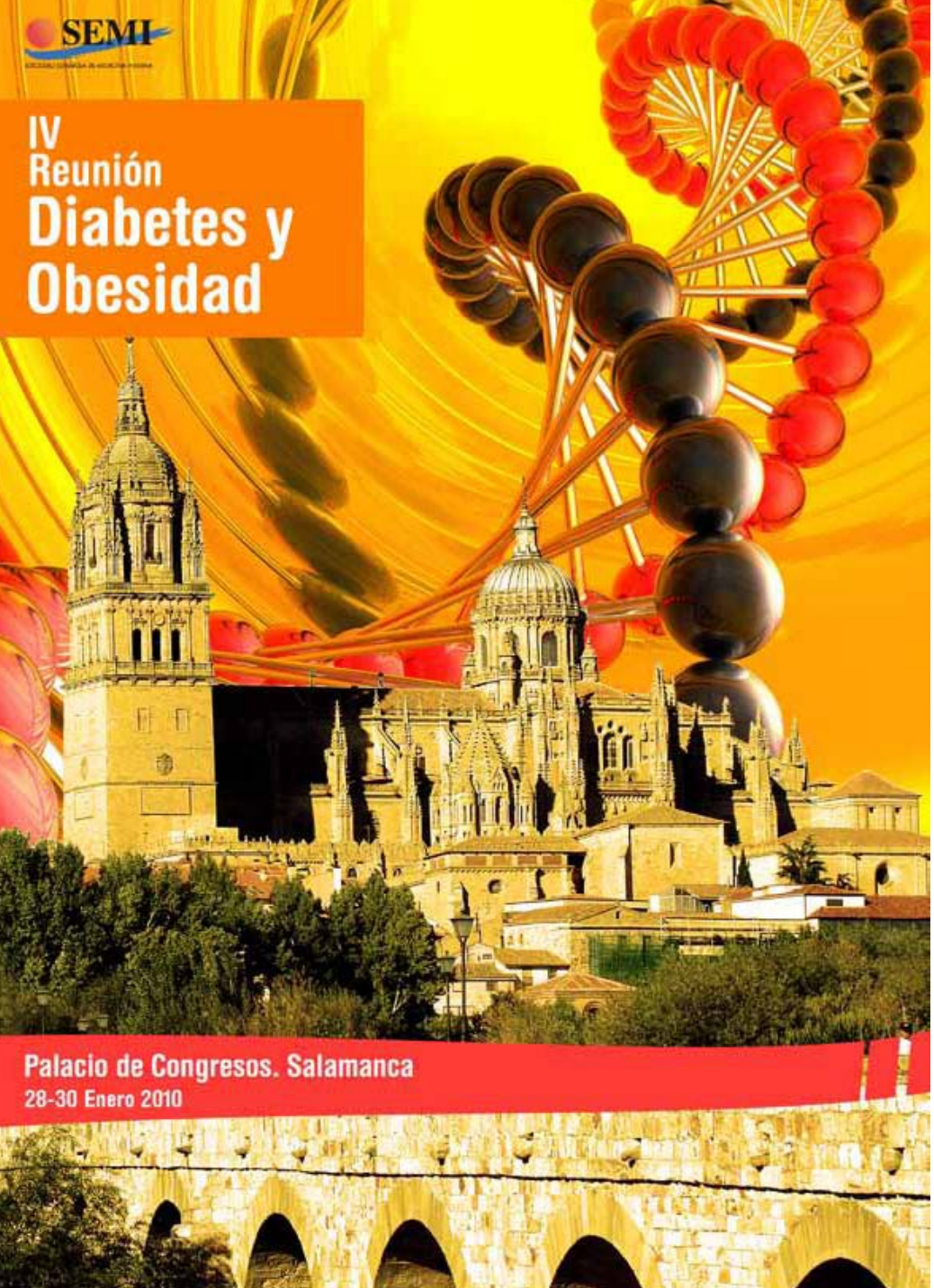


Últimas aportaciones en el tratamiento con ADOS

RECORD
BARI-2

Ricardo Gómez Huelgas
Medicina Interna
Hospital Carlos Haya - Málaga

FÁRMACOS ANTIDIABÉTICOS

METFORMINA **INSULINA** **¿ROSIGLITAZONA?**

Steven E. Nissen

Años 1-2 A.N.

DREAM

ADOPT

PROactive

The NEW ENGLAND JOURNAL of MEDICINE

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

RESULTS

Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

From the Cleveland Clinic, Cleveland. Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.

This article [10.1056/NEJMoa072761] was published at www.nejm.org.

N Engl J Med 2007;356.

Año 2 D.N.

Articles

Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial

The NEW ENGLAND JOURNAL of MEDICINE

JUNE 11, 2009

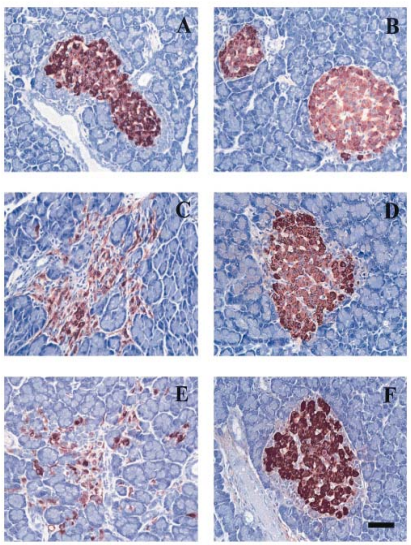
A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease

The BARI 2D Study Group*

ABSTRACT

Rosiglitazona: protección de célula beta

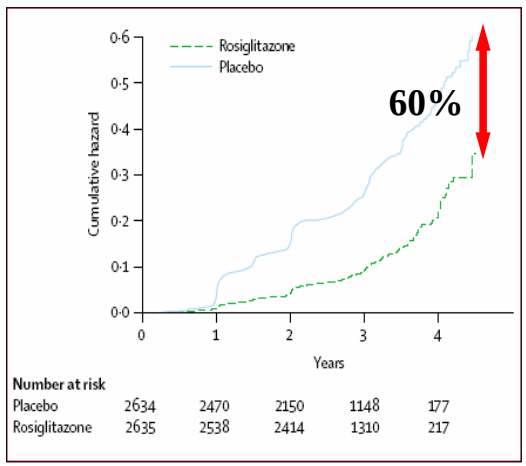
ratas ZDF



Finegood DT. Diabetes 2001;50:1021-9.

DREAM

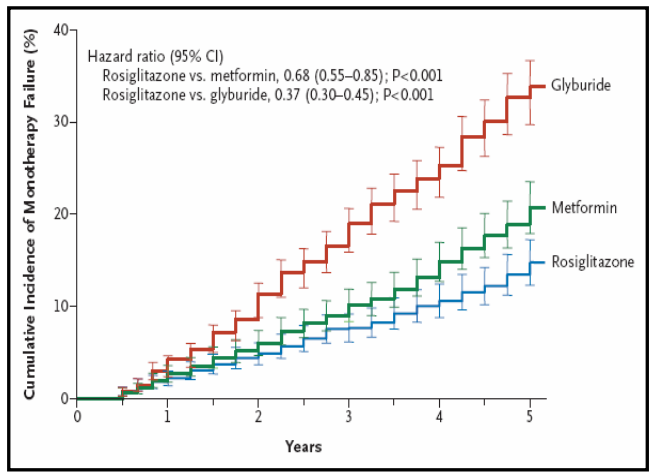
Prediabetes



Lancet 2006;368:1096-1105.

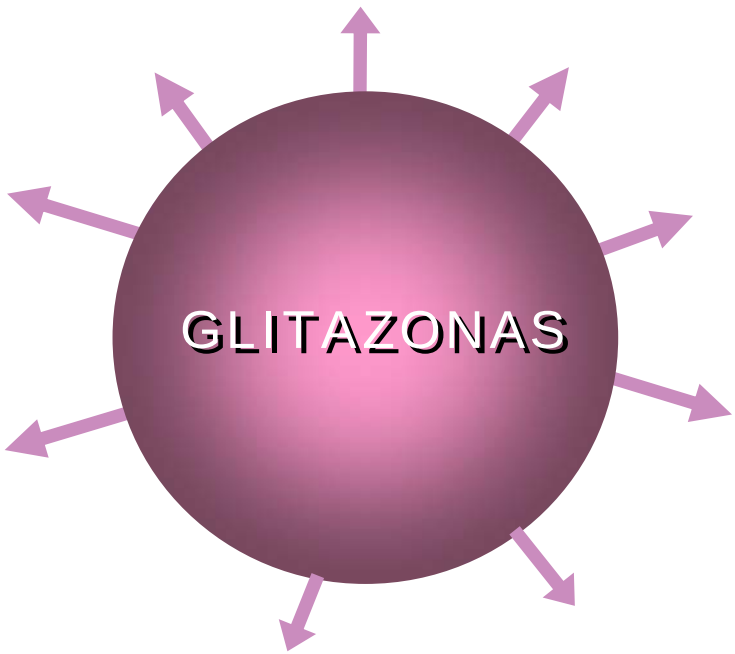
ADOPT

Diabetes de inicio



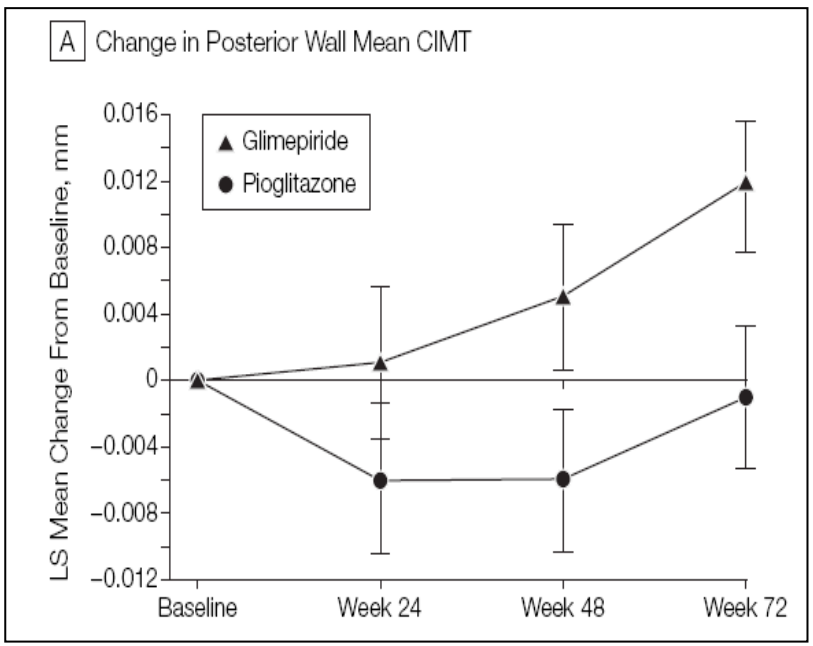
Kahn SE. NEJM 2006;355:2427-43.

