

Curso de formación continua en Cardiología

Resistencia al clopidogrel
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Resistencia al clopidogrel

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Resistencia al clopidogrel

➤ Introducción:

- ❖ El clopidogrel es una tienopiridina que inhibe el receptor P2Y₁₂ de la Adenosina-di- fosfato (ADP).
- ❖ Su uso como antiagregante se ha extendido en los últimos años así como la publicación de artículos referentes a la resistencia al clopidogrel.
- ❖ En 2006 se describe que la resistencia al clopidogrel en voluntarios sanos esta determinada por una variable pre-existente.

Resistencia al clopidogrel

➤ Introducción:

- ❖ El objetivo es esclarecer los distintos formas de resistencia y su correlación con los eventos.

Resistencia al clopidogrel

Mecanismo de acción del clopidogrel:

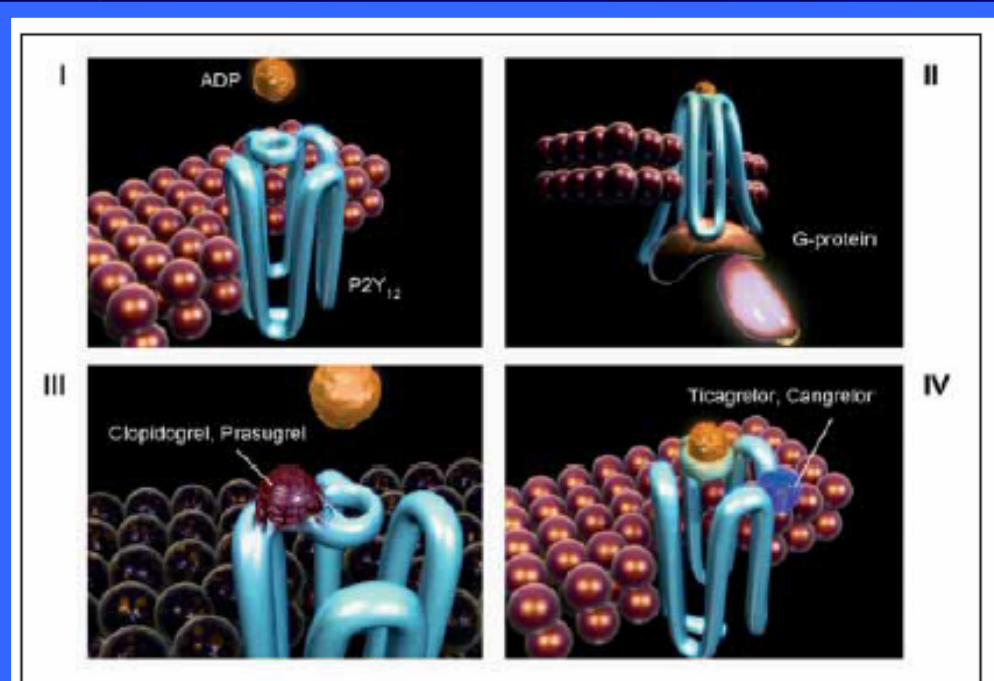
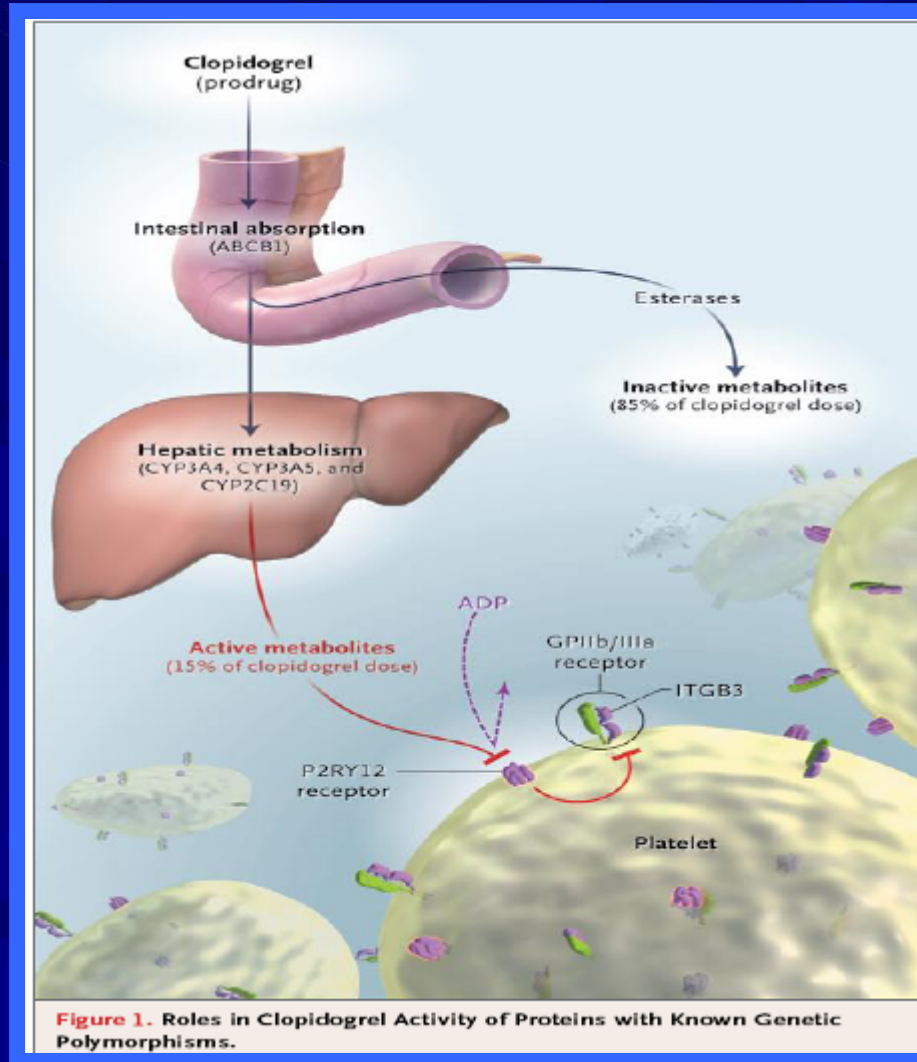


