# Pacientes de Alto Riesgo: Triple Terapia? Riesgo Asociado

XIV Jornadas SOLACI 5 Región Cono Sur

Asunción – Paraguay

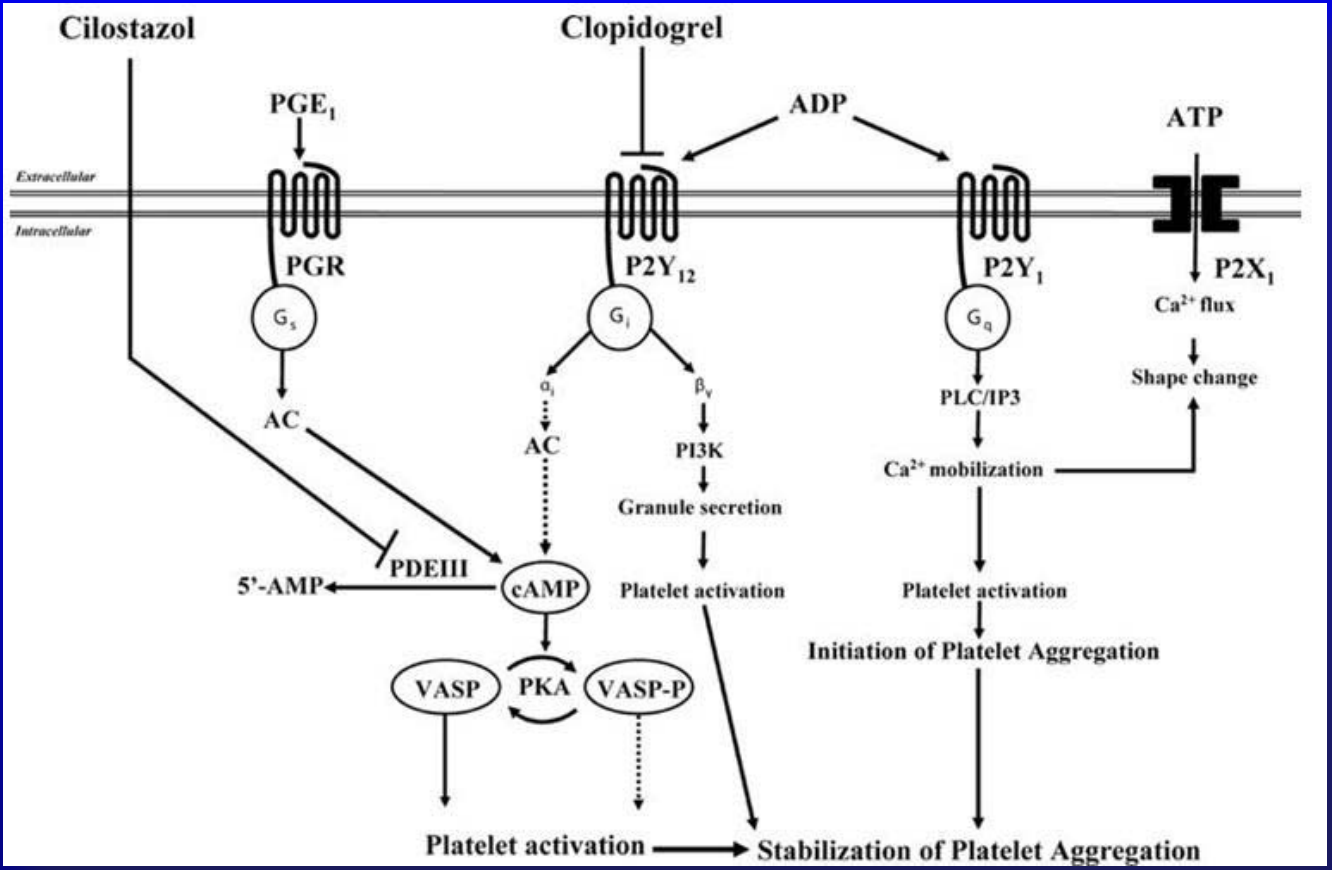
Mayo/2011

# Tratamiento con Clopidogrel

## *Limitaciones*

- Inicio lento de acción, necesitando de pre-tratamiento para mejorar la eficiencia de la ICP
- Niveles modestos de inhibición plaquetária
- Variabilidad de respuesta (Resistencia ≅ 30%)
- Interacción con otras medicaciones (IBPs)
- Variabilidad genética (Polimorfismos – Citocromo P450)

# Triple Terapia
## *Cilostazol*




**Inhibidor de la enzima fosfodiesterase 3 →↑ AMPc intraplaquetario**

# DECLARE DIABETES TRIAL

## *Diseño del Estudio*

n = 400 Diabetes Mellitus

Mayo/2005 a Marzo/2006 5 centros Corea

Angina de Pecho o Stress teste +

**Stent Sirolimus**

n = 200

- **Terapia Triple**
  n =100
  AAS/Clopidogrel
  + Cilostazol
- **Terapia doble**
  n =100
  AAS/Clopidogrel

**Stent Paclitaxel**

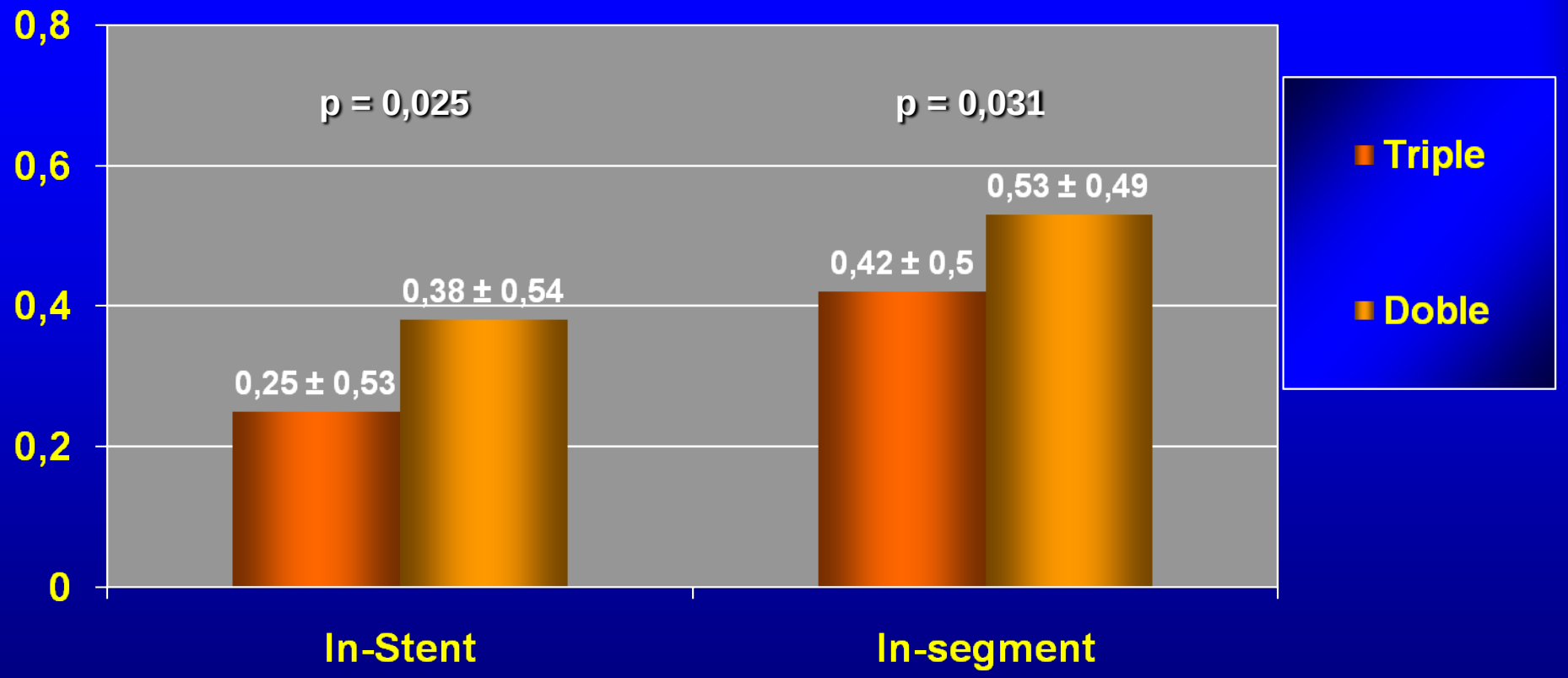
n = 200

- **Terapia Triple**
  n =100
  AAS/Clopidogrel
  + Cilostazol
- **Terapia doble**
  n =100
  AAS/Clopidogrel

Lee SW. J Am Coll Cardiol 2008;51:1181-7

# DECLARE DIABETES TRIAL

## *Primary End Point – Pérdida Tardia (mm)*




Lee SW. J Am Coll Cardiol 2008;51:1181-7

# DECLARE DIABETES TRIAL

## *Efectos Adversos*

| Variable | Triple (n = 200) | Standard (n = 200) | p Value |
|---|---|---|---|
| Bleeding | 3 (1.5%) | 3 (1.5%) | 0.999 |
| Major bleeding | 0 | 0 | |
| Minor bleeding | 3 (1.5%) | 3 (1.5%) | |
| Rash | 15 (7.5%) | 5 (2.5%) | 0.036 |
| Gastrointestinal trouble | 9 (4.5%) | 5 (2.5%) | 0.416 |
| Thrombocytopenia | 0 | 1 (0.5%) | 0.999 |
| Neutropenia | 0 | 0 | 0.999 |
| Hepatic dysfunction | 2 (1.0%) | 1 (0.5%) | 0.999 |
| Drug discontinuation | 29 (14.5%) | 5 (2.5%) | <0.001 |

