

# Estudio Advance

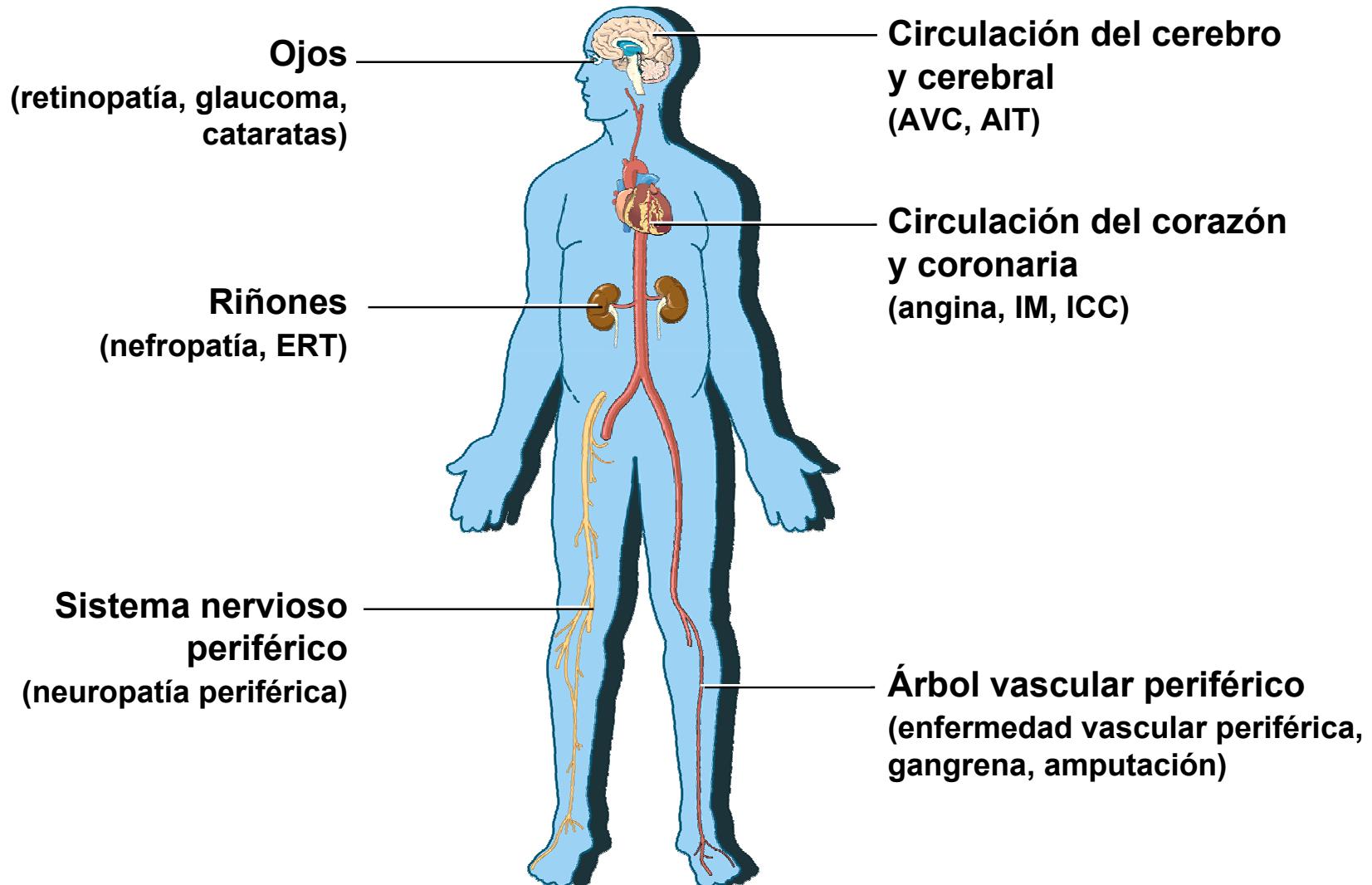
Dr Pedro Conthe\*  
Jefe Sección Medicina Interna  
HGUGM Madrid

**\*No conflicto de intereses**

El Dr P Conthe ha sido consultado y participado como ponente en actividades patrocinadas por BMS, Servier, Astra Zeneca, Menarini, MSD, GSK, Novartis, Lilly, Pfizer, Almirall, Esteve.



# La DM2 enfermedad sistémica

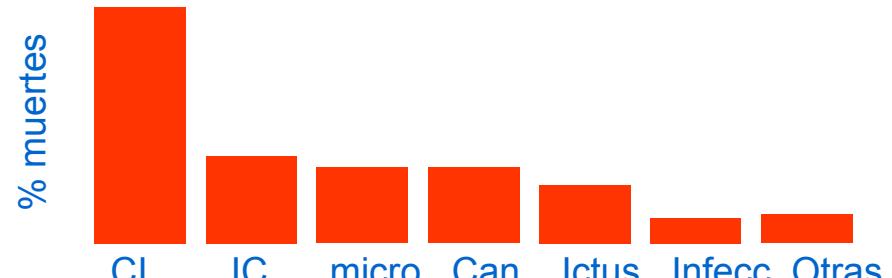


ICC=insuficiencia cardíaca congestiva; ERT=enfermedad renal terminal; IM=infarto de miocardio; AIT=ataques isquémicos transitorios; DMT2=diabetes mellitus tipo 2

Adaptado de International Diabetes Federation. Complications. Disponible en: <http://www.eatlas.idf.org/complications>. Acceso 14 abril de 2006.

# SigloXXI: Diabetes

## Enfermedad vascular



## Seguridad vascular

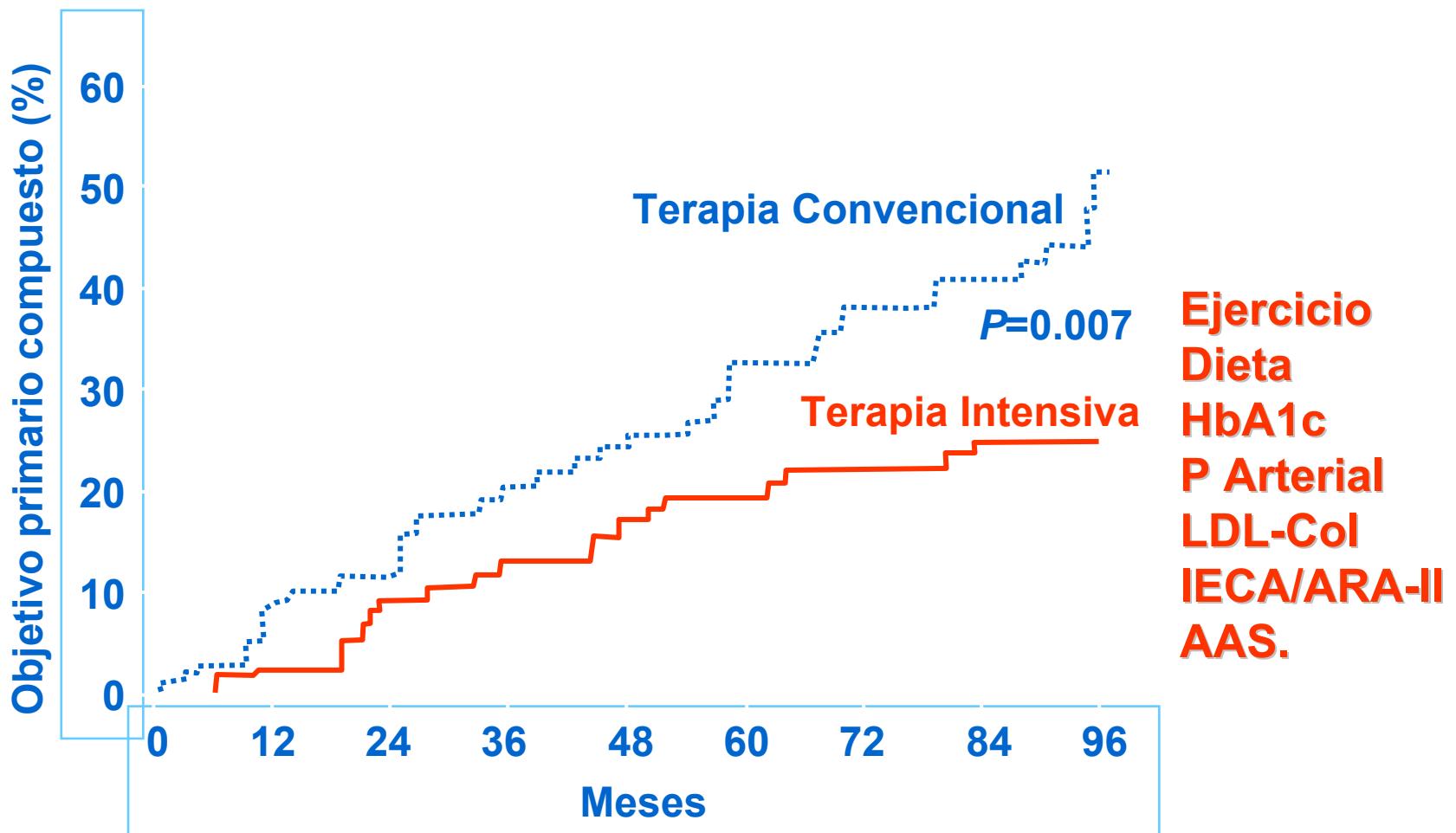


## Protección vascular

No currently marketed therapy for type 2 diabetes has established conclusive evidence of macrovascular benefit Jul 08



# Intervención Multifactorial y Eventos CV en DM2: STENO-2



# Diseño Factorial

## Effects of a fixed combination of perindopril and indapamide ↗@ on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial

ADVANCE Collaborative Group\*

### Summary

**Background** Blood pressure is an important determinant of the risks of macrovascular and microvascular complications of type 2 diabetes, and guidelines recommend intensive lowering of blood pressure for diabetic patients with hypertension. We assessed the effects of the routine administration of an angiotensin converting enzyme (ACE) inhibitor-diuretic combination on serious vascular events in patients with diabetes, irrespective of initial blood pressure levels or the use of other blood pressure lowering drugs.

**Methods** The trial was done by 215 collaborating centres in 20 countries. After a 6-week active run-in period, 11140 patients with type 2 diabetes were randomised to treatment with a fixed combination of perindopril and indapamide or matching placebo, in addition to current therapy. The primary endpoints were composites of major macrovascular and microvascular events, defined as death from cardiovascular disease, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease, and analysis was by intention-to-treat. The macrovascular and microvascular composites were analysed jointly and separately. This trial is registered with ClinicalTrials.gov, number NCT00145925.