Figure 3: Binding of irreversible and reversible P2Y₁₂ receptor antagonists. I, II) ADP binds to the P2Y₁₂ receptor, resulting in a conformational change and G-protein-coupled activation. III) The active metabolites of clopidogrel and prasugrel bind irreversibly to the P2Y₁₂ receptor, deactivating it for the life span of the platelet. IV) Ticagrelor and cangrelor bind reversibly to P2Y₁₂ at a site distinct from that occupied by ADP; reversible antagonism occurs as these agents transform the receptor to an inactive state. Upon dissociation of the reversible agents from this site, the P2Y₁₂ receptor regains its function. Adapted with permission from Husted et al. (34).

Resistencia al clopidogrel

➤ Mecanismo de acción del clopidogrel:



Resistencia al clopidogrel

Tiene 2 pasos hepáticos para su activación, con un 15-20% activo

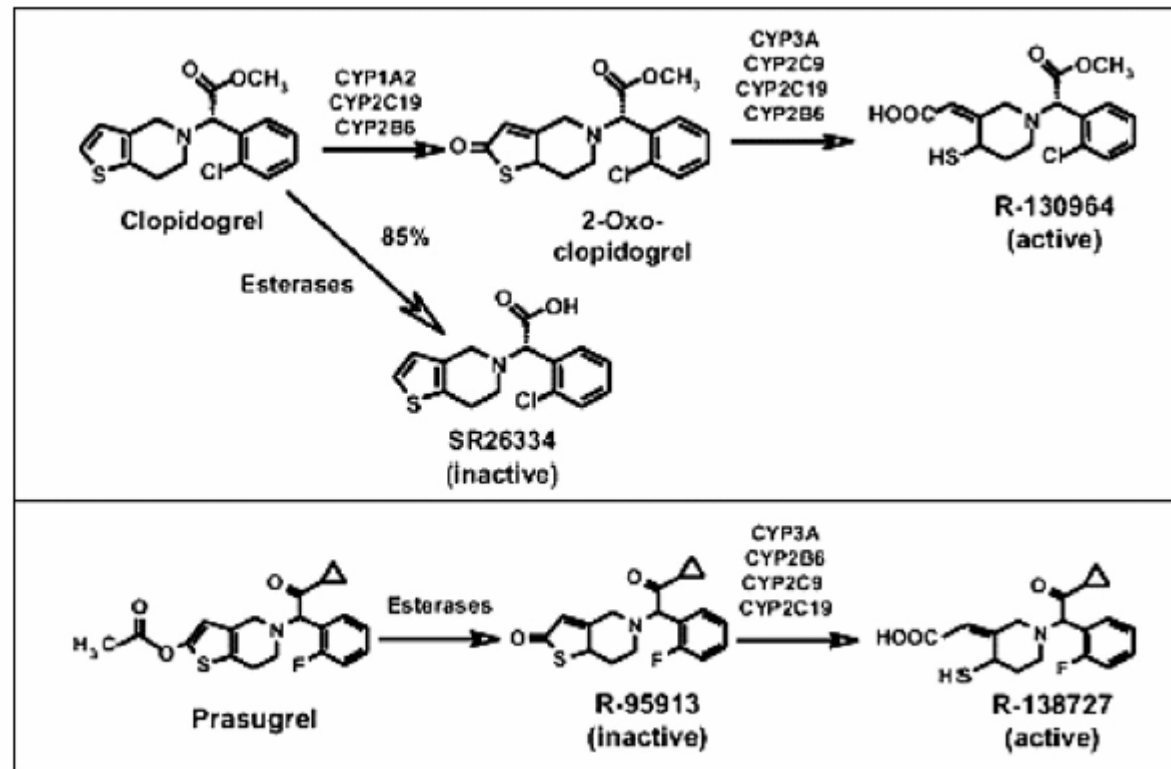


Figure 1. Schematic Representation of the Metabolism of Clopidogrel and Prasugrel

