

Manejo Perioperatorio de los Antiplaquetarios



Nuevos antiagregantes en SCA. ¿Cómo gestionar el cambio? Madrid, 15 de junio

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CONFLICTOS DE INTERÉS

- Honorarios por conferencias:
 - ❖ Eli Lilly Co; Daiichi Sankyo, Inc.; AstraZeneca; Grifols
- Becas:
 - ❖ Sociedad Española de Cardiología

ÍNDICE

- Recomendaciones generales
- Nuevos agentes
- ¿Siempre hay que suspender el tto antiagregante el tiempo recomendado?

RECOMENDACIONES GENERALES

DURATION OF DAPT IN STENTED PATIENTS

➤ ESC guidelines:

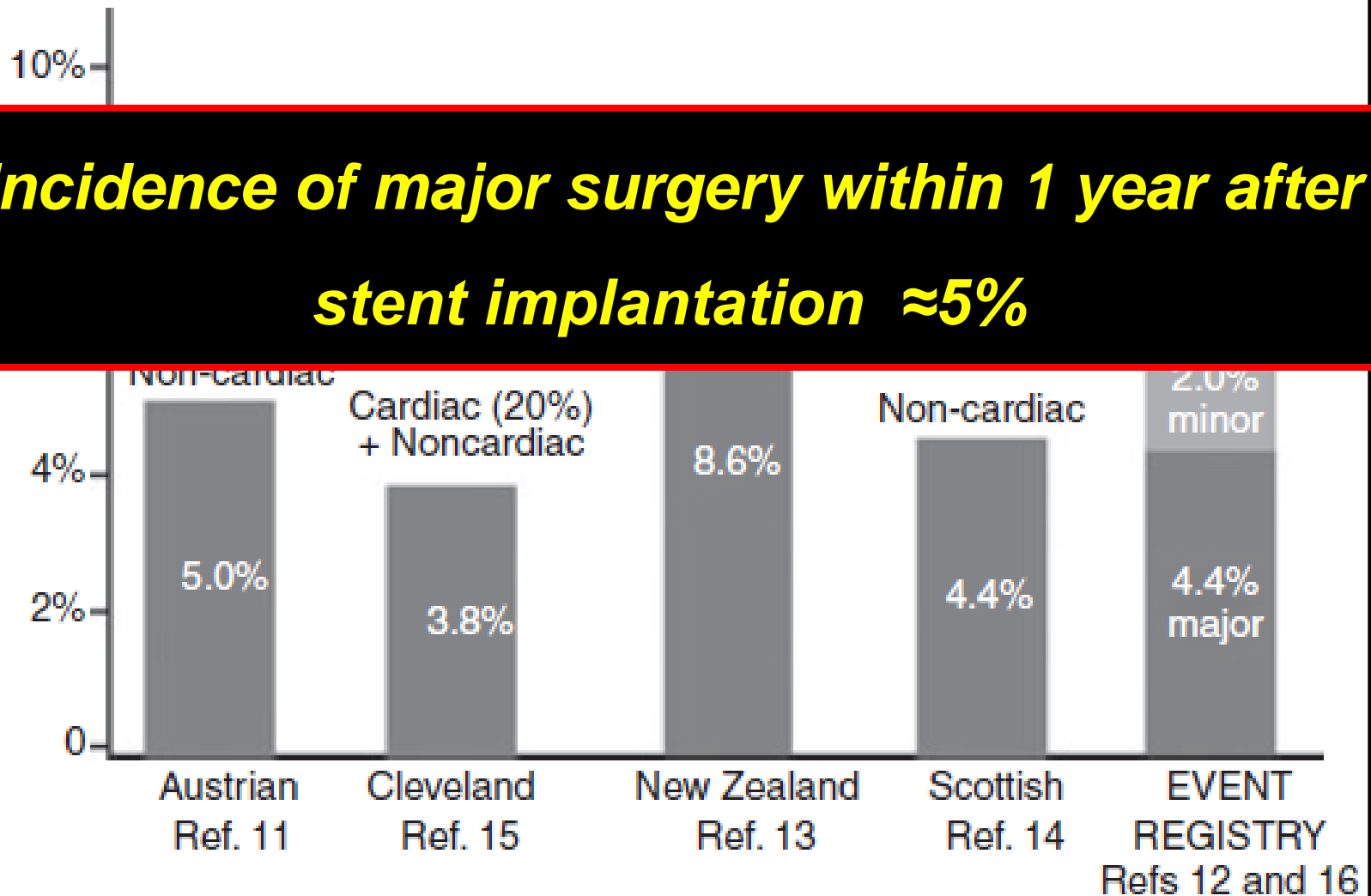
- ❖ ACS: 1 year (irrespective of type of stent)
- ❖ Stable patient – BMS: 1 month
- ❖ DES: 6-12 months

➤ ACC/AHA guidelines:

- ❖ ACS: At least 12 months
- ❖ Non-ACS BMS: 1 month and ideally up to 12 months
- ❖ Non-ACS DES: at least 12 months (if not high risk of bleeding)

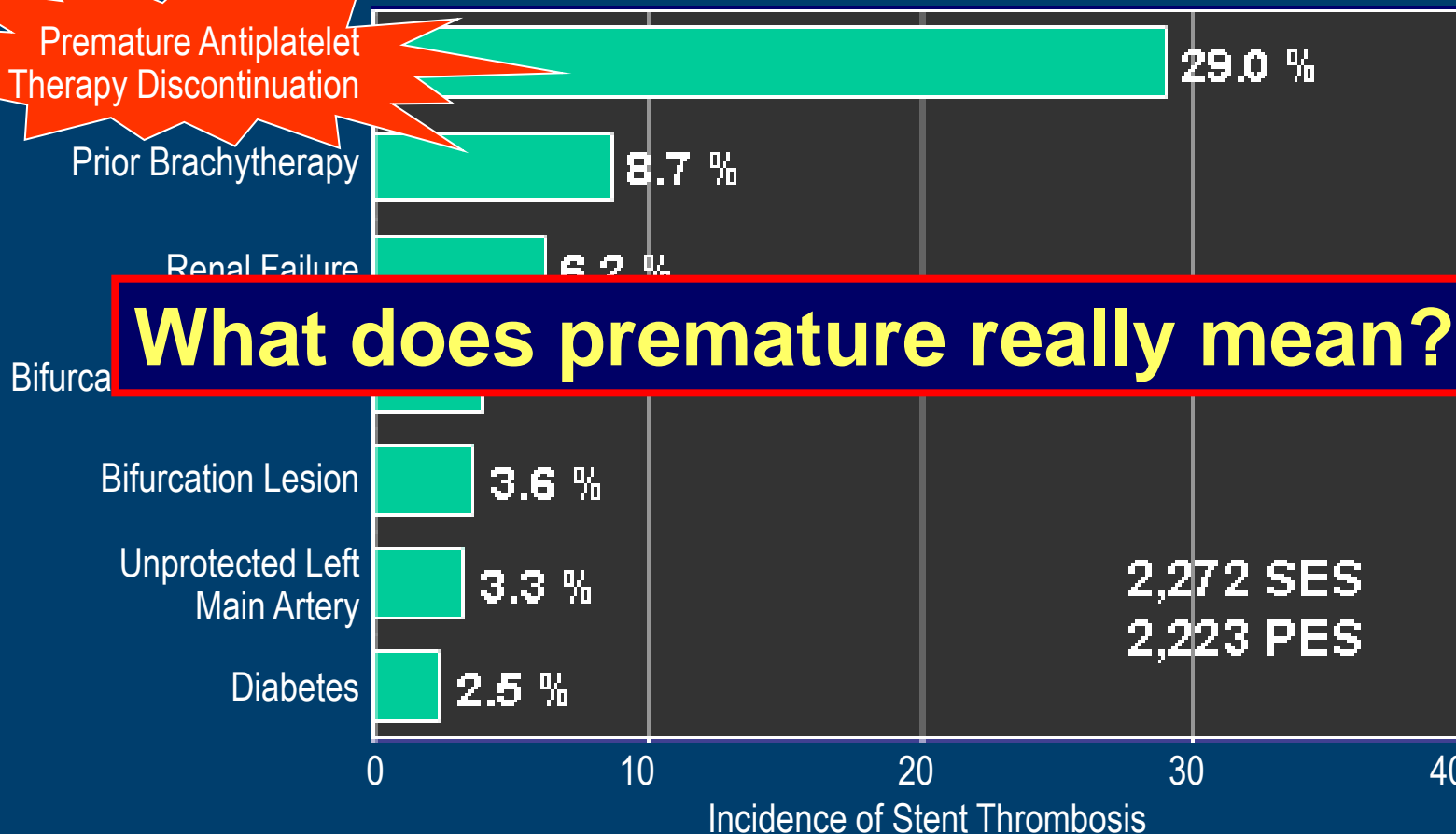
MAJOR SURGERY AFTER PCI

Incidence of major surgery within 1 year after stent implantation $\approx 5\%$



INCIDENCE, PREDICTORS, AND OUTCOME OF THROMBOSIS AFTER DES

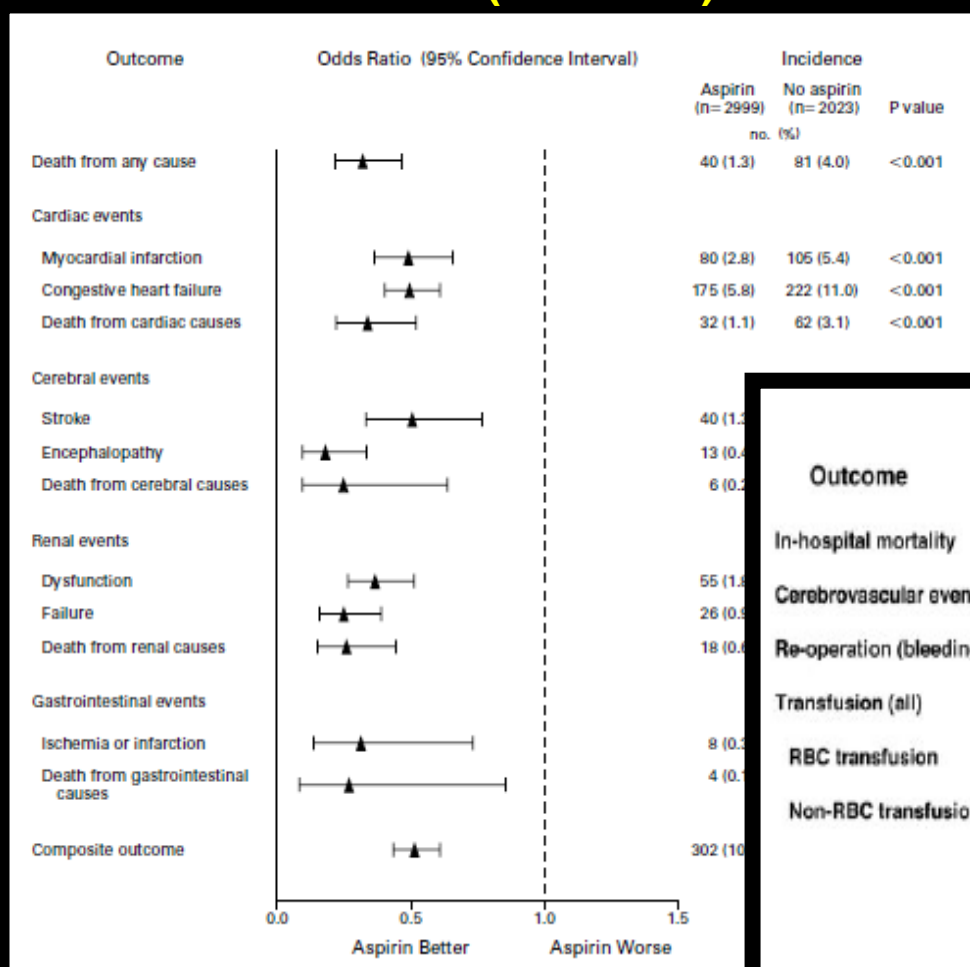
Univariate Predictors of Cumulative Stent Thrombosis