ACCIONES VÁSCULOPROTECTORAS DE LAS GLITAZONAS



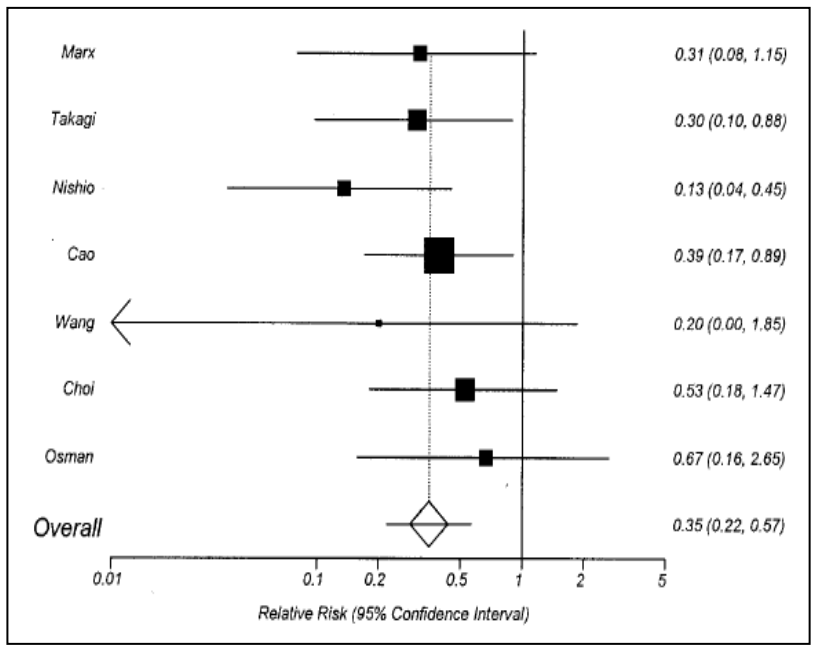
GLITAZONAS
EFECTO ANTIATEROSCLERÓTICO

CHICAGO Trial



Mazzone T. JAMA 2006;296:2572-81.

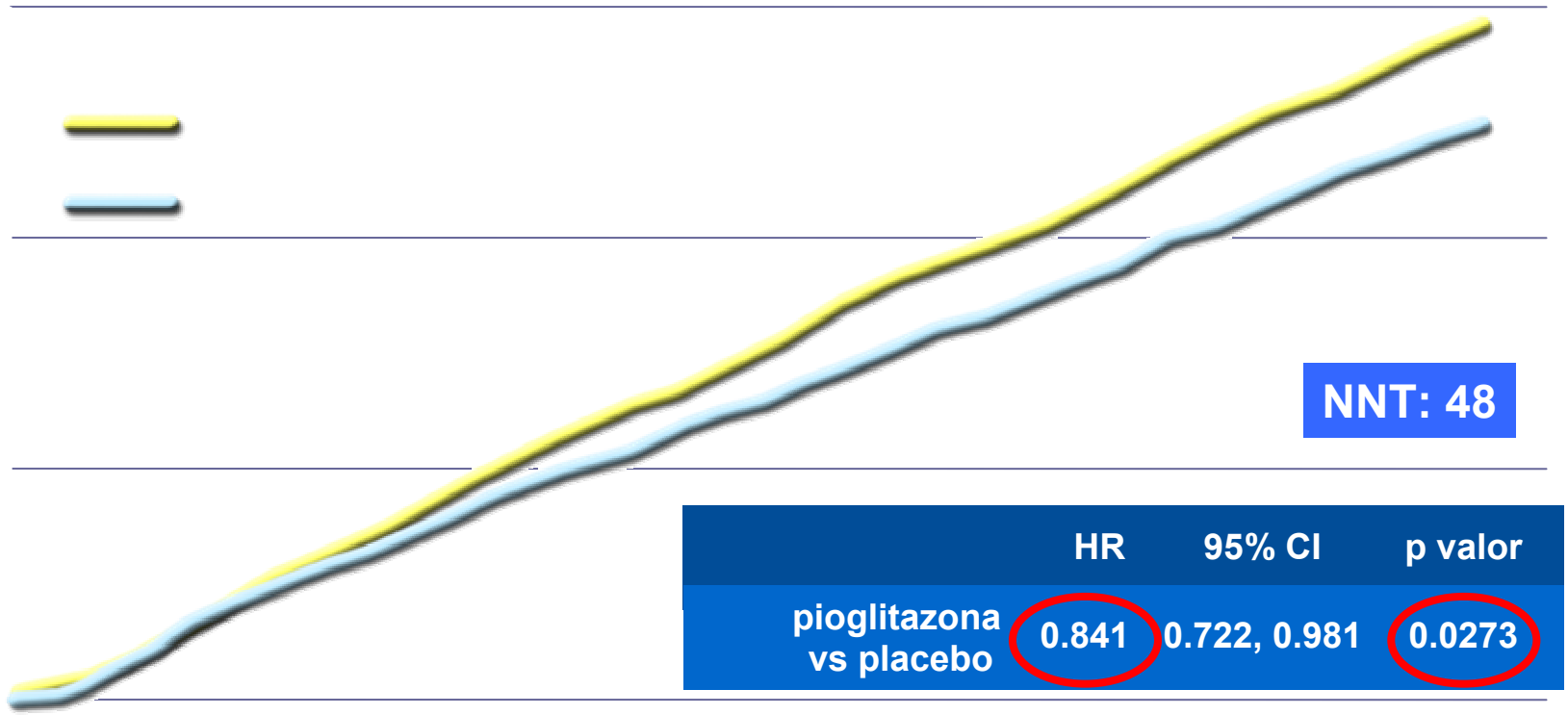
Riesgo de revascularización tras intervención coronaria percutánea



Riche DM. Diabetes Care 2007;30:384-8.

PROactive

Tiempo hasta fallecimiento, IM (excluyendo silente) o ictus



	HR	95% CI	p valor
pioglitazona vs placebo	0.841	0.722, 0.981	0.0273

Lancet 2005; 366: 1279–89

THE LANCET

Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials

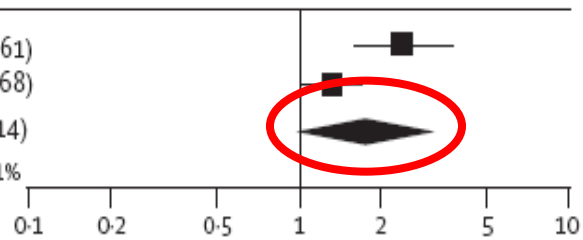
Rodrigo M Lago, Premranjan P Singh, Richard W Nesto

Lancet 2007; 370: 1129–36

Riesgo de I.C.C.

	Weight	Risk ratio (95% CI)
Rosiglitazone trials	46·2%	2·41 (1·61, 3·61)
Pioglitazone trials	53·8%	1·32 (1·04, 1·68)
Total	100·0%	1·74 (0·97, 3·14)

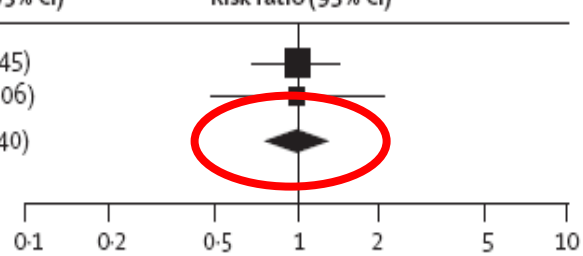
Test for heterogeneity: χ^2=61·27, df=1 (p=0·01), I^2=84·1%
Test for overall effect: Z=1·85 (p=0·07)



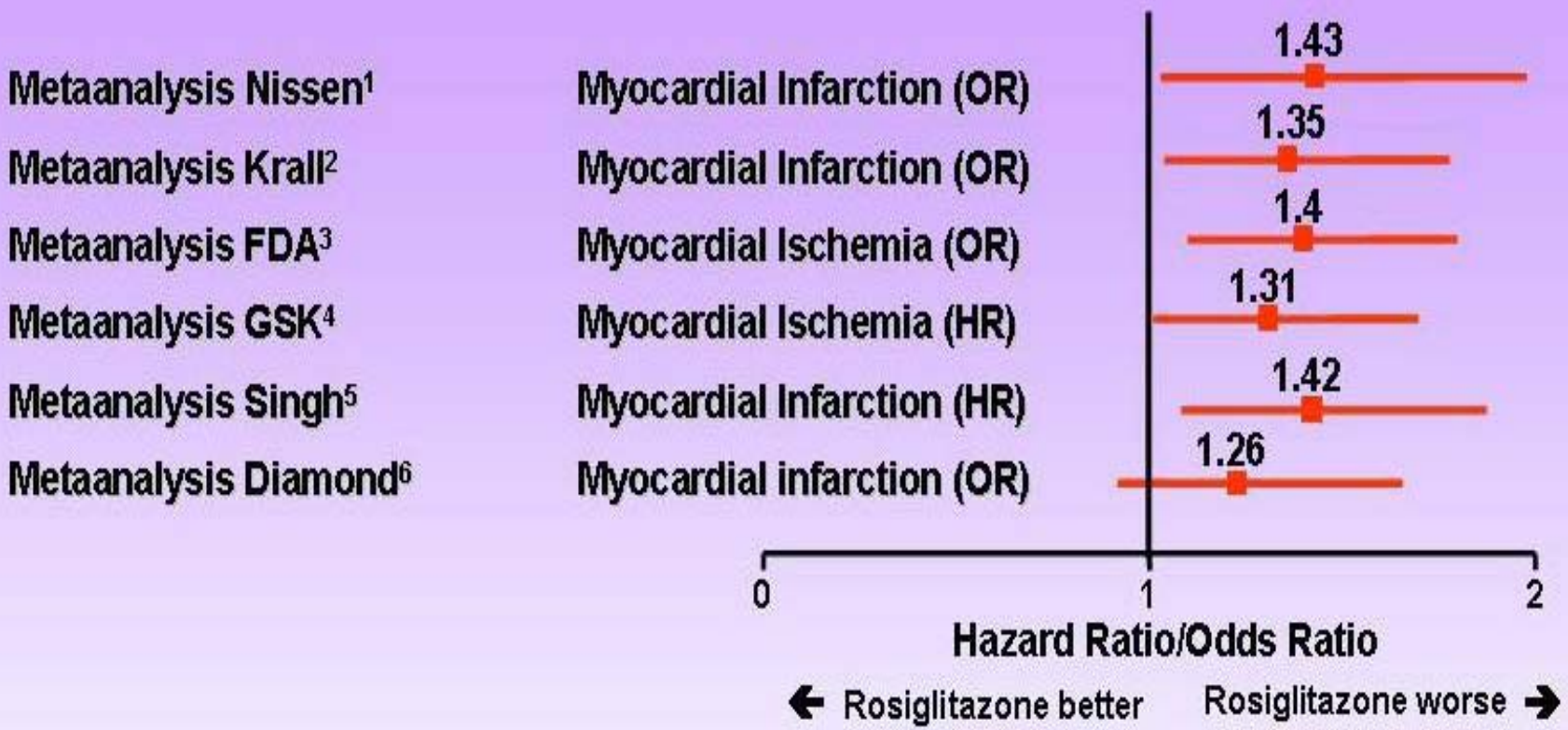
Muerte cardiovascular

	Weight	Risk ratio (95% CI)
Rosiglitazone trials	79·2%	1·01 (0·70, 1·45)
Pioglitazone trials	20·8%	1·01 (0·49, 2·06)
Total	100·0%	1·01 (0·73, 1·40)