Resistencia al clopidogrel

Relación entre no respondedores y eventos clínicos

El registro francés de IAM con ST y sin ST)FAST-MI evaluó prospectivamente la relación de los polimorfismos genéticos que modulaban:

- la absorción: ABCb1
- la activación metabólica: CYP3A5, CYP2C19
- La actividad biológica: P2RY12, ITGB3

Y su relación con muerte y eventos isquémicos en pacientes post IAM.

Resistencia al clopidogrel

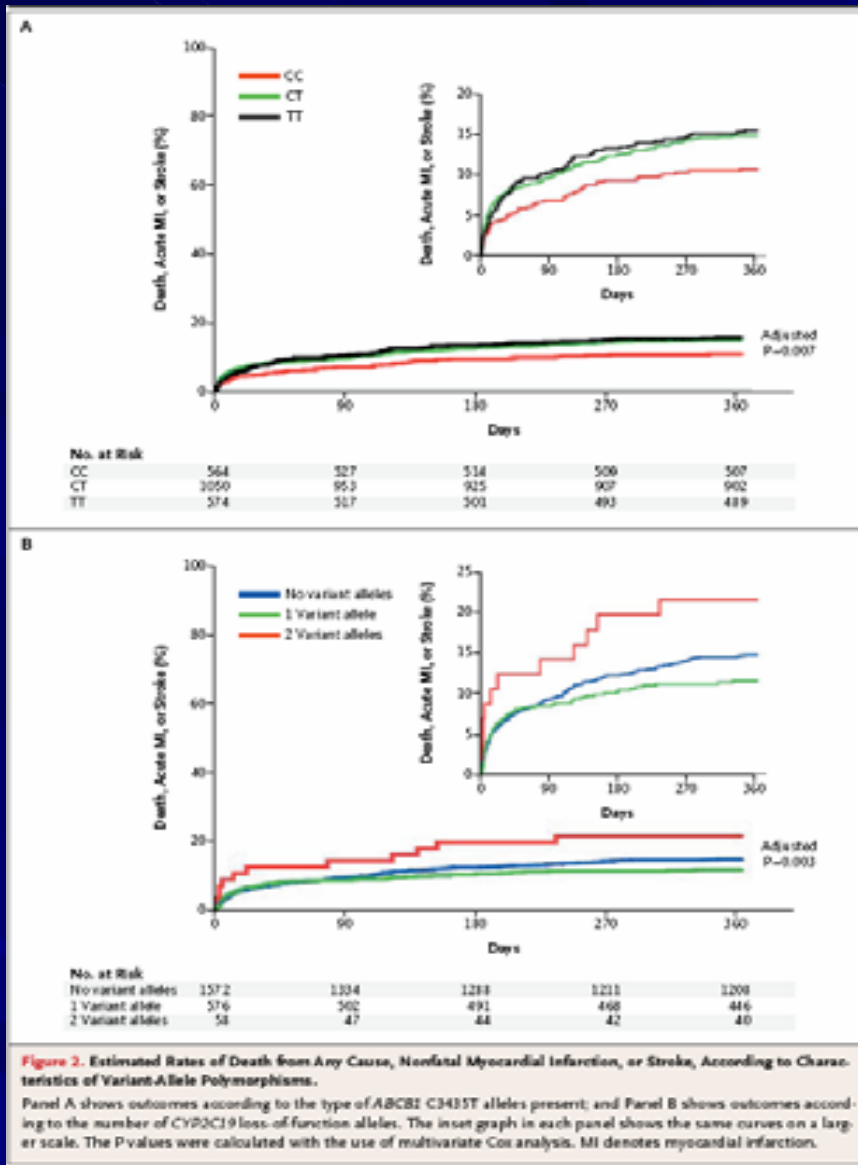
Table 2. Allelic Frequencies of SNPs among the Study Patients, According to Genes.