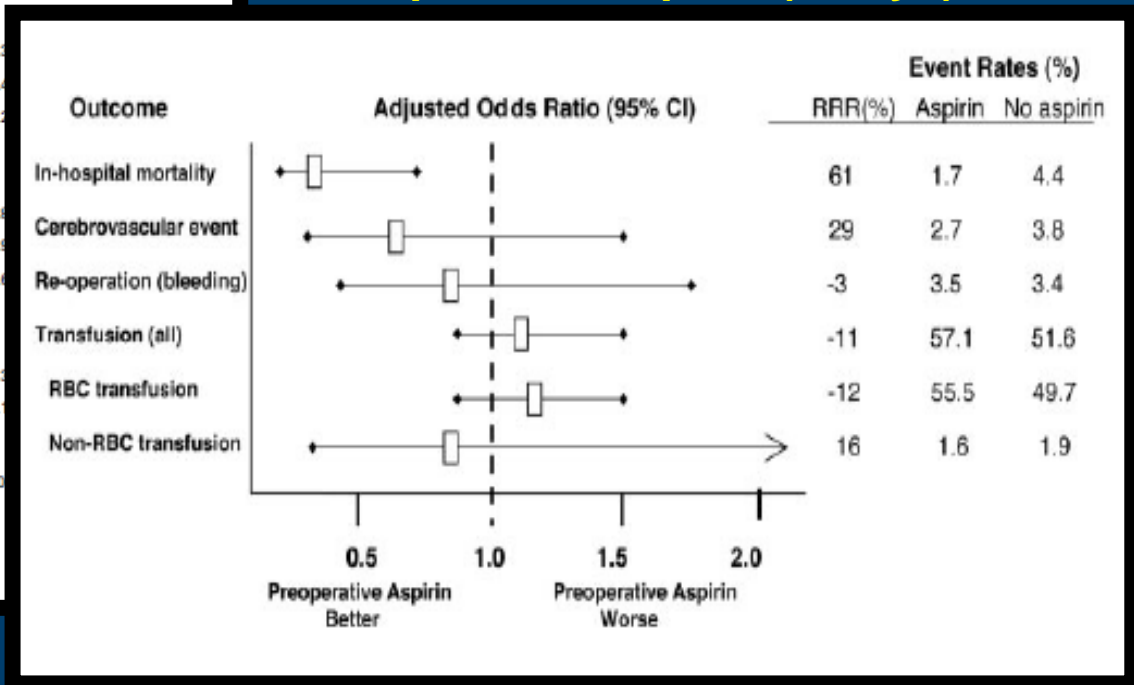
Hazard Ratio for ATP Discontinuation = 89

ASPIRIN AND CABG

After CABG (48 hours)



Preoperative aspirin (5 days)



PERIOPERATIVE DISCONTINUATION OF THIENOPYRIDINES AND MACE

Reference	Population	Time from PCI to NCS	Design	In-hospital results	Thienopyridine
Kaluza et al. ^{13a}	40 patients with NCS after BMS	<6 weeks/mean 13 days	Case series	20% mortality	7/8 not on ticlopidine died
Wilson et al. ^{14b}	207 patients with NCS after BMS	<2 months	Case series	4% MI or stent thrombosis	14% received thienopyridine less than 10 days before NCS
Sharma et al. ^{15a}	47 patients with NCS after BMS	<90 days	Case series	18.4% mortality	6/7 not on ticlopidine died
Reddy et al. ¹⁶	56 patients with NCS after BMS	<15 days	Case series	14% MACE	2/5 stent thromboses not taking clopidogrel
Compton et al. ¹⁸	38 patients with NCS after DES	Median 260 days	Case series	0% MACE	41% taking clopidogrel
Vicenzi et al. ²⁰	103 patients with NCS after stenting	<1 year	Case series	4.9% mortality	Clopidogrel only 'briefly' interrupted
Leibowitz et al. ²⁴	216 patients with NCS after POBA (56%) or BMS (44%)	<6 months/mean 33 days	Case series	12% mortality	Not reported
Schouten et al. ¹⁷	192 patients with NCS after BMS (48%) or DES (52%)	<2 years	Case series	2.6% MACE	5/5 patients with MACE not on clopidogrel
Godet et al. ¹⁹	96 patients with NCS after DES	<3 years/mean 14 months	Case series	2.0% stent thrombosis	37% continued clopidogrel
Rabbitts et al. ²³	520 patients with NCS after DES	<2 years/median 203.5 days	Case series	5.4% MACE	9.1% MACE if continued clopidogrel
Rhee et al. ²¹	141 patients with NCS after DES	<12 months/mean 7.6 months	Case series	5.0% stent thrombosis	Patients with stent thrombosis off clopidogrel longer (12 vs. 51 days)
Assali et al. ²²	78 patients with NCS after DES	>6 months/mean 468 days	Case series	2.6% stent thrombosis, 7.7% death or MI	42% continued clopidogrel
Anwaruddin et al. ²⁵	481 patients with surgery after DES	Mean 1.1 years	Retrospective cohort with multivariable adjustment	2.0% stent thrombosis, 9.0% MACE	37% on clopidogrel, but no effect of discontinuation upon MACE

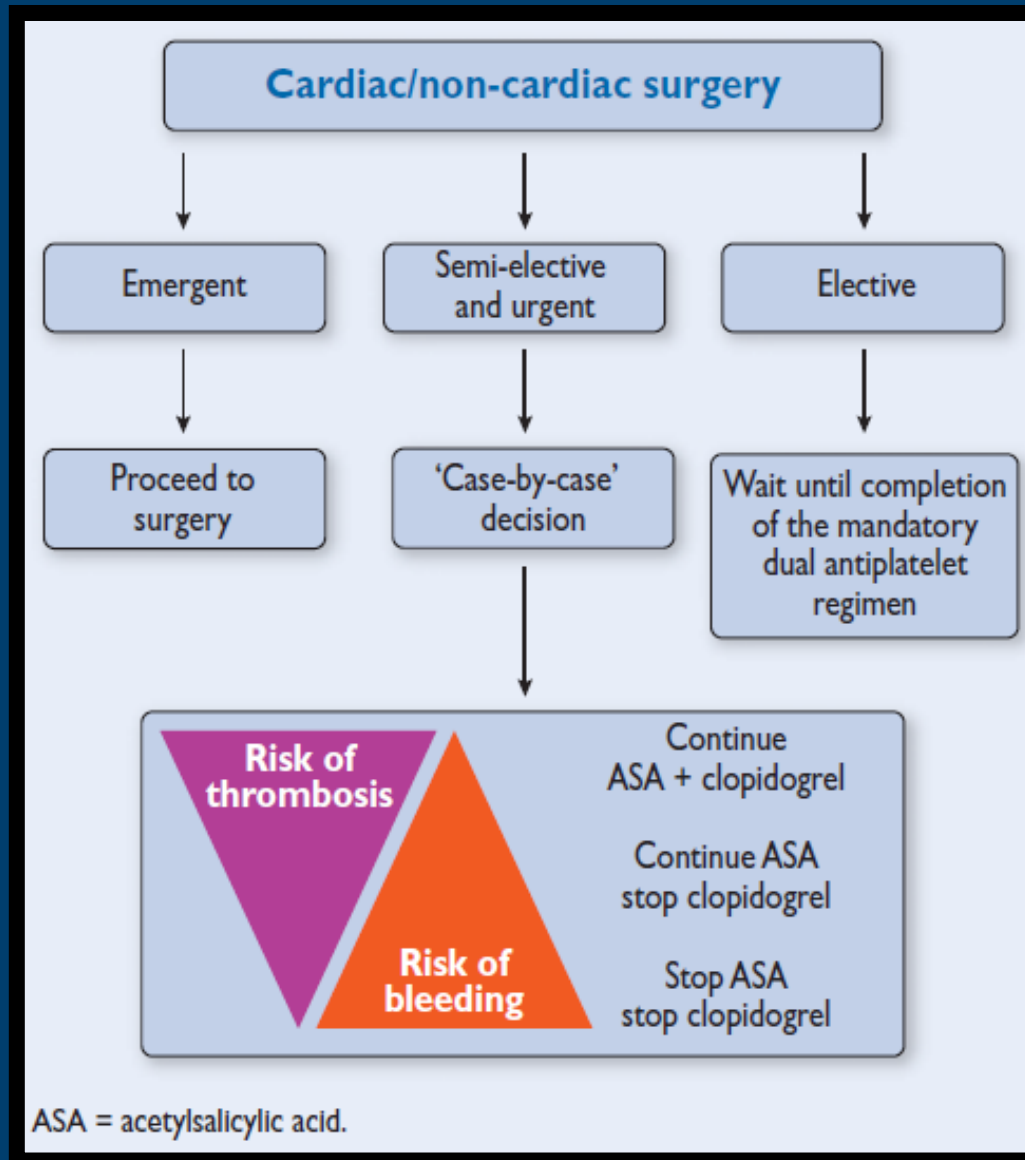
COMMON SENSE

- Knowing the patient **needs** surgery...
 - ❖ No stent: CABG, medical therapy...
 - ❖ If completely necessary: BMS

The less common of the senses...

- Once the patient is stented...
 - ❖ Elective surgery: Wait until completion of DAPT
 - ❖ Semi-elective / Urgent: Wait as much as possible
 - ❖ Emergent: Surgery

ESC GUIDELINES: RECOMMENDATIONS



ESC WG THROMBOSIS: RECOMMENDATIONS

♦ extends also to patients on clopidogrel monotherapy

Minor Surgery: do not stop antiplatelet therapy.

Implement **multidisciplinary consult** in patients with (potential) bleeding complications.
 Low molecular weight heparin: NOT a substitute for platelet inhibiting drugs.
 Avoid **plasmatic anticoagulation** (LMWH, OAC) during surgery.

major surgery and	how to proceed	exception	how to proceed with exception
aspirin for primary prevention ♦	stop aspirin 5 days before surgery ♦		
aspirin in high-risk patients ♦ (diabetes, history of CV events, documented CV disease, increased global risk)	continue aspirin ♦	surgery in closed space, expected major bleeding complications	<ul style="list-style-type: none"> • stop aspirin 5 days before surgery ♦ • consider restarting within 24h ♦
aspirin plus clopidogrel in high risk patients	<ol style="list-style-type: none"> 1. elective surgery: delay until no dual inhibition necessary 2. semi-urgent surgery: continue aspirin ± clopidogrel on a case by case basis 3. urgent surgery (within 24 h): continue aspirin and clopidogrel 	surgery in closed space, expected major bleeding complications	<p><i>If delaying surgery not possible / semi-urgent surgery necessary:</i></p> <ul style="list-style-type: none"> • stop clopidogrel 5 days before surgery, consider bridging (short acting GP IIb/IIIa antagonist) • consider stopping also aspirin in particular patients • consider resuming dual antiplatelet therapy asap

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IF YOU NEED TO STOP...