Test for heterogeneity: χ^2=1·15, df= (p=0·89), I^2=0%
Test for overall effect: Z=0·05 (p=0·96)



Meta-Analysis for Myocardial Infarction with Rosiglitazone



[1]Nissen SE and Wolski K. NEJM 2007; 356:2457-2471; [2]Krall RL. Lancet 2007; 369:1995-1996; [3]FDA-Homepage www.fda.gov; FDA-Hearing 30.07.2007;[4] SPC Avandia®; [5]Singh S et al. JAMA 2007;298:1189-1195; [6]Diamond G et al. Ann Int Med 2007.

Metaanálisis
Críticas metodológicas

-
-
-
-
-
-
-
-

Limitaciones del metaanálisis

RECORD

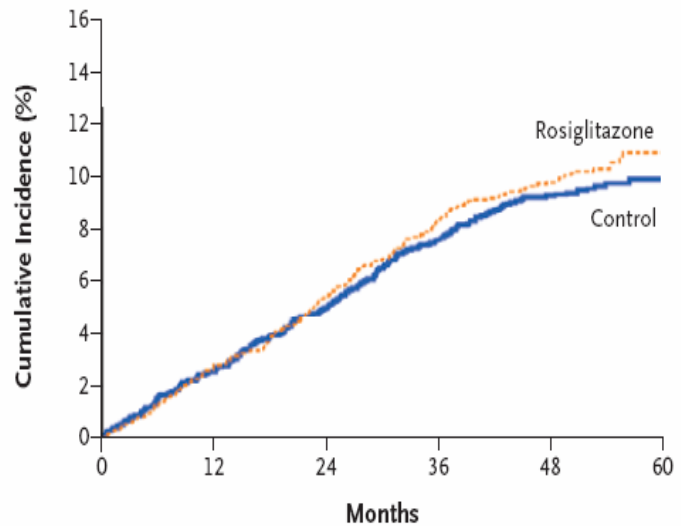
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rosiglitazone Evaluated for Cardiovascular Outcomes — An Interim Analysis

Philip D. Home, D.M., D.Phil., Stuart J. Pocock, Ph.D., Henning Beck-Nielsen, D.M.S.C., Ramón Gomis, M.D., Ph.D., Markolf Hanefeld, M.D., Ph.D., Nigel P. Jones, M.A., Michel Komajda, M.D., and John J.V. McMurray, M.D., for the RECORD Study Group*

A Adjudicated Primary Events



No. at Risk

Control	2227	2087	1980	1878	1694	445
Rosiglitazone	2220	2080	1958	1856	1692	444

Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial

Philip D Home, Stuart J Pocock, Henning Beck-Nielsen, Paula S Curtis, Ramon Gomis, Markolf Hanefeld, Nigel P Jones, Michel Komajda, John JV McMurray, for the RECORD Study Team*

Summary

Background Rosiglitazone is an insulin sensitiser used in combination with metformin, a sulfonylurea, or both, for lowering blood glucose in people with type 2 diabetes. We assessed cardiovascular outcomes after addition of rosiglitazone to either metformin or sulfonylurea compared with the combination of the two over 5–7 years of follow-up. We also assessed comparative safety.

Methods In a multicentre, open-label trial, 4447 patients with type 2 diabetes on metformin or sulfonylurea monotherapy with mean haemoglobin A_{1c} (HbA_{1c}) of 7·9% were randomly assigned to addition of rosiglitazone (n=2220) or to a combination of metformin and sulfonylurea (active control group, n=2227). The primary endpoint was cardiovascular hospitalisation or cardiovascular death, with a hazard ratio (HR) non-inferiority margin of 1·20. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00379769.

Findings 321 people in the rosiglitazone group and 323 in the active control group experienced the primary outcome during a mean 5·5-year follow-up, meeting the criterion of non-inferiority (HR 0·99, 95% CI 0·85–1·16). HR was 0·84 (0·59–1·18) for cardiovascular death, 1·14 (0·80–1·63) for myocardial infarction, and 0·72 (0·49–1·06) for stroke. Heart failure causing admission to hospital or death occurred in 61 people in the rosiglitazone group and 29 in the active control group (HR 2·10, 1·35–3·27, risk difference per 1000 person-years 2·6, 1·1–4·1). Upper and distal lower limb fracture rates were increased mainly in women randomly assigned to rosiglitazone. Mean HbA_{1c} was lower in the rosiglitazone group than in the control group at 5 years.

Interpretation Addition of rosiglitazone to glucose-lowering therapy in people with type 2 diabetes is confirmed to increase the risk of heart failure and of some fractures, mainly in women. Although the data are inconclusive about any possible effect on myocardial infarction, rosiglitazone does not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs.

Funding GlaxoSmithKline plc, UK.

Introduction

Individual oral glucose-lowering medications have limited efficacy,[1,2] and hence are commonly used in combination.[3] In 2000, the thiazolidinediones rosiglitazone and pioglitazone received marketing authorisation for use in combination with metformin and sulfonylureas in Europe. These thiazolidinediones were known to cause fluid retention and possibly heart failure, and both manufacturers were requested to undertake a post-marketing cardiovascular outcome study.[4,5]

From data reported in the UK Prospective Diabetes Study (UKPDS) in 1998, metformin seemed to protect against cardiovascular risk, but uncertainty remained for sulfonylureas.[6,7] After 1999, evidence showed that thiazolidinediones improved some cardiovascular risk markers associated with diabetes—including insulin sensitivity, blood pressure, and coagulation factors.[8,9] However, higher LDL cholesterol concentrations, albeit in the context of improvement in LDL phenotype and unchanged LDL to HDL cholesterol ratio,[10] raised concern about the overall cardiovascular effect of rosiglitazone.

Concerns increased because several peroxisome proliferator-activated receptor (PPAR) γ agonists failed in development as a result of cardiovascular problems in humans or malignancy, in particular bladder tumours, in animals.[11] The PROactive secondary prevention study of the PPARγ agonist pioglitazone was inconclusive for its primary composite cardiovascular endpoint, but showed a reduction for the secondary composite of death, myocardial infarction, and stroke compared with placebo.[12]

For rosiglitazone, which is a PPARγ agonist, an active-comparator cardiovascular outcome study (RECORD) was designed from the time of marketing authorisation.[13] In 2006, the manufacturer (GlaxoSmithKline) submitted to drug regulators a combined analysis of several studies which suggested that, despite large observational studies to the contrary,[14,15] rosiglitazone increased myocardial ischaemia.[16] Nissen and Wolski, using similar data sources, reached similar conclusions.[17] The RECORD steering committee published an unplanned interim analysis at that time.[18]

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See Online/Comment DOI:10.1016/S0140-6736(09)61029-1

* Members listed at the end of paper

Newcastle Diabetes Centre and Newcastle University, Newcastle upon Tyne, UK (Prof P D Home DM); UK Medical Statistics Unit, London School of Hygiene and Tropical Medicine, London, UK (Prof S J Pocock PhD); Department of Endocrinology and Metabolism, Odense, Denmark (Prof H Beck-Nielsen DM SC); GlaxoSmithKline Research and Development, Greenford, UK (P S Curtis PhD); Hospital Clinic, University of Barcelona, Barcelona, Spain (Prof R Gomis MD); Zentrum für Klinische Studien Forschungsbereich Endokrinologie und Stoffwechsel, Dresden, Germany (Prof M Hanefeld MD); GlaxoSmithKline Research and Development, Harlow, UK (N P Jones MA); Université Pierre et Marie Curie Paris 6; Hôpital Pitié-Salpêtrière, Département de Cardiologie, Paris, France (Prof M Komajda MD); and British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK (Prof J V McMurray MD)

Correspondence to: Prof Philip D Home, ICM - Diabetes, The Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, UK phillip.home@newcastle.ac.uk

