



30-31 Octubre 2008 / VALENCIA

Fracaso de la profilaxis antiagregante

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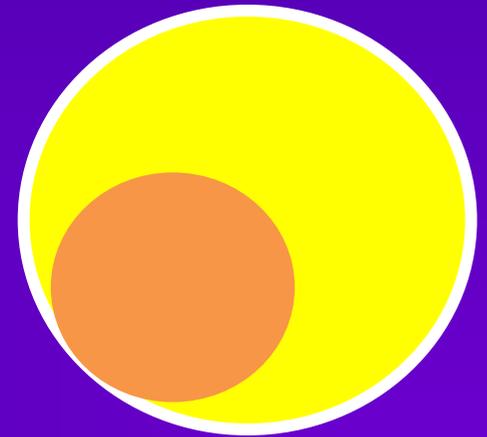
Centrando el tema:

- Primaria
- Secundaria
- AAS
- Trifusal
- Dipyridamol
- Ticlopidina
- Clopidogrel

Fracaso profilaxis antiagregante secundaria

- AAS y clopidogrel:
 - Fallo terapéutico
 - Resistencia farmacológica

NO RESPONDEDORES



No respondedores a AAS

- Fallo terapéutico:
 - Otras causas
 - Incumplimiento
 - Interacciones (ibuprofeno)

Journal of Translational Medicine 

Research **Open Access**

Non-compliance is the predominant cause of aspirin resistance in chronic coronary arterial disease patients

Kenneth A Schwartz*¹, Dianne E Schwartz¹, Kimberly Barber², Mathew Reeves³ and Anthony C De Franco⁴

Published: 29 August 2008



U.S. Food and Drug Administration

September 8, 2006

**Concomitant Use of Ibuprofen and Aspirin:
Potential for Attenuation of the Anti-Platelet Effect of Aspirin**

No respondedores a AAS

- Resistencia a AAS

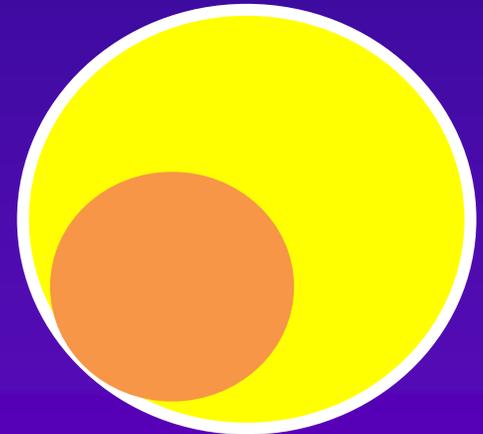
- ¿ Problema ?

- ¿ Cuantificable ?

- ¿ Trascendencia clínica ?

- ¿ Mecanismo ?

- ¿ Alternativas ?



Resistencia a AAS

¿ Problema ?

- 1978 - Mehta :

3 de 10 pacientes, cateterismo, 650 mg AAS

Agregación plaquetaria normal

Atherosclerosis 1978; 31:169-75

- 1991 – Grotemeyer:

29 de 82 pacientes, ACV, 500 mg AAS

Agregación plaquetaria normal

Thromb Res 1991; 63: 587-93

Resistencia a AAS

¿ Problema ?

- 2001 – Gunn:

n = 325, enf cardio-vascular, 325 mg AAS

Agregometría óptica 5.5 % R, 24% semi

PFA-100 9.5 % R

- 2007 – Chen:

n = 468, card isquémica crónica, 80-325 mg AAS

Agregometría modificada 27 % R

Resistencia a AAS

¿ Problema ? 24 %

Volume 153, Issue 2, Pages 175-181 (February 2007)

American Heart Journal

Prevalence of persistent platelet reactivity despite use of aspirin: A systematic review

Marcel M.C. Hovens, MD^a  Jaapian D. Snoep, MSc^a, Jeroen C.J. Eikenboom, MD, PhD^b, Johanna G. van der Bom, MD, PhD^c, Bart J.A. Mertens, PhD^d, Menno V. Huisman, MD, PhD^a

Dosis:

< 100 mg → 36%

> 300 mg → 19%

Método:

Agregometría

optica 6%

Resistencia a AAS

¿ Problema ?

Evaluation of Dose-Related Effects of Aspirin on Platelet Function: Results From the Aspirin-Induced Platelet Effect (ASPECT) Study

Paul A. Gurbel, Kevin P. Bliden, Joseph DiChiara, Justin Newcomer, Willy Weng, Nagaraj K. Neerchal, Tania Gesheff, Srivasavi K. Chaganti, Amena Etherington and Udaya S. Tantry

Circulation 2007;115;3156-3164; originally published online Jun 11, 2007;

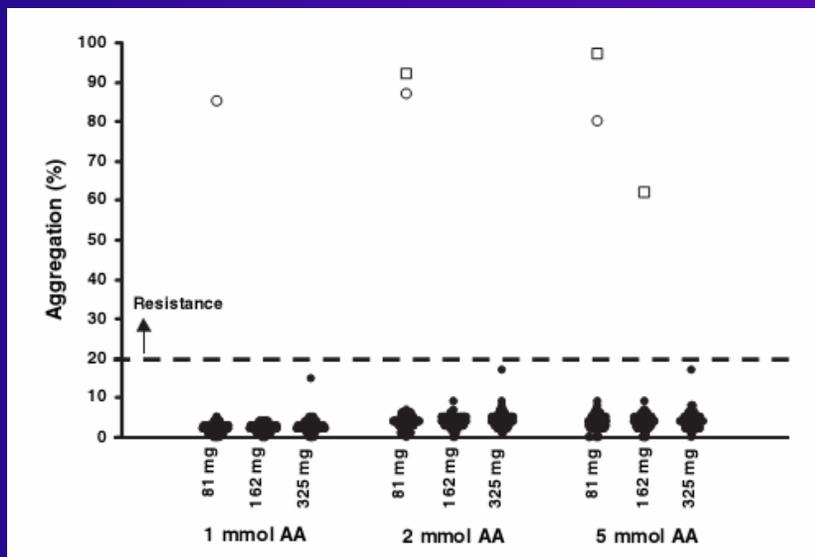


TABLE 2. Effects of Assay and Dose on Measurement of Aspirin Resistance

	Resistance (n)					
	81 mg	162 mg	325 mg	≥1 Dose	2 Doses	3 Doses
LTA						
1 mmol/L AA	1	0	0	1	0	0
2 mmol/L AA	2	0	0	2	0	0
5 mmol/L AA	2	1	0	2	1	0
2 μg/mL Collagen	12	2	1	14	1	0
5 μmol/L ADP	19	11	10	27	7	3
TEG-1 mmol/L AA	5	3	5	11	2	0
VerifyNow	7	4	4	13	2	0
Urinary 11-dehydro-Thromboxane B ₂	31	22	14	42	16	5
PFA-100	32	14	21	42	15	5

