



SOCIEDAD  
ESPAÑOLA DE  
CARDIOLOGÍA

> **CurSOS** de  
**formación**

**Continuada**

## NUEVOS ANTIAGREGANTES EN SCA COMO GESTIONAR EL CAMBIO

# ¿Aspirina en el siglo XXI?

*Antonio Fernández-Ortiz*



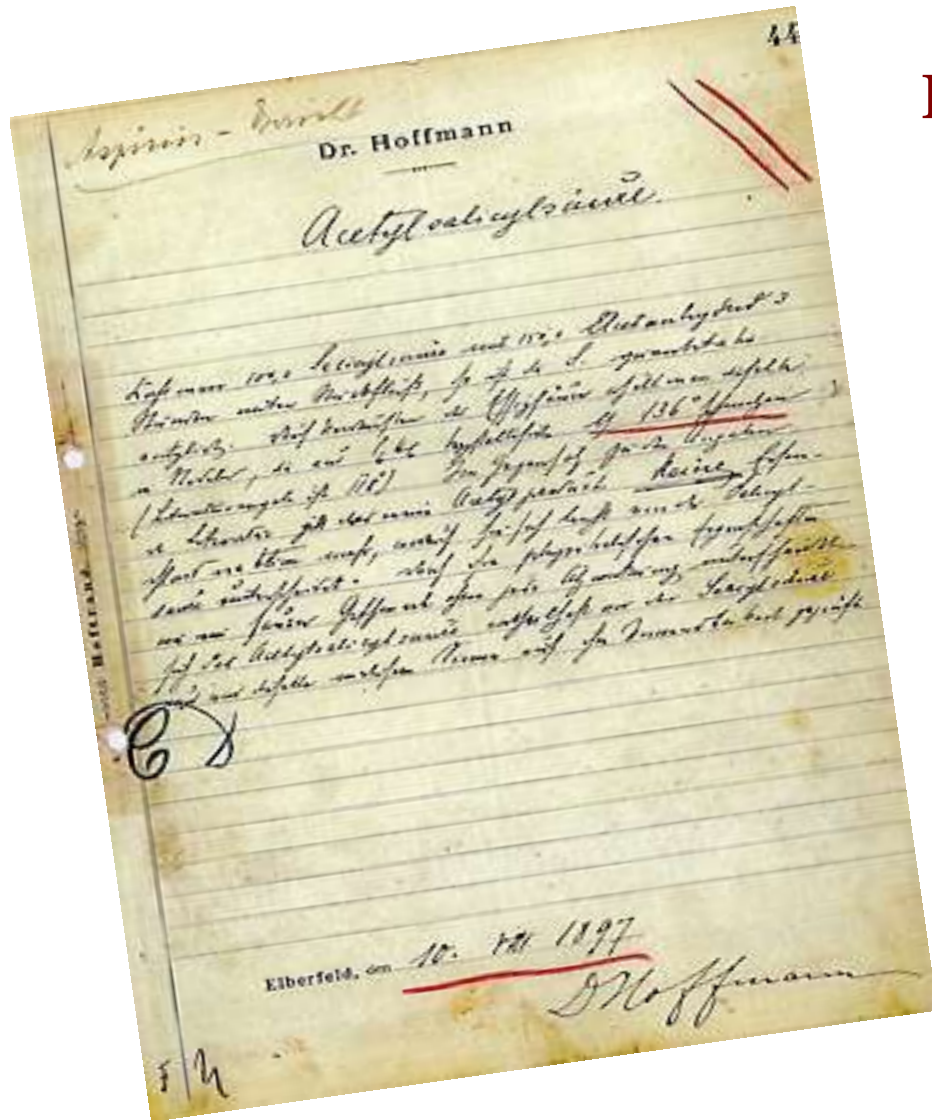
Sección de  
Cardiopatía Isquémica  
y Unidades Coronarias

Grupo de  
Trombosis Cardiovascular

Casa del Corazón  
Madrid, 15 de Junio de 2012

# Aspirin

(From the German acetylspirsaure + chemical suffix – in)



First synthesized in pure form by Felix Hoffman of Friedr. Bayer & Co. in 1897.





DEMAND



# ASPIRIN

Unless you see the "Bayer Cross" package or on tablets you are not getting the genuine Bayer Aspirin proved by millions and prescribed by physicians over twenty-seven years for

- |           |            |
|-----------|------------|
| Colds     | Headache   |
| Neuritis  | Lumbago*   |
| Toothache | Rheumatism |
| Neuralgia | Pain, Pain |

**DOES NOT AFFECT THE HEART**

Each unbroken "Bayer" package contains proven directions. Handy boxes of twelve tablets cost few cents. Drug-gists also sell bottles of 24 and 100.

Aspirin is the trade mark of Bayer Manu-facture of Mononasticumester of Salicylicacid

