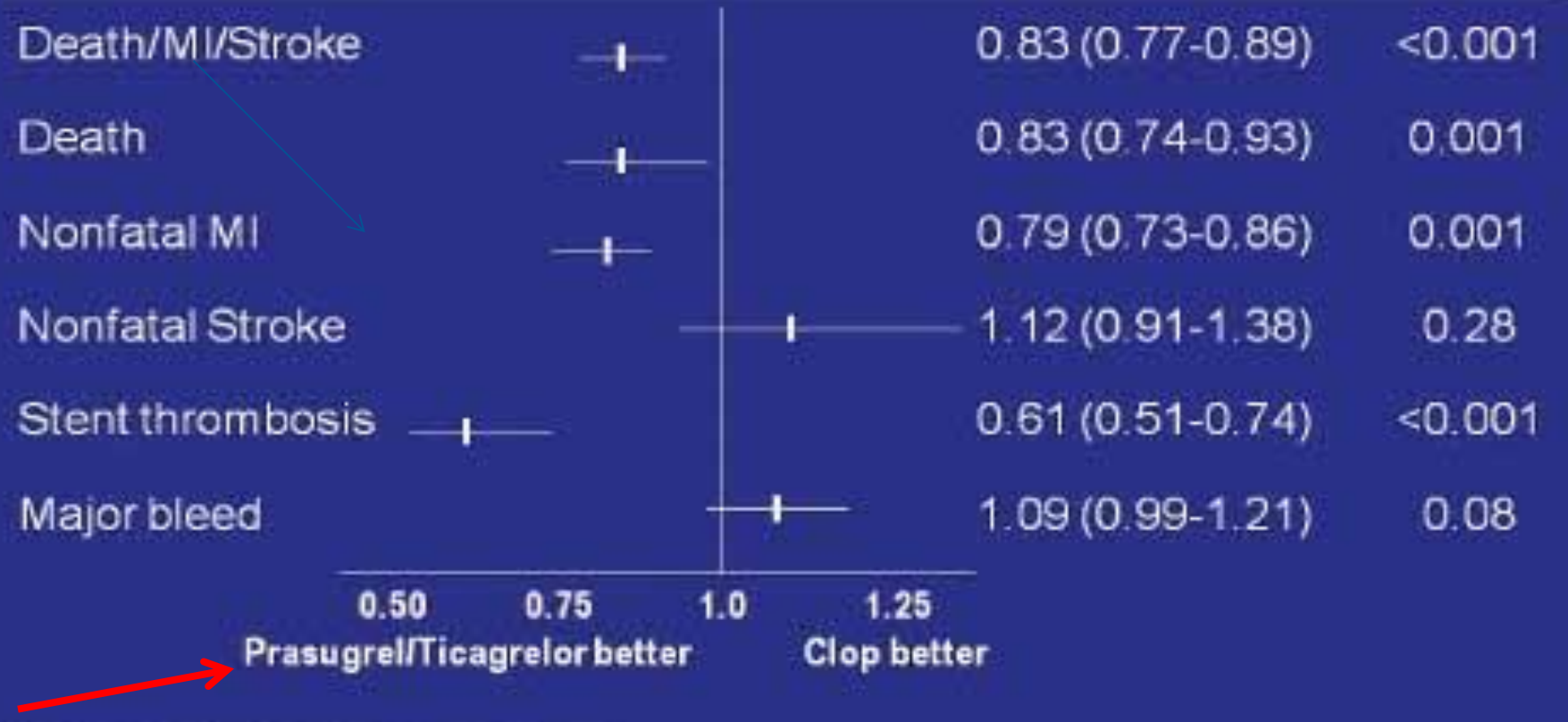

International Journal of Cardiology 158 (2012) 181–185

# Additional financial cost much larger for prasugrel and ticagrelor




International Journal of Cardiology 158 (2012) 181–185

# Meta-Analysis Comparison of Prasugrel, Ticagrelor and Clopidogrel in 3 RCCT* Involving 32,893 Patients




*DISPERSE 2, PLATO, TRITON-TIMI 38

Adapted from Biondi-Zoccai et al. Int J Cardiol 2011;150:325-31

Figure

# PLATO Study
# Clopidogrel vs. Ticagrelor

# PLATO study design

**NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)**
**Clopidogrel-treated or -naive;**
**randomised within 24 hours of index event**
**(N=18,624)**

**Clopidogrel**
**If pre-treated, no additional loading dose;**
**if naive, standard 300 mg loading dose,**
**then 75 mg qd maintenance;**
**(additional 300 mg allowed pre PCI)**

**Ticagrelor**
**180 mg loading dose, then**
**90 mg bid maintenance;**
**(additional 90 mg pre-PCI)**

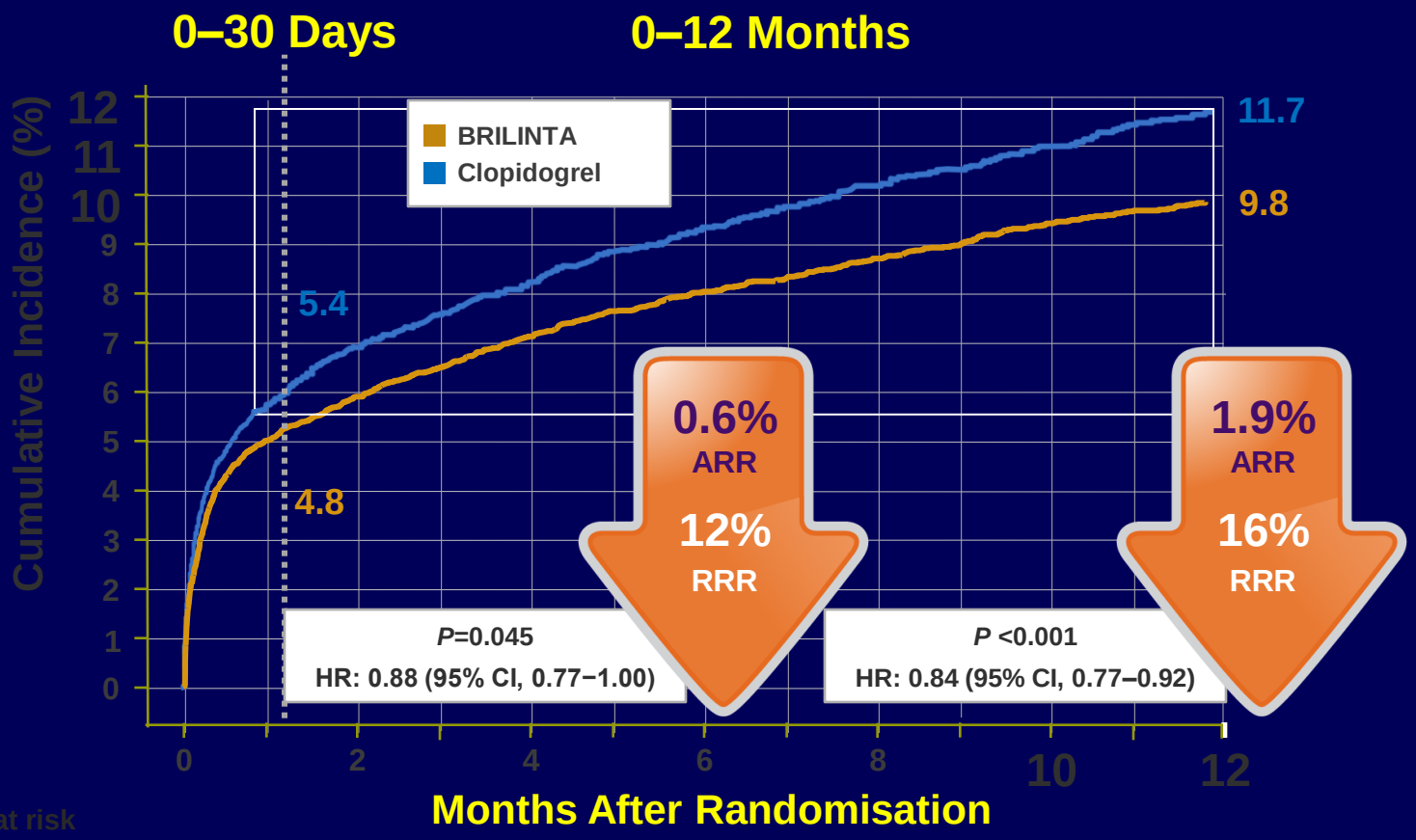
**6–12-month exposure**

**Primary endpoint: CV death + MI + Stroke**
**Primary safety endpint: Total major bleeding**

PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid;
CV = cardiovascular; TIA = transient ischaemic attack

# PLATO: Primary Efficacy Endpoint

(Composite of CV Death, MI, or Stroke)