Lee SW. J Am Coll Cardiol 2008;51:1181-7

# DECLARE – LONG TRIAL

## *Diseño del Estudio*

n = 499 Lesiones ≥ 25 mm Stent Zotarolimus ≥ 30 mm

Diciembre/2007 a Diciembre/2008 10 centros Corea

Angina Estable o SCA

**Terapia Triple**

n = 250

**Terapia Doble**

n = 249

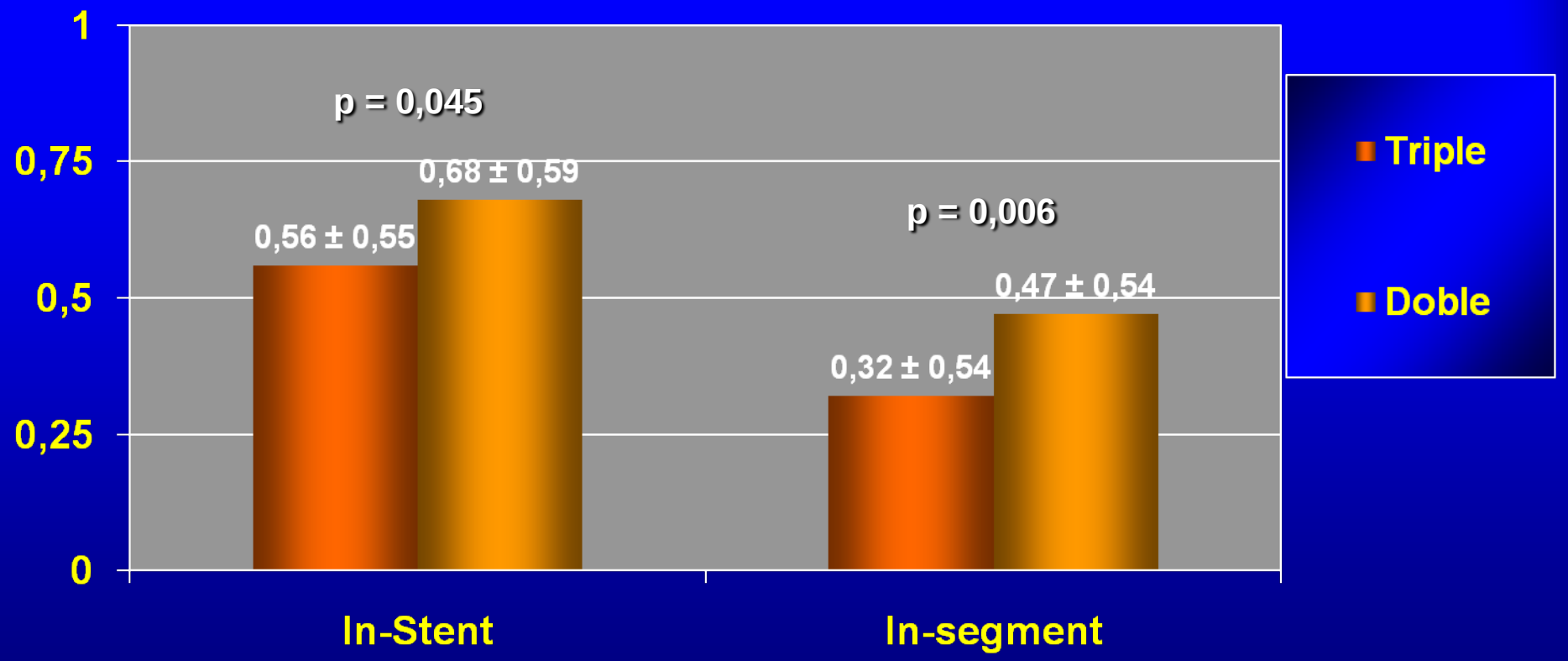
**Primary Endpoint**

In Stent Late – Loss – 8 meses

Lee SW. J Am Coll Cardiol 2011;57:1264-70

# DECLARE DIABETES TRIAL

## *Primary End Point – Late Loss (mm)*




Lee SW. J Am Coll Cardiol 2011;57:1264-70

# DECLARE DIABETES TRIAL

## *Efectos Adversos*

| Variable | Triple (n = 250) | Dual (n = 249) | p Value |
|---|---|---|---|
| Bleeding complications | 18 (7.2%) | 17 (6.8%) | 0.87 |
| Major bleeding | 6 (2.4%) | 2 (0.8%) | 0.16 |
| Minor bleeding | 1 (0.4%) | 1 (0.4%) | 0.99 |
| Minimal bleeding | 11 (4.4%) | 14 (5.6%) | 0.53 |
| Headache | 11 (4.4%) | 2 (0.8%) | 0.01 |
| Palpitation | 4 (1.6%) | 1 (0.4%) | 0.18 |
| Rash | 8 (3.2%) | 7 (2.8%) | 0.80 |
| Gastrointestinal trouble | 6 (2.4%) | 2 (0.8%) | 0.16 |
| Thrombocytopenia | 1 (0.4%) | 0 | 0.99 |
| Neutropenia | 1 (0.4%) | 0 | 0.99 |
| Hepatic dysfunction | 0 | 4 (1.6%) | 0.06 |
| Drug discontinuation | 47 (18.8%) | 28 (11.2%) | 0.02 |

