

Cursos de la Casa del Corazón 2012

Nuevos antiagregantes en SCA. Como gestionar el cambio

¿Pruebas de función plaquetaria-genotipado en la práctica clínica diaria?



Antonio Tello Montoliu, MD, PhD

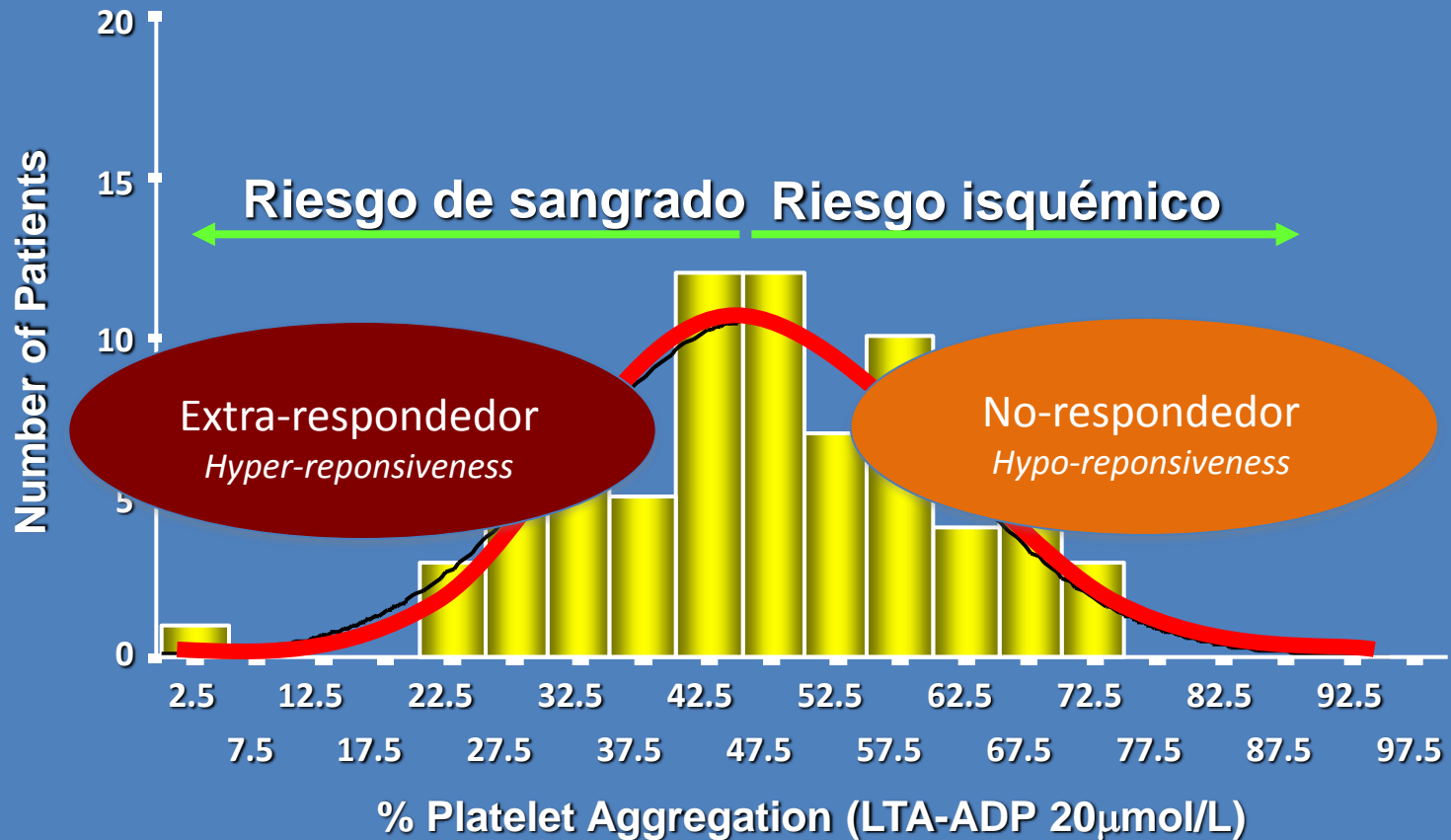
University of Florida College of Medicine-Jacksonville

Conflictos de interés

- No declara.

Respuesta a fármacos antiplaquetarios

Variabilidad individual en la respuesta a la terapia antiagregante



Genetic Factors

-Aspirin:

-Polymorphisms GP IIa subunit (PI^A); COX-1 (C50T); CYP (2C9); UDP (UGT1A6); FXIII(Val34Leu)

-Clopidogrel:

- Polymorphism CYP (2C19); GPIa; P2Y₁₂; GPIIIa

Antiplatelet drugs response variability

Clinical Factors

- Poor compliance.
- Drug interactions:
 - Aspirin vs NSAID
 - Clopidogrel vs PPI, statins, CCB, coumadin.
- Clinical characteristics:
 - ACS
 - DM/insulin resistance
 - Elevated BMI.

Cellular Factors

- Accelerated platelet turnover.
- Upregulation of platelet signaling pathways.
- Dysregulation of Ca⁺² metabolism. increase oxidative stress.

Métodos Laboratorio

Test	Basis	Able to monitor	Advantages	Disadvantages
Turbidometric aggregometry	Platelet aggregation	Aspirin P2Y ₁₂ inhibitors	Historical gold standard	Large sample volume Complex sample preparation Time-consuming
Impedance aggregometry	Platelet aggregation	Aspirin P2Y ₁₂ inhibitors	Whole-blood assay	Large sample volume Complex sample preparation Time-consuming
VASP phosphorylation state (flow cytometry)	P2Y ₁₂ activation-dependent signaling	P2Y ₁₂ inhibitors	Whole-blood assay Very small sample volume Most specific for assessing P2Y ₁₂ blockers effect Can be shipped to core lab	Complex sample preparation Requires flow cytometer and experienced technician
Thromboxane A ₂ metabolites	Serum thromboxane B ₂ (stable blood metabolite) Urinary 11-dehydro thromboxane B ₂ (stable urine metabolite) /creatinine	Aspirin	Evaluation of COX-1 inhibition (aspirin target) Most specific for assessing aspirin effect Can be shipped to core lab	Not entirely platelet-specific
Platelet surface P-selectin, activated GP IIb-IIIa, leukocyte-platelet aggregates (flow cytometry)	Changes in platelet surface due to activation	Aspirin P2Y ₁₂ inhibitors	Whole-blood assays Small sample volume Can be shipped to core lab	Complex sample preparation Requires flow cytometer and experienced technician

Point-of-care

Test	Basis	Able to monitor	Advantages	Disadvantages
Bleeding time	Cessation of blood flow by platelet plug after a blade incision (e.g. in the forearm)		Physiological In vivo surrogate for potential of clinical bleeding	Crude approach Operator-dependent Low reproducibility (e.g. dependant of temperature, cuff pressure, direction of the incision)
VerifyNow®	Platelet aggregation	Aspirin P2Y ₁₂ inhibitors	Whole-blood assay Small sample volume Very simple and rapid No sample preparation True point-of-care (no pipetting required)	Limited by hematocrit and platelet count range No instrument adjustment
Multiplate® analyzer	Multiple electrode aggregometry (electric impedance)	Aspirin P2Y ₁₂ inhibitors	Whole-blood assay Small sample volume Simple and rapid	Requires pipetting
TEG® PlateletMapping™ system	Platelet contribution to clot strength	Aspirin P2Y ₁₂ inhibitors	Whole-blood assay Global evaluation of haemostasis (clot formation and lysis)	Limited studies Requires pipetting
Plateletworks™	Platelet aggregation	Aspirin P2Y ₁₂ inhibitors	Whole-blood assay Minimal sample preparation	Not well studied yet Requires pipetting
Impact® cone-and-plate(let) analyzer	Shear-induced platelet adhesion	Aspirin P2Y ₁₂ inhibitors	Whole-blood assay Small sample volume Importance of shear for platelet function No sample preparation Simple and rapid	Not widely used Requires pipetting
PFA-100®	Cessation of high shear blood flow by platelet plug	Aspirin P2Y ₁₂ inhibitors (Innovance PFAP2Y PFA-100 system)	Whole-blood assay Simple and rapid Small sample volume No sample preparation	Dependent on vWF and hematocrit Minimal pipetting Does not correlate well with clopidogrel therapy Do not assess the whole range of platelet response

Métodos de Genotipado

Test	Muestra	Base	Tiempo
Sondas	Sangre	PCR	dias
AmpliChip	Sangre (mucosa bucal)	Microarrays	8 horas
Infiniti	Sangre	Microarrays	3-8 horas
Verigene	Sangre	Microarrays	2.5 horas
Spartan	Mucosa Bucal	Microarrays	1 hora

Características a considerar para una potencial aplicación a la práctica clínica

1. Facilidad de uso en la “cabecera del paciente”
2. Volumen de muestra pequeño
3. Tiempo razonable
4. Datos consistentes que demuestren relación con eventos clínicos
5. Capacidad para detectar todo el espectro de respuestas
6. Capacidad para guiar el manejo terapéutico

Agregometría de transmisión óptica

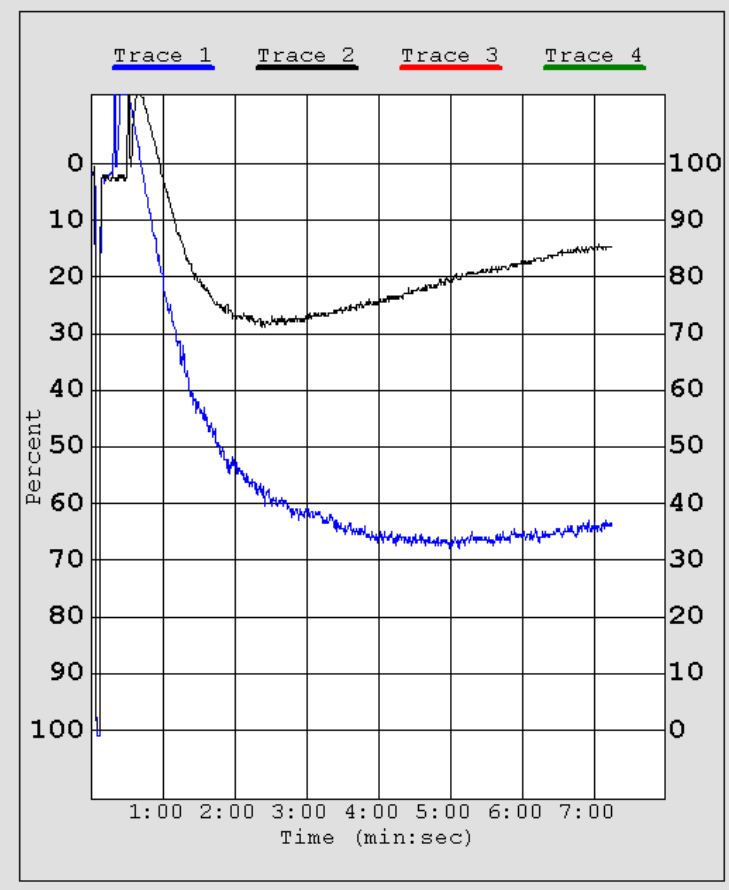
AGGREGATION OF BLOOD PLATELETS BY ADENOSINE DIPHOSPHATE AND ITS REVERSAL

By PROF. G. V. R. BORN

Department of Pharmacology, Royal College of Surgeons of England, London

NATURE

June 9, 1962 Vol. 194



Pruebas basadas en laboratorio

Limitaciones

- No de fácil uso
- Requieren tiempo
- Requieren personal entrenado
- Requieren equipamiento....caro
- No tienen disponibilidad generalizada
- En general.... *Alto coste*



multiplate[®]

THE NEW STANDARD FOR PLATELET DIAGNOSTICS



Attachment of the test cell to the analyzer.