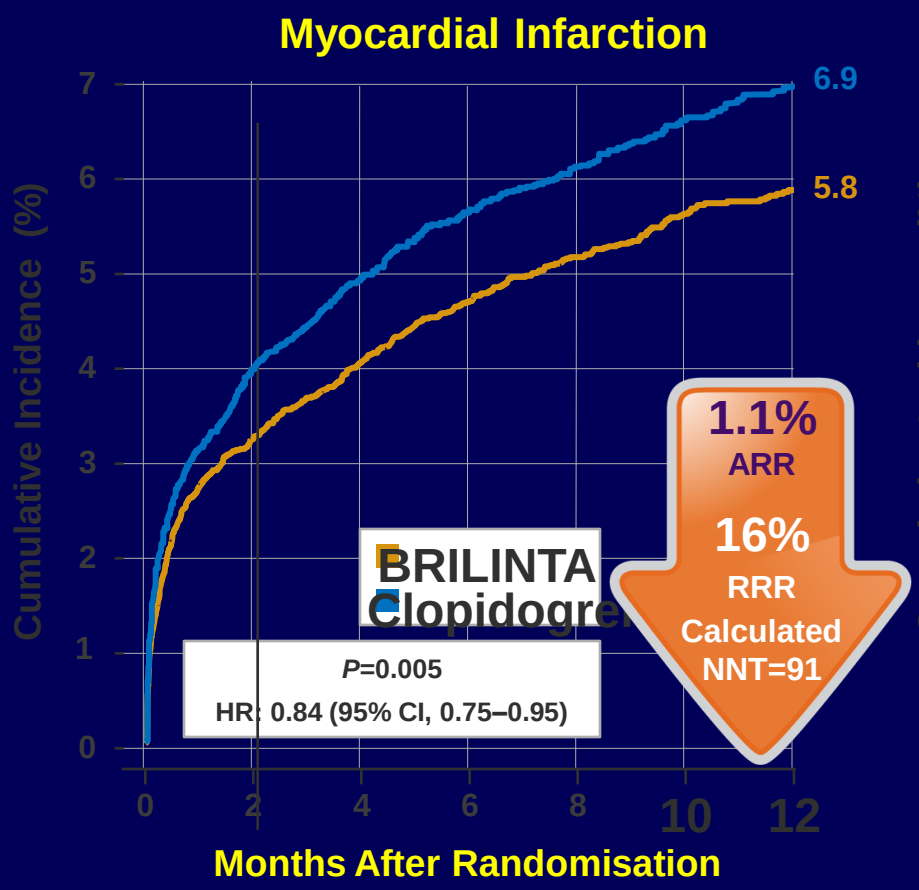


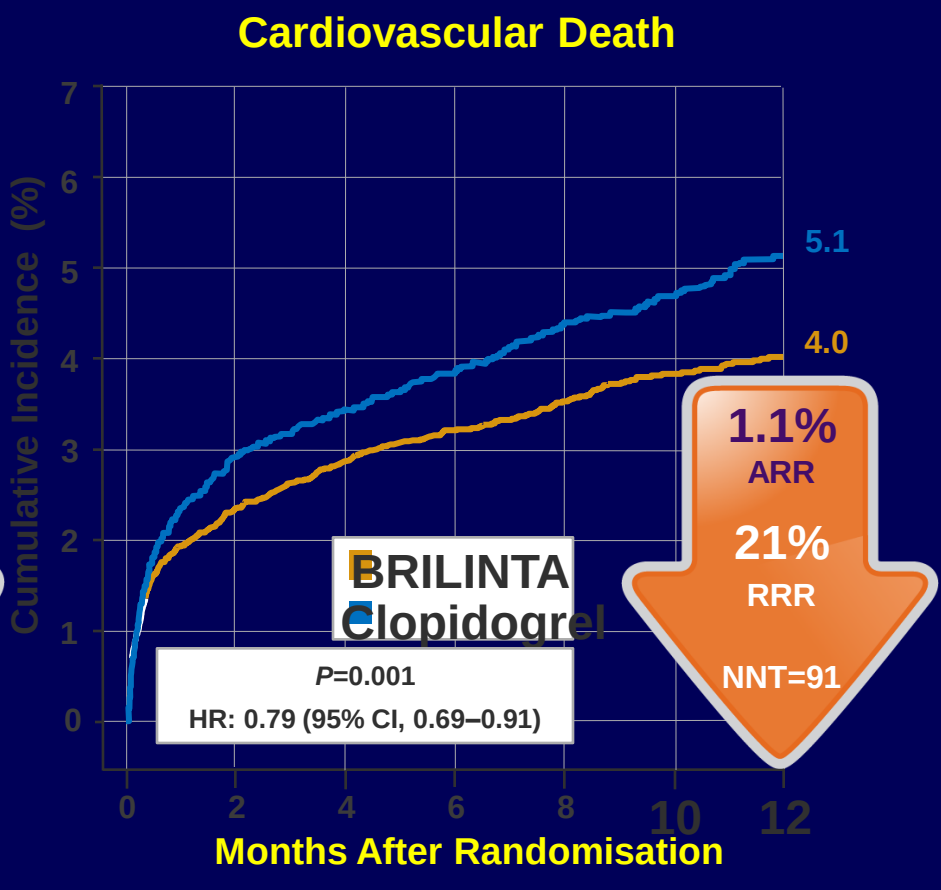

| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| BRILINTA | 9,333 | 8,628 | 8,460 | 8,219 | 6,743 | 5,161 | 4,147 |
| Clopidogrel | 9,291 | 8,521 | 8,362 | 8,124 | 6,650 | 5,096 | 4,047 |

*Both groups included aspirin.* *NNT at one year.

Wallentin L, et al. *N Engl J Med.* 2009;361:1045–1057.

# PLATO: Secondary Efficacy Endpoints

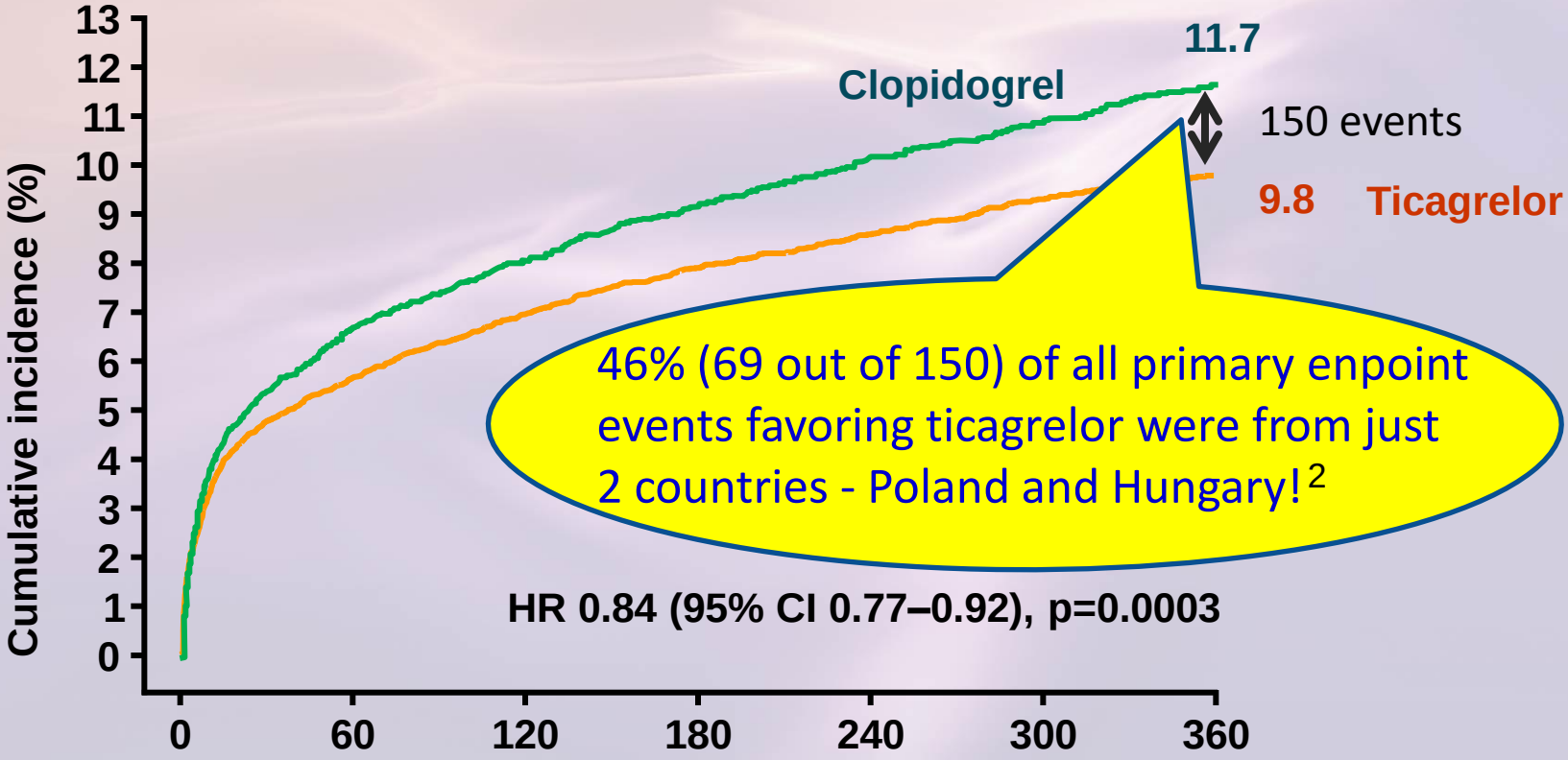



*Both groups included aspirin.*


Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.
Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057. Supplement.
BRILINTA: Summary of Product Characteristics, 2010.

# Primary efficacy_PLATO study
## event (composite of CV death, MI or stroke)




K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

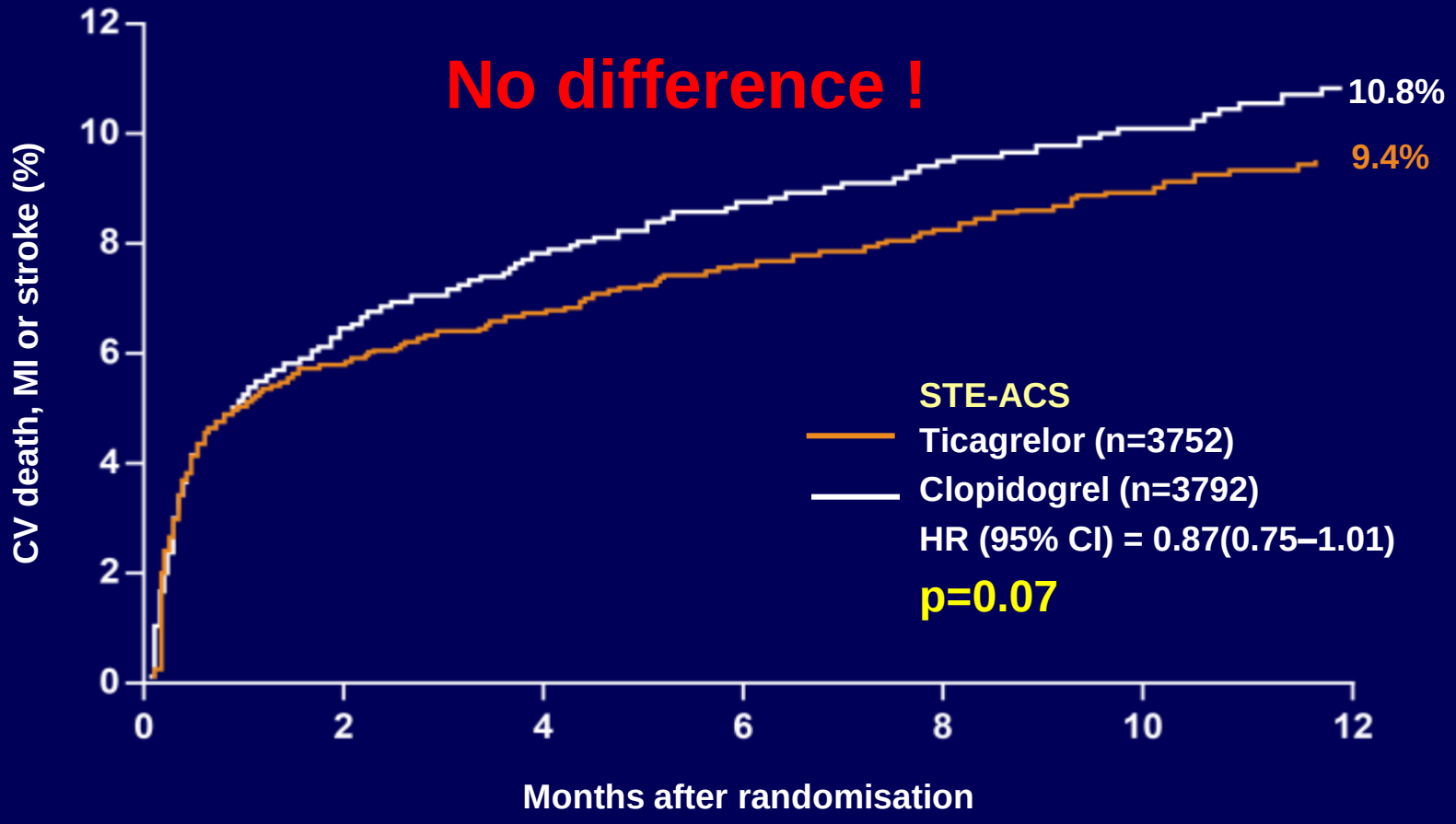
| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ticagrelor | 9,333 | 8,628 | 8,460 | 8,219 | 6,743 | 5,161 | 4,147 |
| Clopidogrel | 9,291 | 8,521 | 8,362 | 8,124 | 6,743 | 5,096 | 4,047 |

[1] Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.

[2] DiNicolantonio JJ, Tomek A, Inactivations, deletions, non-adjudications, and downgrades of clinical endpoints on ticagrelor, Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.07.020

# PLATO STE-ACS (STEMI)
# Primary composite endpoint

[Steg 2010:J–L]




ACS, acute coronary syndromes; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; STE, ST-segment elevation.

