

***Intervenciones coronarias:  
Optimizando la farmacología***

**Conrad Simpendorfer MD FACC  
Heart & Vascular Institute  
Cleveland Clinic**

# Caso clínico

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- **Mujer de 59 años , fumadora, sin empleo**
- **Hipertensa, diabética (mal controladas)**
- **AIT hace 1 año, hemorragia digestiva hace 3 años.**
- **Aspirina, Metformina, lisinopril, simvastatina**
- **Presentación: 2 días de dolor precordial recurrente**

# Caso clínico

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- Troponina (+), Glicemia: 156mg/dl, HgA1C : 8.1%
- Creatinina : 1.36mg/dl
- Tratamiento inicial:  
Aspirina 325mg, heparina, NTG e.v.,  
metoprolol 50mg x2 , Clopidogrel 600mg

29-SEP-2012 03:51:18

CCF

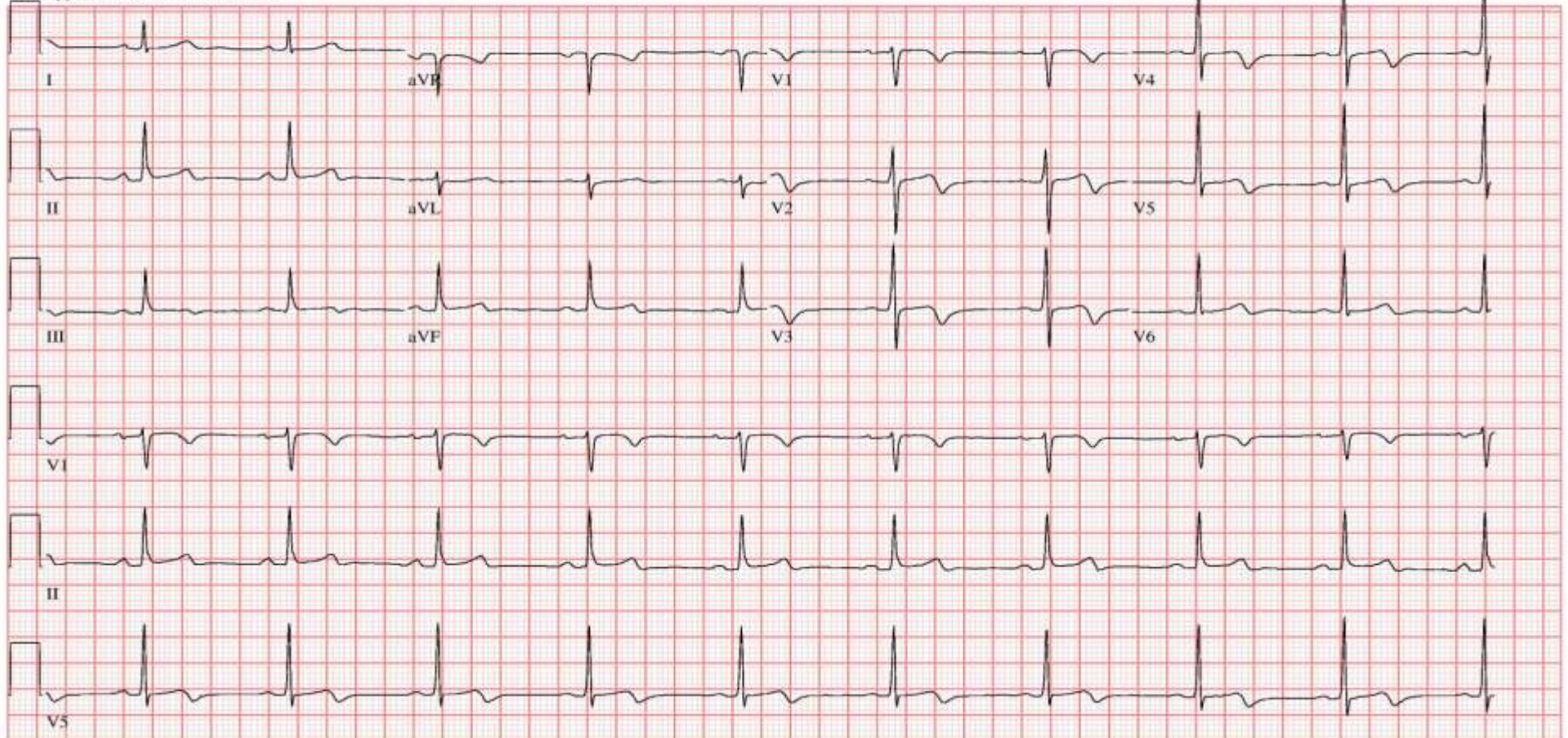
SINUS BRADYCARDIA  
ANTEROLATERAL T WAVE ABNORMALITY, MYOCARDIAL CHANGES  
ABNORMAL ECG

Technician: 926  
Test ind:

Referred by: RAVI NAIR

Newly Acquired

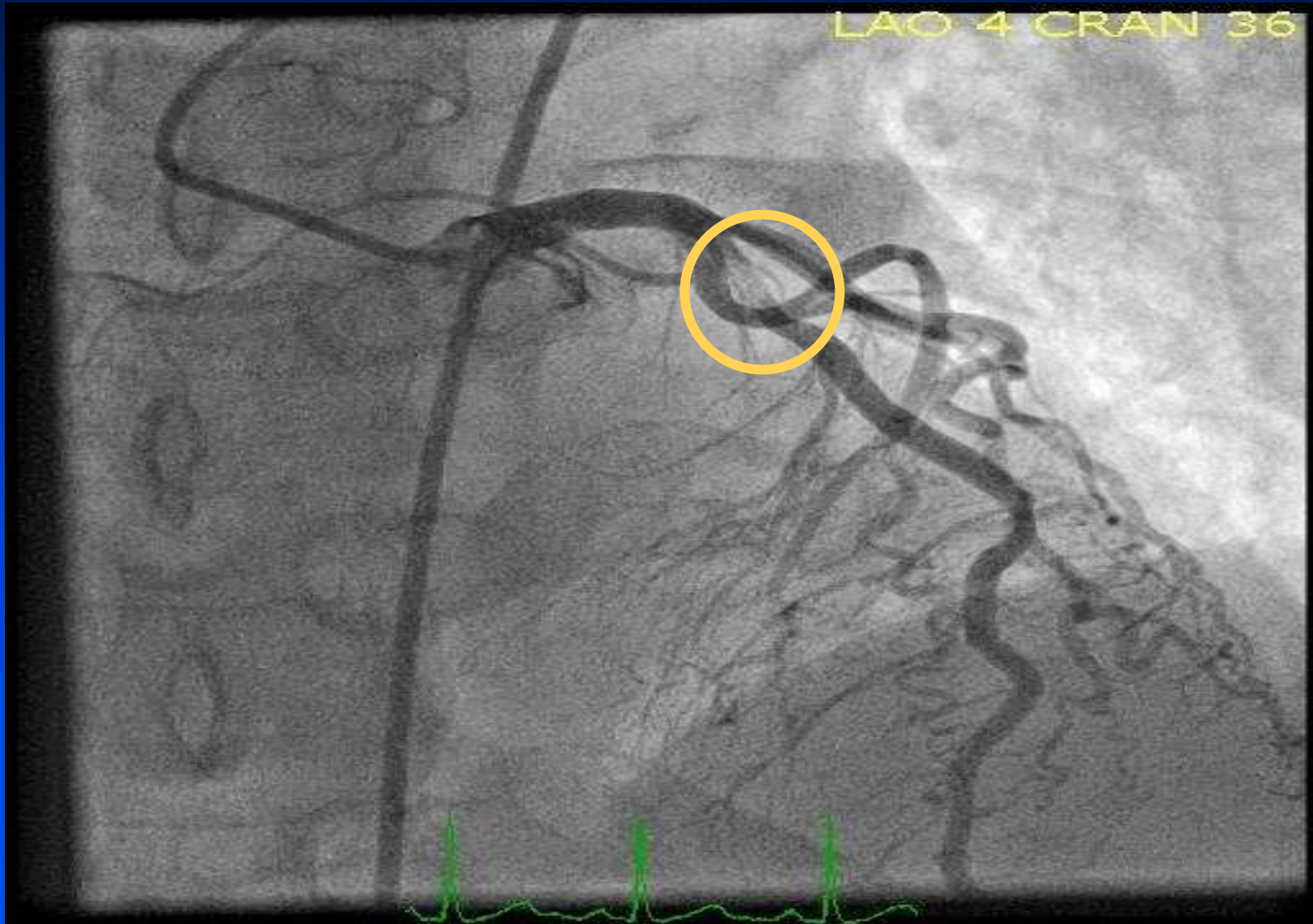
Test Type: ECG COMP W INTERP



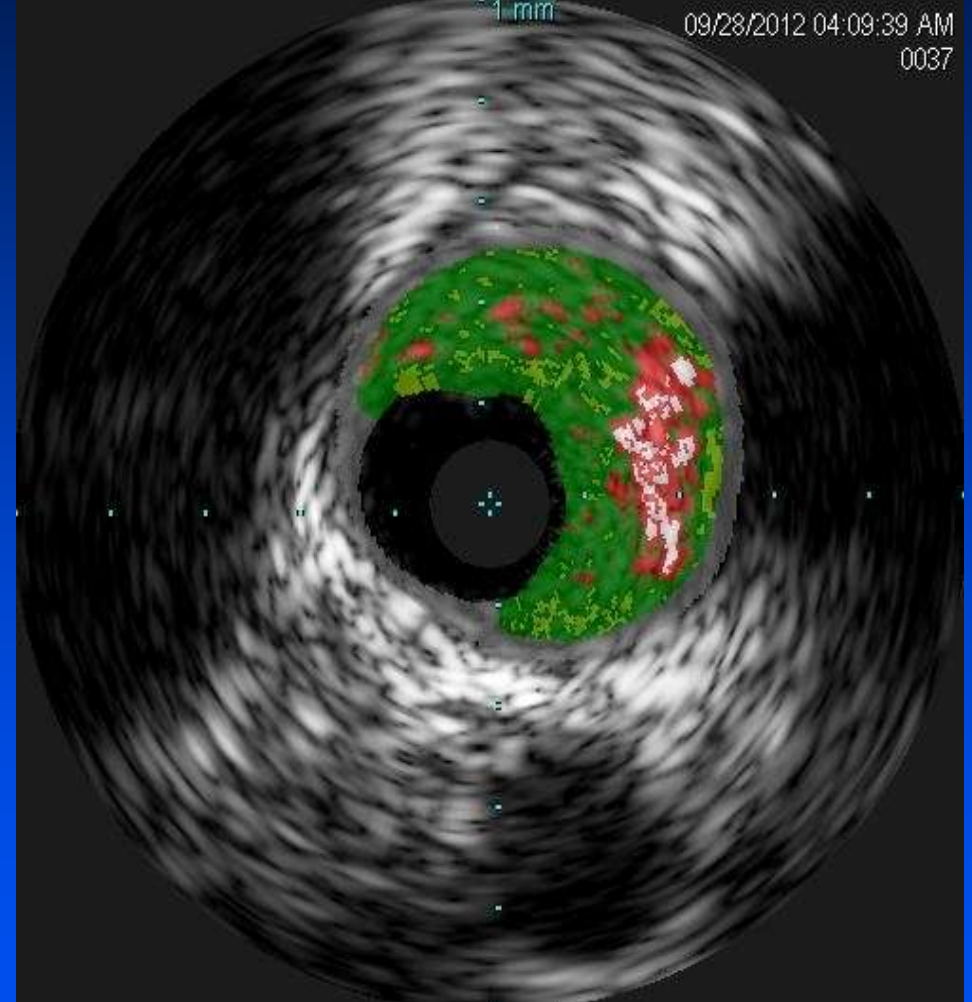
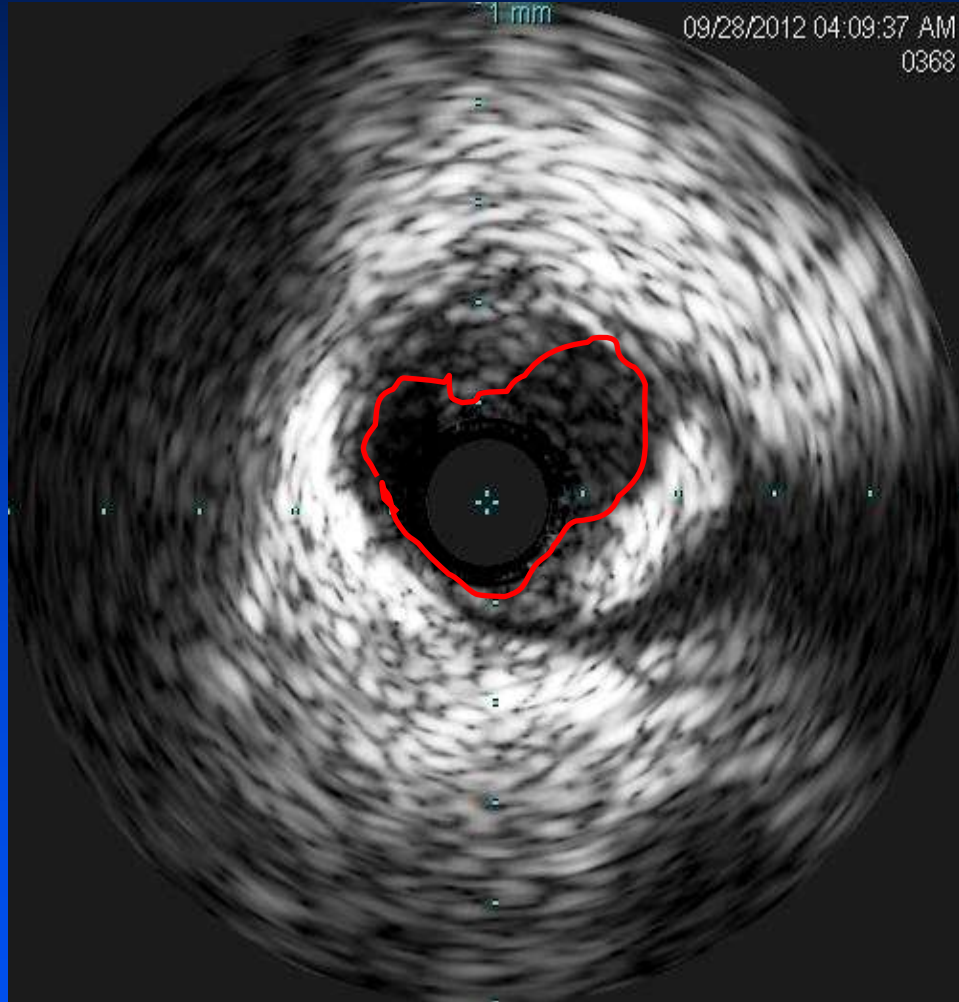
25mm/s 10mm/mV 100Hz 7.1.1 12SL 237 CID: 29

EID: Newly Acquired EDT: ORDER: 450084572 ACCOUNT: 0999

# Coronariografía



# IVUS



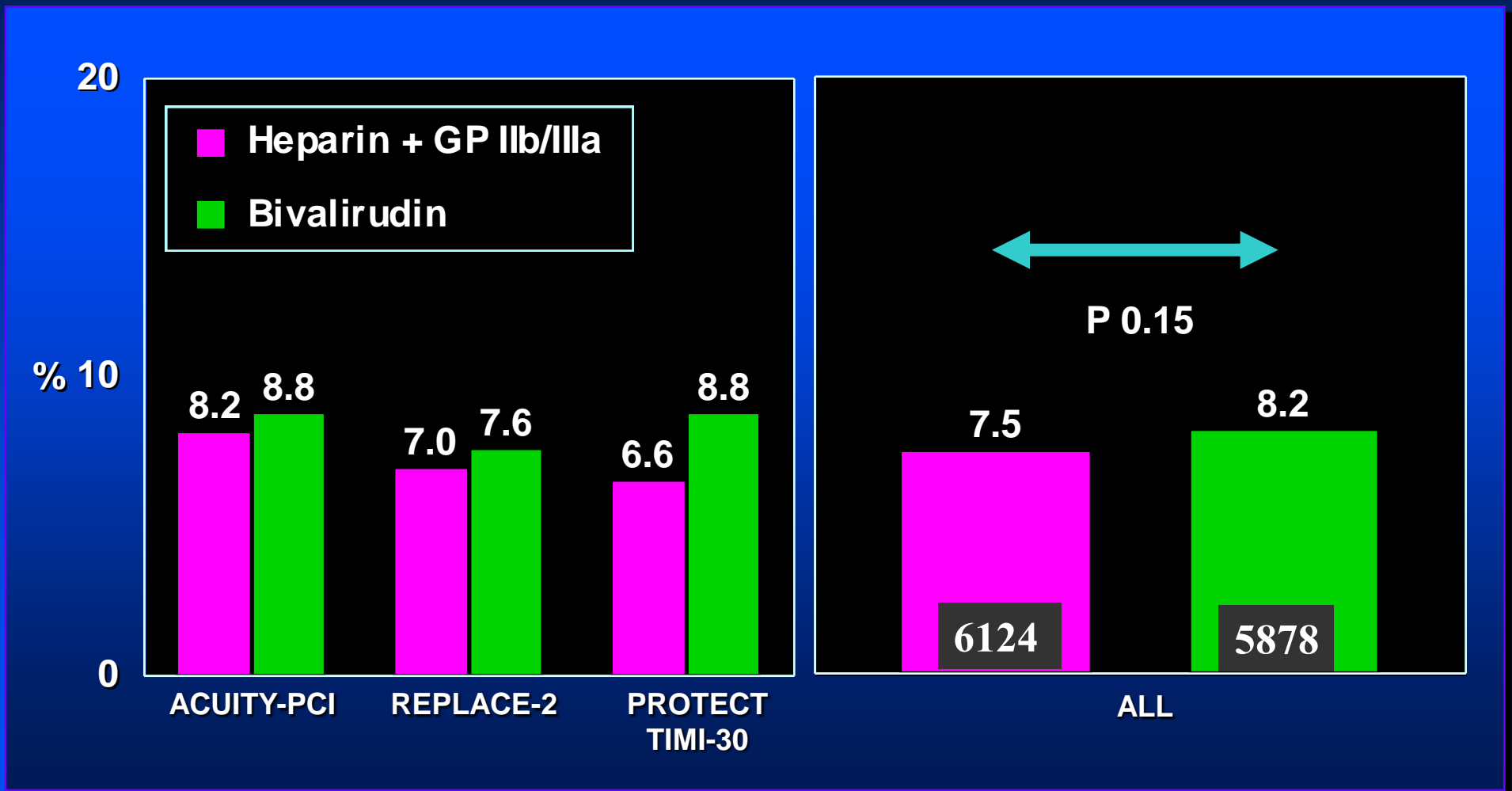
# Heparina +/- GP2b/3a



# Heparin + GP IIb/IIIa vs Bivalirudin Trials

Patients with ACS Undergoing PCI

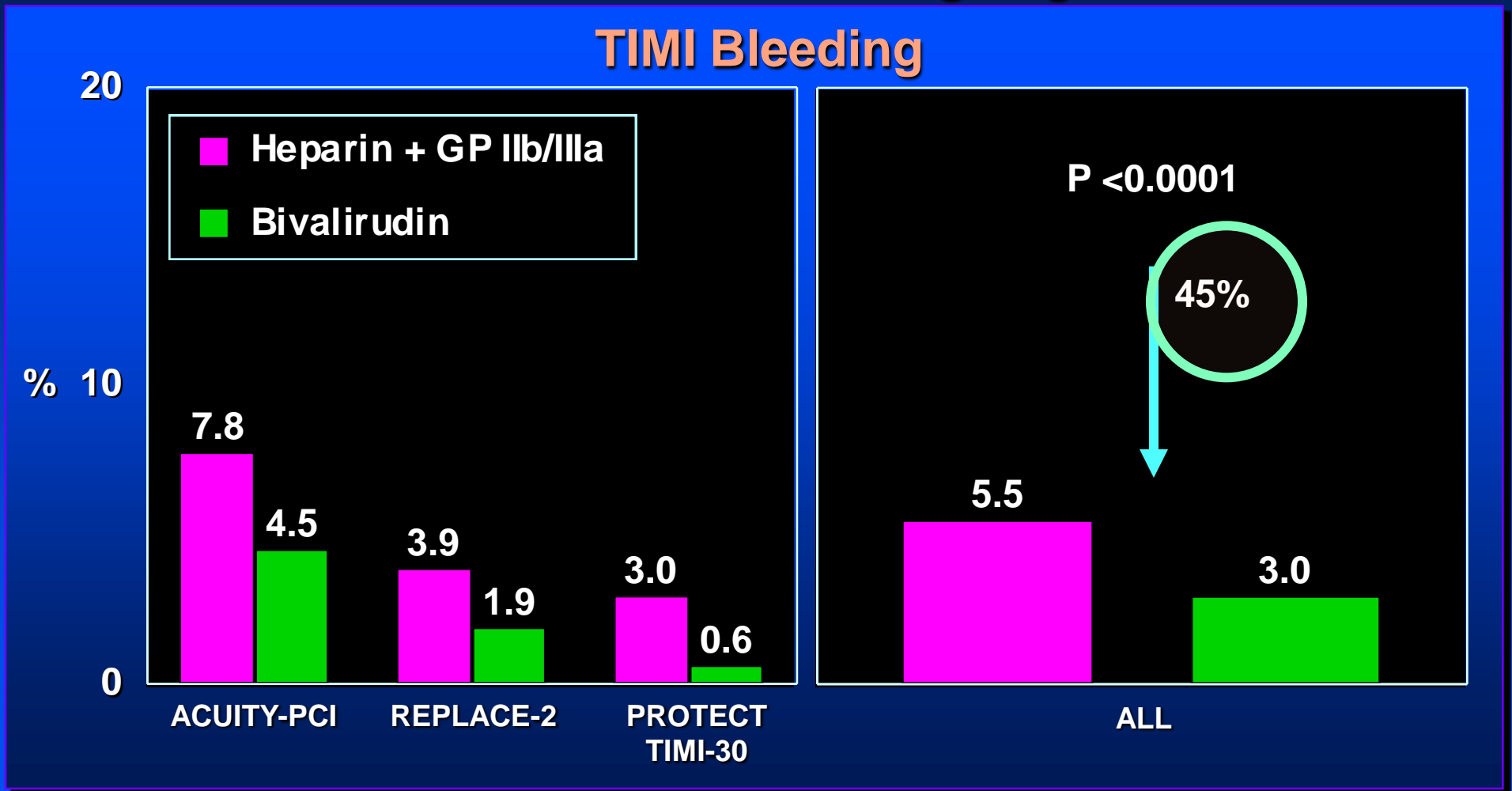
## Composite Ischemia





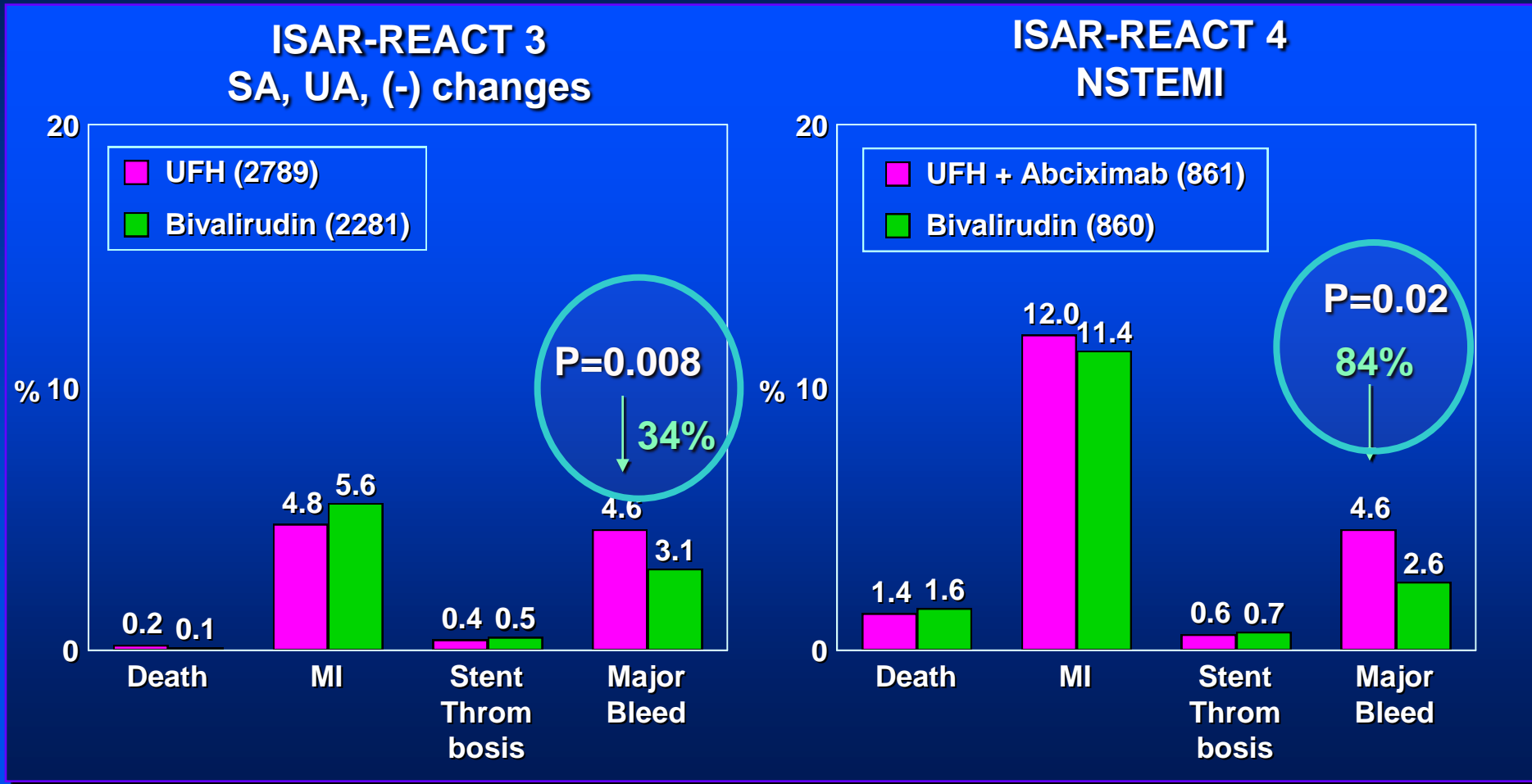
# Heparin + GP IIb/IIIa vs Bivalirudin Trials