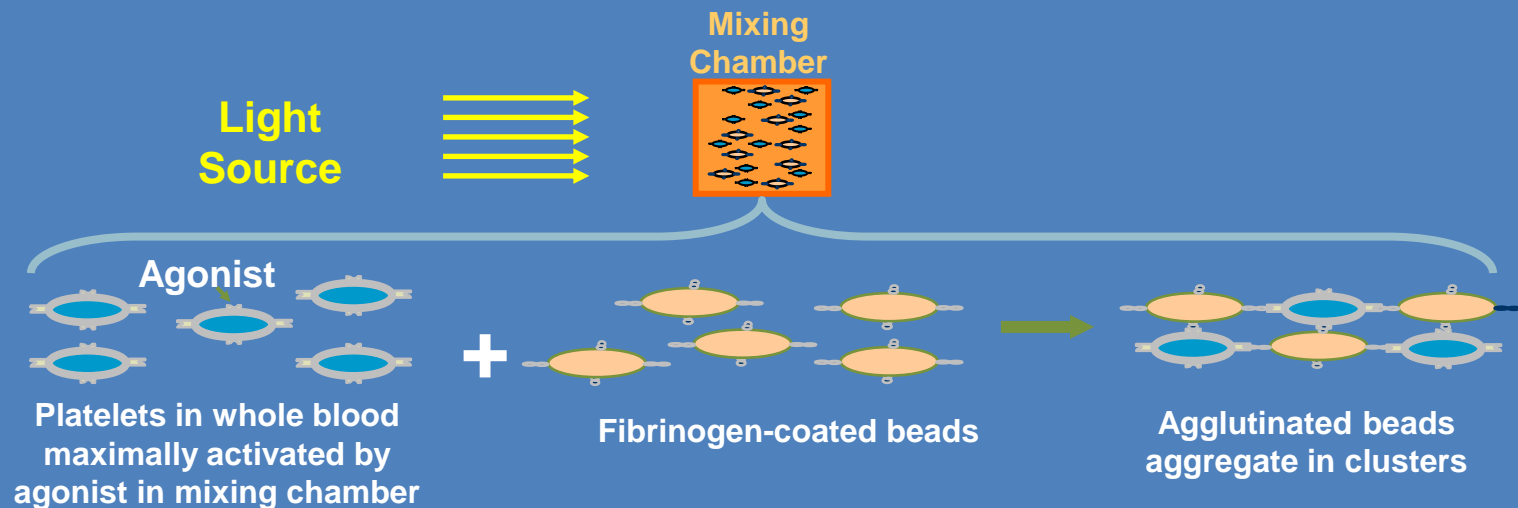
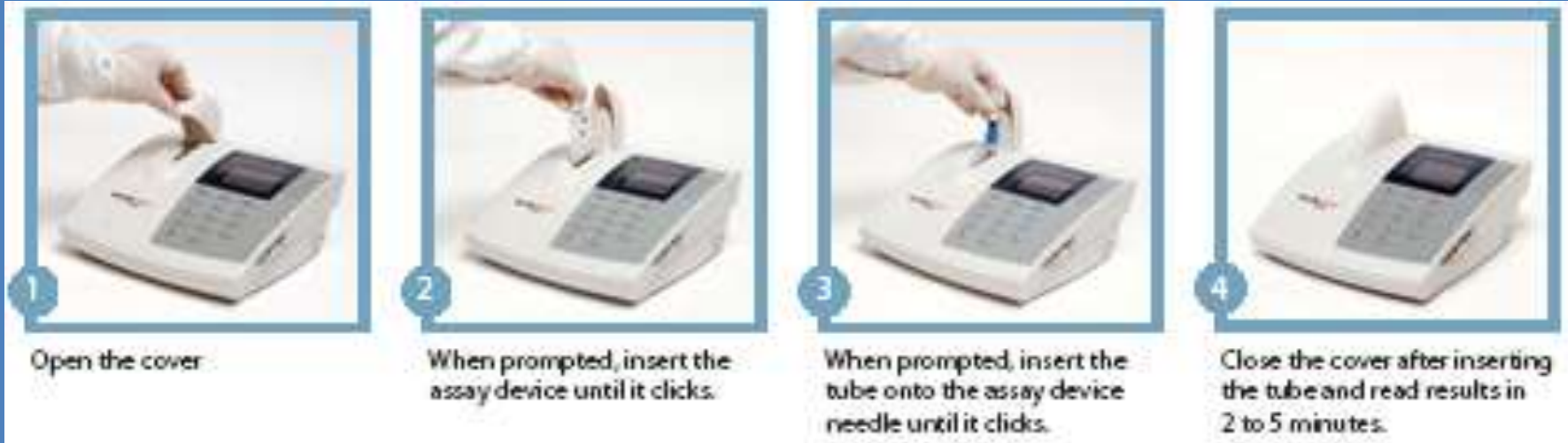
Software guided pipetting procedures.



300 μ l sample volume per analysis
(mini test cell with 175 μ l volume
available for research use).

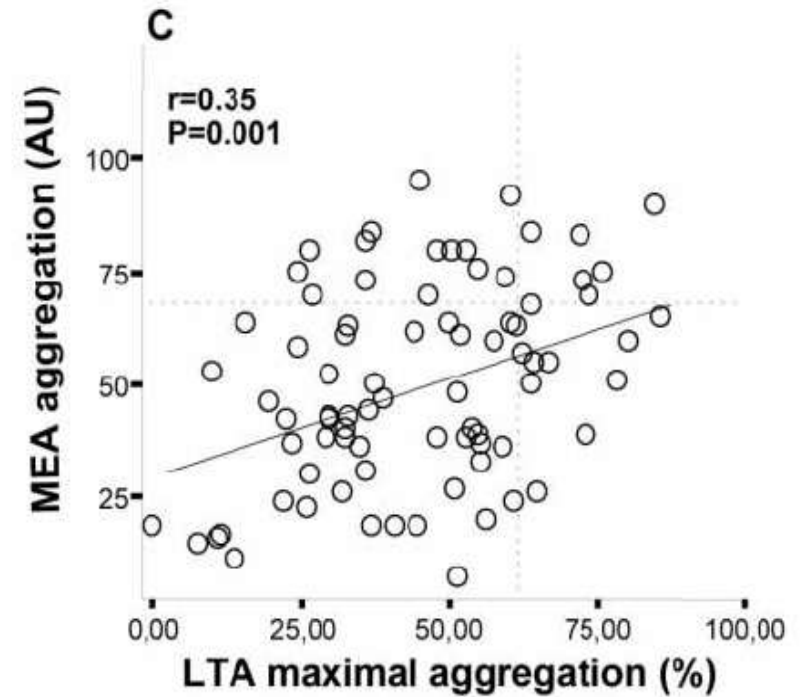
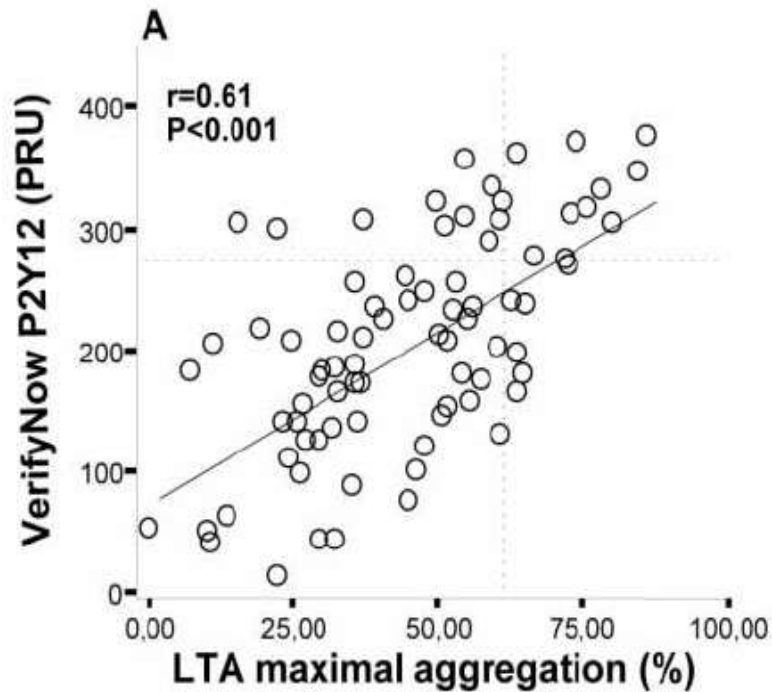
VerifyNow Assay