| Nucleotide Change and Genotype ^a | Patients without Outcome Event (N = 1914) | Patients with Outcome Event (N = 294) | P Value† |
|---|---|---------------------------------------|----------|
| P2RY12 | | | |
| C→A (rs16844673) | | | 0.96 |
| No. of patients with data | 1879 | 290 | |
| GA—no. (%) | 3 (<1) | 0 | |
| AA—no. (%) | 1886 (>99) | 190 (100) | |
| G31T (rs6809499) | | | |
| No. of patients with data | 1861 | 283 | 0.42 |
| TT—no. (%) | 47 (2) | 6 (2) | |
| GT—no. (%) | 471 (25) | 81 (28) | |
| GG—no. (%) | 1343 (72) | 194 (69) | |
| C34T (rs6785910) | | | |
| No. of patients with data | 1897 | 288 | 0.36 |
| TT—no. (%) | 192 (10) | 22 (8) | |
| CT—no. (%) | 777 (41) | 116 (40) | |
| CC—no. (%) | 928 (49) | 150 (52) | |
| ITGB3 | | | |
| T→C (rs5918) | | | 0.86 |
| No. of patients with data | 1878 | 288 | |
| CC—no. (%) | 41 (2) | 6 (2) | |
| CT—no. (%) | 501 (27) | 80 (28) | |
| TT—no. (%) | 1334 (71) | 202 (70) | |
| ABCB2 | | | |
| C3415T (rs1045642) | | | 0.04 |
| No. of patients with data | 1898 | 290 | |
| TT—no. (%) | 489 (26) | 81 (28) | |
| CC—no. (%) | 167 (9) | 57 (20) | |
| CT—no. (%) | 902 (48) | 148 (51) | |
| CYP3A5 | | | |
| A6986G, CYP3A5*3 (rs176746) | | | 0.69 |
| No. of patients with data | 1886 | 285 | |
| GG—no. (%) | 1373 (83) | 243 (85) | |
| AA—no. (%) | 20 (1) | 3 (1) | |
| AG—no. (%) | 293 (16) | 39 (14) | |

Table 2. (Continued.)

| Nucleotide Change and Genotype ^a | Patients without Outcome Event (N = 1914) | Patients with Outcome Event (N = 294) | P Value† |
|---|---|---------------------------------------|----------|
| CYP2C19 | | | |
| G681A, CYP2C19*2 (rs4244285) | | | 0.17 |
| No. of patients with data | 1890 | 288 | |
| AA—no. (%) | 43 (2) | 10 (3) | |
| AG—no. (%) | 500 (26) | 64 (22) | |
| GG—no. (%) | 1347 (71) | 214 (74) | |
| G636A, CYP2C19*3 (rs4966972) | | | |
| No. of patients with data | 1896 | 291 | 0.97 |
| AG—no. (%) | 1 (<1) | 0 | |
| GG—no. (%) | 1895 (>99) | 291 (100) | |
| A10, CYP2C19*4 (rs28399504) | | | |
| No. of patients with data | 1899 | 290 | 0.31 |
| GG—no. (%) | 1882 (99) | 286 (99) | |
| GA—no. (%) | 17 (1) | 4 (1) | |
| C1297T, CYP2C19*5 | | | |
| No. of patients with data | 1887 | 289 | 0.97 |
| CT—no. (%) | 1 (<1) | 0 | |
| CC—no. (%) | 1886 (>99) | 289 (100) | |
| Any CYP2C19 loss-of-function SNP (*2, *3, *4, or *5) | | | |
| No. of patients with data | 1914 | 294 | 0.045 |
| No variant allele—no. (%) | 1355 (71) | 218 (74) | |
| 1 Variant allele—no. (%) | 513 (27) | 64 (22) | |
| 2 Variant alleles—no. (%) | 46 (2) | 12 (4) | |
| C806T, CYP2C19*17 (rs12248160) | | | |
| No. of patients with data | 1877 | 287 | 0.18 |
| TT—no. (%) | 89 (5) | 11 (4) | |
| CT—no. (%) | 167 (9) | 77 (27) | |
| CC—no. (%) | 1191 (63) | 199 (69) | |

Resistencia al clopidogrel



Existen 3 polimorfismos de CYP2C19

El CYP2C19*1 corresponde a la función normal.

Los CYP2C19*2 y CYP2C19*3 pierden su función dando "pobre metabolización"

Los "pobres metabolizadores" se clasifican en:

Pobres con 2 alelos e intermedios con 1 alelo mutado.

NEJM2009;340(4):363-75

JACC2010;56(4):321-41

Resistencia al clopidogrel

- Resumen: de los 2208 pacientes tratados con clopidogrel se evaluó la relación entre las determinantes genéticas a la respuesta del clopidogrel y los eventos cardiovasculares.
- Las variantes genéticas del CYP2C19 que resultan en la pérdida de su función, se asocian a muerte, IAM o stroke. 21.5 vs 13.3 or 1.98 (IC 1.71-7.51)