## Contra el dolor...



# ASPIRINA

UNICAMENTE AUTENTICA CON LA:   
Rechácense todas las imitaciones

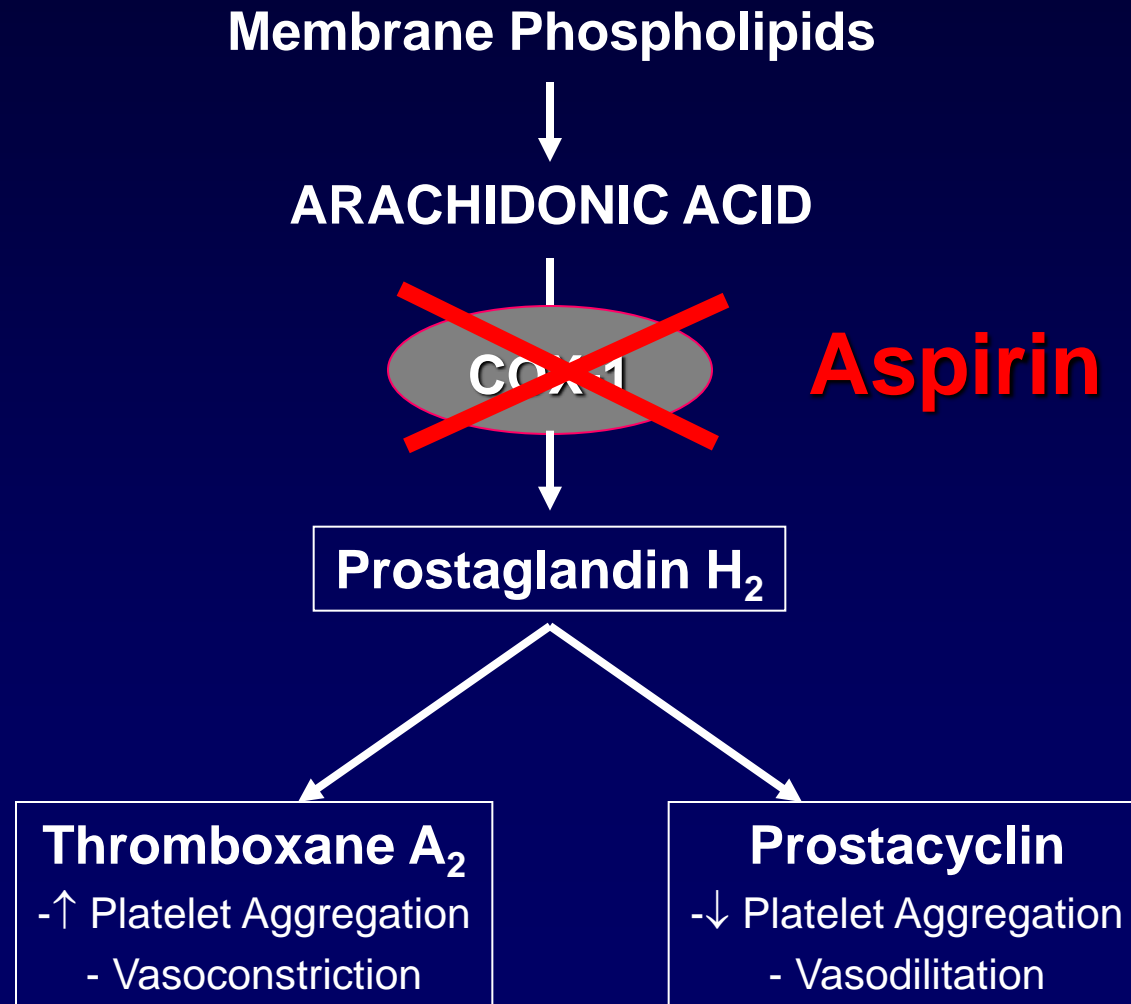
# Tabletas "Bayer" de ASPIRINA



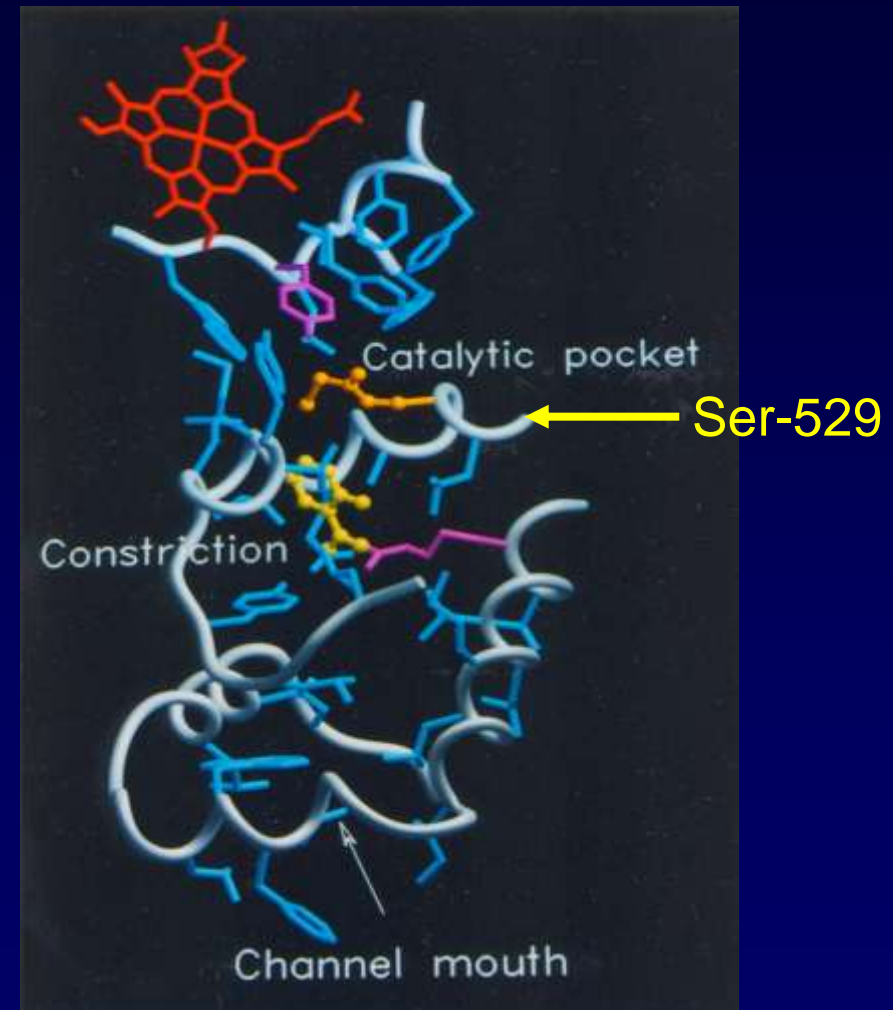
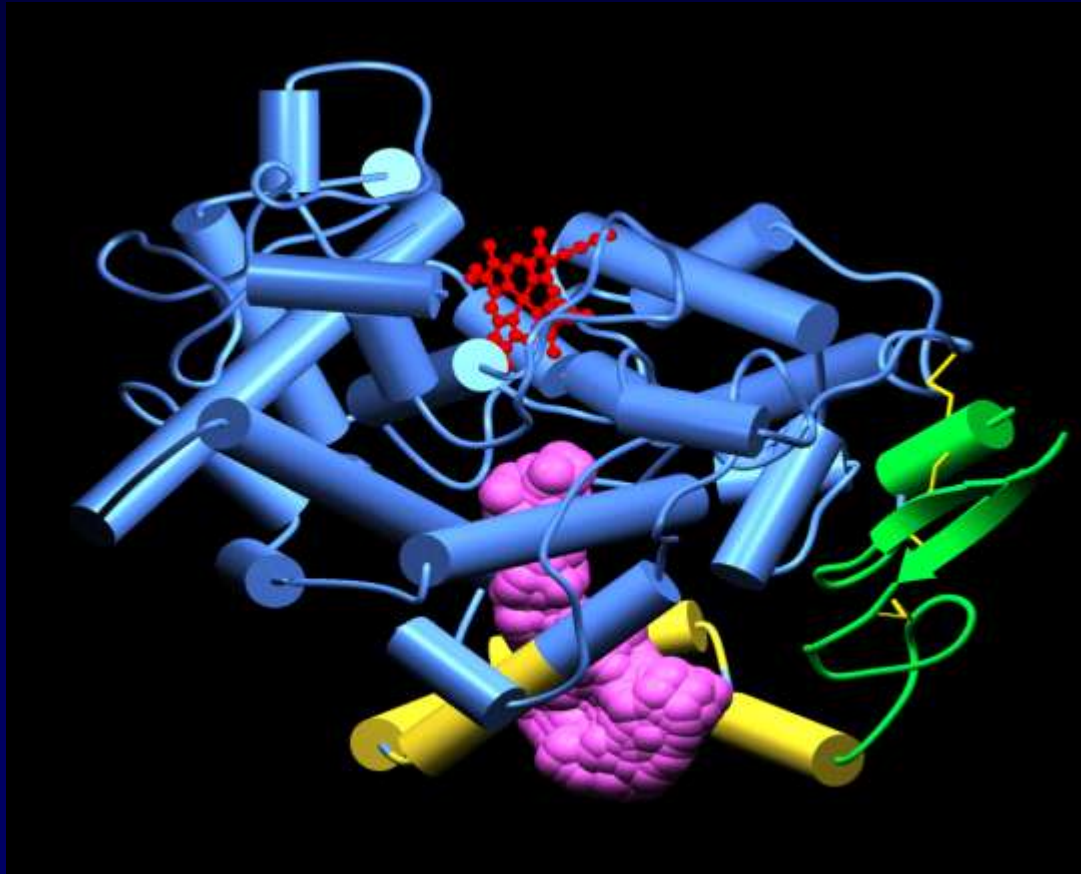
## El fin del sufrimiento