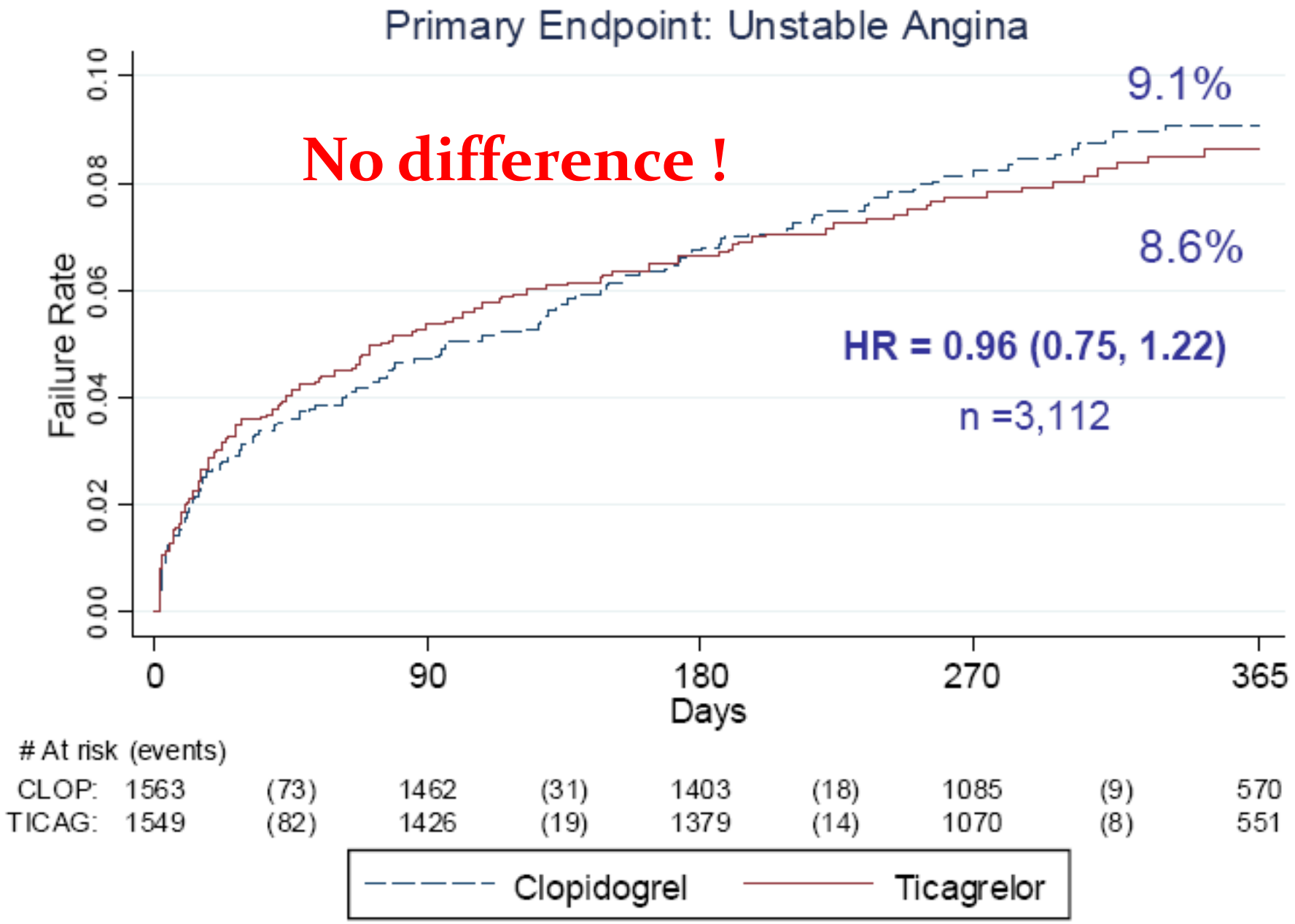
Steg PG, et al. *Circulation* 2010;122:2131–2141;
Wallentin L, et al. N Engl J Med 2009;361:1045–1057.

# STEMI Subgroup_PLATO Study

## *Efficacy end-points @ 12 months*

| | Clopidogrel | Ticagrelor* | HR | ARR |
|---|---|---|---|---|
| CV death/MI/stroke | 10.8% | 9.4% | **0.87** (0.75-1.01) | **1.4%** p=0.07 |
| CV death | 5.5% | 4.5% | **0.83** (0.67-1.02) | **1%** p=0.07 |
| Stroke | 1% | 1.7% | 1.63 (1.07-2.48) | ↑ **0.7%** p=0.02 |

Steg et al Circulation 2010; 122: 2131-41.






FDA website: AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM221383

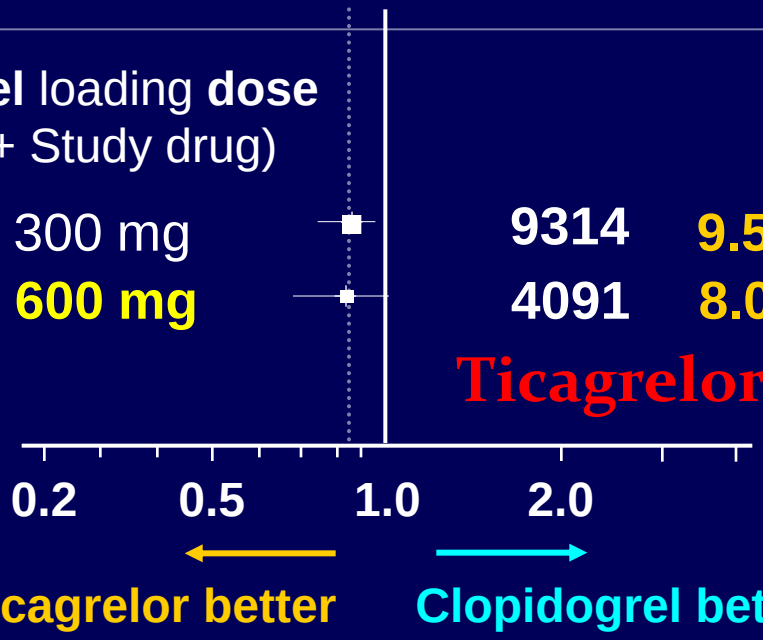
# Ticagrelor: Efficacy Across Patient Subgroups

| Characteristic | | Total Patients | KM% at Month 12 Tic | KM% at Month 12 Clop | HR (95% CI) | Interaction *P-value* |
|---|---|---|---|---|---|---|
| Overall Treatment Effect | | 18624 | 9.8 | 11.7 | 0.84 (0.77, 0.92) | |
| Age | < 65 years | 10643 | 7.2 | 8.5 | 0.85 (0.74, 0.97) | |
| | < 75 years | 15744 | 8.6 | 10.4 | 0.82 (0.74, 0.91) | 0.2166 |
| | ≥ 75 years | 2878 | 16.8 | 18.3 | 0.94 (0.78, 1.12) | |
| Sex | Male | 13336 | 9.2 | 11.1 | 0.85 (0.76, 0.95) | 0.8182 |
| | Female | 5288 | 11.2 | 13.2 | 0.83 (0.71, 0.97) | |
| Body Weight | < 60 kg | 1312 | 13.1 | 17.3 | 0.75 (0.56, 0.99) | 0.3615 |
| | ≥ 60 kg | 17256 | 9.5 | 11.2 | 0.86 (0.78, 0.94) | |
| Prior Non-hemorrhagic Stroke /TIA | No | 17462 | 9.2 | 11.1 | 0.84 (0.76, 0.93) | 0.8351 |
| | Yes | 1152 | 19.0 | 20.8 | 0.87 (0.66, 1.13) | |
| Diabetes Mellitus | No | 13962 | 8.4 | 10.2 | 0.83 (0.74, 0.92) | 0.4882 |
| | Yes | 4662 | 14.1 | 16.2 | 0.88 (0.76, 1.03) | |
| Final Diagnosis | Uns. Angina | 3112 | 8.6 | 9.1 | 0.96 (0.75, 1.22) | 0.4085 |
| | NSTEMI | 7955 | 11.4 | 13.9 | 0.83 (0.73, 0.94) | |
| | STEMI | 7026 | 8.5 | 10.1 | 0.84 (0.72, 0.98) | |
| | Other | 489 | 9.1 | 14.7 | 0.58 (0.34, 1.00) | |


Supplement to: Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57

CC-29

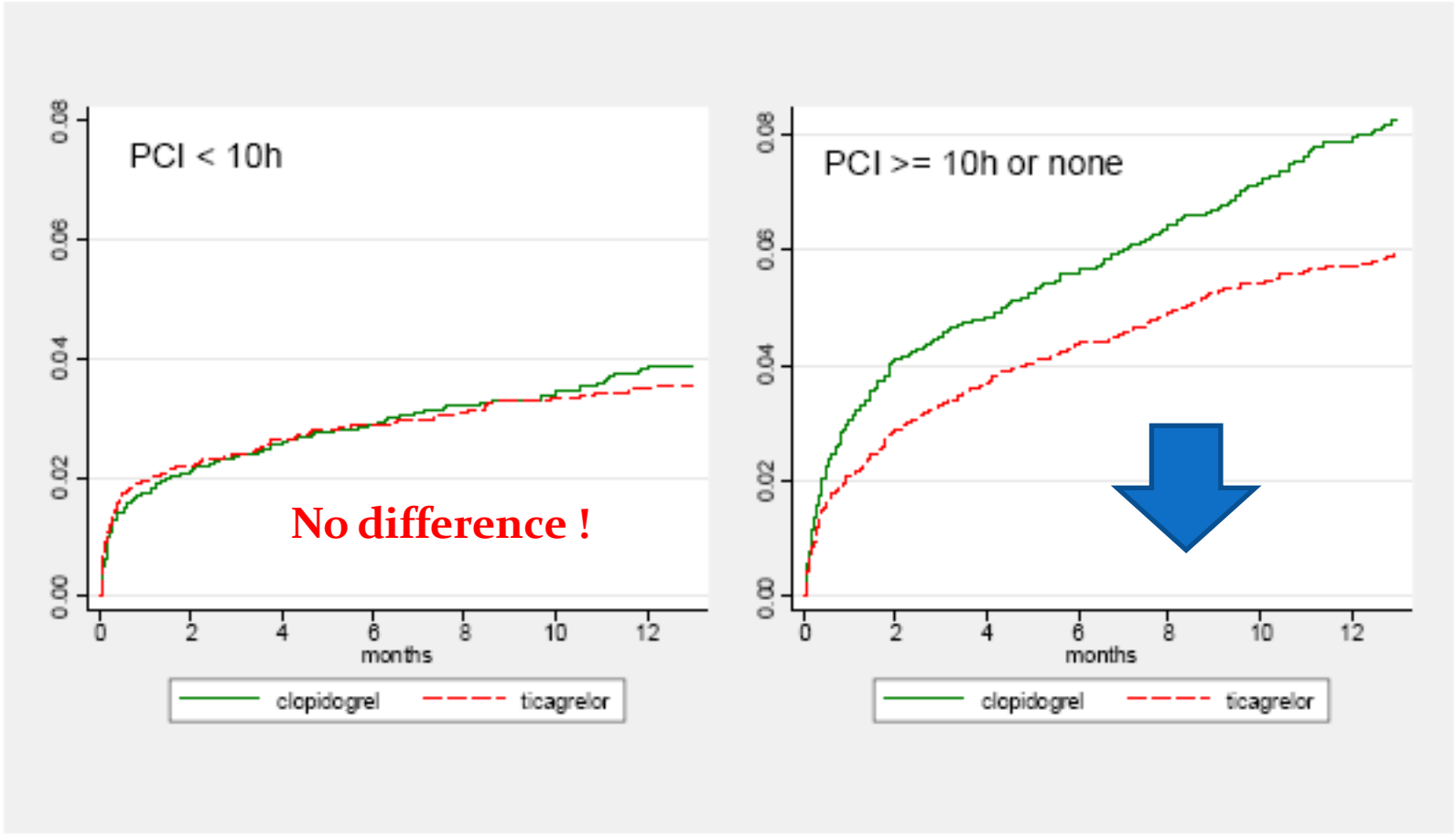
# Primary efficacy endpoint by clopidogrel loading dose




| Characteristic | Hazard Ratio (95% CI) | Total Patients | KM % at Month 12 Ti. | KM % at Month 12 Cl. | HR (95% CI) | p value (Interaction) |
|---|---|---|---|---|---|---|
| **Clopidogrel** loading **dose** (Pre-rand. + Study drug) | | | | | | 0.917 |
| 300 mg | | 9314 | 9.5 | 11.2 | 0.85 (0.74, 0.96) | |
| **600 mg** | | 4091 | 8.0 | 9.5 | 0.83 (0.67, 1.03) | |
| | | | Ticagrelor | 9.6 | | |