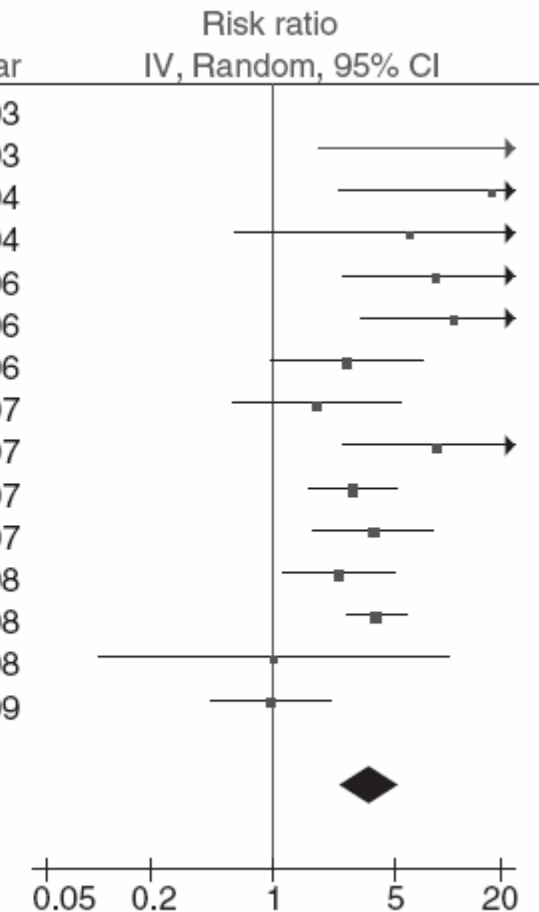
Resistencia al clopidogrel

- Los polimorfismos de CYP2C19 justificarían el 12% de la variabilidad de la respuesta y su valor predictivo positivo de la pérdida de la función del polimorfismo se estima entre 12-20%
- Los polimorfismos genéticos se relacionan con distintas etnias ej. 50% Chinos, 34% Negros, 25% blancos, 19% Mexicanos.
- En el estudio TRITON TIMI 38 Prasugrel vs Clopidogrel y trombolíticos en IAM, el 95% tenía el polimorfismo CYP2C19*2.
- Los que presentan una variante alelica tienen 26-31% menos del metabolito activo, los que presentan 2 variables 46-55%

Resistencia al clopidogrel

- El metaanálisis de la relación de los no respondedores mediada por agregación y eventos clínicos

| Study or Subgroup | Non-responders | | Responders | | Weight | Risk ratio | |
|-------------------|----------------|-------|------------|-------|--------|----------------------|------|
| | Events | Total | Events | Total | | IV, Random, 95% CI | Year |
| Gurbel 2003 | 0 | 29 | 0 | 63 | | Not estimatable | 2003 |
| Muller 2003 | 2 | 12 | 0* | 93 | 1.5% | 36.15 (1.84–36.15) | 2003 |
| Matetzky 2004 | 6 | 15 | 1 | 45 | 3.0% | 18.00 [2.35, 137.71] | 2004 |
| Mobley 2004 | 2 | 11 | 1 | 33 | 2.4% | 6.00 [0.60, 59.93] | 2004 |
| Campo 2006 | 7 | 14 | 3 | 51 | 6.3% | 8.50 [2.52, 28.69] | 2006 |
| Cuisset 2006 | 9 | 23 | 3 | 83 | 6.3% | 10.83 [3.19, 36.75] | 2006 |
| Hochholzer 2006 | 7 | 199 | 8 | 603 | 7.9% | 2.65 [0.97, 7.22] | 2006 |
| Schwonberg 2007 | 4 | 14 | 6 | 37 | 7.1% | 1.76 [0.58, 5.32] | 2007 |
| Frere 2007 | 11 | 54 | 3 | 127 | 6.2% | 8.62 [2.50, 29.69] | 2007 |
| Angiolillo 2007 | 17 | 45 | 17 | 128 | 12.2% | 2.84 [1.59, 5.08] | 2007 |
| Buonamici 2007 | 9 | 105 | 16 | 699 | 9.9% | 3.74 [1.70, 8.25] | 2007 |
| Geisler 2008 | 15 | 312 | 13 | 638 | 10.5% | 2.36 [1.14, 4.90] | 2008 |
| Gurbel 2008 | 54 | 101 | 27 | 196 | 14.3% | 3.88 [2.62, 5.76] | 2008 |
| Liu 2008 | 1 | 13 | 2 | 26 | 2.4% | 1.00 [0.10, 10.04] | 2008 |
| Yong 2009 | 7 | 49 | 21 | 142 | 9.9% | 0.97 [0.44, 2.13] | 2009 |
| Total (95% CI) | | 996 | | 2964 | 100.0% | 3.53 [2.39, 5.20] | |