Lee SW. J Am Coll Cardiol 2011;57:1264-70

# CILON-T TRIAL

## *Diseño del Estudio*

n = 960 Stents Medicados

Setiembre/2006 a Juño/2009 5 centros Corea del Sur

Angina del Pecho o Stress Test +

**Terapia Triple**

n = 477

**Terapia Doble**

n = 483

**Primary Endpoint**

MACE – Muerte Cardiaca, IM no fatal, RLB isquemia, AVCI – 6 m

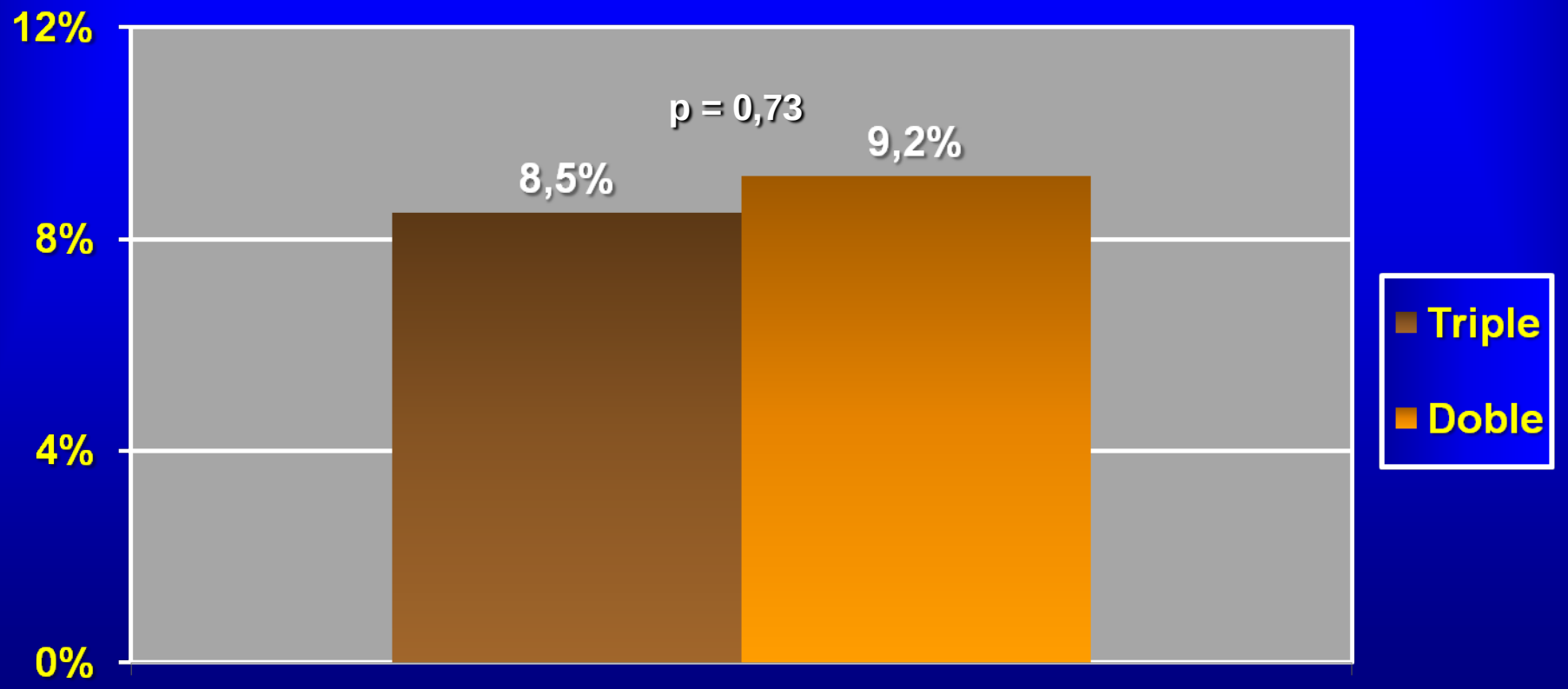
**Secondary Endpoint**

PRU (VerifyNow)– Alta Hospitalaria e 6 m

Suh J.W. J Am Coll Cardiol 2011;57:290-1

# CILON – T TRIAL
## *Endpoint Primário*

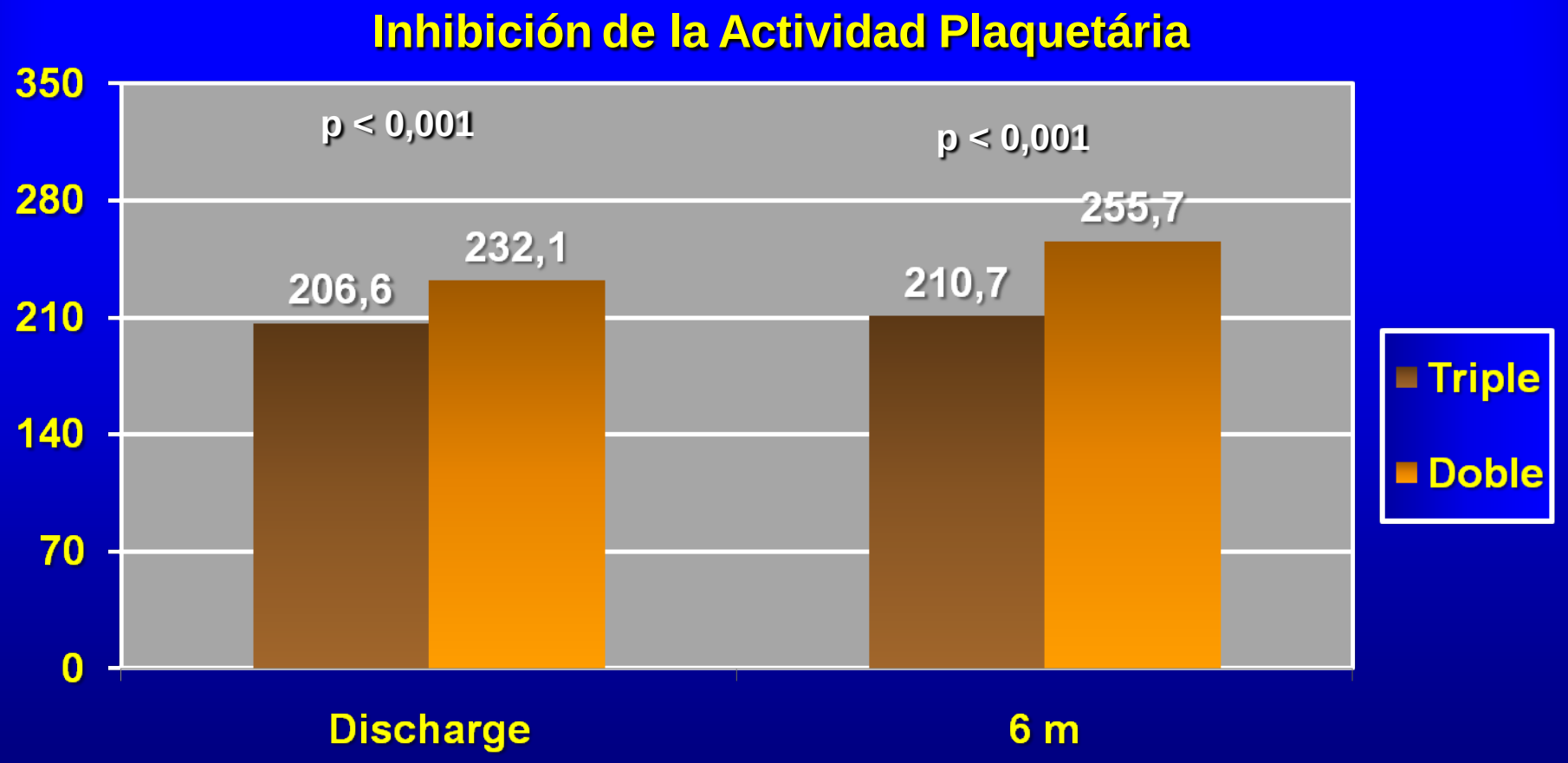
**Muerte Cardíaca, IAM no Fatal, RVB isquemia y AVC 6 m**




Suh J.W. J Am Coll Cardiol 2011;57:290-1

# Reactividad Plaquetária

## *Endpoint Secundário*




Suh J.W. J Am Coll Cardiol 2011;57:290-1

# CILON – T TRIAL

## *Efectos Adversos*

| Variable | TAT (n = 457) | DAT (n = 458) | p Value |
|---|---|---|---|
| Bleeding complications | | | 0.511 |
| TIMI major | 2 (0.4%) | 1 (0.2%) | |
| TIMI minor | 1 (0.2%) | 0 (0%) | |
| Drug discontinuation | 30 (6.6%) | 3 (0.7%) | <0.001 |
| Heart rate, beats/min | | | |
| Baseline | 69.7 (11.9) | 69.2 (12.7) | 0.62 |
| 6 months | 73.3 (12.0) | 68.4 (13.7) | <0.001 |

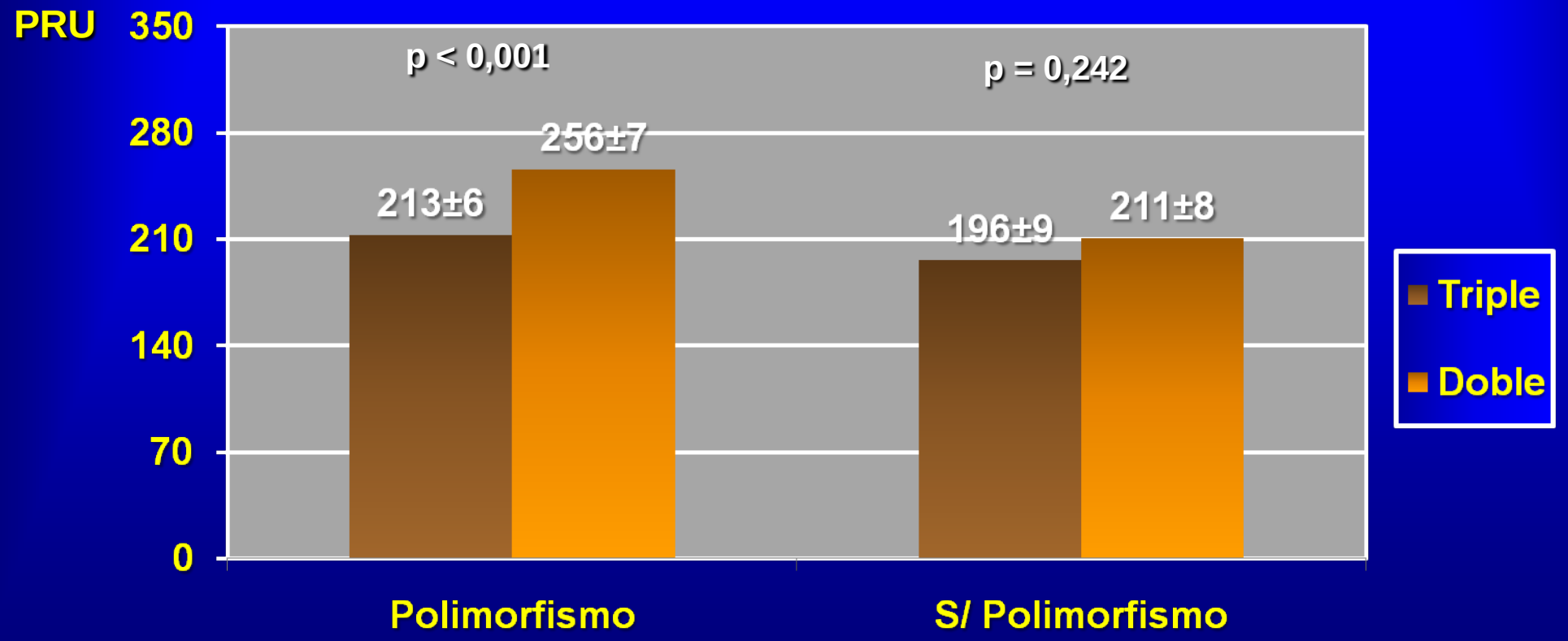
Suh J.W. J Am Coll Cardiol 2011;57:290-1

# CILON T TRIAL

## *Polimorfismo CYP2C19*

**n = 474 Portadores de Polimorfismo**

**Reactividad Plaquetária - Teste VerifyNow**




Park K. Heart 2011;97:641-647

# Anti Coagulación Oral
## *Warfarina - Indicaciones*

- Fibrilación Atrial
- Válvulas Mecánica Cardíacas
- Trombo Mural Ventrículo Izquierdo
- Trombosis Venosa Profunda
- Embolismo Pulmonar