Patients with ACS Undergoing PCI



# UFH ± Abciximab vs Bivalirudin

## 30-Day Events

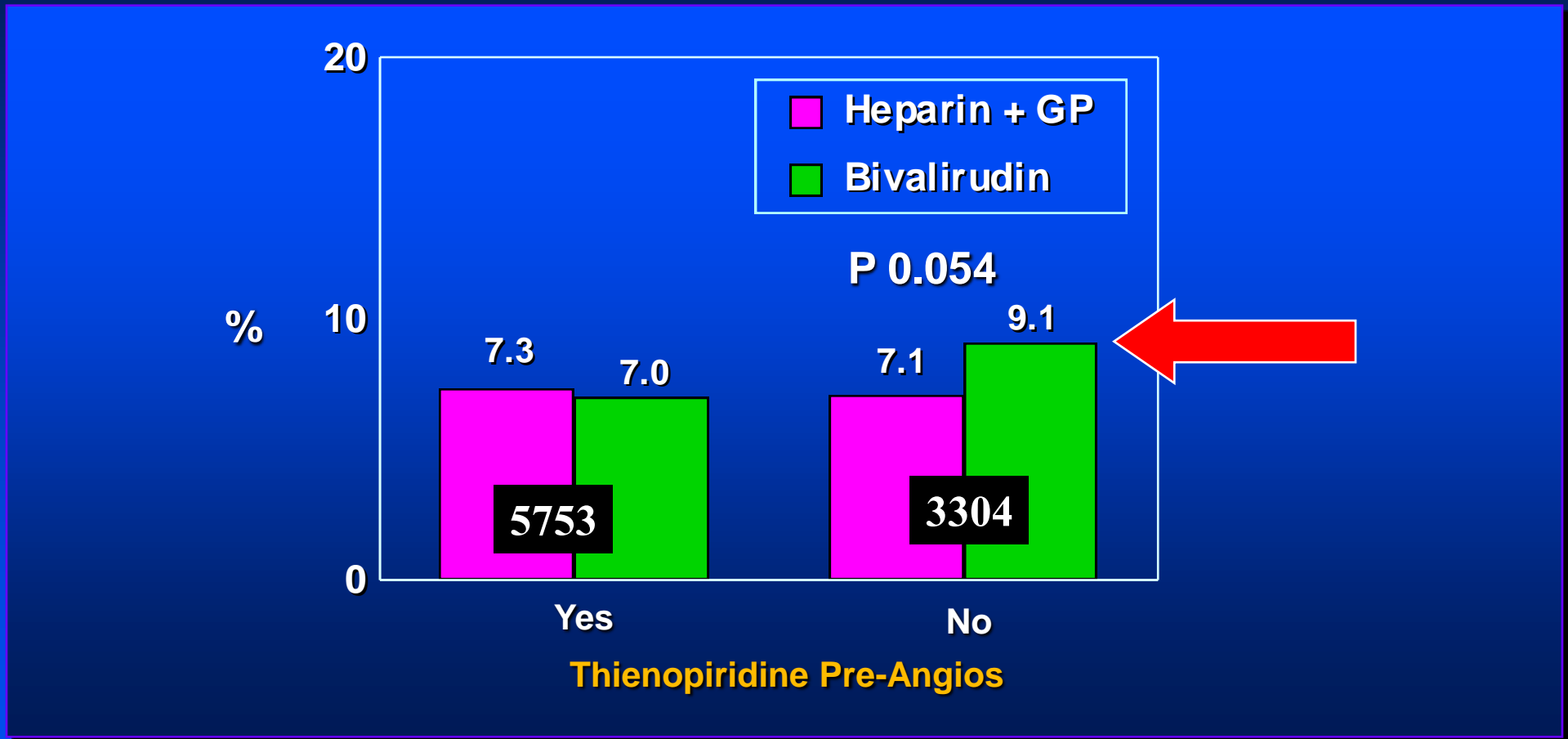


A Kastrati NEJM 2008;359:688-96

NEJM 2011;365:1980-9

# ACUITY: Thienopiridine Pre-Treatment

## Composite Ischemia



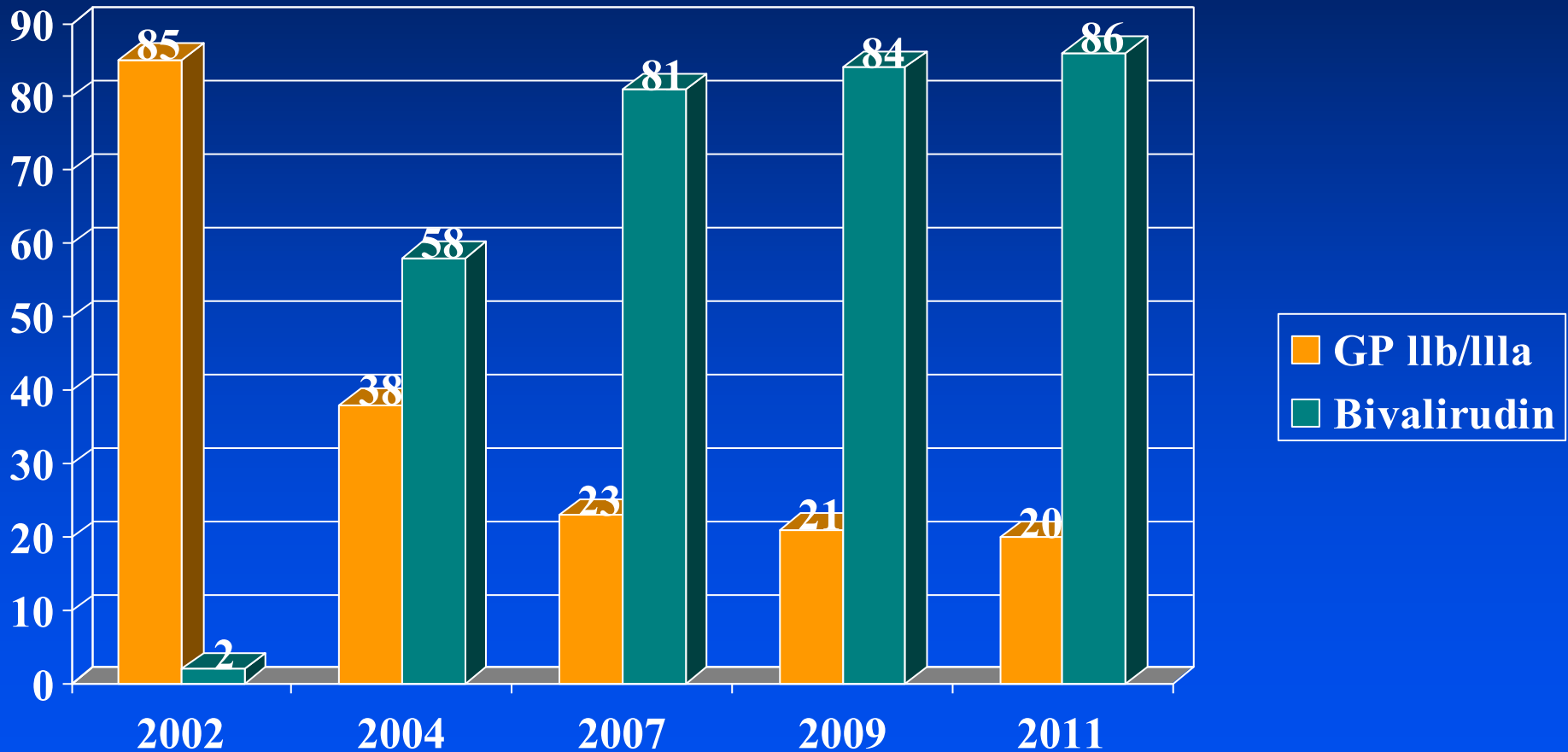
# Heparina+GP2b/3a vs Bivalirudina:

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- **Bivalirudina se asocia a una incidencia significativamente menor de sangrados mayores.**
- **La incidencia de eventos isquémicos es similar con ambas drogas (excepción: pacientes con bivaluridina no pre-tratados con Clopidogrel)**

# Anticoagulation in PCI

*CLEVELAND CLINIC*



# 2011 ACCF/AHA/SCAI Guidelines for PCI

## Anticoagulantes - antitrombina

I   IIa   IIb   III

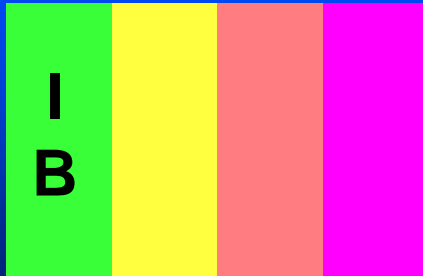


**Bivaluridina es de utilidad independiente de tratamiento previo con heparina.**

# ESC 2011 NSTE-ACS Guidelines

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## Anticoagulantes



- Bivaluridina como alternativa a Heparina+GPI en estrategia invasiva temprana, particularmente en pacientes de alto riesgo de sangrado.

# Cual es el rol actual de inhibidores GPIIb/IIIa en intervenciones coronarias?



EUROPEAN  
SOCIETY OF  
CARDIOLOGY\*

European Heart Journal (2008) **29**, 429–431  
doi:10.1093/eurheartj/ehm624

EDITORIAL

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## Platelet glycoprotein IIb/IIIa receptor inhibitors—end of an era?

Marco Roffi<sup>1\*</sup> and Debabrata Mukherjee<sup>2</sup>



# Precaución!

## CRUSADE Registry

- 27% de los pacientes tuvieron exceso de dosificación de Eptifibatide y Tirofiban:

Mujeres, >75 años, bajo peso, E.renal

- Consecuencias:

17% sangrado mayor

50% aumento de mortalidad

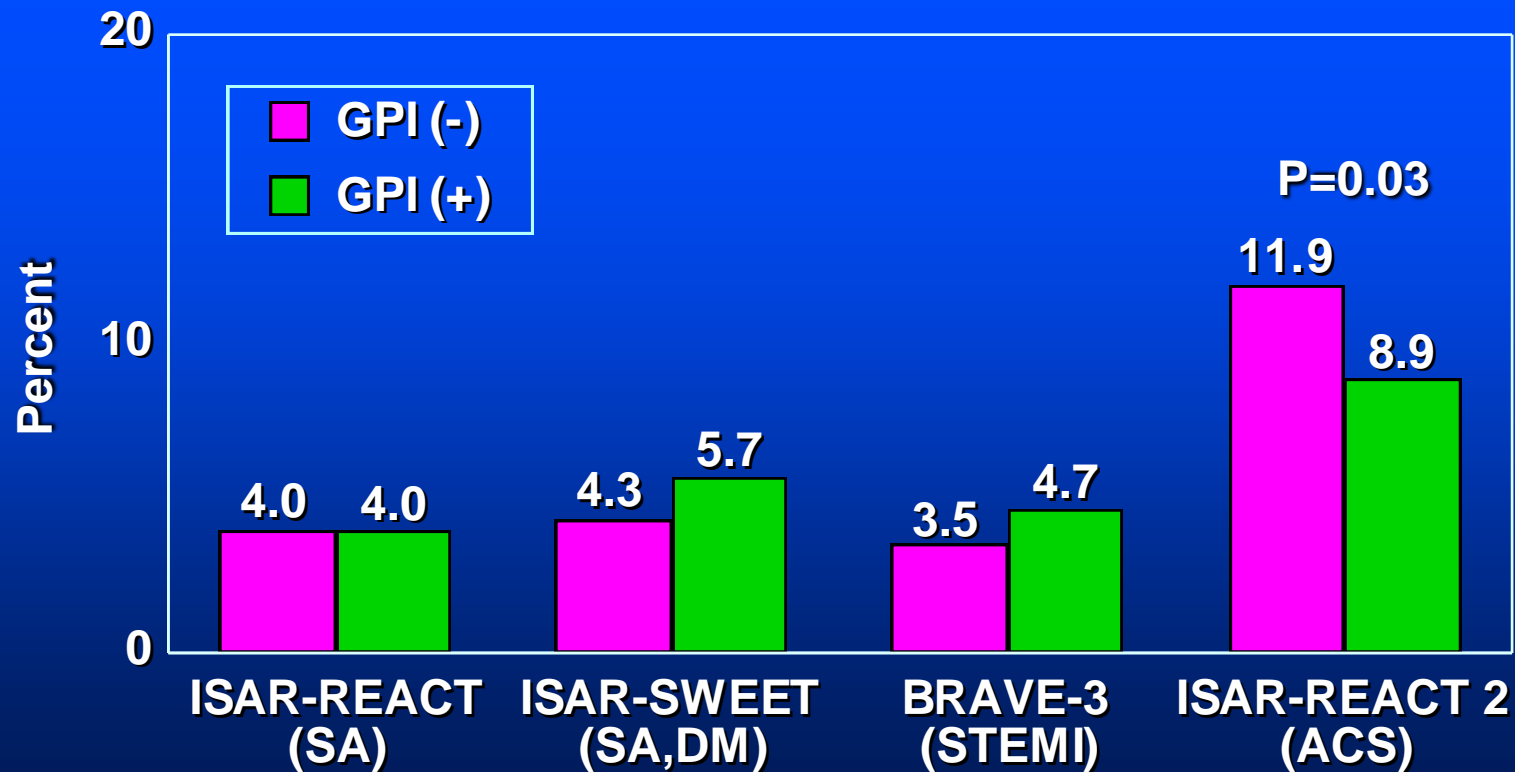
# GPI's : interrogantes ?

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- **Beneficio en pacientes con stents, aspirina y Clopidogrel?**
- **Administración temprana (**upstream**) o durante el procedimiento (**downstream**)?**
- **Son necesarias las infusiones prolongadas?**

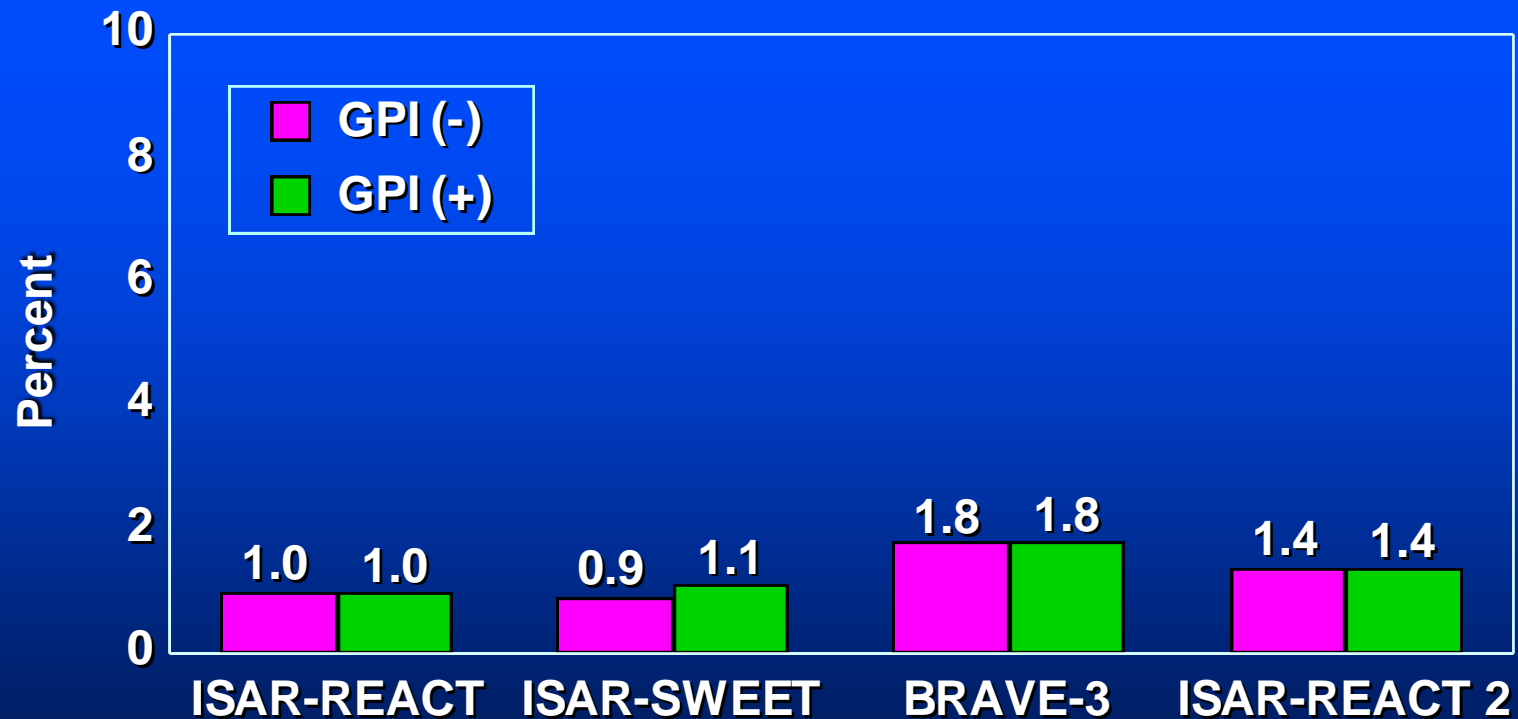
# GPI in PCI (Stenting + Thienopyridine Pre-loading)

30-day Death / MI / Urgent TVR



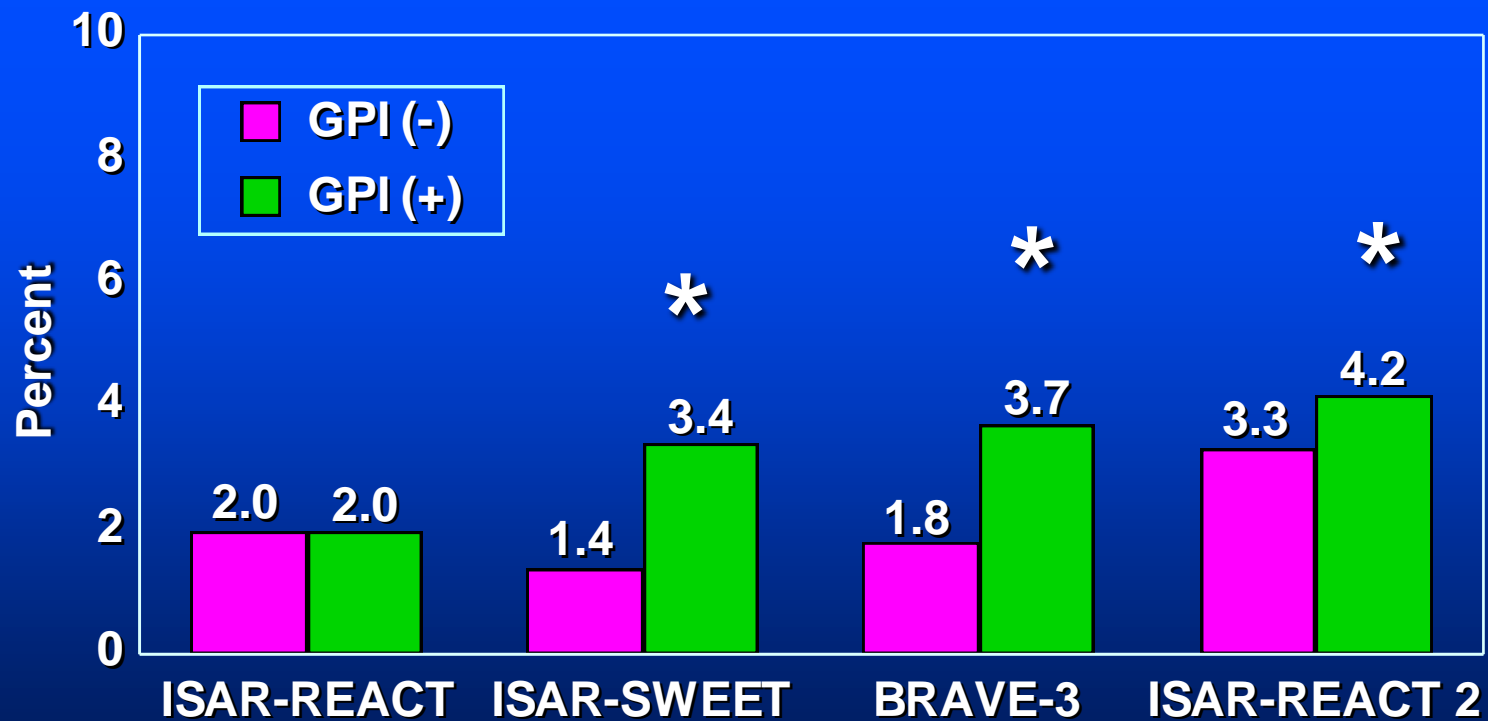
# GPI in PCI (Stenting + Thienopyridine Pre-loading)

## TIMI - Major Bleeding



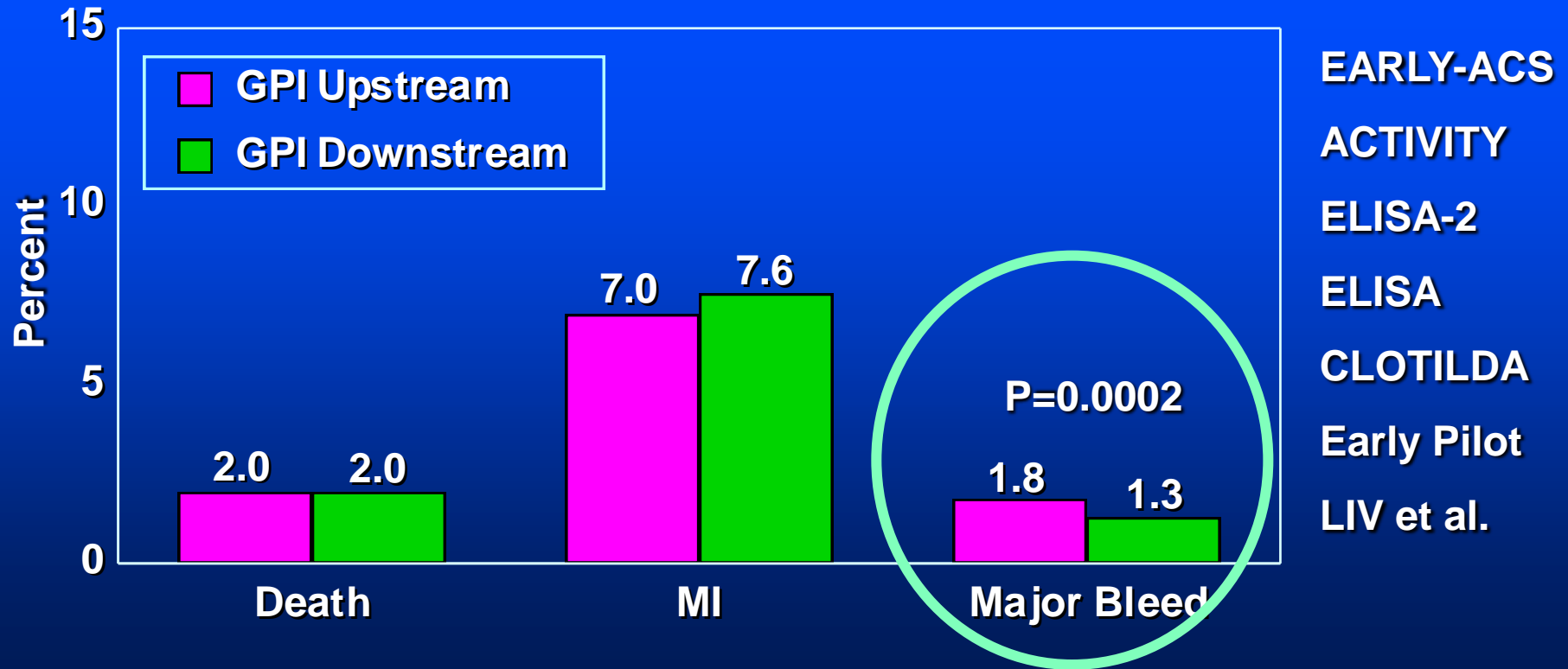
# GPI in PCI (Stenting + Thienopyridine Pre-loading)