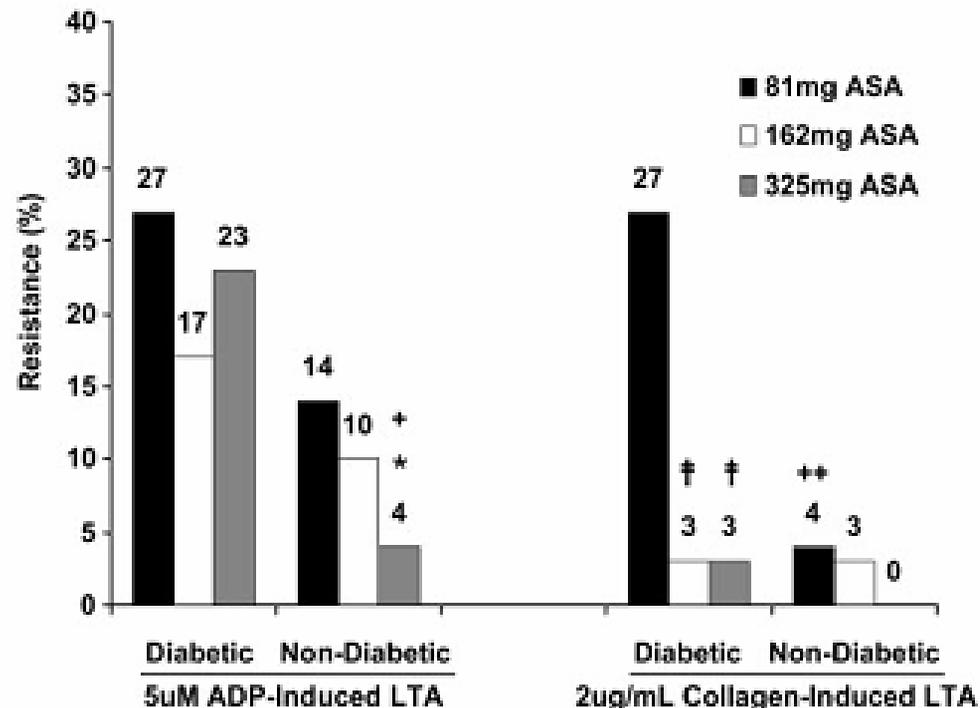
Resistencia a AAS

¿ Problema ?

The Effect of Aspirin Dosing on Platelet Function in Diabetic and Nondiabetic Patients

An Analysis From the Aspirin-Induced Platelet Effect (ASPECT)

Joseph DiChiara, I
Thomas A. Suarez,



007

No respondedores a AAS

- Resistencia a AAS

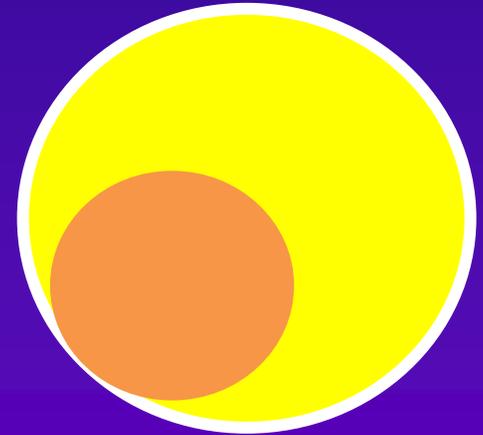
Problema

¿ Cuantificable ?

¿ Trascendencia clínica ?

¿ Mecanismo ?

¿ Alternativas ?



Resistencia a AAS

¿ Cuantificable ?



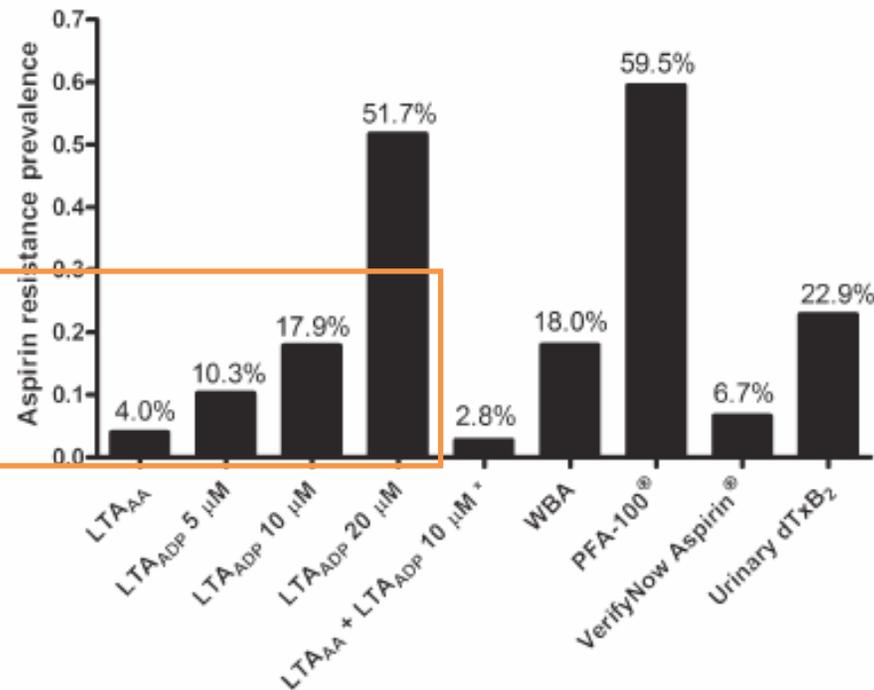
European Heart Journal (2007) 28, 1702–1708
doi:10.1093/eurheartj/ehm226

Clinical research
Coronary heart disease

A comparison of six major platelet function tests to determine the prevalence of aspirin resistance in patients with stable coronary artery disease

Marie Lordkipanid
Donald A. Palisaiti

urgeon¹,



Aggregometría
óptica

No respondedores a AAS

- Resistencia a AAS

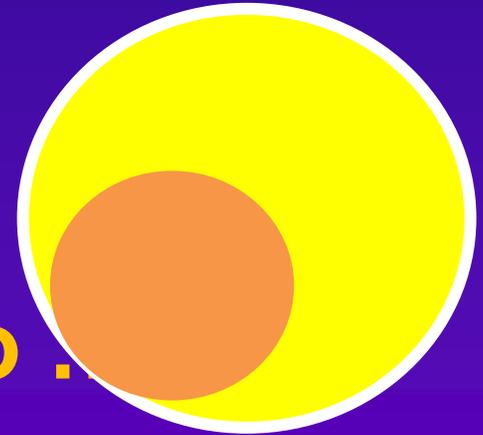
Existe

Cuantificable , pero .

¿ Trascendencia clínica ?

¿ Mecanismo ?

¿ Alternativas ?