- Tubo de sangre entera, sin pipeteado
- Resultados en menos de 5 minutos



Correlación con Gold Standard

Respuesta al clopidogrel

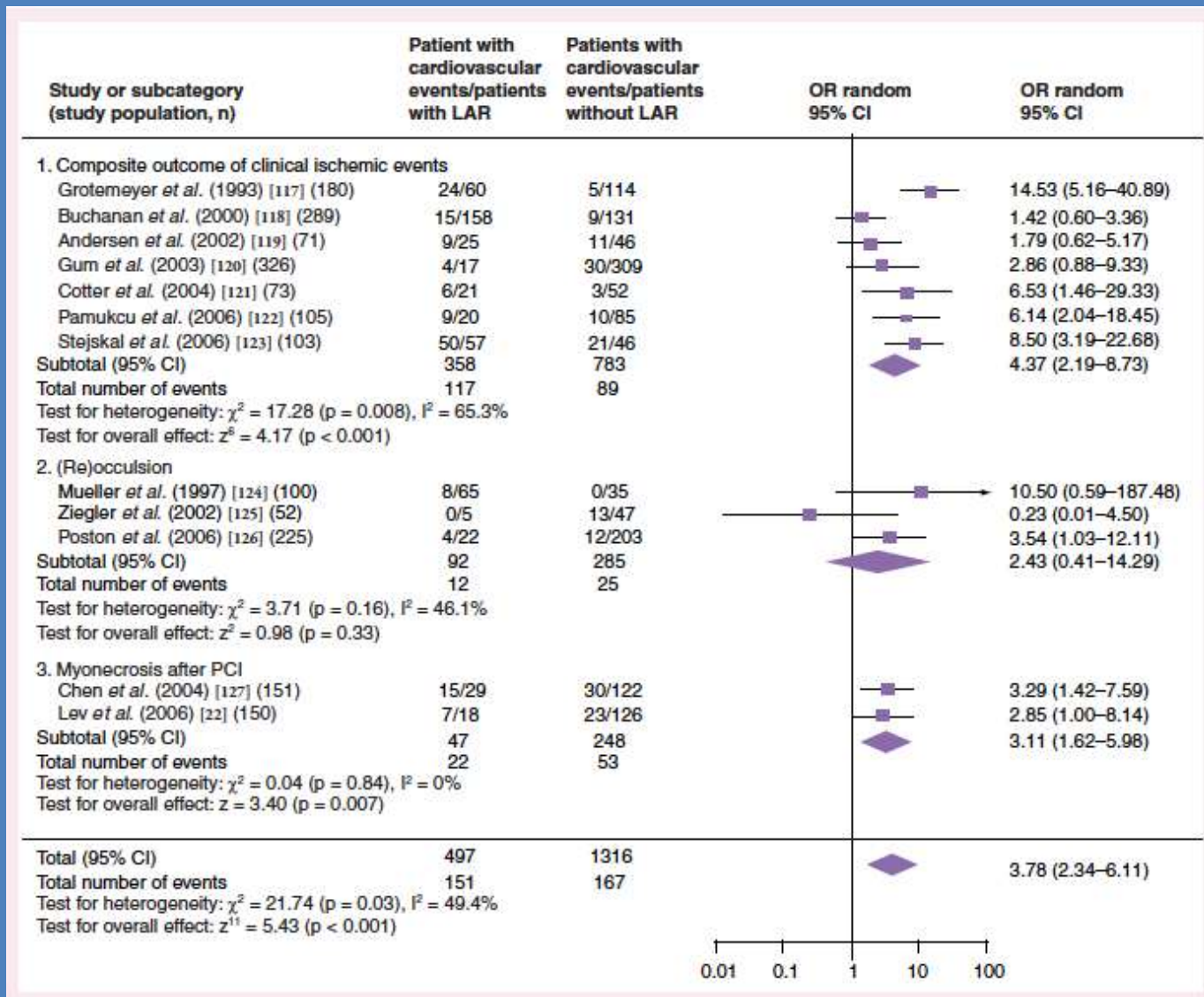


Point-of-care Genotipado

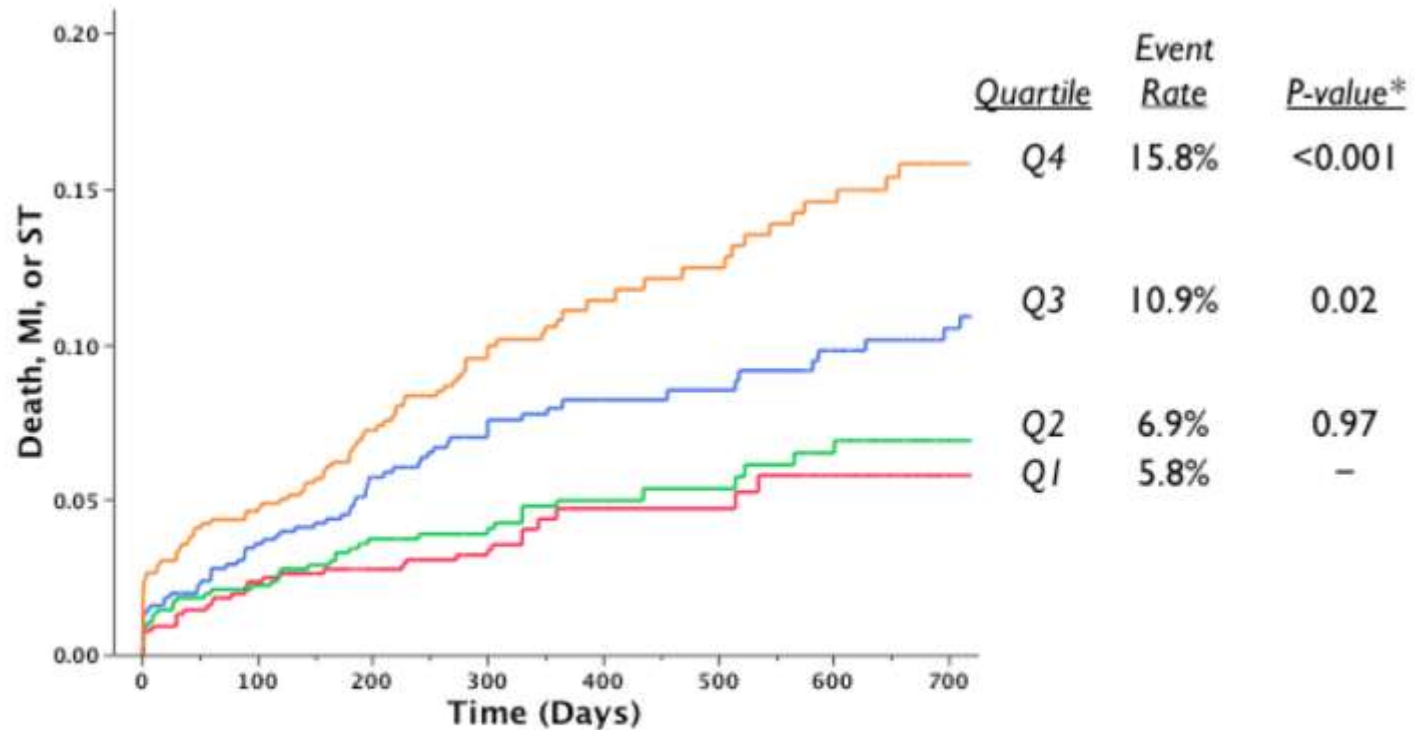


Relación con eventos clínicos

Aspirina



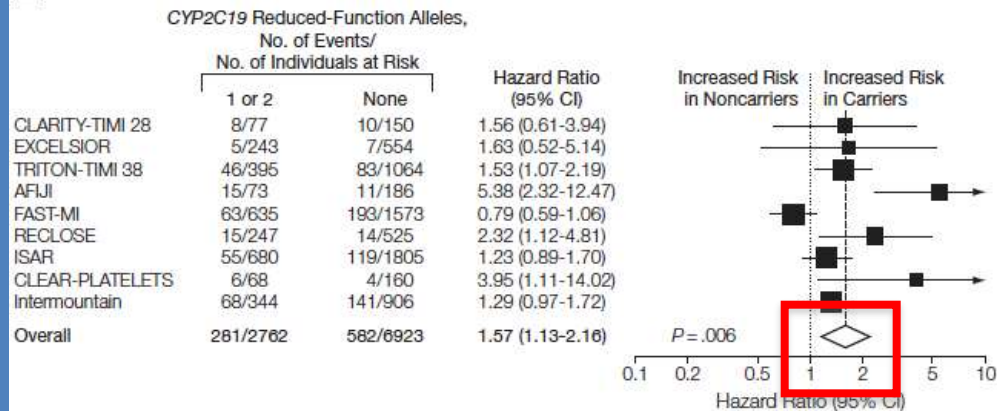
On-Clopidogrel Platelet Reactivity & Ischemic Events Post-PCI: A Patient-Level Meta-Analysis



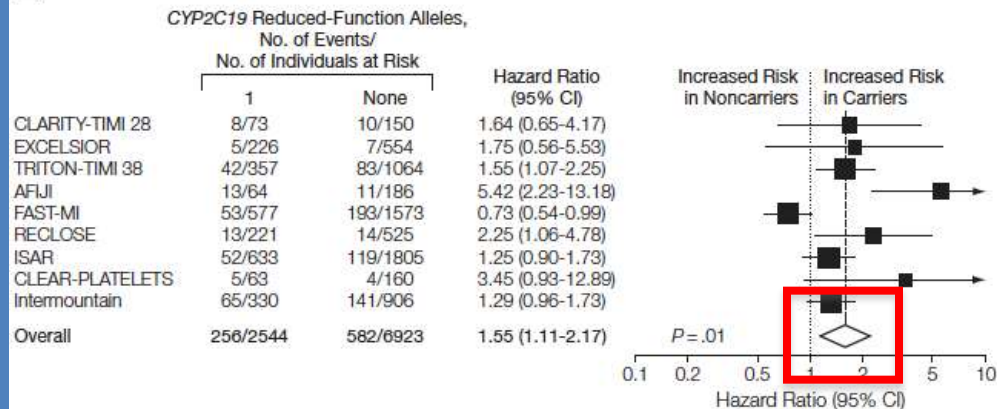
No. at risk				
Q1	765	639	179	169
Q2	761	611	249	237
Q3	757	595	294	271
Q4	758	588	252	224

Non-ACS pts with high reactivity : HR 2.47 (1.79–3.40), P<0.0001

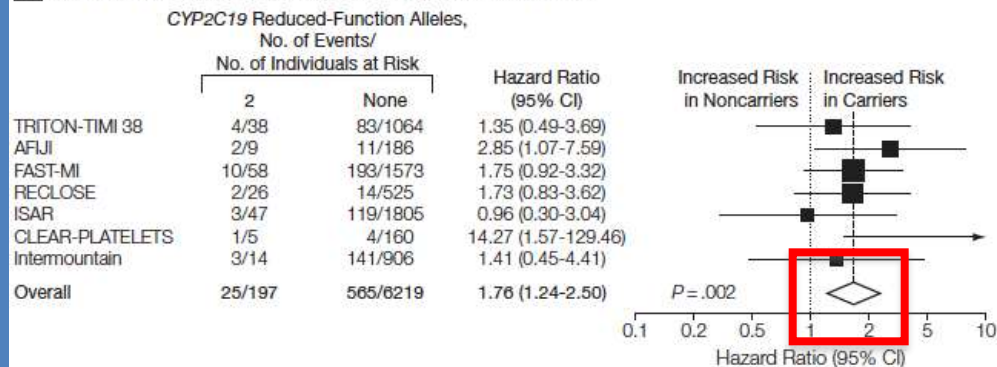
A Carriers of 1 or 2 CYP2C19 Reduced-Function Alleles vs Noncarriers



B Carriers of 1 CYP2C19 Reduced-Function Alleles vs Noncarriers



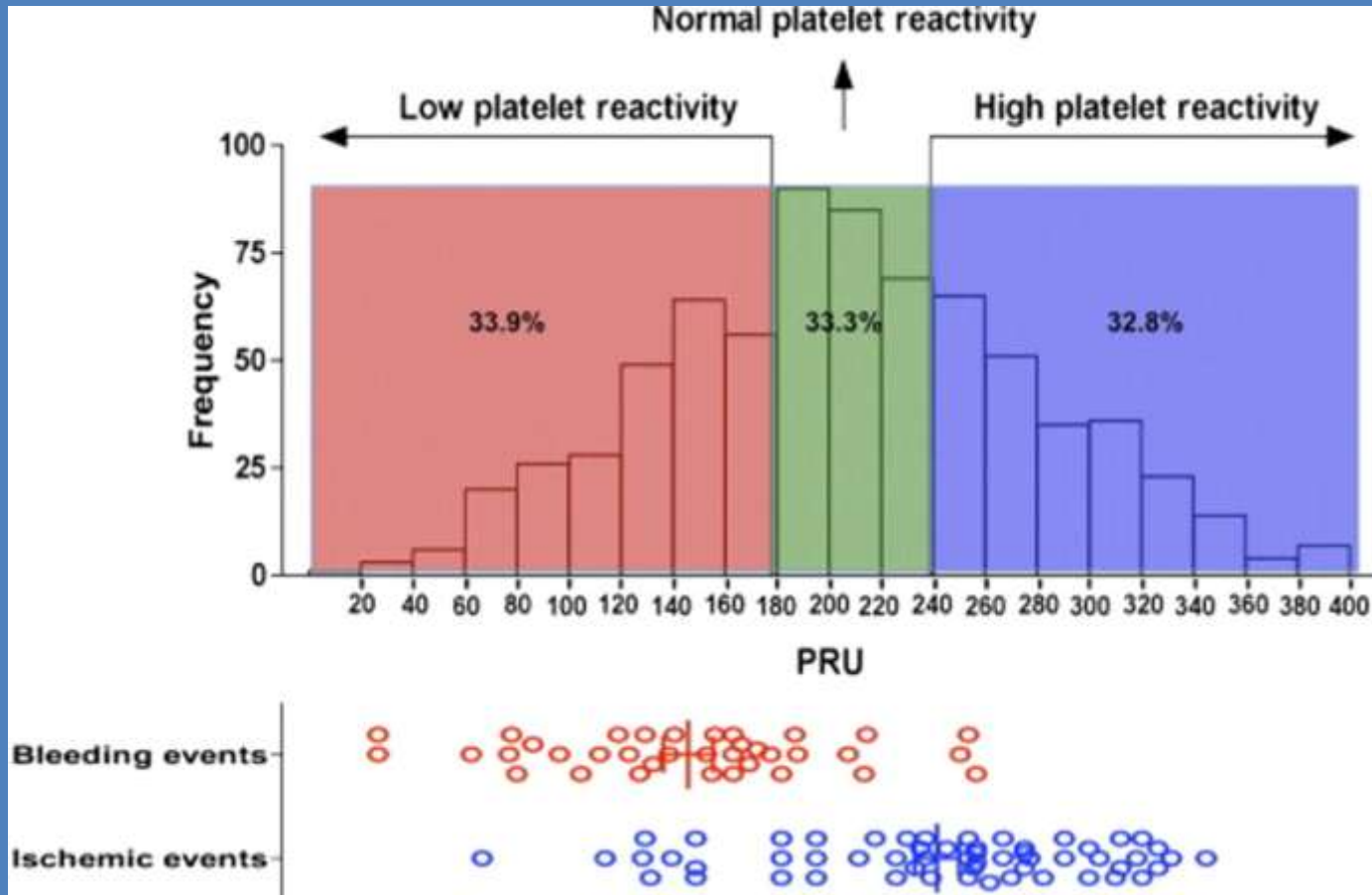
C Carriers of 2 CYP2C19 Reduced-Function Alleles vs Noncarriers