## TIMI - Minor Bleeding



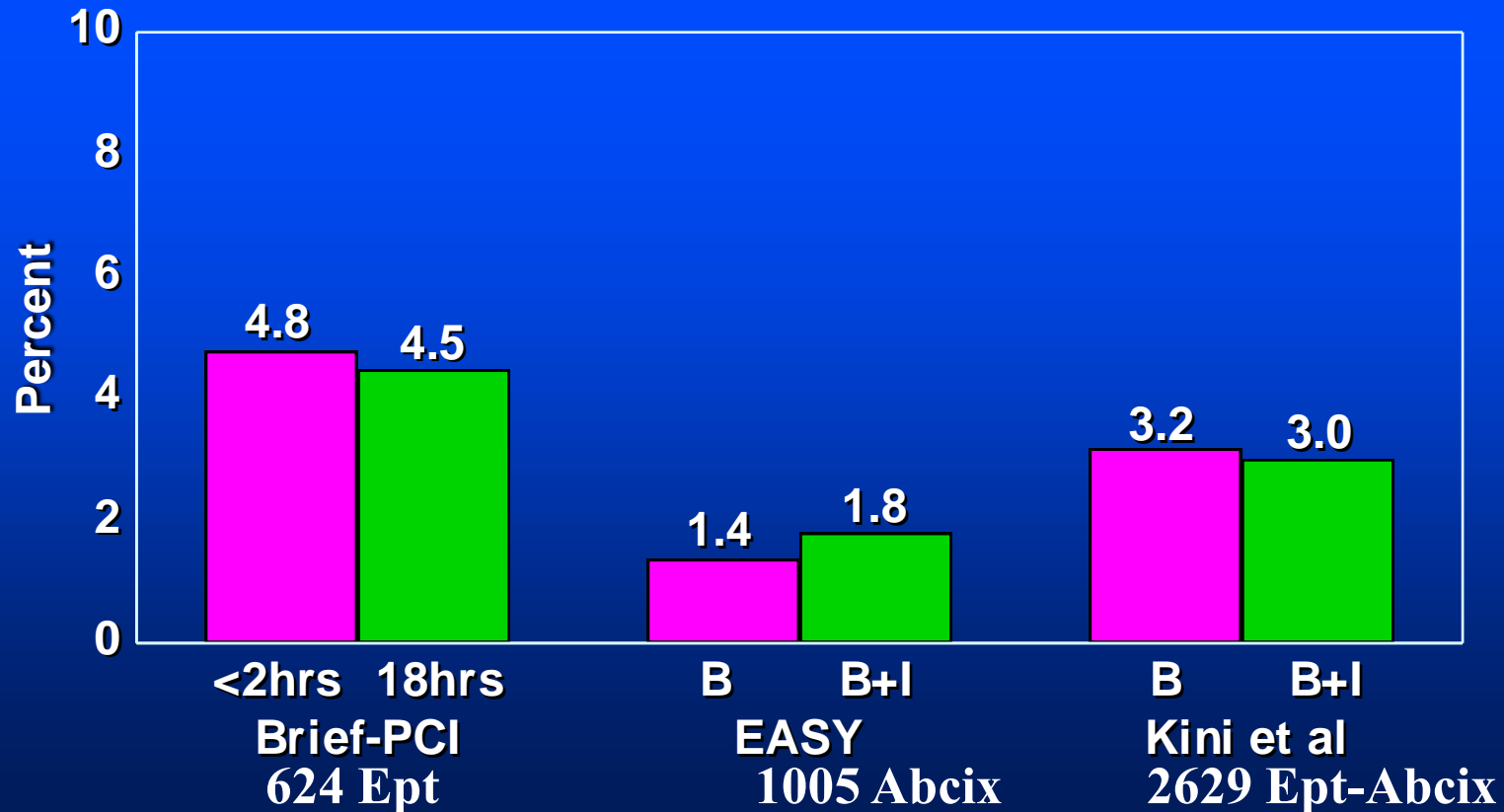
# Meta-Analysis GPI in High Risk ACS Undergoing Invasive Rx

7 RCT - 19,929 pts  
30-Day Events



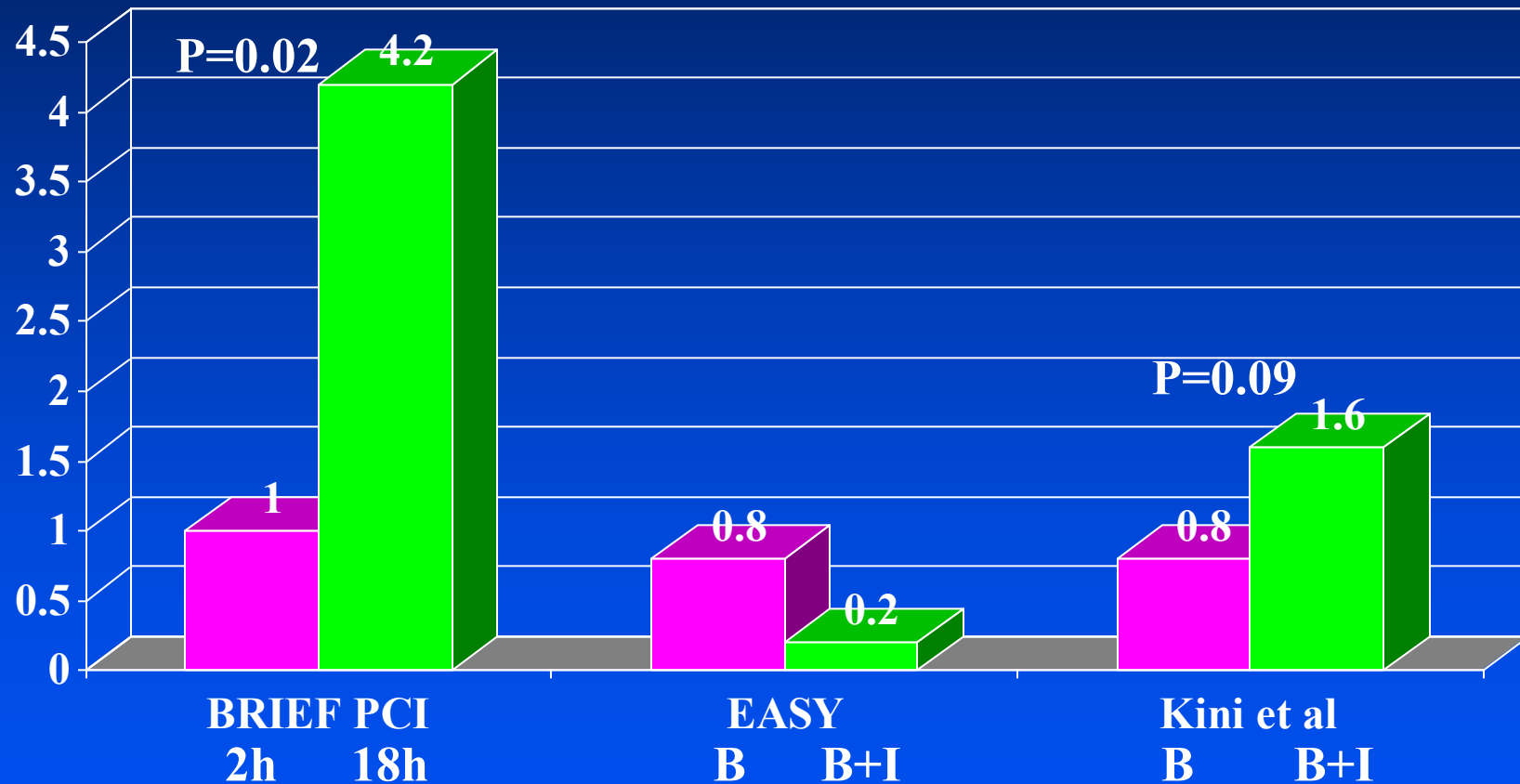
# GPIIb/IIIa Duration of Infusion

## 30-day Death / MI / Urgent TVR



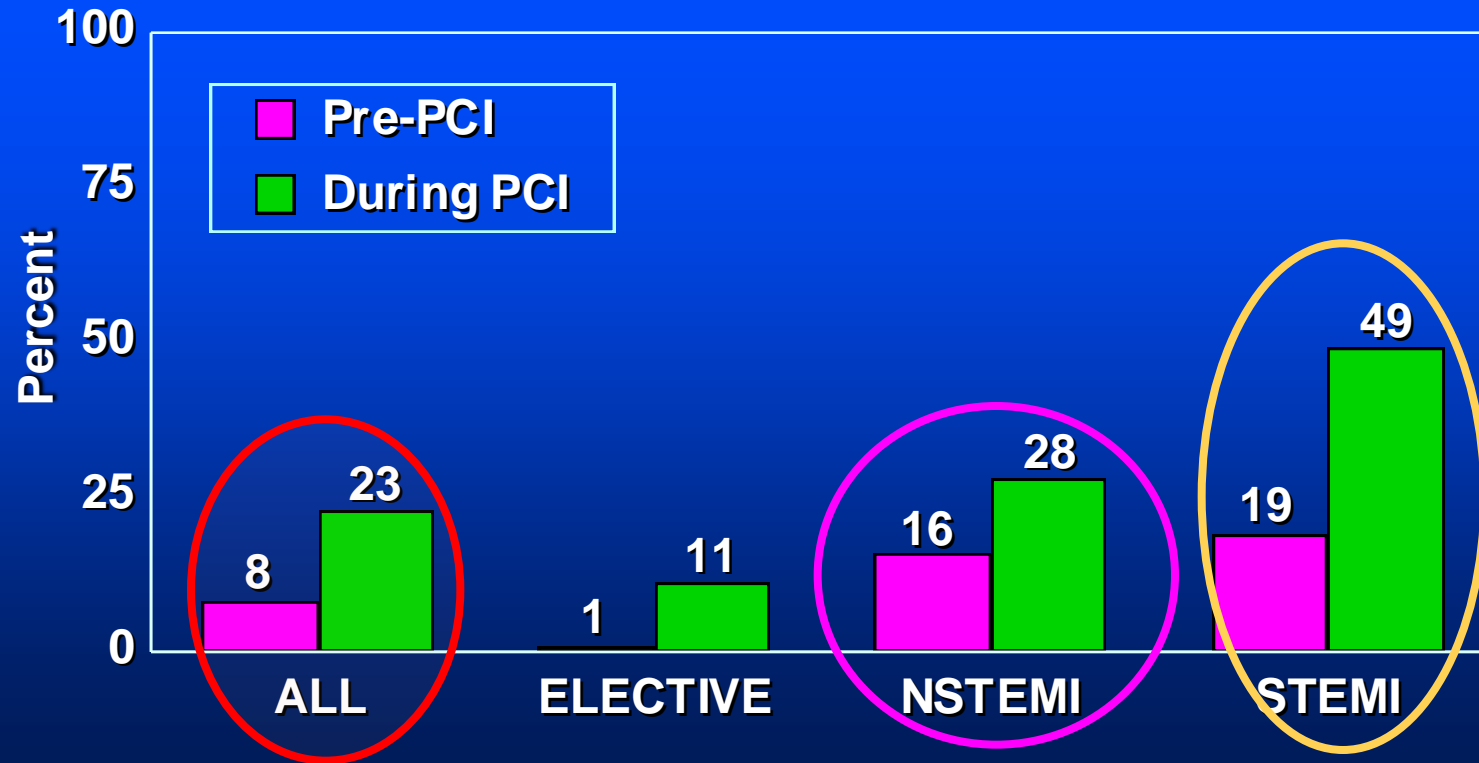
# GPI : Duration of infusion

## Major bleeding





# GPI Utilization in PCI Euro Heart Survey



## **En pacientes que han recibido una dosis de carga de Clopidogrel ,el agregar un inhibidor GP 2b/3a...**

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- **Logra mayor inhibición plaquetaria**
- **En intervenciones electivas no reduce los eventos clinicos**
- **En sindromes coronarios agudos,especialmente en TnT (+),reduce eventos isquémicos sin aumento en sangrados mayores, pero con mas sangrados menores.**

# Como optimizar el uso de inhibidores GP en intervenciones coronarias ?

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- Uso selectivo:

NSTEMI de alto riesgo

STEMI (++ trombosis, presentación temprana),  
intracoronario?

Pacientes sin premedicación de tienopiridina

# Inhibidores GP

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- Prevenir sangrado

Identificar pacientes de alto riesgo

Evitar administración pre-PCI “upstream”

Infusiones breves

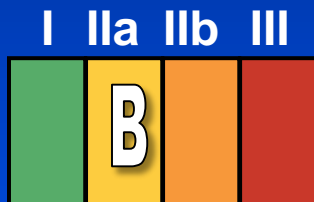
Cuidados con vía de acceso (radial).

# 2011 ACCF/AHA/SCAI Guidelines for PCI

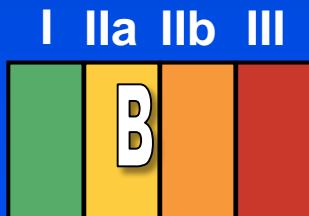
## Inhibidores GP IIb/IIa



En pacientes con UA/NSTEMI de alto riesgo (Troponinas +) en heparina y no pretratados con Clopidogrel.



En pacientes con UA/NSTEMI de alto riesgo pretratados con Clopidogrel



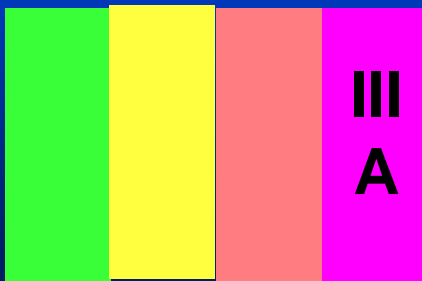
En angioplastia electiva con heparina en pacientes no pretratados con Clopidogrel.

# ESC 2011 NSTE-ACS Guidelines

## GPIIb/IIIa receptor inhibitors



- Pacientes en DTAP, se recomienda agregar inhibidores GP en PCI de alto riesgo (Tn +, trombo), si el riesgo de sangrado es bajo.



- No se recomiendan de rutina previo a la angiografía en la estrategia invasiva.

A 3D medical illustration of a blood vessel. The vessel lumen is filled with red blood cells. A large, yellowish, irregular plaque is attached to the vessel wall. Several yellow, disc-shaped platelets are floating in the blood. The overall background is a dark red color.

## ***Antiplaquetarios orales:***

- Cual droga?***
- Duración del tratamiento***

# Clopidogrel o ...



**Effient**<sup>TM</sup>  
*prasugrel HCl* tablets

**COMING SOON!**





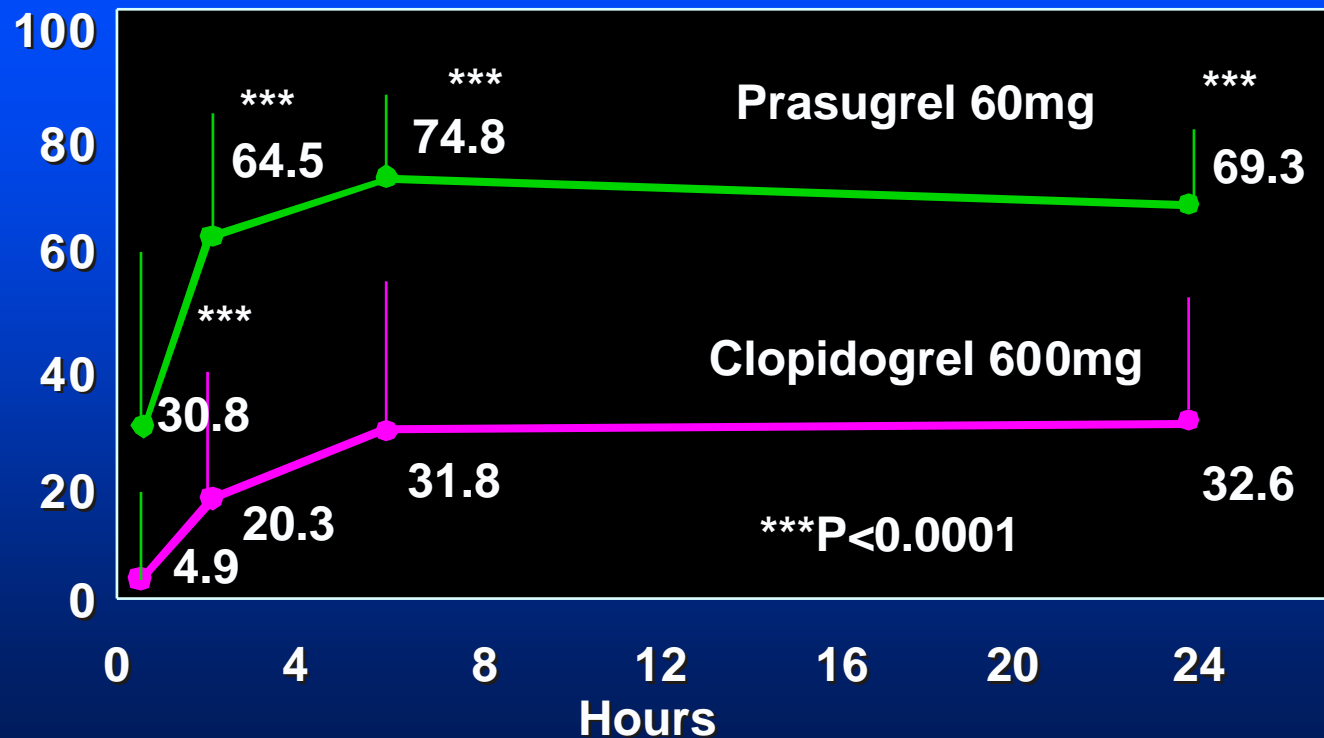
# Inhibidores P2Y<sub>12</sub>

	<i><b>Clopidogrel</b></i>	<i><b>Prasugrel</b></i>	<i><b>Ticagrelor</b></i>
<b>Clase</b>	Tienopiridina	Tienopiridina	Triazolopirimidina
<b>Reversibilidad</b>	Irreversible	Irreversible	Reversible
<b>Comienzo</b>	2-4 hrs	30 min	30 min
<b>Duración</b>	3 – 10 dias	5 – 10 dias	3 – 4 dias
<b>Suspender previo cirugía</b>	5 dias	7 dias	5 dias
<b>Activación</b>	Prodroga x2	Prodroga x1	Directa

# Principle TIMI 44

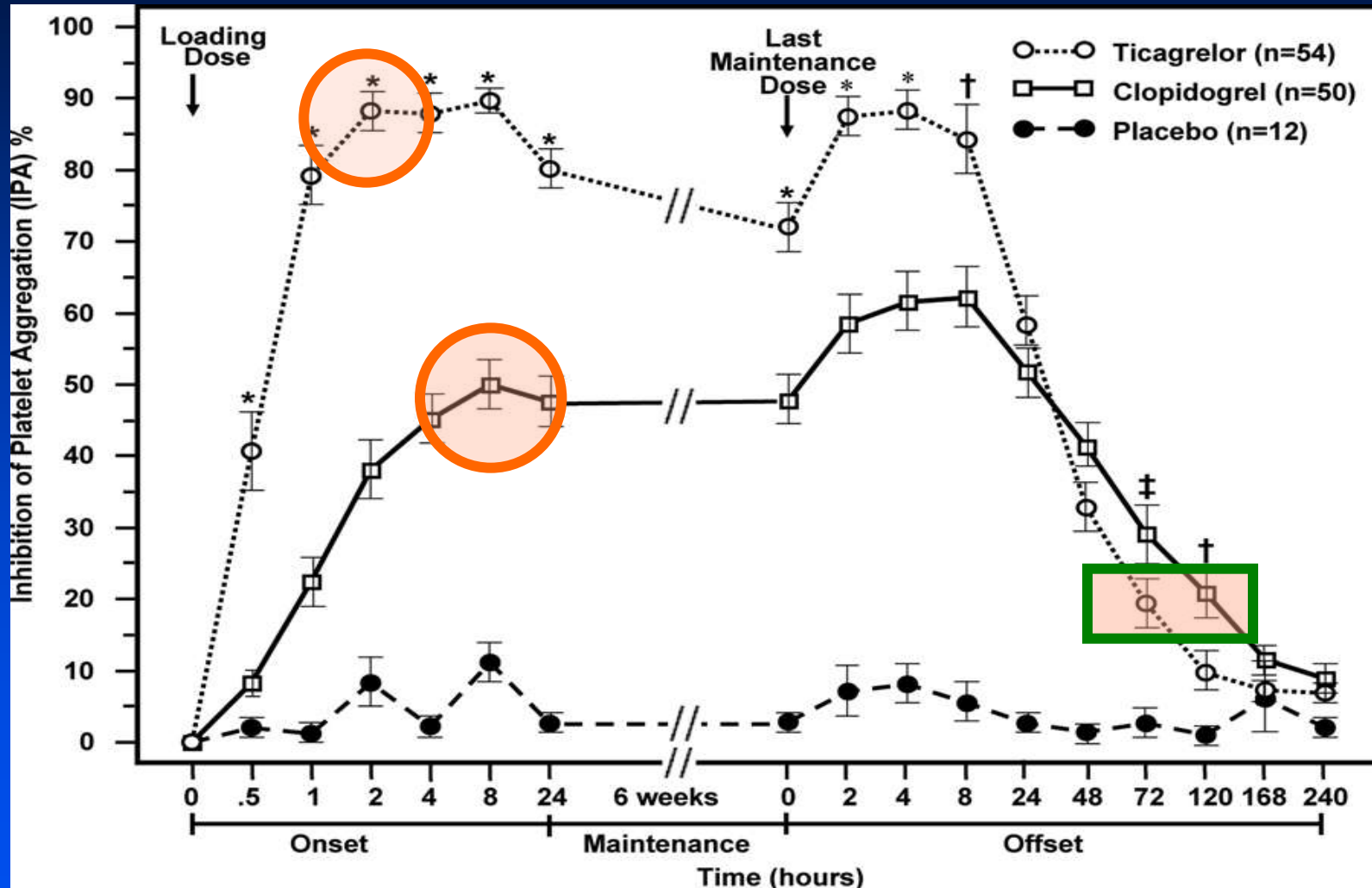
## Inhibition Platelet Aggregation

IPA (20  $\mu$ m ADP, %)