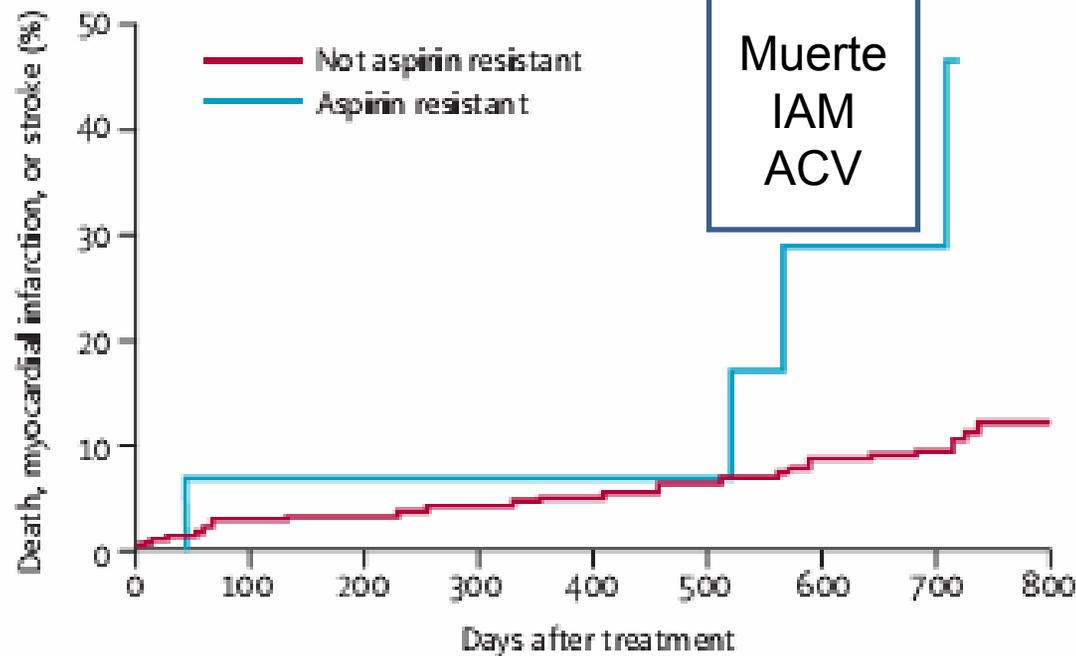


Resistencia a AAS

¿ Trascendencia clínica ?

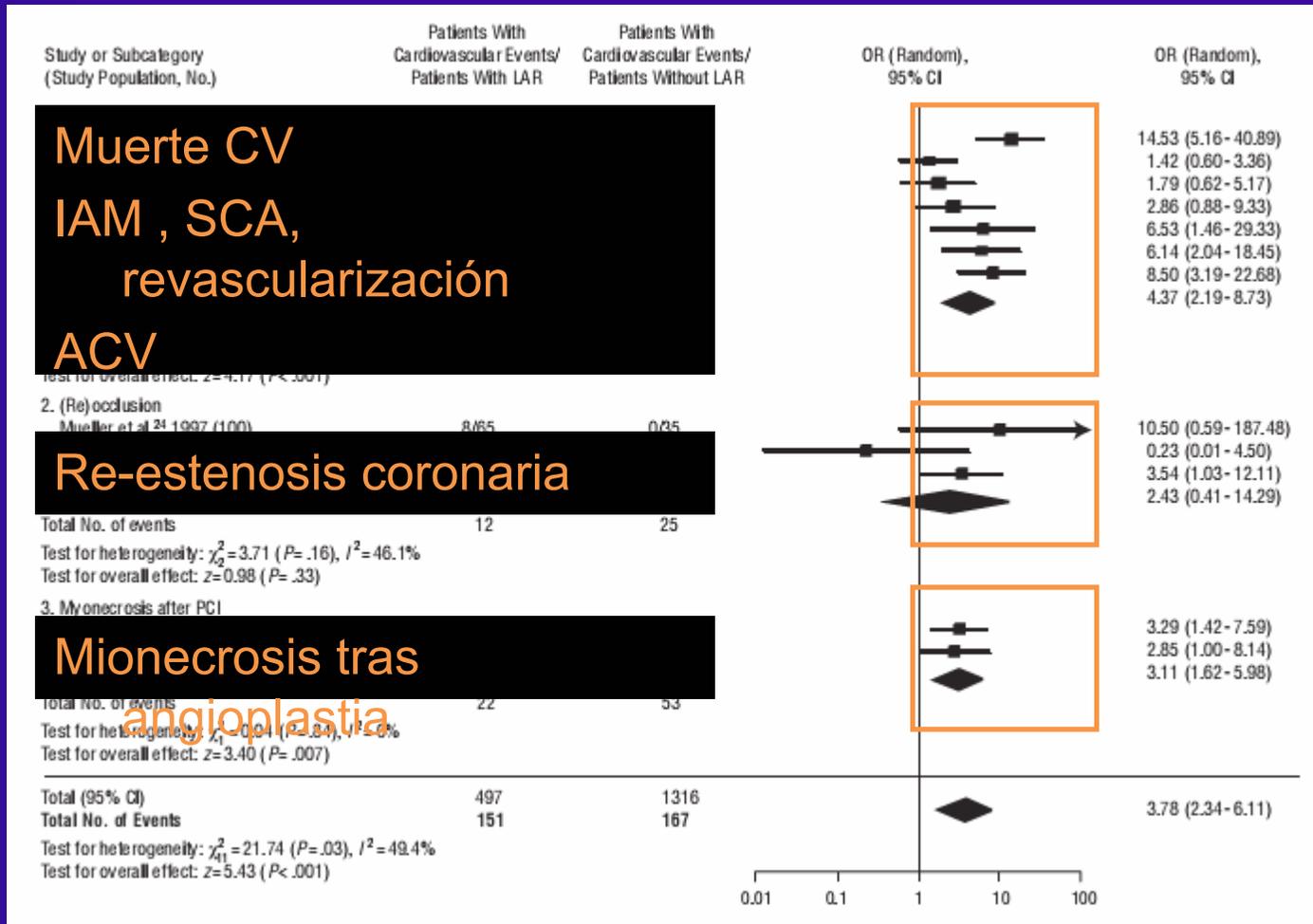
A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease

Gum, P. JACC 2003;41:961-5



Resistencia a AAS

¿ Trascendencia clínica ?