- Clopidogrel: 5 days
- Prasugrel: 7 days
- Ticagrelor: 5 days
- Bridging therapy with tirofiban
 - ❖ Only reports of case series



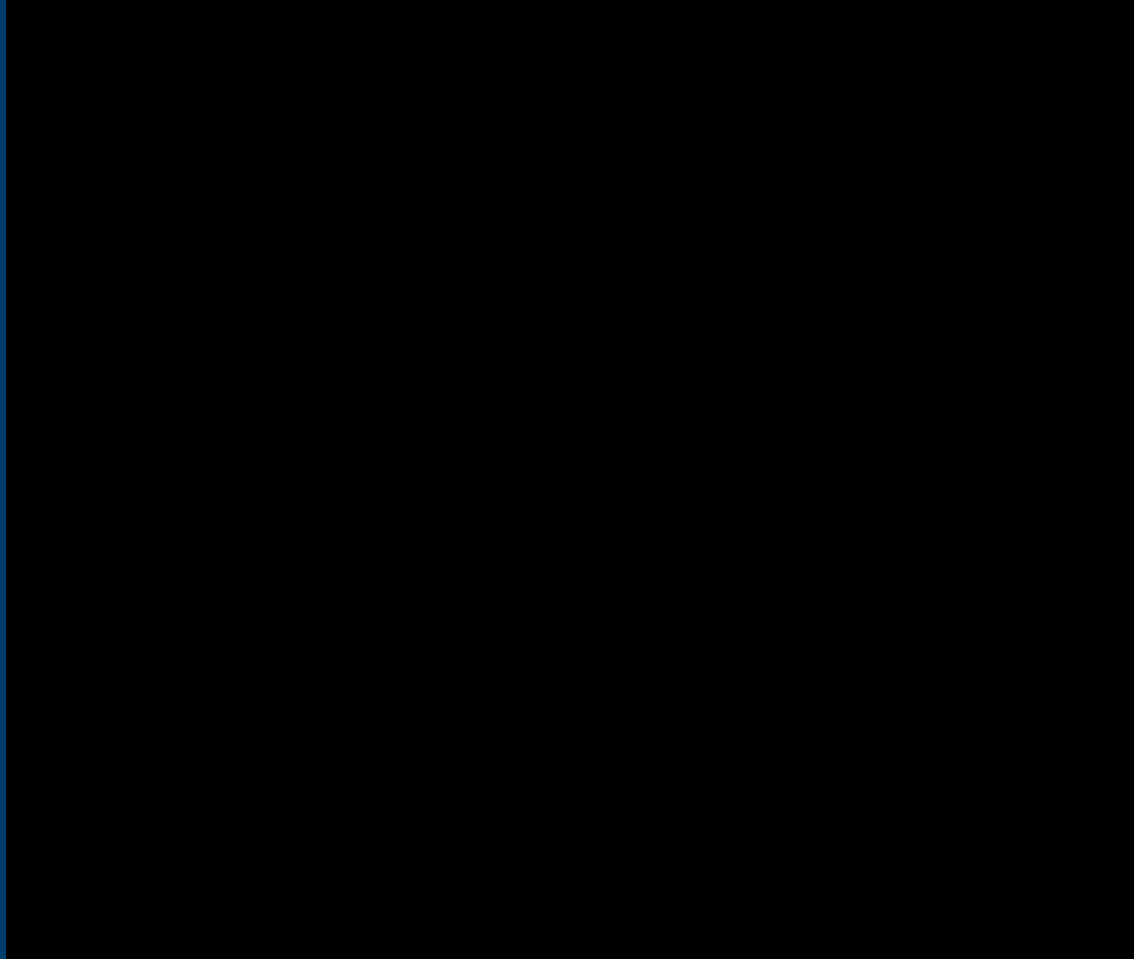
NUEVOS FÁRMACOS ANTIPLAQUETARIOS

P2Y₁₂ INHIBITORS

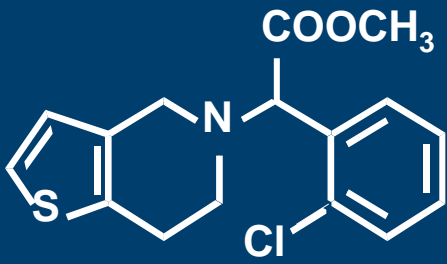
More potent with less variability

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor	Elinogrel
Group	Thienopyridine	Thienopyridine	CPTP	ATP analog	Quinazolinedione
Administration	oral	oral	oral	IV	IV and oral
Receptor blockade	irreversible	irreversible	reversible	reversible	reversible
Onset of action	2-8 h	30 min-4 h	30 min – 2 h	seconds	seconds
Offset of action	7-10 days	7-10 days	3-5 days	60-90 minutes	50 min (IV) 12 h (oral)
CYP drug interactions	yes	no	yes	no	no

Prasugrel Binding to P2Y₁₂



CLOPIDOGREL: METABOLISM



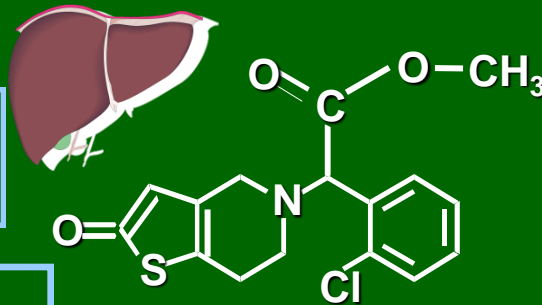
Clopidogrel

Esterases

Inactive Metabolites
(85% clopidogrel)

CYP 1A2
CYP 2B6
CYP 2C19

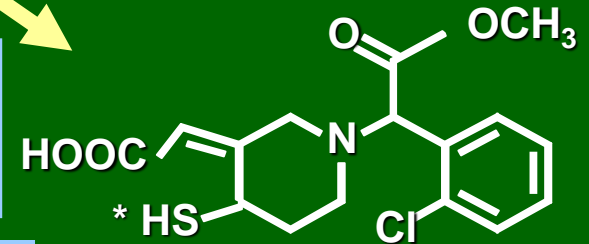
Hepatic
metabolism



2-oxo compound

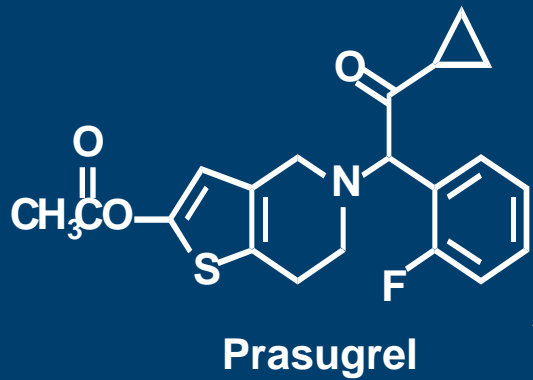
CYP 3A4(5)
CYP 2C9
CYP 2C19
CYP 2B6

Hepatic
metabolism

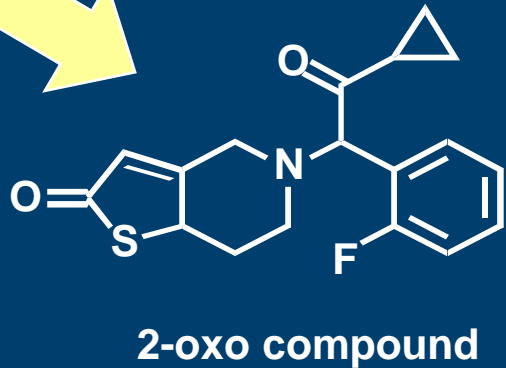


Active Metabolite

PRASUGREL: METABOLISM

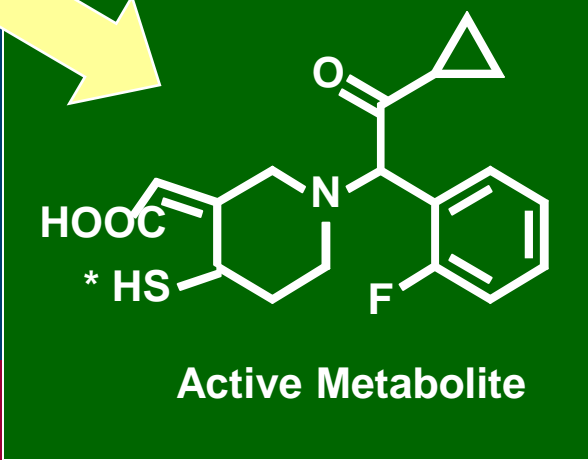
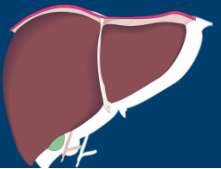


Pre-hepatic metabolism
Blood and intestine esterases

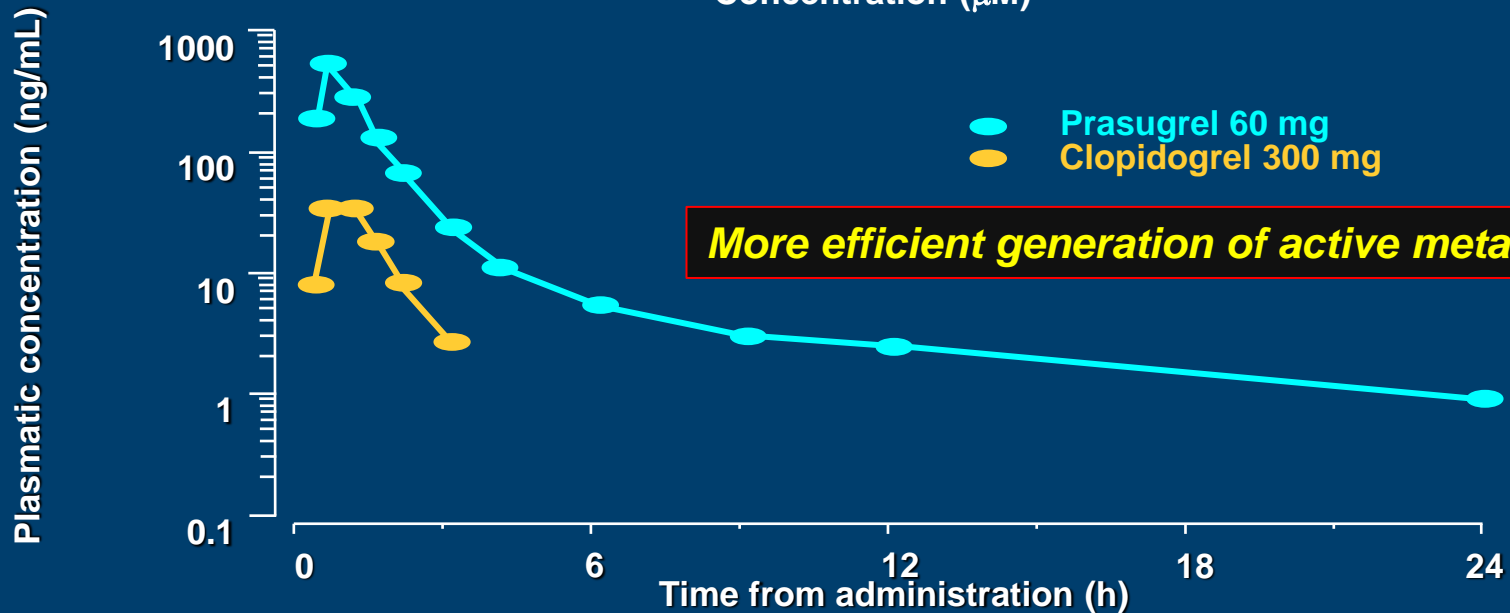
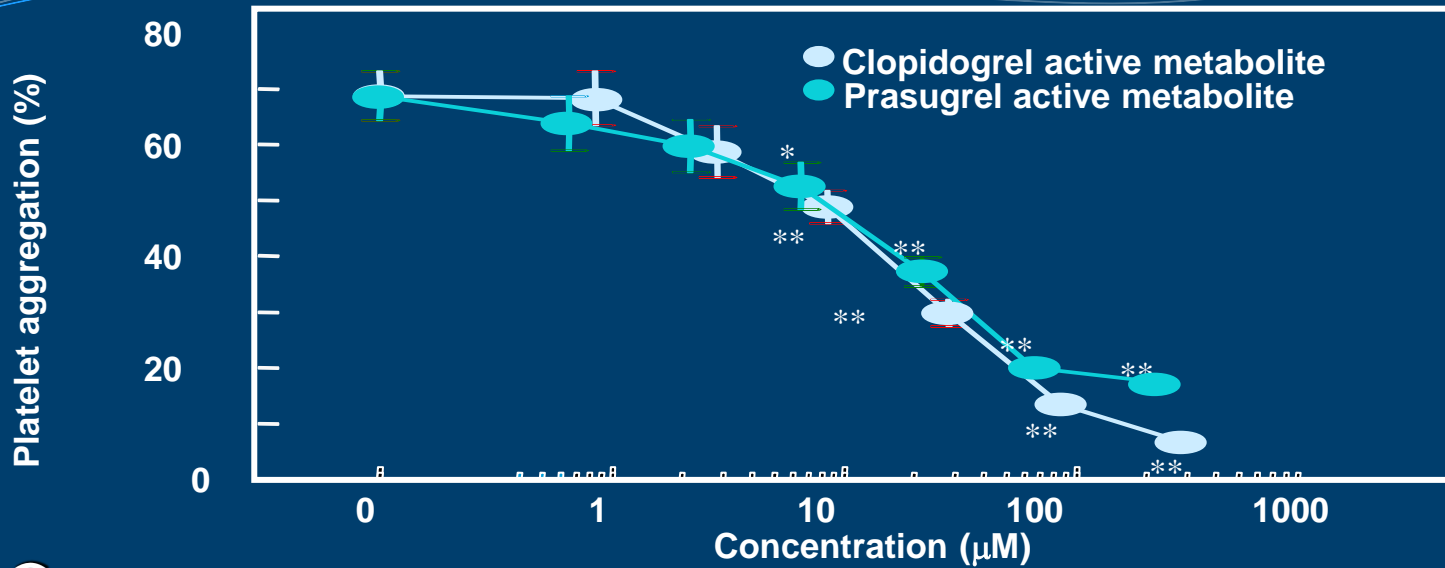