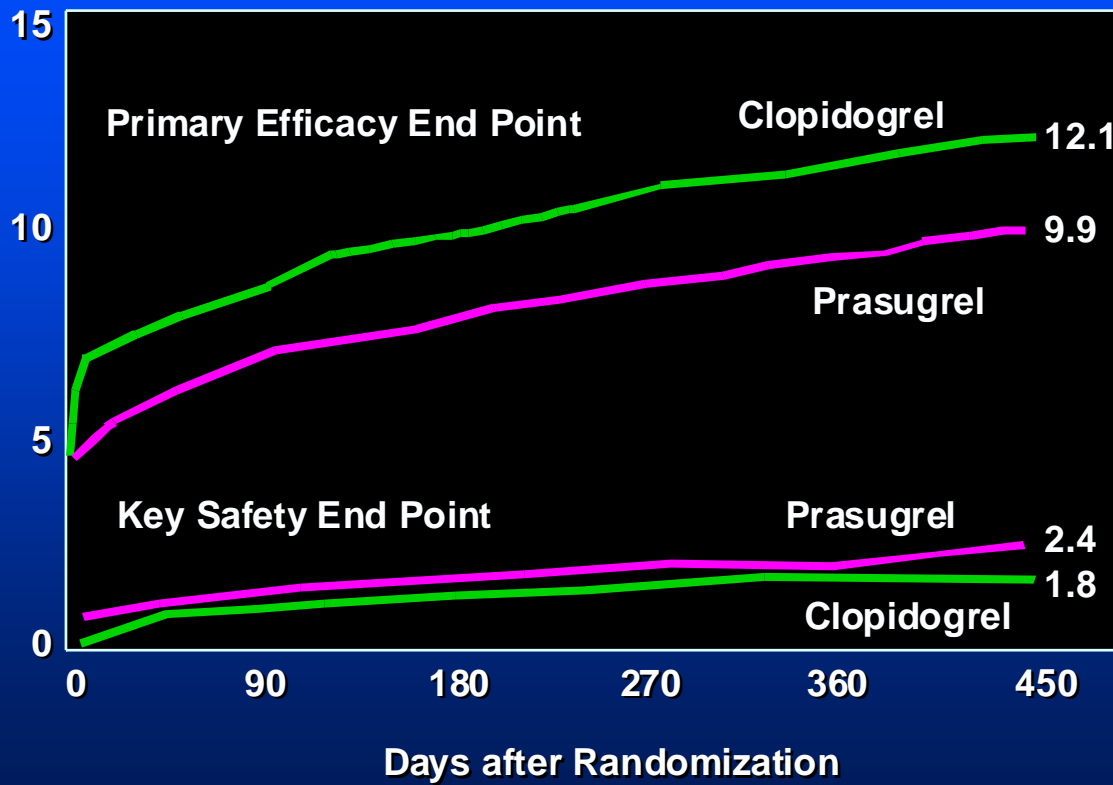
# ONSET/OFFSET Study

## Antiplatelet Effects of Ticagrelor vs Clopidogrel



# TRITON-TIMI 38

End Point (%)



↓ 138 Events

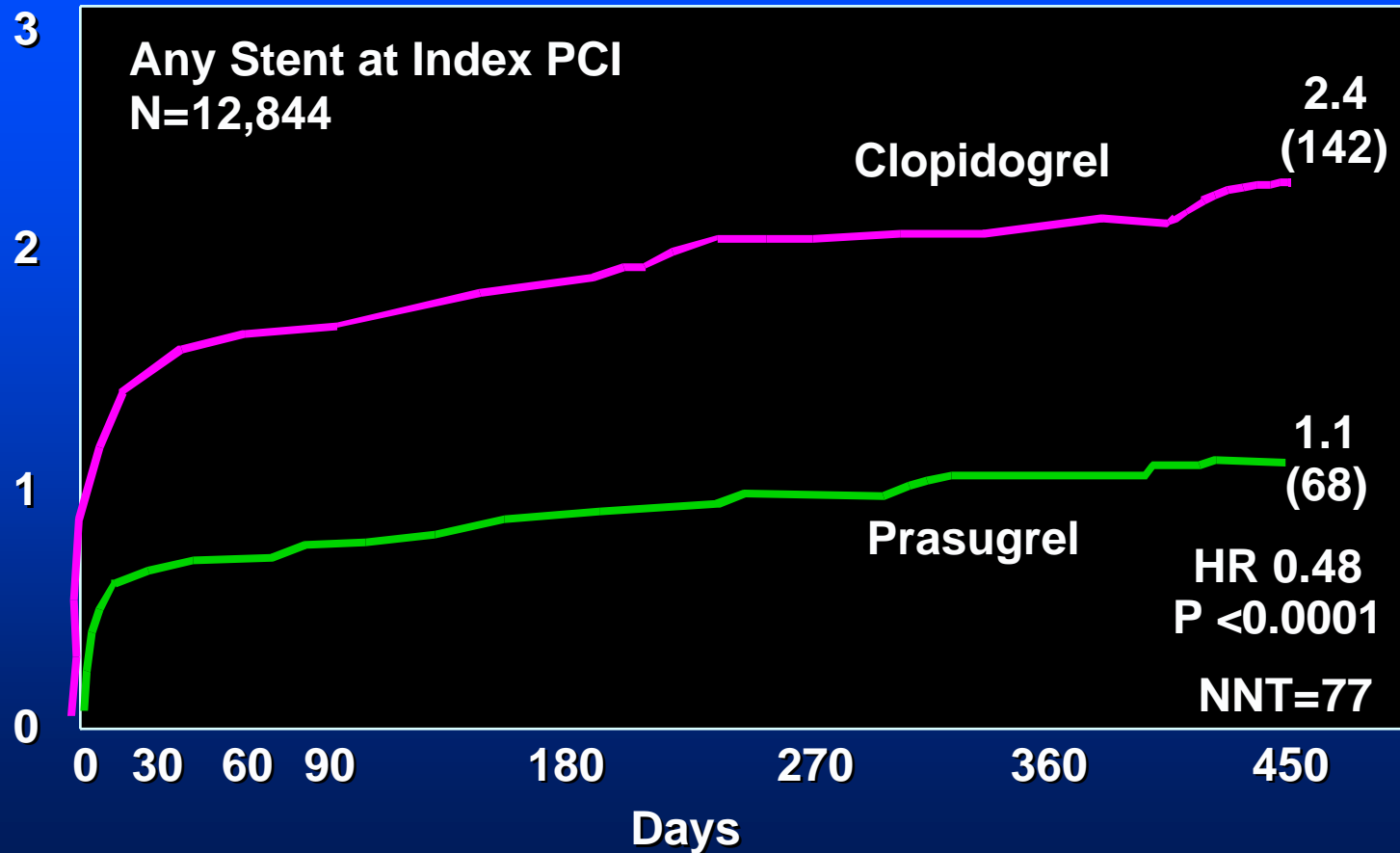
Hazard ratio, 0.81;  
95% CI, 0.73-0.90;  
P<0.001

↑ 35 Events

Hazard ratio, 1.32;  
95% CI, 1.03-1.68;  
P=0.03

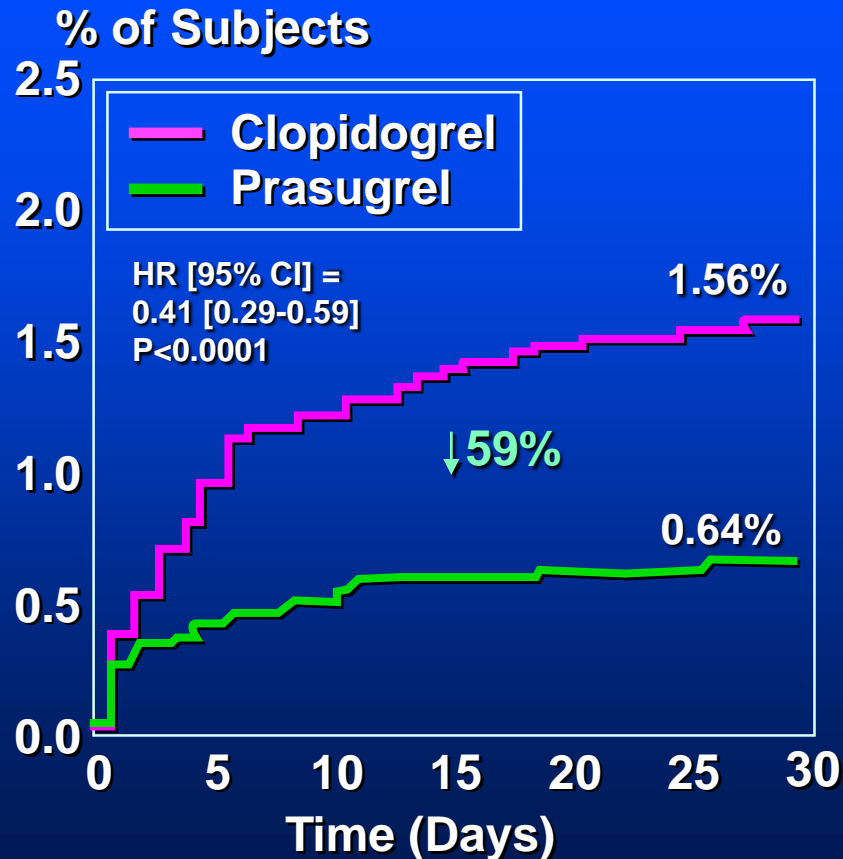
# TRITON-TIMI 38: Stent Thrombosis (ARC Definite + Probable)

Endpoint (%)

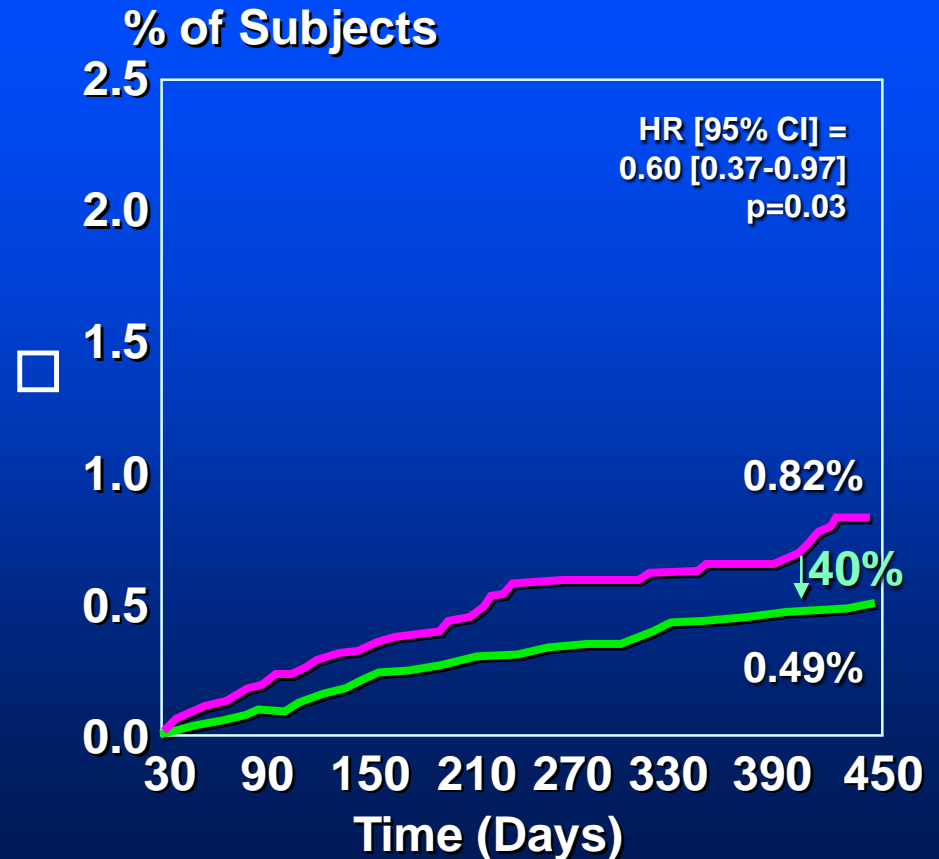


# TRITON TIMI-38: ARC Def/Prob ST

## Early ST

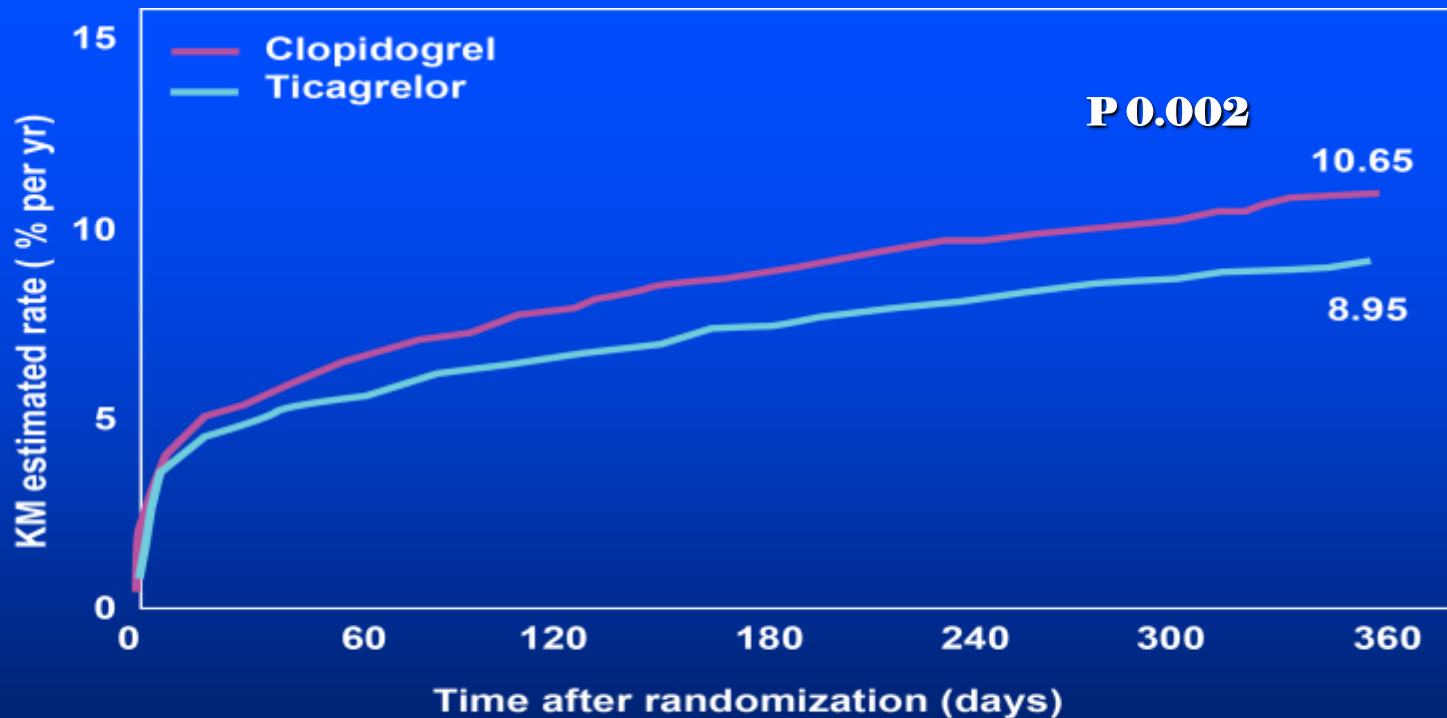


## Late ST



# PLATO: Planned Invasive Strategy

## CV Death, MI, Stroke



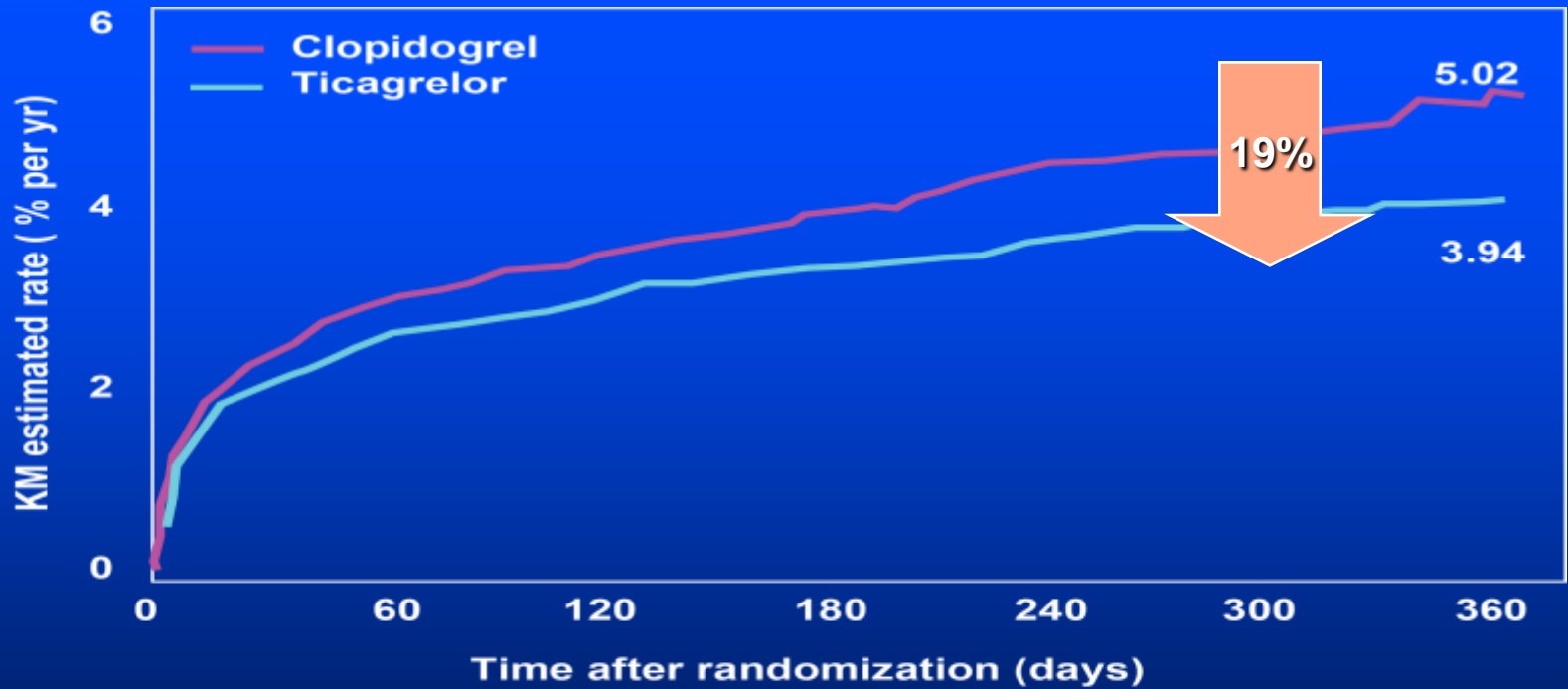
16%

Number at risk

Clopidogrel	6676	6129	6034	5881	4815	3680	2965
Ticagrelor	6732	6236	6134	5972	4889	3735	3048

# PLATO: Planned Invasive Strategy

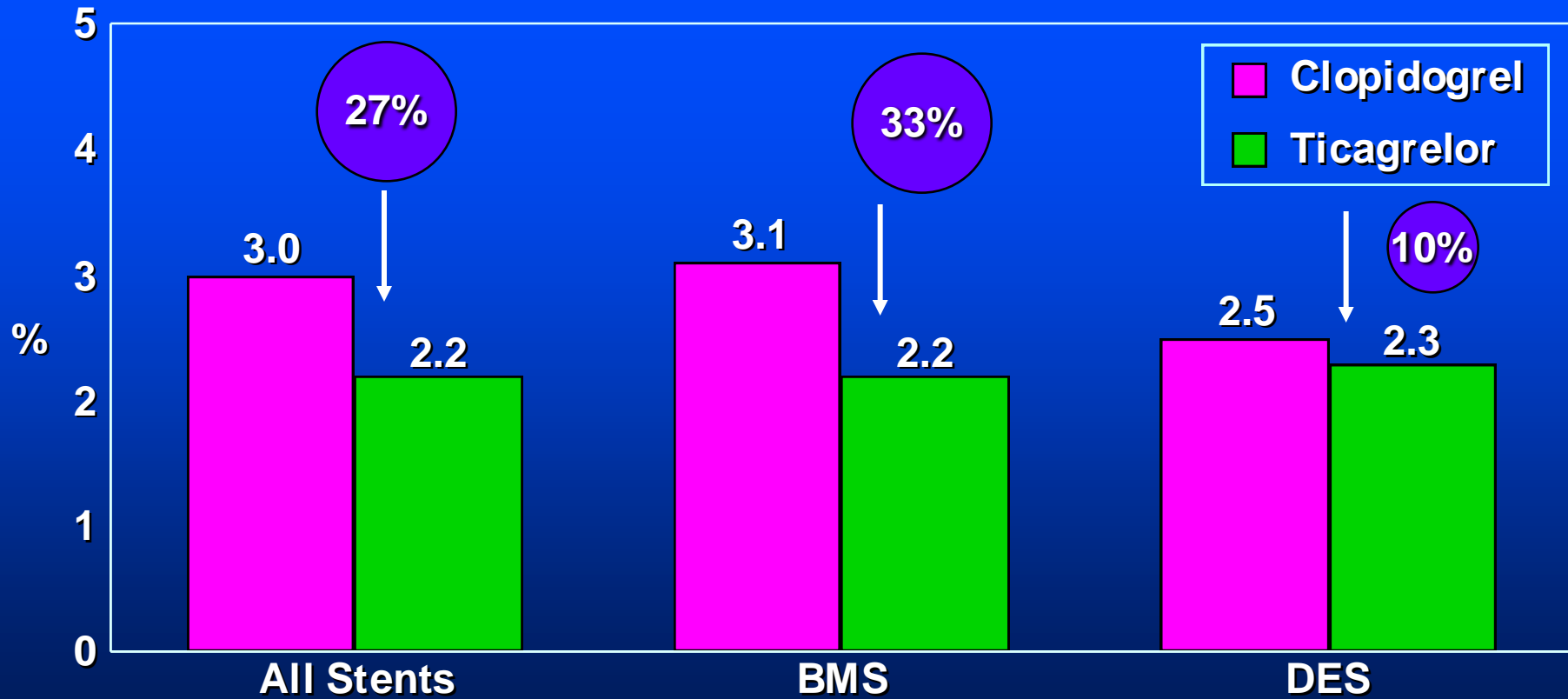
## All-Cause Mortality



Number at risk	0	60	120	180	240	300	360
Clopidogrel	6676	6376	6331	6209	5114	3917	3164
Ticagrelor	6732	6439	6375	6241	5141	3951	3233