**Ticagrelor vs. Clopidogrel 600 mg loading dose -> the same efficacy**

# Deaths by PCI within 10h

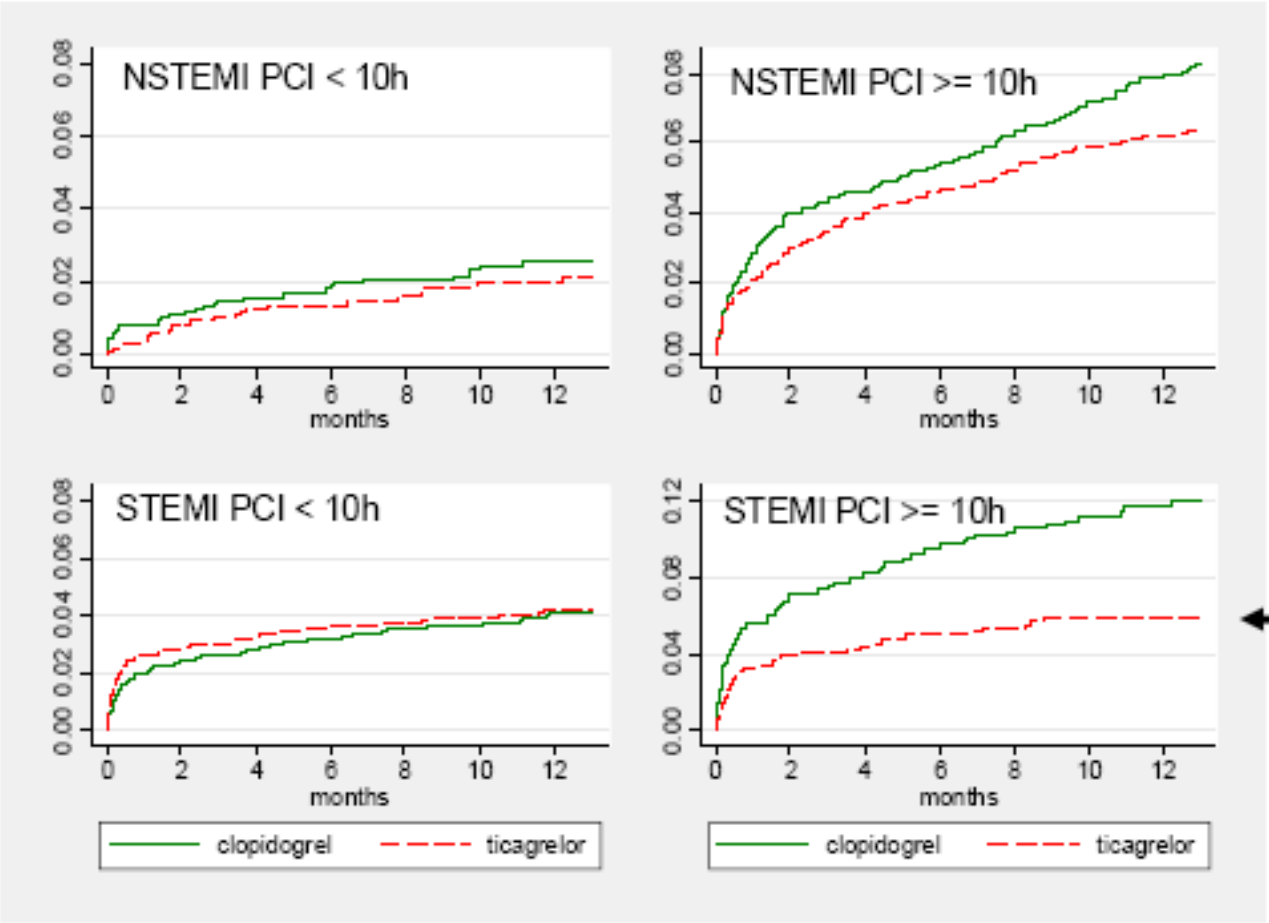





FDA website: AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM221383

# Deaths by PCI within 10h & MI Type

**No difference !**

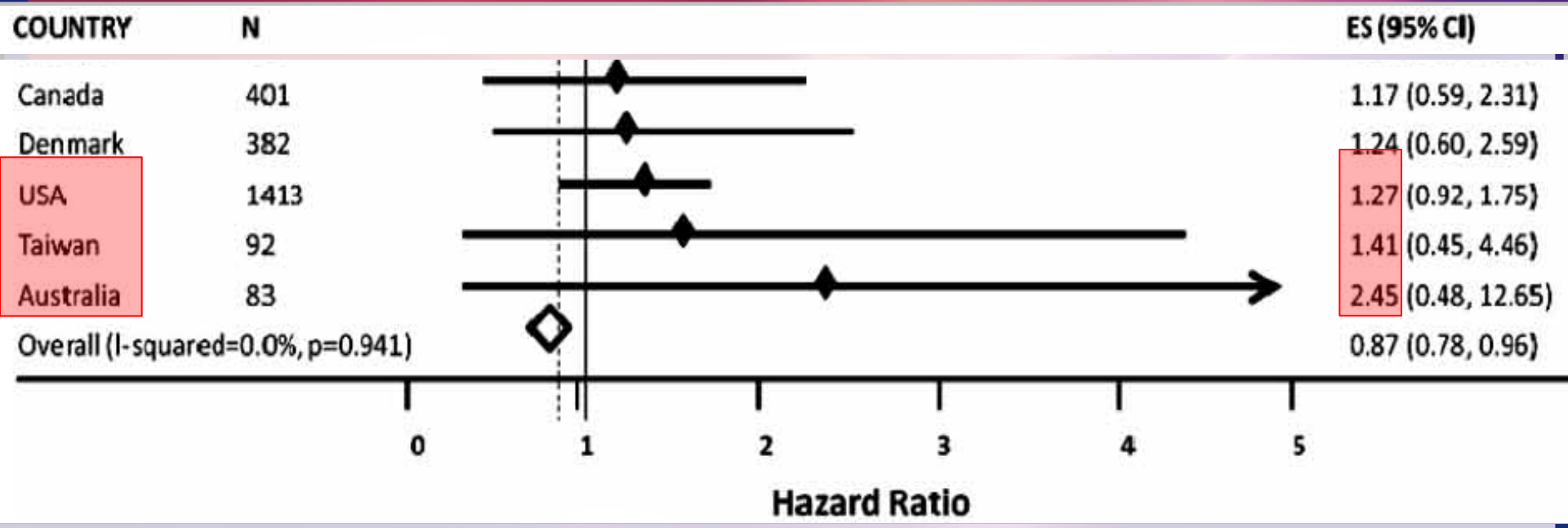



Note different scale



FDA website: AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM221383

# Regional Disparity in Primary Efficacy _ PLATO Study




| Characteristic | Hazard Ratio (95% CI) | Total Patients | KM % at Month 12 Ti. | KM % at Month 12 CI. | HR (95% CI) | *P* value (Interaction) |
|---|---|---|---|---|---|---|
| Region | | | | | | 0.05 |
| Asia/Australia | | 1714 | 11.4 | 14.8 | 0.80 (0.61, 1.04) | |
| Central/South America | | 1237 | 15.2 | 17.9 | 0.86 (0.65, 1.13) | |
| Europe/Middle East/Africa | | 13859 | 8.8 | 11.0 | 0.80 (0.72, 0.90) | |
| North America | | 1814 | 11.9 | 9.6 | 1.25 (0.93, 1.67) | |

Serebruany VL, et al. *Thromb Haemost* 2011;105:752-9

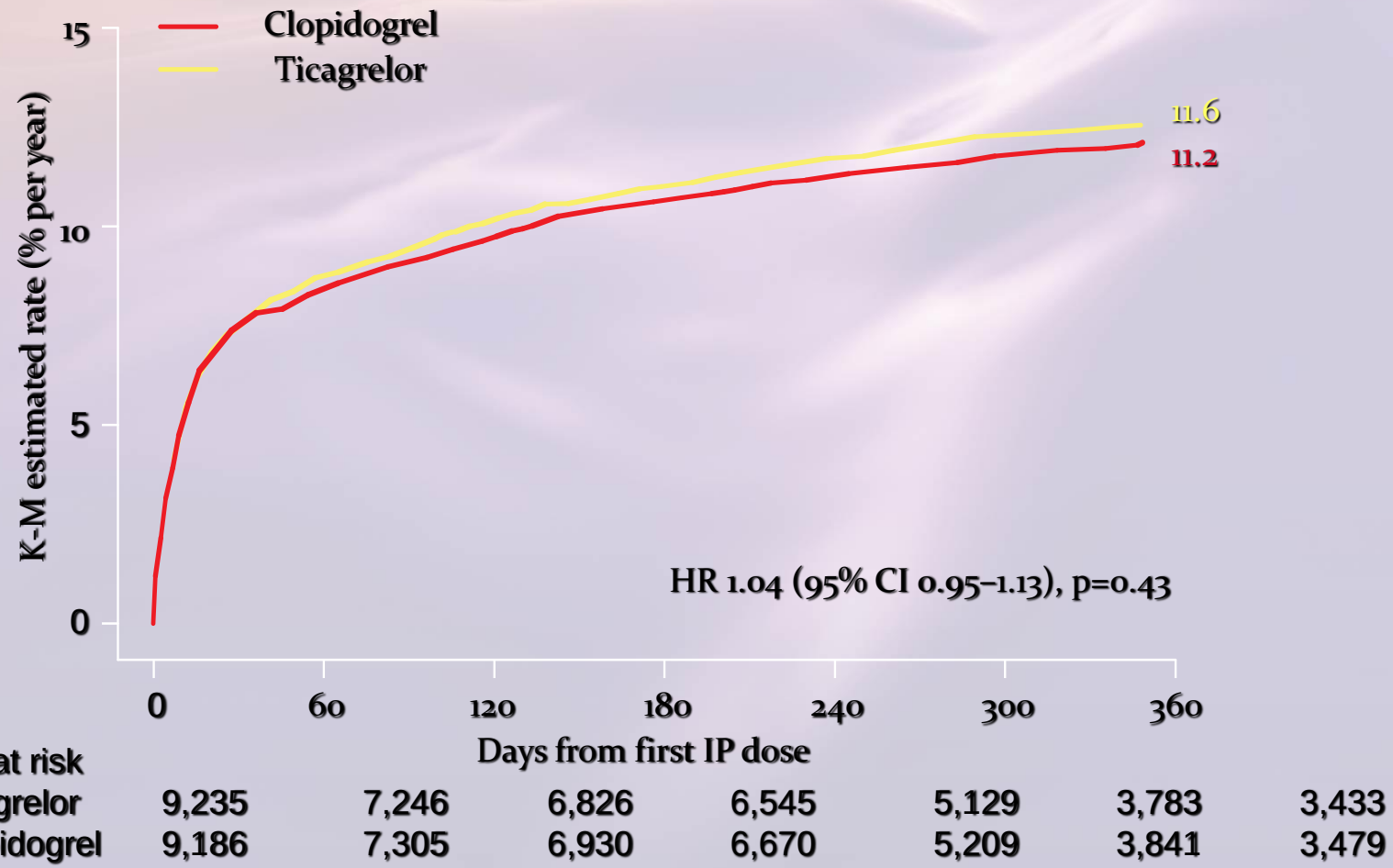
# Recommendations of international guidelines for $P2Y_{12}$ inhibitors use in ACS patients

| | | ESC /EACTS 2010<br>Myocardial revascularization guidelines | ESC 2011<br>NSTEACS guidelines | ACC/AHA 2009<br>Focused STEMI guidelines update | ACCF/AHA/ SCAI 2011<br>Focused PCI & NSTEACS, STEMI guidelines updates | ACCF/AHA 2012<br>UA/NSTEMI guidelines |
|---|---|---|---|---|---|---|
| NSTEACS | Clopidogrel | **I C** | I B | - | I B | **I B** |
| | **Ticagrelor** | **I B** | **I B** | - | **I B** | **I B** |
| STEMI | Clopidogrel | **I C** | - | I C | I B | - |
| | **Ticagrelor** | **I B** | - | Not approved yet by FDA | **I B** | - |