* : a correction of 0.5 patient was applied

Resistencia al clopidogrel y su relación con eventos

Table 1. CYP2C19*2 Polymorphisms and Cardiovascular Outcomes

| Source, Year (Region) | Patients, n (Age, Years) | Disease | Clopidogrel Dosage | Duration of Follow-Up (Months) | Outcome (n) | Frequency of Genotype, n (%) | | | RR (95% CI) | Adjustment |
|---|--------------------------|---------|---|--------------------------------|---|------------------------------|------------|------------|--|---|
| | | | | | | *1/*1 | *1/*2 | *2/*2 | | |
| Trenk et al., 2008 (Germany) (21) | 797 (mean: 66.4) | CAD | LD 600 mg MD 75 mg day ⁻¹ | 12 | Death and MI (24) | 552 (69.3) | 228 (28.6) | 17 (2.1) | 0.67 (0.25–1.78)† | None |
| Simon et al., 2009 (France) (22) | 2178 (mean: 70.1) | AMI | LD 300 mg MD 75 mg day ⁻¹ | 12 | Death from any cause (225) | 1561 (71.7) | 564 (25.9) | 53 (2.4) | 0.89 (0.68–1.18)† | None |
| Collet et al., 2009 (France) (2) | 259 (18–45) | MI | LD n.d. MD 75 mg day ⁻¹ | 100 | Death, MI, urgent coronary revascularization (26) Stent thrombosis (12) | 186 (71.8) | | 73 (28.2) | 5.38 (2.32–12.47) 6.04 (1.75–20.80) | BMI smoking, diabetes, stent implantation, STEMI, use of proton-pump inhibitors |
| Mega et al., 2009 (United States) (17) | 1459 (mean: 60.1) | ACS | LD 300 mg MD 75 mg day ⁻¹ | 15 | Death from CV causes, MI, stroke (129) Stent thrombosis (18) | 1064 (72.9) | | 395 (27.1) | 1.53 (1.07–2.19) 3.09 (1.19–8.00) | None |
| Sibbing et al., 2009 (Germany) (4) | 2485 (mean: 66.5) | CAD | LD 600 mg MD 75 mg day ⁻¹ | 1 | Stent thrombosis (17) | 1805 (73) | 633 (25) | 47 (2) | 3.81 (1.45–10.02) | Age, diabetes, ACS, type of stent |
| Giusti et al., 2009 (Italy) (3) | 772 (mean: 68.3) | ACS | LD 600 mg MD 75 mg day ⁻¹ | 6 | Stent thrombosis + cardiac mortality (29) Stent thrombosis (24) | 525 (68) | 221 (28.6) | 26 (3.4) | 2.70 (1.00–8.42) 3.43 (1.01–12.78) | Residual platelet reactivity, traditional CV risk factors, clinical and procedural risk factors |
| Shuldiner et al., 2009 (United States) (15) | 93‡ (mean: 65) | CAD | LD 300/600 mg day ⁻¹ MD 75 mg day ⁻¹ | 12 | MI, unplanned target and nontarget lesion revascularization, hospitalization, death from CV causes (n not reported) | 66 (70.9) | 27 (29.1) | | 3.40 (1.36–8.46) | Age, gender, race |

Advertencia de la FDA de resistencia al clopidogrel

- ✓ A comienzo del 2009 la FDA recomienda el estudio genético y probable considerar dosis altas de clopidogrel.
El 5 de Mayo 2009 se aclara que los pobres metabolizadores tienen poca agregación con clopidogrel y que la dosis óptima no se conoce.
- ✓ La 2ª advertencia del 2009 sugiere abolir el uso de clopidogrel en los pacientes con polimorfismo CYP2C19 con déficit funcional o por inhibición del CYP2C19 por drogas (Omeprazol).
- ✓ La tercera advertencia Marzo 2010, sugiere al médico tratante evaluar alternativas terapéuticas o estrategias terapéuticas para los "pobres metabolizadores"
Asimismo se menciona el aumento de los eventos clínicos en esta población.

Resistencia al clopidogrel

Alternativas desde el punto de vista clínico

➤ Modificar la dosis:

La escasez de datos con respecto a los “pobres respondedores” no avalan su uso solo de acuerdo a la genotipificación.

El uso de 600mg de carga o doble carga mejoran la inhibición plaquetaria y el mantenimiento de 150mg también, algunos pacientes no tienen respuestas. No se ha demostrado en los eventos cardiovasculares mayores (MACE) en todas las poblaciones.

