Bloqueo del sistema renina-angiotensina en el paciente diabético tipo 2
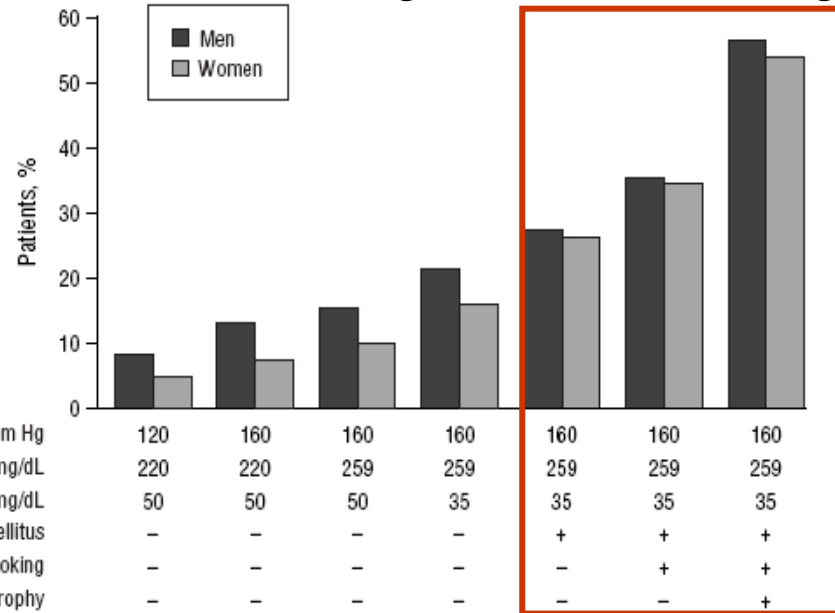
A quién?

Pablo Gómez
Nefrologia –Unidad HTA
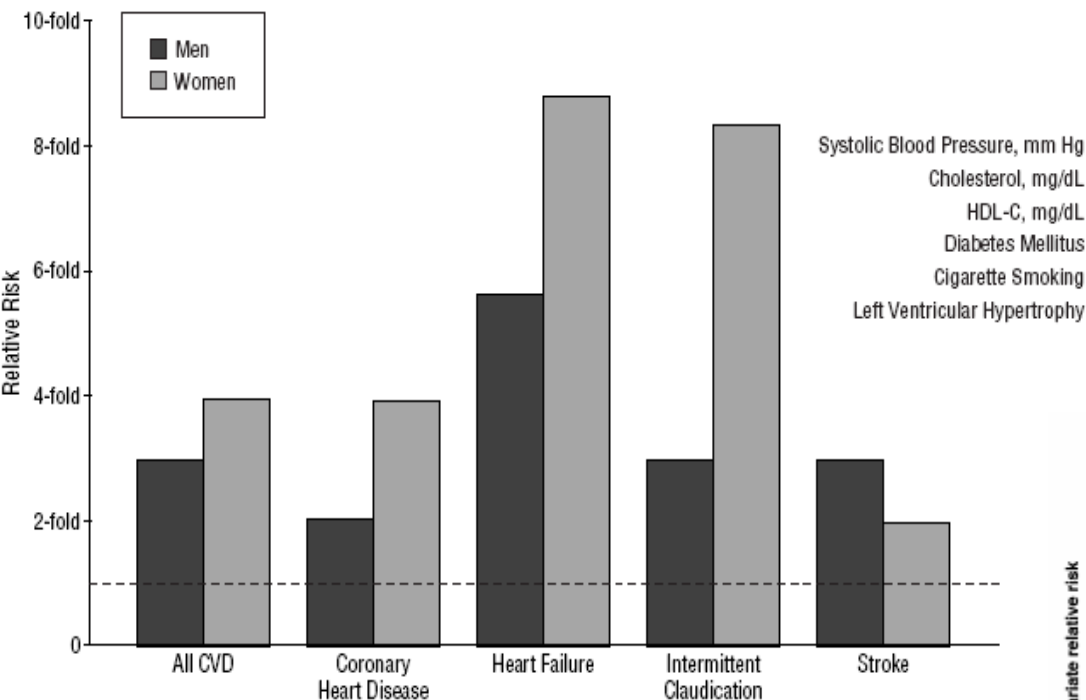Hospital del SAS ,Jerez