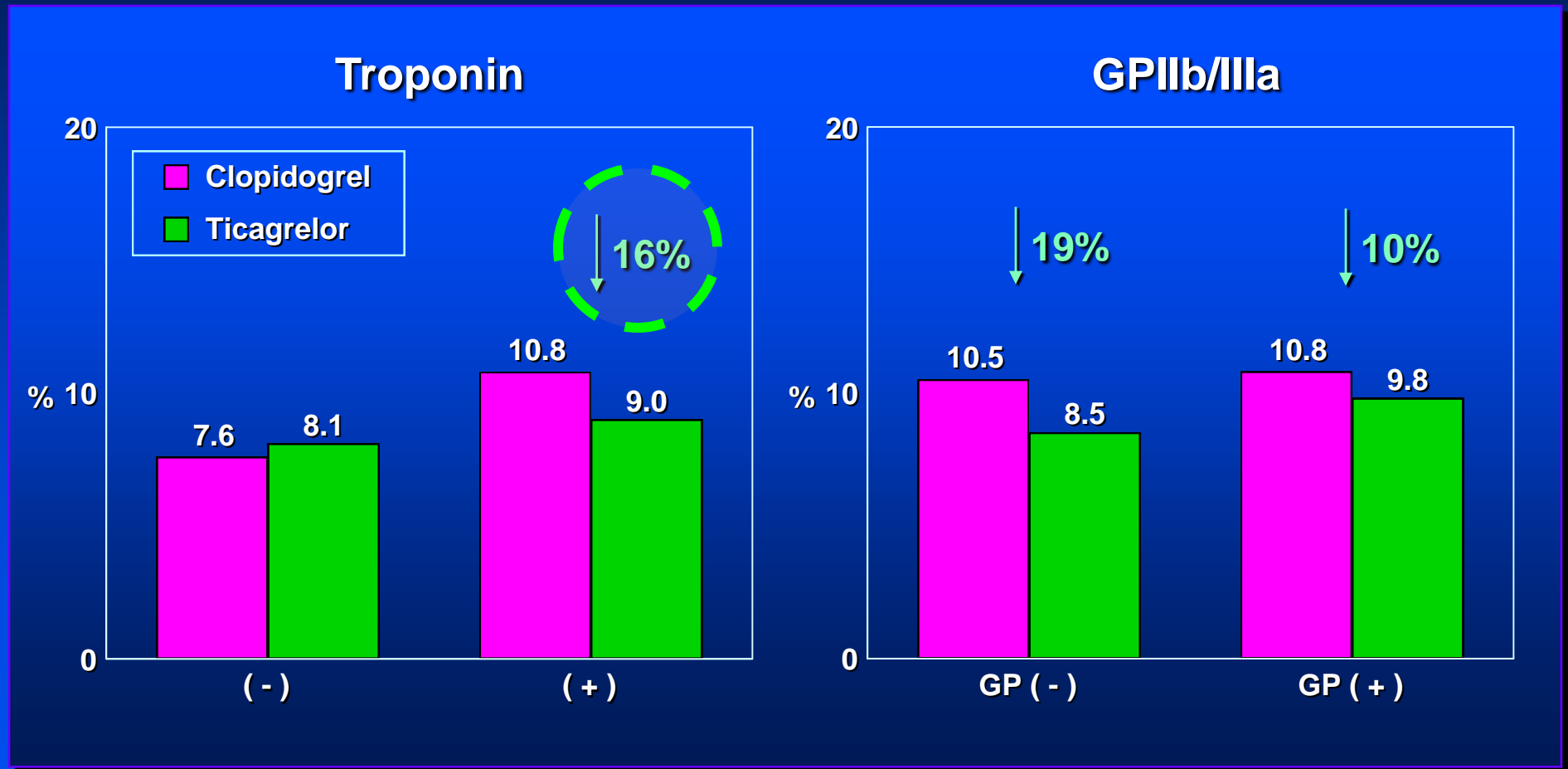


# PLATO: Stent Thrombosis

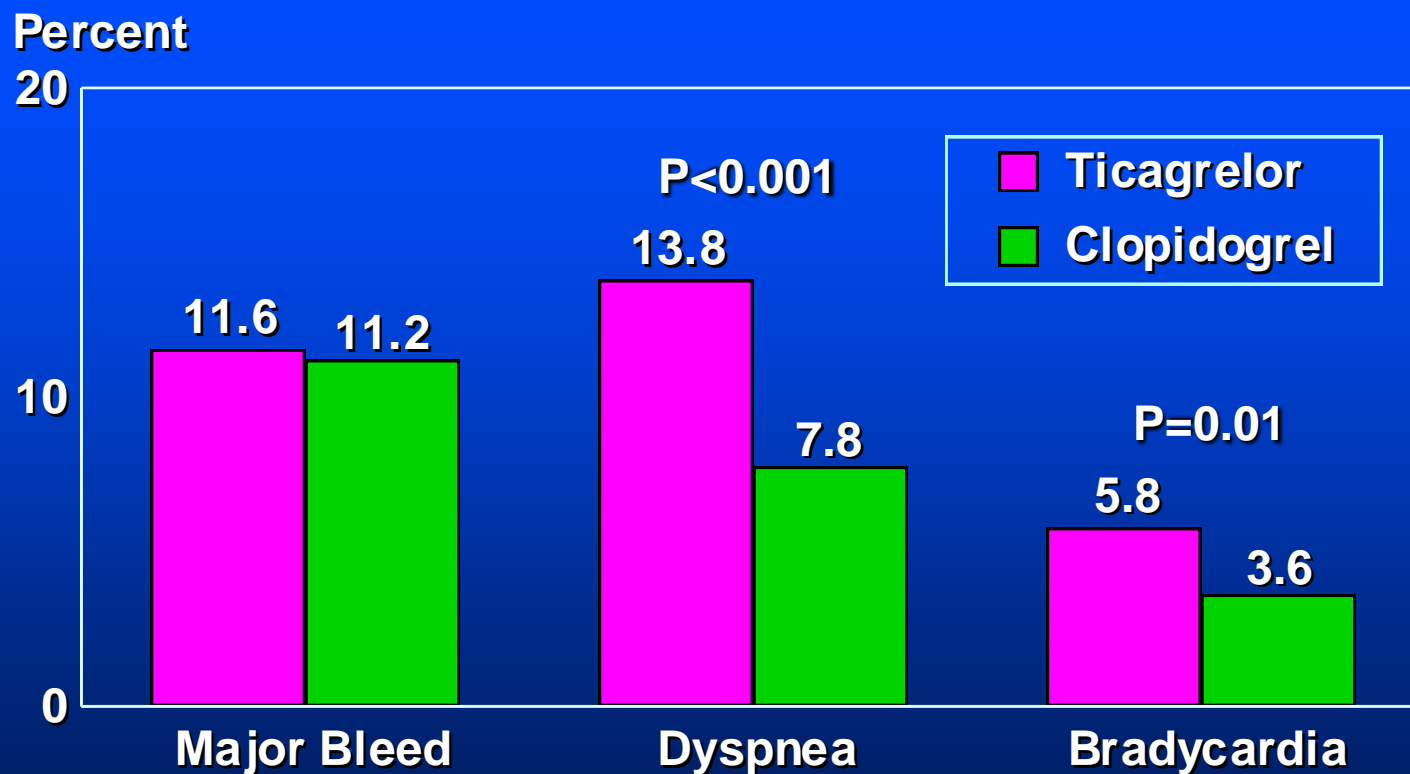


# PLATO (PCI Patients)

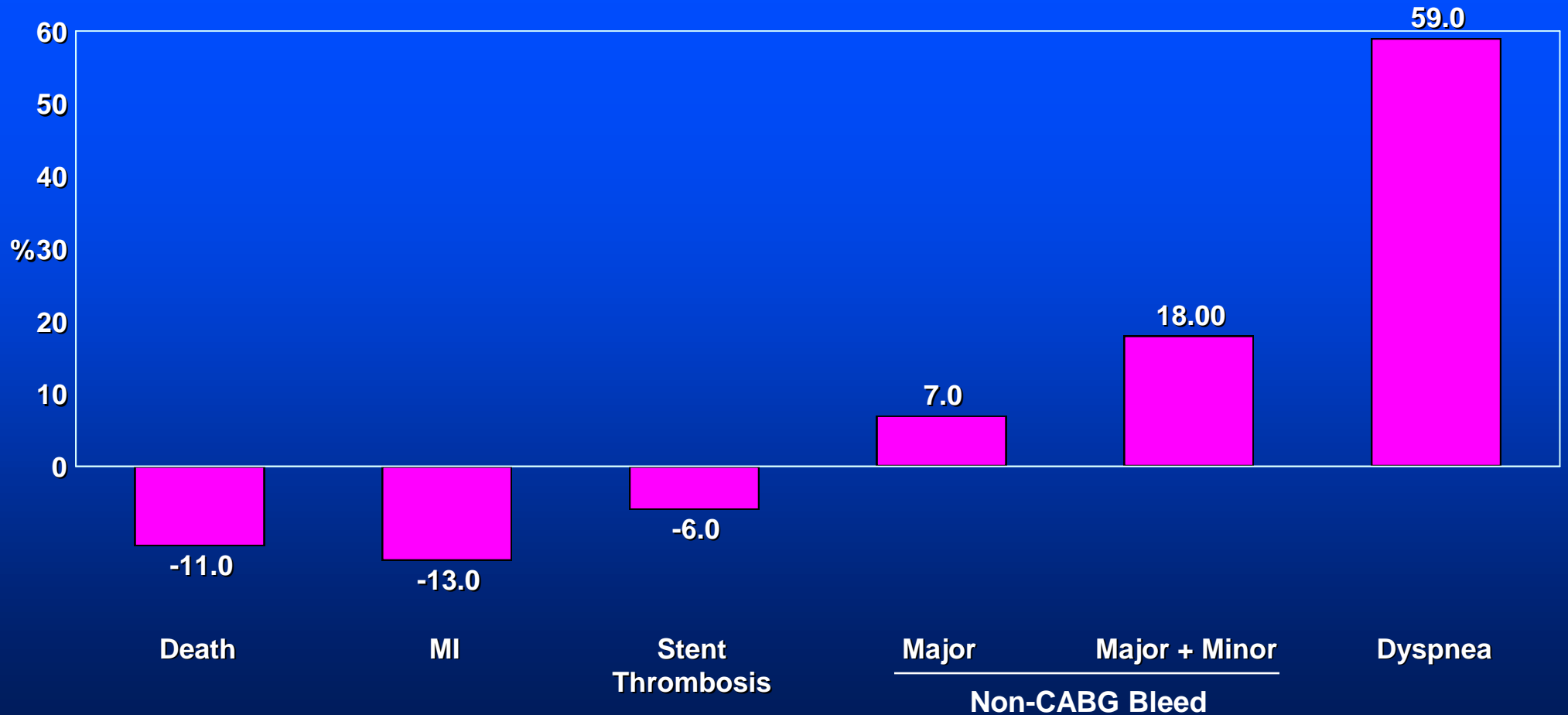
## 1-Year CV Death, MI, Stroke



# PLATO: Adverse Events

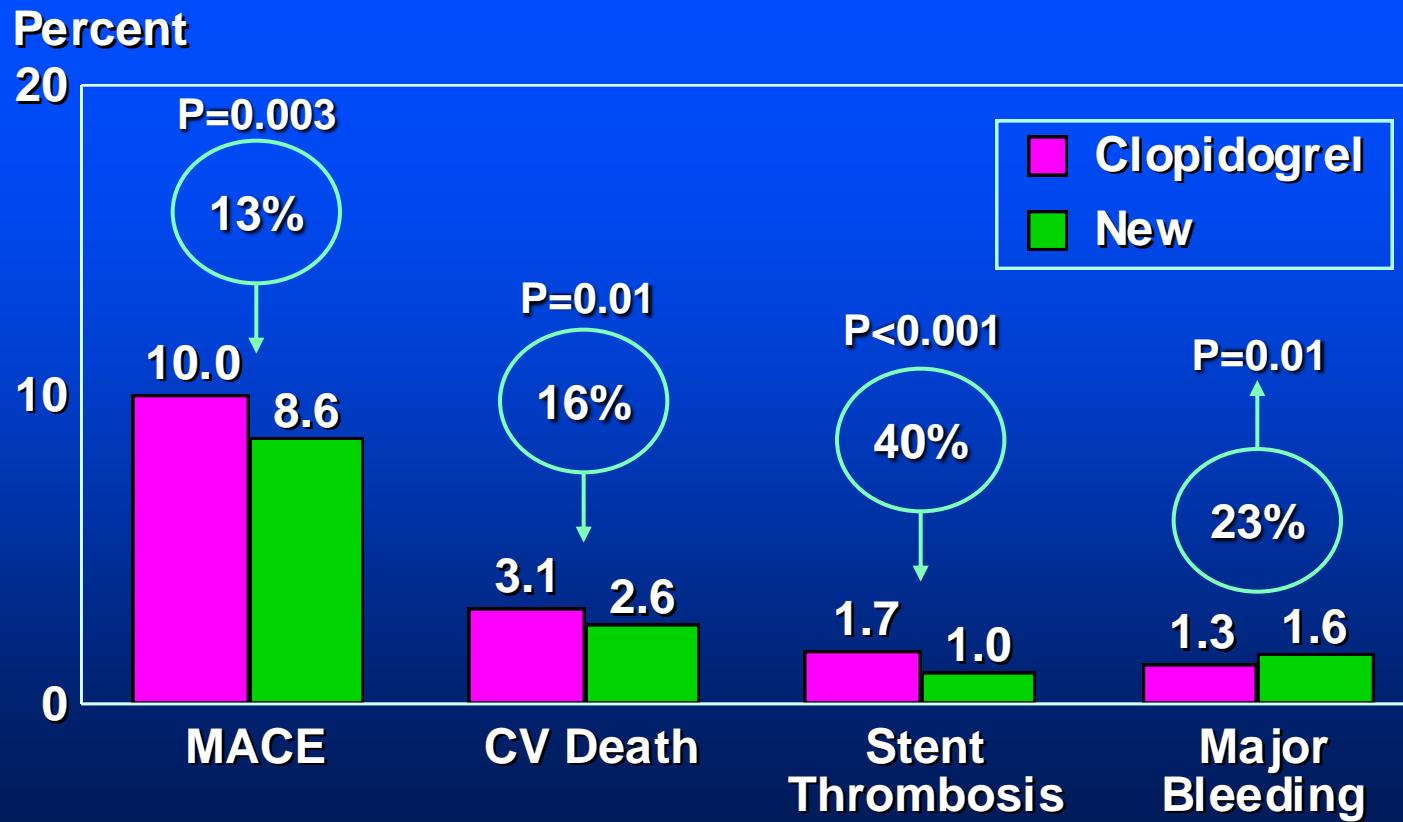


# PLATO Events x 1000 PCI Patients on Ticagrelor Compared to Clopidogrel



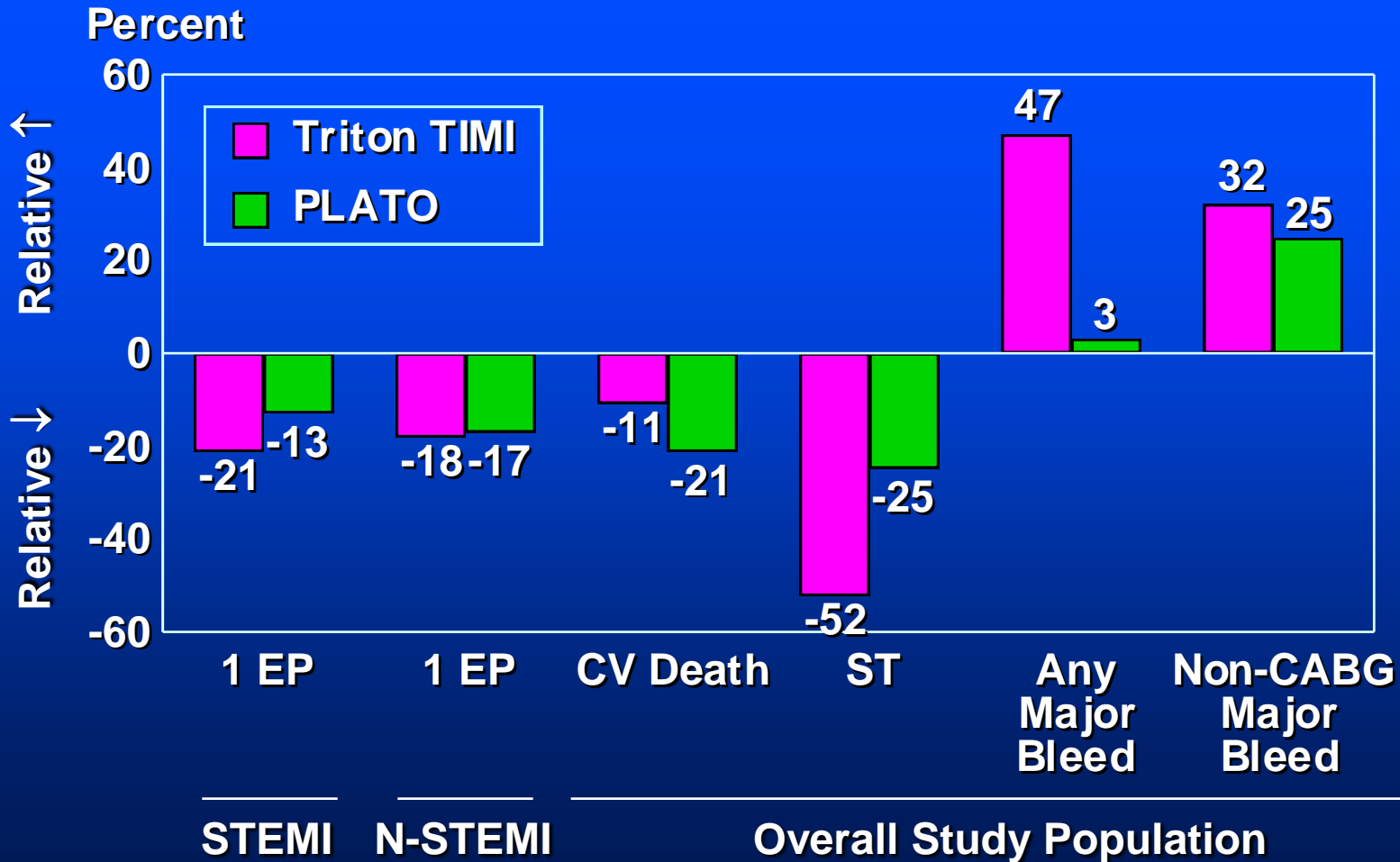
# Clopidogrel vs New P2Y<sub>12</sub> Inhibitors in ACS Patients Undergoing PCI

Meta-Analysis 5 Studies: 42,198 pts



JUMBO  
TRITON  
PLATO  
CHAMPION  
CH-PLATFORM

# Clopidogrel Compared to Prasugrel/Ticagrelor in PCI



# 2011 ACCF/AHA/SCAI Guideline for PCI

## Oral Antiplatelet Therapy

Opciones para dosis de carga de inhibidores P2Y<sub>12</sub> en pacientes que reciben stents incluyen:

I    IIa    IIb    III



a. Clopidogrel 600 mg (ACS y non-ACS ).

b. Prasugrel 60 mg (ACS ).

c. Ticagrelor 180 mg (ACS ).

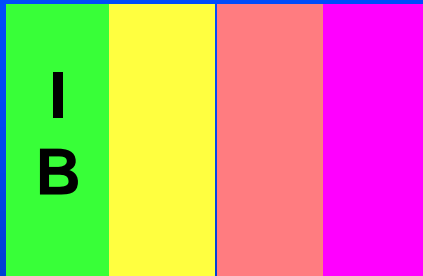
I    IIa    IIb    III



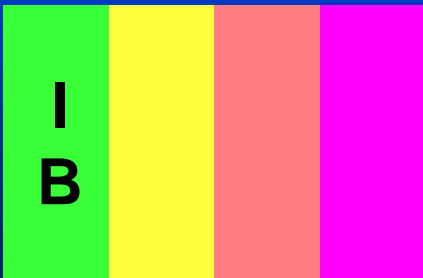
Prasugrel esta contraindicado en pacientes con antecedente de AVE o AIT

# ESC 2011 NSTE-ACS Guidelines

## Oral antiplatelet agents



- **Ticagrelor** se recomienda para pacientes de mediano-alto riesgo, incluso aquellos pre-tratados con Clopidogrel

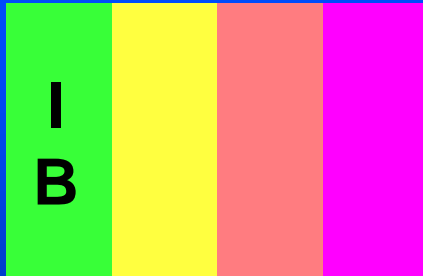


- **Prasugrel** en pacientes que no han recibido Clopidogrel (especialmente diabeticos) que van a PCI, a menos que haya riesgo de sangramiento mayor.



# ESC 2011 STE-ACS Guidelines

## Oral antiplatelet agents



- Clopidogrel 600mg para PCI en pacientes **que no pueden tomar** Ticagrelor o Prasugrel.



- Clopidogrel 150mg/dia por 7 dias puede considerarse en pacientes con riesgo bajo de sangrado.

# TRILOGY ACS



# ESC congress news

**MONDAY 27 AUGUST**

M U N I C H 2 0 1 2

**Neutral results from first prasugrel-clopidogrel test in medically managed ACS**



# Conclusiones : nuevos inhibidores de P2Y<sub>12</sub>

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- ↑ Inhibición plaquetaria, mas intensa
- ↓ Inhibición plaquetaria mas rápida
- ↓ Reduce eventos isquémicos
- ↓ Reducen trombosis de stent
- ↑ Aumenta eventos de sangrado

# Nuevos inhibidores P2Y<sub>12</sub> : limitantes

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- **Mayores de 75 años, < 60 kg , AVE, riesgo de sangrado (Prasugrel)**
- **Disnea, bradicardia (Ticagrelor)**
- **Costo \$\$\$**
- **Adherencia al tratamiento: costo, efectos laterales, dosificación 2 x dia.**

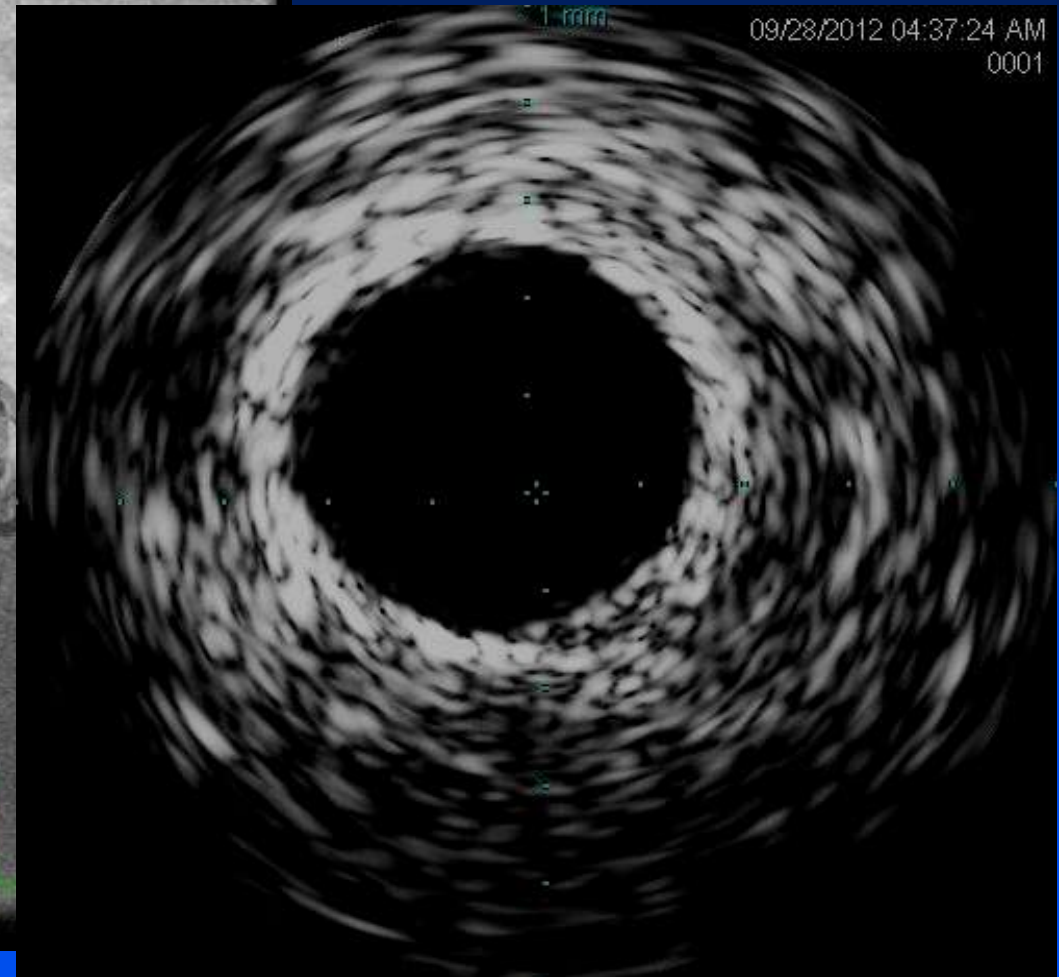
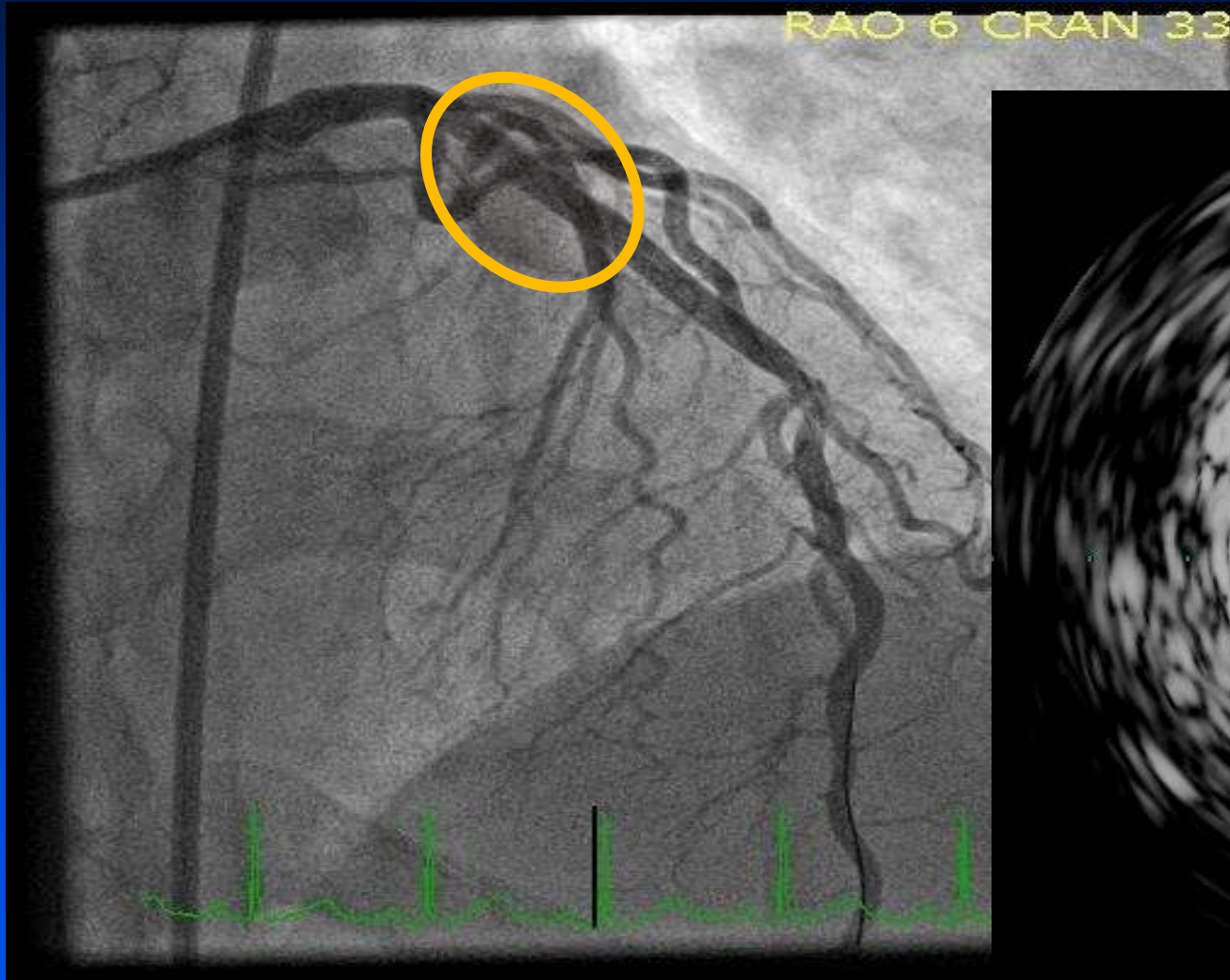
# Nuevos Antiplaquetarios

## Uso “selectivo”

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- Post trombosis de stent
- Pacientes a alto riesgo de trombosis de stent
- “Resistencia” a Clopidogrel ?
  - a) Polimorfismo genético
  - b) Test de agregación plaquetaria
- Angioplastia Primaria?
- Manejo peri-operatorio en pacientes con stents medicados.