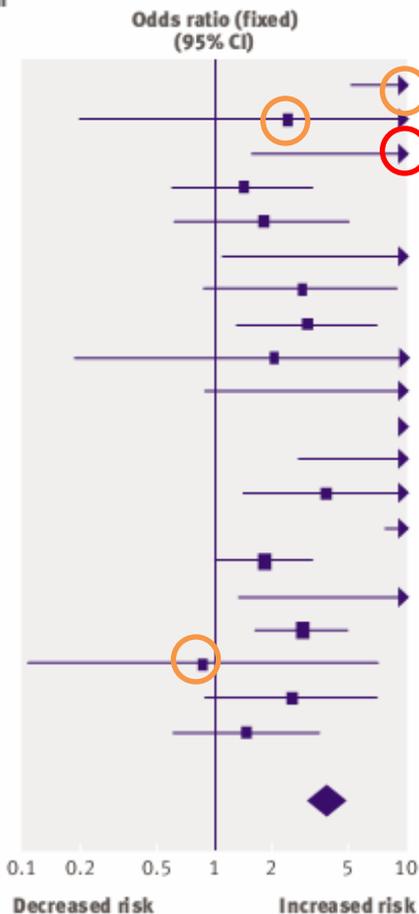
Resistencia a AAS

¿ Trascendencia clínica ?

BM

Study	No with event/ No of aspirin resistant patients	No with event/ No of aspirin sensitive patients
Grotemeyer et al ^{w13}	24/60	5/114
McCabe et al ^{w9}	2/22	1/25
Mueller et al ^{w10}	8/41	0/55
Buchanan et al ^{w6}	15/158	9/131
Andersen et al ^{w5}	9/25	11/46
Grundmann et al ^{w3}	12/12	23/41
Gum et al ^{w7}	4/17	30/309
Chen et al ^{w16}	19/29	47/122
Cotter et al ^{w2}	1/9	3/52
Faraday et al ^{w18}	1/2	1/28
Stejskal et al ^{w4}	61/73	1/30
Borna et al ^{w1}	17/20	15/44
Chen et al ^{w17}	10/22	17/95
Gurbel et al ^{w19}	27/45	11/146
Hobikoglu et al ^{w8}	42/69	62/135
Yilmaz et al ^{w12}	7/8	7/20
Zhang et al ^{w20}	41/67	67/189
Berrouschot et al ^{w15}	1/30	8/210
Poston et al ^{w11}	7/49	9/146
Pamukcu et al ^{w14}	8/52	20/182
Total (95% CI)	810	2120

Test for heterogeneity:
 $\chi^2=60.69$, $df=19$, $P<0.001$, $I^2=68.7\%$
 Test for overall effect: $z=11.93$, $P<0.001$



ovascular
 a-analysis
 id Michael R
 008; EAP

No respondedores a AAS

- Resistencia a AAS

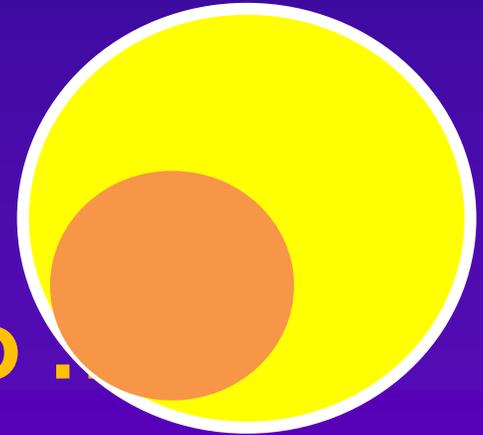
Existe

Cuantificable , pero .

Trascendencia clínica

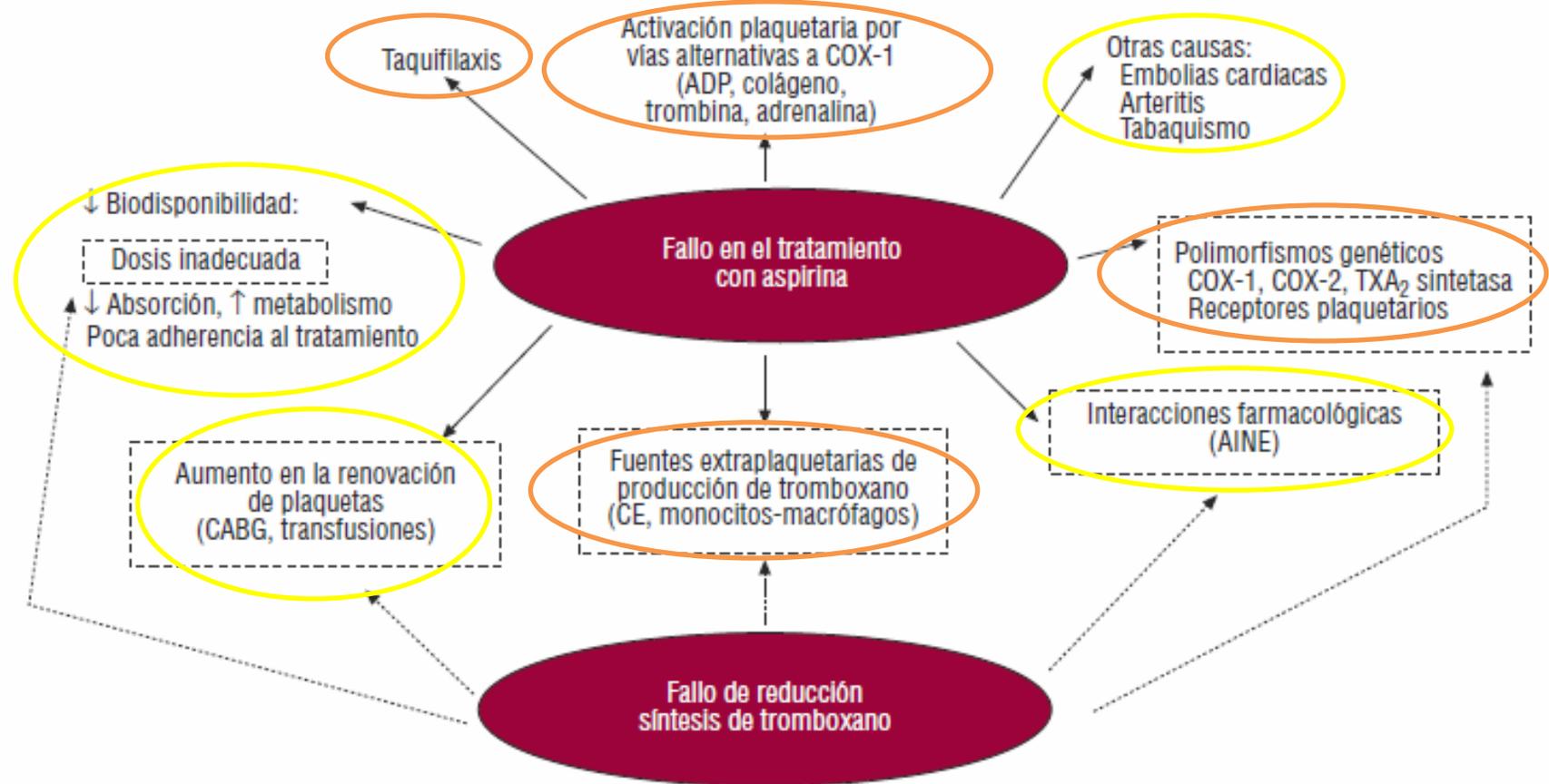
¿ Mecanismo ?