Hepatic metabolism

- CYP 3A4(5)
- CYP 2C9
- CYP 2C19
- CYP 2B6



ACTIVE METABOLITE

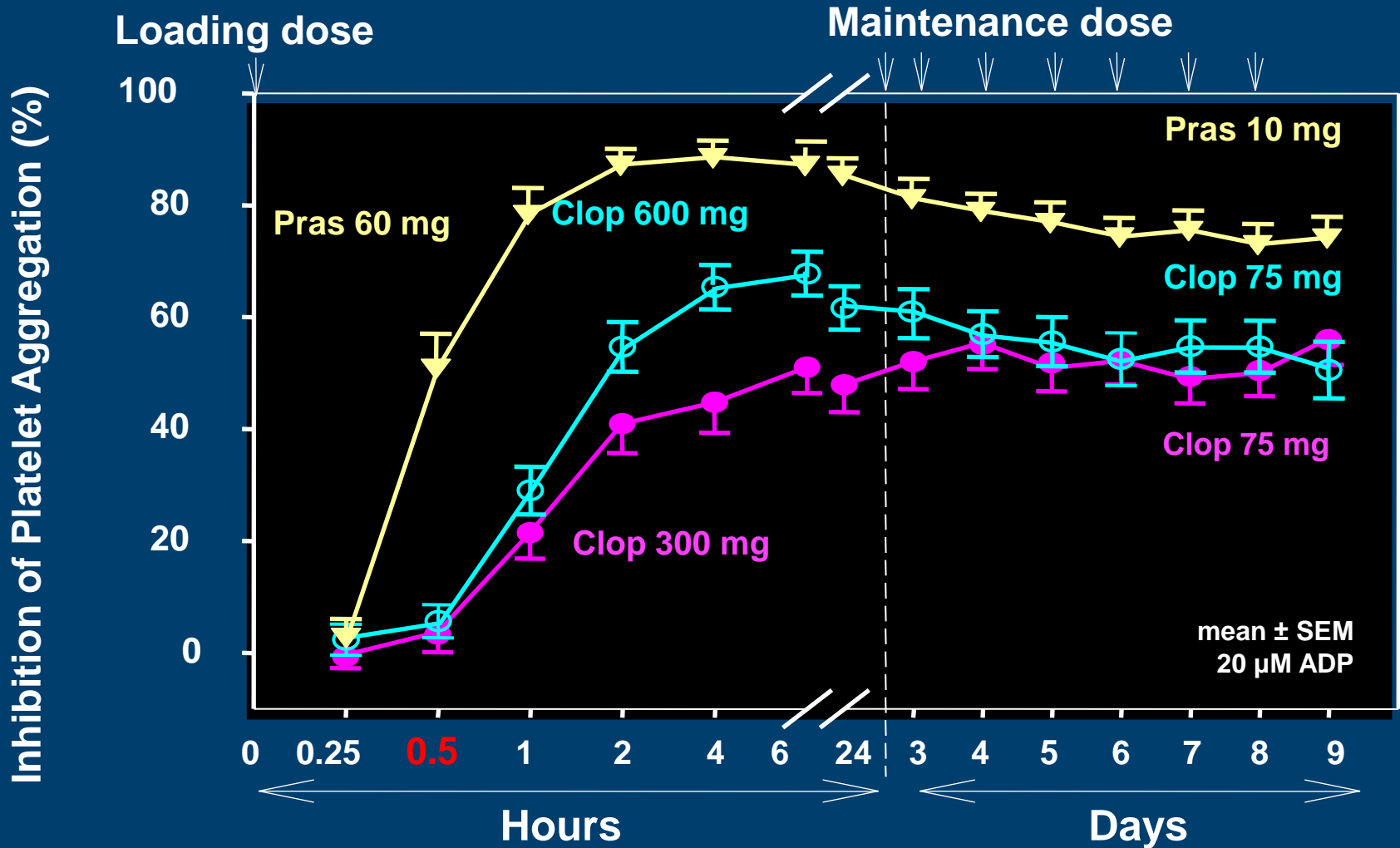


More efficient generation of active metabolite

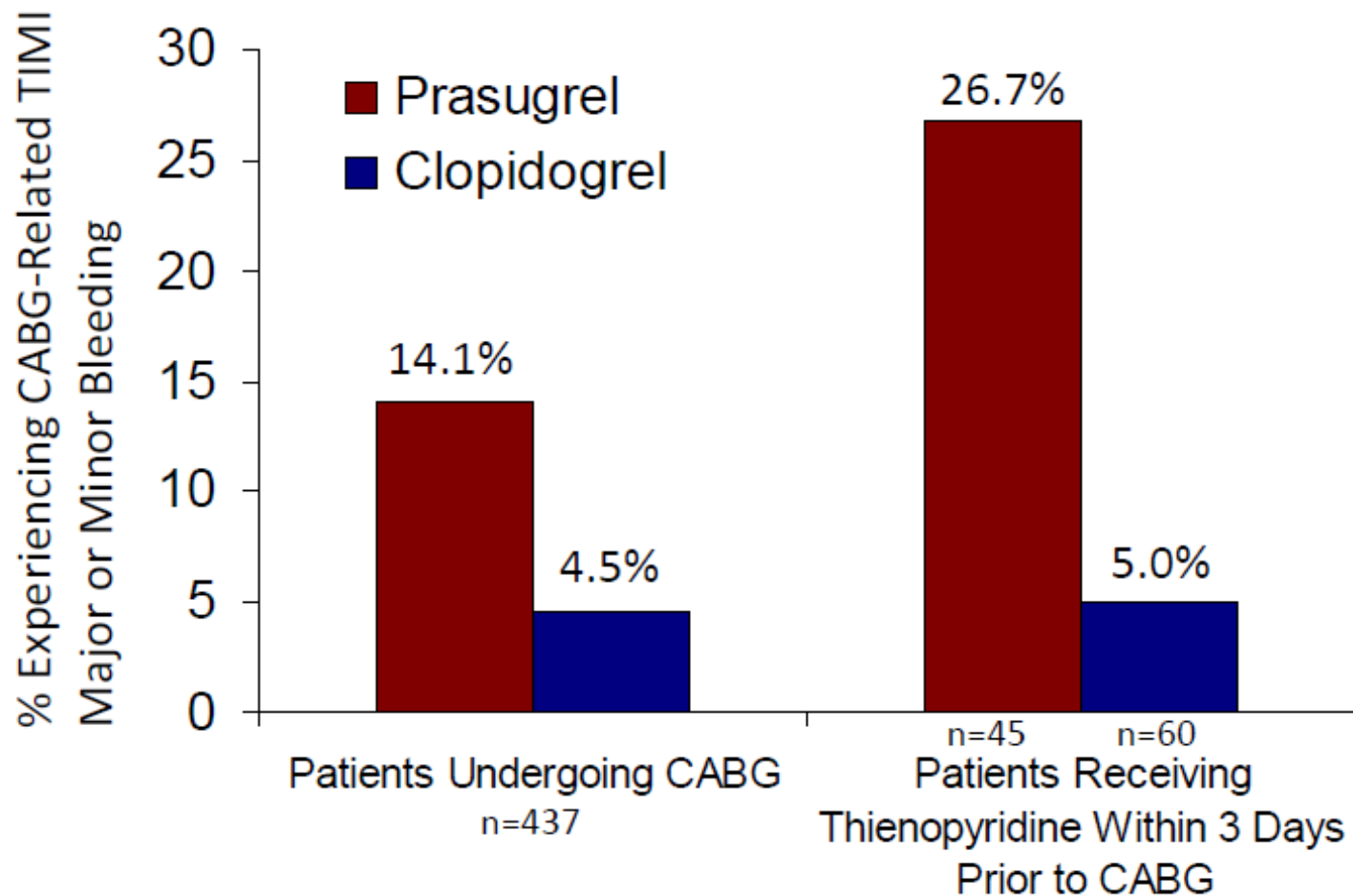
Sugidachi A et al. J Thromb Haemost 2007;5:1545-51.

Payne CD et al. J Cardiovasc Pharmacol 2007;50:555-562.