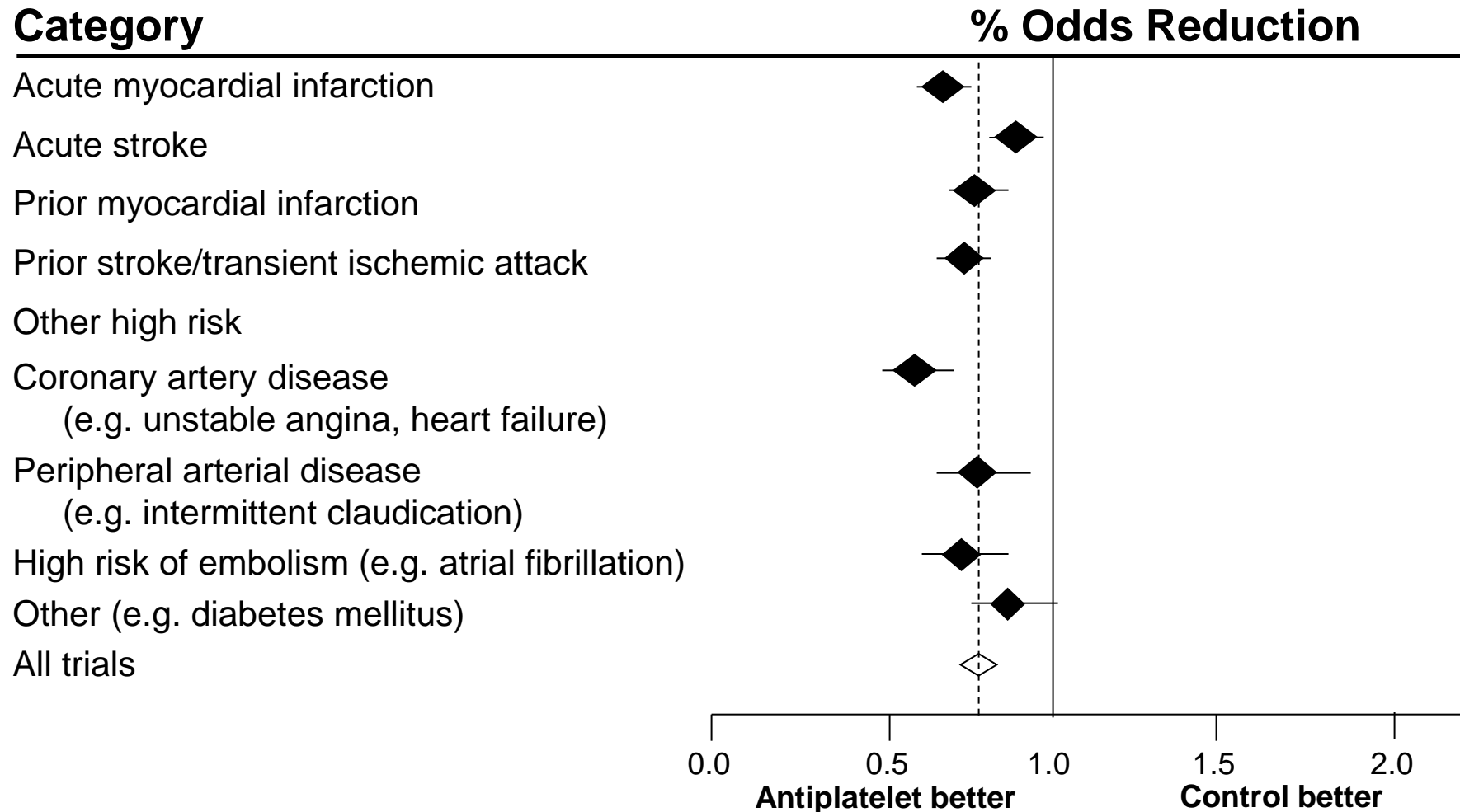
# Metabolic Pathways of Arachadonic Acid



# Acetylation of Ser-529 Obstructs the COX-1 Channel Just Below the Catalytic Pocket



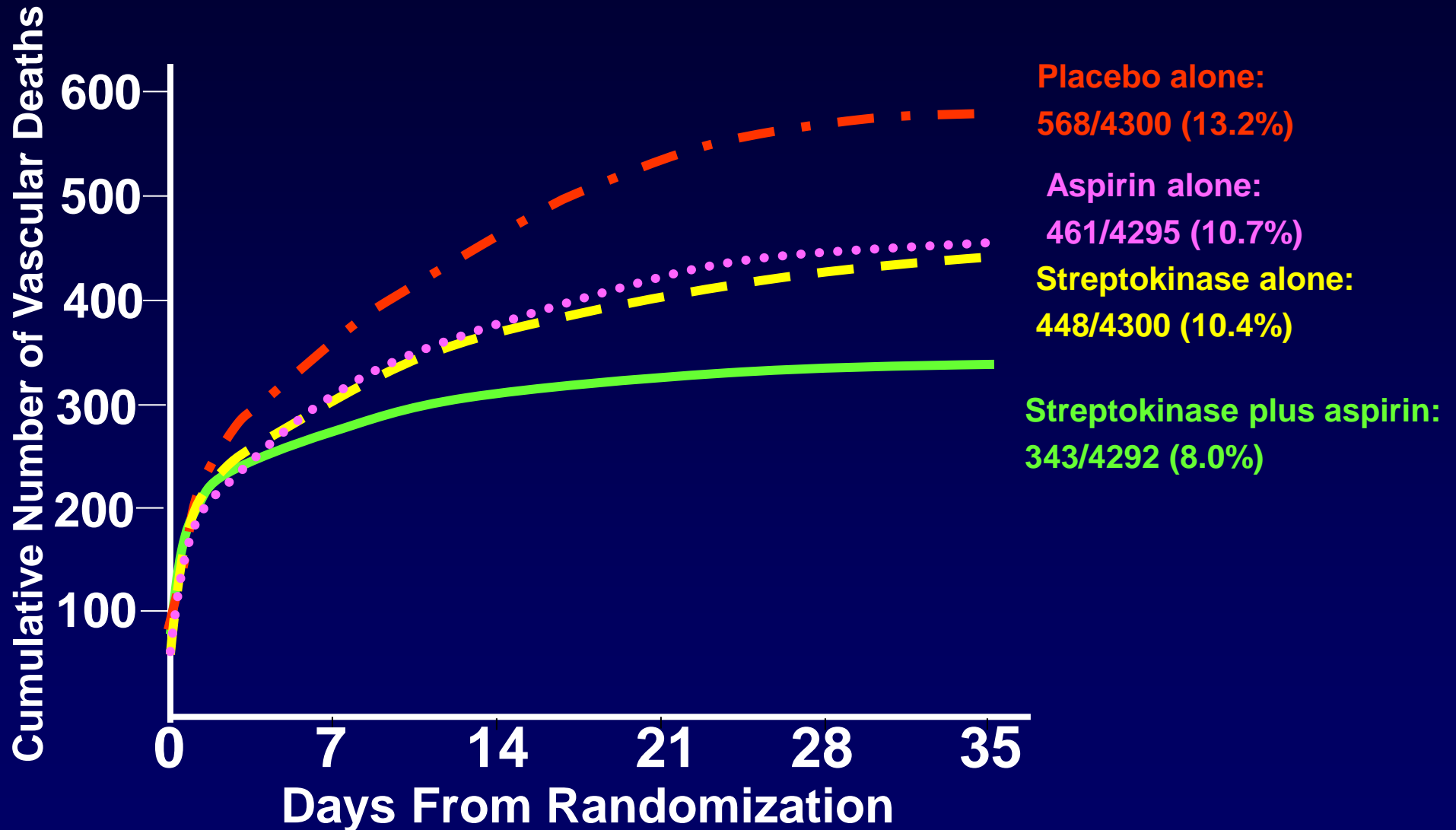
# Antithrombotic Trialists' Collaboration (ATC): Efficacy of Antiplatelet Therapy on Vascular Events



\*Vascular events = myocardial infarction, stroke or vascular death

Antithrombotic Trialists' Collaboration. *BMJ* 2002; 324: 71–86.