Table 3. Effect of Different Clopidogrel Dosing Protocols on Patient Outcomes

| Study | Regimen | Metric | Results |
|--|--|---|--|
| ARMYDA-4 RELOAD (42)* 503 stable AP or non-STEMI ACS patients on chronic C for more than 10 d | 600 mg load vs. placebo | 30-d MACE defined as cardiac death, MI, or TVR | No benefit in overall cohort. In non-STEMI ACS patients, 600 mg load reduced MACE (16.3% to 6.4%); no change in MACE in stable AP. |
| HORIZONS-AMI (43) 3602 STEMI patients | 600 mg vs. 300 mg C load | 30-d MACE defined as all-cause death, stroke, reinfarction, unplanned revascularization for ischemia, or major bleeding | 600-mg dose was an independent predictor of lower 30-d MACE |
| CURRENT OASIS-7* 25,098 ACS patients (41a) | High-dose C – 600-mg loading dose, then 150 mg for 7 d, then 75 mg daily to 30 d; standard dose C – 300 mg loading dose, then 75 mg daily to 30 d | 30-d MACE defined as cardiovascular death, MI, or stroke | No benefit in overall cohort. In subgroup of 17,232 PCI patients, 15% reduction in MACE in high-dose group with a 42% reduction in definite ST, but increased bleeding |

Resistencia al clopidogrel

Alternativas desde el punto de vista clínico

➤ Adicionar Cilostazol:

inhibe la plaqueta por vías diferentes a la aspirina y tienopiridinas.

Es un inhibidor selectivo de la fosfodiesterasa tipo 3 y altera la recaptación de ADP y la producción de PGI₂ óxido nítrico endotelial.

➤ Adicionar OMEGA-3

➤ Prasugrel:

El subestudio de plaquetas se realizó en un pequeño subgrupo del TRITON_TIMI 38 y mostró mayor inhibición comparado con 75/150mg de Clopidogrel con reducción de los eventos y un incremento del sangrado MAYOR SOBRE TODO EN <60kg, >70años y stroke o TIA previos.

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Table 4. Ongoing Trials Evaluating Antiplatelet Therapy Tailored by Genotyping and/or Phenotype Assessment

| Study | Design | No. of Patients | Population | Selection Criterion | Outcome | Follow-Up |
|--|--|-----------------|---|--|---|----------------------------------|
| Trials Evaluating Pharmacodynamic and/or Pharmacokinetic Outcomes | | | | | | |
| GIFT (NCT00992420) PI: M.J. Price | Observational, prospective cohort study (GRAVITAS substudy) (PD study) | Up to 2000 | Stable CAD or NSTEMI ACS undergoing DES | Patients with high residual platelet activity (HRPA) 12- to 24-h post-DES randomized to: 1) standard 75 mg clopidogrel, or 2) high-dose clopidogrel (additional 600 mg followed by 150 mg daily) | Association of CYP2C19 genotype with RPA (VerifyNow) on standard dose of clopidogrel or incremental change RPA on high-dose clopidogrel | 6 mo |
| Clopidogrel Pharmacogenomics Project (NCT01097343) PI: J. Dharmavaram PI: J.S. Rossi | Randomized, open-label, crossover, phase 0 (PD/PK study) | 200 | Stable CAD | Screen for CYP2C19*2 LOF allele; randomize eligible patients to clopidogrel 75 mg or 150 mg daily × 30 d and then crossover | Change in RPA (VerifyNow, optical aggregometry); measurement of active metabolites | 90 d |
| CLOVIS-2 (NCT00822666) PI: J.-P. Collet PI: G. Montalescot | Randomized, open-label, phase III, crossover (PD/PK study) | 120 | Post-MI, <45 y and enrolled in AFJJI registry | Comparison of 2 loading strategies of clopidogrel (300 mg vs. 900 mg) in 2 genetic profiles: wild-type 2C19*1 and carriers of 2C19*2 (homozygous or heterozygous) | Inhibition of RPA (IRPA) by optical aggregometry; measurement of active metabolites | 6 h postclopidogrel loading dose |
| Role of CYP2C19 Polymorphism in the Drug Interaction Between Clopidogrel and Omeprazole (NCT01094275) PI: S. Nadipalli PI: T. Delac | Observational, case-crossover, phase IV (PD/PK study) | 75 | Healthy volunteers | Subjects with CYP2C19*2/*3 LOF allele, and age- and gender-matched wild-type control randomized to clopidogrel + omeprazole vs. clopidogrel × 1 wk, and crossover | Platelet inhibitory response to clopidogrel; measurement of active metabolites | 3 wk |
| ELEVATE-TIMI 56 PI: J.L. Mega (58a) | Randomized treatment sequence (PD study) | 275 | Stable CAD | Patients on clopidogrel 75 mg and genotyped for CYP2C19 alleles will be treated with biweekly dose of clopidogrel *(75 mg to 300 mg daily, depending on genotype). | Change in RPA (VerifyNow, VASP) | 8 wk |
| PREDICT Pilot Study (NCT00747656) PI: M.J. Price | Observational prospective cohort (PD study) | 42 | Stable CAD on clopidogrel therapy | Patients with HRPA on clopidogrel 75 mg and genotyped for CYP2C19 alleles treated with double-dose clopidogrel (150 mg) | Change in RPA (VerifyNow) | 7 d |
| ACCEL-2C19 (NCT01012193) PI: Y.-H. Jeong | Randomized, active-control, single-blind (PD study) | 134 | Stable CAD, elective PCI | Patients genotyped for CYP2C19 variants randomized to high-dose clopidogrel (150 mg) + ASA 200 mg vs. cilostazol 100 mg bid + 75 mg clopidogrel + ASA 200 mg (triple therapy) | Inhibition of maximum platelet aggregation (optical aggregometry; VerifyNow) | 30 d |
| ACCELAMI2C19 (NCT00915733) PI: I.-S. Kim | Randomized, active-control, open-label (PD study) | 80 | Acute MI, post-PCI | Patients genotyped for CYP2C19 variants randomized to high-dose clopidogrel (150 mg) + ASA 100 mg vs. cilostazol 100 mg bid + 75 mg clopidogrel + ASA 100 mg (triple therapy) | Inhibition of maximum platelet aggregation (optical aggregometry; VerifyNow) | 30 d |