* I C for administration before angiography

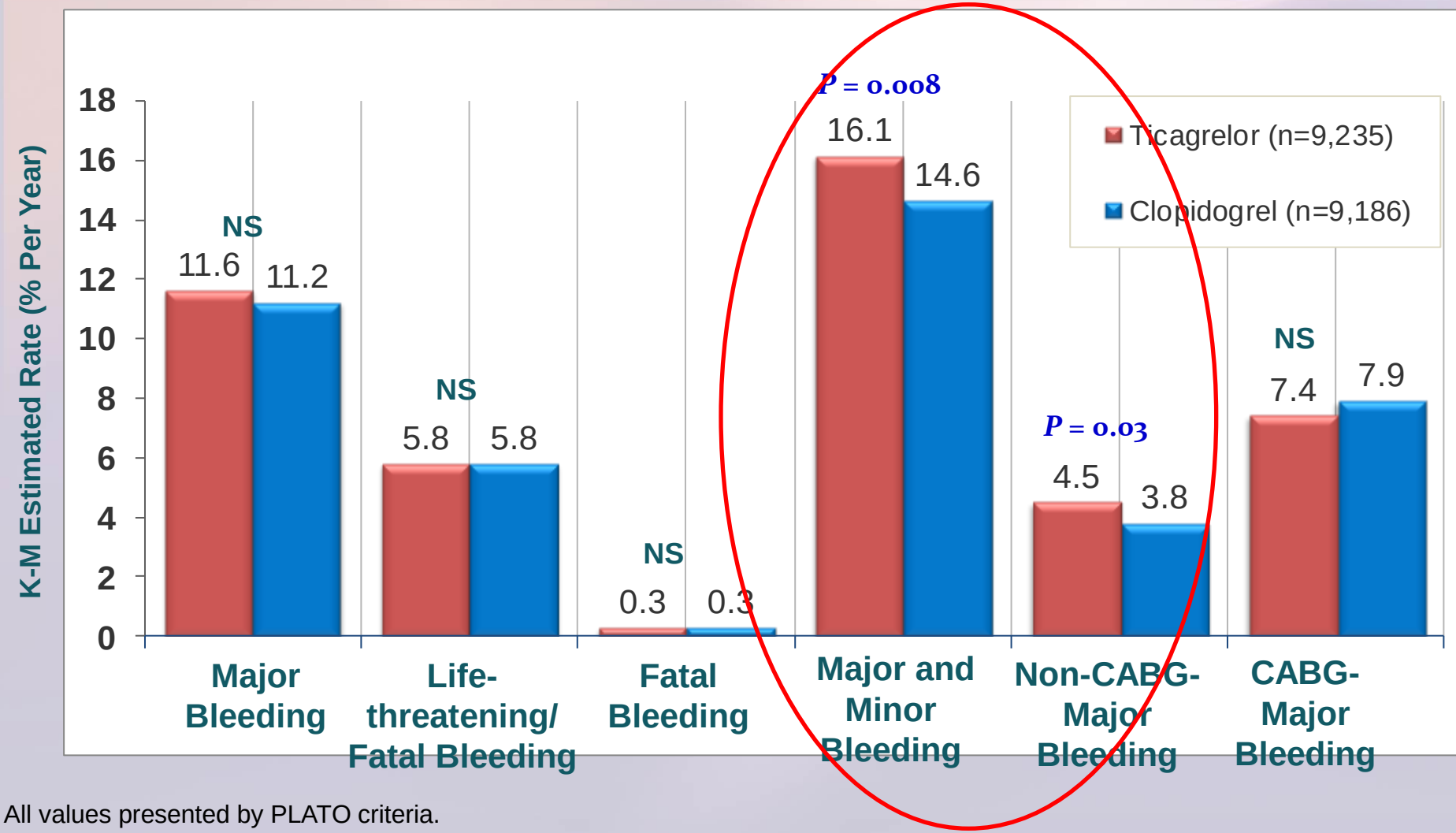
# PLATO : Time to Major Bleeding – Primary Safety Event

PLATO 研究顯示，Ticagrelor 的 bleeding risk 與 Plavix® 相當




Wallentin L et al. *N Engl J Med.* 2009 Sep 10;361(11):1045-57.

# Bleeding_PLATO Study

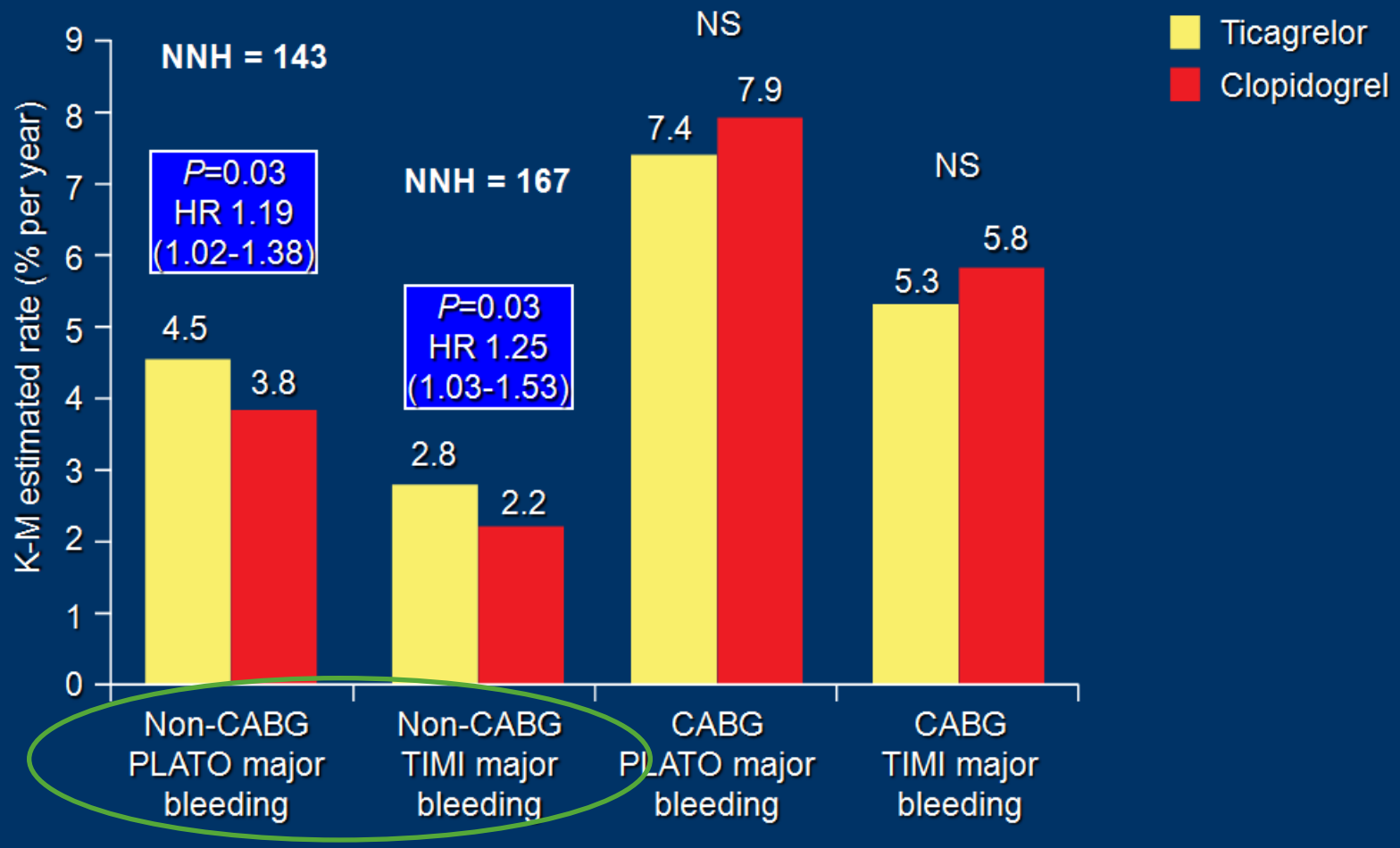



All values presented by PLATO criteria.
*Both groups included aspirin.*



Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.

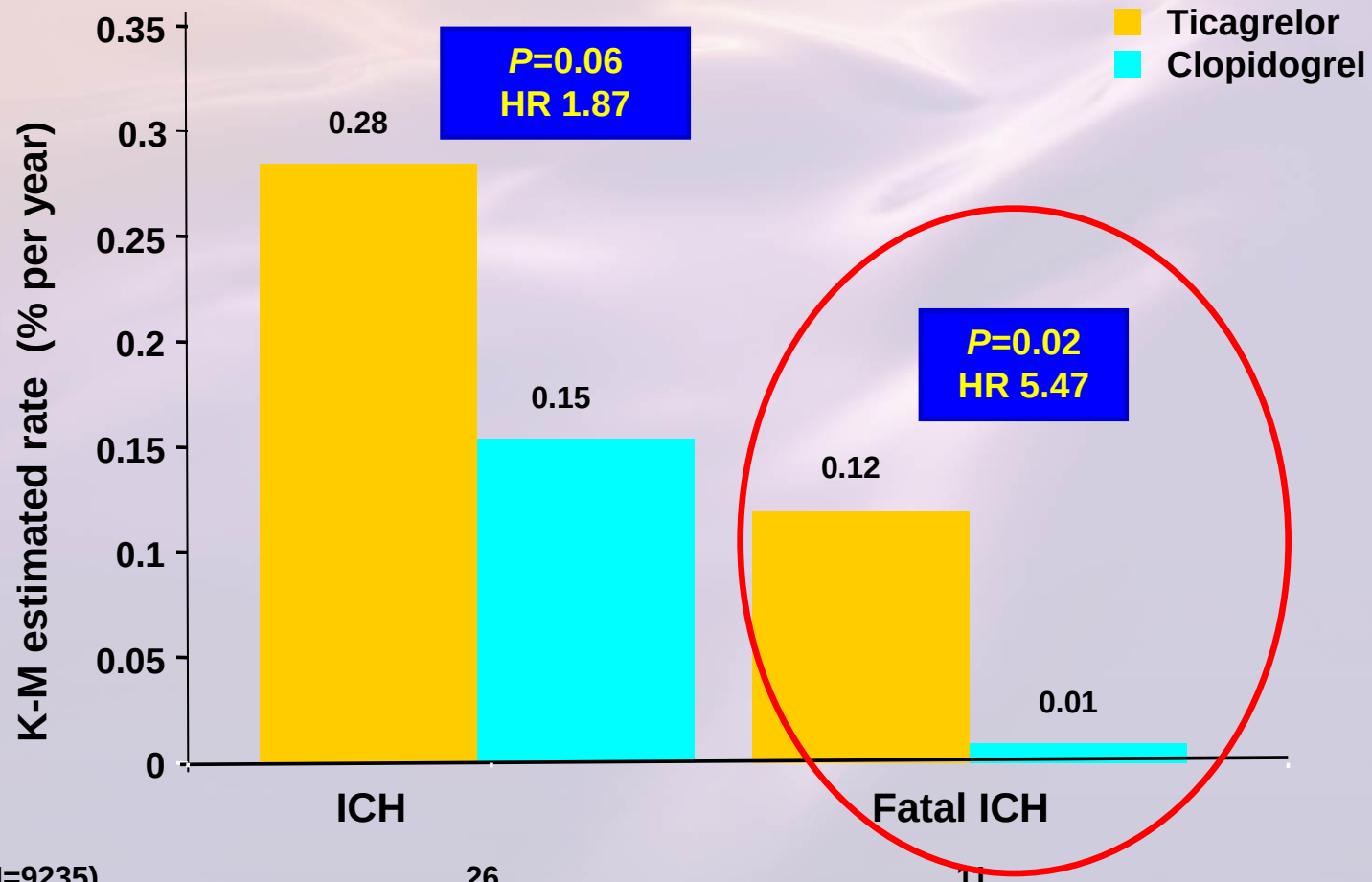
# Non-CABG and CABG-related major bleeding






Wallentin L et al. *N Engl J Med.* 2009 Sep 10;361(11):1045-57.