Espectro de respuestas

Ventana terapéutica

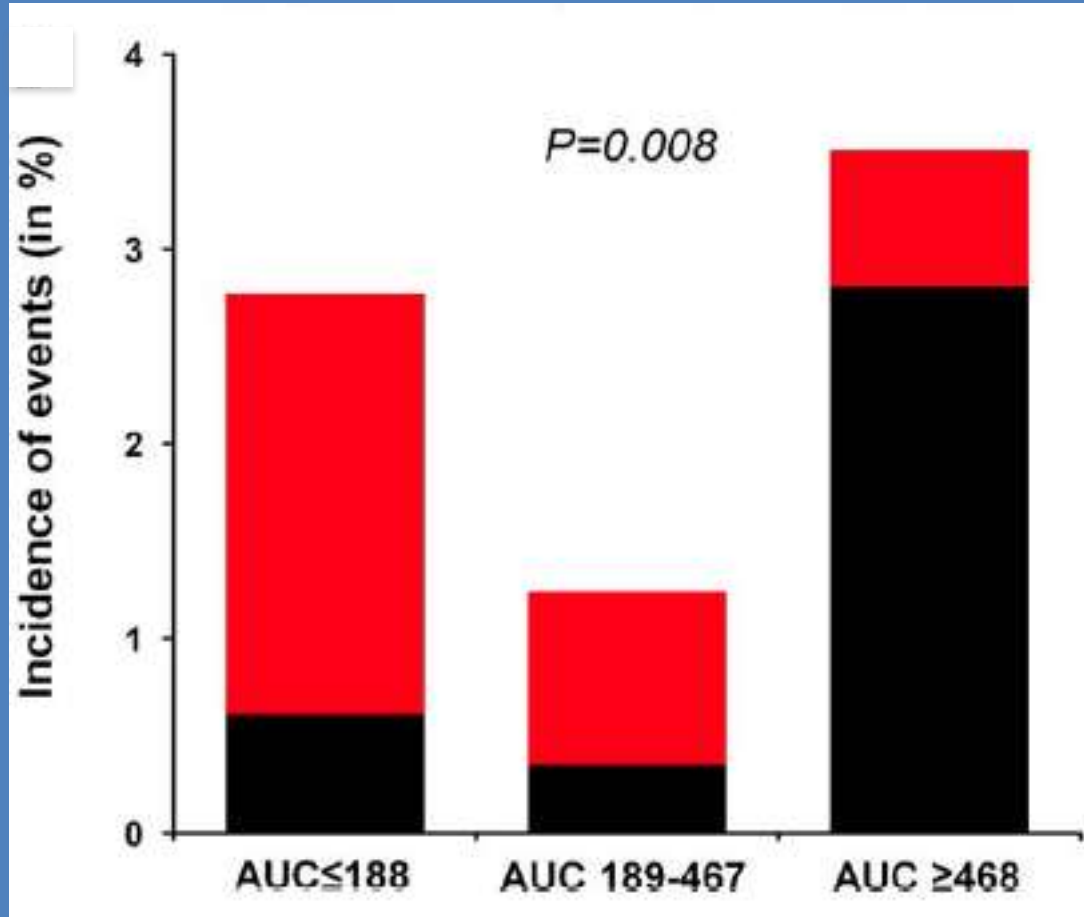
VerifyNow-P2Y12 Assay



Espectro de respuestas

Ventana terapéutica

Multiplate analyzer



Tailoring Treatment with Tirofiban in patients showing

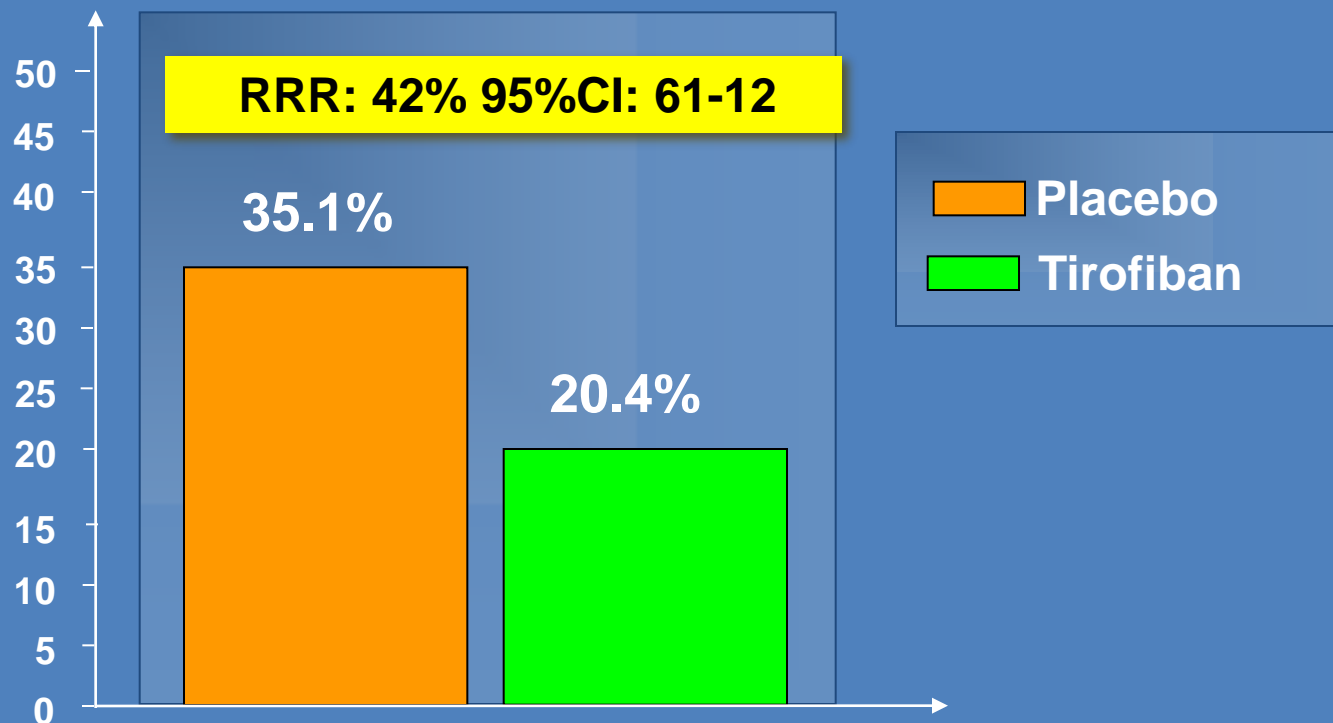
Resistance to aspirin and/or Resistance to clopidogrel

Patients with stable, unstable low risk CAD undergoing elective PCI
being ASA and/or clopidogrel resistance using Verify Now

Primary Endpoint

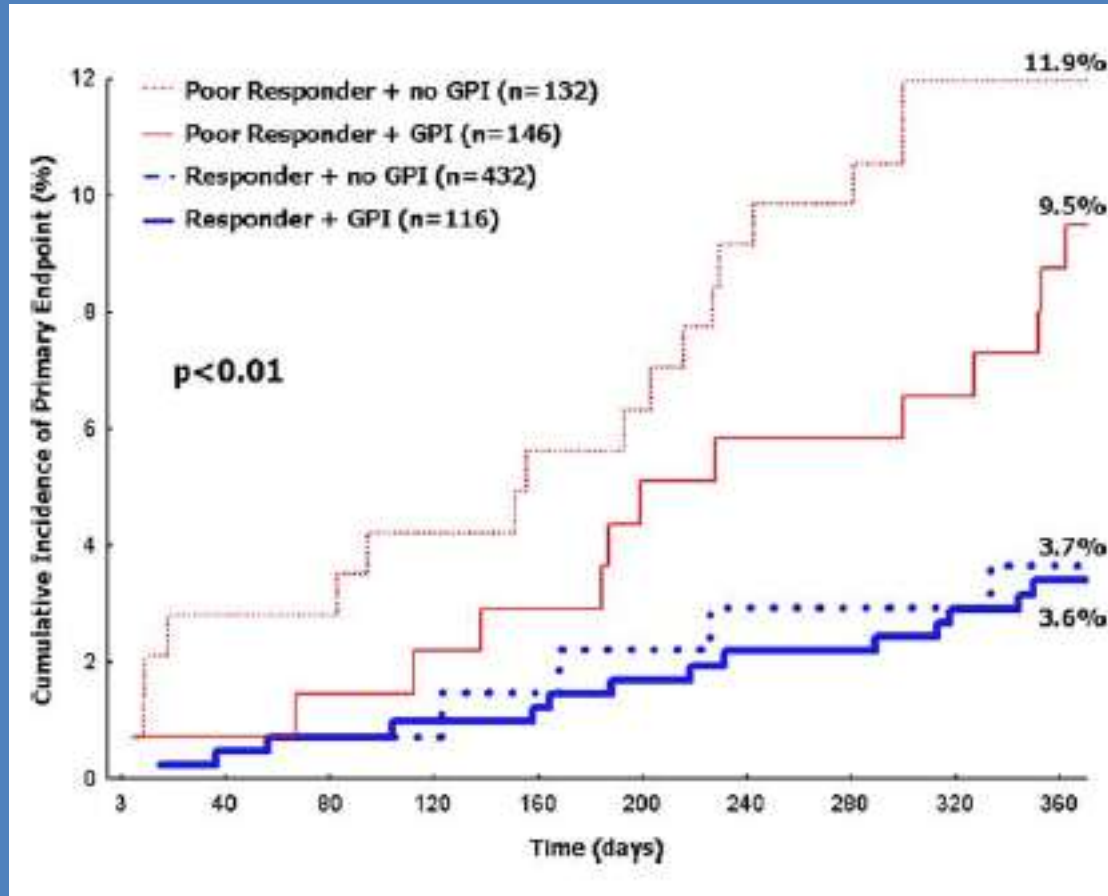
Tp >3×ULN w/in 48 hs

P=0.009 for superiority



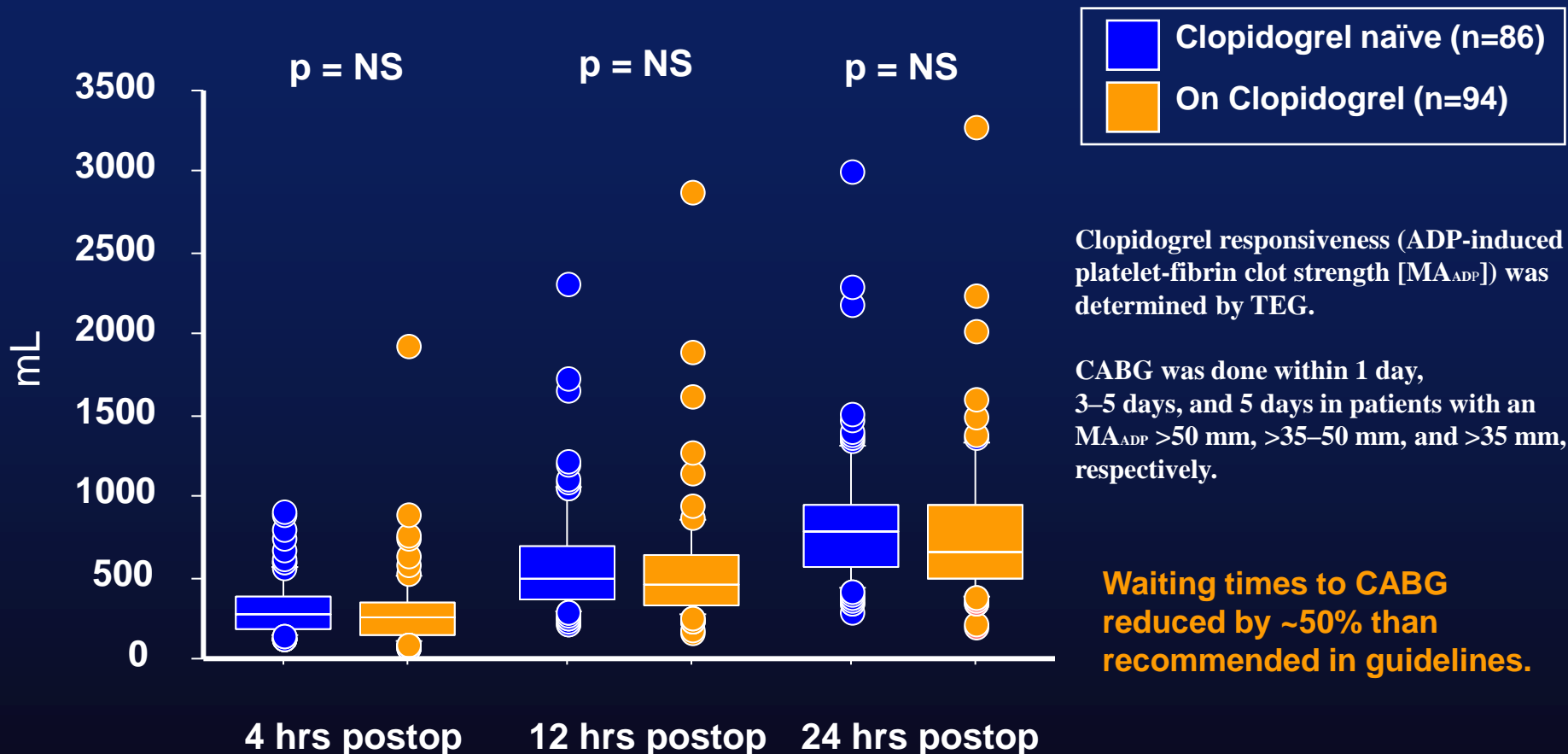
Tailoring Treatment with Tirofiban in patients showing Resistance to aspirin and/or Resistance to clopidogrel