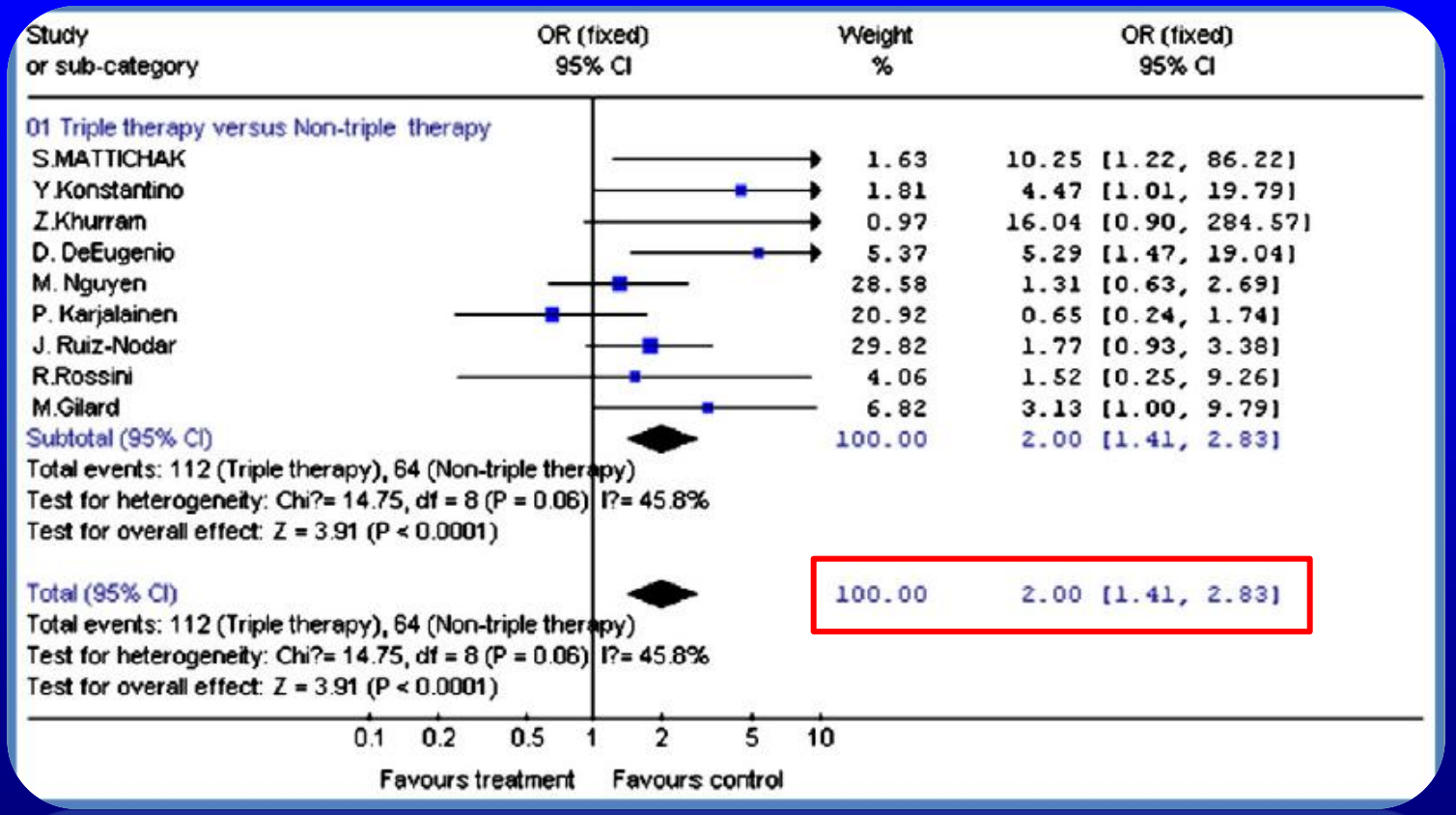
**5 a 10% ICP pacientes necesitan anti coagulación crónica**