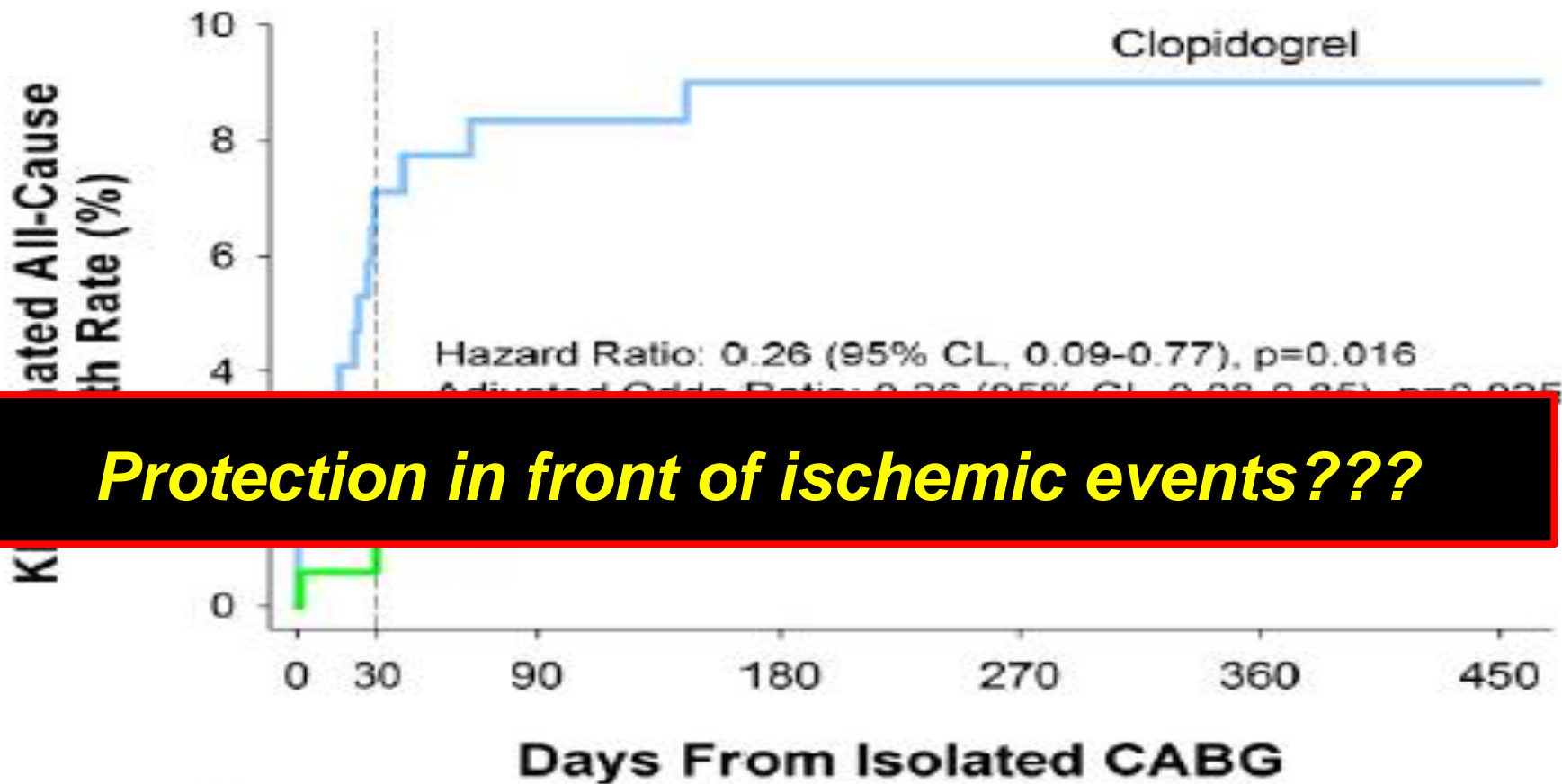
PRASUGREL: RAPID ONSET OF ACTION AND GREATER IPA



PRASUGREL: CABG



PRASUGREL: CABG

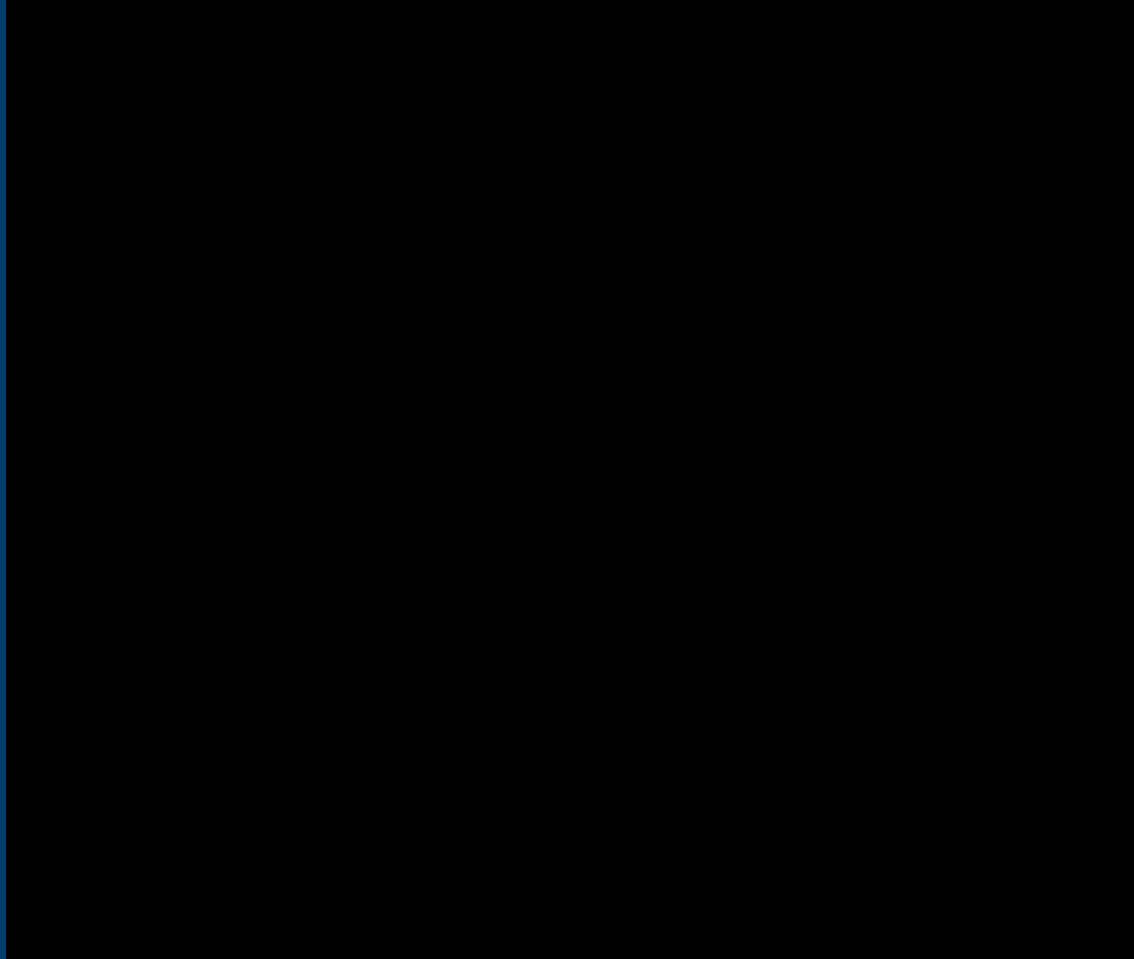


Protection in front of ischemic events???

Number at risk

Clopidogrel	173	153	143	124	92	51	9
Prasugrel	173	165	149	125	89	55	15

Ticagrelor Binding to P2Y₁₂



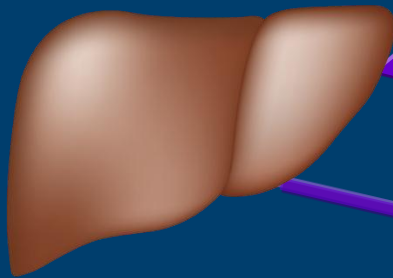
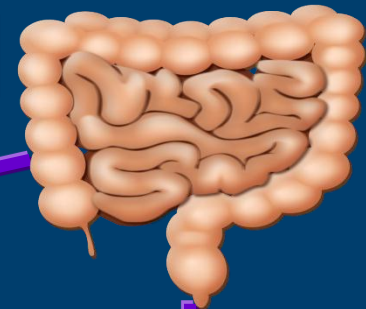
TICAGRELOR

A **non-thienopyridine**, in the chemical class CPTP (CycloPentylTriazoloPyrimidine)

Direct acting: Hepatic metabolism not required for activity

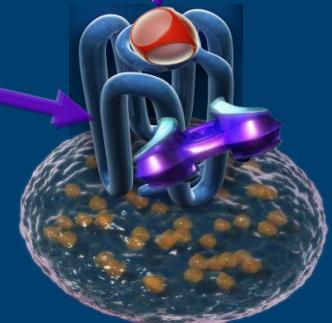


Rapid intestinal absorption

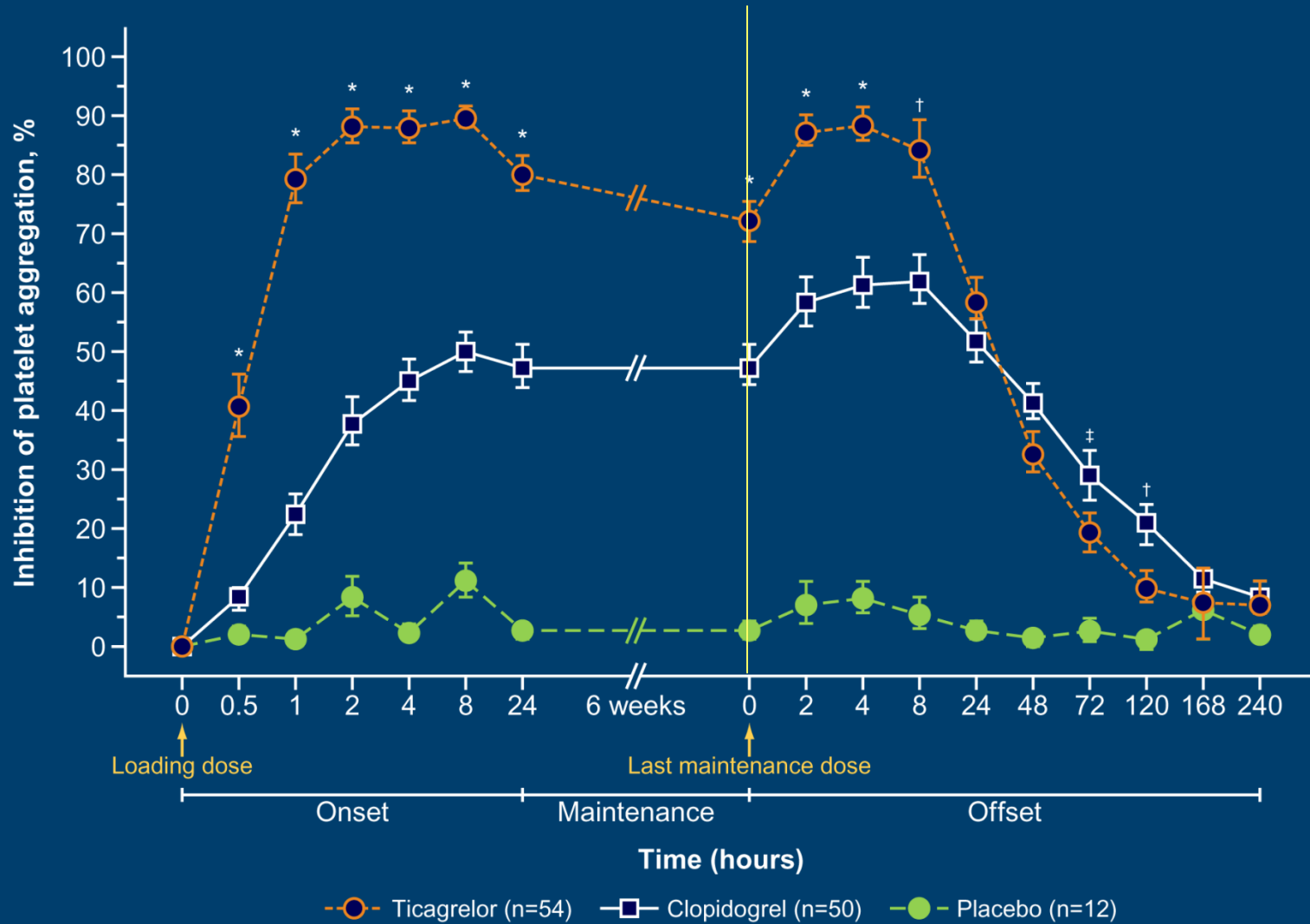


Active metabolite: AR-C124910XX (half-life ~10 hours) accounts for ~30% to 40% of total activity