Lancet 2007; 370: 829-40

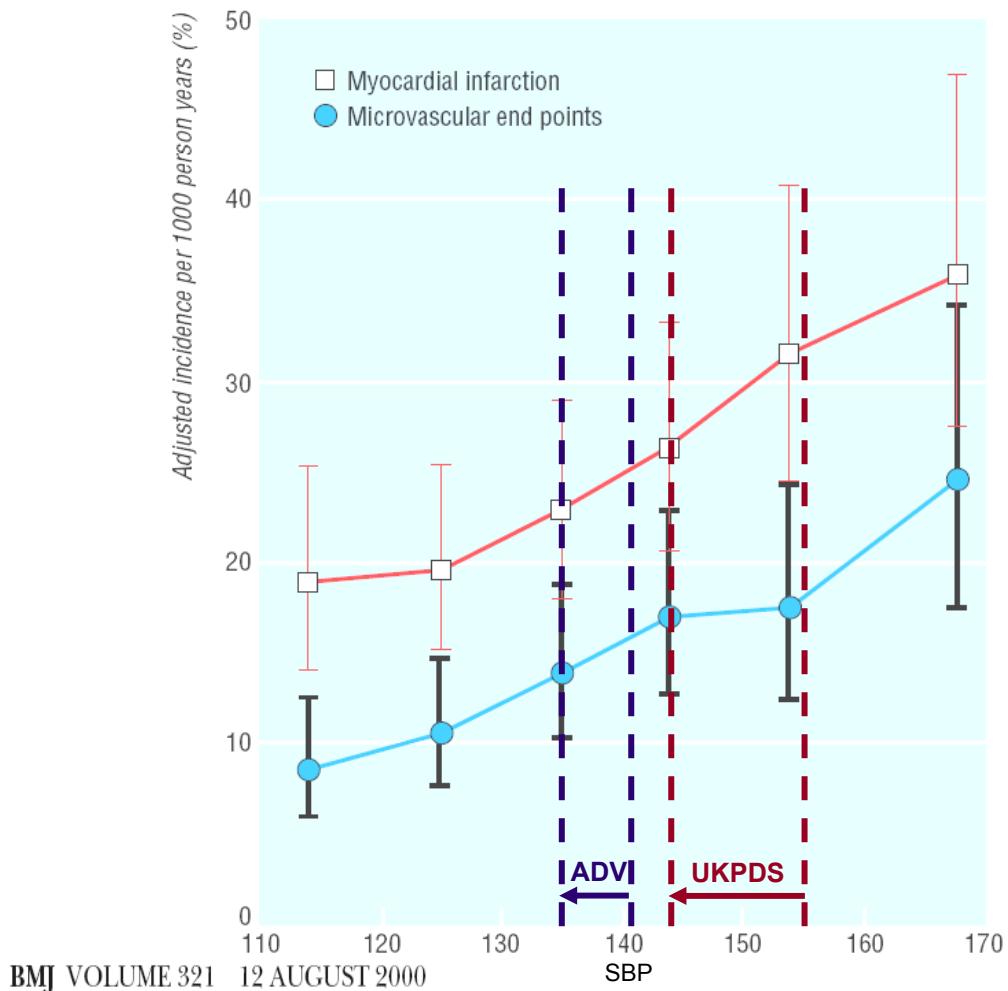
Published Online  
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DOI:10.1016/S0140-6736(07)61303-8

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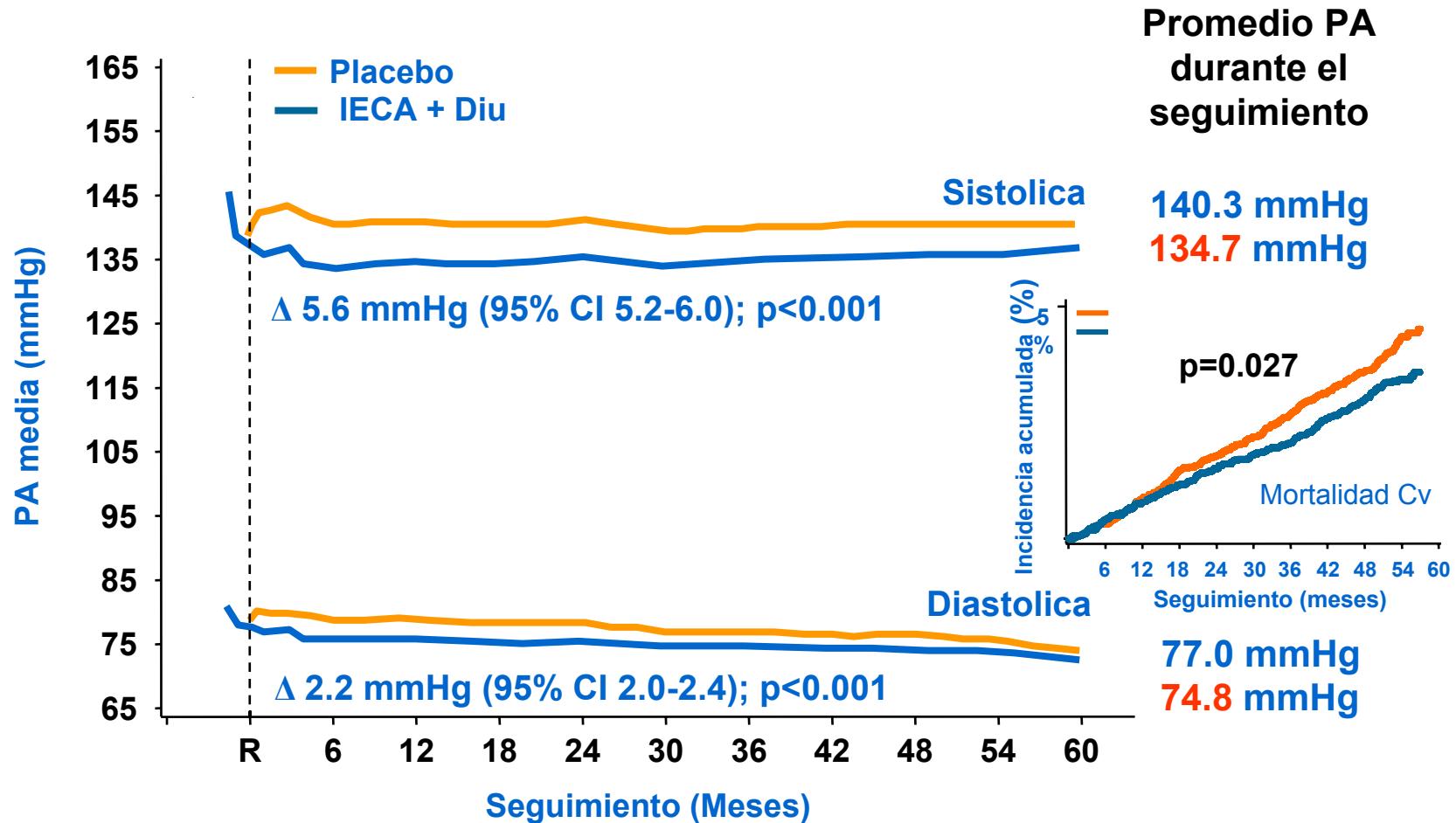
\*Collaborators listed at end of paper

Correspondence to:  
Dr Anushka Patel FRACP  
Cardiovascular Division,  
The George Institute for  
International Health, University  
of Sydney, PO Box M201,  
Missenden Road, Sydney,  
NSW 2050, Australia

# Reducción de la PA en el contexto de UKPDS: UK Prospective Diabetes Study



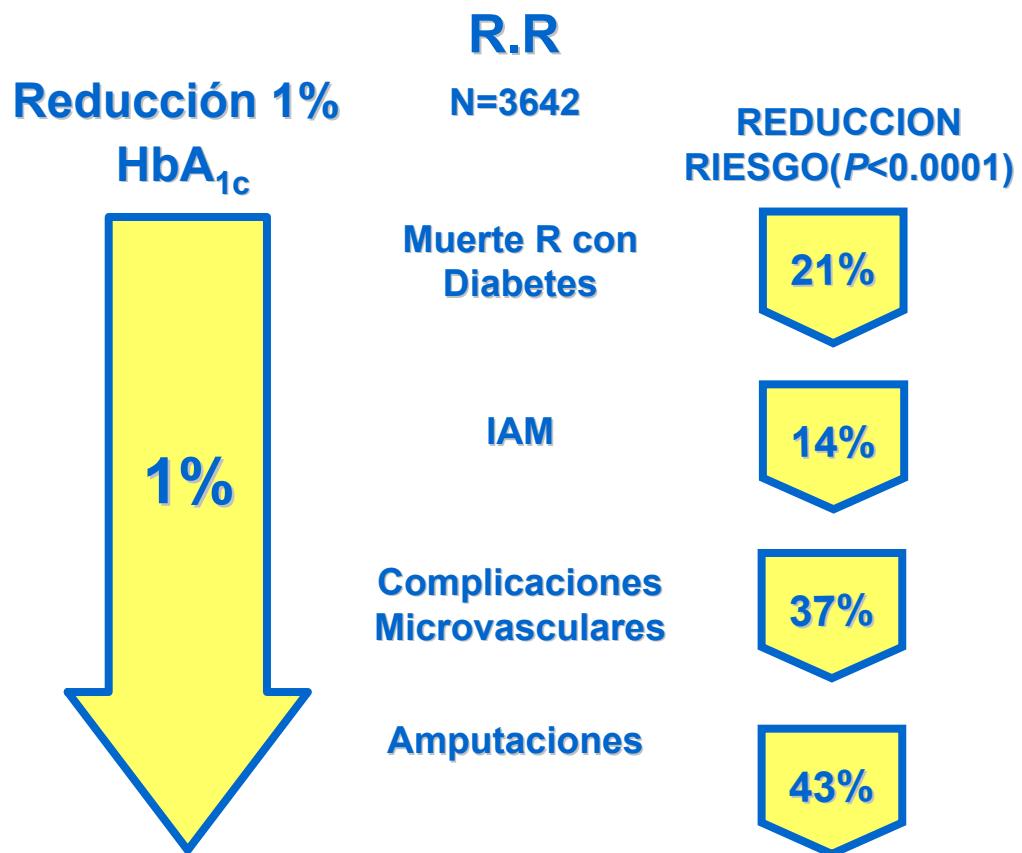
# Advance: mayor reducción de presión arterial



# y el control glucémico?

Estudios Previos:

DCCT (1993) y UKPDS (1998) demostraron que un control estricto de HbA<sub>1c</sub> ayuda a prevenir las complicaciones diabéticas



<sup>1</sup>Liebl A. *Diabetologia* 2002; 45:S23–S28.