King III. J Am Coll Cardiol 2008;51:172-209

# Anti Coagulación Oral en ICP

## *Meta–Análisis → Riesgo de Sangrado >*

**9 estudios** **Triple n = 1.428** **No Triple n = 3.753**

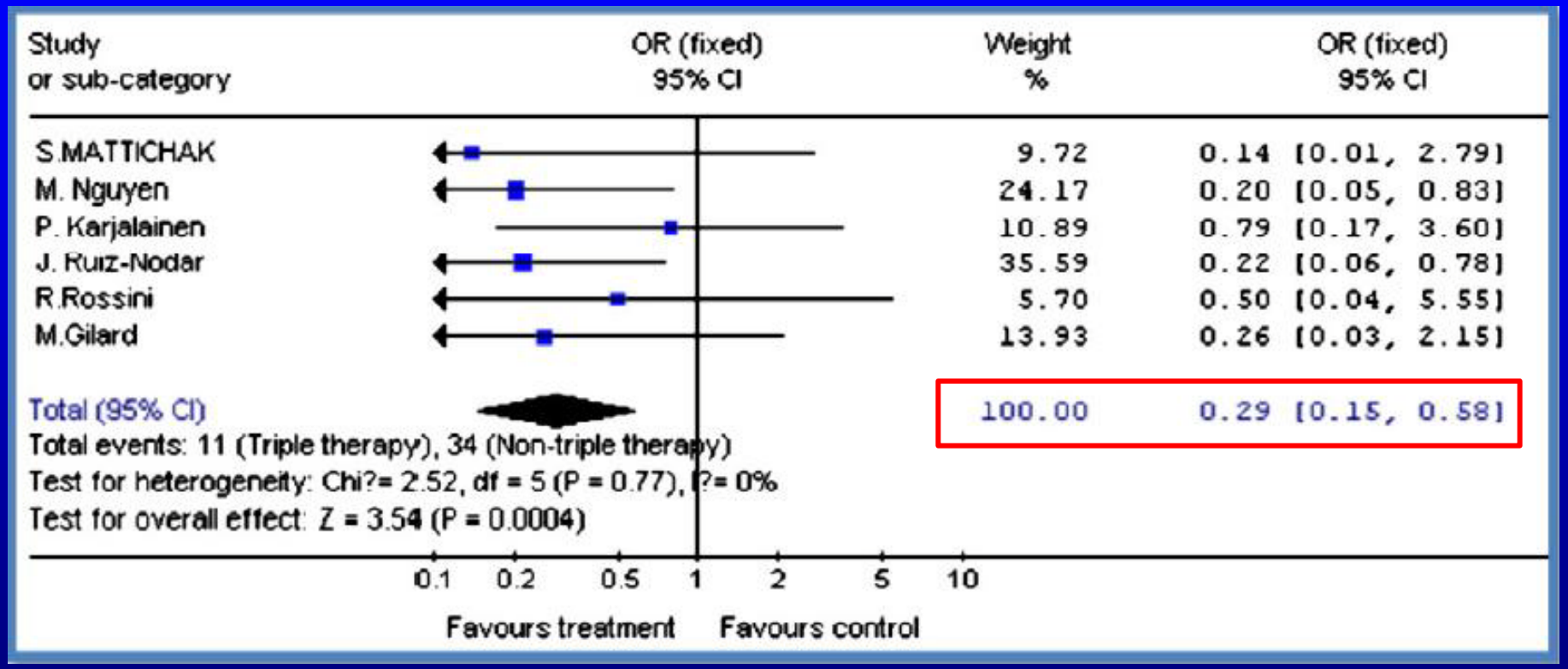



Gao F. Interv J Cardiol 2011;148:96-101

# Anti Coagulación Oral en ICP

## *Meta–Análisis → Riesgo de AVC*

### Triple vs No Triple Terapia

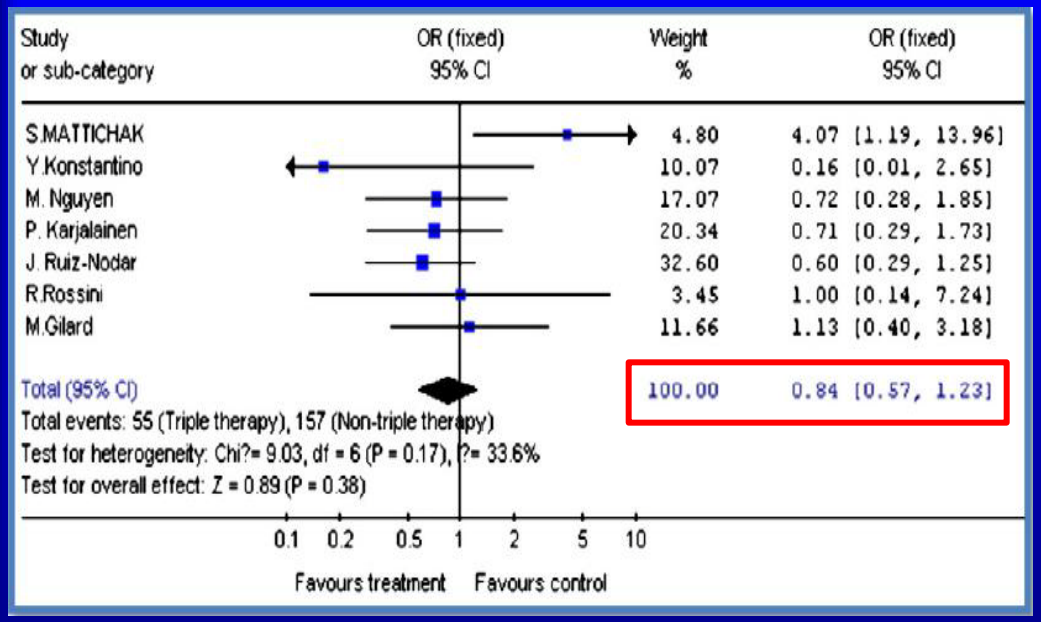



Gao F. Interv J Cardiol 2011;148:96-101

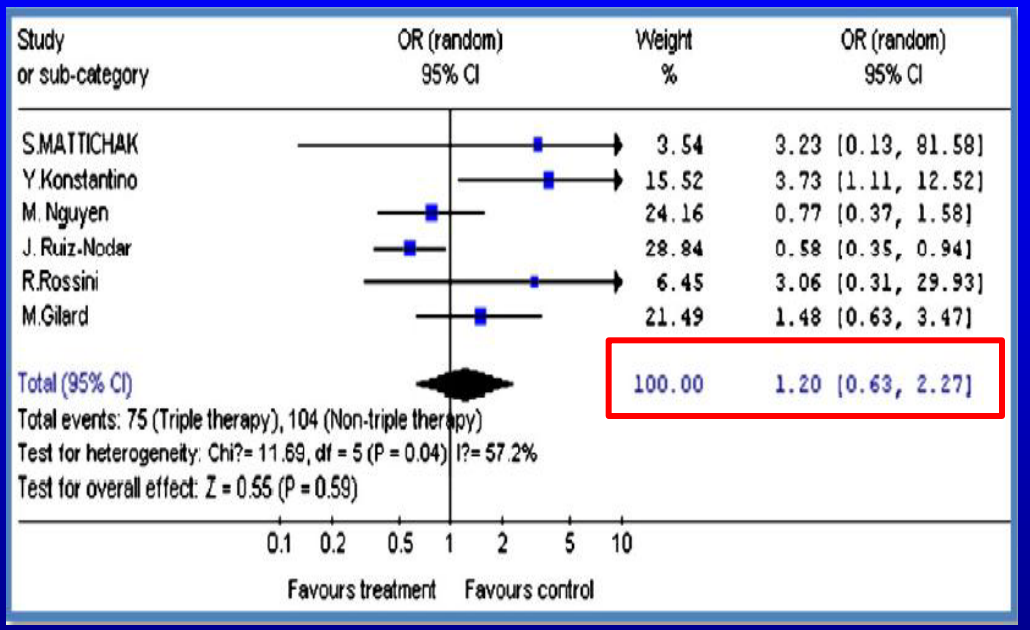
# Anti Coagulación Oral en ICP

## *Meta – Análisis → Riesgo de IAM y Muerte*

### Triple vs No Triple Terapia




**IAM**




**Muerte**

Gao F. Interv J Cardiol 2011;148:96-101

# Guidelines ESC

## *Management of Atrial Fibrillation and ICP*

- **ICP SCA o Electiva**
- **Evitar lo uso del DES (lesiones largas, vasos pequeños, diabetes, etc)**
- **Utilizar la Vía Radial**
- **INR – 2,0 a 2,5**

**Terapia Triple**

**Anticoagulante oral + AAS ≤ 100mg/dia + Clopidogrel 75 mg/dia**

**Duración ≤ 1 m**

Eur Heart J 2010;31:2369-2429
Eur Heart J 2010;31:2501-2555

# Guideline Update for ICP

## *ACC/AHA/SCAI 2007*

| Antiplatelet Agents/Anticoagulants: Warfarin | | | |
|---|---|---|---|
| Manage warfarin to an INR of 2.5 to 3.5 for post-MI patients when clinically indicated or for those not able to take aspirin or clopidogrel. | 1. Managing warfarin to an INR equal to 2.0 to 3.0 for paroxysmal or chronic atrial fibrillation or flutter is recommended, and in post-MI patients when clinically indicated (e.g., atrial fibrillation, left ventricular thrombus). | *I (A)* | Modified recommendation (changed text) |
| | 2. Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. | *I (B)* | New Recommendation |
| | 3. In patients requiring warfarin, clopidogrel, and aspirin therapy after PCI, an INR of 2.0 to 2.5 is recommended with low dose aspirin (75 mg to 81 mg) and a 75-mg dose of clopidogrel. | *I (C)* | New recommendation |

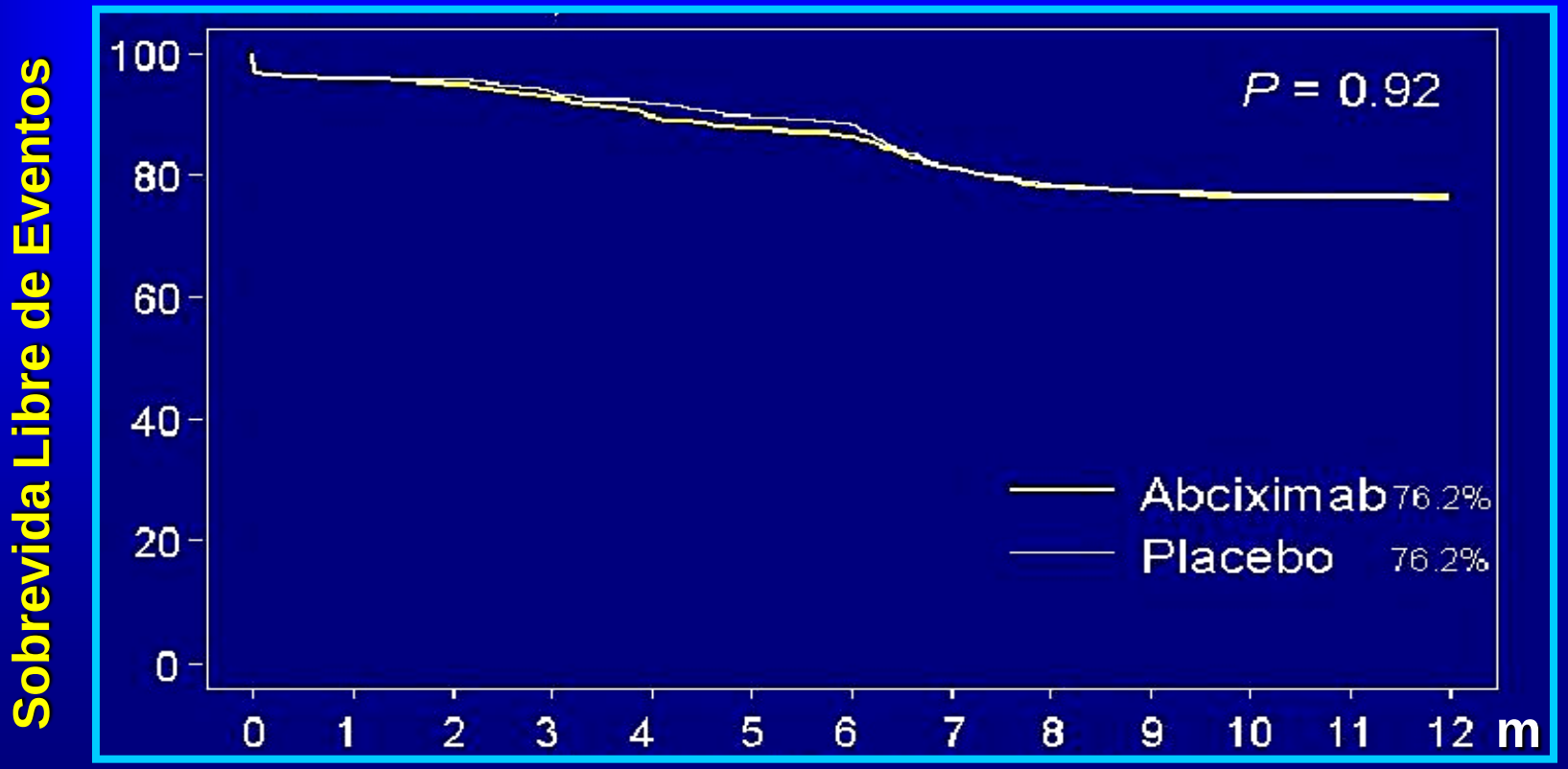
King III SB J Am Coll Cardiol 2008;51:172-209