# Caso clínico



# Caso clínico

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- Pre – stent

Aspirina, Clopidogrel 600mg, heparina

- Durante PCI

Bivaluridina, Inhibidor GPIIb/IIa (-).

- Post – stent

Aspirina 81 mg, Clopidogrel 75 mg

A photograph of two frigatebirds on a nest. The male bird on the left has a large, inflated red gular sac and a black head. The female bird on the right has a black head and a white breast. They are sitting on a nest made of sticks and twigs, surrounded by green foliage. The background is a blurred, golden-brown field.

**Muchas gracias**

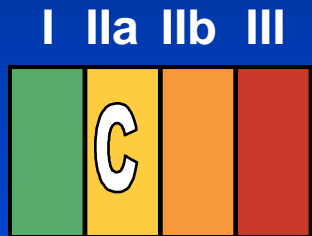


# Duracion de tratamiento antiplaquetario

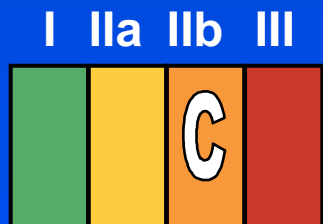
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**Aspirina debe continuarse en forma indefinida**



**Continuar Clopidogrel, Prasugrel or Ticagrelor mas de 12 meses puede considerarse en pacientes con stents medicados.**



**Continuar doble terapia antiplaquetaria (DAPT) puede considerarse en pacientes con stents medicados.**

# Oral Antiplatelet Therapy (cont.)



The duration of P2Y<sub>12</sub> inhibitor therapy after stent implantation should generally be as follows:

- a)** In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y<sub>12</sub> inhibitor therapy should be given for at least 12 months. Options include: 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).

# Postprocedural Antiplatelet Therapy

After PCI, aspirin should be continued indefinitely.

The duration of P2Y<sub>12</sub> inhibitor therapy after stent implantation should generally be as follows:

- a) In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y<sub>12</sub> 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).



**NEW**

**Angiomax<sup>®</sup>**  
(bivalirudin)

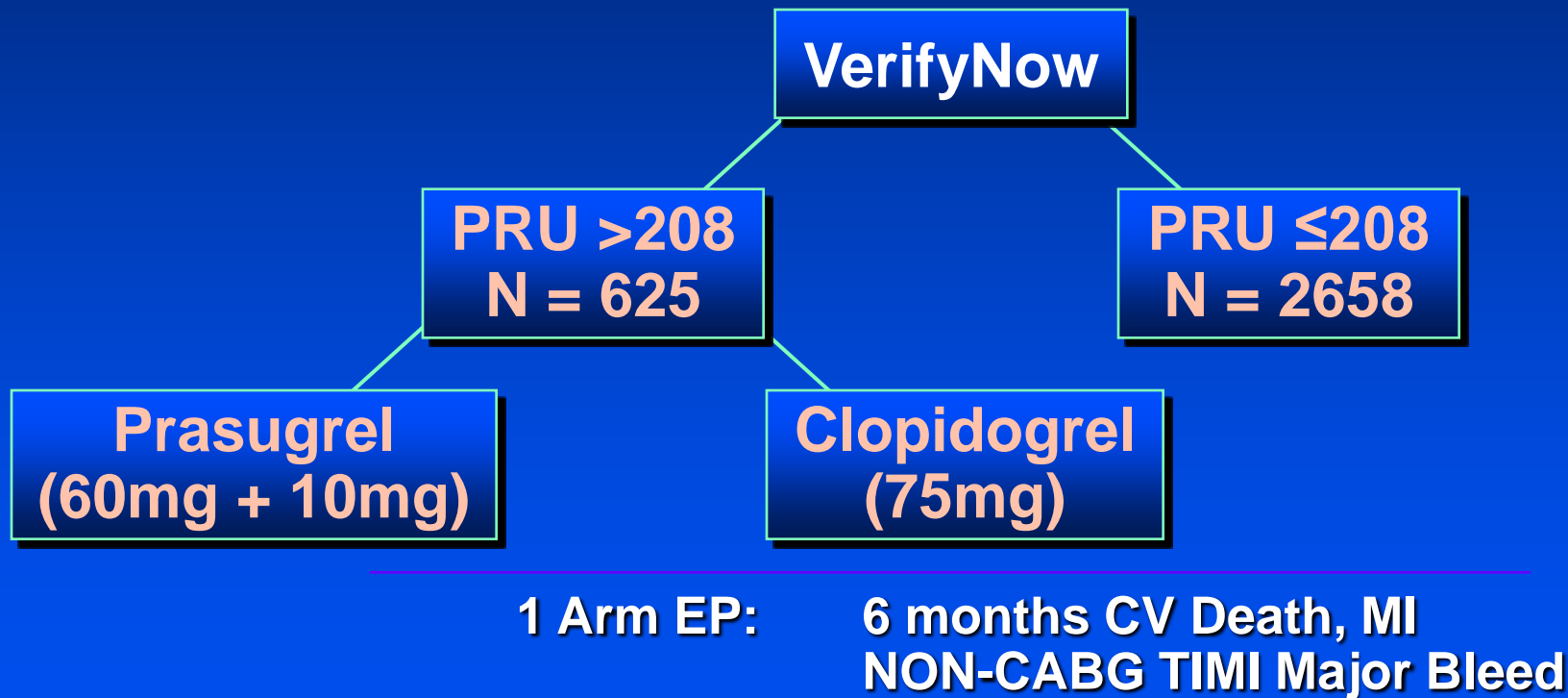
FOR INJECTION

# TRIGGER-PCI

## Prasugrel vs Clopidogrel in HTPR

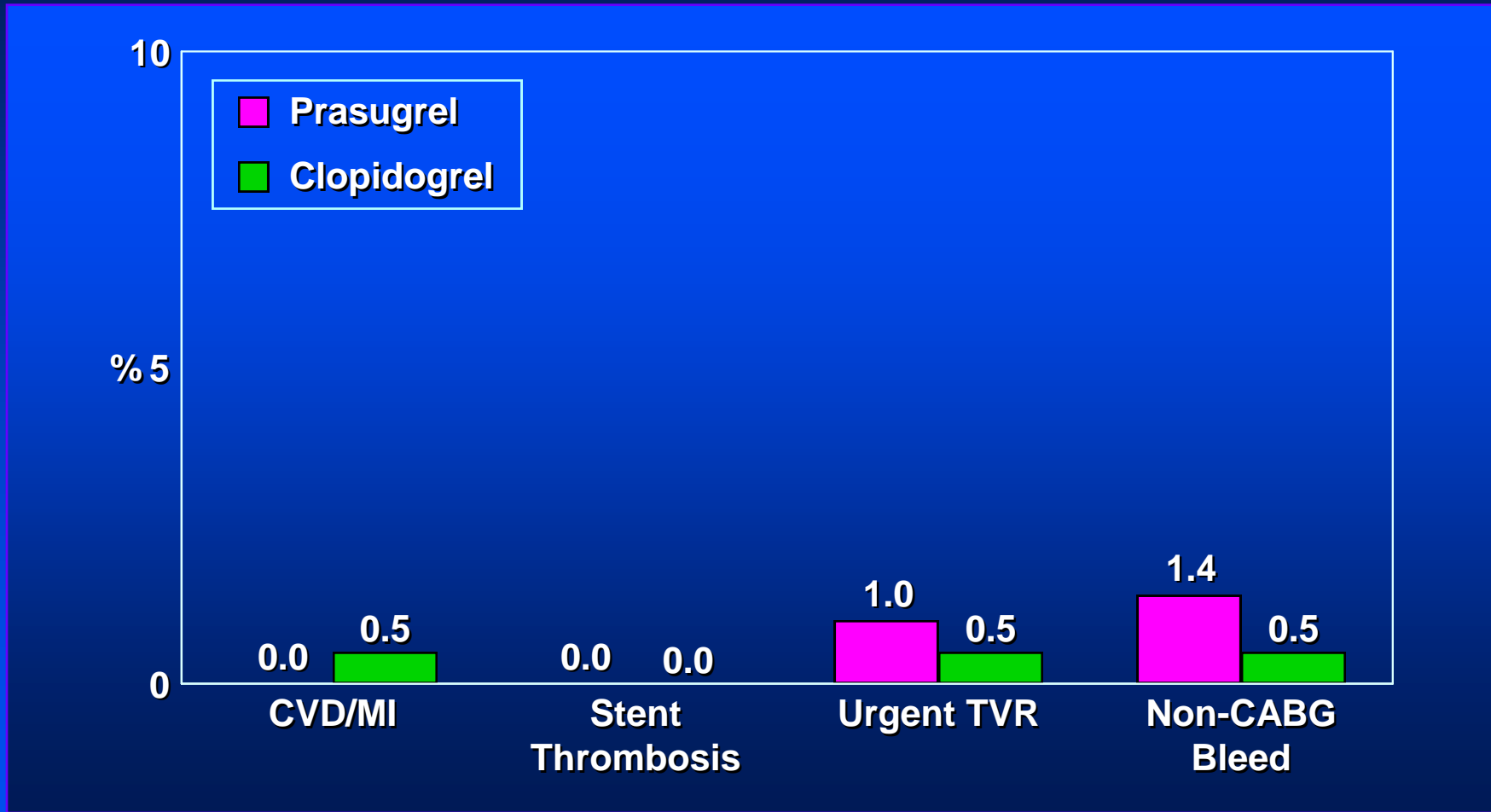
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3492 Pts  
Successful Elective DES  
Clopidogrel 600 mg