Guión

- Riesgo vascular en diabetes mellitus

- Implicación del SRA en el daño vascular del diabético

- Evidencias de protección vascular con bloqueantes del SRA en la diabetes mellitus tipo 2

Pablo Gómez
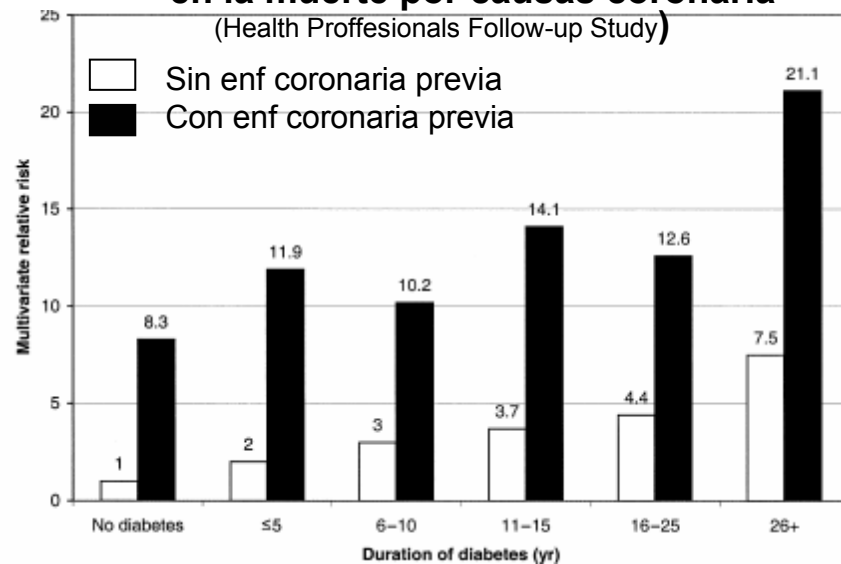Hospital de Jerez

Aumento de enfermedad CV en la diabetes mellitus

% de sujetos diagnosticados de enf. coronaria según los factores de riesgo

**RR de eventos CV en diabetes mellitus**

Men
Women

10-fold
8-fold
6-fold
4-fold
2-fold
0

Relative Risk

All CVD | Coronary Heart Disease | Heart Failure | Intermittent Claudication | Stroke

60
50
40
30
20
10
0

Patients, %

Men
Women

Systolic Blood Pressure, mm Hg	120	160	160	160	160	160	160
Cholesterol, mg/dL	220	220	259	259	259	259	259
HDL-C, mg/dL	50	50	50	35	35	35	35
Diabetes Mellitus	–	–	–	–	+	+	+
Cigarette Smoking	–	–	–	–	–	+	+
Left Ventricular Hypertrophy	–	–	–	–	–	–	+

Efecto de duración de diabetes en la muerte por causas coronaria
(Health Proffesionals Follow-up Study)

☐ Sin enf coronaria previa
■ Con enf coronaria previa

25
20
15
10
5
0

Multivariate relative risk

| No diabetes | ≤5 | 6–10 | 11–15 | 16–25 | 26+ |

1 — 8.3
2 — 11.9
3 — 10.2
3.7 — 14.1
4.4 — 12.6
7.5 — 21.1

Duration of diabetes (yr)

Kannel and McGee,Circulation 59,8, 1979
Cho et al J Ame Coll Cardiol 40,954,2002
Barret-Connor et al Arch Intern Med 164,934,2004