# ISAR – REACT I Trial

## *Seguimento Clínico 1 ano*

**n = 2.159 ICP eletiva ( s/ desnivelamento ST ou troponina +)**

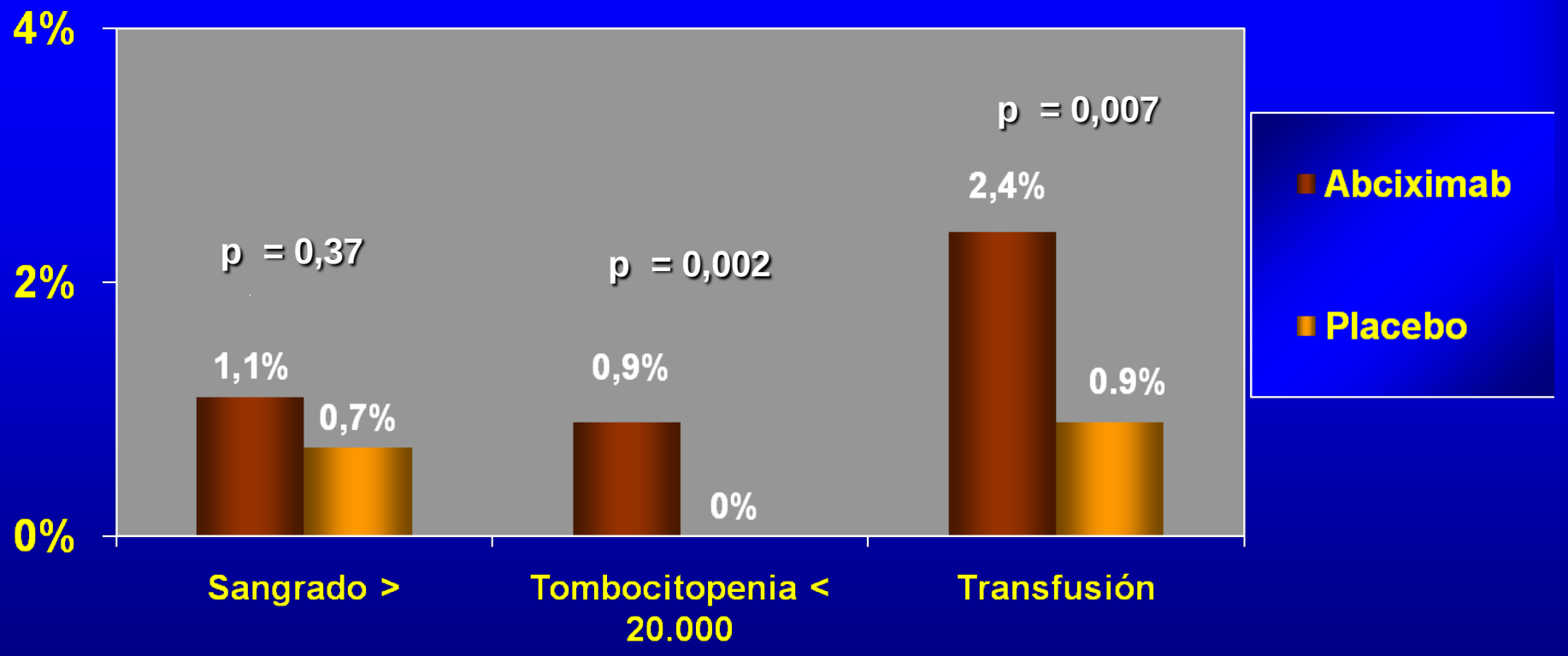
**Clopidogrel 600mg ≥ 2 hs + AAS**




Kastrati N Engl J Med 2004;350:232-8

# ESTUDO ISAR - REACT

## *Complicaciones 30 dias*




Kastrati N Engl J Med 2004;350:232-8

# Guidelines ESC/EACTS

## *GPIIb/IIIa en la ICP Electiva*

| Elective PCI | | | |
|---|---|---|---|
| Antiplatelet therapy | | Class[a] | Level[b] |
| | ASA | I | B |
| | Clopidogrel | I | A |
| | Clopidogrel - pretreatment with 300 mg loading dose >6 h before PCI (or 600 mg >2 h before) | I | C |
| | + GPIIb–IIIa antagonists (bailout situation only) | IIa | C |

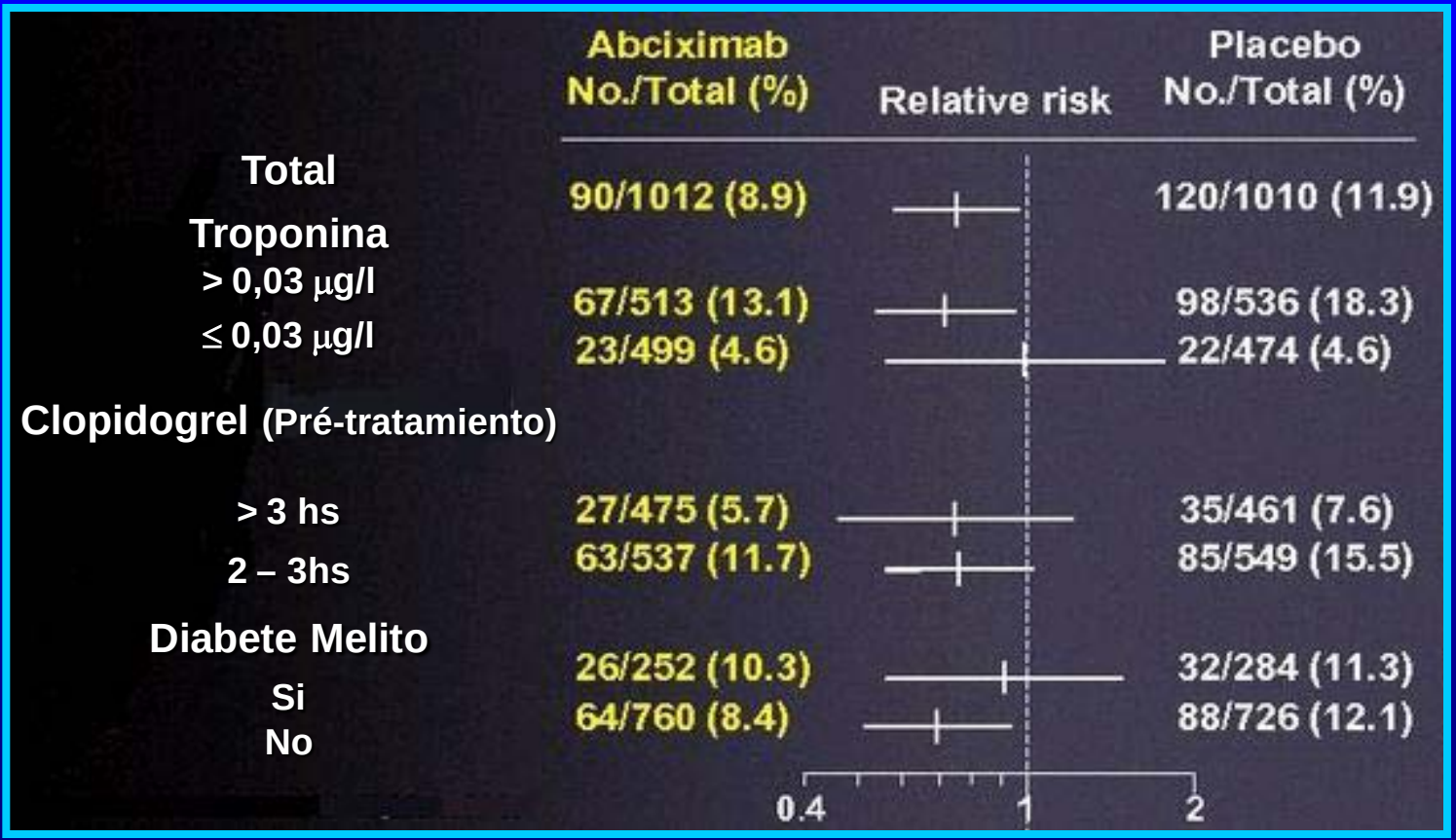
Eur Heart J 2010;31:2501-2555

# ISAR – REACT II Trial

## *Análise de Subgrupos*

**n = 2159** **Implante de Stent - SCASEST**

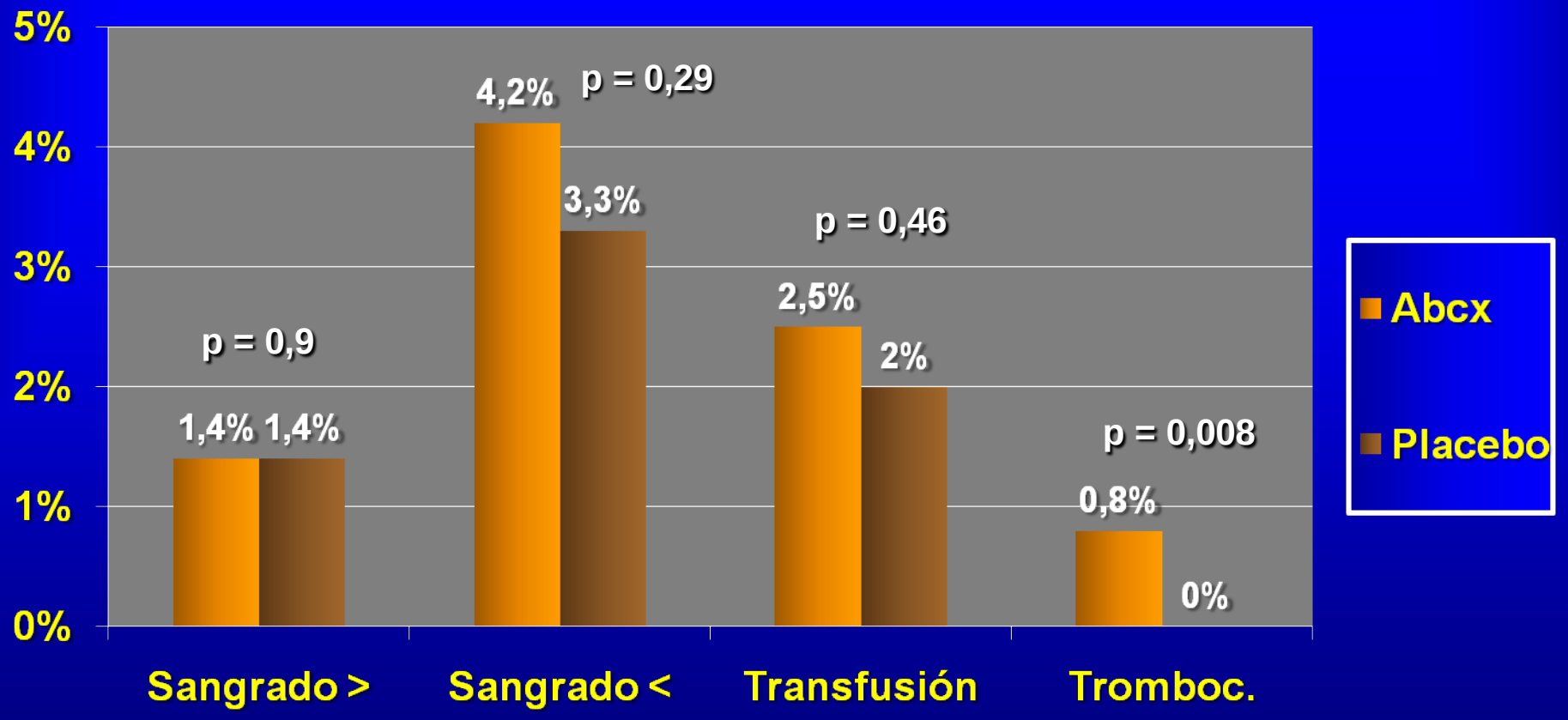
**Marcadores (+) o Alteración ST → Clopidogrel 600mg ≥ 2 hs + AAS 500mg**