RECORD

4,447 pacientes DM2
en monoterapia

randomizados
t: 5,5 años

Criterios
inclusión / exclusión

metformina
- añadir rosiglitazona
- añadir sulfonilurea

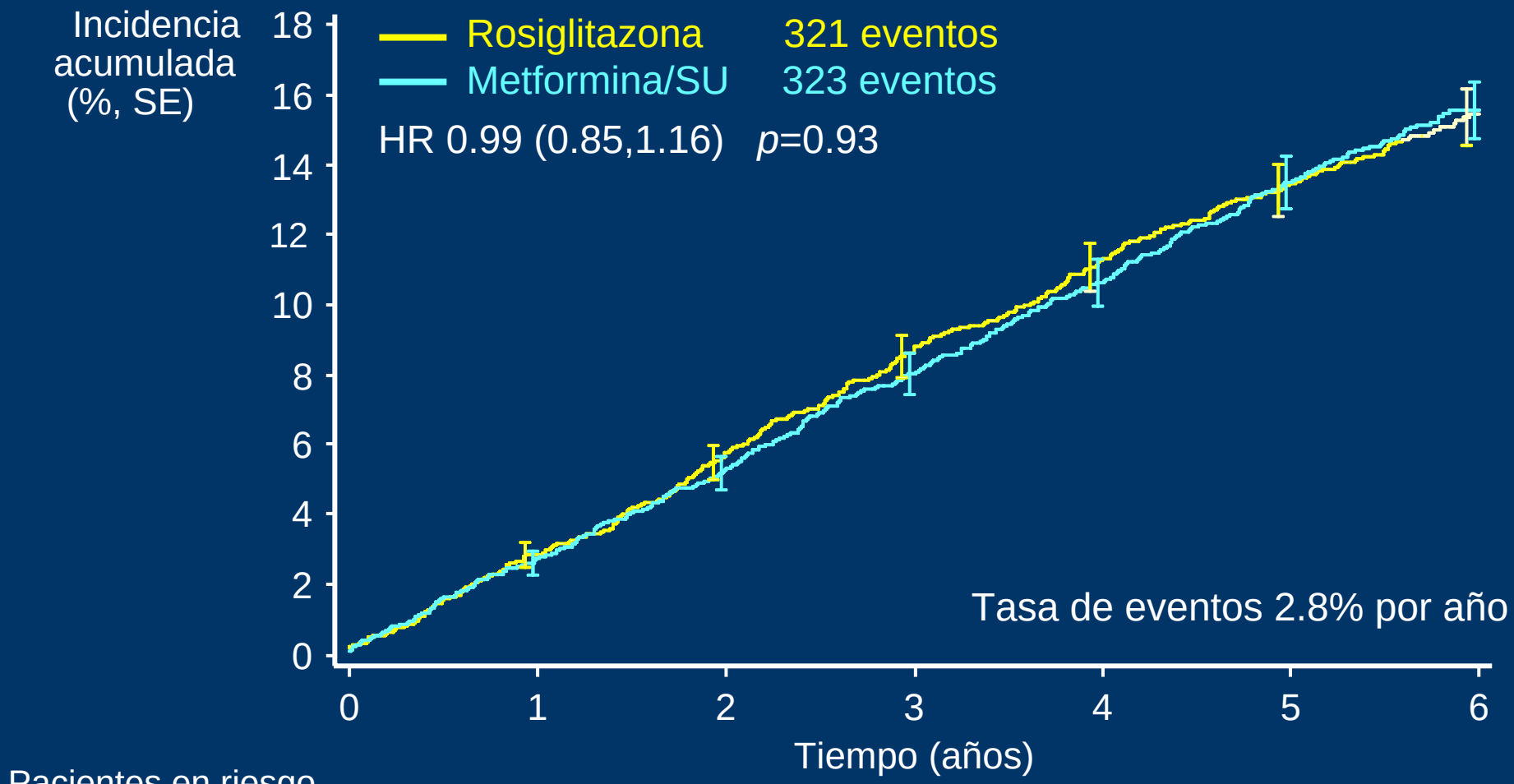
sulfonilurea
- añadir rosiglitazona
- añadir metformina

- edad 40-75 años
- IMC >25
- HbA1c 7-9%

- sin MACE 3 meses
- sin IC
- sin Cx CV programada

variable principal: muerte / hospitalización CV

Hospitalización CV o muerte CV

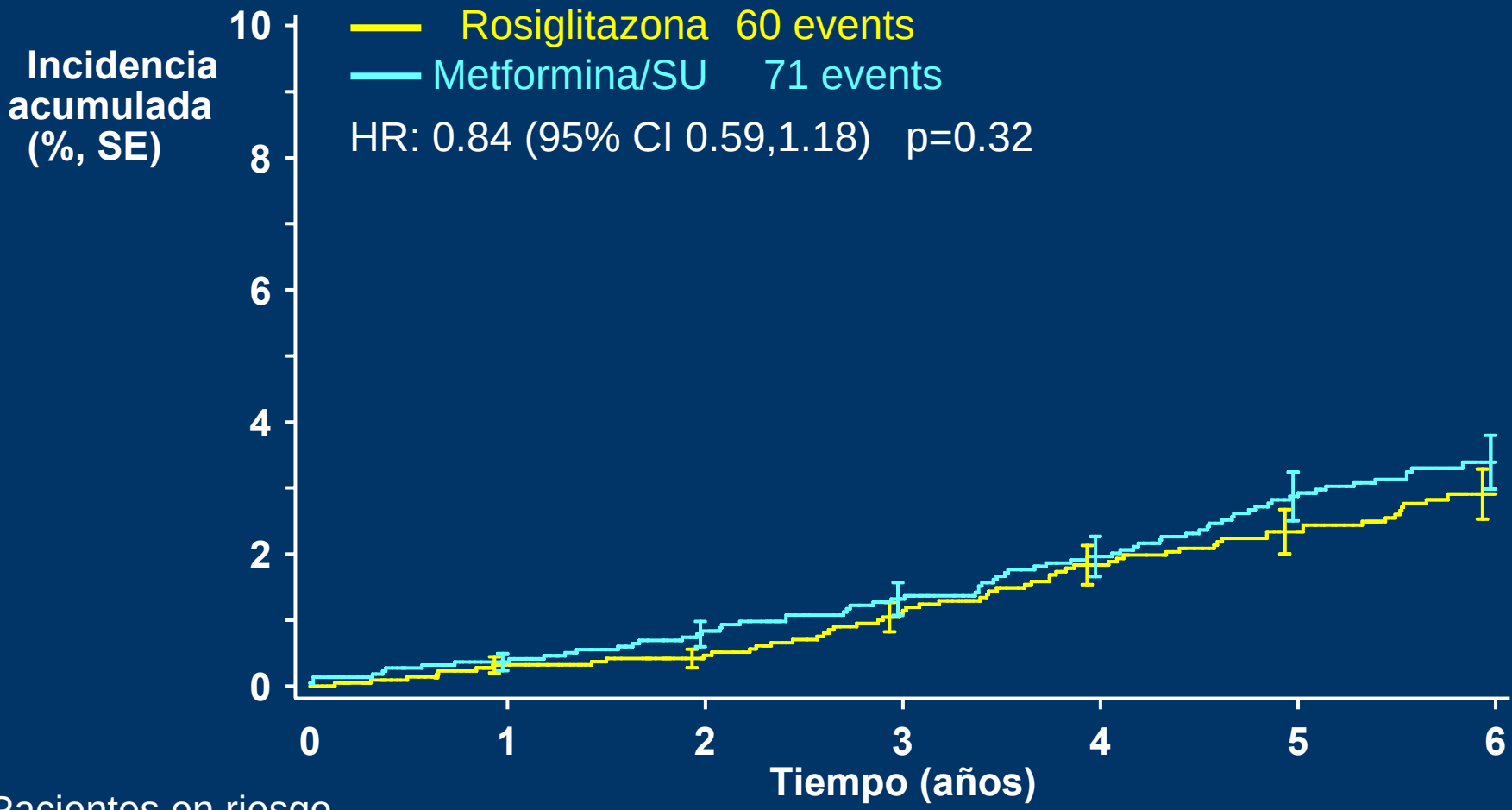


Pacientes en riesgo

Rosiglitazona	2220	2086	1981	1883	1795	1720	918
Metformina/SU	2227	2101	1995	1895	1798	1697	908

RECORD®

Muerte CV

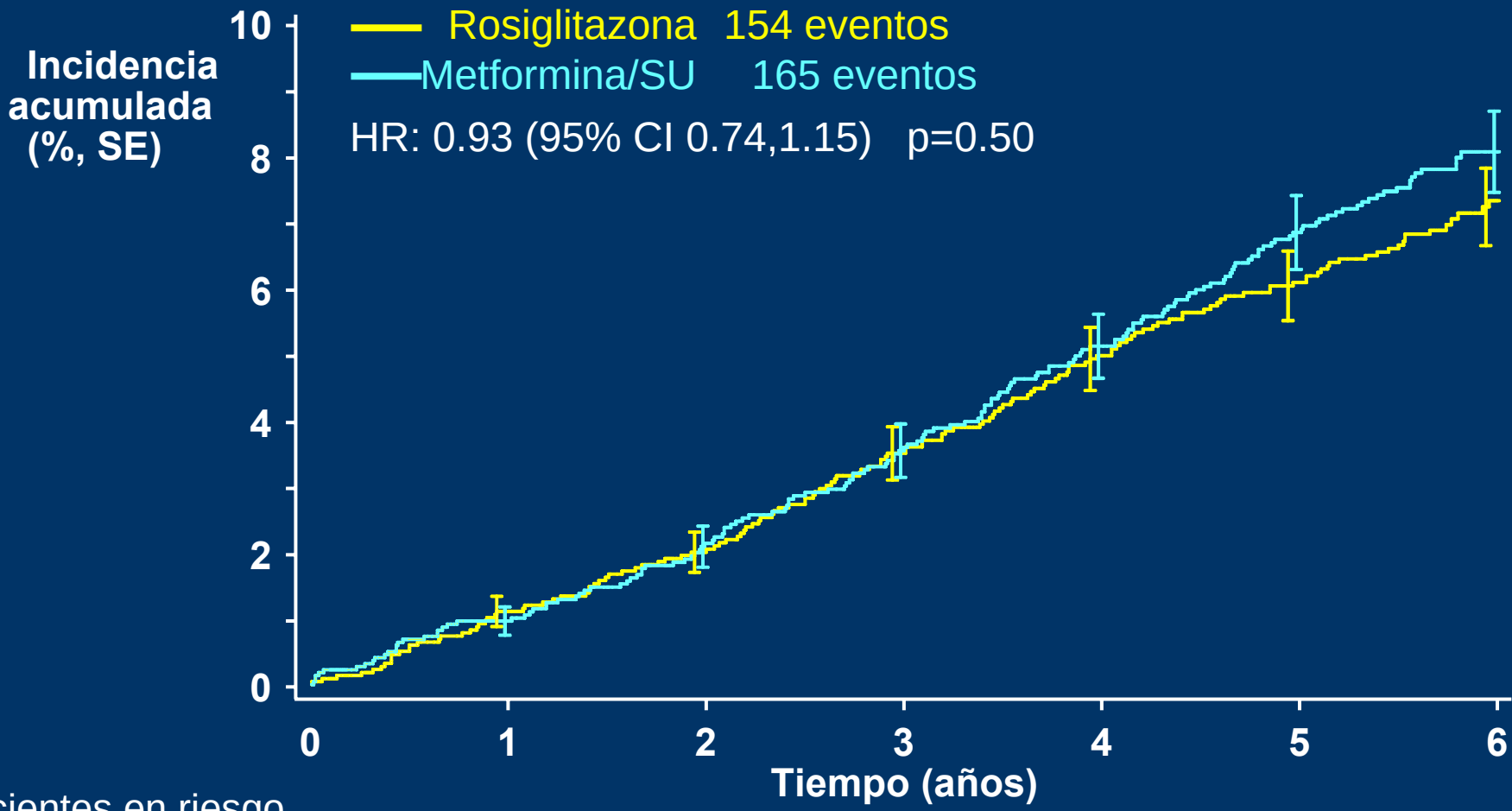


Pacientes en riesgo

Rosiglitazona	2220	2139	2084	2032	1972	1918	1042
Metformina/SU	2227	2148	2085	2025	1965	1893	1017