Pablo Gómez
Hospital de Jerez

# Relación entre edad y enf. CV en diabetes mellitus
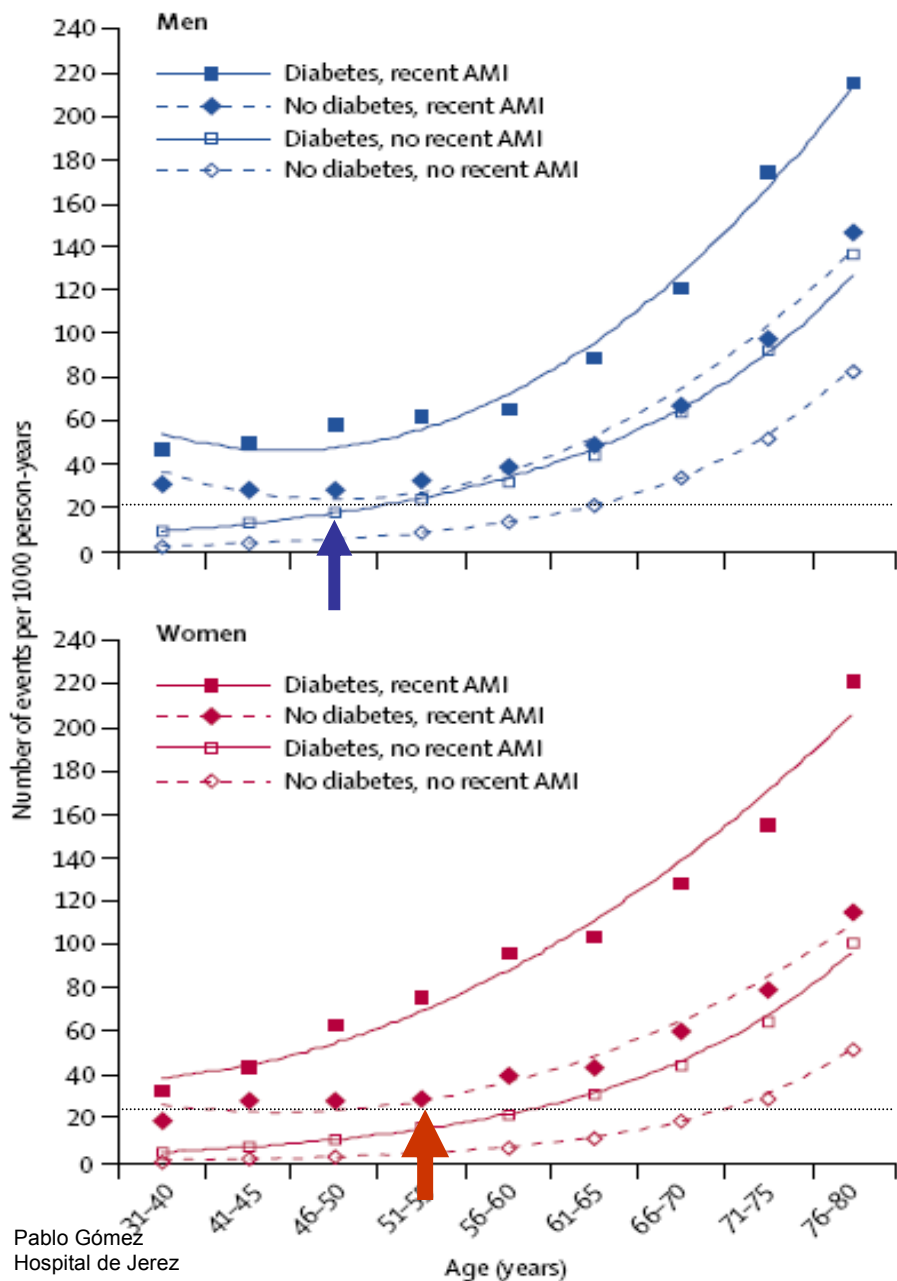
-La diabetes confiere un equivalente de riesgo igual a 15 años de vida.