Kastrati A. JAMA 2006;295:1531-38

# ISAR REACT II TRIAL

## *Complicações*



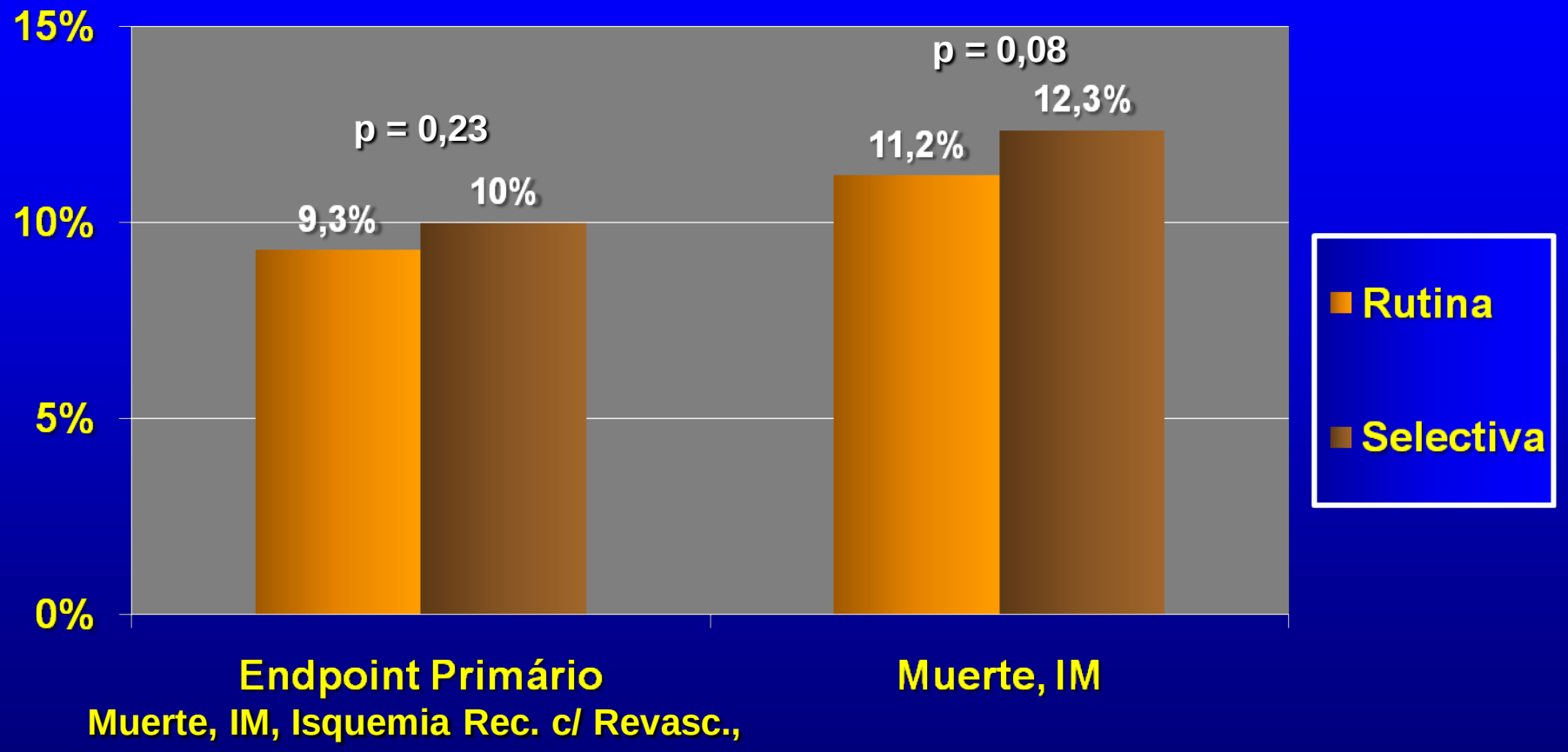

Kastrati A. JAMA 2006;295:1531-38

# EARLY ACS TRIAL

## *Upstream vs Deferred Eptifibatide*

n = 9492 29 países 440 centros SCASEST Alto Riesgo → Estrategia Invasiva

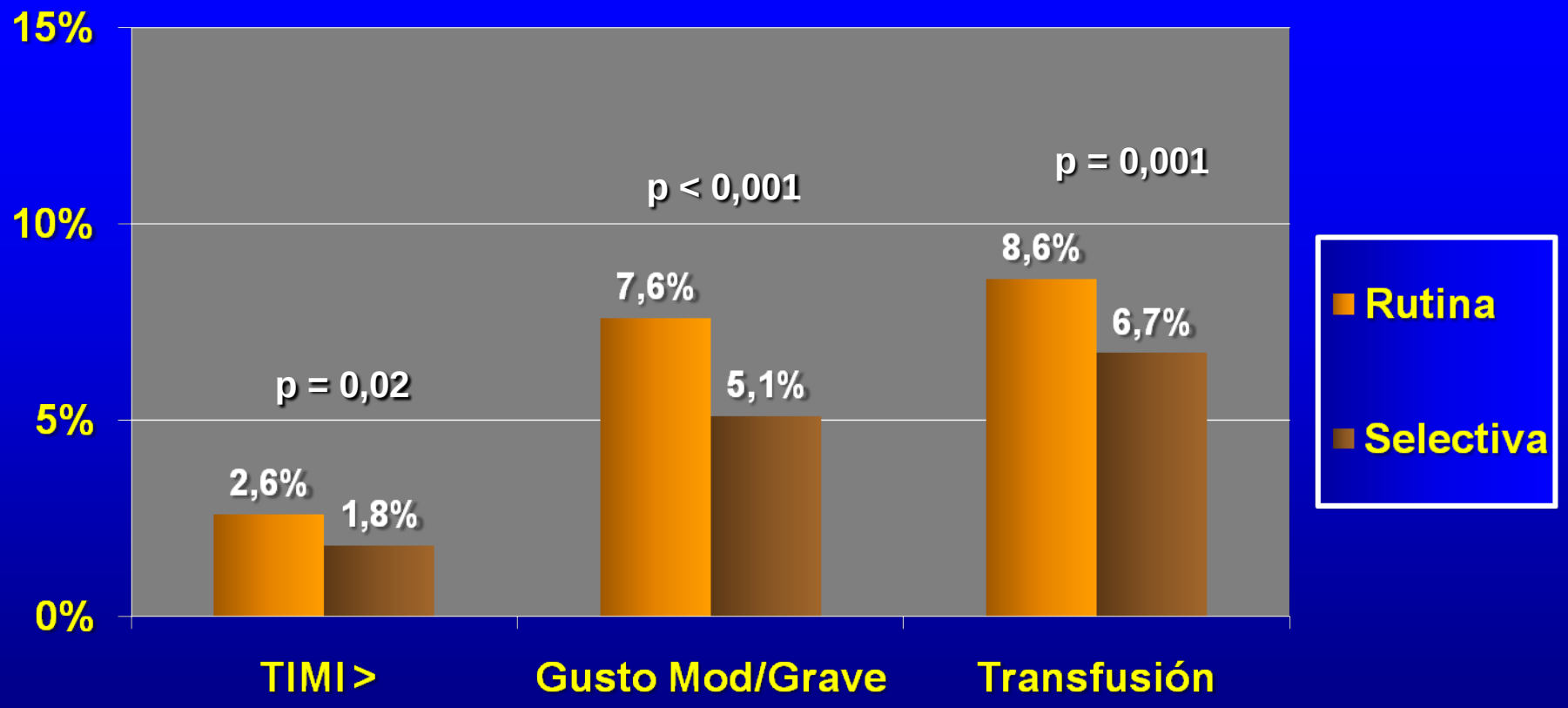
AAS + Heparina + Clopidogrel (75%)