¿ Alternativas ?



No respondedores a AAS

¿ Mecanismo ?



No respondedores a AAS

- Resistencia a AAS

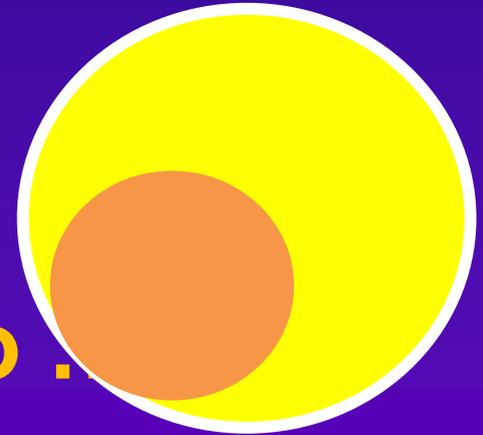
Existe

Cuantificable , pero .

Trascendencia clínica

Mecanismo

¿ Alternativas ?



Resistencia a AAS ¿ Alternativas ?

OFFICIAL COMMUNICATION OF THE SSC

Aspirin resistance: position paper of the Working Group on
Aspirin Resistance

J Thromb Haemost 2005; 3: 1309–11.

- La alternativa es desconocida
- No realizar estudios de resistencia
- No tomar decisiones clínicas basadas en ellos

Resistencia a AAS ¿ Alternativas ?

¿ Aumentar dosis de AAS ?

NO

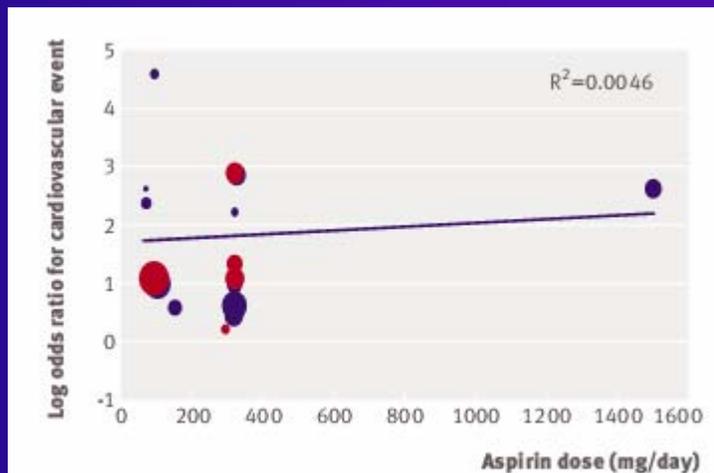


Fig 4 Dose related effect of aspirin on cardiovascular outcome

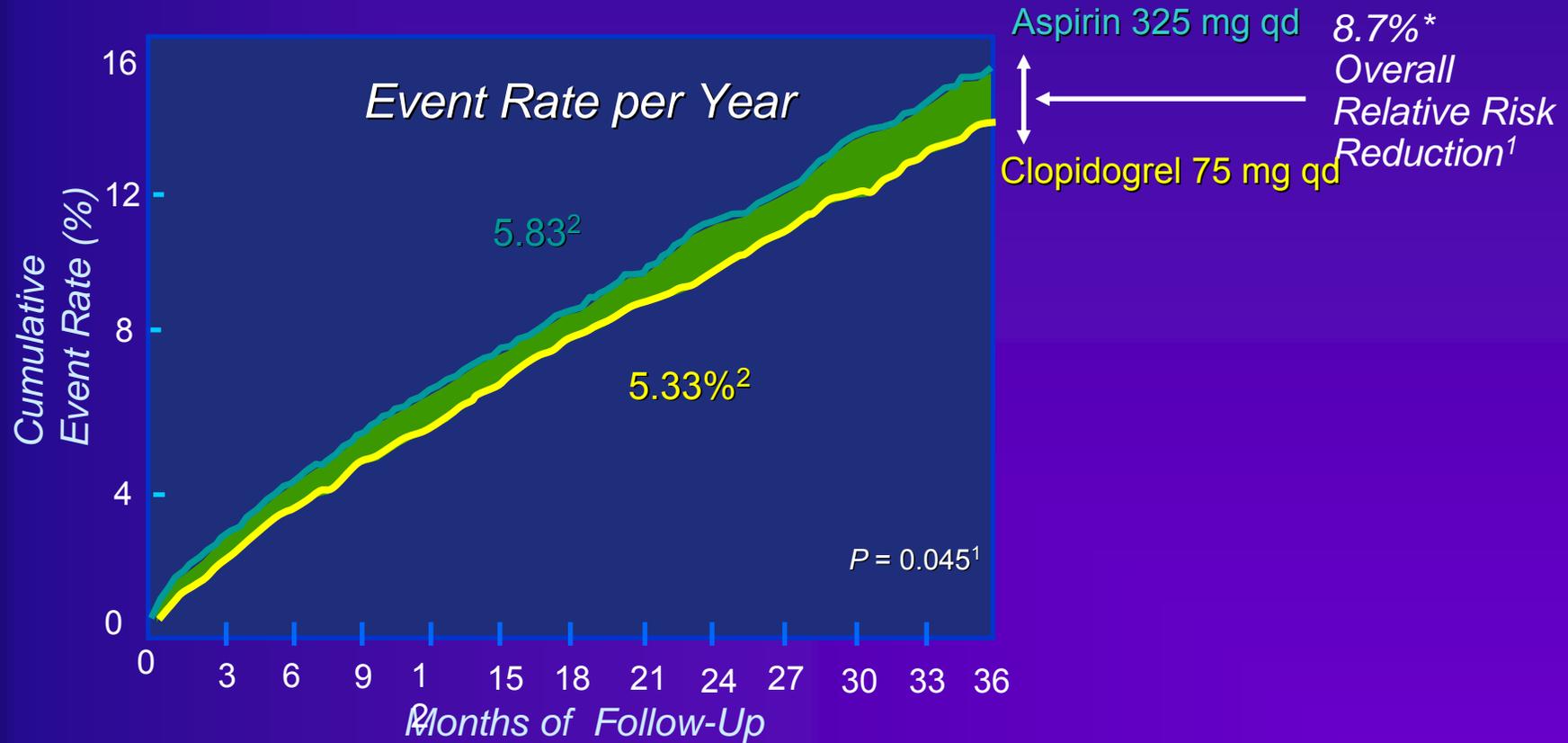
dosis de mantenimiento puede reducirse a 81-100 mg/día de por vida. Es más, dosis altas de aspirina pueden tener importantes efectos adversos al inhibir la COX endotelial (isoforma COX-2) y reducir así la síntesis de PGI₂, un importante cardioprotector (fig. 1).

Rev Esp Cardiol. 2008;61(5):501-13

BMJ 2008;336;195-198;

No respondedores a AAS ¿ Alternativas ?