RECORD®

Muerte CV, infarto de miocardio o ictus

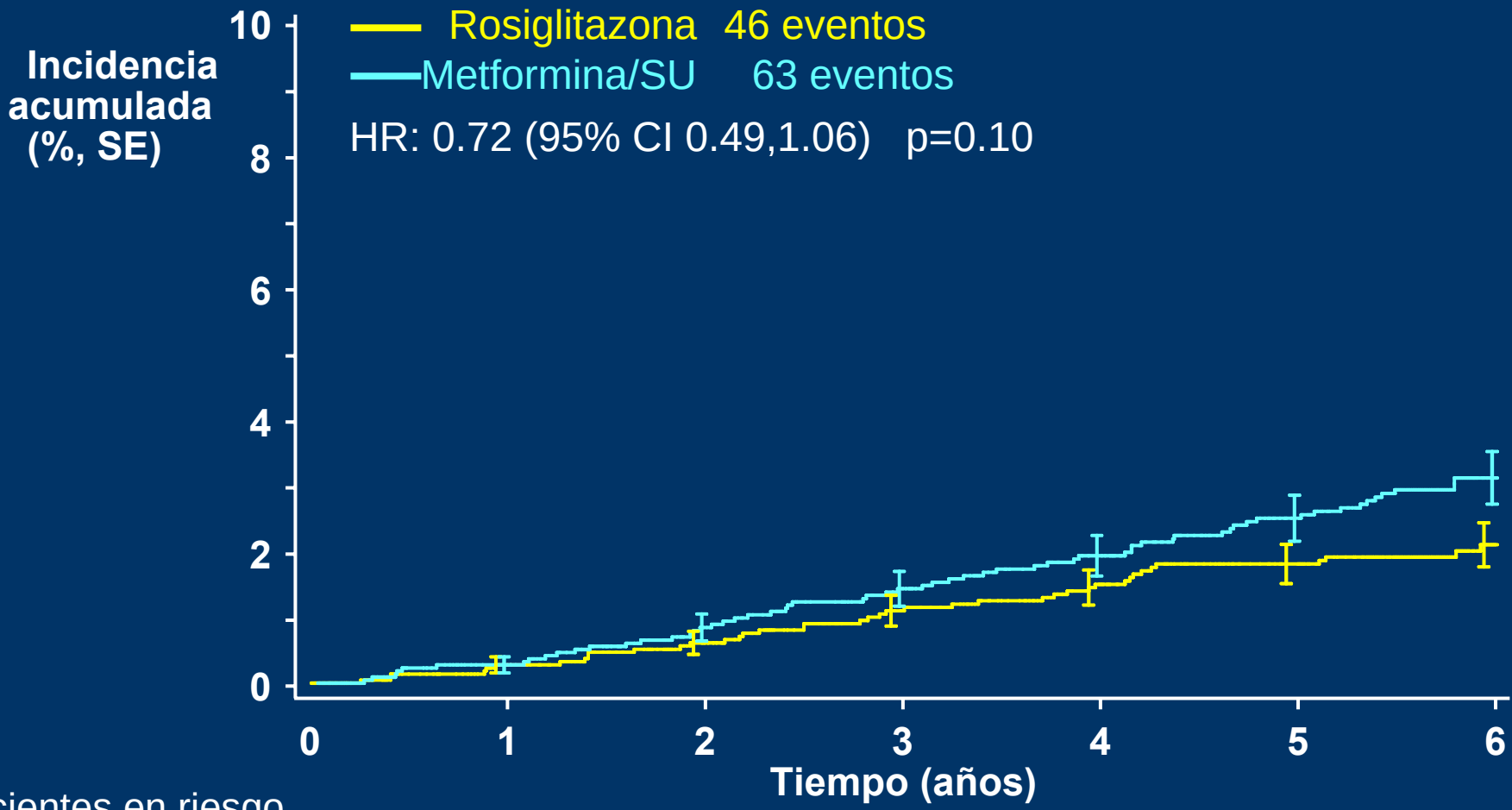


Pacientes en riesgo

Rosiglitazona	2220	2121	2052	1982	1912	1852	994
Metformina/SU	2227	2135	2057	1978	1901	1816	970

RECORD®

Ictus, fatal y no-fatal

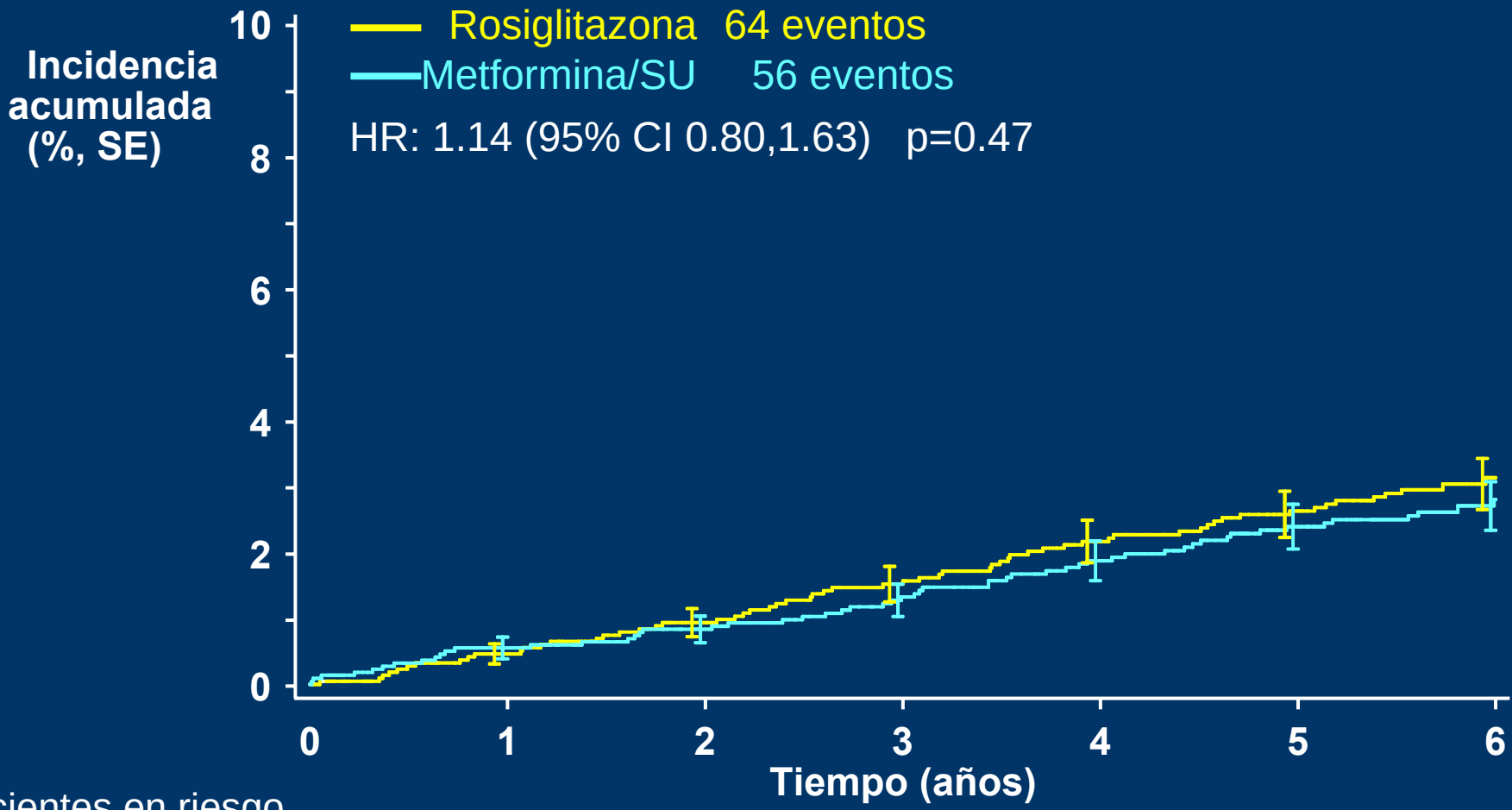


Pacientes en riesgo

Rosiglitazona	2220	2132	2070	2009	1947	1891	1024
Metformina/SU	2227	2142	2068	1998	1930	1851	991

RECORD®

Infarto, fatal y no-fatal



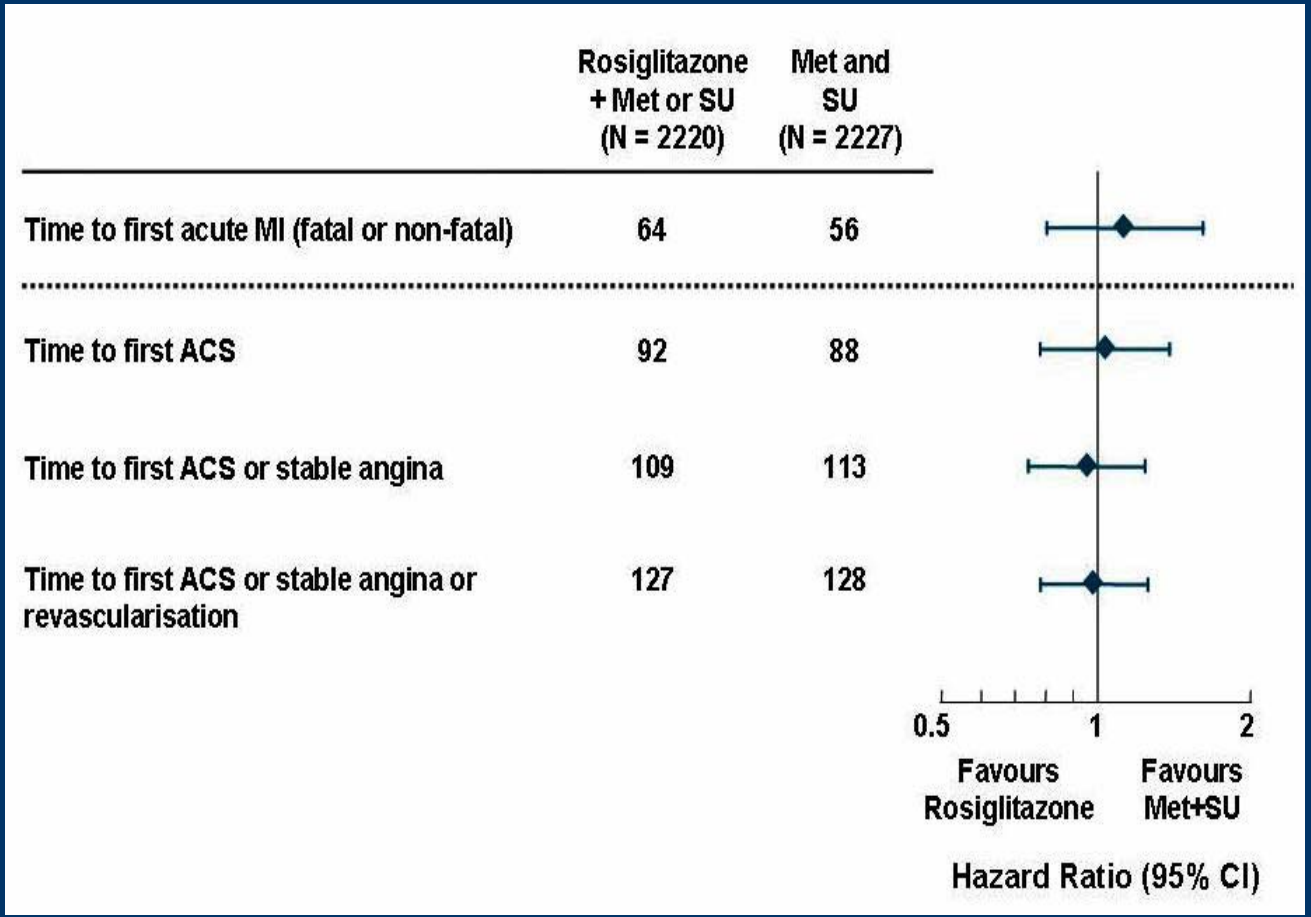
Pacientes en riesgo

Rosiglitazona	2220	2128	2066	2005	1937	1879	1012
Metformina/SU	2227	2141	2074	2005	1936	1858	996