Seguimiento al año



TARGET CABG

Primary Endpoint: 24 hr Chest Tube Output

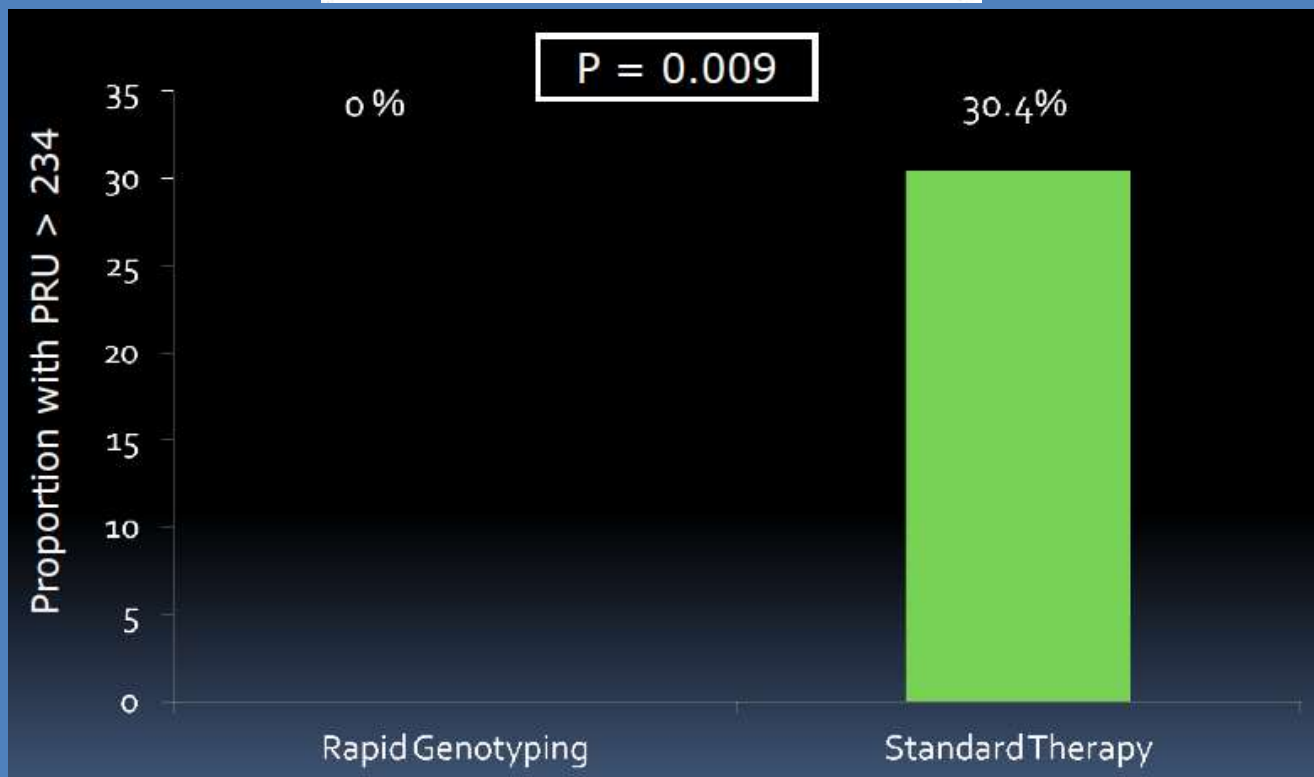
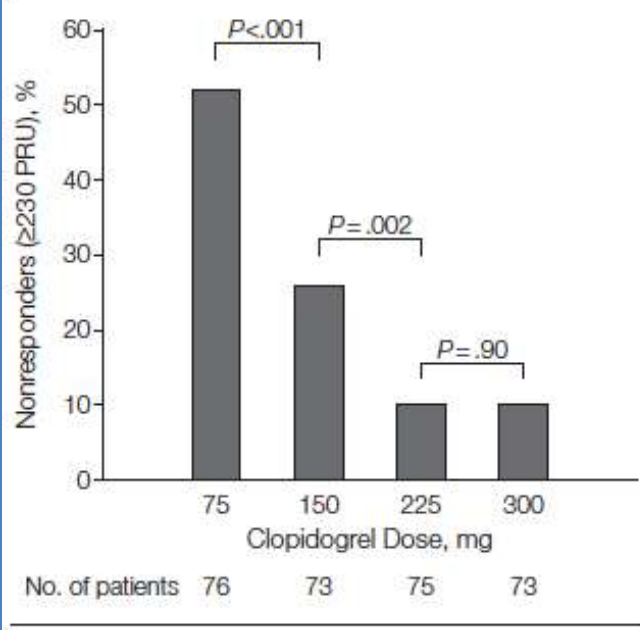


Clopidogrel responsiveness (ADP-induced platelet-fibrin clot strength [MA_{ADP}]) was determined by TEG.

CABG was done within 1 day, 3–5 days, and 5 days in patients with an MA_{ADP} >50 mm, >35–50 mm, and >35 mm, respectively.

Waiting times to CABG reduced by ~50% than recommended in guidelines.

The line in the box indicates the median and the box reaches from the the 25th and the 75 th percentile. The whiskers range from the 10th to the 90th percentile. The circles above and below the whiskers are outliers



Pruebas de función plaquetaria:

1. Variado surtido de pruebas que nos permiten evaluar todas la facetas de la función plaquetaria
2. Nos ayudan a cuantificar la respuesta a fármacos (*responder/ non reponder / Hyper responder*)
3. Valor pronóstico (*Ventana terapéutica*)
4. Potencial para guiar el manejo clínico (*tailoring therapy*).

Pero.....

- Variado surtido de pruebas que nos permiten evaluar todas la facetas de la función plaquetaria
 - *Pero cual????*

Point-of-care

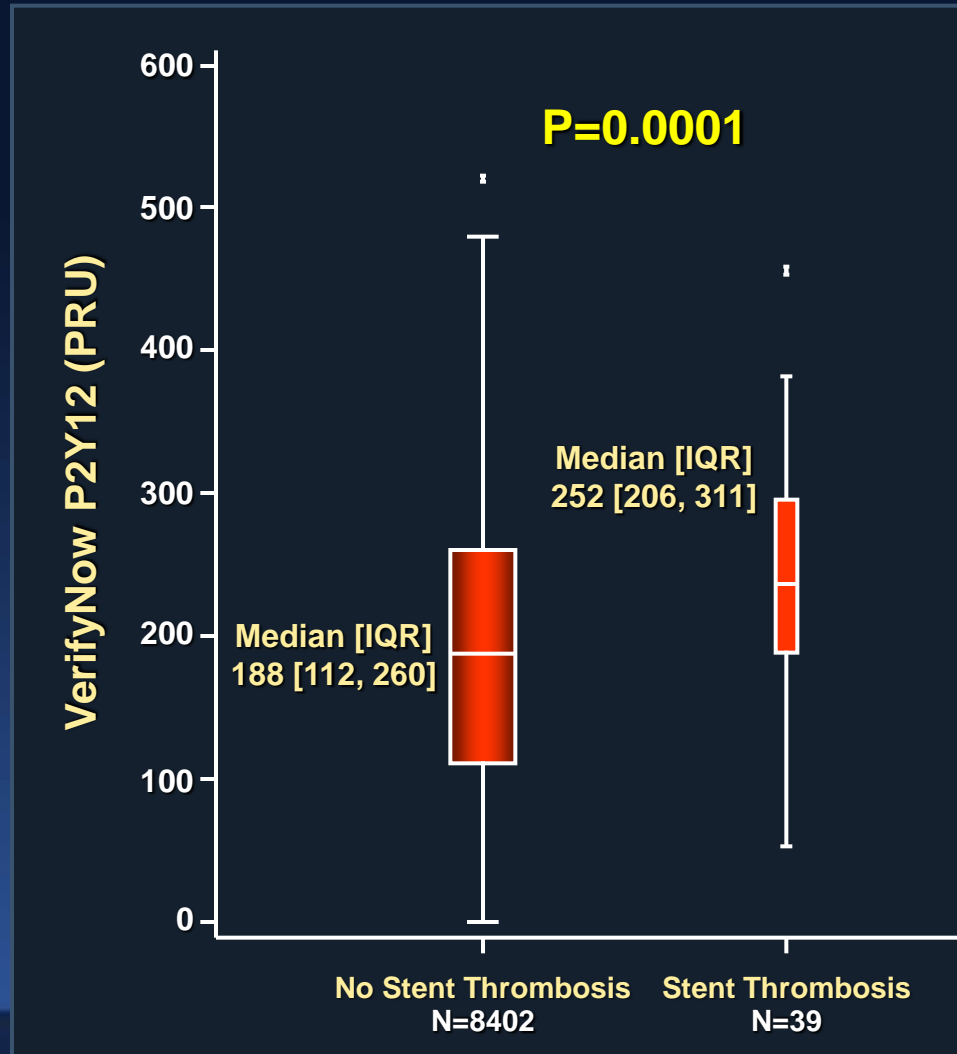
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TEG® PlateletMapping™ system	Platelet contraction			Limited studies Requires pipetting
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Cual es el mejor?
Que punto de corte?
En que momento?

Pero.....

- Variado surtido de pruebas que nos permiten evaluar todas la facetas de la función plaquetaria
 - *Pero cual????*
- Nos ayudan a cuantificar la respuesta a fármacos (responder/ non reponder / Hyper responder)
 - *Pero esto importa de verdad?*