Año 2008

Advance

VADT

Accord

Mortalidad  
(%)

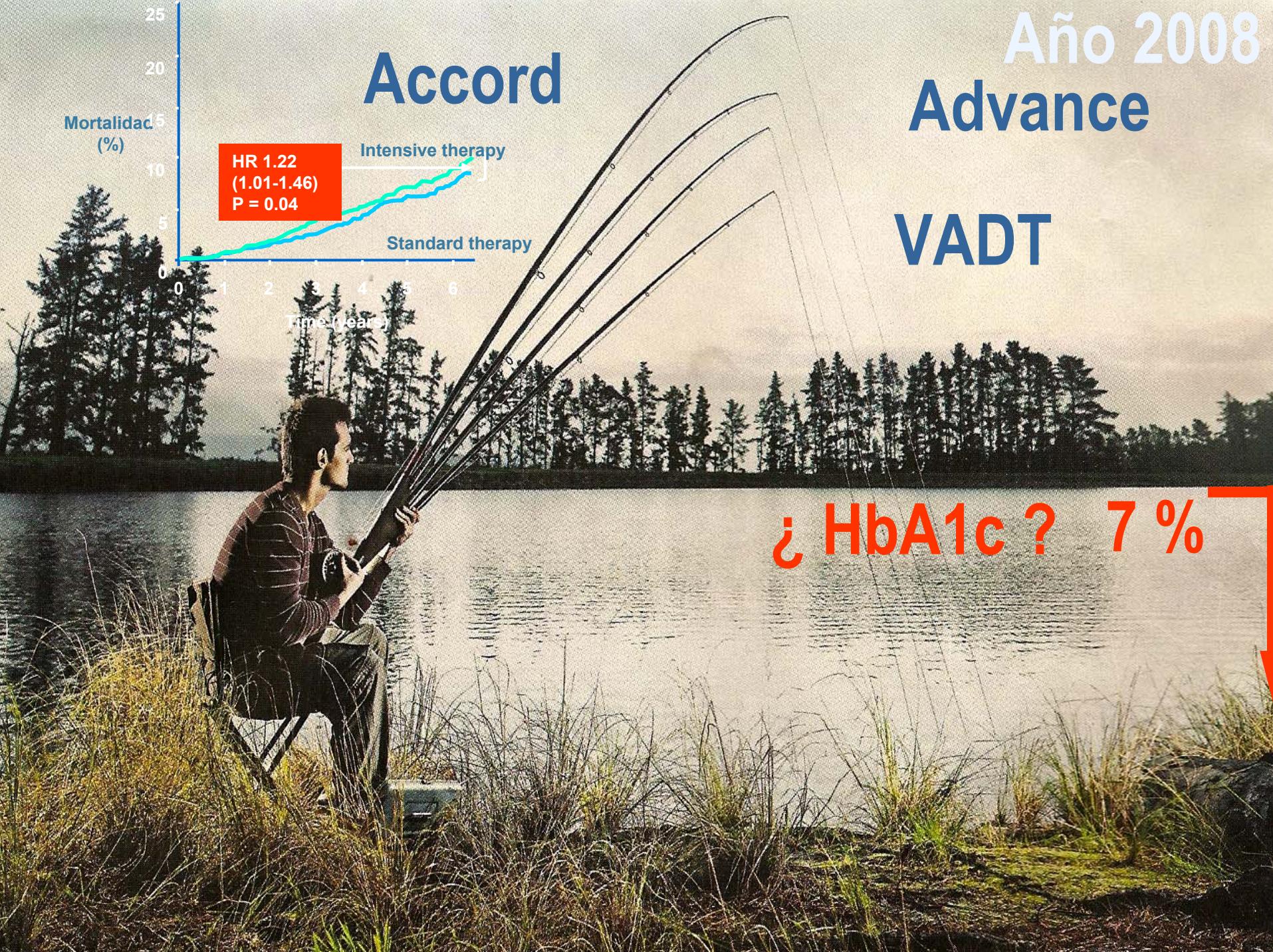
HR 1.22  
(1.01-1.46)  
 $P = 0.04$

Intensive therapy

Standard therapy

Time (years)

¿ HbA1c ? 7 %



ORIGINAL ARTICLE

# Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group\*

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## ABSTRACT

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### BACKGROUND

In patients with type 2 diabetes, the effects of intensive glucose control on vascular outcomes remain uncertain.

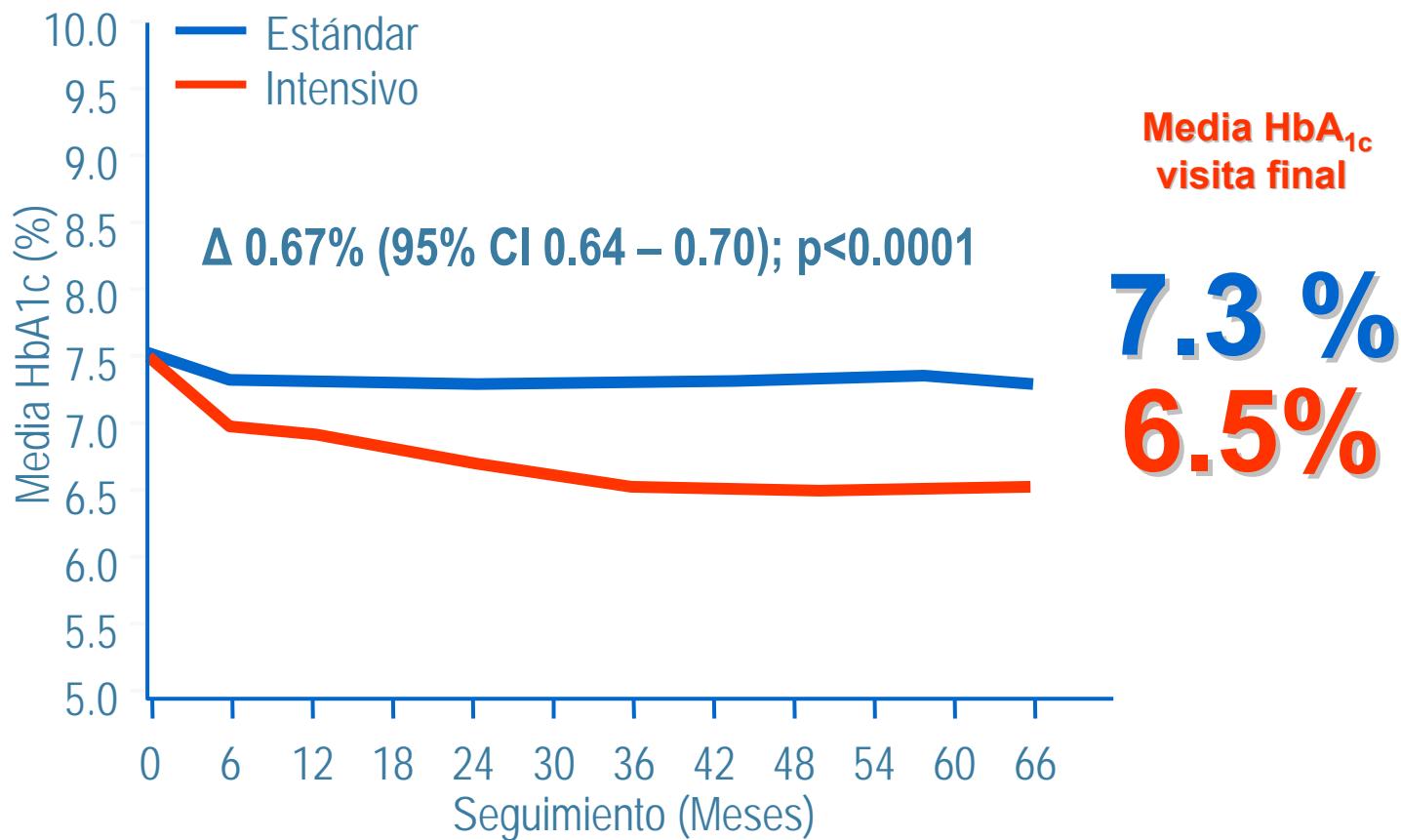
### METHODS

We randomly assigned 11,140 patients with type 2 diabetes to undergo either standard glucose control or intensive glucose control, defined as the use of gliclazide (modified release) plus other drugs as required to achieve a glycated hemoglobin value of 6.5% or less. Primary end points were composites of major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy), assessed both jointly and separately.

The members of the Writing Committee of the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) Collaborative Group are listed in the Appendix. Address reprint requests to Dr. Anushka Patel at the Cardiovascular Division, George Institute for International Health, University of Sydney, P.O. Box M201, Missenden Rd., Sydney, NSW 2050, Australia, or at [apatel@george.org.au](mailto:apatel@george.org.au).

\*Members of the ADVANCE Collaborative Group are listed in the Supplementary Appendix (available with the full text of this article at [www.nejm.org](http://www.nejm.org)).

# Reducción progresiva y significativa de HbA<sub>1c</sub>



# Perfil de los pacientes en ADVANCE

## Características Basales:

- Edad 66 años
- HbA<sub>1c</sub> 7.5%
- IMC 28 kg/m<sup>2</sup>
- PAS 145 mm Hg
- Duración de la diabetes: 8 años
- Historia de enfermedad macrovascular 32%  
enfermedad microvascular 10%

# Estrategia para el Control Glucémico Intensivo

Titulación de la Dosis a criterio facultativo con el objetivo de  $\text{HbA}_{1\text{c}} \leq 6.5\%:$

- Glicazida en todos los pacientes (primera línea, cambio de otra SU, adición a metformina)
- Incremento de la dosis de Glicazida hasta 4 comprimidos/día (120 mg)
- Adición de otros antidiabéticos orales
- Adición de insulina