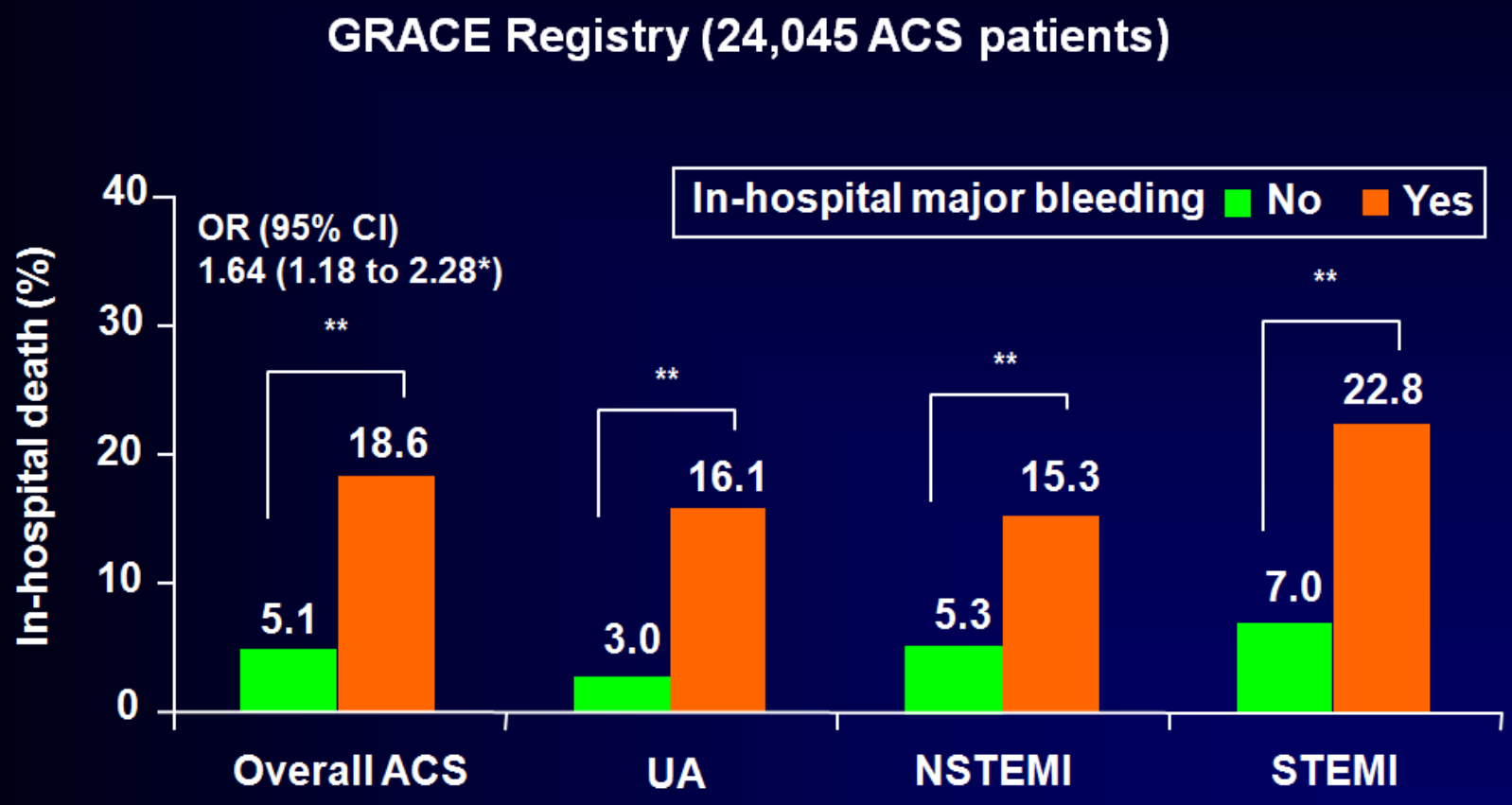
# Intracranial bleeding




| | | |
|---|---|---|
| Ticagrelor (N=9235) | 26 | 11 |
| Clopidogrel (N=9186) | 14 | 1 |

Wallentin L et al. *N Engl J Med.* 2009 Sep 10;361(11):1045-57.

# Major Bleeding is Associated with an Increased Risk of Hospital Death in ACS Patients

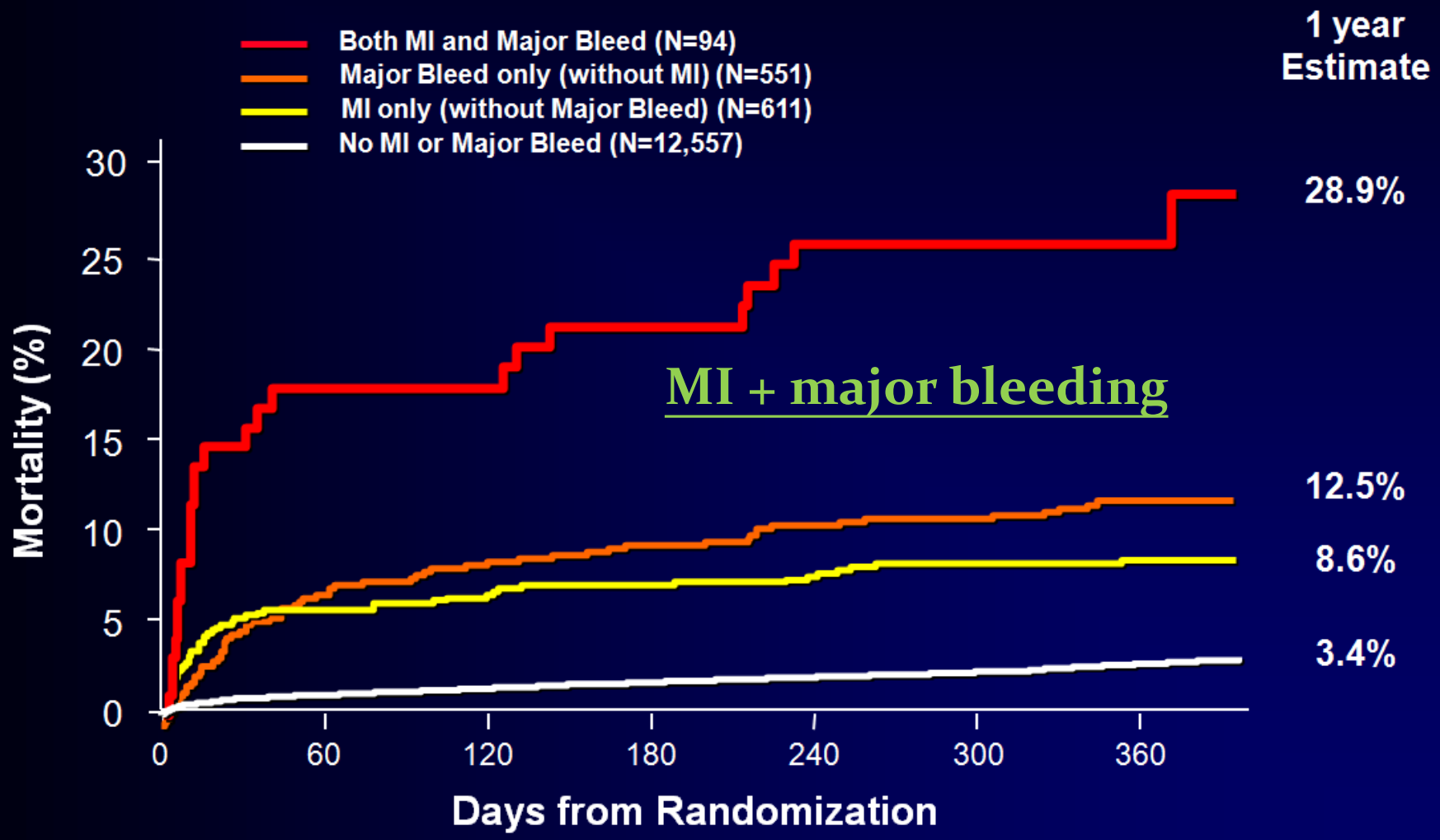



*After adjustment for comorbidities, clinical presentation and hospital therapies

**p<0.001 for differences in unadjusted death rates

Moscucci M. *Eur Heart J* 2003;24:1815-23.

# Impact of MI and Major Bleeding within First 30 Days on Risk of 1-Year Mortality




Stone GW. *JAMA* 2007; 298:2497-506

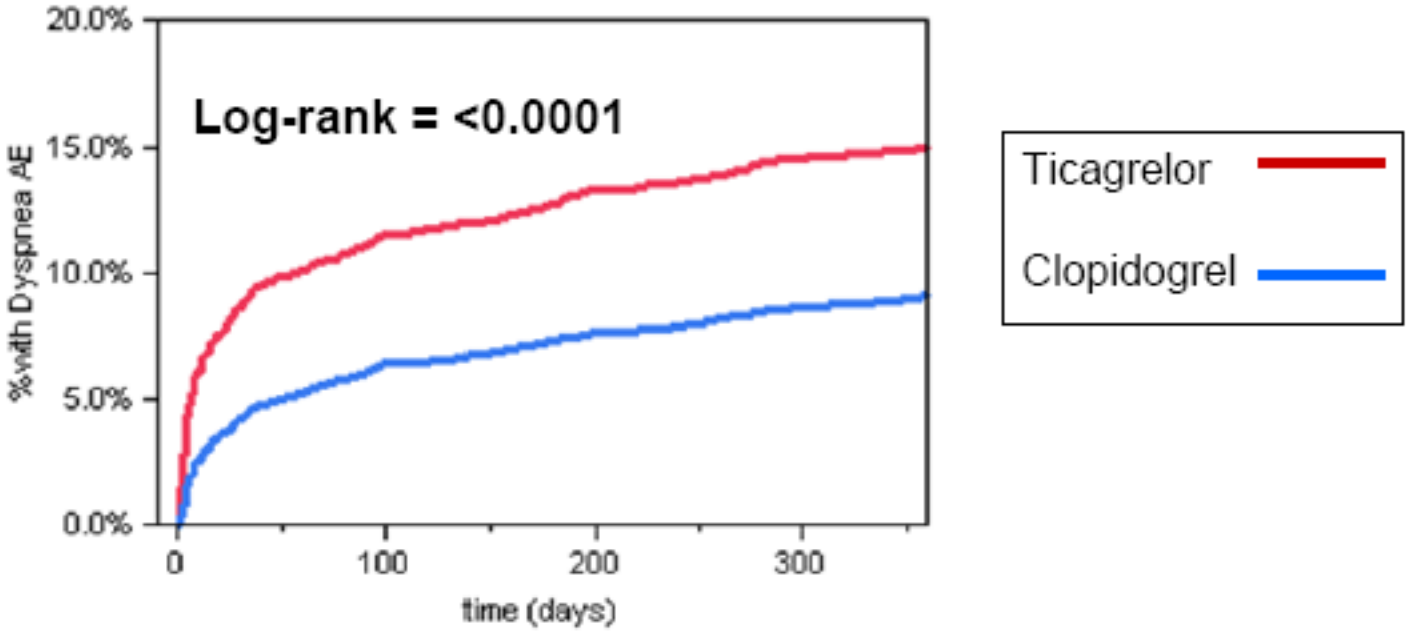
# Safety_PLATO Study

| All patients | Ticagrelor (n=9,235) | Clopidogrel (n=9,186) | p value* |
|---|---|---|---|
| **Dyspnoea, %** | | | |
| Any | 13.8 | 7.8 | <0.001 |
| With discontinuation of study treatment | 0.9 | 0.1 | <0.001 |
| **Neoplasms arising during treatment, %** | | | |
| Any | 1.4 | 1.7 | 0.17 |
| Malignant | 1.2 | 1.3 | 0.69 |
| Benign | 0.2 | 0.4 | 0.02 |