# Aspirin in Acute Myocardial Infarction: ISIS-2

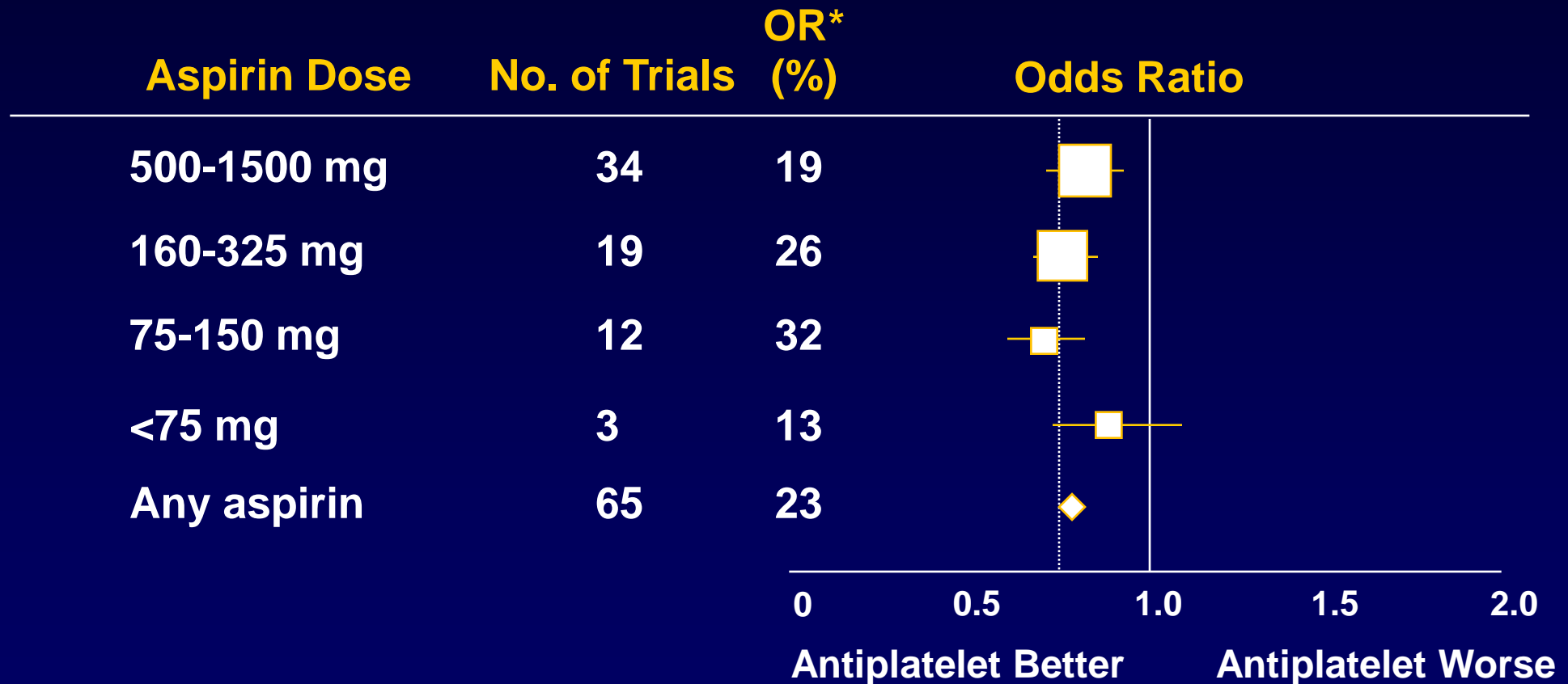


# Aspirina en el siglo XXI (?)

- ¿cuál es la dosis óptima?
- ¿es útil en prevención primaria?
- ¿resistencia a la aspirina?



# Indirect Comparisons of ASA Doses on Vascular Events in High-Risk Patients



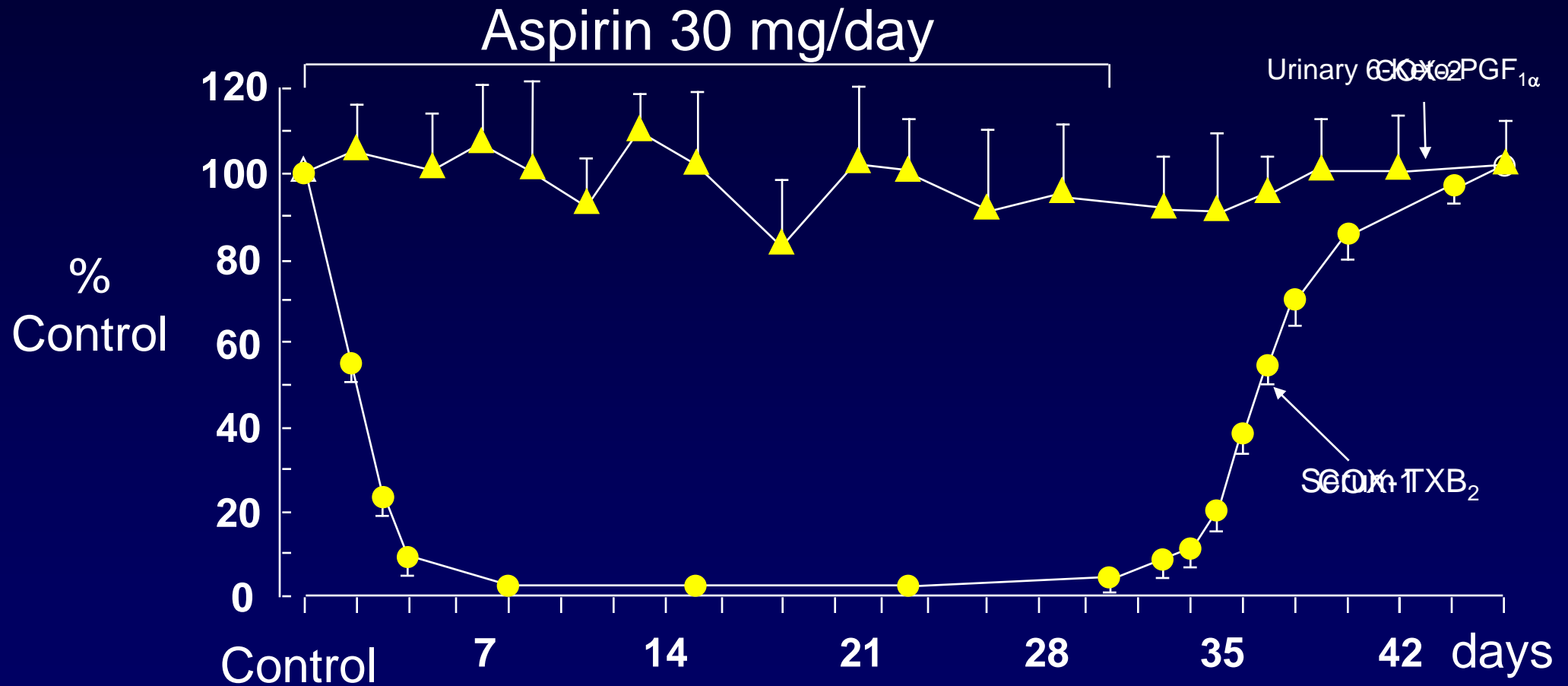
\* Odds reduction.

Treatment effect  $P < .0001$ .

ASA, acetylsalicylic acid.

Adapted with permission from BMJ Publishing Group. Antithrombotic Trialists' Collaboration. *BMJ*. 2002;324:71-86.