Reversible binding to P₂Y₁₂ receptor (different site than ADP): half life ~8 h

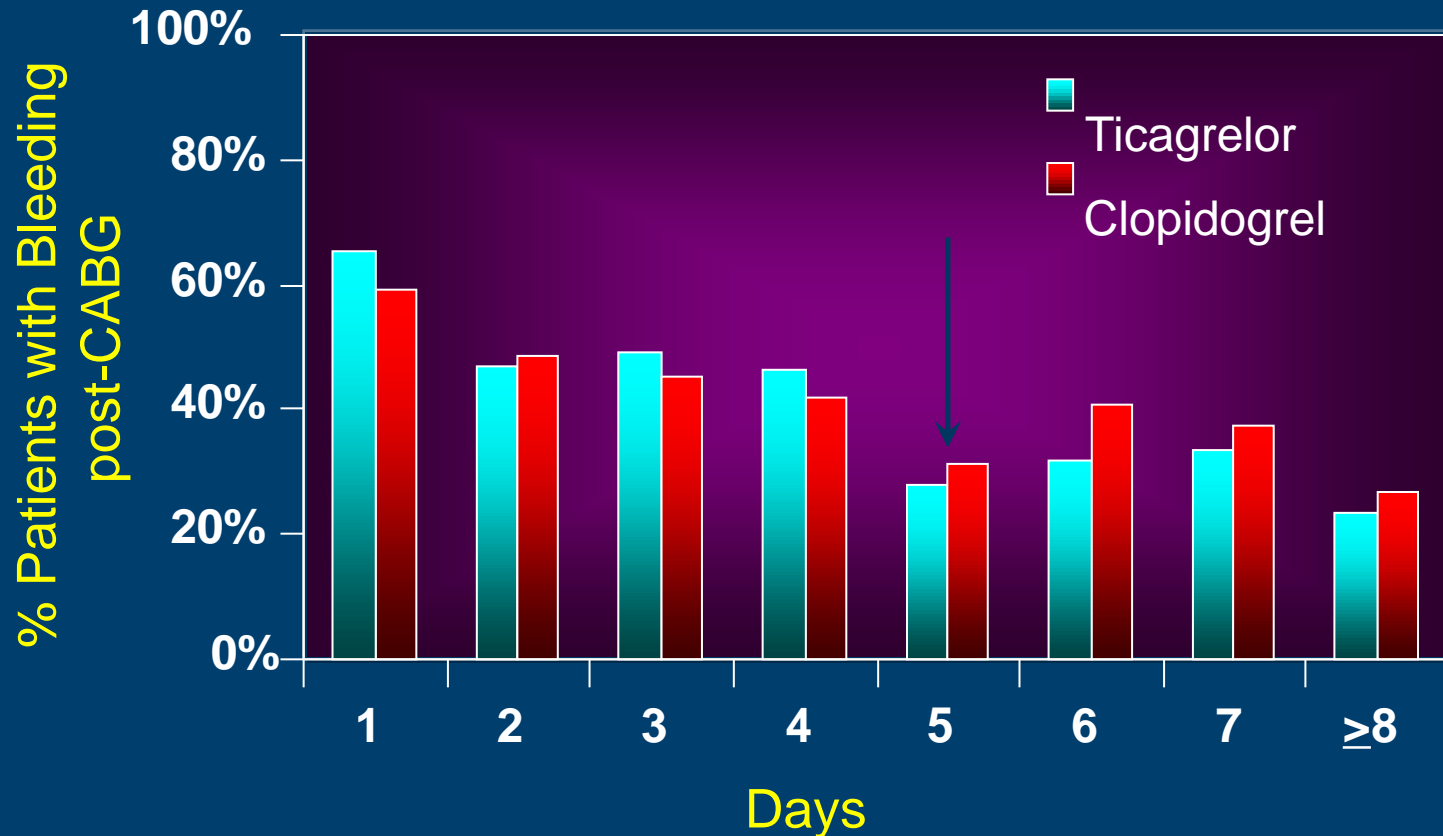


TICAGRELOR: RAPID ONSET / OFFSET & GREATER IPA



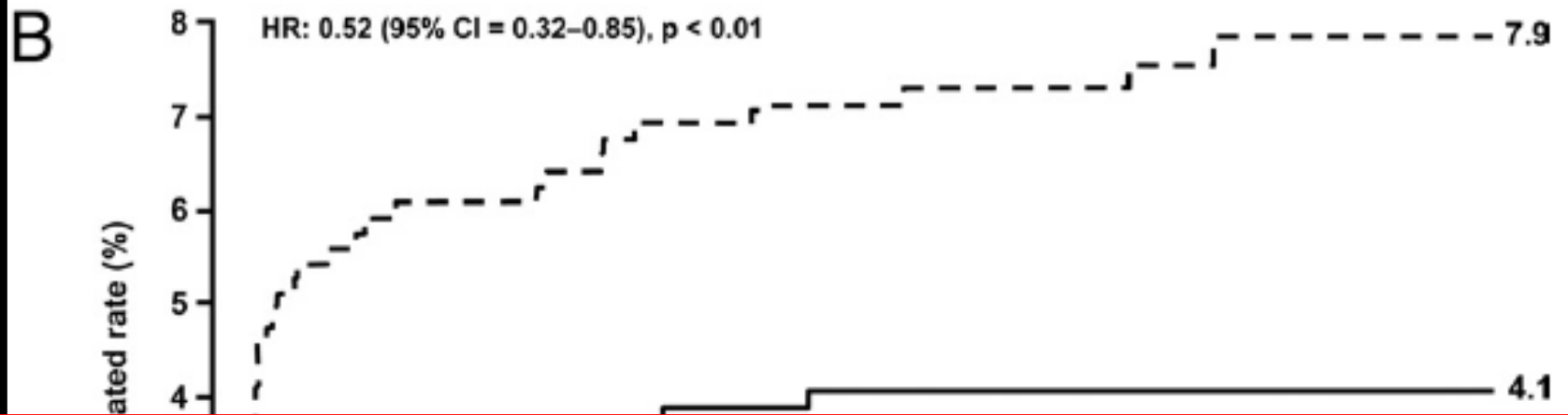
TICAGRELOR: CABG

Major Fatal/Life-Threatening Bleeding by Days from Last Dose of Treatment to CABG

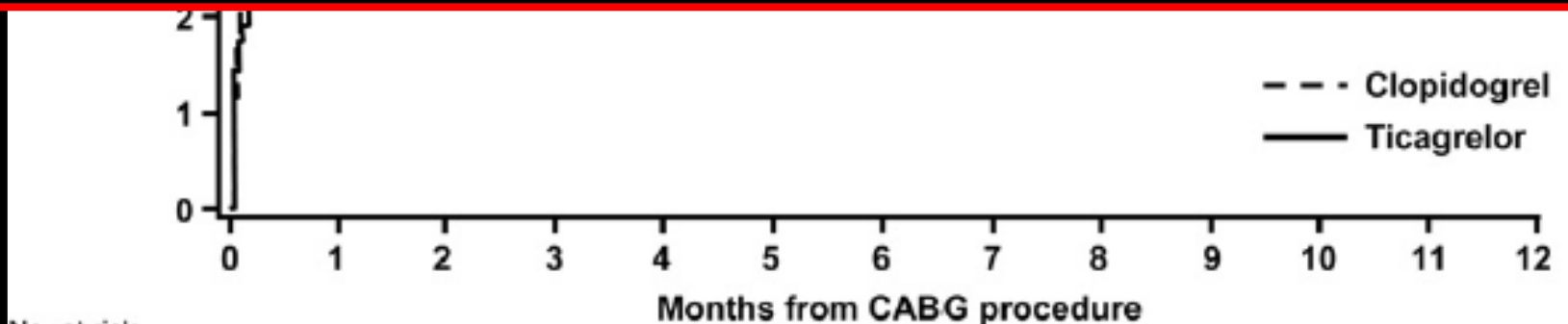


Bleeding differences favor ticagrelor ≥ 5 days post discontinuation

TICAGRELOR: CABG



Protection in front of ischemic events???

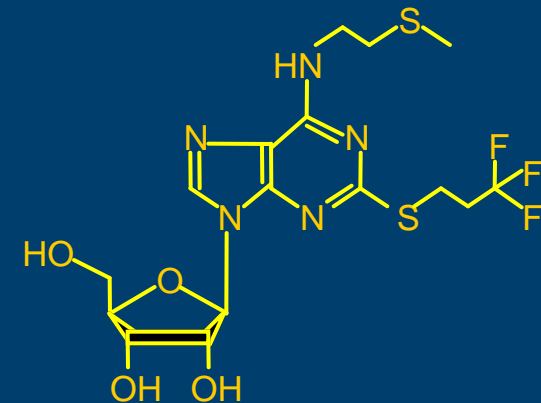
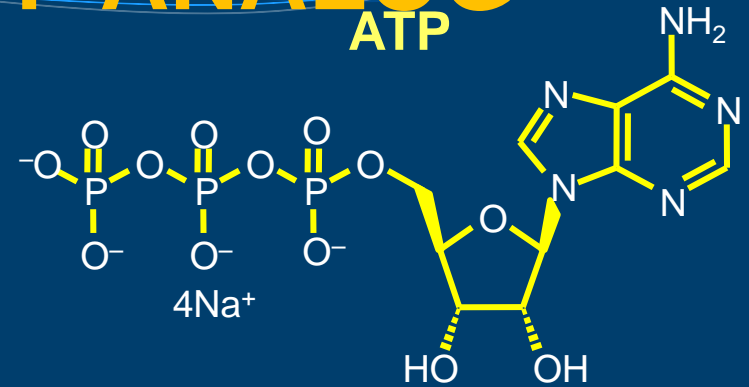
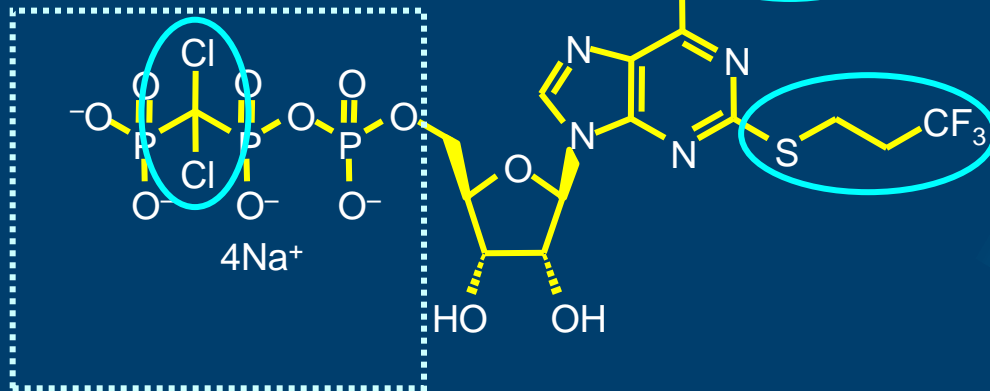