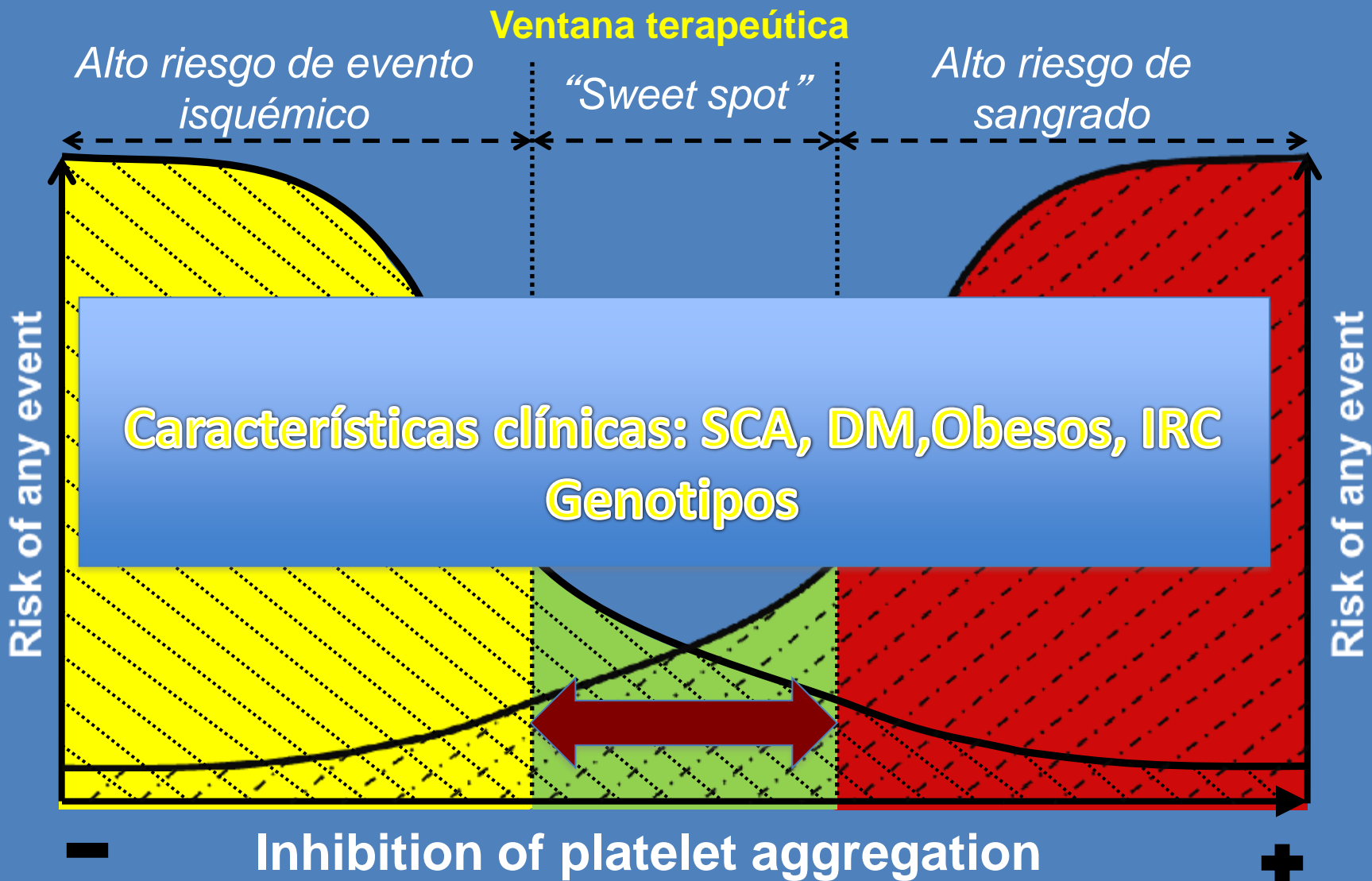
ADAPT-DES: ADP Platelet Responsiveness in Pts with and without Definite/Probable Stent Thrombosis within 30 Days



Pero.....

- Variado surtido de pruebas que nos permiten evaluar todas la facetas de la función plaquetaria
 - *Pero cual????*
- Nos ayudan a cuantificar la respuesta a fármacos (responder/ non reponder / Hyper responder)
 - *Pero esto importa de verdad?*
- Valor pronóstico (Ventana terapéutica)
 - *Pero sirve para todos?*

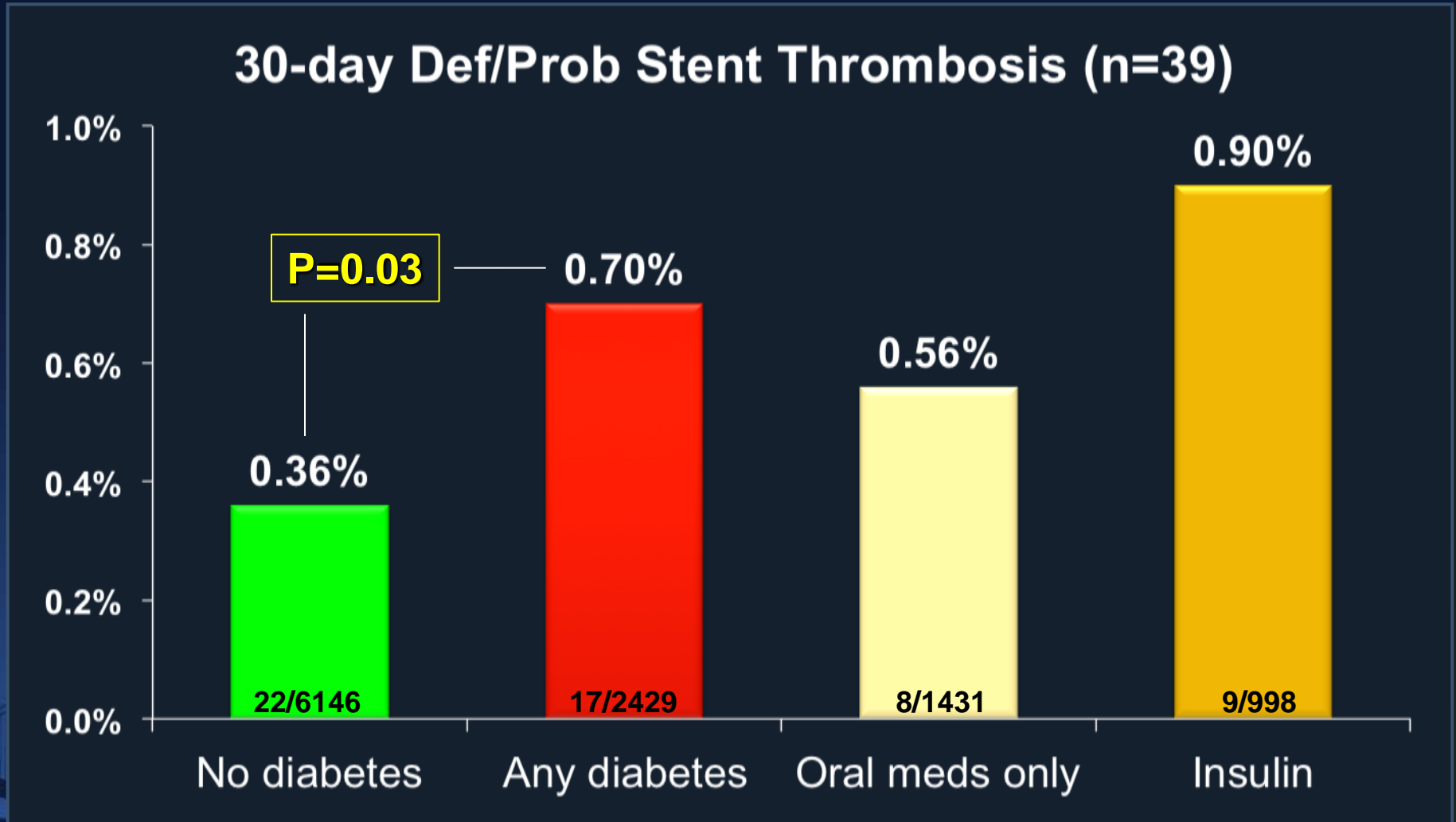
Espectro de respuestas



 Riesgo isquémico

 Riesgo de sangrado

ADAPT-DES: Relationship between diabetes* and stent thrombosis



Pero.....

- Variado surtido de pruebas que nos permiten evaluar todas la facetas de la función plaquetaria
 - *Pero cual????*
- Nos ayudan a cuantificar la respuesta a fármacos (responder/ non reponder / Hyper responder)
 - *Pero esto importa de verdad?*
- Valor pronóstico (Ventana terapéutica)
 - *Pero sirve para todos?*
- Potencial para guiar el manejo clínico (tailoring therapy).
 - *Pero hay evidencia?*

Ensayos clínicos en función plaquetaríá

Negativos

ARCTIC

Mensajes para “llevar a casa”

- Nos queda por definir que herramienta(s) es la más apropiada.
- También que puntos de corte.
- Cual será el mejor escenario clínico para utilizarlo.

No “uno para todos”

2011 ACCF/AHA/SCAI Guideline for PCI Platelet Function Testing



Platelet function testing may be considered in patients at high risk for poor clinical outcomes.



In clopidogrel-treated patients with high platelet reactivity, alternative agents, such as prasugrel or ticagrelor, might be considered.



No Benefit

The routine clinical use of platelet function testing to screen clopidogrel-treated patients undergoing PCI **is not recommended.**



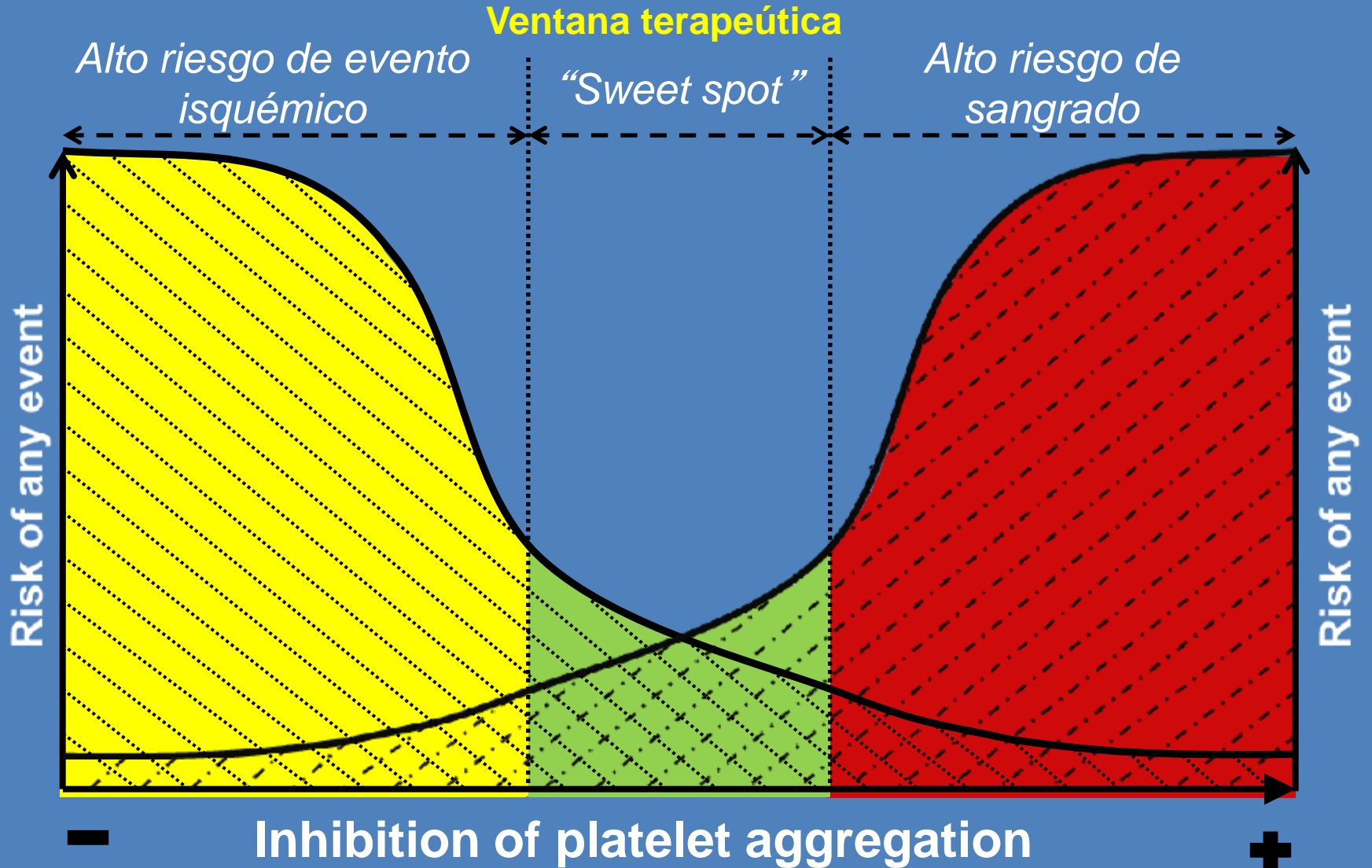
Helping Cardiovascular Professionals
Learn. Advance. Heal.