-Para IM, ICTUS o muerte de cualquier causa los hombres y mujeres diabéti-cos entran en alto riesgo a las edades de 47,9 y 54,3 años, respectivamente. Si se incluye revascularizacion corona-ria o carótida se reduce a 41,3 y 47,7.
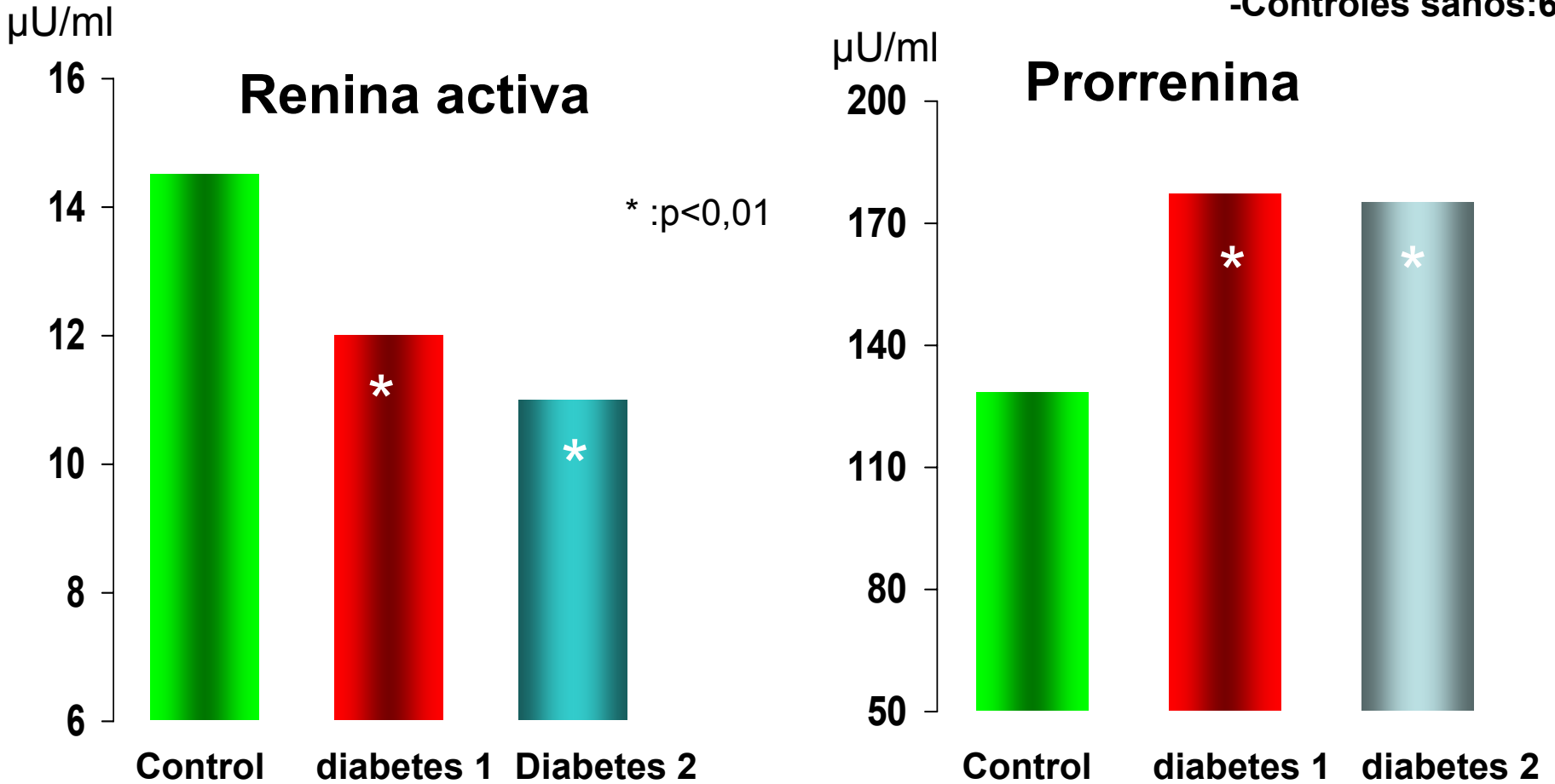
Pablo Gómez
Hospital de Jerez