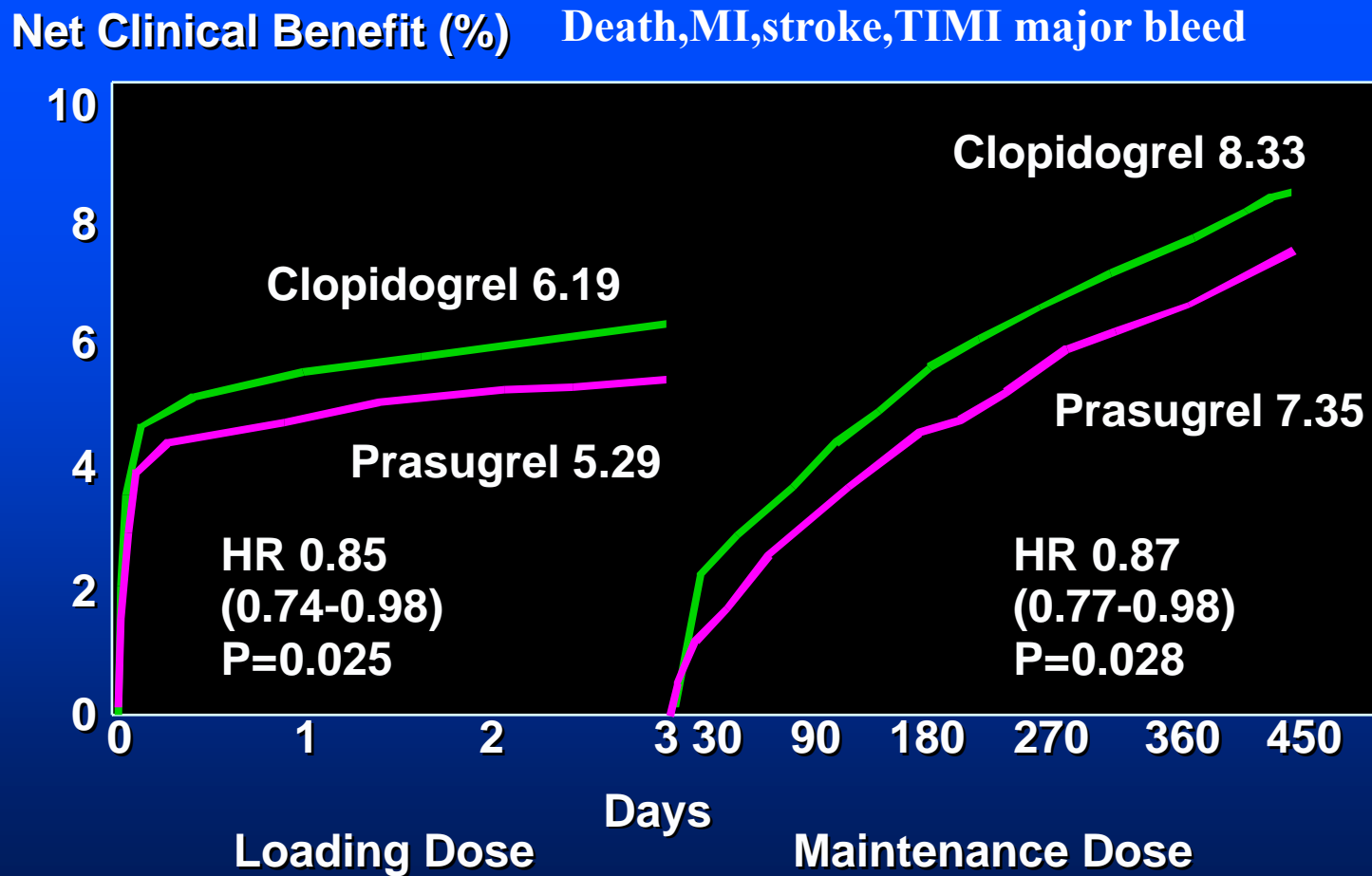


# TRIGGER PCI

## 6-Month Events

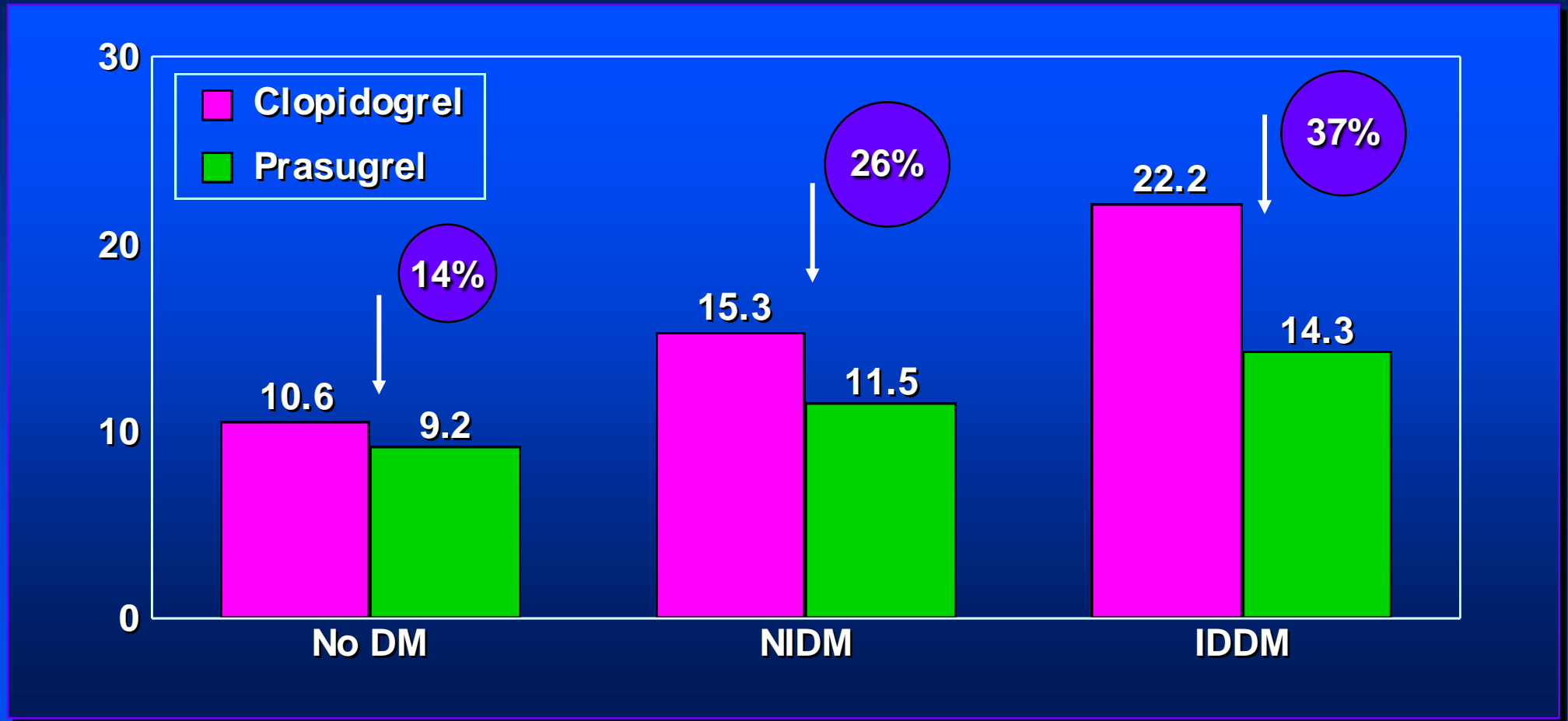


# TRITON-TIMI 38



# TRITON-TIMI 38: Diabetic Status

## CV Death, MI, Stroke

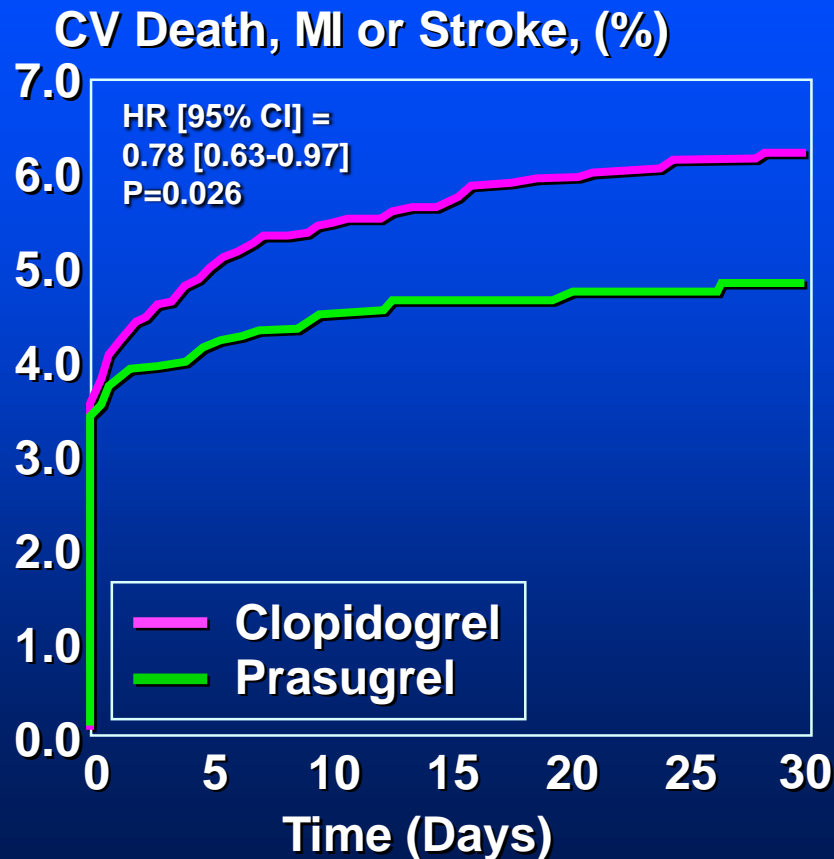




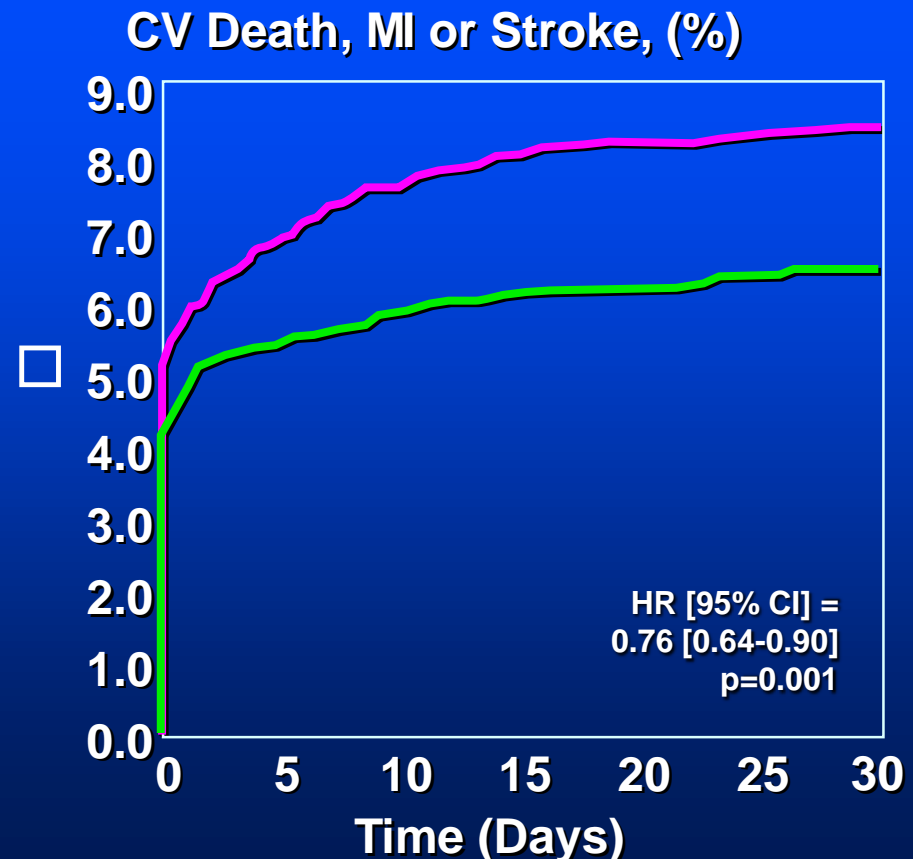
# TRITON TIMI-38

## Clopidogrel vs Prasugrel ± GP Inhibitors

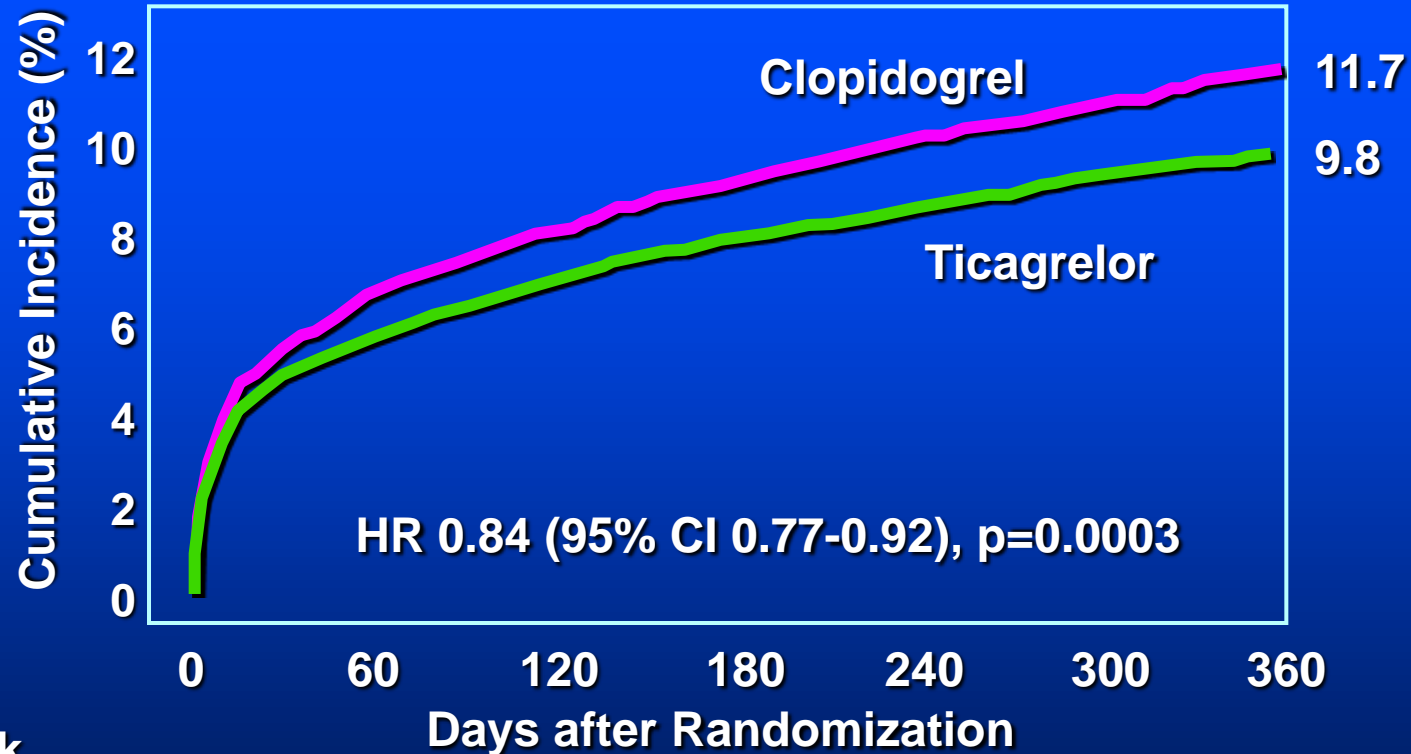
### No GP IIb/IIIa Inhibitor Used



### GP IIb/IIIa Inhibitor Used

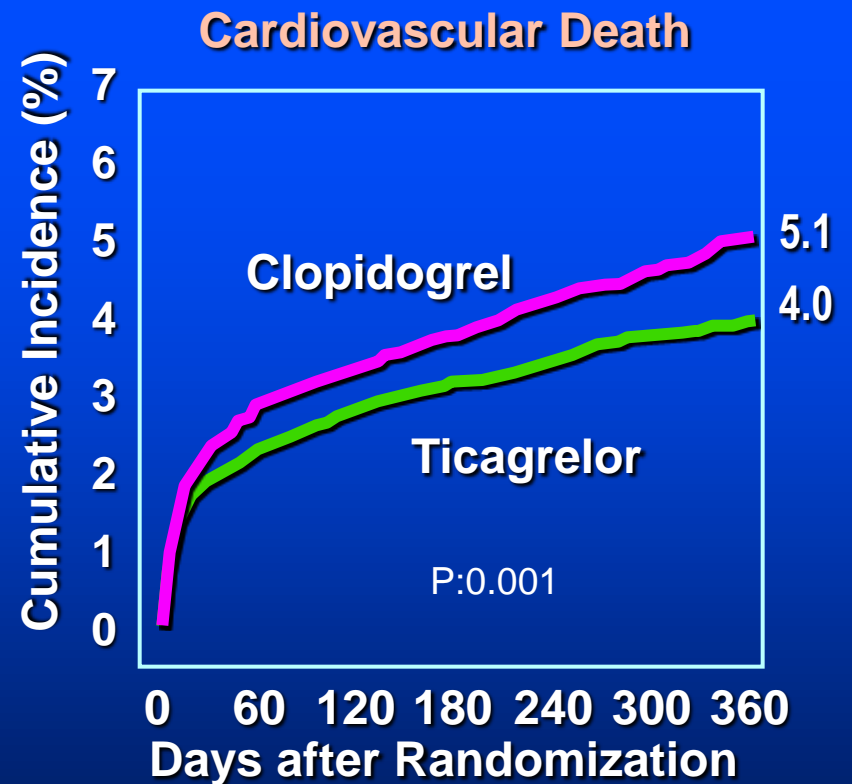
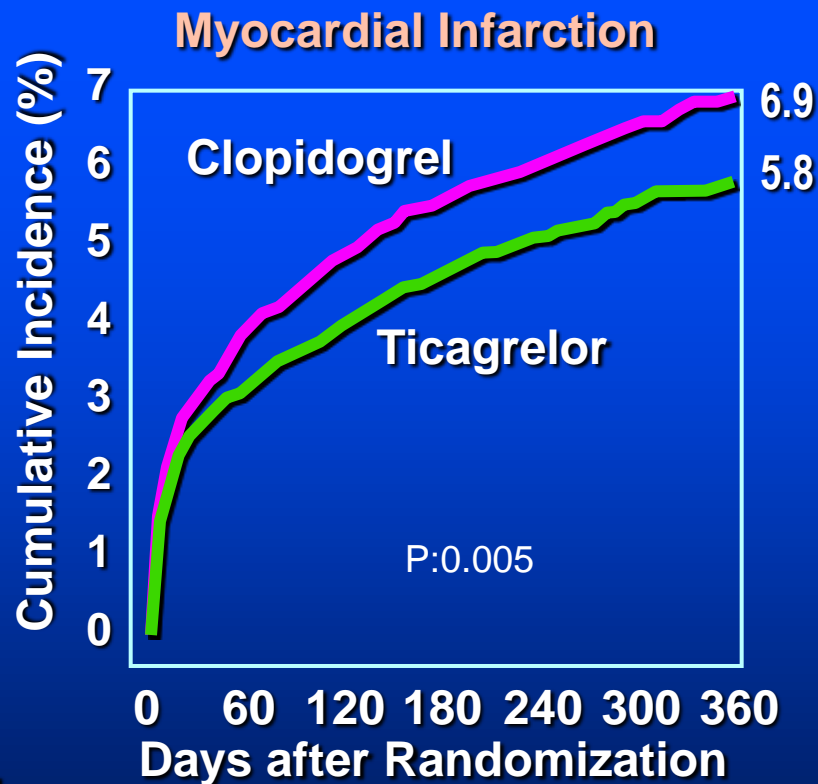


# PLATO: Primary Efficacy Event (CV Death, MI or Stroke)



No. at risk	Days after Randomization						
Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6743	5096	4047

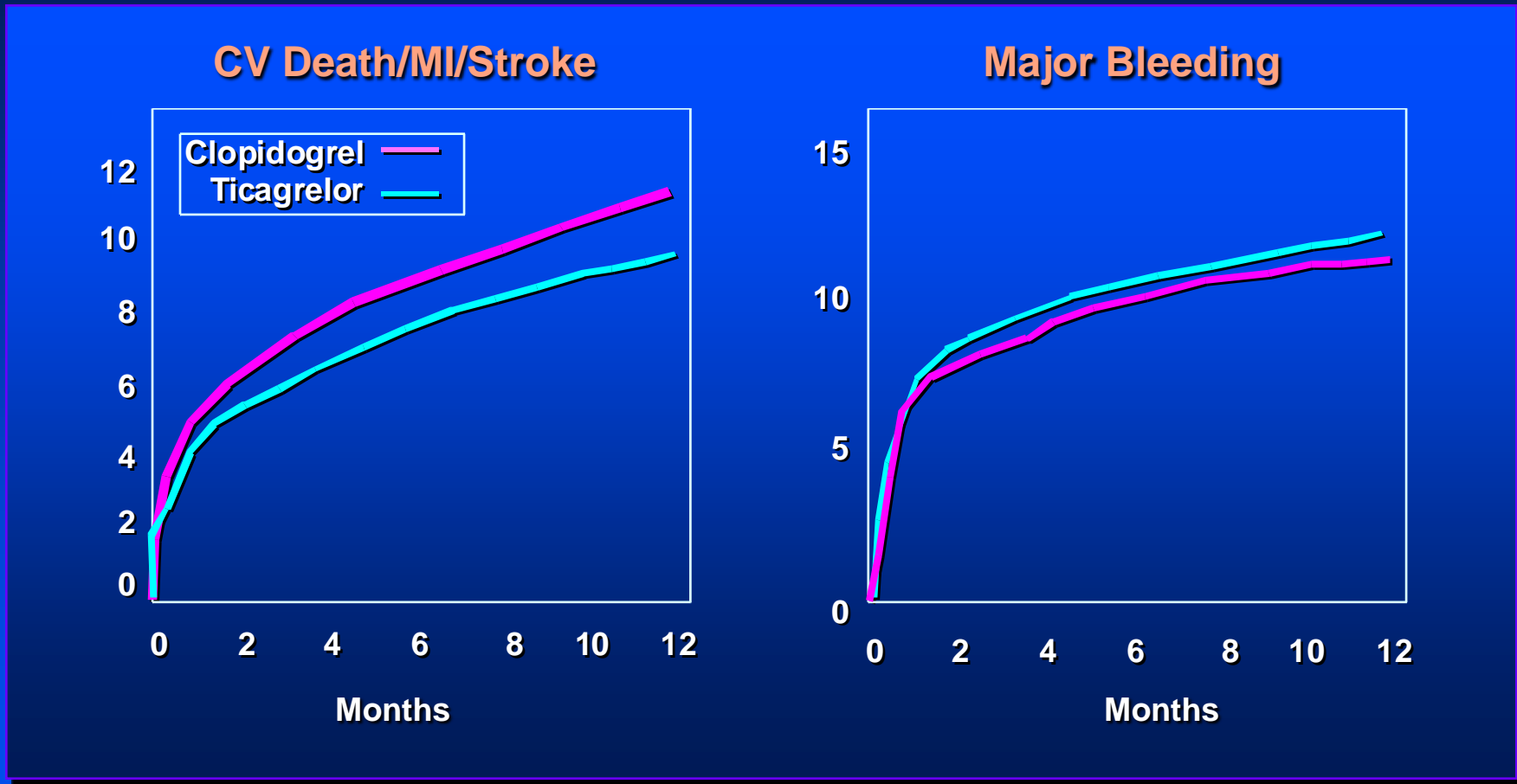
# PLATO: Secondary Efficacy Endpoints



No. at risk	0	60	120	180	240	300	360
Ticagrelor	9333	8678	8520	8279	6796	5210	4191
Clopidogrel	9291	8560	8405	8177	6703	5136	4109

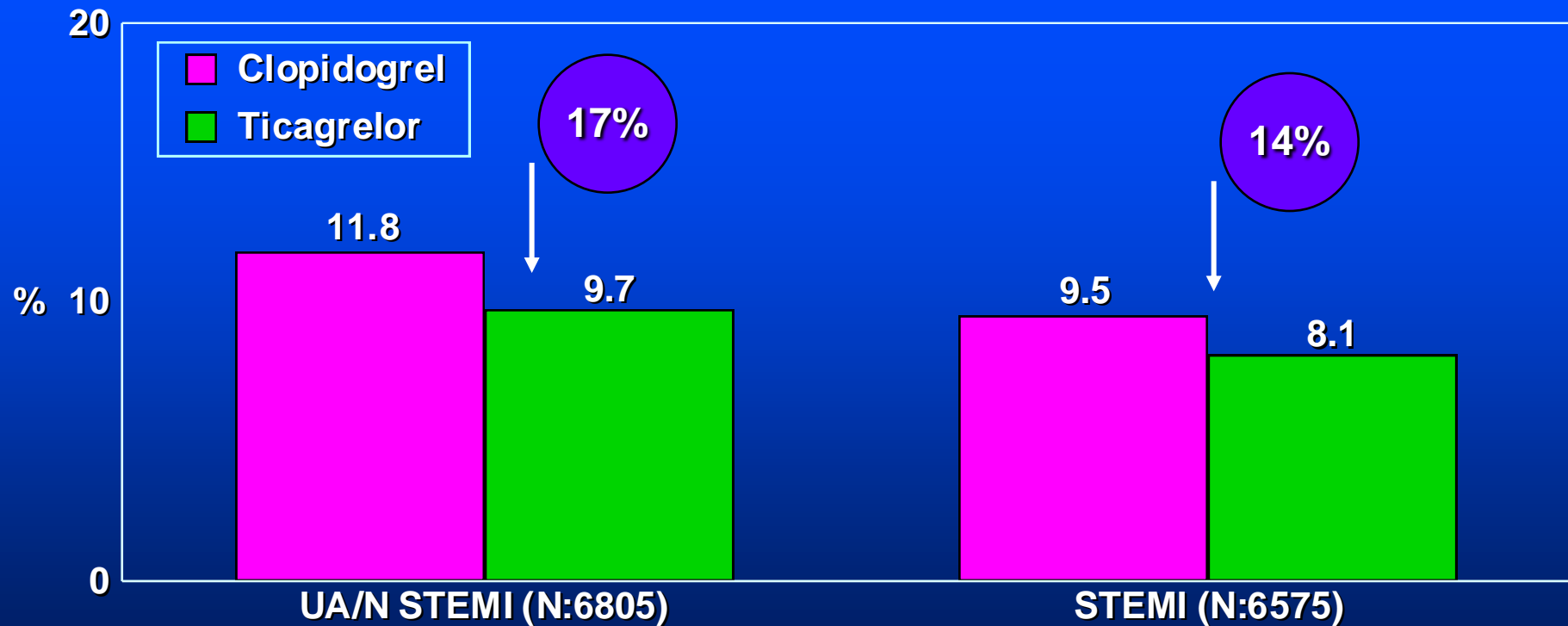
No. at risk	0	60	120	180	240	300	360
Ticagrelor	9333	8294	8822	8626	7119	5482	4419
Clopidogrel	9291	8865	8780	8589	7079	5441	4364