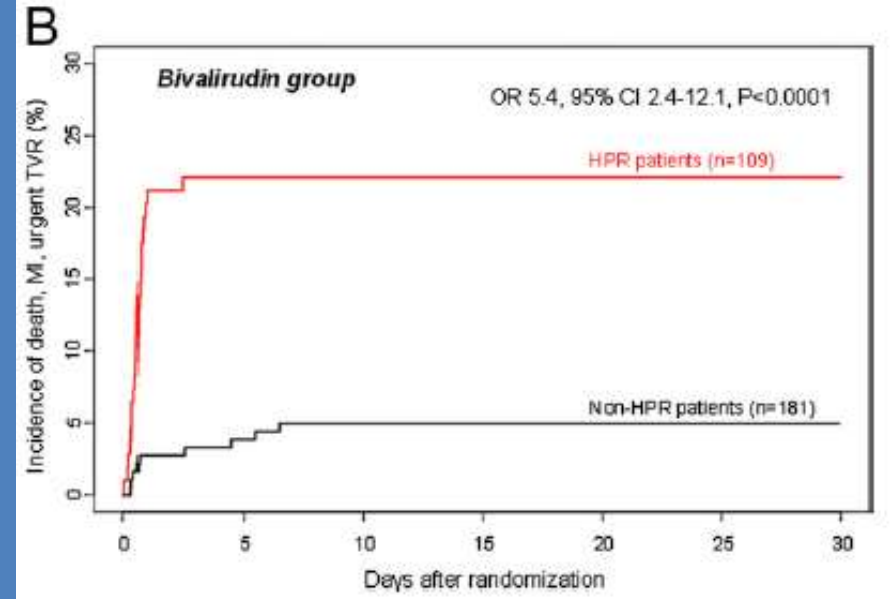
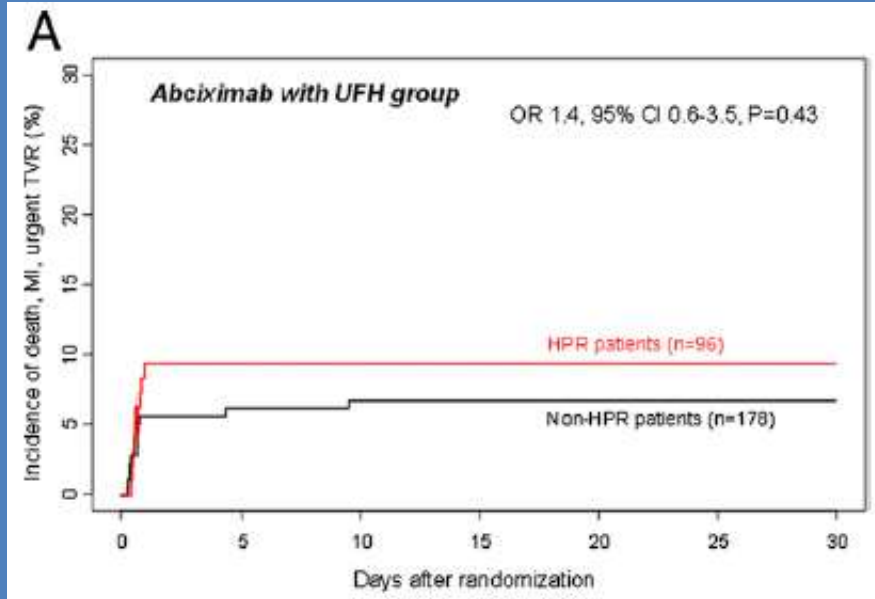
Relación con eventos clínicos Aspirina

	LTA AA		OR (95% CI)	P-value
	NAPR (n = 481)	HAPR (n = 444)		
	< 20% aggregation, no. (%)	> 20% aggregation, no. (%)		
Death, MI, ST, stroke	29 (6.0)	45 (10.1)	1.76 (1.08–2.86)	0.020
Death	4 (0.8)	11 (2.5)	3.03 (0.96–9.58)	0.048
MI	21 (4.4)	31 (7.0)	1.64 (0.93–2.91)	0.08
ST	3 (0.6)	6 (1.4)	2.18 (0.54–8.78)	0.26
Stroke	6 (1.2)	4 (0.9)	0.72 (0.20–2.57)	0.61
	VerifyNow Aspirin			
	NAPR (n = 324)	HAPR (n = 98)	OR (95% CI)	P-value
	< 454 ARU, no. (%)	> 454 ARU, no. (%)		
Death, MI, ST, stroke	19 (5.9)	13 (13.3)	2.46 (1.17–5.17)	0.015
Death	5 (1.5)	4 (4.1)	2.71 (0.71–10.31)	0.13
MI	13 (4.0)	6 (6.1)	1.56 (0.58–4.22)	0.38
ST	1 (0.3)	2 (2.0)	6.73 (0.60–75.02)	0.07
Stroke	2 (0.6)	3 (3.1)	5.08 (0.84–30.87)	0.05

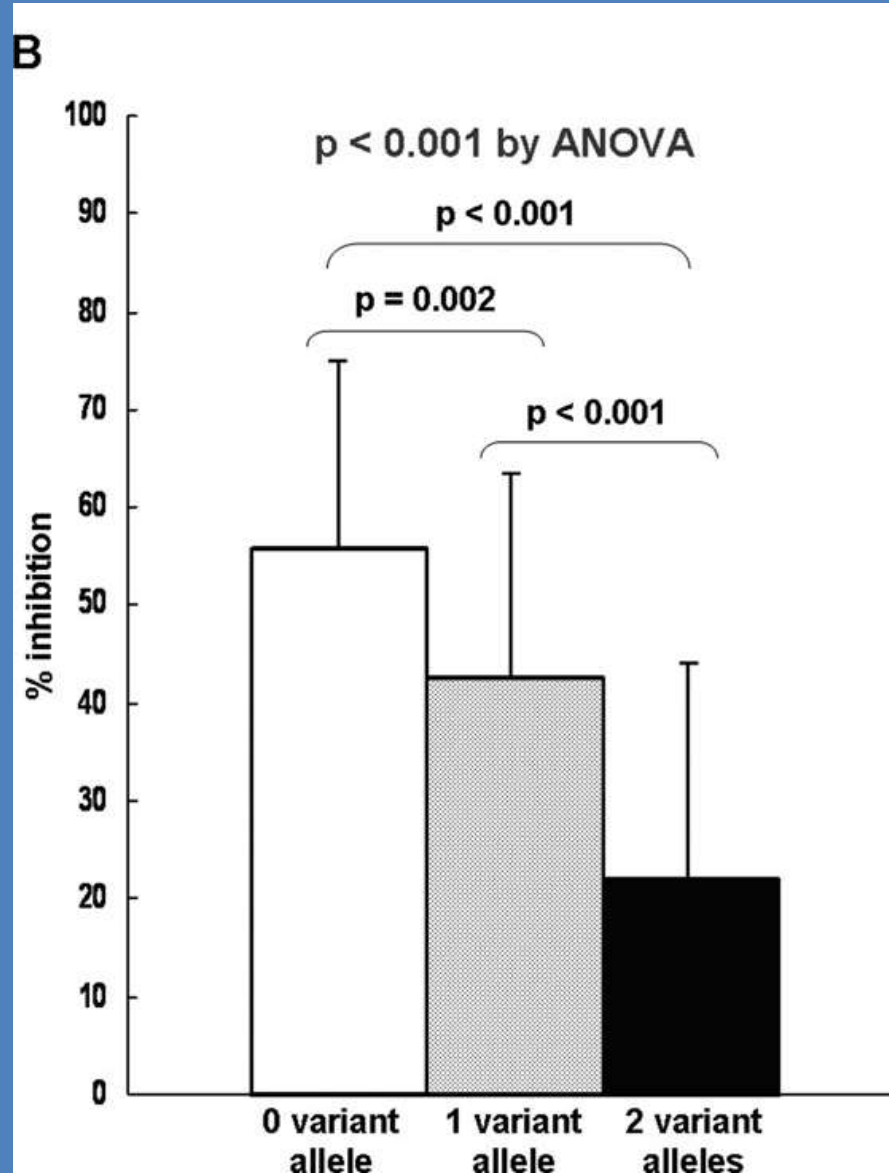
Espectro de respuestas

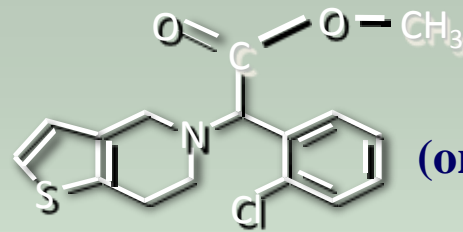


ISAR-REACT-4 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment-4) Platelet Substudy



Respuesta a clopidogrel modificada por polimorfismo





Clopidogrel

(oral ingestion of pro-drug)

Genetic targets

MDR-1

Intestinal absorption

CYP enzyme system

Two sequential steps:

One step: CYP3A4, CYP3A5, CYP2C9, CYP1A2

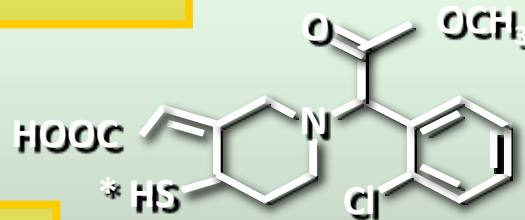
Both steps: CYP2B6, CYP2C19

**Hepatic generation
of active metabolite**

Platelet membrane receptors

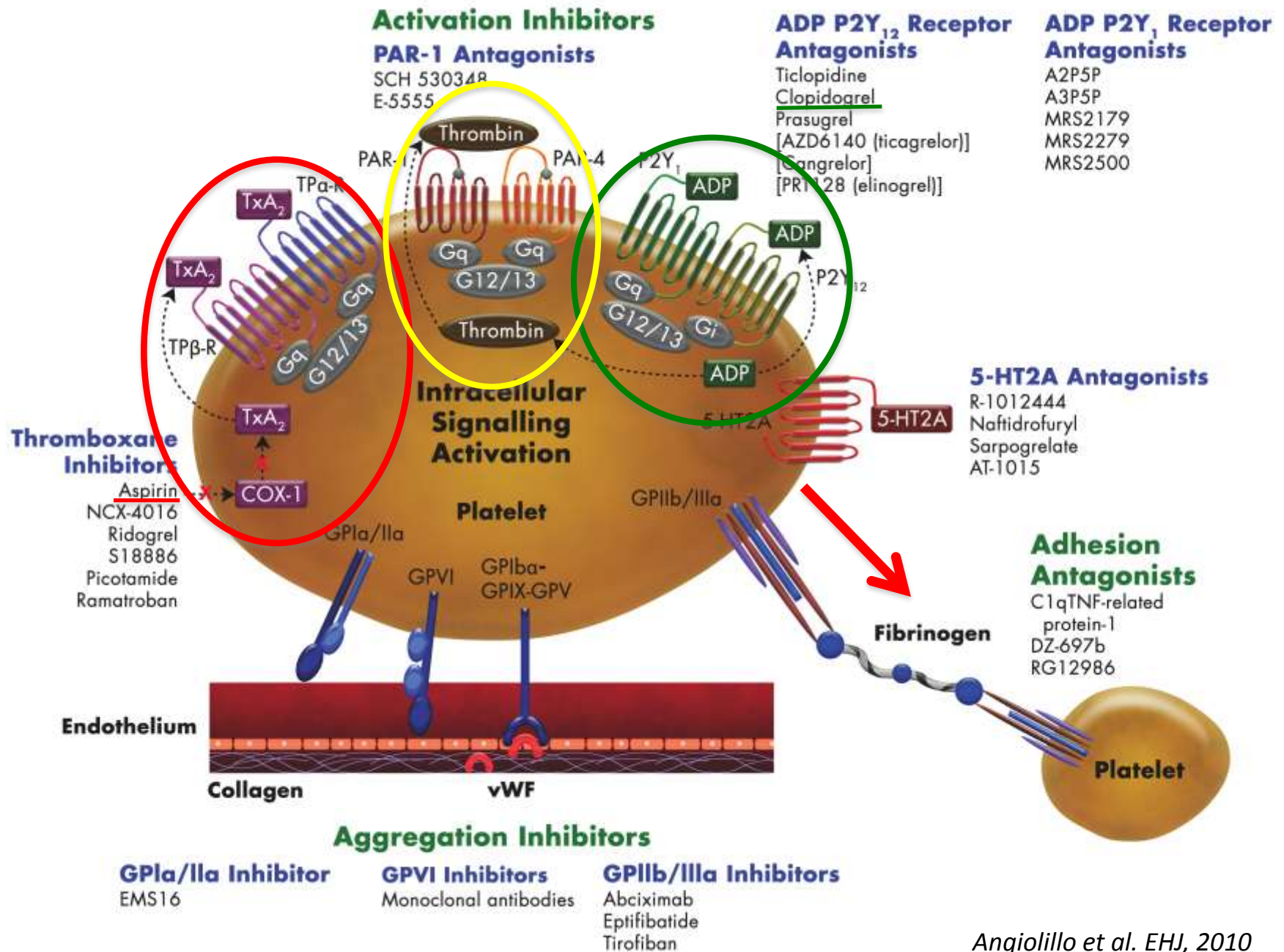
P2Y₁₂, GP IIb/IIIa, GP Ia

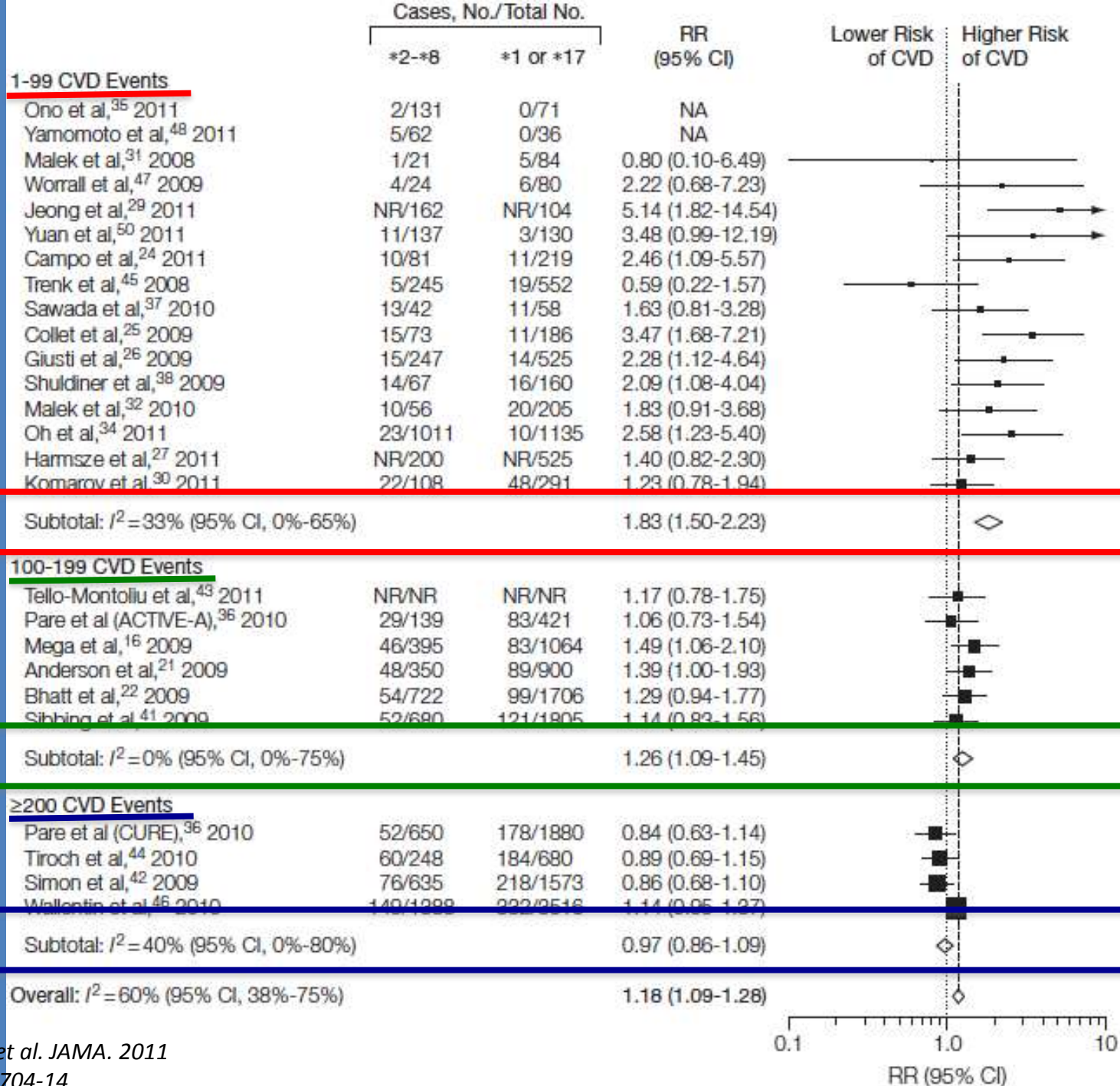
Platelet inhibition



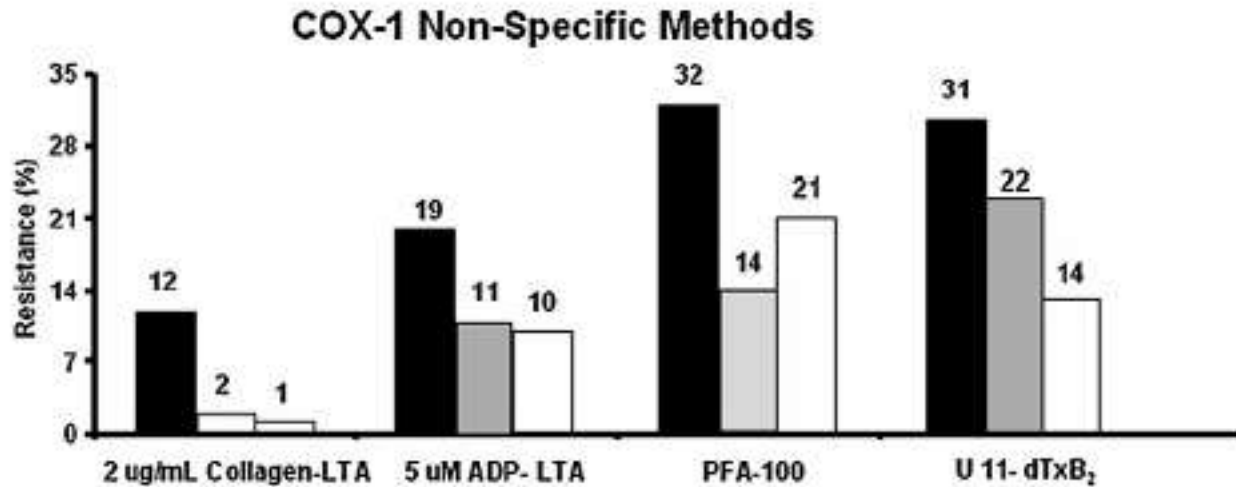
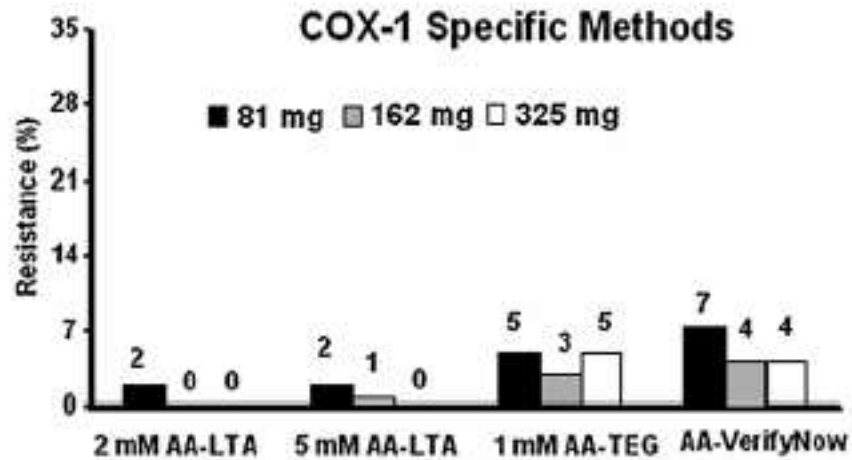
* HS

Fisiología plaquetaria





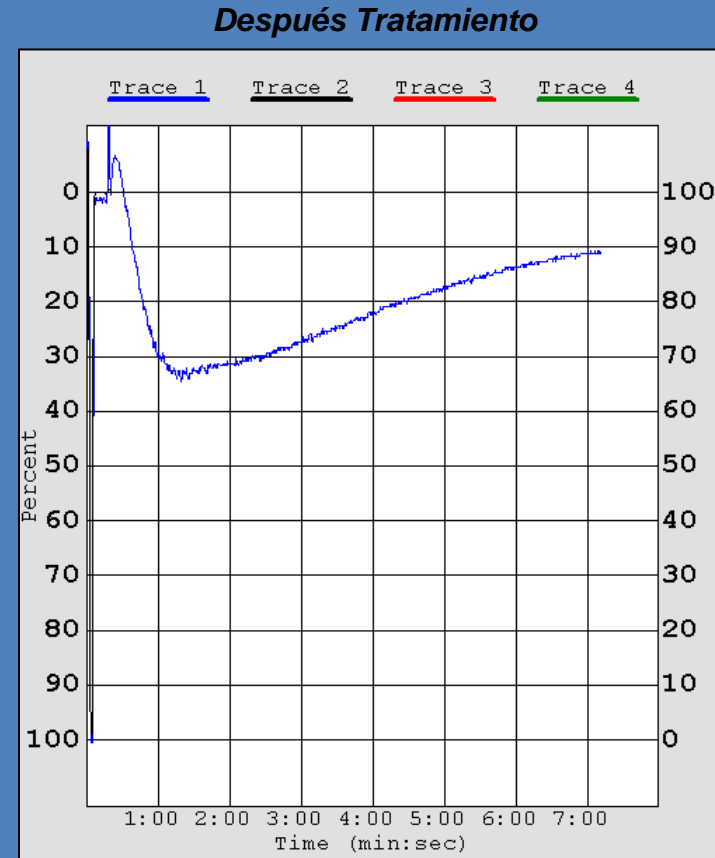
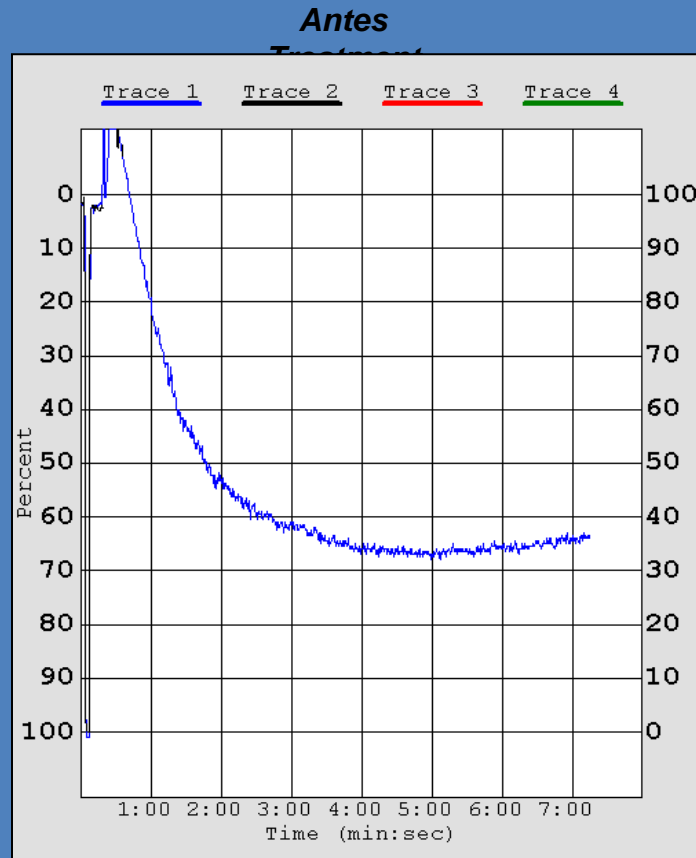
Respuesta a aspirina



Respuesta a fármacos antiplaquetarios

Definiciones

- Hiper / Hipo: Definiciones basadas en test de laboratorio



Cambio absoluto: 68%-32%= **36%**

Cambio Relativo: (68%-32%)/68% * 100 = **53%**

On-treatment platelet reactivity: **32%**

Respuesta a fármacos antiplaquetarios

Definiciones

Fallo al tratamiento

CURE