Giuliano RP N Engl J Med 2009;360:2165-75

# EARLY ACS TRIAL

## *Upstream vs Deferred Eptifibatide*




Giuliano RP N Engl J Med 2009;360:2165-75

# SCASEST Medio y Alto Riesgo

## *Guidelines ACCF/AHA - Inhibidores GPIIb/IIIa*

**Patients with definitive UA/NSTEMI at Medium or High Risk → Invasive Strategy:**

**ASA (Level Evidence A) + 1 of the following**

**Before PCI**

- **Clopidogrel (Level Evidence B)**
- **IV GP IIb/IIIa Inhibitor (Level Evidence A) (Eptifibatide or Tirofiban)**

**At Time of PCI**

- **Clopidogrel (Level Evidence A)**
- **Prasugrel (Level Evidence B)**
- **IV GP IIb/IIIa (Level Evidence A)**

Wright RS. J Am Coll Cardiol 2011;57:1920-1959

# Guidelines SCASEST Medio y Alto Riesgo

## *Inhibidores GPIIb/IIIa – ACCF/AHA*

**Class IIb (Level of Evidence B)**

**Invasive Strategy → The use of upstream GP IIb/IIIa inhibitors may be considered in High Risk UA/NSTEMI already receiving ASA and Thienopyridine who are not otherwise at high risk for bleeding**

Wright RS. J Am Coll Cardiol 2011;57:1920-1959

# Guidelines SCASEST Medio y Alto Riesgo

## *Inhibidores GPIIb/IIIa*

| NSTE-ACS | ESC/EACTS | | |
|---|---|---|---|
| **Antiplatelet therapy** | | | |
| | ASA | I | C |
| | Clopidogrel (with 600 mg loading dose as soon as possible) | I | C |
| | Clopidogrel (for 9–12 months after PCI) | I | B |
| | Prasugrel[d] | IIa | B |
| | Ticagrelor[d] | I | B |
| | + GPIIb–IIIa antagonists<br>(in patients with evidence of high intracoronary thrombus burden) | | |
| | Abciximab (with DAPT) | I | B |
| | Tirofiban, Eptifibatide | IIa | B |
| | Upstream GPIIb–IIIa antagonists | III | B |
| **Anticoagulation** | | | |
| Very high-risk of ischaemia[e] | UFH (+GPIIb–IIIa antagonists) or | I | C |
| | Bivalirudin (monotherapy) | I | B |

Eur Heart J 2010;31:2501-2555

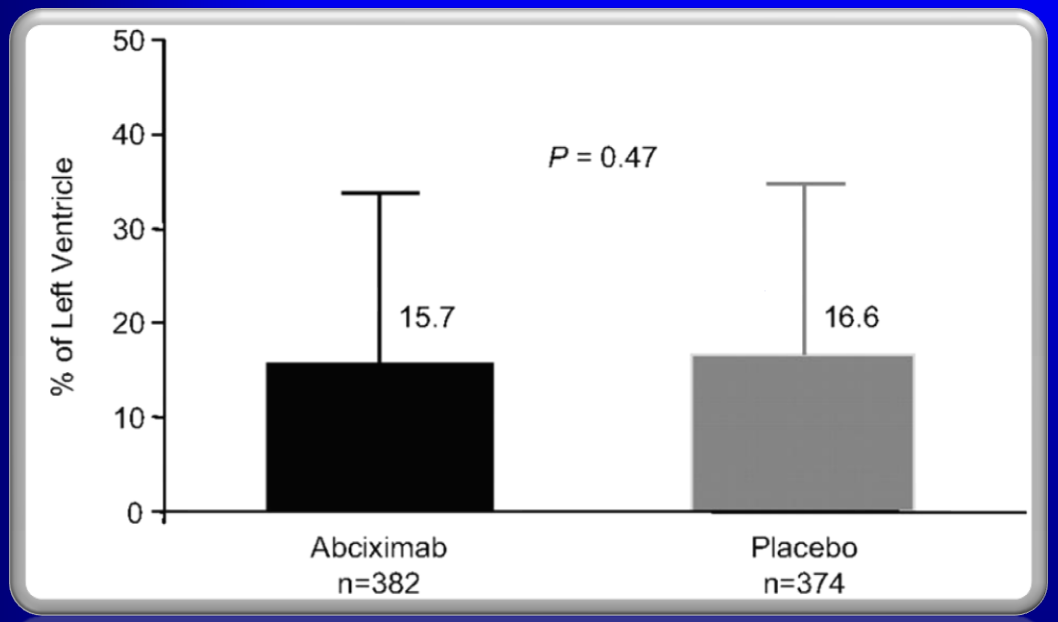
**Aún necessitamos del Abciximab en pacientes con SCA con elevación de ST pré-tratados con clopidogrel en la dosis de ataque ?**

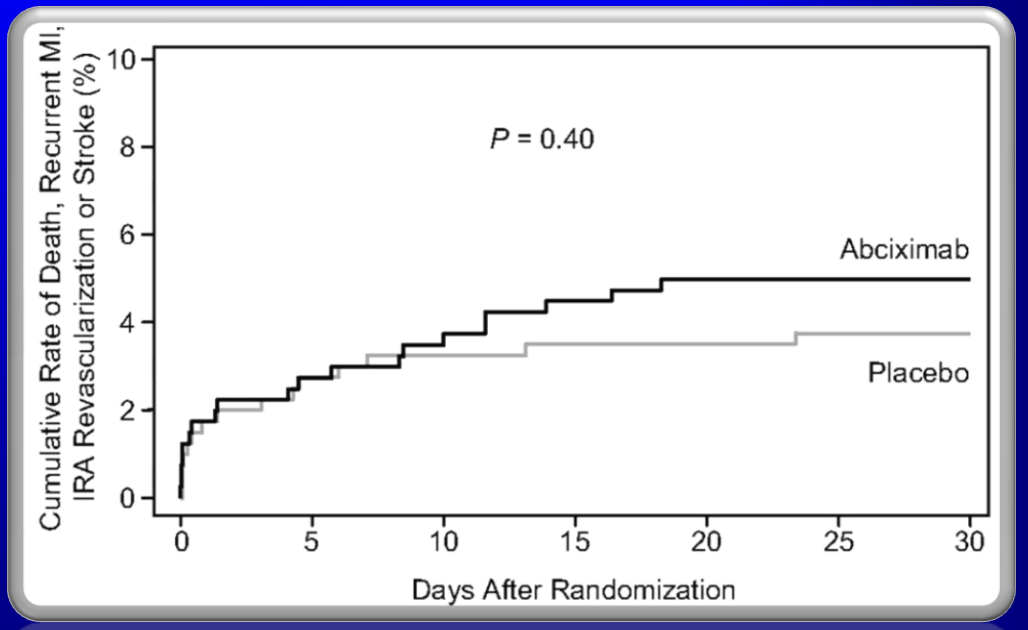
# BRAVE 3 TRIAL

## *Endpoint Primario*

n = 800 IAM < 24 h → ICP

Clopidogrel 600mg + AAS 500mg + Heparina 5000u




Enpoint Primario

Extensión del Infarto (SPECT)

Mehilli J. Circulation 2009;119:1933-40

# BRAVE TRIAL

## *Eventos Clínicos 30 dias*

| | Abciximab (n=401), n (%) | Placebo (n=399), n (%) | *P* |
|---|---|---|---|
| Death | 13 (3.2) | 10 (2.5) | 0.53 |
| Recurrent MI | 6 (1.5) | 6 (1.5) | 0.99 |
| IRA revascularization | 3 (0.8) | 4 (1) | 0.70 |
| Death, recurrent MI, IRA revascularization | 19 (4.7) | 14 (3.5) | 0.38 |
| Stroke | 1 (0.3) | 1 (0.3) | 1.0 |
| TIMI major bleeding | 7 (1.8) | 7 (1.8) | 0.99 |
| TIMI minor bleeding | 15 (3.7) | 7 (1.8) | 0.09 |
| Blood transfusion | 12 (3.0) | 13 (3.3) | 0.83 |
| Profound thrombocytopenia | 6 (1.5) | 0 | 0.03 |

Mehilli J. Circulation 2009;119:1933-40

# Diretrizes IAM
## *Inhibidores GP IIb/IIIa*

| STEMI | AHA/ACC | | |
|---|---|---|---|
| GPIIb/IIIa antagonists | | | |
| | Abciximab | IIa | A |
| | Eptifibatide | IIa | B |
| | Tirofiban | IIa | B |
| | Upstream GPIIb/IIIa antagonists | IIb | B |

| STEMI | ESC/EACTS | | |
|---|---|---|---|
| GPIIb/IIIa antagonists (in patients with evidence of high intracoronary thrombus burden) | | | |
| | Abciximab | IIa | A |
| | Eptifibatide | IIa | B |
| | Tirofiban | IIb | B |
| | Upstream GPIIb/IIIa antagonists | III | B |

Kushner FG. Circulation 2009;54:2205-2241
Eur Heart J 2010;31:2501-2555