No. at risk

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

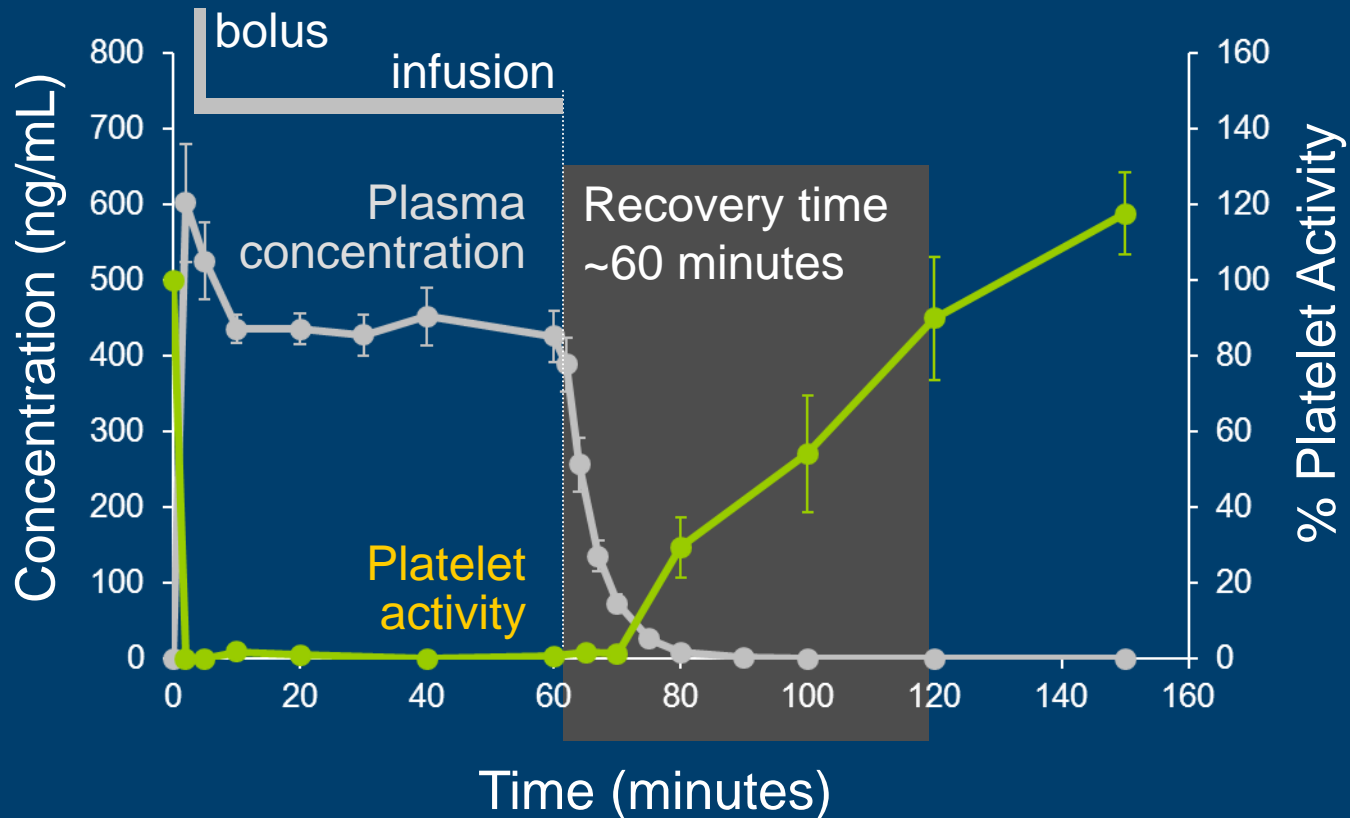
CANGRELOR: ATP ANALOG

Cangrelor (IV)



- ATP analog
- Direct-acting P2Y₁₂ antagonist
- Reversible receptor binding
- No hepatic or renal metabolism: NO interactions
- Extremely short half-life: **2-5 minutes**
- Instant onset of action: steady-state in 30 minutes
- Platelet function recovered in 60-90 minutes
- Great IPA: >90%

CANGRELOR: PHARMACODYNAMICS



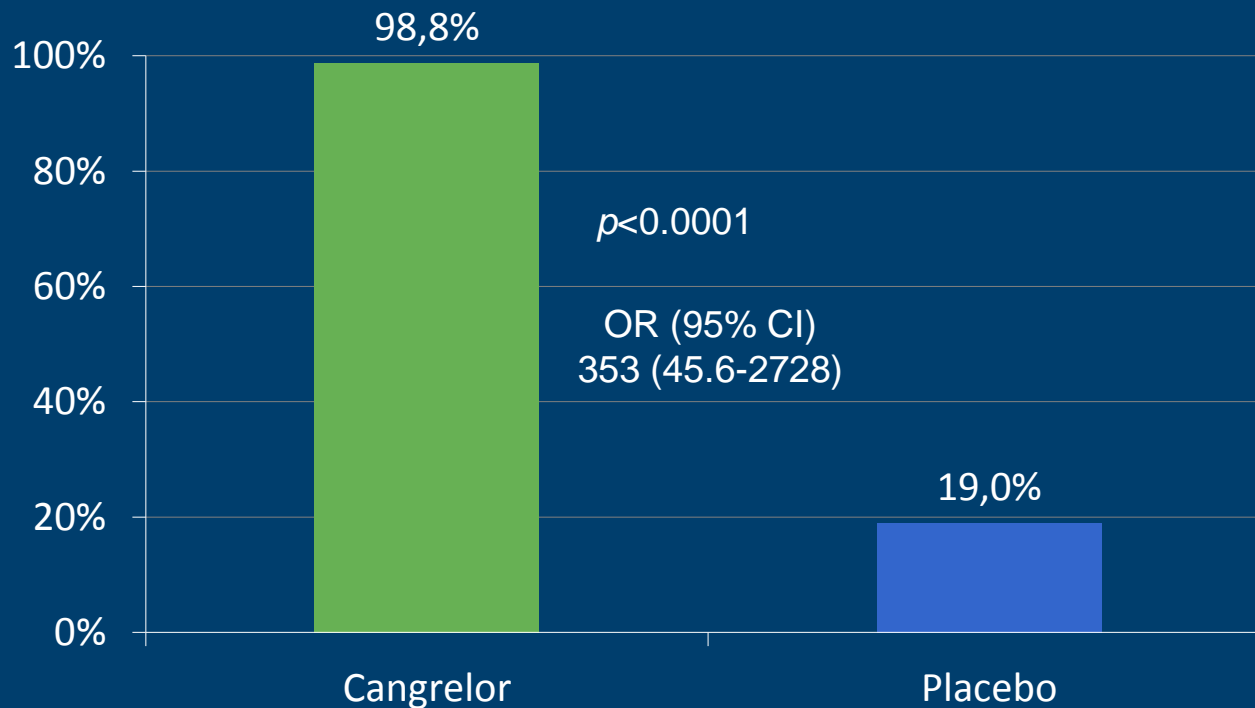
dose 30ug/kg then 4ug/kg/min

CANGRELOR: BRIDGE

Primary endpoint



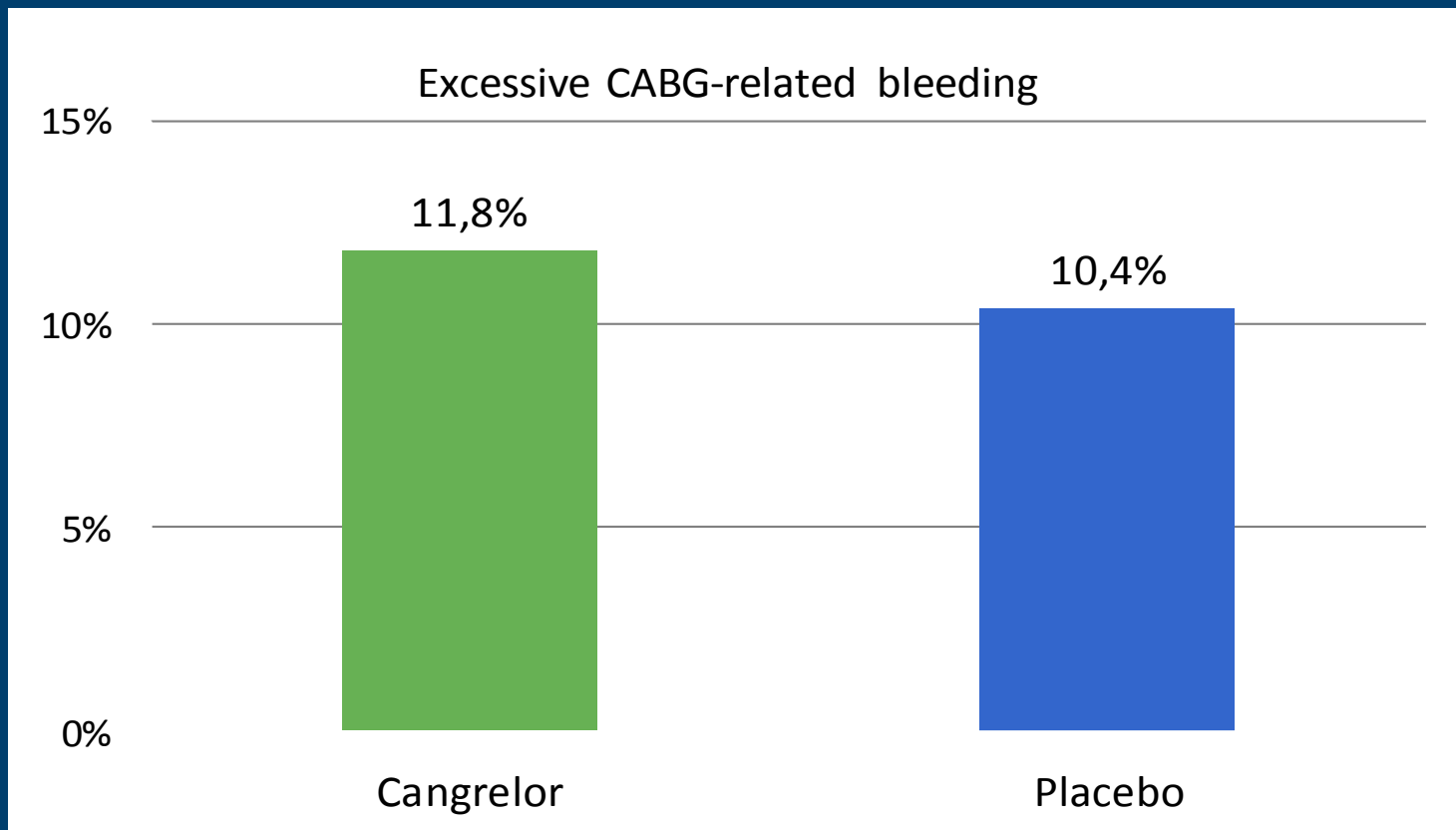
- Percent of patients with PRU<240 for all on-treatment samples:



CANGRELOR PRE-CABG



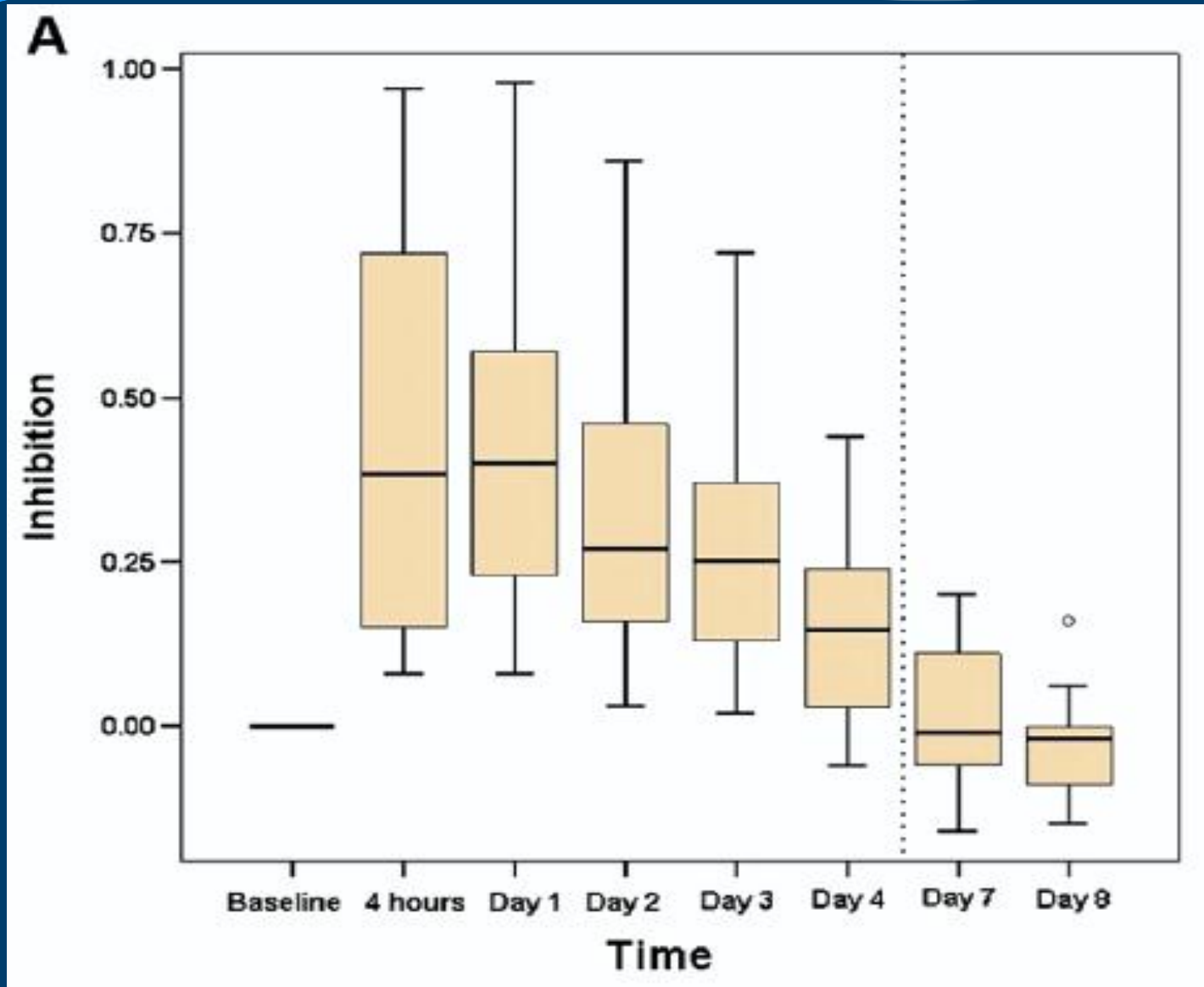
Patients with an ACS or treated with a coronary stent (BMS or DES) on a thienopyridine awaiting CABG.



N indicates number of patients with valid samples in the intention to treat population; PRU= P2Y12 reaction units; Data expressed as mean±SD

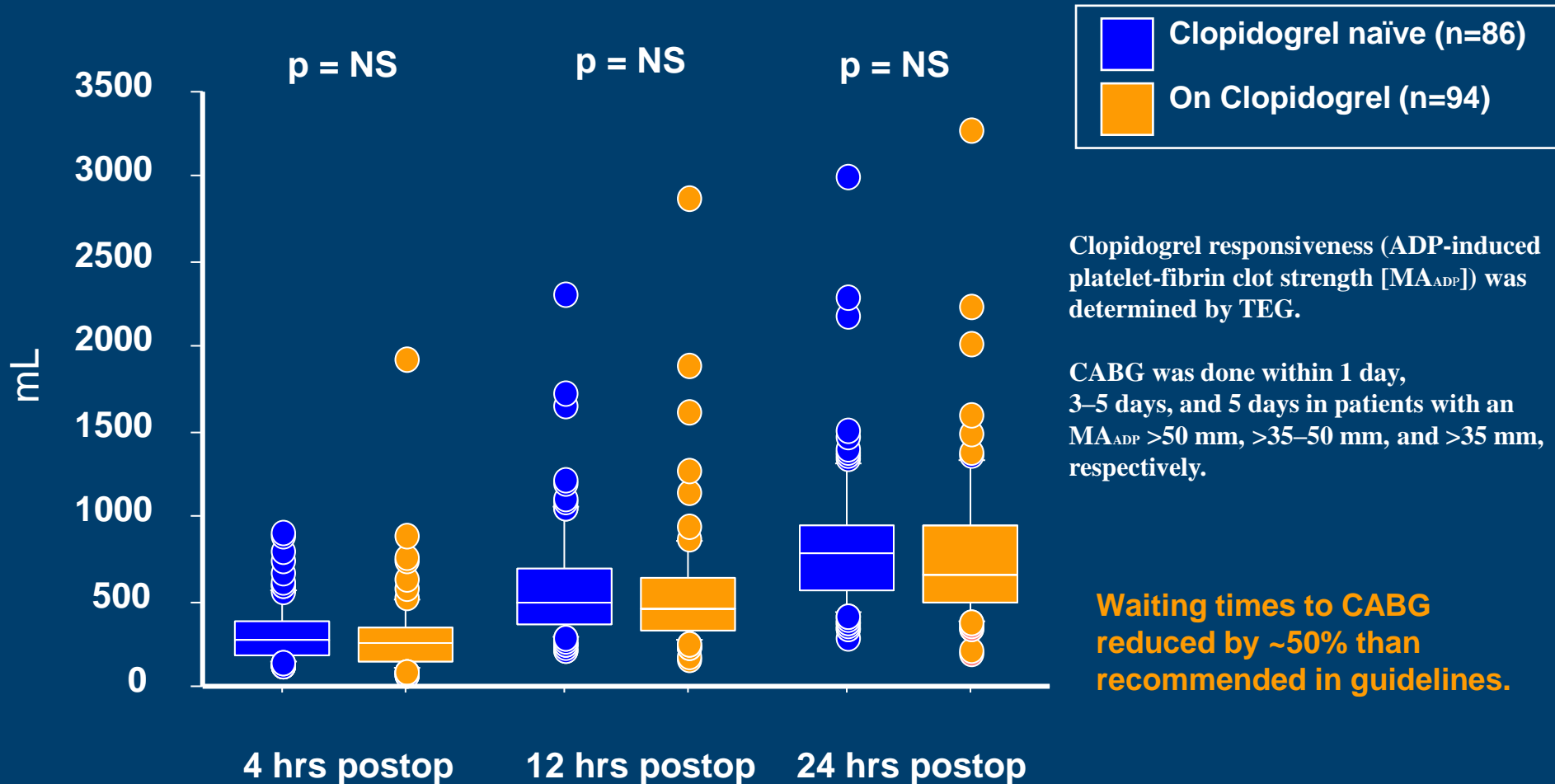
**¿SIEMPRE HAY QUE SUSPENDER
LOS ANTIAGREGANTES EL
TIEMPO RECOMENDADO?**

CLOPIDOGREL: OFFSET OF ACTION



CLOPIDOGREL: TIME TO CABG

TARGET-CABG: Primary Endpoint: 24 hr Chest Tube Output

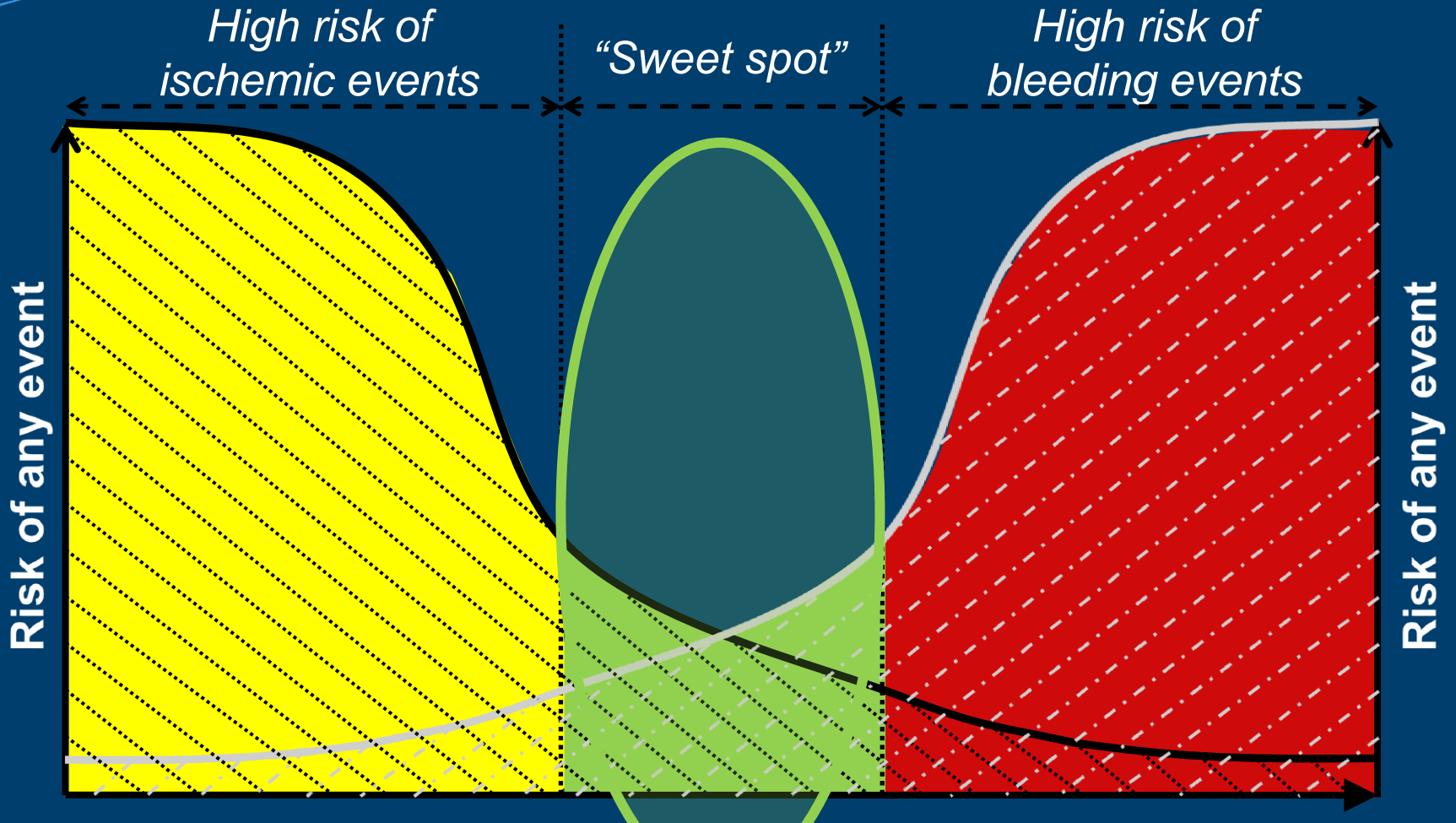


¿¿Sirve la misma talla para todo el mundo??



**Tratamiento
“individualizado”**

THERAPEUTIC WINDOW



The lower the bleeding risk, the higher the ischemic risk

CONCLUSIONES

CONCLUSIONES

- Usar el **sentido común** en pacientes con stent:
 - ❖ Cirugía electiva: Esperar hasta completar DAPT
 - ❖ Semi-electiva / Urgente: Esperar lo que sea posible (individualizar)
 - ❖ Emergente: Cirugía
- Considerar mantener DAPT en cirugía de bajo riesgo
- Mantener AAS excepto en situaciones de riesgo de sangrado extremadamente alto
- Si hay que suspender, como regla general:
 - ❖ Clopidogrel: 5 días
 - ❖ Prasugrel: 7 días
 - ❖ Ticagrelor: 5 días
- Tests de función plaquetar pueden ayudar a individualizar

GRACIAS POR SU ATENCIÓN