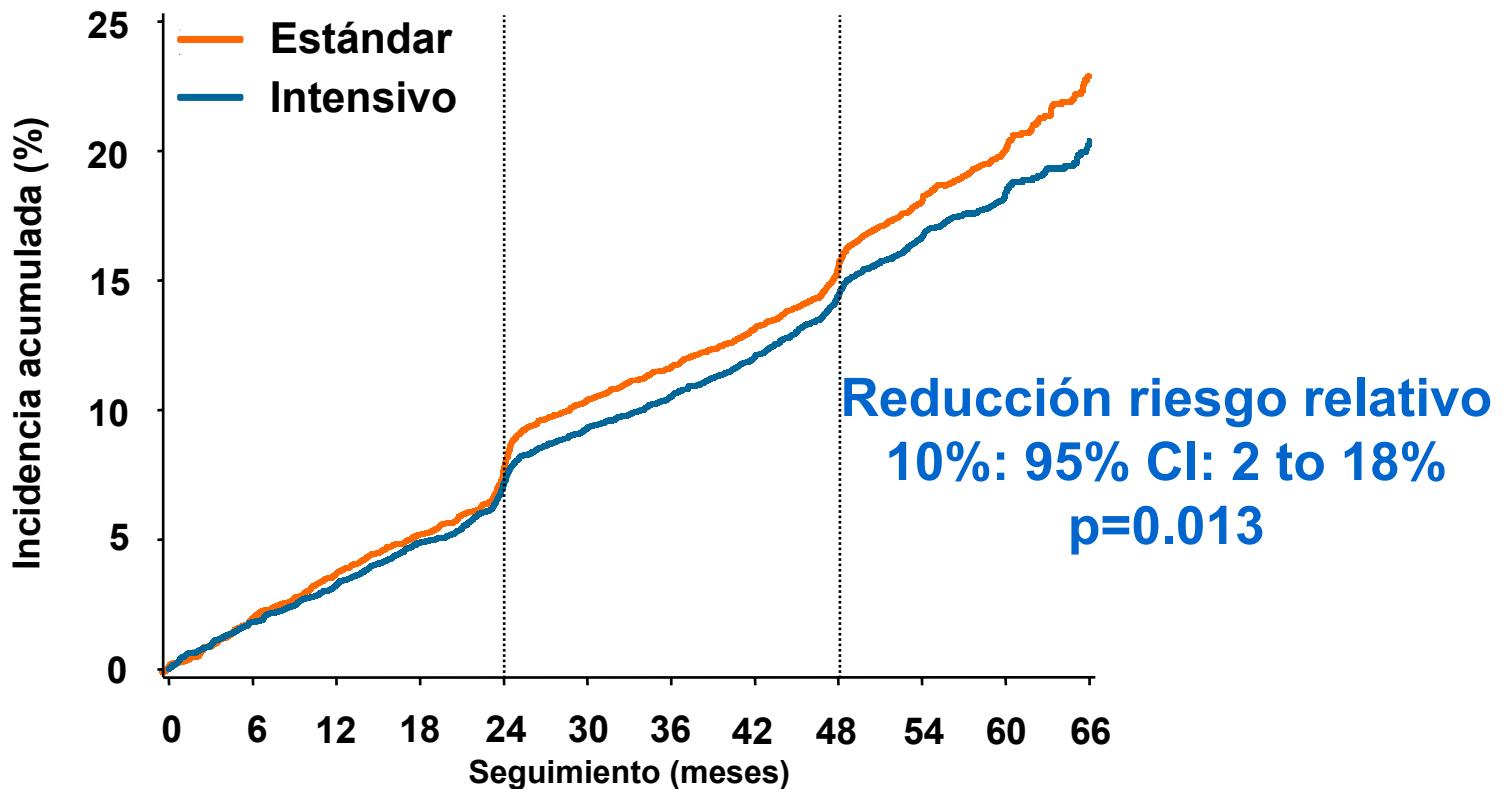
**120 mg glicazida en el 70% de los pacientes**

# ADVANCE: Fármacos hipoglucemiantes al final del seguimiento

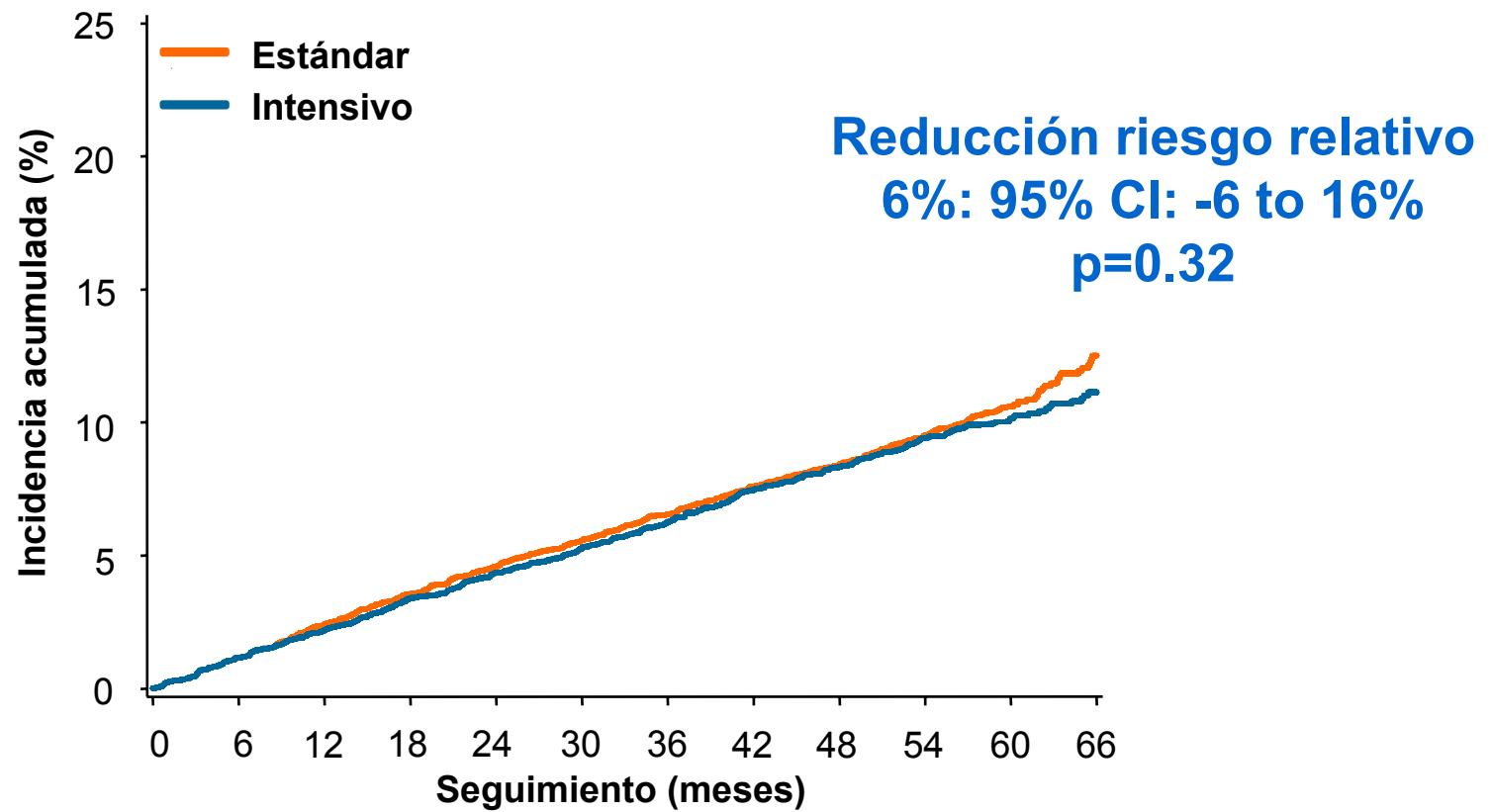
	Tratamiento Aleatorio	
	Intensivo (n=4828)	Estándar (n=4741)
glicazida	91%	-
Otra Sulfonilurea	-	57%
Metformina	74%	67%
Glitazonas	17%	11%
Acarbosa	19%	13%
Glinidas	1%	3%
Insulina	40%	24%

# Objetivo Combinado Primario

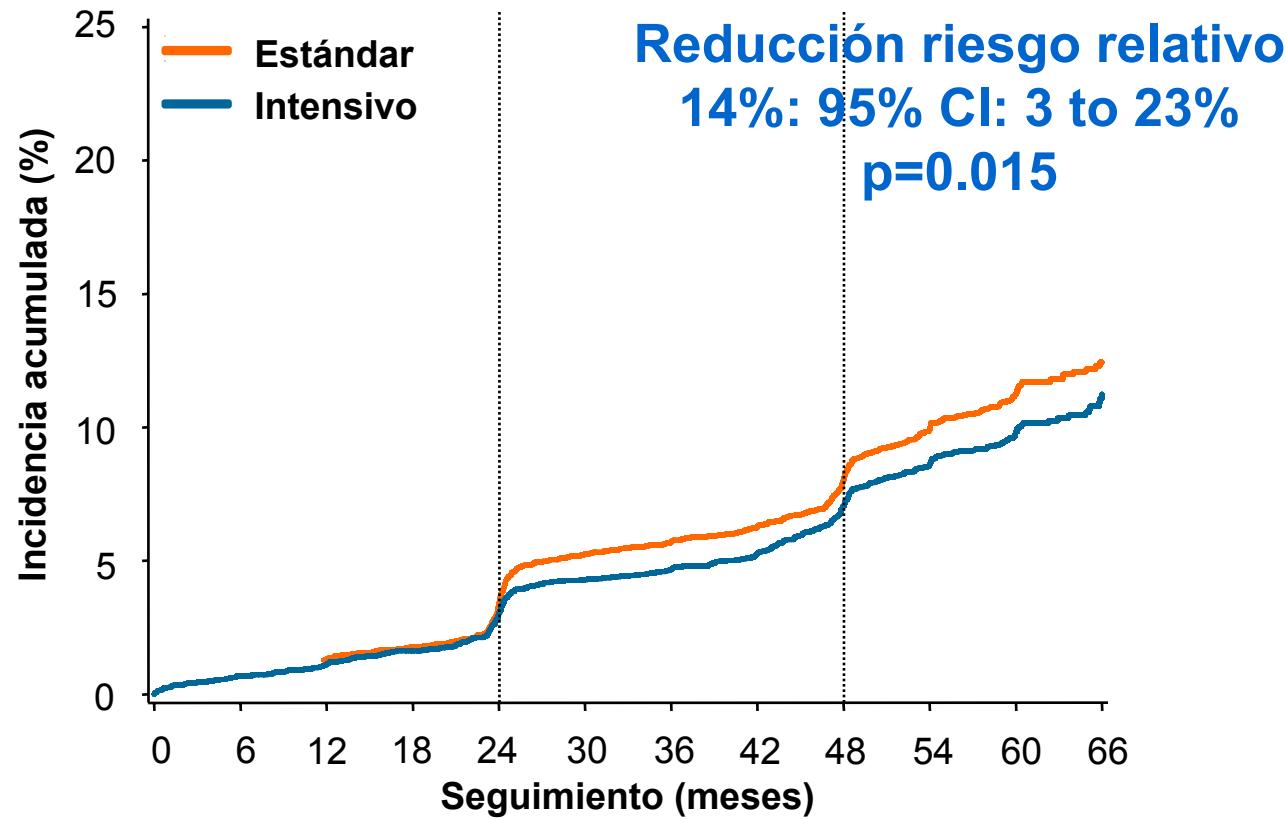
## *Complicaciones micro y macrovasculares*