# PLATO: Efficacy + Safety



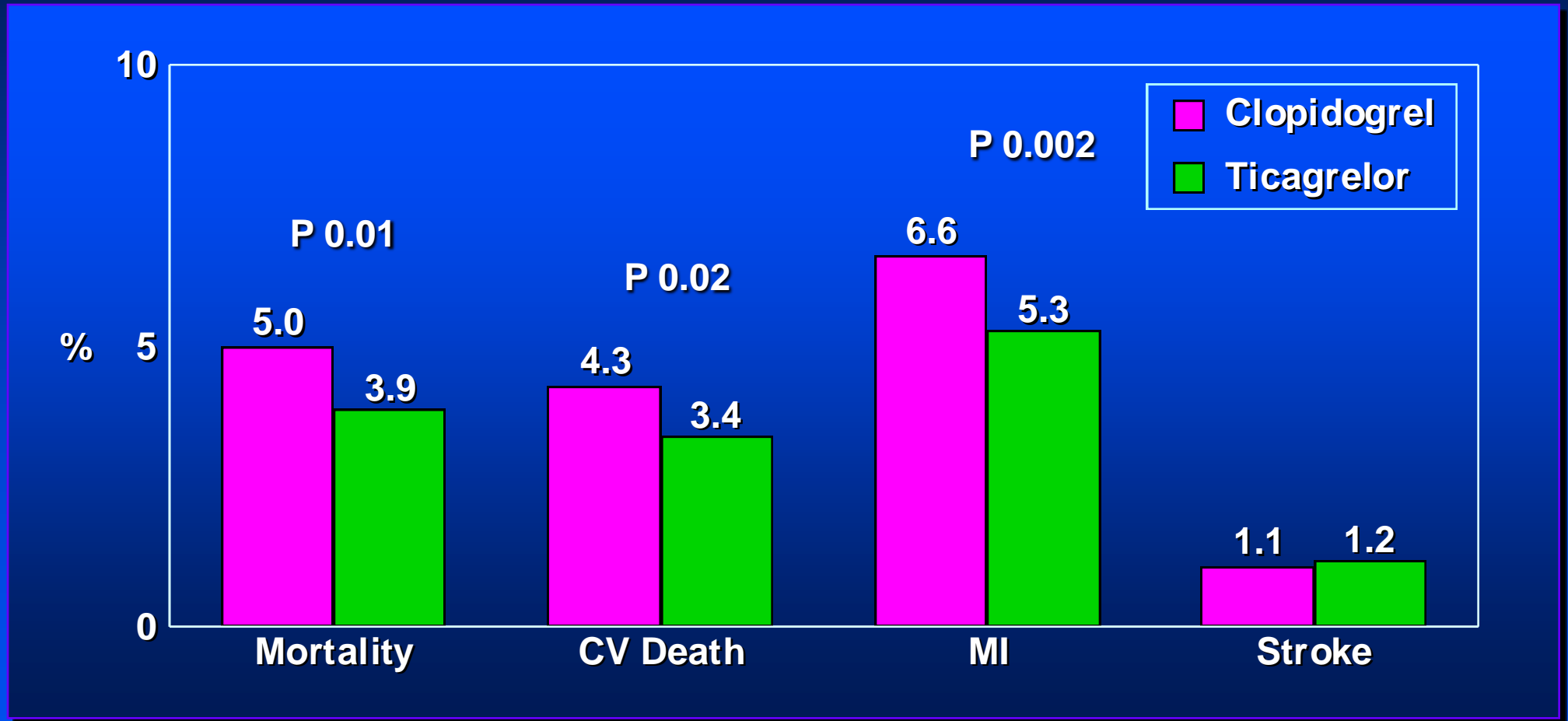
# PLATO: PCI Patients

## CV Death, MI, Stroke

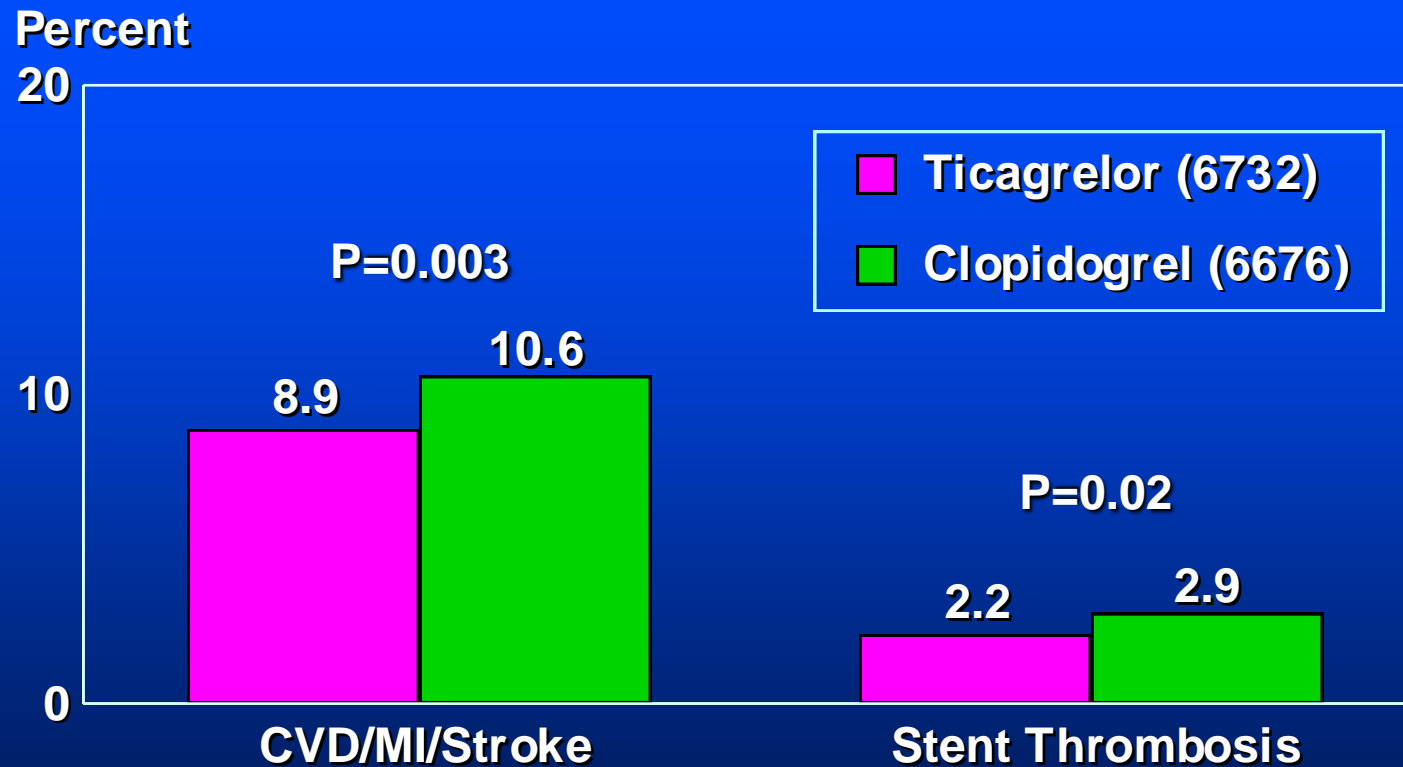


# PLATO: PCI Patients

## 1-Year Events

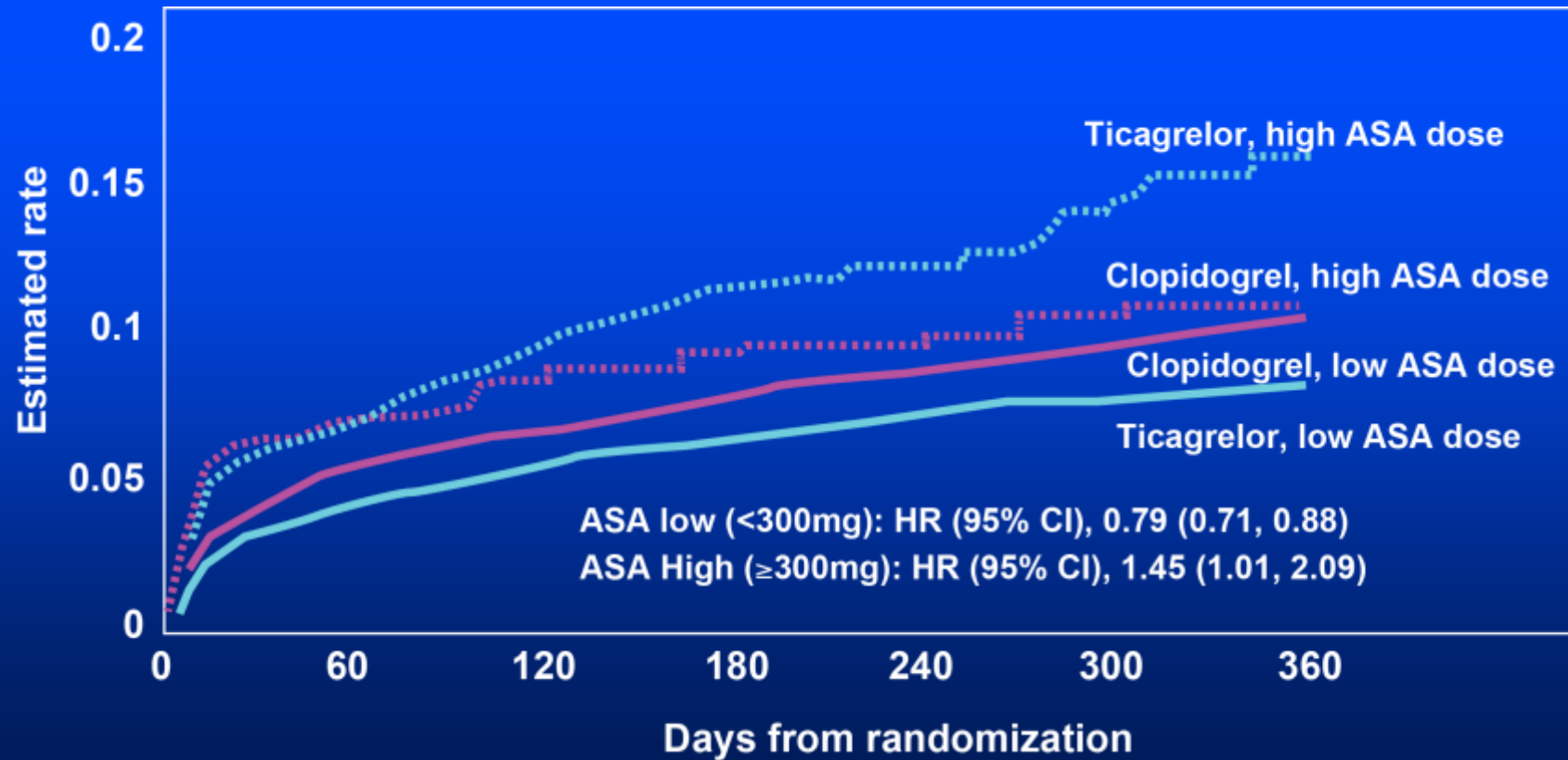


# PLATO: Planned Invasive Group



# PLATO: Aspirin Dose

## CV Death, MI, Stroke

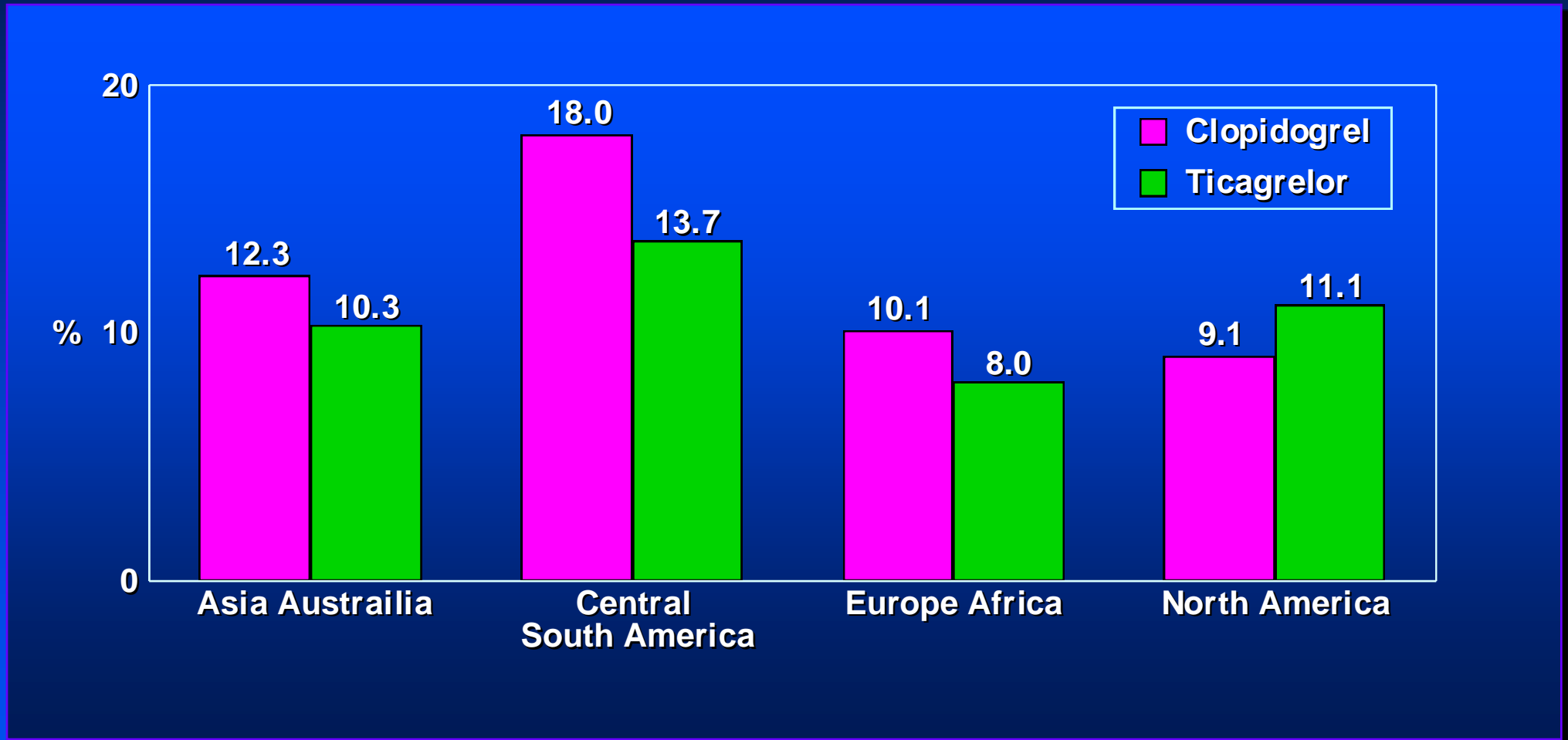




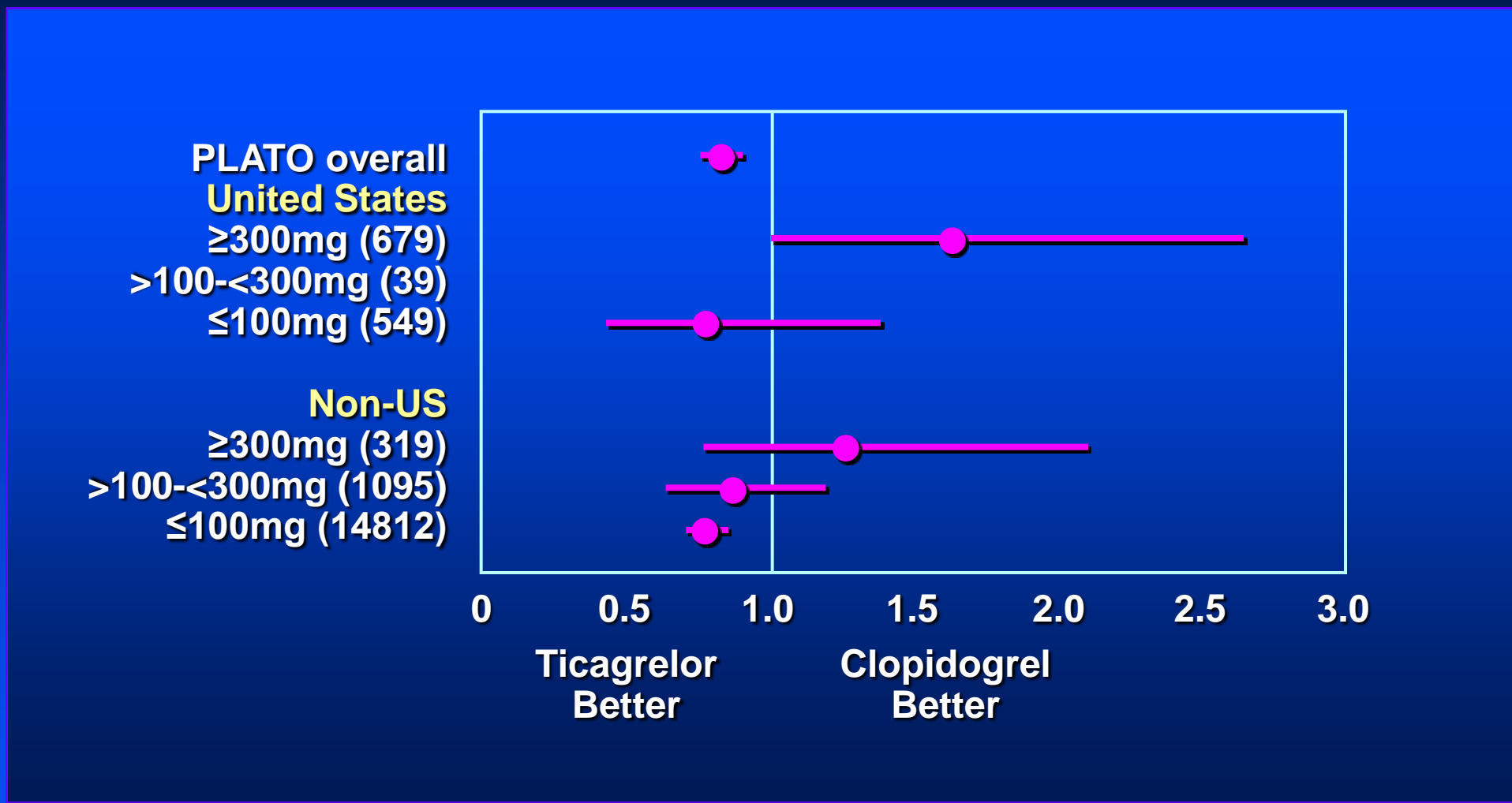
# PLATO: PCI Patients

## Geographic region

CV Death, MI, Stroke

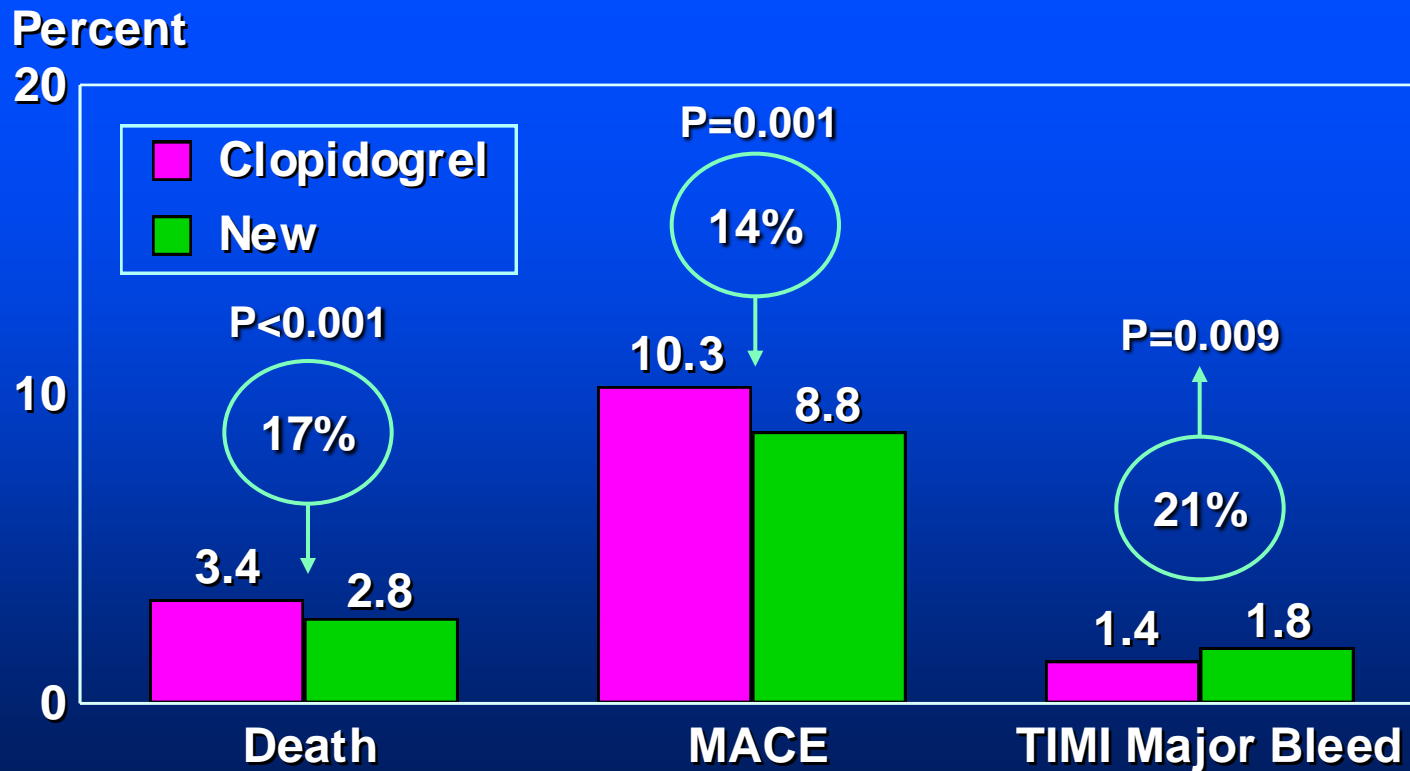


# PLATO: Outcomes by Region & Aspirin Dose



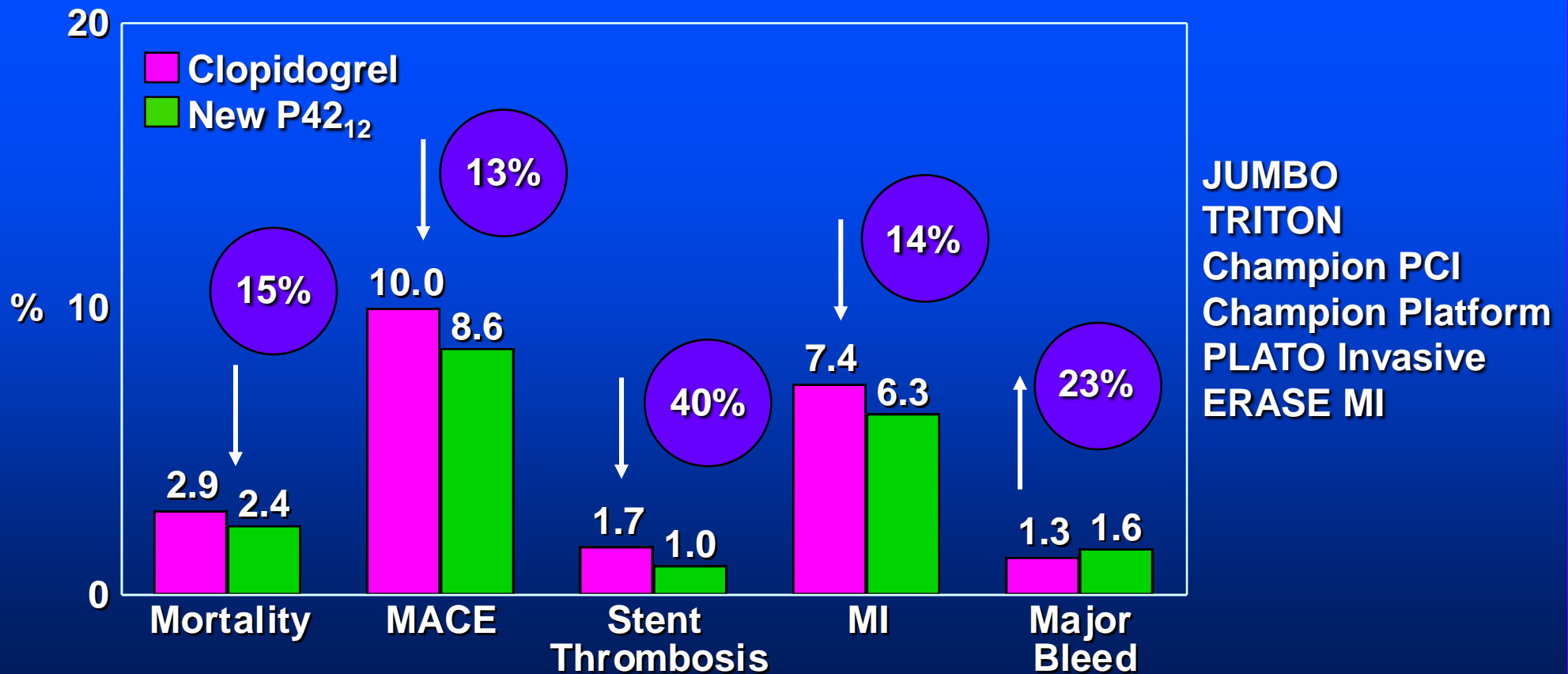
# Clopidogrel vs New P2Y<sub>12</sub> Inhibitors in ACS

Meta-Analysis 8 Studies: 48,599 pts



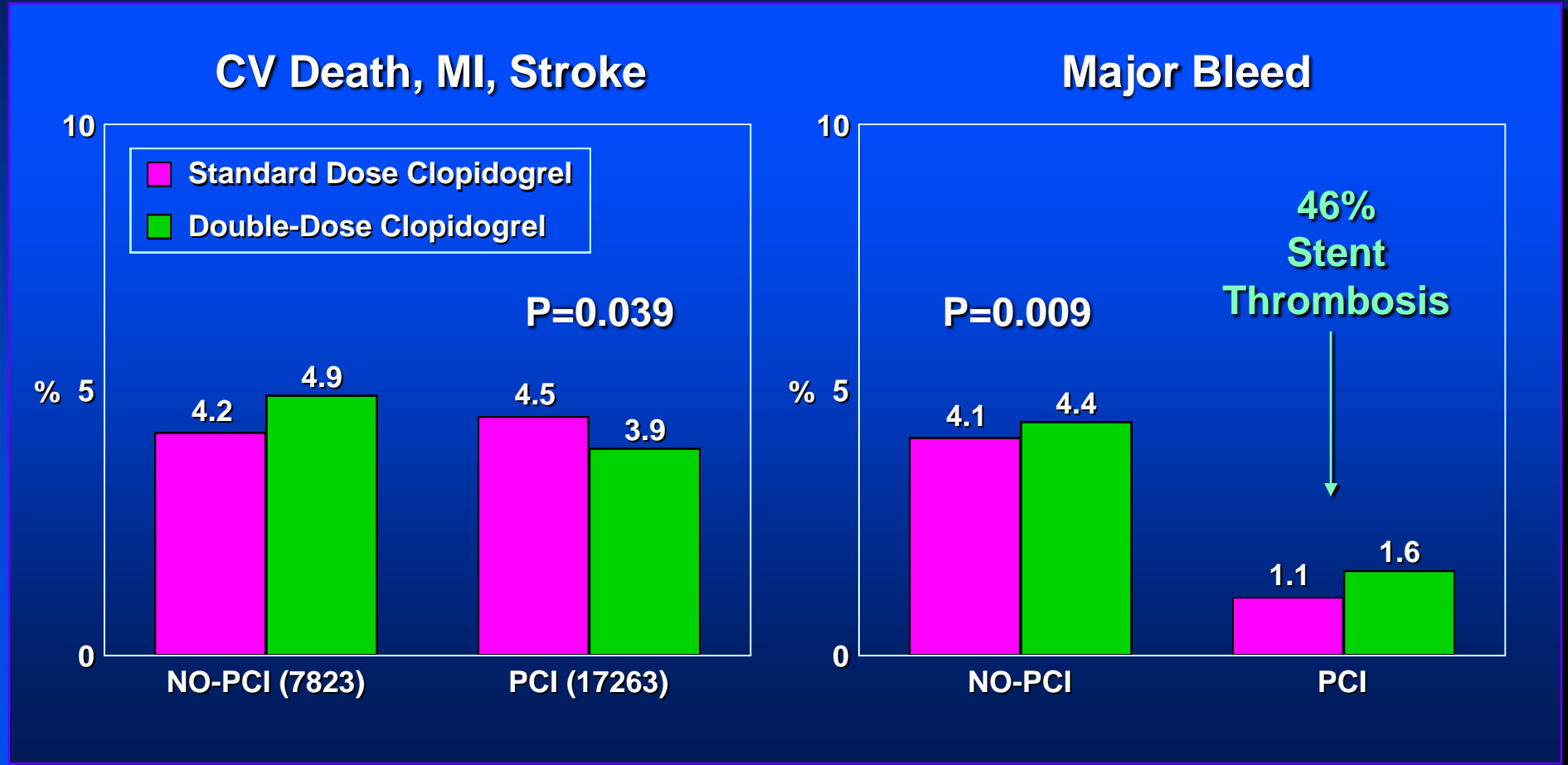
# Meta-Analysis: Clopidogrel vs New P2Y<sub>12</sub> Inhibitors all PCI patients

6 Studies - 42,198 Patients



# CURRENT – OASIS 7

## 30-Day Events

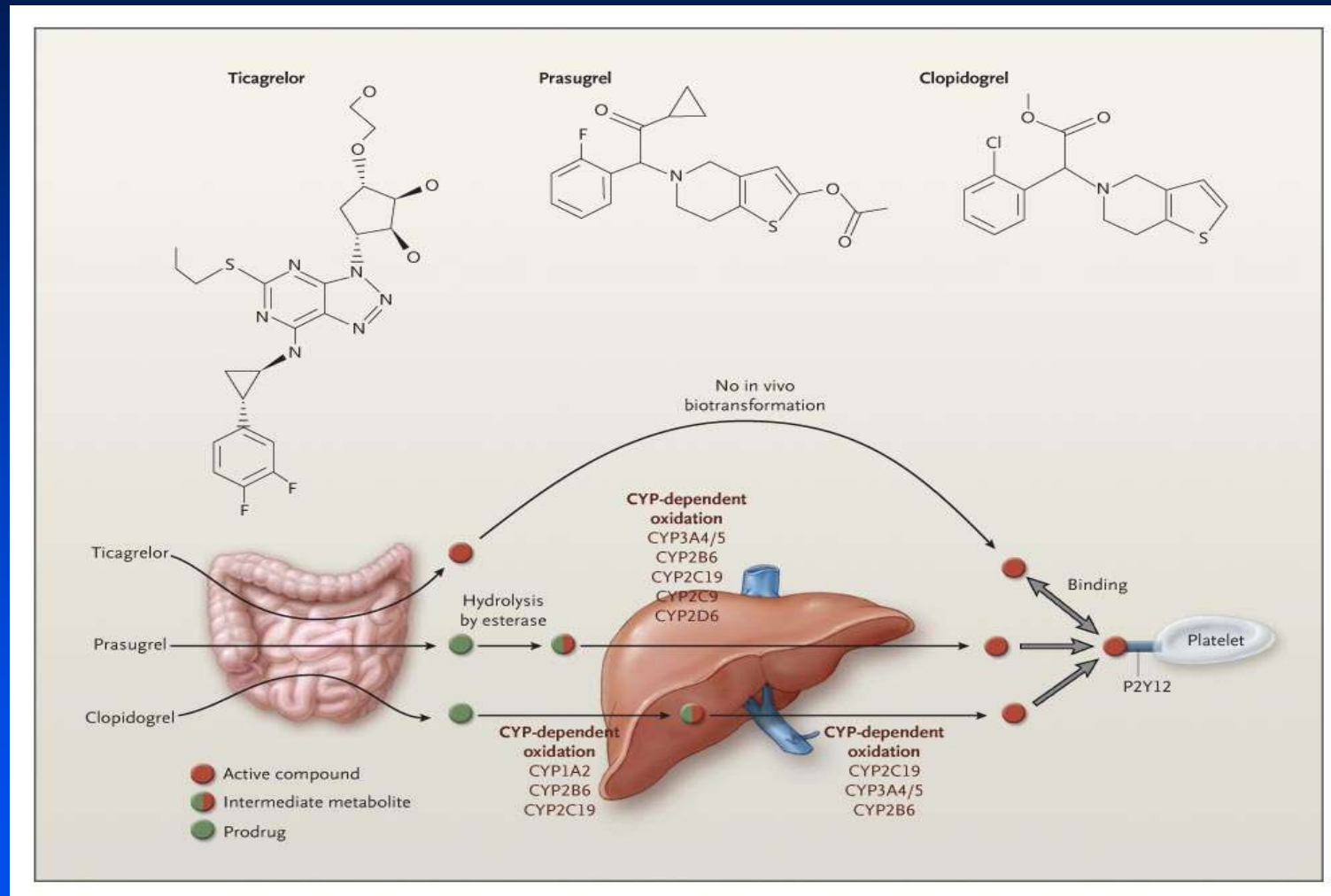


# Heparina+GPI vs Bivalirudin

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- **REPLACE-2:** PCI electiva o urgente
- **ACUITY :** SCA
- **HORIZONS-AMI:** STEMI

# Biotransformacion de Clopidogrel, Prasugrel y Ticagrelor.



Schömig A. N Engl J Med 2009;361:1108-1111.

# TRITON- TIMI 38 : eficacia analisis de subgrupos