Guión

- Riesgo vascular en diabetes mellitus

- **Implicación del SRA en el daño vascular del diabético**

- Evidencias de protección orgánica con bloqueantes del SRA en la diabetes mellitus tipo 2

Pablo Gómez
Hospital de Jerez

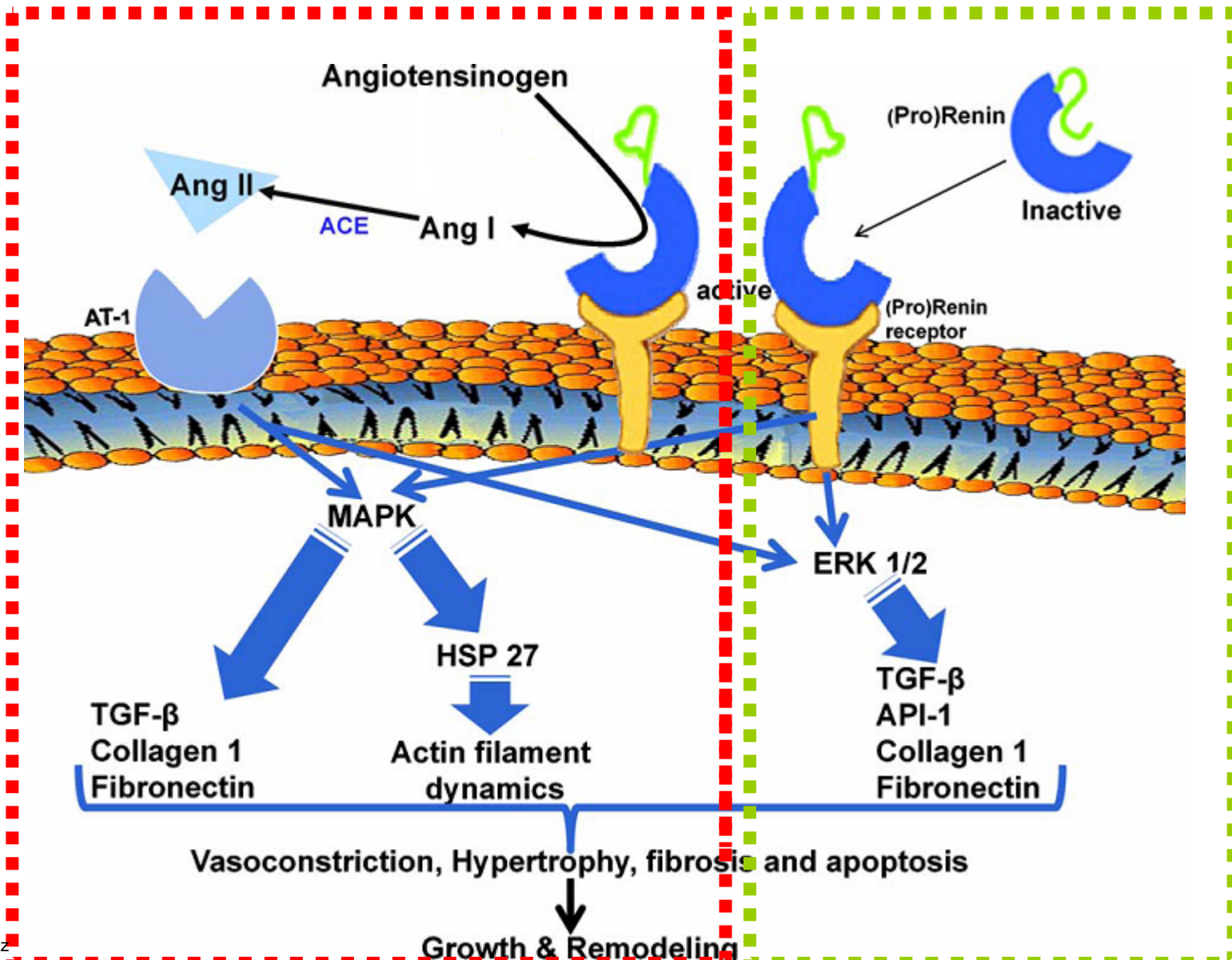# Sistema renina-angioten-aldos. y daño vascular