Resistencia al clopidogrel

Alternativas desde el punto de vista clínico

Table 2. Pharmacodynamic Studies of Platelet Responsiveness to Different Clopidogrel Dosing Protocols

| Study | Regimen | Metric | Results |
|---|---|---|---|
| ISAR-CHOICE (33) 60 elective PCI patients; C-naïve | C, 300, 600, 900 mg LD | Platelet aggregometry, active thiol metabolite of C | 600 mg dose had highest active drug metabolite level and platelet suppression compared with the 300 mg dose. |
| von Beckerath et al. (34) 60 patients after successful PCI; 600 mg C load | C, 150 mg daily vs. 75 mg daily (MD) | 30-d platelet function | C, 150 mg daily had more intense platelet inhibition. |
| OPTIMUS study (35) 40 patients with type 2 DM and documented suboptimal response to C | C, 150 mg daily vs. 75 mg daily (MD) | Repeat platelet function testing after 30 d | 150 mg dose improved rates of platelet inhibition, but 60% of patients still had suboptimal C effect. |
| Fontana et al. (36) 81 patients with recent PCI and documented suboptimal platelet inhibition on C 75 mg daily | C increased to 150 mg daily C (MD) | Repeat platelet function testing after 15 d | C, 150 mg daily improved platelet inhibition. |
| PRINC trial (37) 60 patients undergoing PCI; C, 600 mg LD | 2 h after initial C-load, either 600 mg C or placebo, then second randomization to 150 mg C vs. 75 mg C daily | Platelet inhibition at 2, 4, and 7 h, and 1 wk | 600 mg load × 2 at 2 h apart produced better inhibition than 600 mg acutely; 150 mg daily results in better inhibition than 75 mg after 1 wk. |
| VASP-02 (38) 153 patients undergoing elective PCI | C, 150 mg versus 75 mg daily for 4 wk; after 2 wk, platelet inhibition checked and low responders increased to 150 mg daily | Platelet inhibition at 2 and 4 wk | At 2 wk, 150 mg C produced better platelet inhibition. In low responders, 150 mg C improved platelet inhibition. |
| Price et al. (40) 45 volunteers | C, 300, 600, 900 mg LD | Platelet inhibition at baseline and 1 through 7 h | 600 mg and 900 mg had more intense platelet inhibition than 300 mg, no difference between 600 mg and 900 mg. |
| Montalescot et al. (ALBION) (41) 103 patients with NSTEMI | C, 300, 600, 900 mg LD | ADP-induced IPA at 24 h | LDs greater than 300 mg provided greater antiplatelet effect than 300 mg |

ADP indicates adenosine diphosphate; ALBION, Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis; C, clopidogrel; DM, diabetes mellitus; IPA, inhibition of platelet aggregation; ISAR-CHOICE, Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 Higher Oral Doses for Immediate Clopidogrel Effect; LD, loading dose; MD, maintenance dose; NSTEMI, non-ST-segment elevation myocardial infarction; OPTIMUS, Optimizing Antiplatelet Therapy in Diabetes Mellitus; PCI, percutaneous coronary intervention; PRINC, Plavix Response in Coronary Intervention; and VASP-02, Vasodilator-Stimulated Phosphoprotein-02 Randomized Study.

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Conclusiones

- ❖ Existen múltiples variabilidades individuales de respuestas al clopidogrel.
- ❖ Estas variables incluyen factores genéticos y clínicos.
- ❖ Algunos genotipos podrían asociarse a hiporeactividad plaquetaria tanto a nivel biológico como clínico.
- ❖ Los polimorfismos genéticos de CYP2C19*2 con las 2 variantes alelicas pierden su función pero su impacto clínico queda aún por confirmarse.
- ❖ El valor predictivo del estudio genético queda por confirmarse.
- ❖ Hasta la actualidad no parece ser razonable el estudio genotípico para la toma de decisiones.