# Selective Cumulative Inhibition of Platelet TXA<sub>2</sub> Production by Low-Dose Aspirin in Healthy Subjects



Patrignani, Filabozzi & Patrono, J Clin Invest 1982; 69:1366-72

# BRAVO: Bleeding By ASA dose

## Outcomes by Aspirin Dose in Placebo Study Drug Patients

	Low Dose, 75-162 mg/d (n=2410)	Higher Dose, 162-326 mg/d (n=2179)
<b>Primary end point</b>	<b>16.4</b>	<b>18.6</b>
<b>Death, MI, stroke</b>	<b>6.2</b>	<b>6.1</b>
<b>Death</b>	<b>2.8</b>	<b>1.7</b>
<b>MI</b>	<b>2.0</b>	<b>2.1</b>
<b>Stroke</b>	<b>2.1</b>	<b>2.8</b>
<b>Internal bleeding</b>	<b>2.4</b>	<b>3.3</b>
<b>Any bleeding</b>	<b>11.1</b>	<b>15.4</b>
<b>Transfusion</b>	<b>1.0</b>	<b>2.0</b>



# ASA Dose Comparison

## Primary Outcome and Bleeding

	ASA 75-100 mg	ASA 300-325 mg	HR	95% CI	P
CV Death/MI/Stroke					
PCI (2N=17,232)	4.2	4.1	0.98	0.84-1.13	0.76
No PCI (2N=7855)	4.7	4.4	0.92	0.75-1.14	0.44
Overall (2N=25,087)	4.4	4.2	0.96	0.85-1.08	0.47
Stent Thrombosis	2.1	1.9	0.91	0.73-1.12	0.37
TIMI Major Bleed	1.03	0.97	0.94	0.73-1.21	0.71
CURRENT Major Bleed	2.3	2.3	0.99	0.84-1.17	0.90
CURRENT Severe Bleed	1.7	1.7	1.00	0.83-1.21	1.00

**GI Bleeds: 30 (0.24%) v 47 (0.38%), P=0.051**

No other significant differences between ASA dose groups

**Table. Vascular Disorders for Which Aspirin Has Been Shown to Be Effective and Lowest Effective Dose**

Disorder	Lowest Effective Daily Dose (mg)
Transient ischemic attack and ischemic stroke*	50
Men at high cardiovascular risk	75
Hypertension	75
Stable angina	75
Unstable angina*	75
Severe carotid artery stenosis*	75
Polycythemia vera*	100
Acute myocardial infarction	160
Acute ischemic stroke*	160

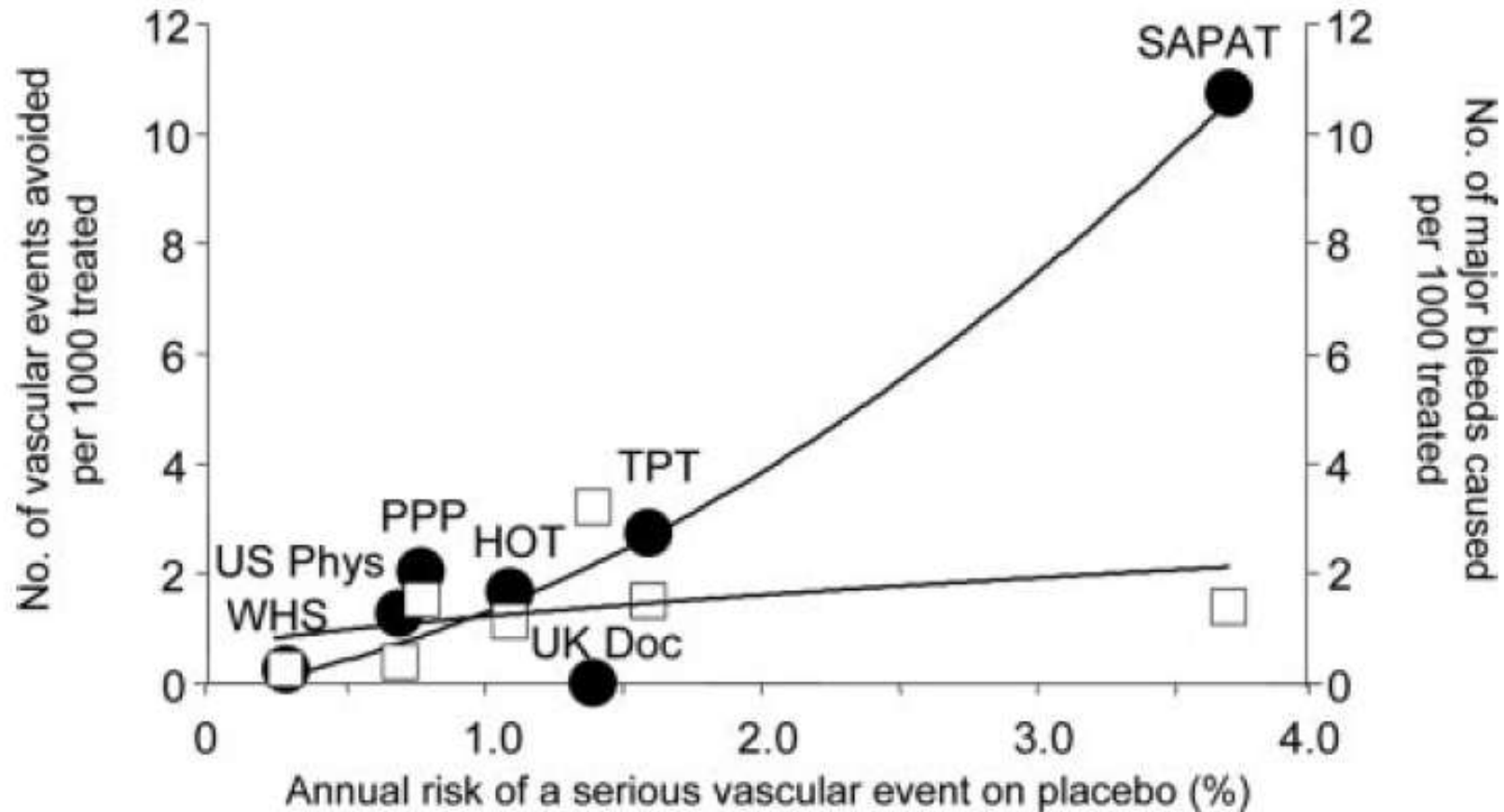
\*Higher doses have been tested in other trials and not found to confer any greater risk reduction.

# Aspirina

## Relación beneficio / riesgo

	Nº eventos evitados / 1000 tratados / año	Nº hemorragias GI / 1000 tratados / año
Bajo riesgo	1-2	1-2
HTA esencial	1-2	1-2
Angina estable	10	1-2
Infarto previo	20	1-2
Angina inestable	50	1-2