¿ Cambiar a clopidogrel ?



CAPRIE Study
MI, Ischemic Stroke, or Vascular Death (N=19,185)

No respondedores a AAS ¿ Alternativas ?

¿ Cambiar a clopidogrel ?

SI

Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study

Lancet Neurology 2008; 7:875-884

PRoFESS: Clopidogrel = AAS + DP

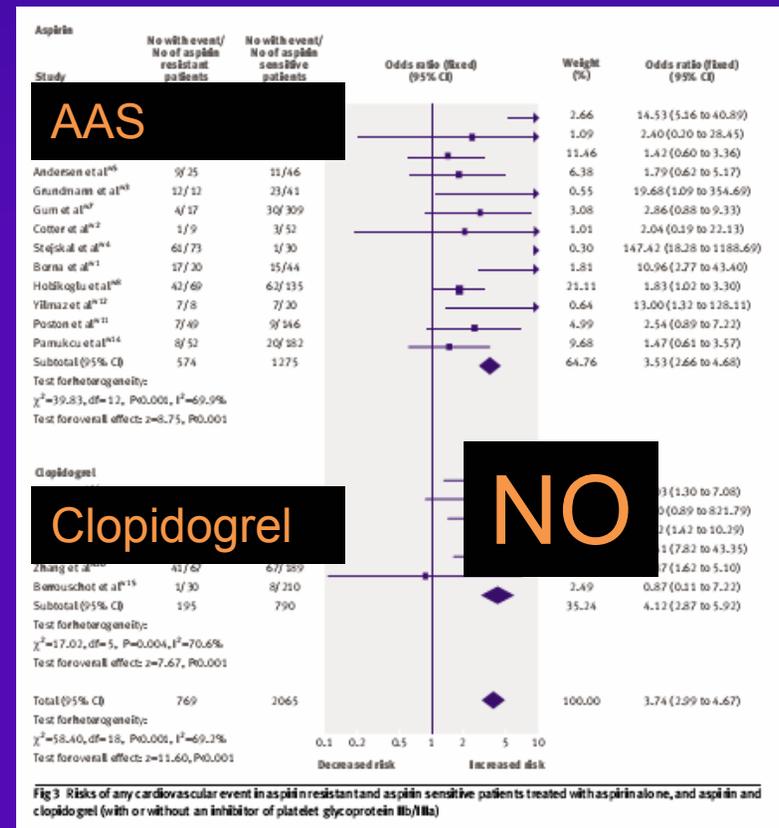
CAPRIE: Clopidogrel > AAS

Resistencia a AAS ¿ Alternativas ?

¿ Doble antiagregación ?

($R^2=0.0046$; fig 4). Moreover, concomitant therapy with clopidogrel or tirofiban (an inhibitor of platelet glycoprotein IIb/IIIa), or both, provided no benefit to those patients identified as aspirin resistant (aspirin and clopidogrel, 3.06, 1.99 to 4.70; aspirin alone, 2.52, 1.79 to 3.56; fig 3).

BMJ 2008;336;195-198;



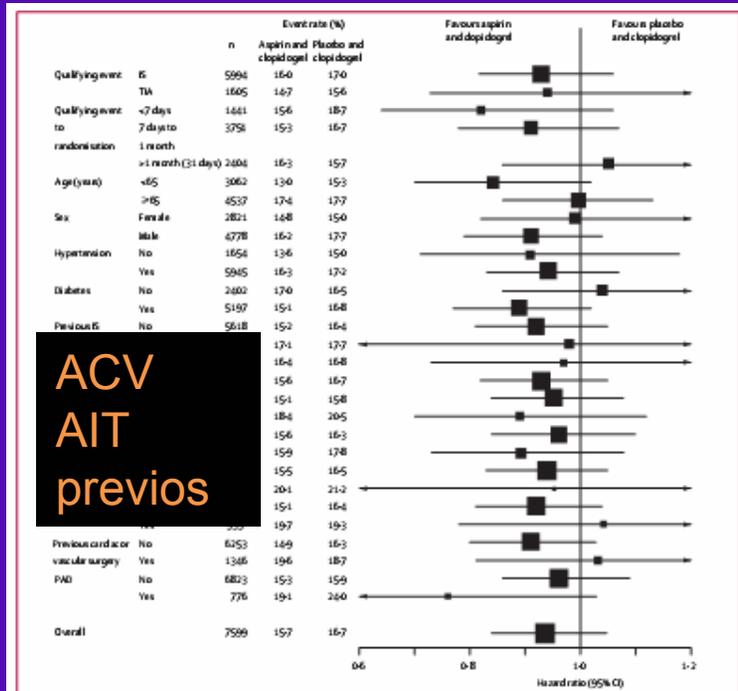
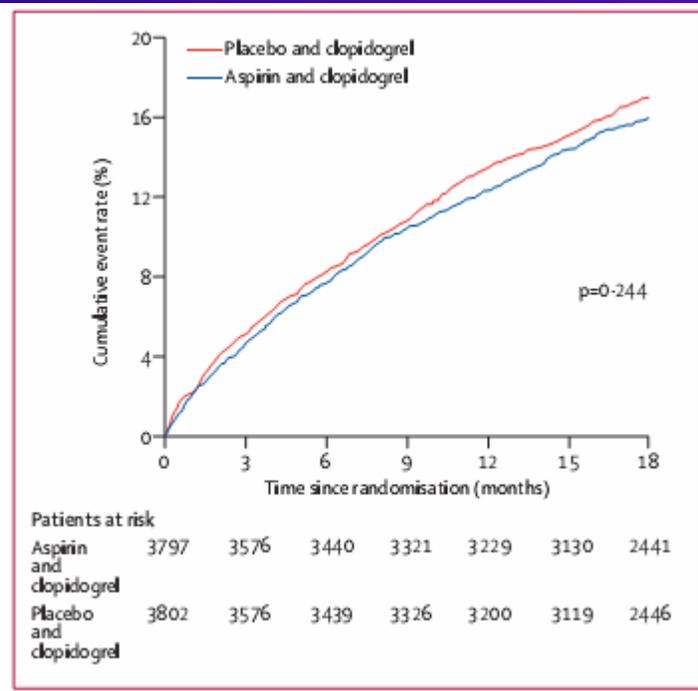
No respondedores a AAS ¿ Alternativas ?