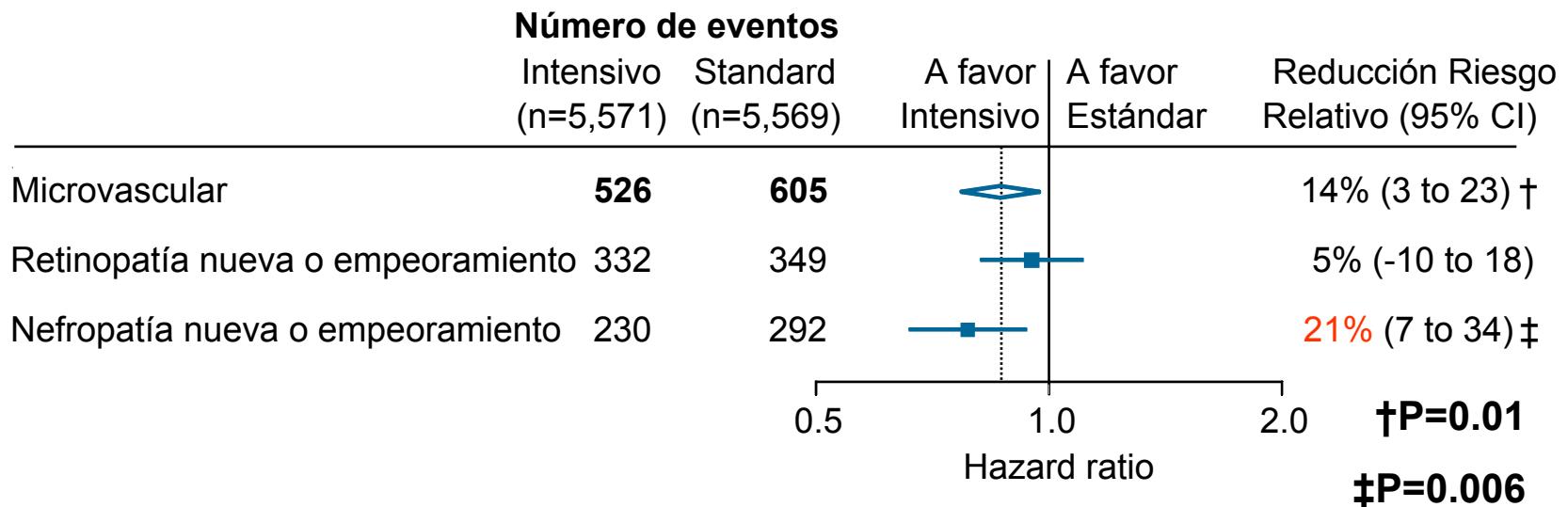
# Complicaciones Macrovasculares



# Complicaciones Microvasculares

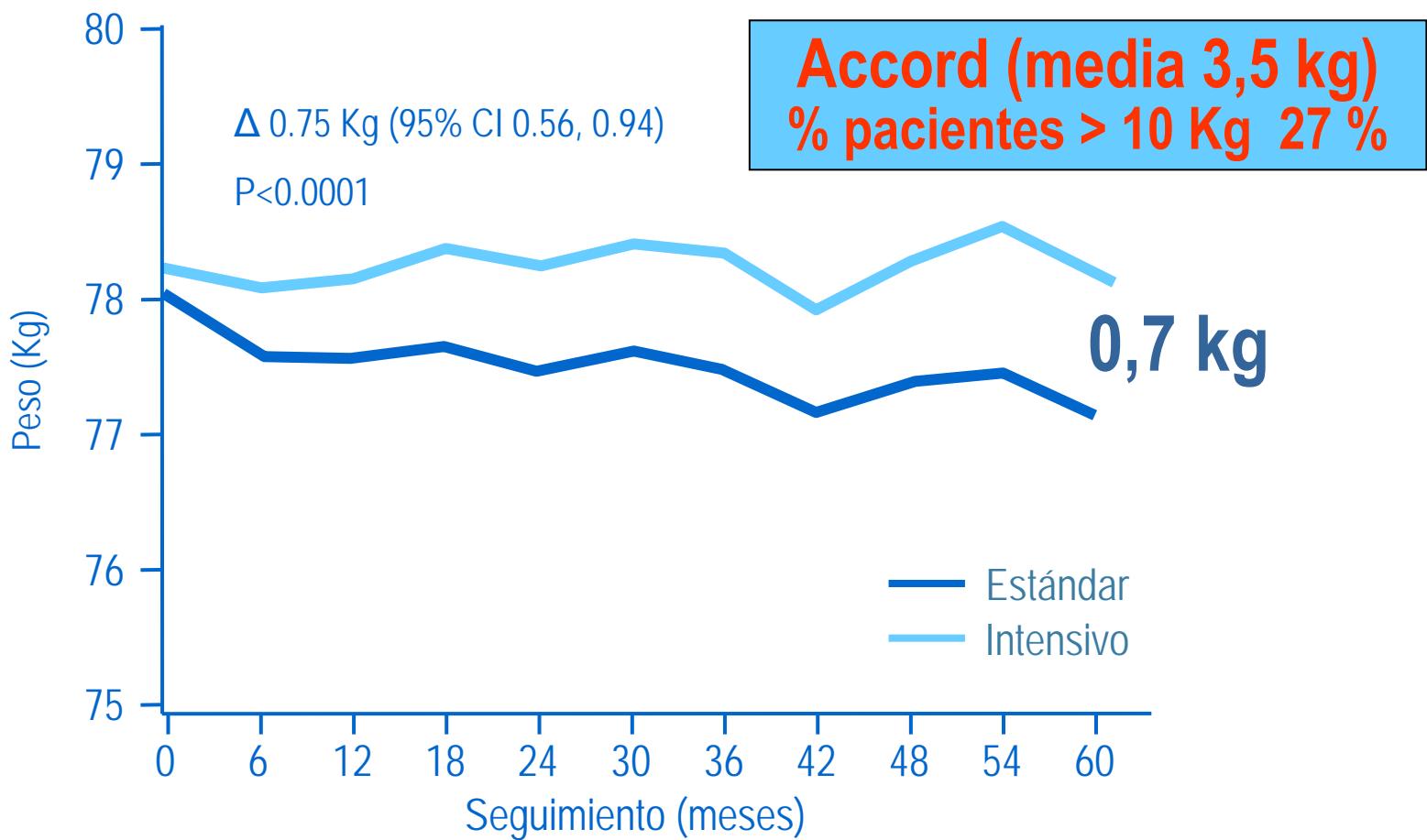


# Complicaciones Microvasculares

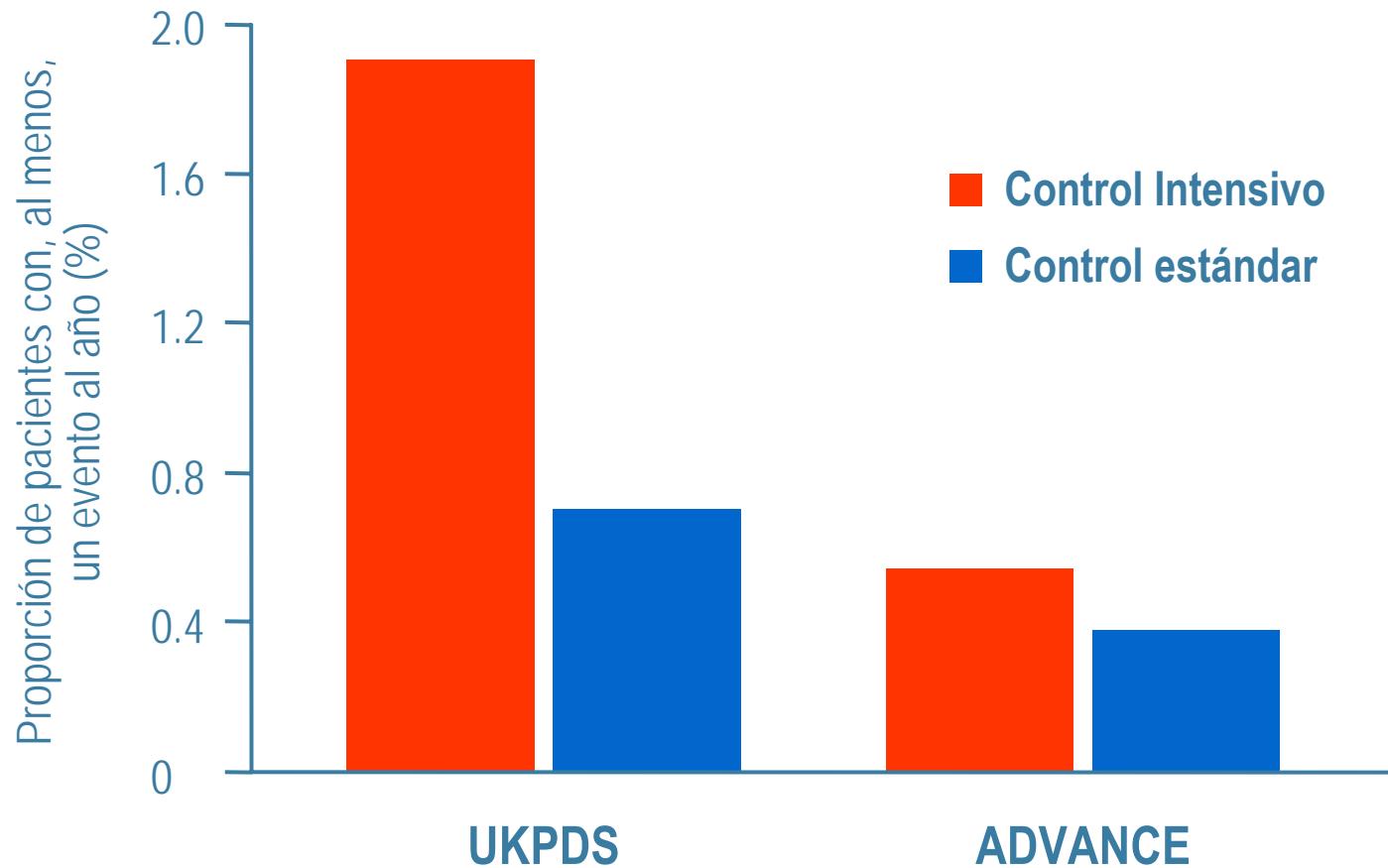


+ hospitalizaciones ( 44,9 vs 42,8)  
+ visitas (x2)