# Efficacy and safety of low-dose aspirin in low-risk subjects



# Recomendación ADA (2004) en PREVENCIÓN PRIMARIA:

75-162 mg /día en DM tipo I o DM tipo II >40 años o FRCV asociados

## JPAD

Primary prevention trial

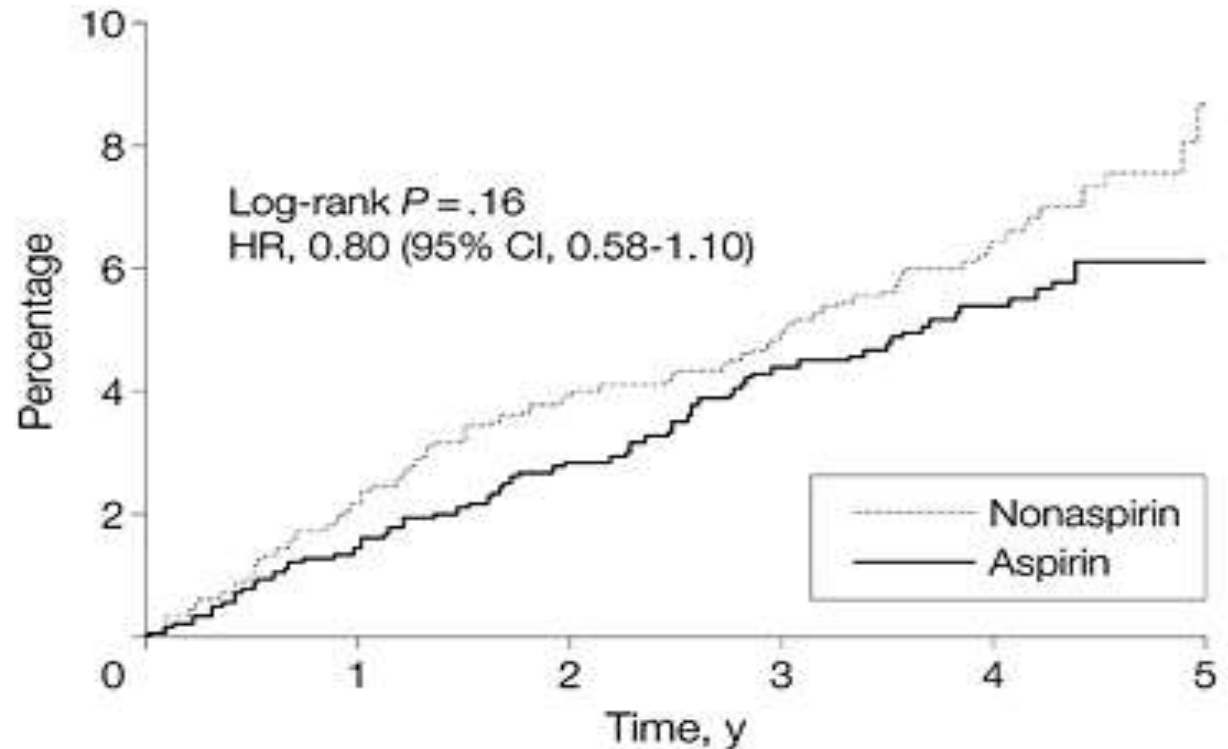
2537 DM II pts

Aspirin vs placebo

Mean FU 4,37 years

Primary EP:

- Isch. heart disease
- Stroke
- Peri. arterial disease



No. at risk

Nonaspirin	1277	1220	1165	1117	813	135
Aspirin	1262	1210	1159	1095	806	140



# ¿Resistencia a aspirina ?

## Definición

### Clínica

Fracaso de la aspirina en la prevención de eventos trombóticos cardiovasculares

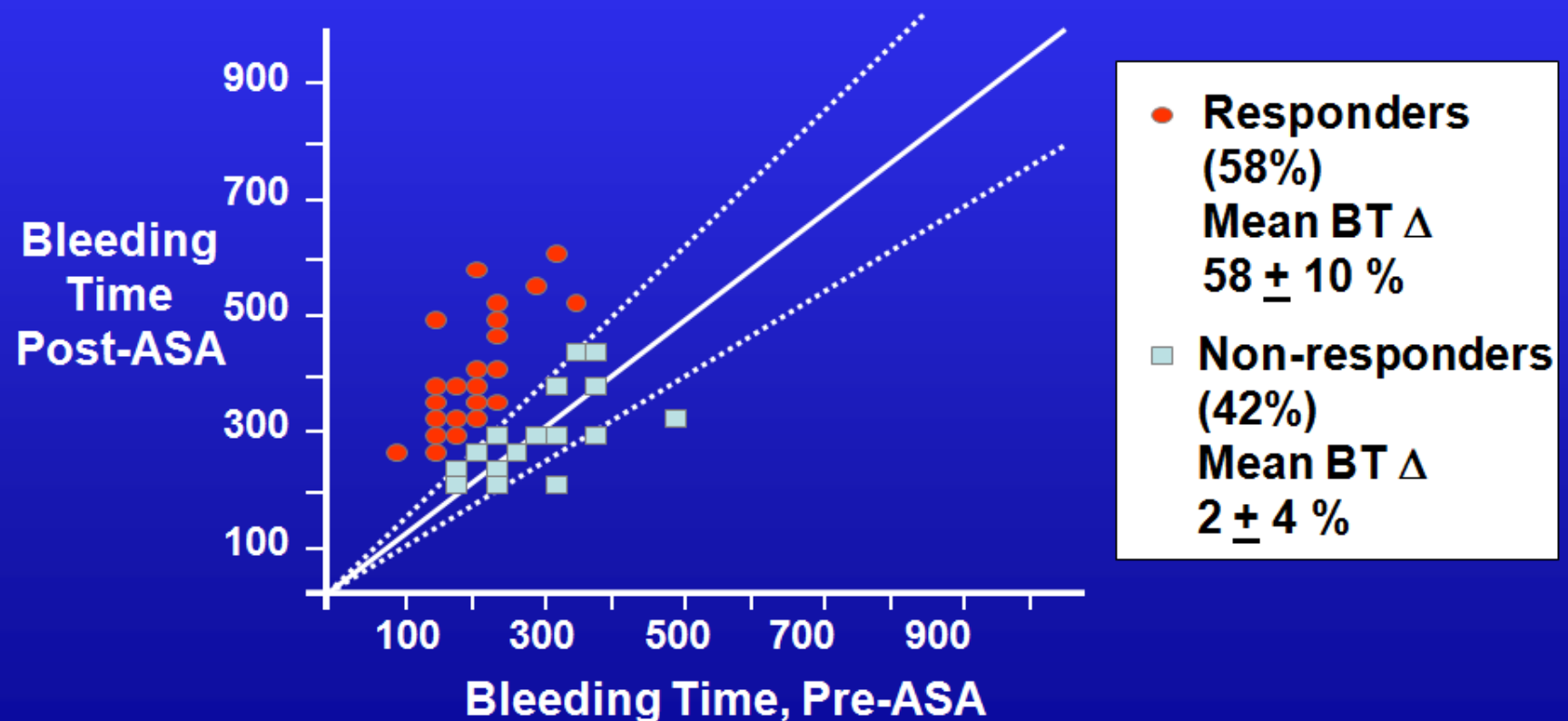
### Laboratorio

Escaso o nulo efecto inhibitorio de la aspirina sobre la función plaquetaria



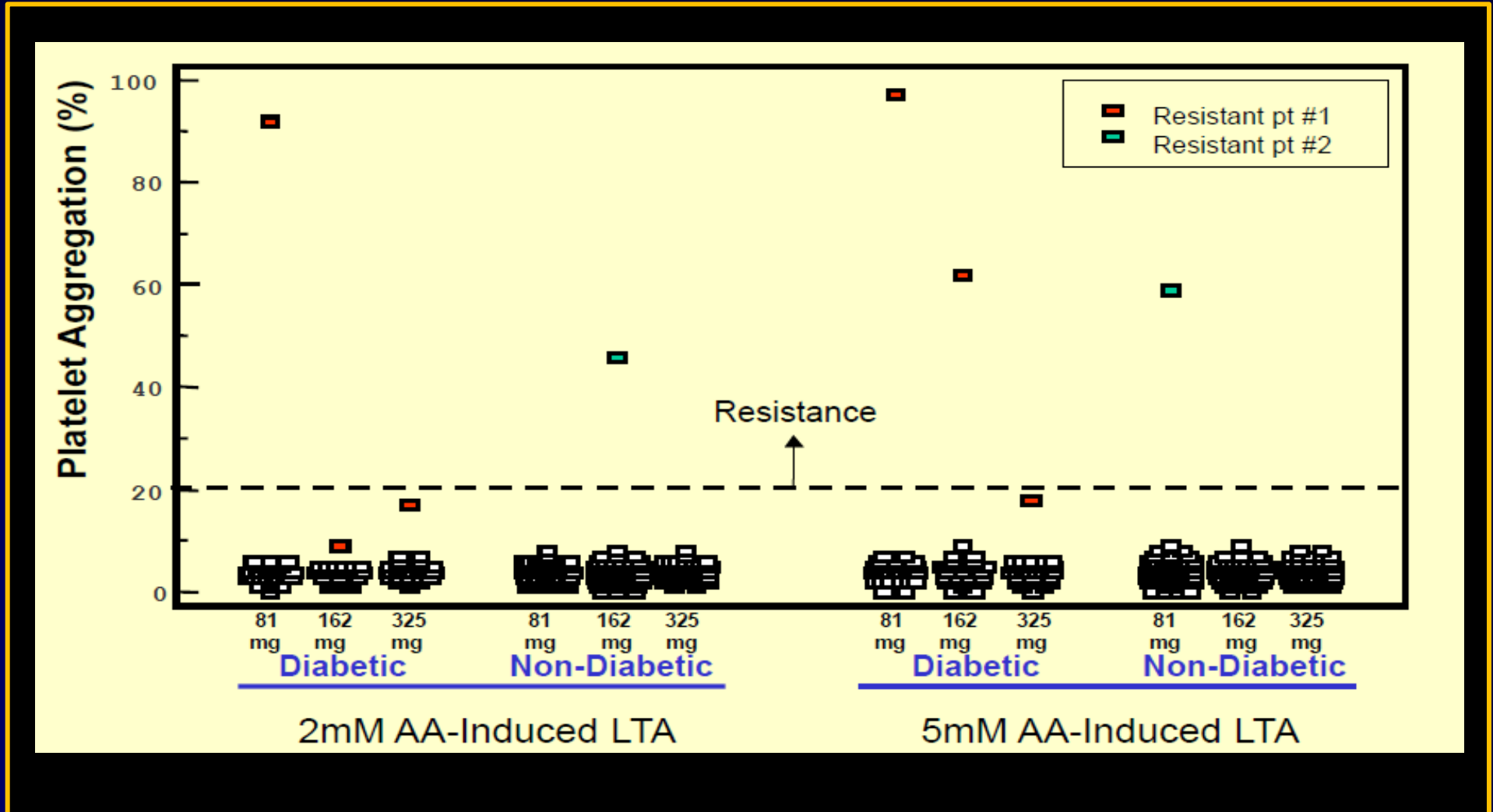
# Interpatient Variability in Aspirin Response - Bleeding Time