*p values were calculated using Fischer's exact test

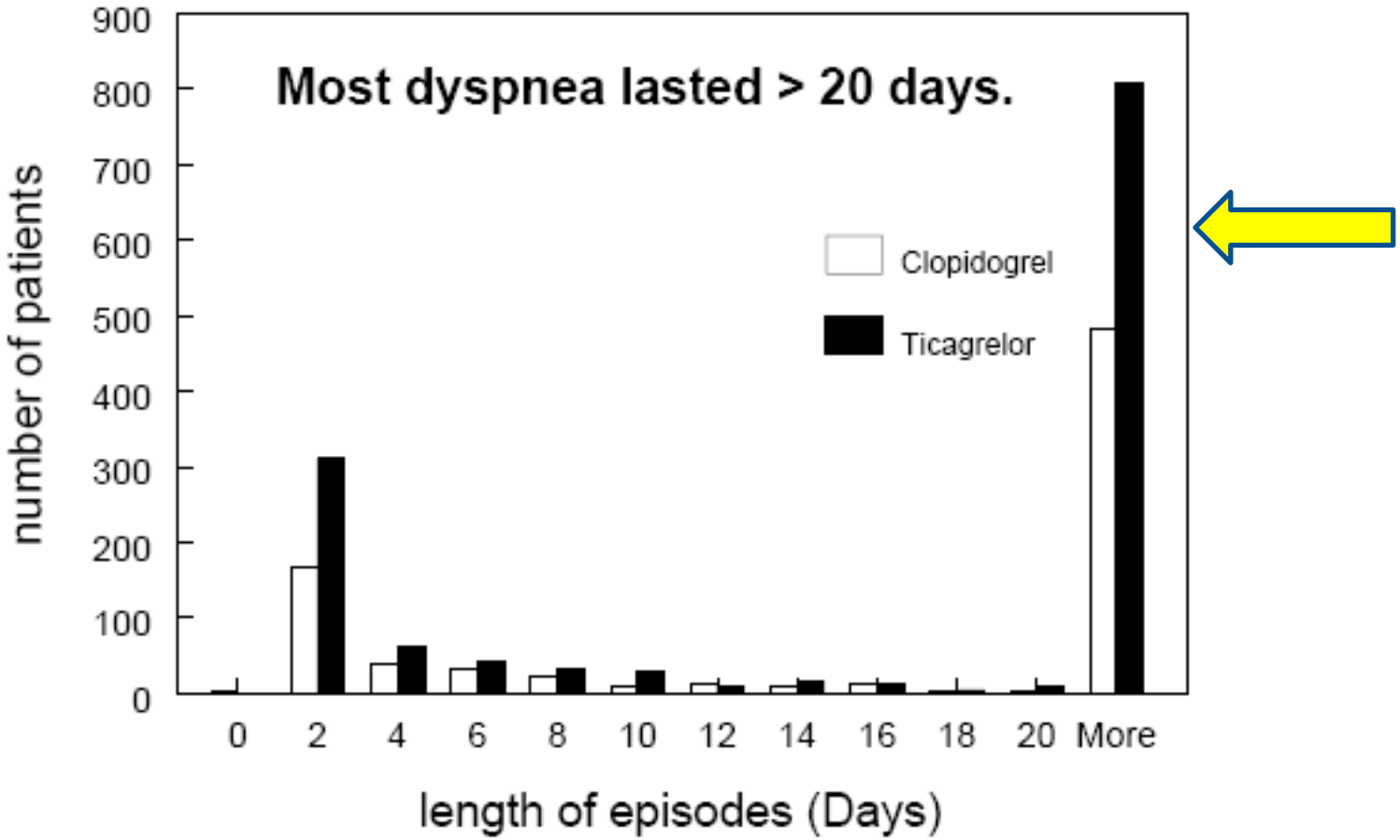
Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.

# Dyspnea time to event analysis




| Group | # failed | # censored | KM% failed |
|---|---|---|---|
| Ticagrelor | 1344 | 7891 | 14.6% |
| Clopidogrel | 803 | 8383 | 8.7% |

# Dyspnea


Most dyspnea lasted > 20 days.
number of patients
900
800
700
600
500
400
300
200
100
0
Clopidogrel
Ticagrelor
0
2
4
6
8
10
12
14
16
18
20
More
length of episodes (Days)

# Holter monitoring_PLATO Study

| Holter monitoring at first week | Ticagrelor (n=1,451) | Clopidogrel (n=1,415) | p value |
|---|---|---|---|
| Ventricular pauses ≥3 seconds, % | 5.8 | 3.6 | 0.01 |
| Ventricular pauses ≥5 seconds, % | 2.0 | 1.2 | 0.10 |
| **Holter monitoring at 30 days** | **Ticagrelor (n= 985)** | **Clopidogrel (n=1,006)** | **p value** |
| Ventricular pauses ≥3 seconds, % | 2.1 | 1.7 | 0.52 |
| Ventricular pauses ≥5 seconds, % | 0.8 | 0.6 | 0.60 |

# Bradycardia related events_PLATO Study

| Bradycardia-related event, % | Ticagrelor (n=9,235) | Clopidogrel (n=9,186) | p value |
|---|---|---|---|
| Pacemaker Insertion | 0.9 | 0.9 | 0.87 |
| Syncope | 1.1 | 0.8 | 0.08 |
| Bradycardia | 4.4 | 4.0 | 0.21 |
| Heart block | 0.7 | 0.7 | 1.00 |

- In previous ticagrelor clinical study, AE - asymptomatic ventricular pauses was observed.
- In PLATO, patients with an increased risk of bradycardic events (eg, patients without a pacemaker who have **sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope) were excluded**

# Laboratory parameters_PLATO Study

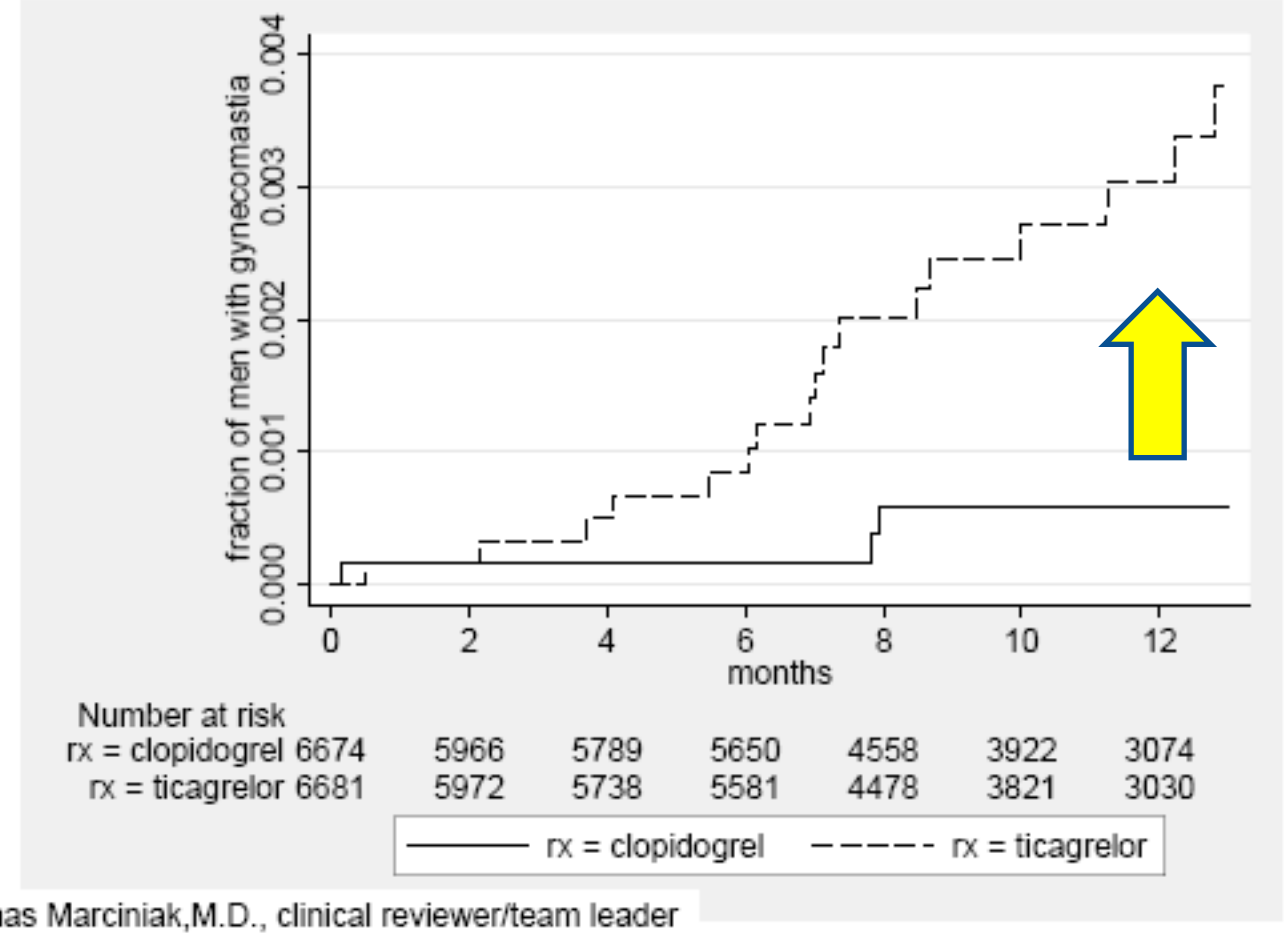
| All patients | Ticagrelor (n=9,235) | Clopidogrel (n=9,186) | p value* |
|---|---|---|---|
| % increase in creatinine from baseline | | | |
| At 1 month | 10 ± 22 | 8 ± 21 | <0.001 |
| At 12 months | 11 ± 22 | 9 ± 22 | <0.001 |
| Follow-up visit | 10 ± 22 | 10 ± 22 | 0.59 |
| % increase in uric acid from baseline | | | |
| At 1 month | 14 ± 46 | 7 ± 44 | <0.001 |
| At 12 months | 15 ± 52 | 7 ± 31 | <0.001 |
| Follow-up visit | 7 ± 43 | 8 ± 48 | 0.56 |

Values are mean % ± SD; *p values were calculated using Fisher's exact test

# Hormonally-related AEs

| Characteristic | Ticagrelor | Clopidogrel | RR |
|---|---|---|---|
| All patients | N= 9235 | N= 9186 | |
| Females only | N= 2634 | N= 2603 | |
| Males only | N= 6601 | N= 6583 | |
| | n(percent) | n(percent) | |
| Vaginal bleeding (females) | 22 (0.84) | 17 (0.65) | 1.3 |
| Gynecomastia/ swelling/ mass (males) | 17 (0.26) | 3 (0. 05) | 5.2 |
| Prostate cancer (males) | 13 (0.19) | 12 (0.18) | 1.1 |
| BPH (males) | 10 (0.15) | 8 (0.12) | 1.3 |
| Breast Cancer (females) | 4 (0.15) | 10 (0.38) | 0.4 |
| Sexual Dysfunction (males) | 3 (0.05) | 11 (0.17) | 0.3 |
| Cervical/ uterine malignancy (females) | 1 (0) | 0 (0) | 0 |

# Gynecomastia, breast swelling or breast mass




Thomas Marciniak,M.D., clinical reviewer/team leader

# Premature discontinuation of study drugs

| All patients | Ticagrelor n(%) | Clopidogrel n(%) | p value* |
|---|---|---|---|
| Premature discontinuation | 2186 (23.4) | 1999(21.5%) | 0.002 |
| Because of adverse event | 690 (7.4) | 556 (6.0) | <0.001 |
| Because of dyspnea | 79 (0.9) | 13 (0.1) | <0.001 |
| Because of patient's unwillingness to continue | 946 (10.1) | 859 (9.2) | 0.04 |
| Other reasons | 550 (5.9) | 584 (6.3) | 0.27 |

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.