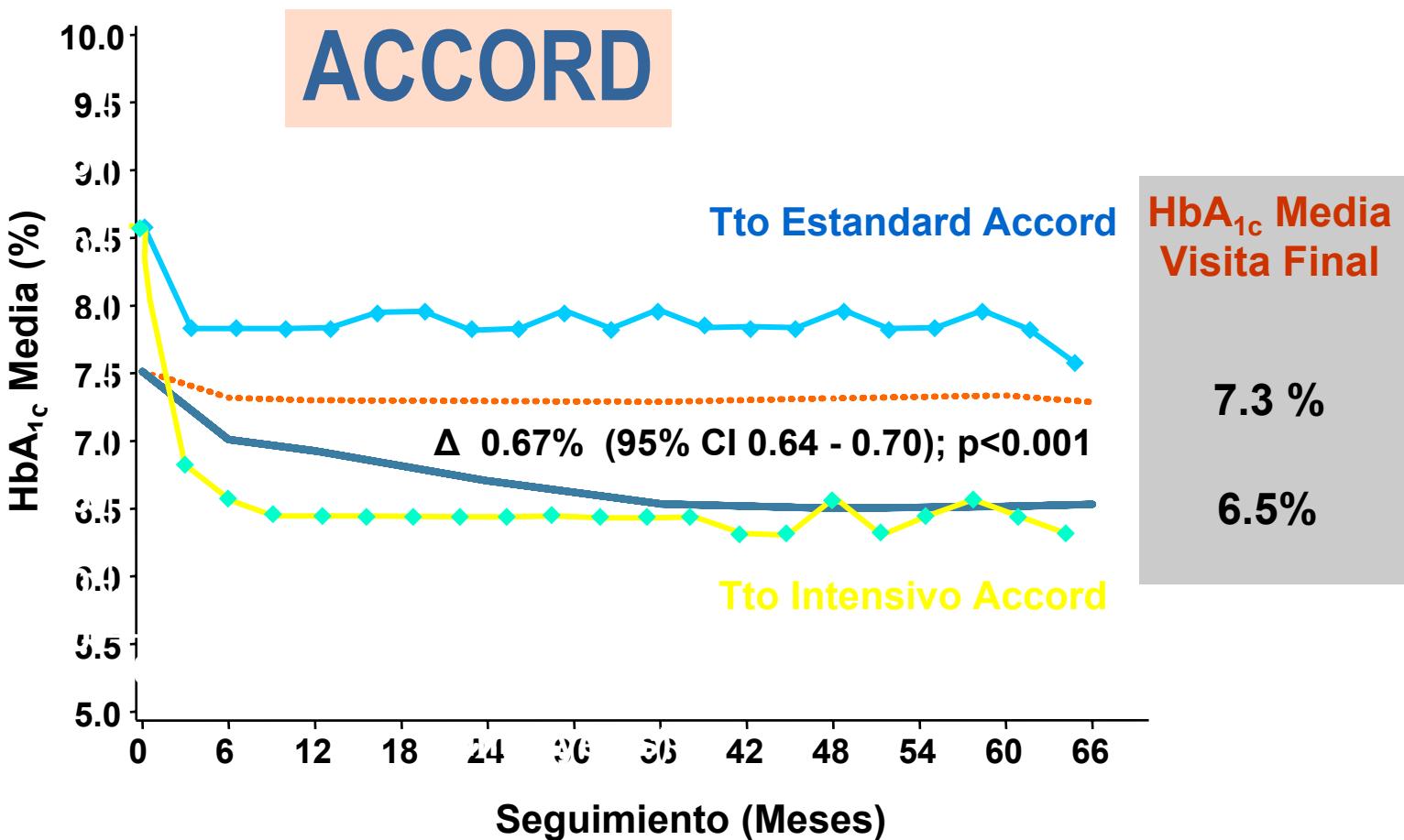
# Neutralidad en el Peso



# Tasa Comparativa de Hipoglucemias Graves entre UKPDS y ADVANCE



# Hemoglobina A<sub>1c</sub>



# Farmacos, Hipoglucemia y mortalidad

	ADVANCE	ACCORD
Media HbA <sub>1c</sub>	6.4 %	6.4 %
Hipoglucemias graves	2.5 %	16.2 %
% de fármacos utilizados		
secretagogos	92 %	87 %
metformina	74 %	95 %
glitazonas	17 %	92 %
insulina	40%	77%
MUERTE CUALQUIER CAUSA %	8.9 vs. 9.6	5.0 vs. 4.0

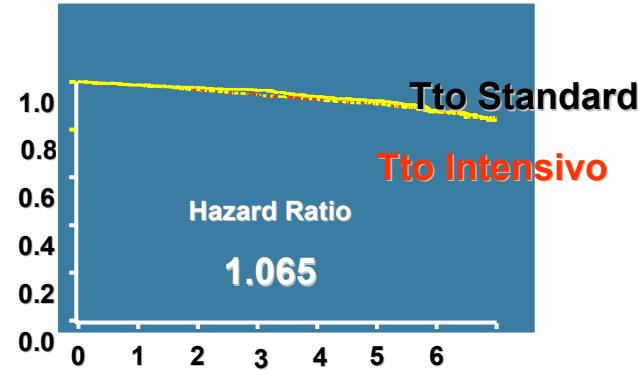
# VADT: perfil y pronóstico

1791 pacientes, 97% varones

Duration of DM	11.5 ± 7.7*
Age (years)	60.4 ± 9.5*
BMI ( $\text{kg}/\text{m}^2$ )	31.3 ± 4.6*
HbA1c (on OAA max dose or insulin)	9.4 ± 1.5*
Hypertension	72 %
Macrovascular events	40 %
Diabetic neuropathy	43 %
Retinopathy	62 %