¿ Doble antiagregación **AAS + Clopidogrel**

NO



Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial
Lancet 2004; 364: 331-37

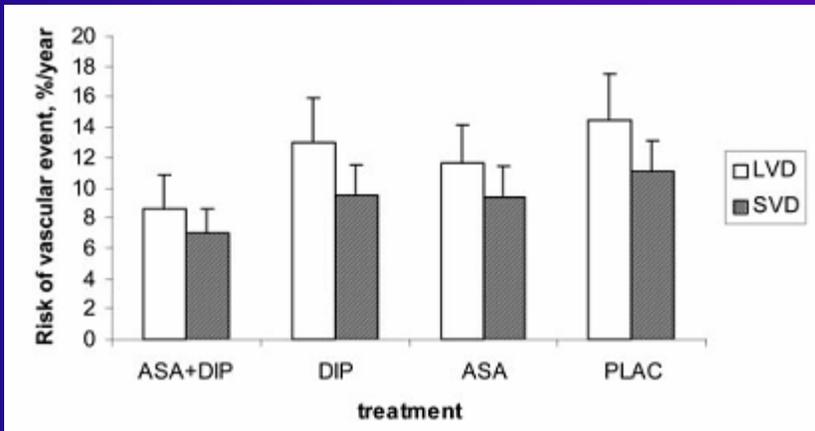


No respondedores a AAS ¿ Alternativas ?

¿ Doble antiagregación ?

Dipyridamole plus aspirin versus aspirin alone in secondary prevention after TIA or stroke: a meta-analysis by risk

Journal of Neurology, Neurosurgery, and Psychiatry 2008;79:1218-1223



(AAS 25 mg + Dipyridamol 200 mg) x 2

SI, salvo
cardiopatía isquémica

No respondedores a AAS ¿ Alternativas ?

¿ Triple antiagregación ?

NO

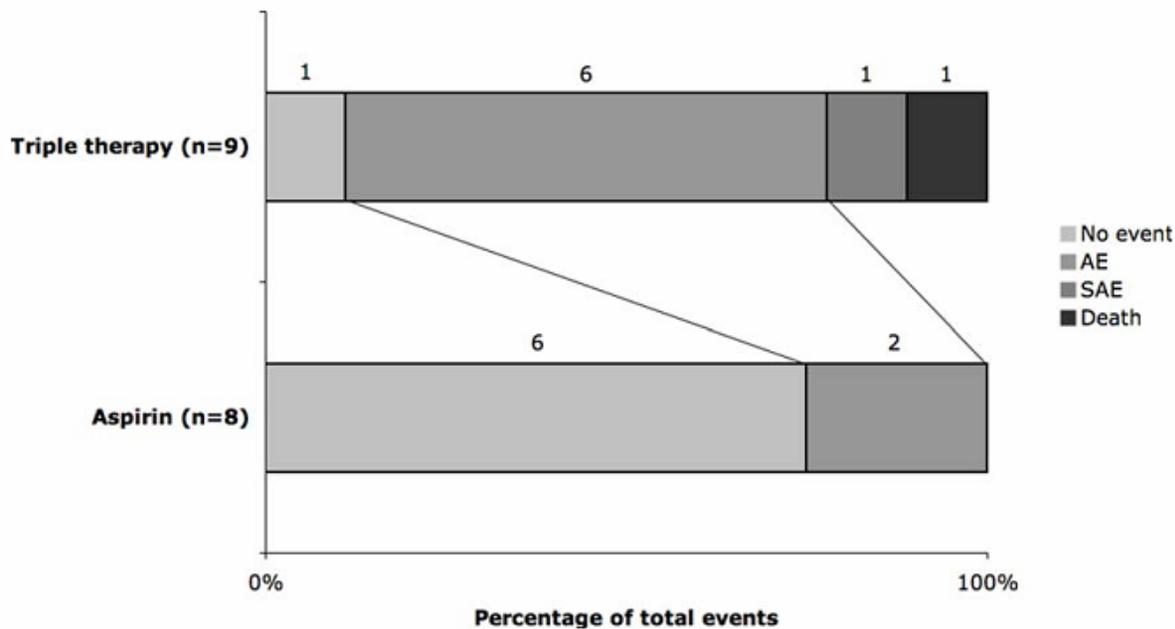
OPEN ACCESS Freely available online

PLoS one

A Randomised Controlled Trial of Triple Antiplatelet Therapy (Aspirin, Clopidogrel and Dipyridamole) in the Secondary Prevention of Stroke: Safety, Tolerability and Feasibility

Nikola Sprigg, Laura J. Gra

Stroke Trials Unit, Institute of Neurosciences



No respondedores a AAS ¿ Alternativas ?

¿ Anticoagulación ?

NO

Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial

Lancet Neurology 2007; 6:115-124

Oral anticoagulants versus antiplatelet therapy for preventing further vascular events after transient ischaemic attack or minor stroke of presumed arterial origin

A Algra, ELLM De Schryver, J van Gijn, LJ Kappelle, PJ Koudstaal

Cochrane Database of Systematic Reviews 2008 Issue 4



No respondedores a Clopidogrel

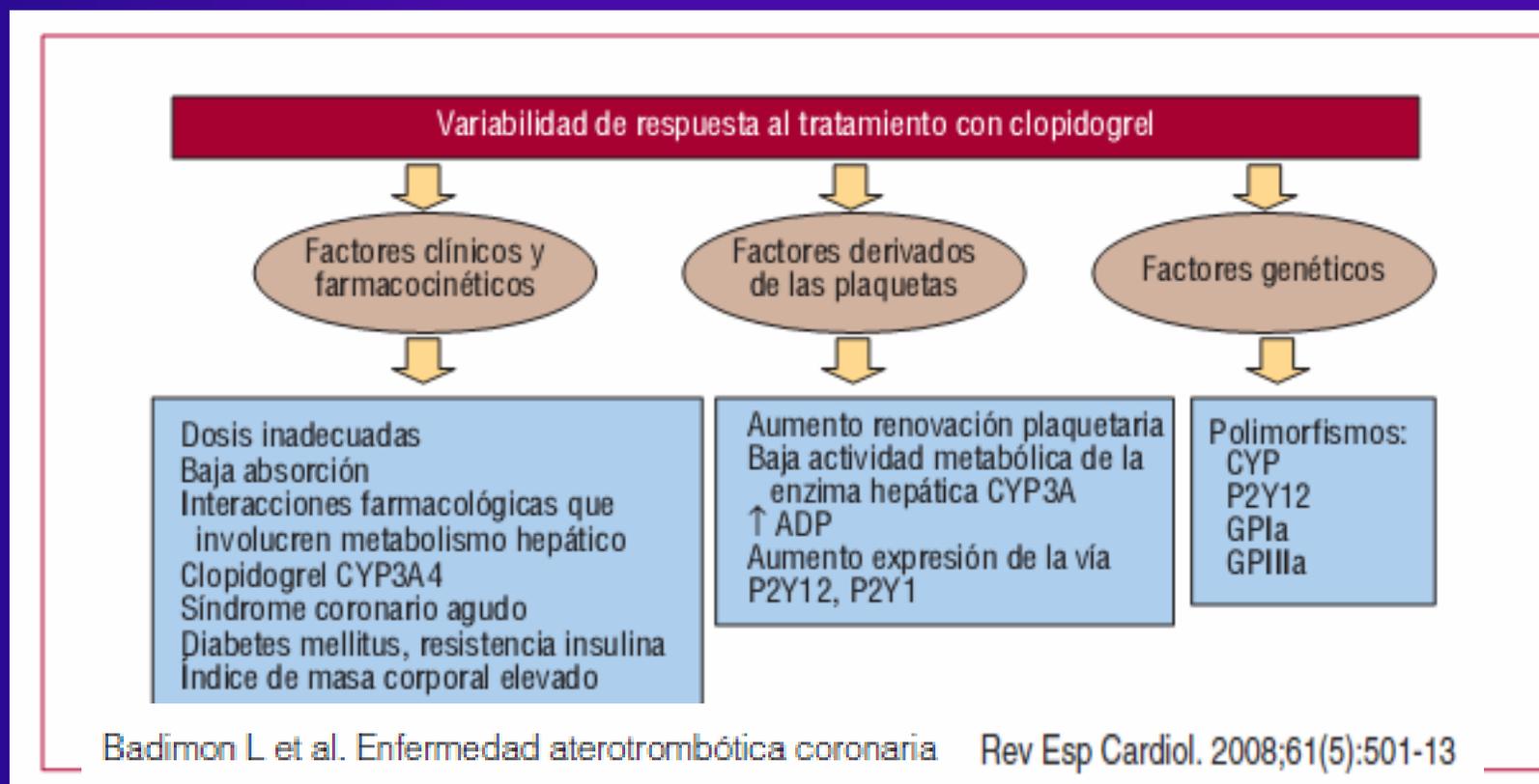
Adjusted Clopidogrel Loading Doses According to Vasodilator-Stimulated Phosphoprotein Phosphorylation Index Decrease Rate of Major Adverse Cardiovascular Events in Patients With Clopidogrel Resistance A Multicenter Randomized Prospective Study