RECORD®

RECORD: no existe tendencia a más eventos coronarios con rosiglitazona

Análisis post hoc



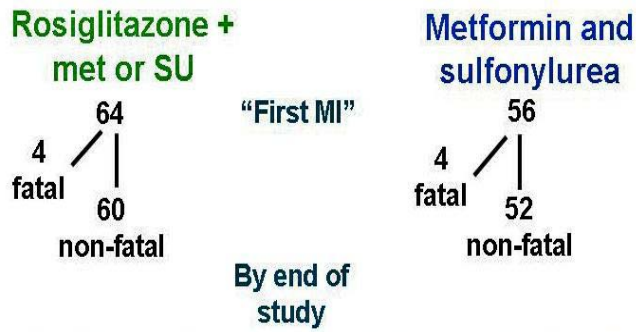
RECORD: no existe mayor mortalidad coronaria con rosiglitazona

Análisis post hoc

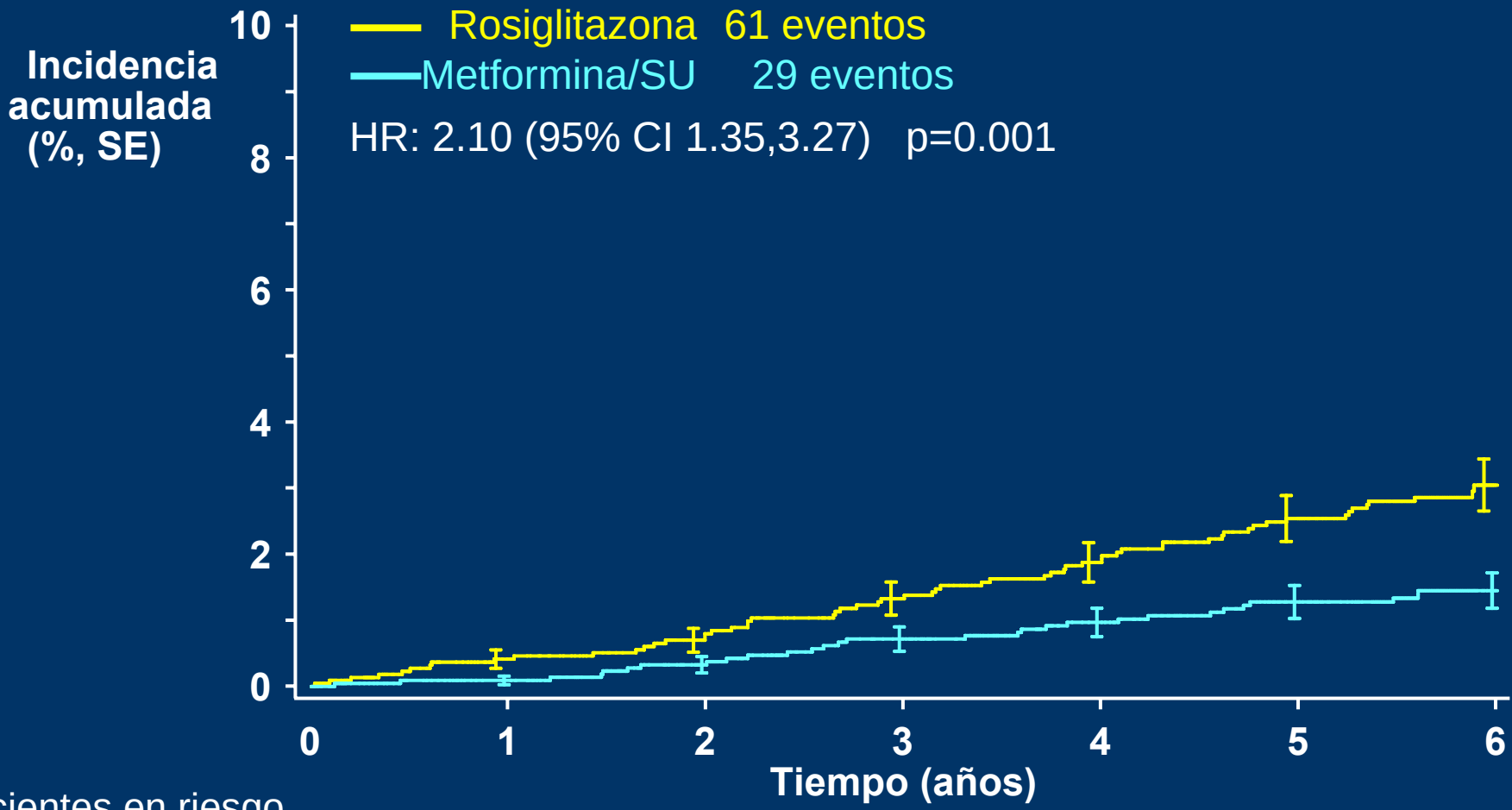
Total population

	Rosiglitazone+ Met or SU (n=2220) Patients	Metformin and sulfonylurea (n=2227) Patients
Deaths		
• Acute MI	7	10
• Sudden	8	12

Outcomes after "first" acute MI



ICC, fatal y no-fatal



Pacientes en riesgo

Rosiglitazona	2220	2130	2069	2008	1994	1884	1017
Metformina/SU	2227	2146	2078	2014	1949	1877	1012

RECORD®

Insuficiencia cardiaca y Rosilitazona
Factores predictores

RECORD. Análisis post-hoc

- **Edad ≥60 años**
- **Perímetro de cintura ≥104 cm**
- **Micro/proteinuria**
- **Betabloqueantes**

La cardiopatía isquémica no incrementa el riesgo

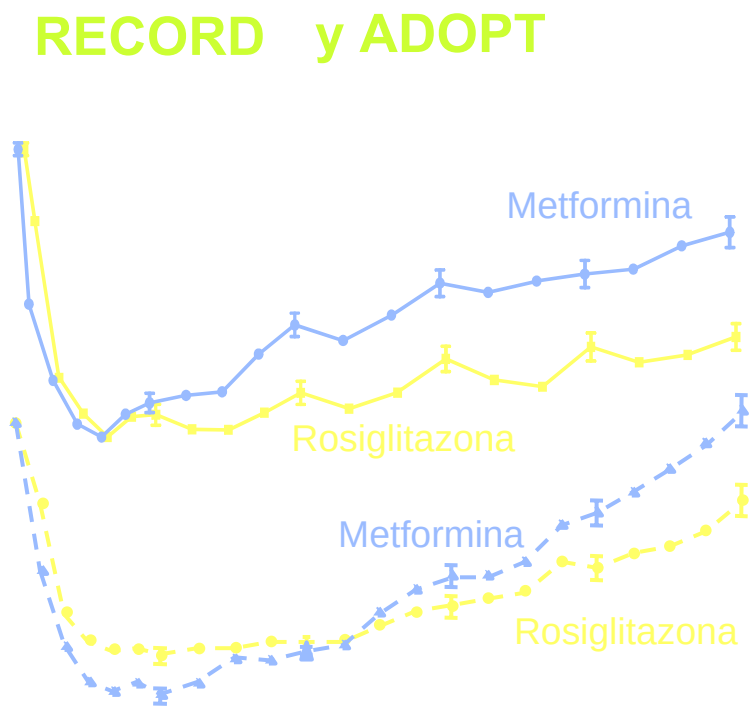
RECORD®

Tiempo hasta la fractura

Rosiglitazona 2220	2116	2031	1955	1864	1778	950
Metformina/SU2227	2123	2037	1959	1888	1805	958

RECORD®

HbA_{1c} a lo largo del tiempo: RECORD y ADOPT



RECORD®

¿Cuáles son los puntos débiles del estudio?