\* Mean ± SD

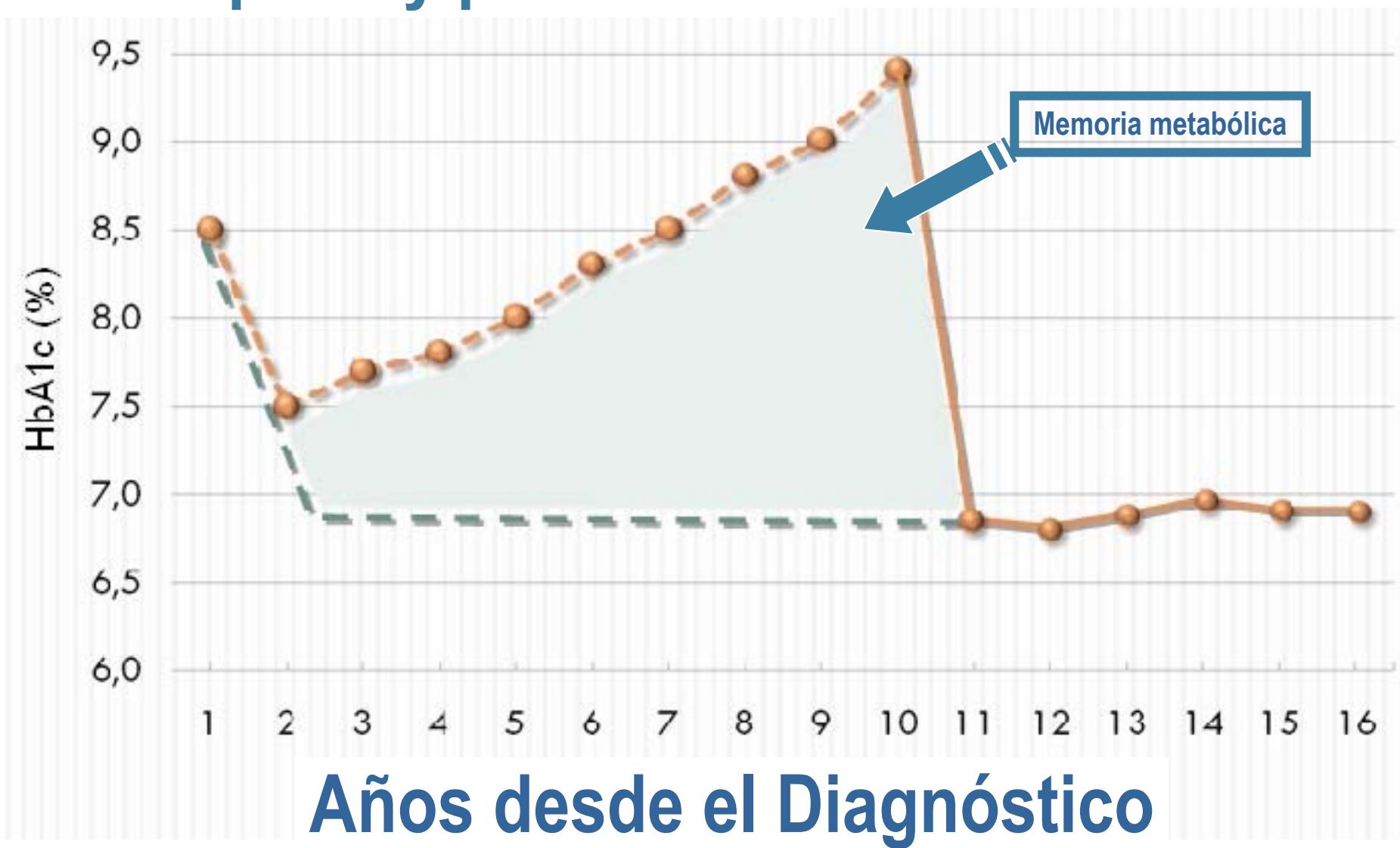
HbA1c basal 9,4 %  
HbA1c final 6,9%



## Predictores de Primer evento

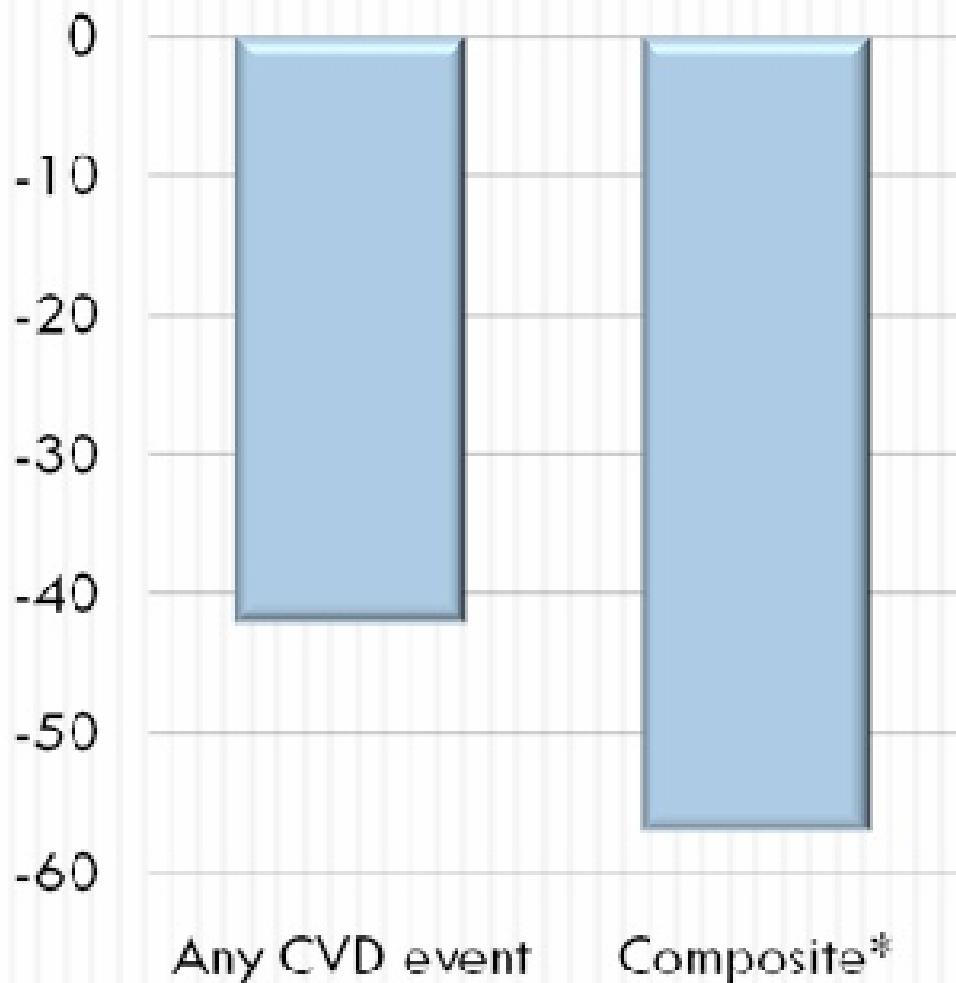
Evento previo	3.003
Edad	1.333
Duración DM 2	1.019
HDL	0.823
Hba1c alcanzada	1.095
Hipoglucemia	2.062

# VADT: perfil y pronóstico

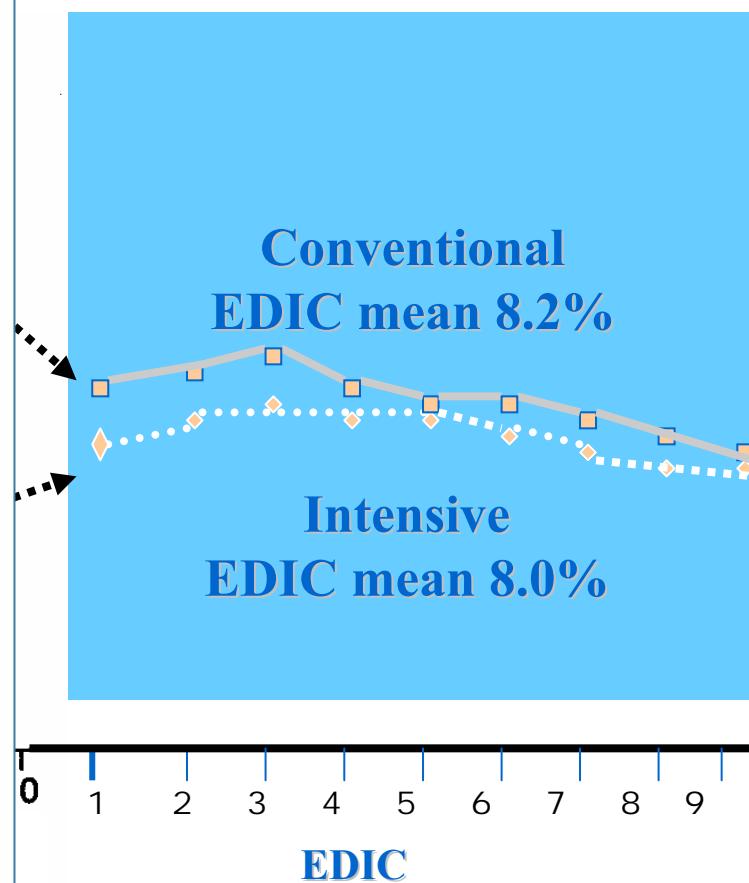


# DCCT / EDIC

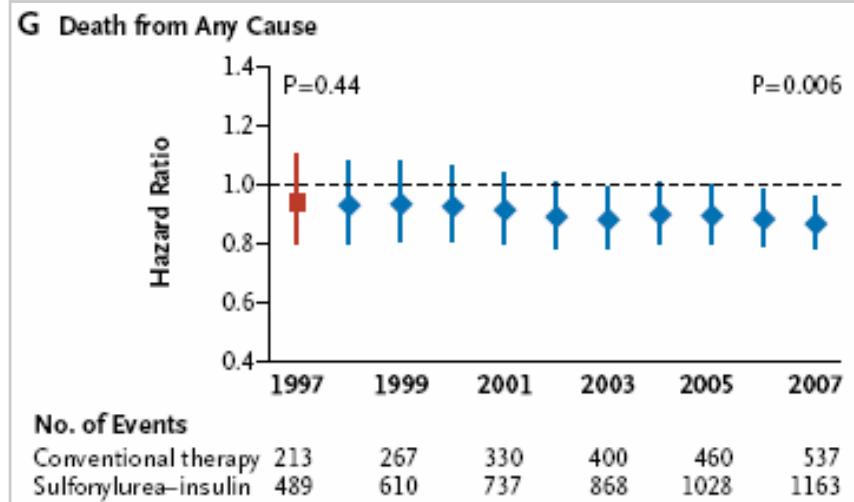
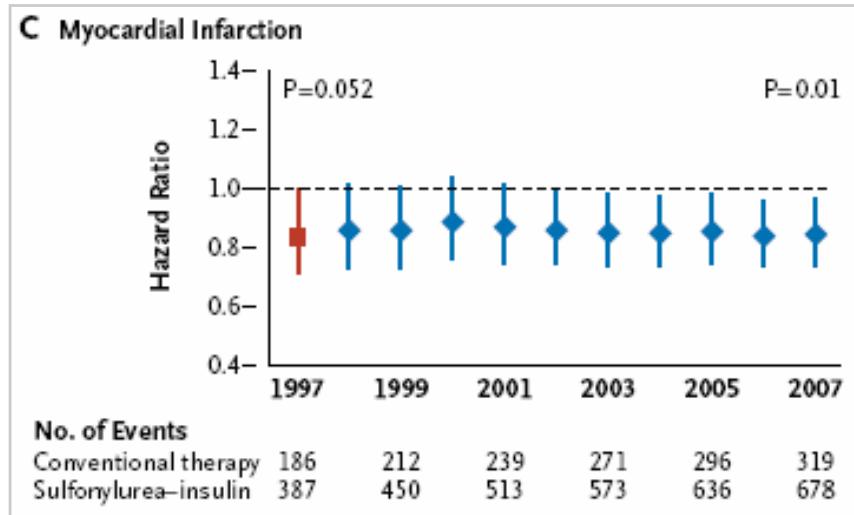
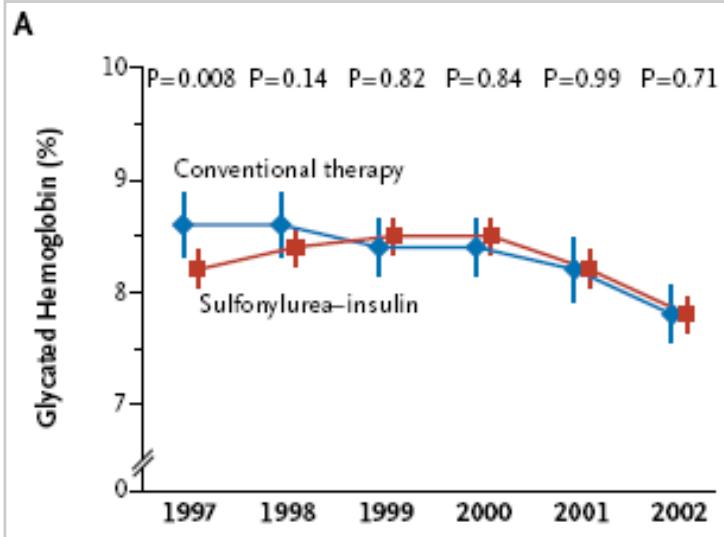
Cardiovascular disease  
during mean 17 yrs follow-up