Aspirin, 325 mg daily in 40 CABG patients

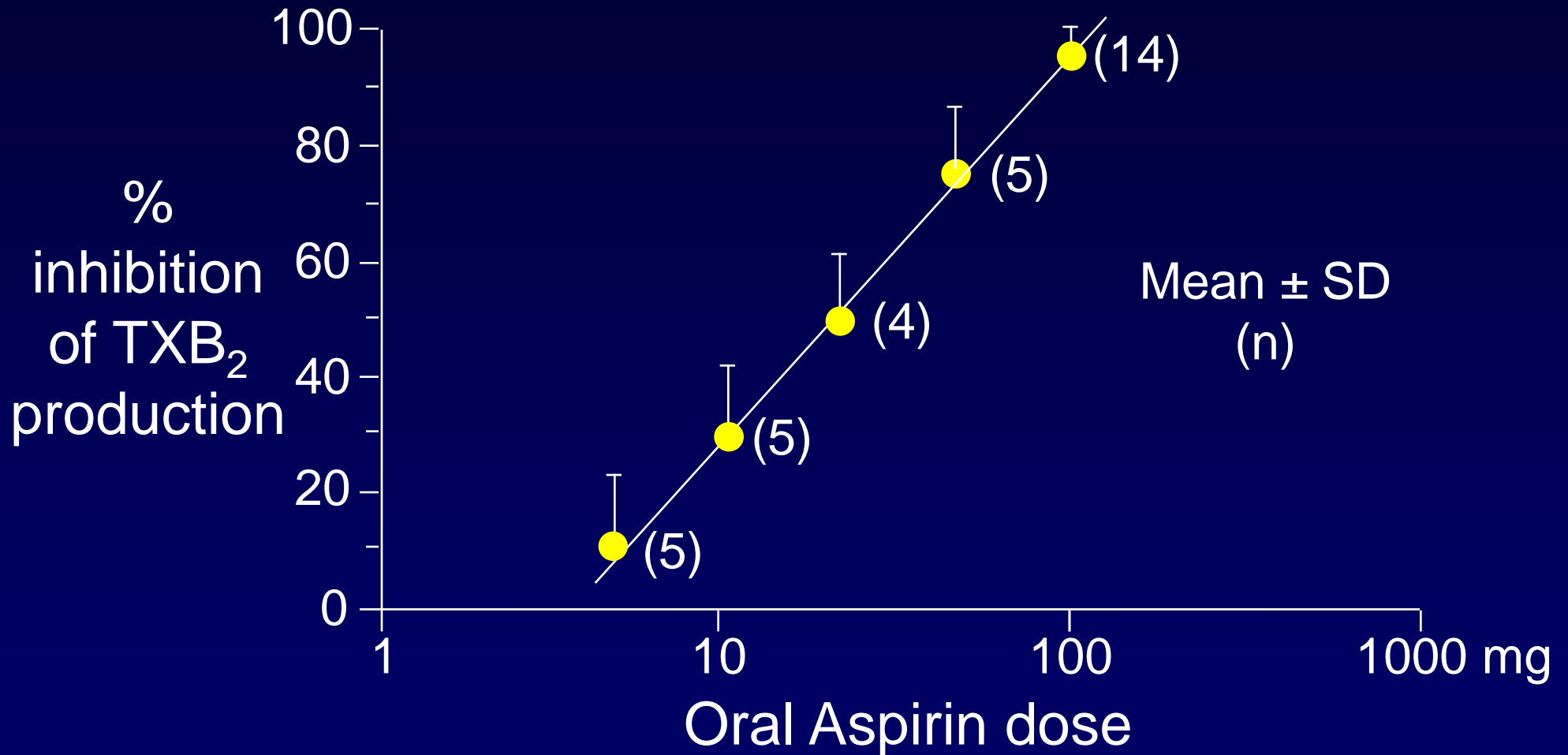


# ASPIRINA - DIABETES

Prevalence "ASA resistance" using COX-1 specific assays



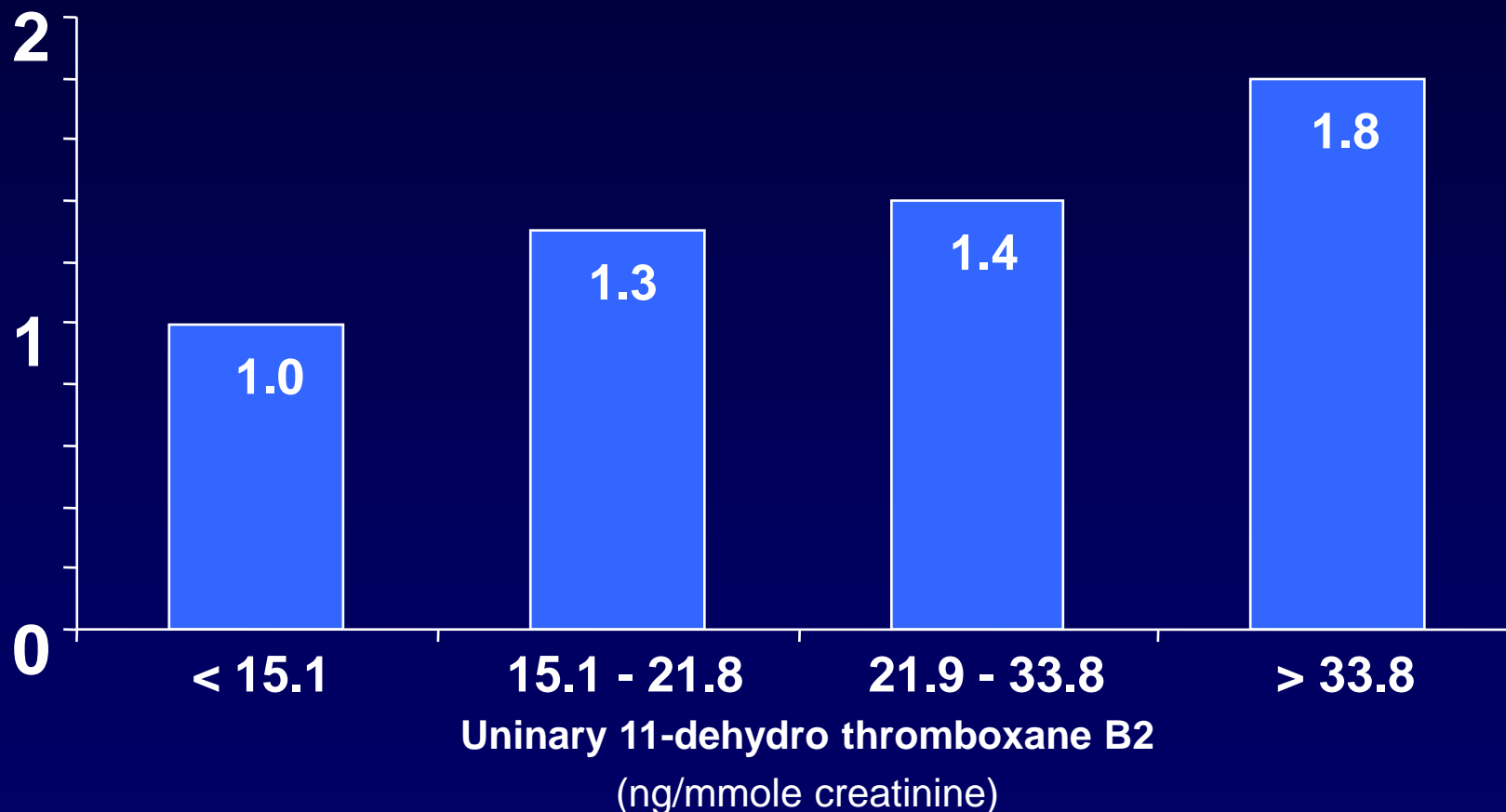
# Log-linear Inhibition of Platelet Cyclooxygenase Activity by Aspirin in Healthy Subjects