Pablo Gómez
Hospital de Jerez
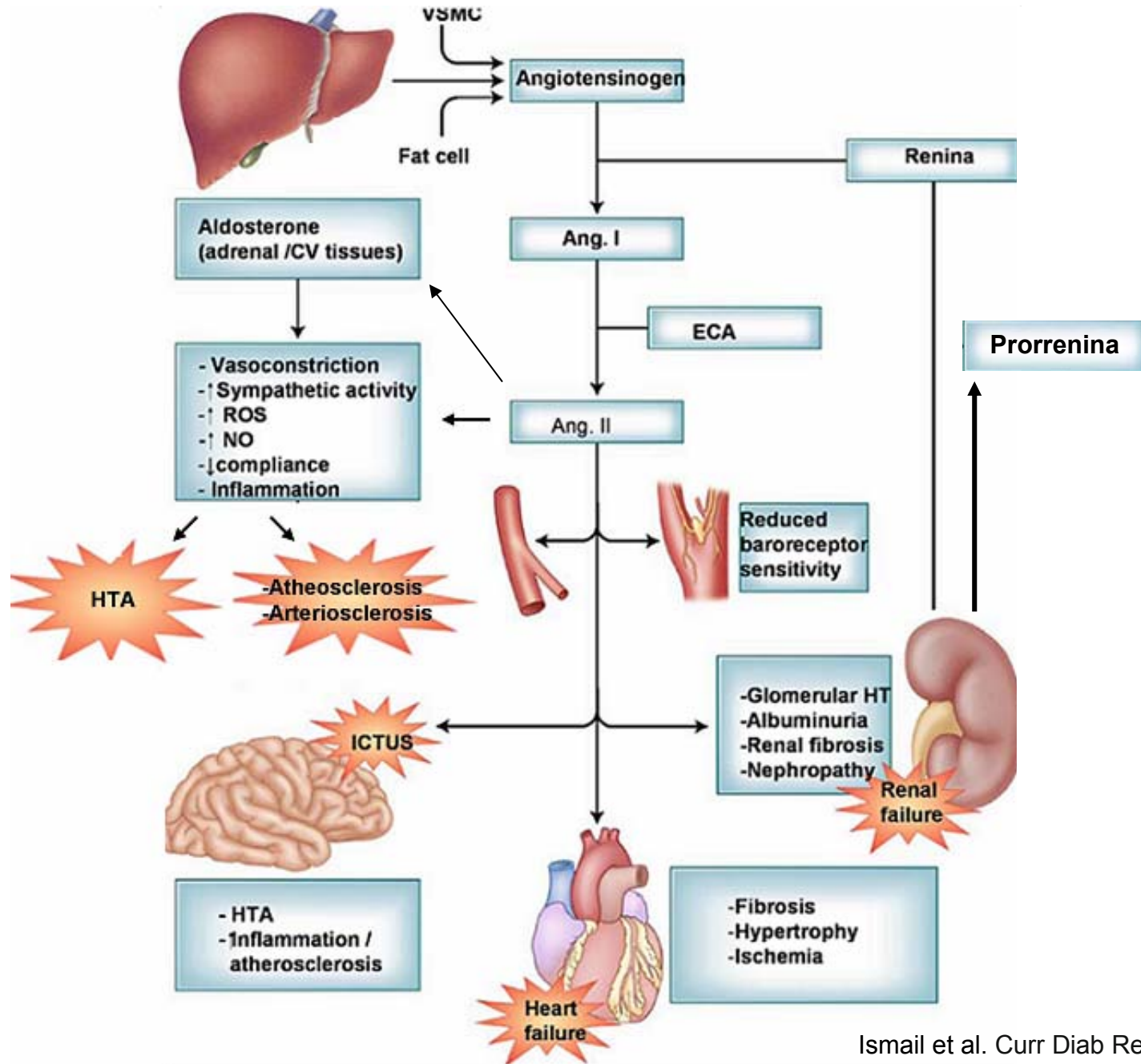
Valores plasmáticos de renina y prorrenina en la diabetes mellitus