EDIC Observation



# UKPDS 10 años después...



# **ADVANCE: Efecto sobre los principales Criterios de Eficacia**

## **Control Glucémico Intensivo y Progresivo**

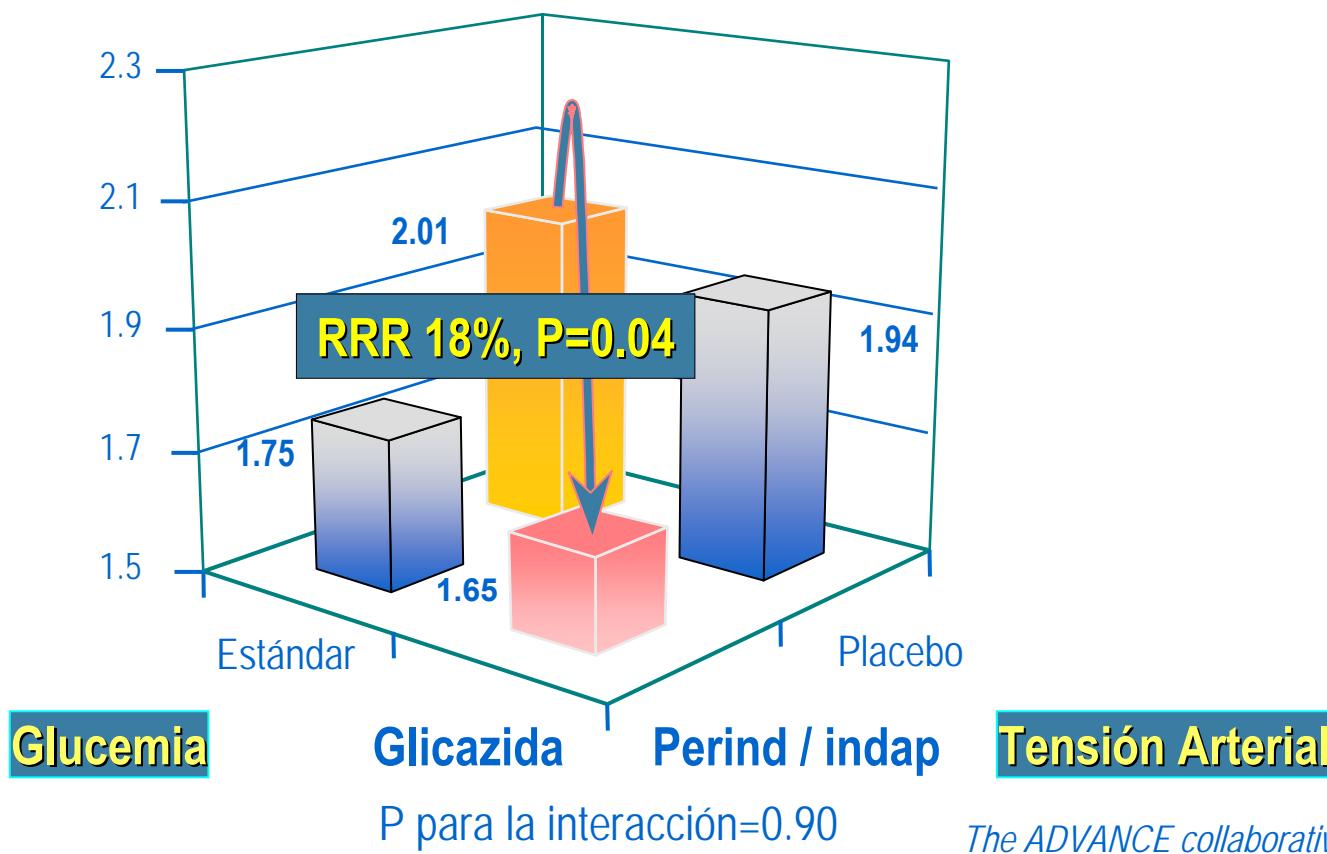
- 10% Reducción Criterio Primario Combinado
- 14% Reducción Complicaciones Microvasculares\*
  - 21% Reducción Nefropatía\*
- Reducción no significativa Mortalidad Total (-7%) o Cardiovascular (-12%)

# Beneficios conjuntos

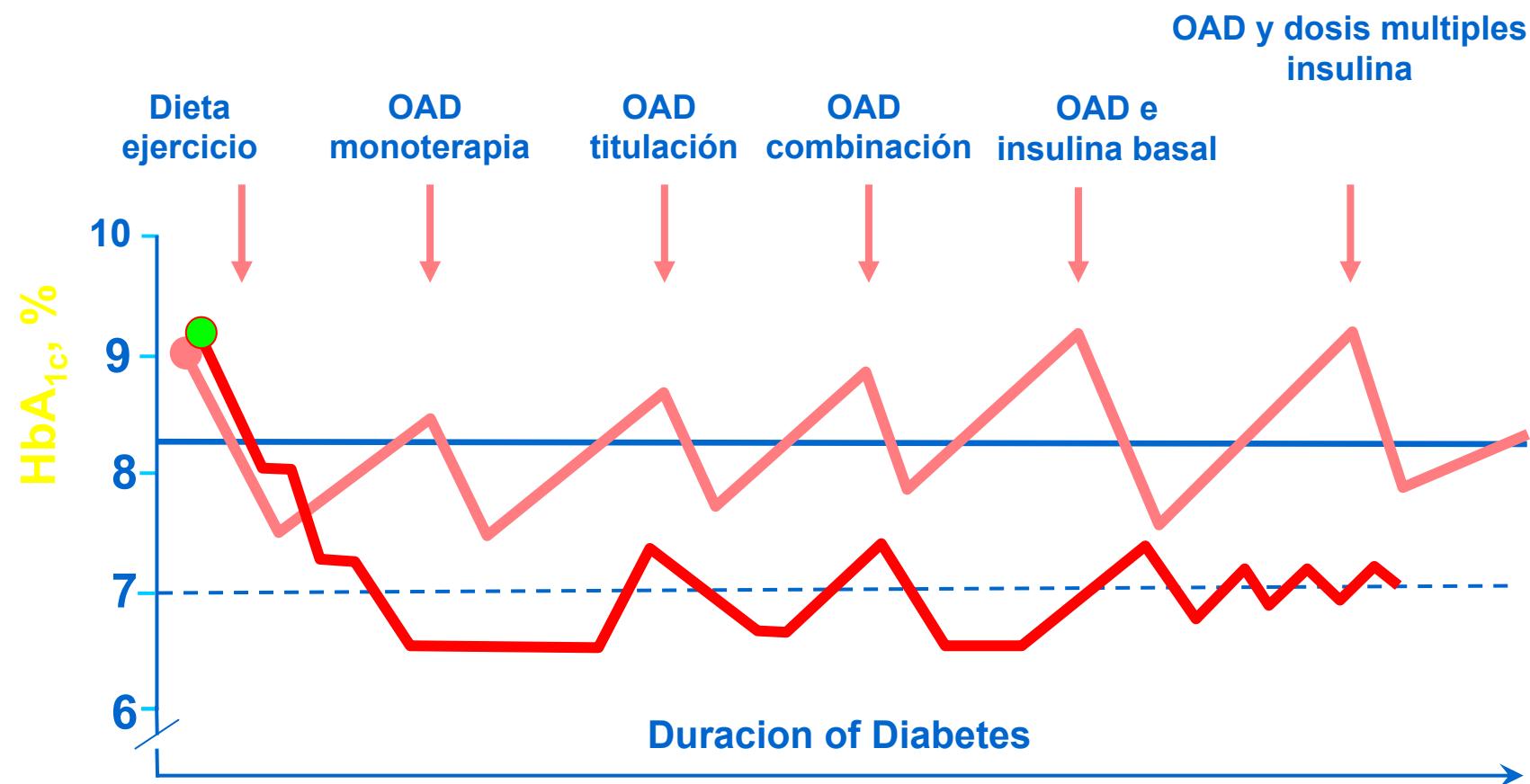
Reducción sistemática de Presión Arterial y Control Intensivo de la Glucemia

Mortalidad Total

Tasa de Eventos Anuales %

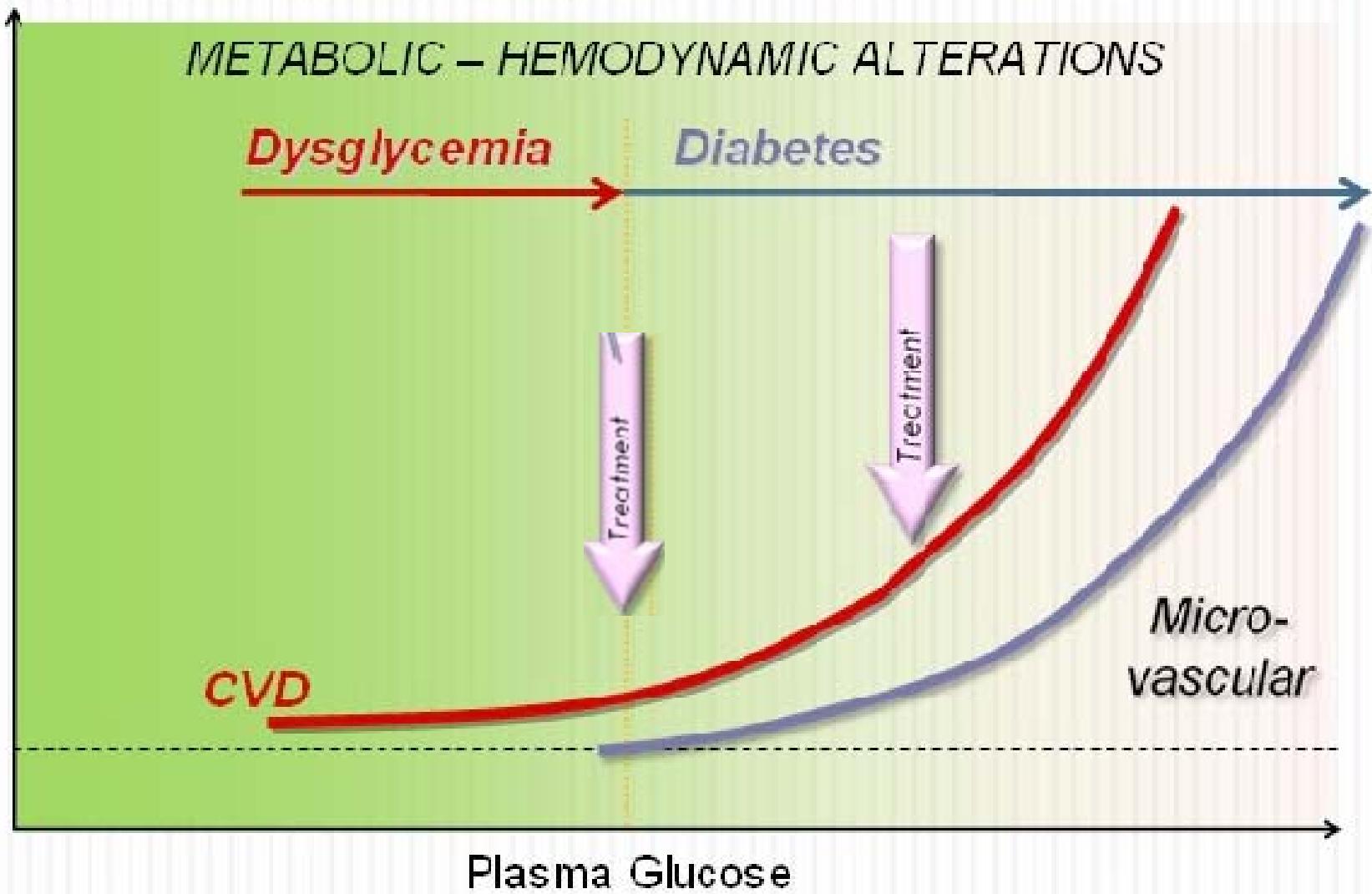


# Tratamiento combinado precoz con antidiabéticos orales



# Por qué esperar ?

Relative Risk



# **Conclusiones**

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- 1.-Preciso utilizar estrategias seguras en descenso y consecución de objetivos de control metabólico dentro de tto integrador**
  
- 2.-Especial atención a la Hipoglucemia**
  
- 3.-Objetivo General de control glucémico en DM 2 (**¡PRECOZMENTE!**) Hb a1c < 7 %**



**ADVANCE**  
Collaborative Group