Patrignani, Filabozzi & Patrono, J Clin Invest 1982; 69:1366-72

# Thromboxane Biosynthesis on Aspirin and CV Events

Odds Ratio for MI, Stroke or CV Death



# Aspirin “resistance” and risk of cardiovascular morbidity: systematic review and meta-analysis

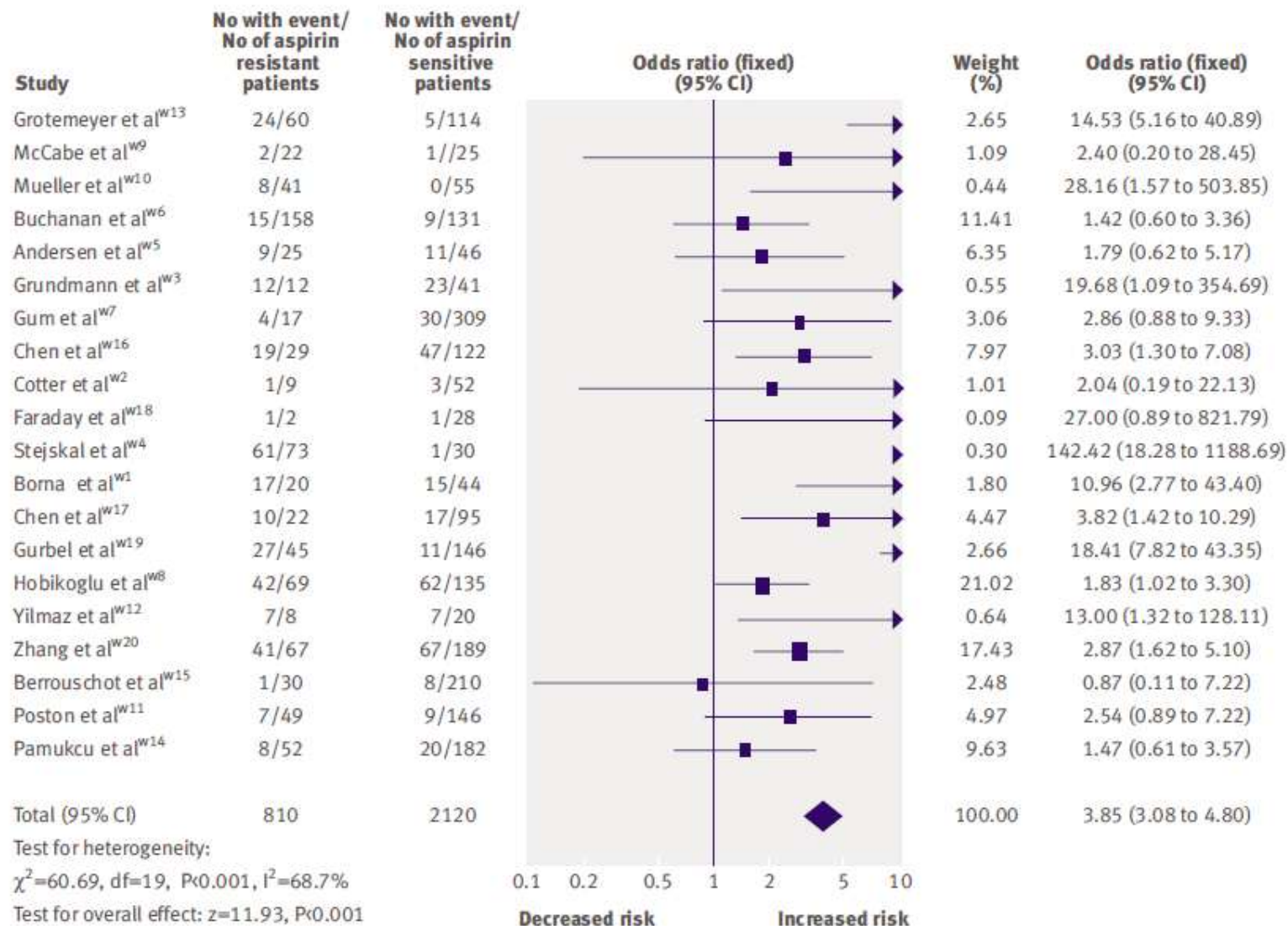


Fig 2 Risk of any cardiovascular event in aspirin resistant patients

**Dosis e  
intervalo  
prescrito**



**Regimen  
administrado**



**Concentración  
del fármaco  
en el lugar  
de acción**

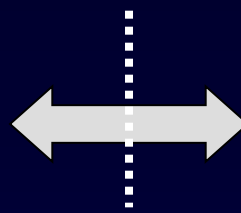


**Intensidad y  
duración del  
efecto  
farmacológico**



**Efecto  
clínico**

# FARMACOCINÉTICA



# FARMACODINÁMICA

- Velocidad y grado de absorción
  - Masa corporal
- Unión a proteínas plasmáticas
  - Distribución en los fluidos
- Velocidad y vía de eliminación

- Interacción droga-receptor
- Estado funcional del receptor

Tratamientos concomitantes

Cumplimiento del tratamiento

Dosis e intervalo prescrito

Regimen administrado

Concentración del fármaco en el lugar de acción

Intensidad y duración del efecto farmacológico

Efecto clínico

Errores medicación

- Variables fisiológicas (.edad.)
- Factores patológicos (.insuf. renal o hepática)
- Variantes genéticas de enzimas o receptores clave
- Interacción con otros fármacos

Tipo o sustrato del paciente



# Conclusiones sobre aspirina en el siglo XXI



- Continua siendo el *gold-standard* del tratamiento antitrombotico en la enfermedad cardiovascular.
  - Se recomienda utilizar las dosis más pequeñas que se haya demostrado eficaces.
- No tenemos evidencia suficiente para aceptar la existencia de resistencia a la aspirina. En cualquier caso el beneficio global de la aspirina supera con creces los recortes de una supuesta resistencia.