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 11, 2009 VOL. 360 NO. 24

A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease

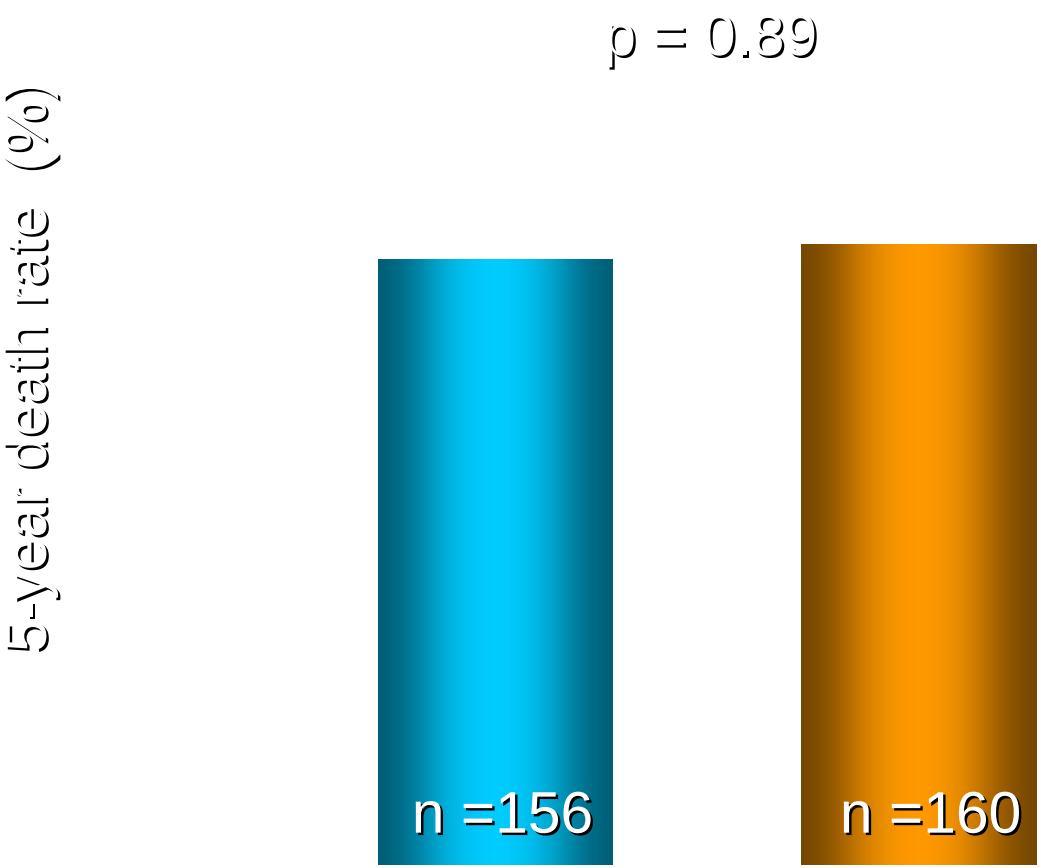
2 estrategias terapéuticas

en diabéticos tipo 2 con
enfermedad coronaria estable

- INSULÍN - SENSIBILIZANTES vs
  INSULÍN - PROVEEDORES

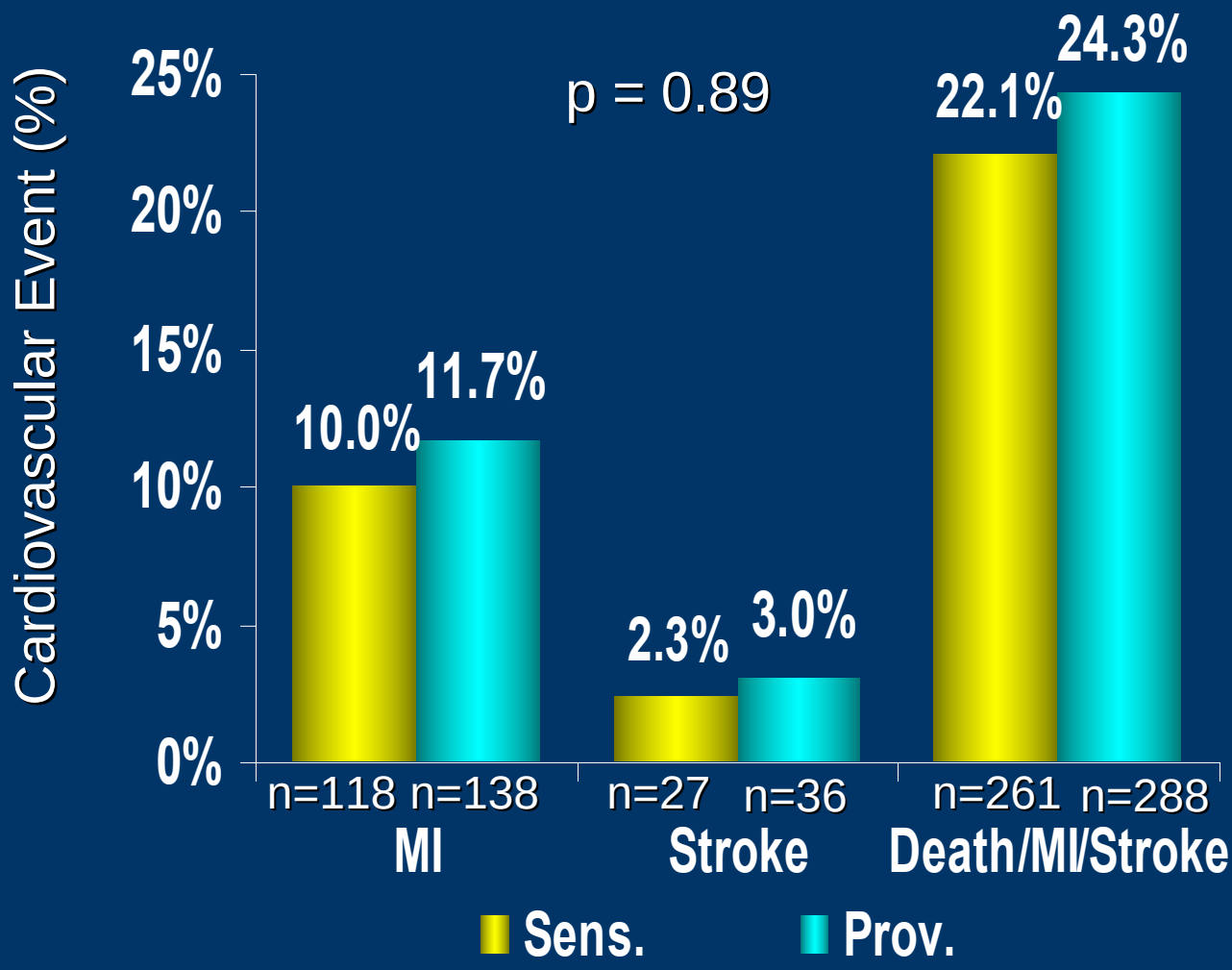
- TERAPIA MÉDICA INTENSIVA vs
  REVASCULARIZACIÓN PRECOZ

BARI 2D Trial: Primary Endpoint



BARI 2D Study Group, NEJM 2009

BARI 2D Trial: Secondary Endpoint



BARI 2D Study Group, NEJM 2009

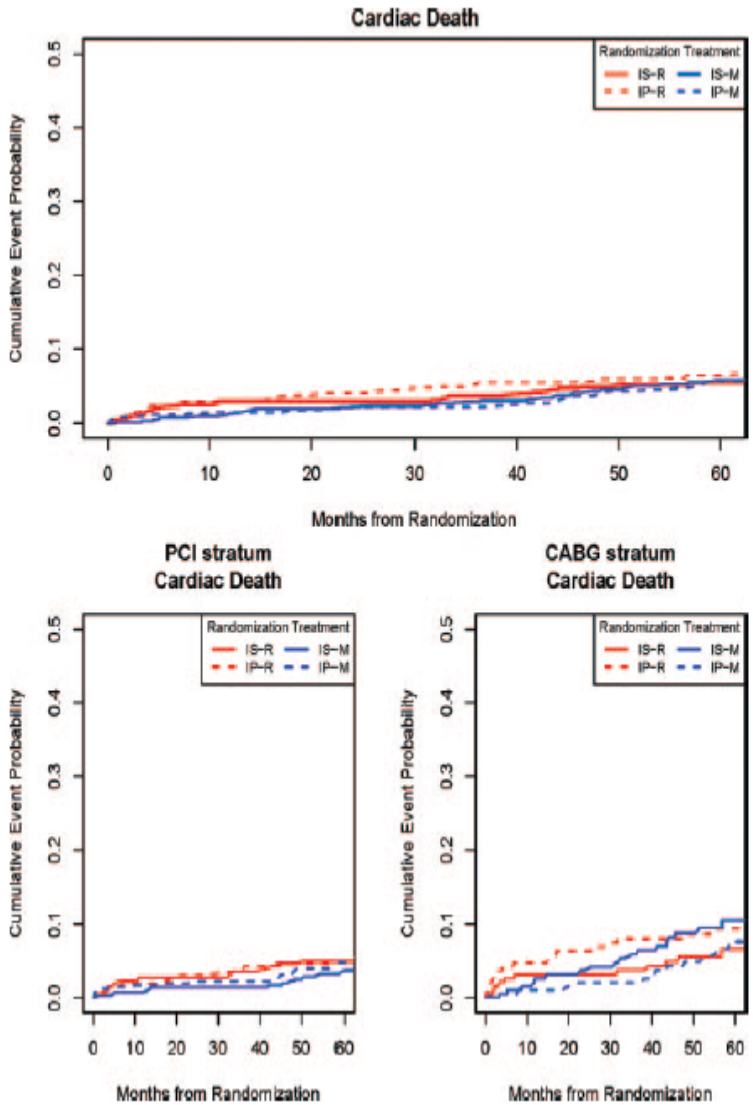
Circulation

Circulation. 2009;120:2529-2540.

The Bypass Angioplasty Revascularization Investigation 2 Diabetes Randomized Trial of Different Treatment Strategies in Type 2 Diabetes Mellitus With Stable Ischemic Heart Disease

Impact of Treatment Strategy on Cardiac Mortality and Myocardial Infarction

Bernard R. Chaitman, MD; Regina M. Hardison, MS; Dale Adler, MD; Suzanne Gebhart, MD;



Circulation

Circulation. 2009;120:2529-2540.

The Bypass Angioplasty Revascularization Investigation 2 Diabetes Randomized Trial of Different Treatment Strategies in Type 2 Diabetes Mellitus With Stable Ischemic Heart Disease

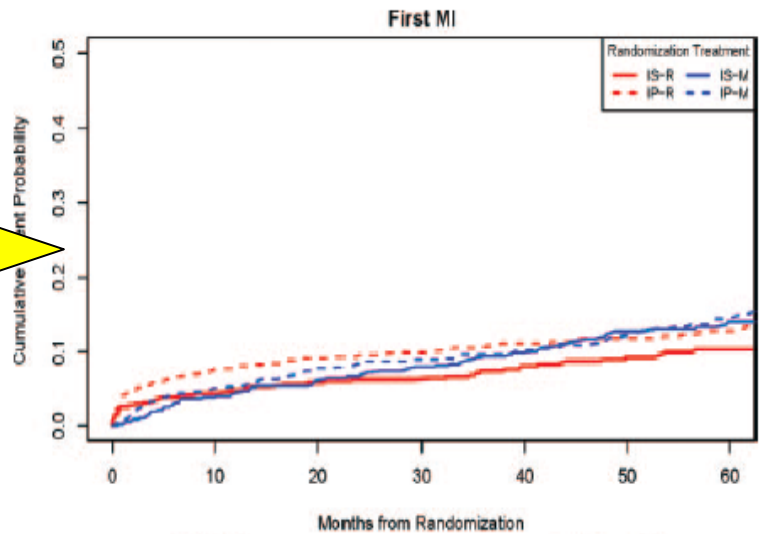
Impact of Treatment Strategy on Cardiac Mortality and Myocardial Infarction

Bernard R. Chaitman, MD; Regina M. Hardison, MS; Dale Adler, MD; Suzanne Gebhart, MD;

En pacientes coronarios estables con DM2:

T. Médico Intensivo
=
Revascularización

Insulín sensibilizantes
=
Insulín proveedores



Enfermedad coronaria de BAJO RIESGO

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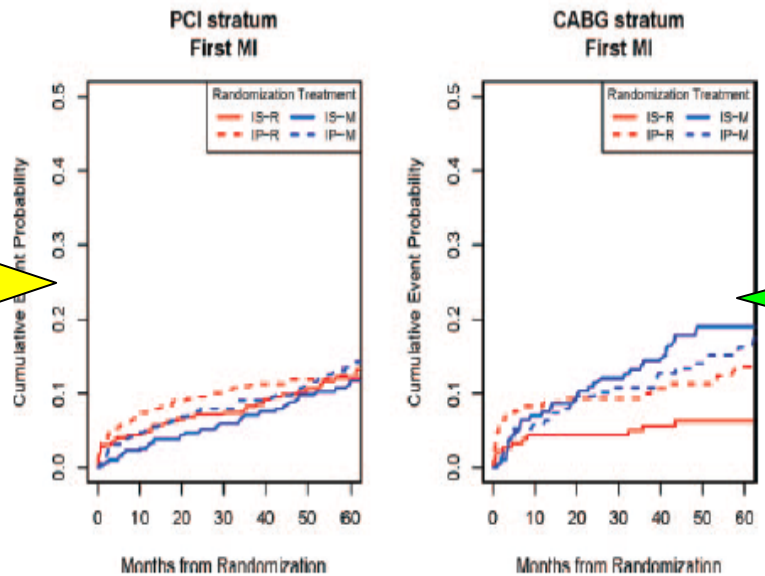
T. Médico Intensivo

Insulín sensibilizantes
=
Insulín proveedores



Estrategia en
enfermedad coronaria AVANZADA

↓

Bypass
+
Metformina / Rosiglitazona

RECORD & BARI-2
CONCLUSIONES

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¿Cómo minimizar los efectos secundarios de las TZD?

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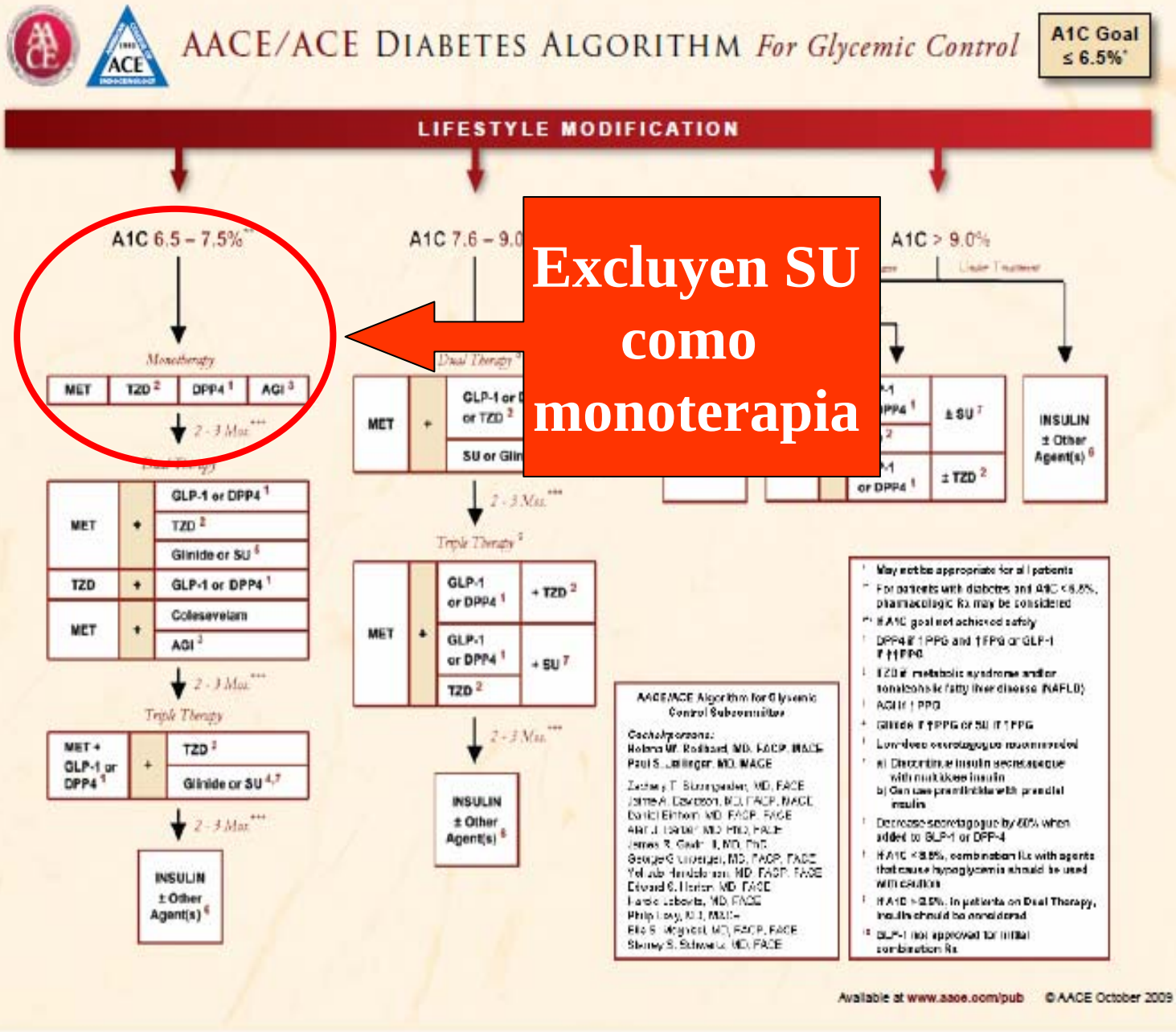
FÁRMACOS ANTIDIABÉTICOS

METFORMINA

INSULINA

¿ROSIGLITAZONA?


AACE/ACE DIABETES ALGORITHM For Glycemic Control
A1C Goal ≤ 6.5%*
LIFESTYLE MODIFICATION
A1C 6.5 – 7.5%**
A1C 7.6 – 9.0
A1C > 9.0%
Excluyen SU como monoterapia
Monotherapy
MET
TZD 2
DPP4 1
AGI 3
2 - 3 Mos.***
Dual Therapy
MET + GLP-1 or DPP4 1
MET + TZD 2
MET + Glinide or SU 5
TZD + GLP-1 or DPP4 1
MET + Colesevelam
MET + AGI 3
Triple Therapy
MET + GLP-1 or DPP4 1 + TZD 2 + Glinide or SU 4,7
MET + GLP-1 or DPP4 1 + TZD 2
MET + GLP-1 or DPP4 1 + SU 7
TZD 2
INSULIN ± Other Agent(s) 6
± SU 7
± TZD 2
AACE/ACE Algorithm for Glycemic Control Subcommittee
Available at www.aace.com/pub
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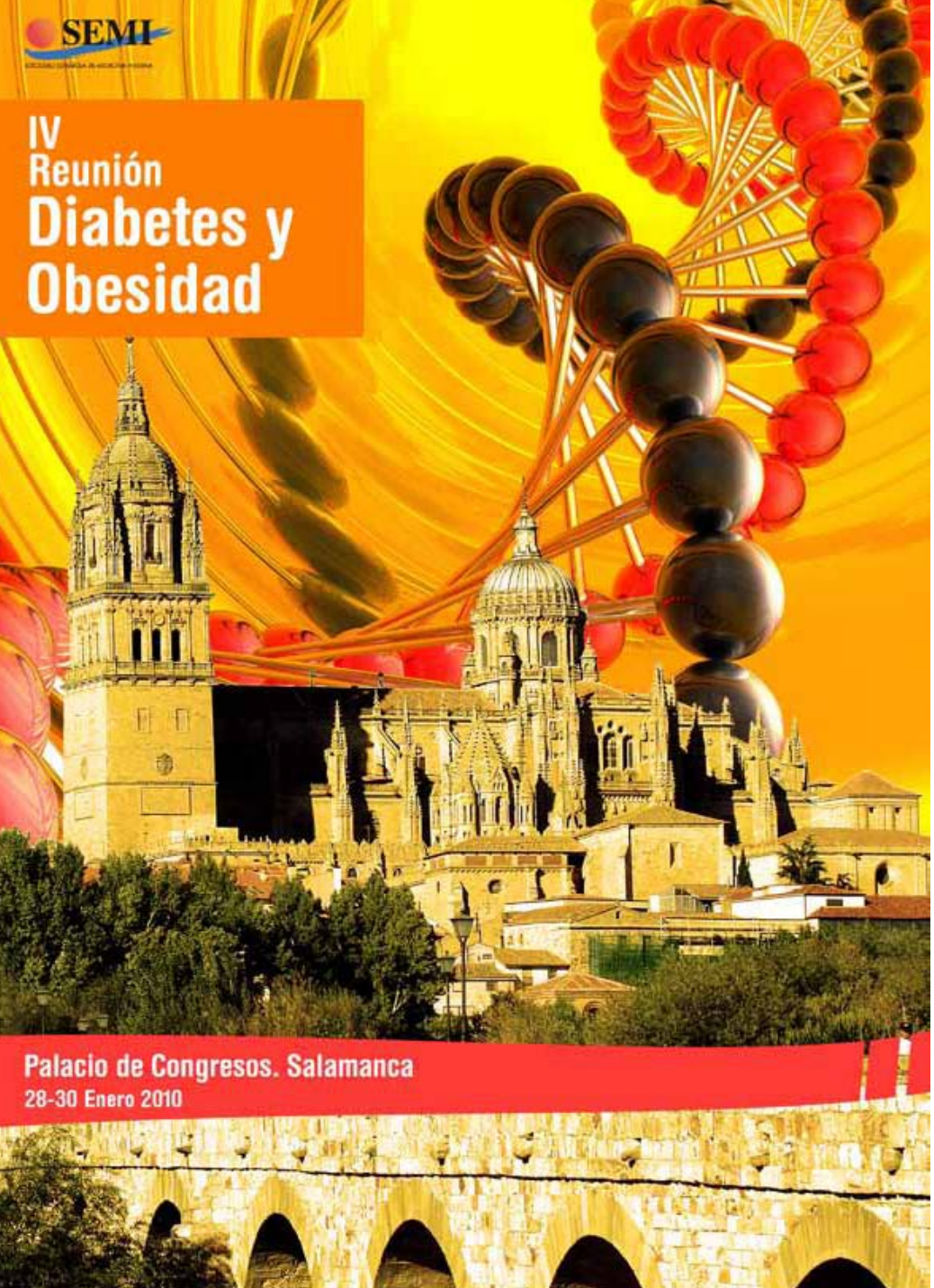

MUCHAS GRACIAS POR SU ATENCIÓN