# Therapeutic considerations

- Based on **1,000** patients admitted to hospital for ACS, using ticagrelor instead of clopidogrel for 12 months resulted in
  - 14 fewer deaths; 15 more major+minor bleeds
  - 11 fewer myocardial infarctions ; 6 more non-CABG bleeds
  - 6–8 fewer cases with stent thrombosis
  - 9 more discontinuation because of dyspnoea
- Treating with ticagrelor instead of clopidogrel for one year
  - For every 54 patients, one event of CV death, MI or stroke was prevented
  - For every 91 patients, one MI/CV death was prevented

# Comparison of Indications of Different Antiplatelets

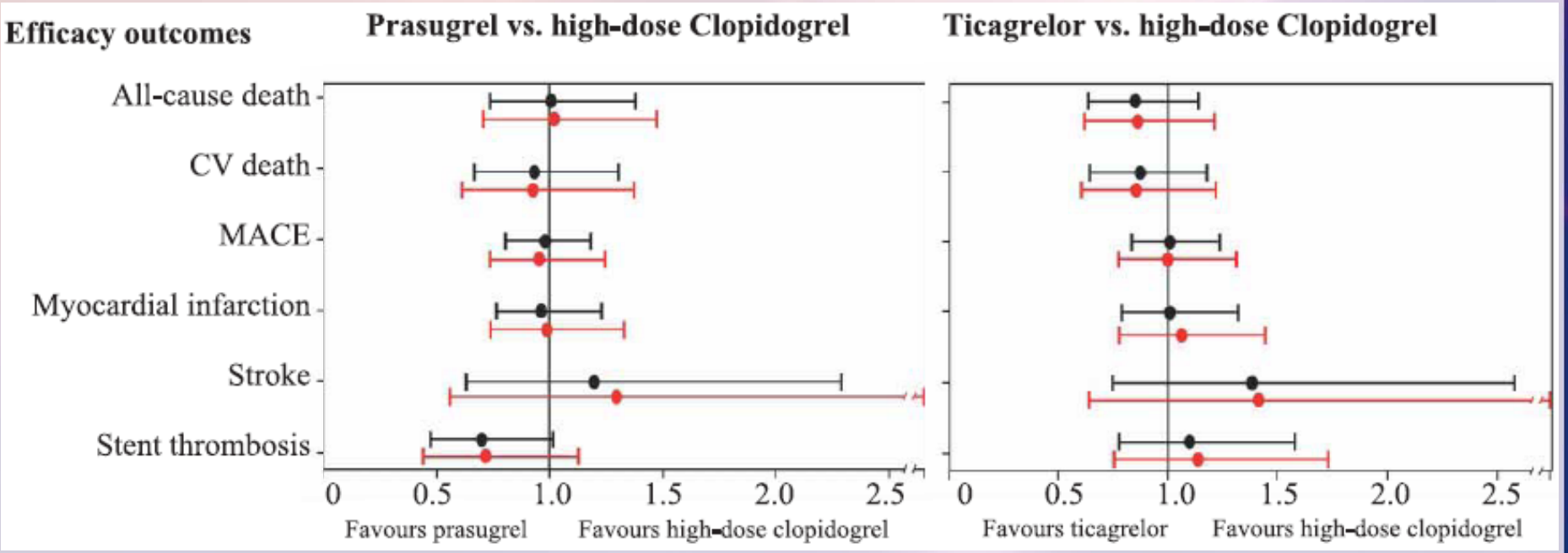
| | ACS | | | IS | PAD |
|---|---|---|---|---|---|
| | PCI | Medically managed | CABG | | |
| **Plavix** | √ | √ | √ | √ | √ |
| **Ticagrelor** | √ | √ | √ | | |
| **Prasugrel** | √ | | | | |

**Plavix**: indicated to prevent atherothrombosis events in multiple vascular beds (cerebrovascular, coronary and peripheral arterial bed).

**Ticagrelor** with ASA: indicated for the prevention of atherothrombotic events in adult patients with unstable angina, NSTEMI or STEMI. The indication is for only one vascular bed.

# Other Comparisons of Current Antiplatelet Drugs

# Efficacy of high dose clopidogrel did not differ from prasugrel or ticagrelor



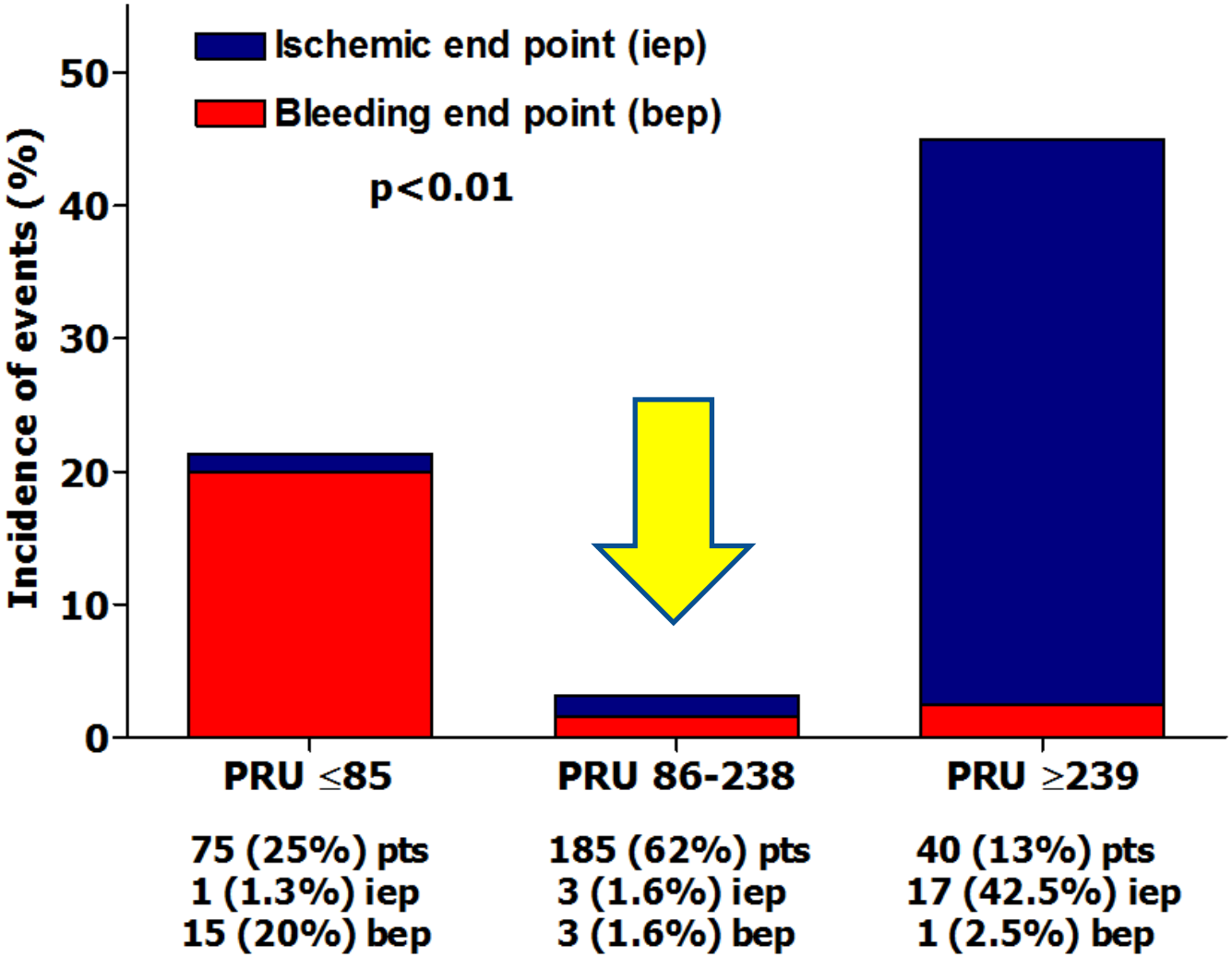

all included studies (black) and subgroup analysis in ACS patients (red)

14 randomised controlled trials enrolling patients scheduled for and/or undergoing PCI with randomisation to high- and standard-dose clopidogrel, prasugrel and ticagrelor, on top of ASA, were included in the analysis.
(high- vs. standard-dose clopidogrel: 9 trials, prasugrel vs. high-dose clopidogrel: 2 trials, prasugrel vs. standard-dose clopidogrel: 2 trials, ticagrelor vs. standard-dose clopidogrel: 1 trial)

Steiner S, et al. Thromb Haemost 2012;108:318-27.

# PRU Values and Window Effect

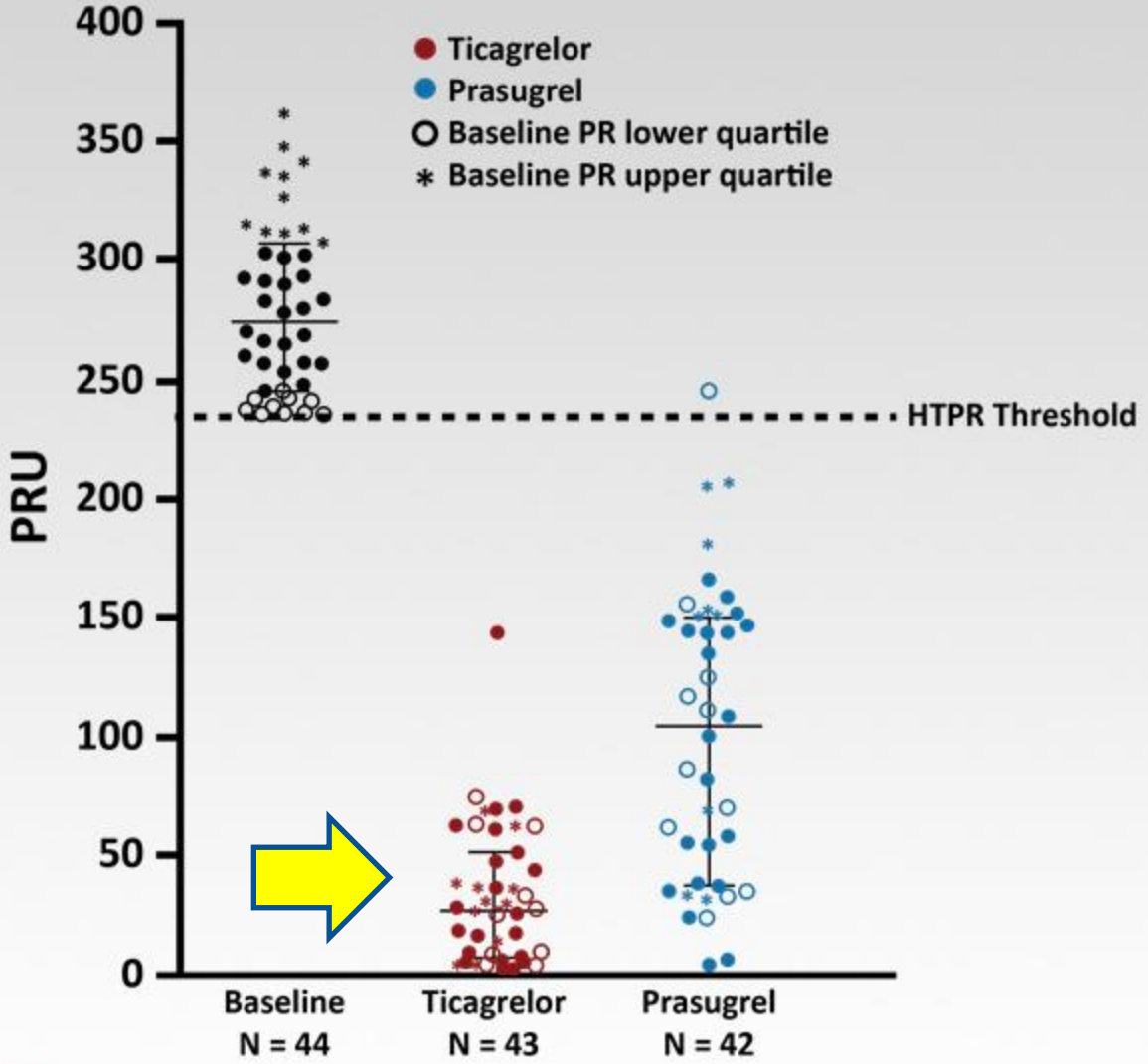
VerifyNow® System




J Am Coll Cardiol 2011;57:2474–83

Accumetrics

# ACS Patients With HTPR on Clopidogrel 24 h Post-PCI Randomized to Ticagrelor 90 mg Twice Daily or Prasugrel 10 mg Daily




Alexopoulos D, et al.[9]

# Conclusions

# Conclusion

- For unstable angina or STEMI patients, the risks of CV death, MI and stroke between Plavix and ticagrelor are not significantly different.
- From PLATO study, non-CABG major bleeds and major+minor bleeds were substantially increased with ticagrelor.
- Use newer antiplatelet agents, such as prasugrel or ticagrelor, preferably when a sufficient **platelet inhibition could not be achieved after the use of high-dose clopidogrel or the occurrence of stent thrombosis.**
- **Antiplatelet agents should be used according to personal conditions and/or co-morbidities.**

Mehta SR, et al. Lancet 2010;376:1233-43; Geng DF, et al. Cardiology 2012;122:148-57; Rajan L, et al. Curr Cardiol Rep 2011;13:303-11.

Thanks for Your Attention !