Journal of the American College of Cardiology
Volume 51, Issue 14, 8 April 2008, Pages 1404-1411

- A mayor dosis, mayor antiagregación
- 14 % resistentes (no más eventos cardíacos)
- No más sangrado
- VASP – guiado: cero eventos ($p < 0.007$)

No respondedores a Clopidogrel

- Mecanismos



No respondedores a Clopidogrel

Interacciones

- Estatinas

Statins do not adversely affect post-interventional residual platelet aggregation and outcomes in patients undergoing coronary stenting treated by dual antiplatelet therapy

European Heart Journal Advance Access originally published online on May 24, 2008
European Heart Journal 2008 29(13):1635-1643; doi:10.1093/eurheartj/ehn212

High-dose atorvastatin does not negatively influence clinical outcomes among clopidogrel treated acute coronary syndrome patients—A Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) analysis

American Heart Journal
Volume 155, Issue 5, May 2008, Pages 954-958

No respondedores a Clopidogrel

Interacciones

- Omeprazol:

Influence of Omeprazole on the Antiplatelet Action of Clopidogrel Associated With Aspirin The Randomized, Double-Blind OCLA (Omeprazole CLopidogrel Aspirin) Study

Journal of the American College of Cardiology
Volume 51, Issue 3, 22 January 2008, Pages 256-260

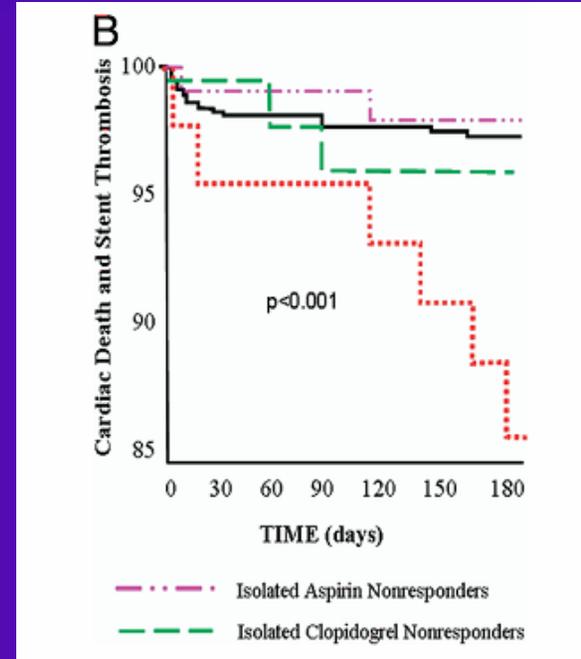
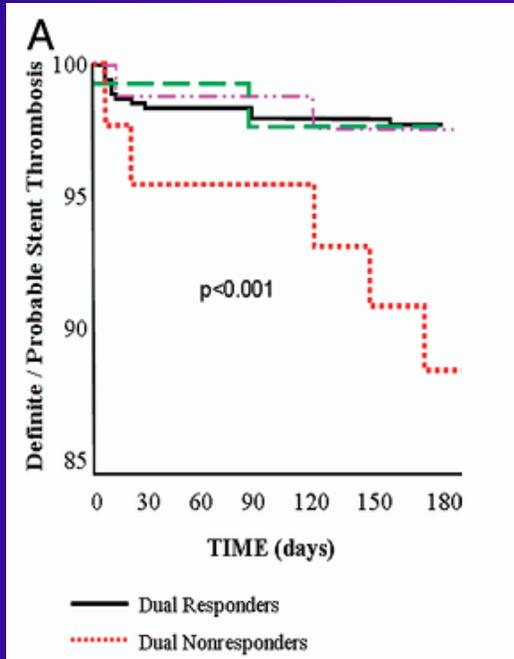
AAS + Clopidogrel + Omeprazol

¿ Más reestenosis stent ?

No respondedores a AAS y Clopidogrel

Incidence and Clinical Impact of Dual Nonresponsiveness to Aspirin and Clopidogrel in Patients With Drug-Eluting Stents

JACC Vol. 52, No. 9, 2008
August 26, 2008:734-9



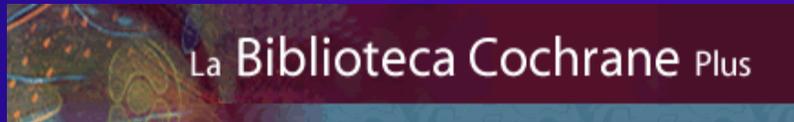
ASCET trial

(ASpirin non-responsiveness and Clopidogrel Endpoint Trial)

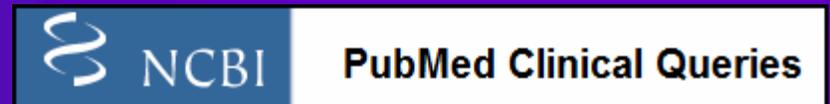
Tailoring Treatment with Tirofiban in
patients showing Resistance to aspirin
and/or Resistance to clopidogrel

3T/2R

GRAVITAS



tenemos un problema



**Sin conflicto de
intereses**

AAS: inhibe ciclooxigenasa 1