N:- diabetes:- 18 tipo1
-17 tipo 2
-Controles sanos:69

μU/ml

Renina activa

* :p<0,01

16 —
14 —
12 —
10 —
8 —
6 —

Control — diabetes 1 — Diabetes 2

μU/ml

Prorrenina

200 —
170 —
140 —
110 —
80 —
50 —

Control — diabetes 1 — diabetes 2

Pablo Gómez
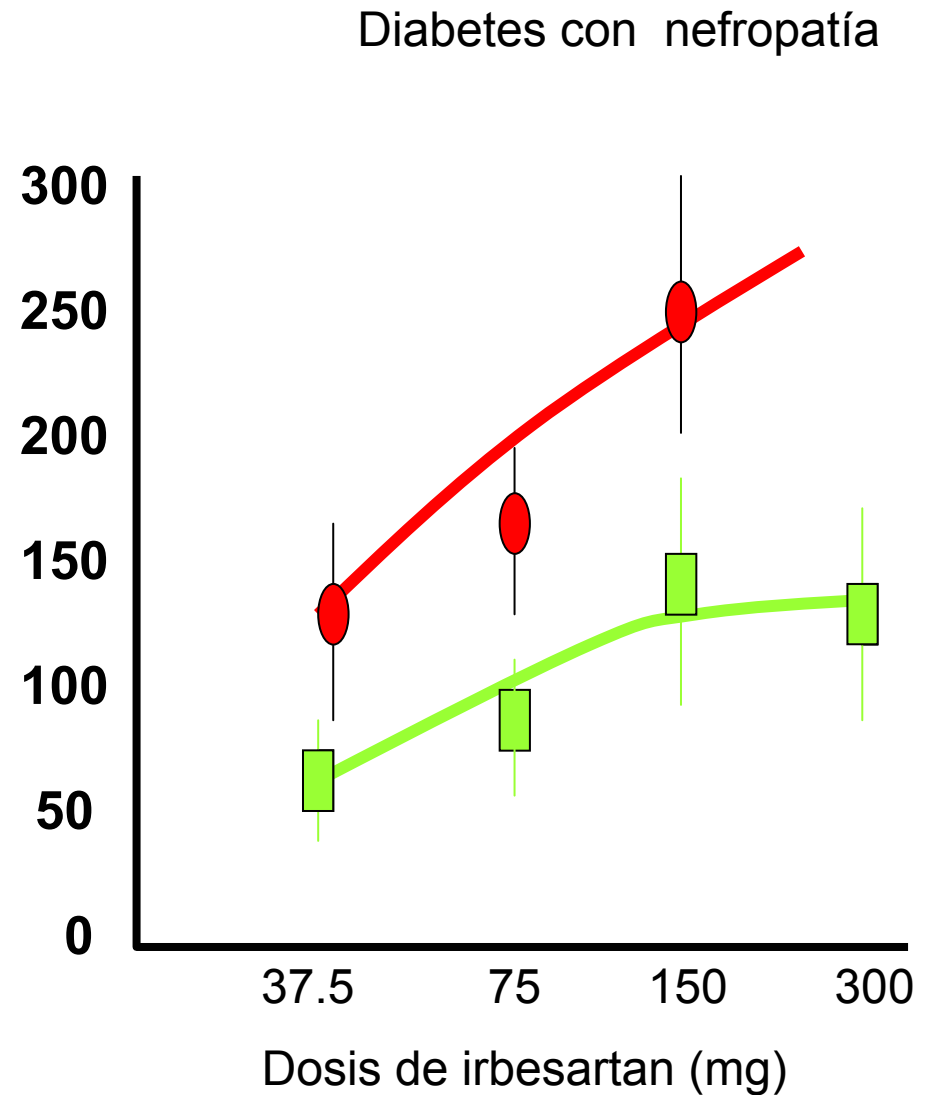Hospital de Jerez

Stankovic et al J Am Soc Nephroll 17:3293,2006

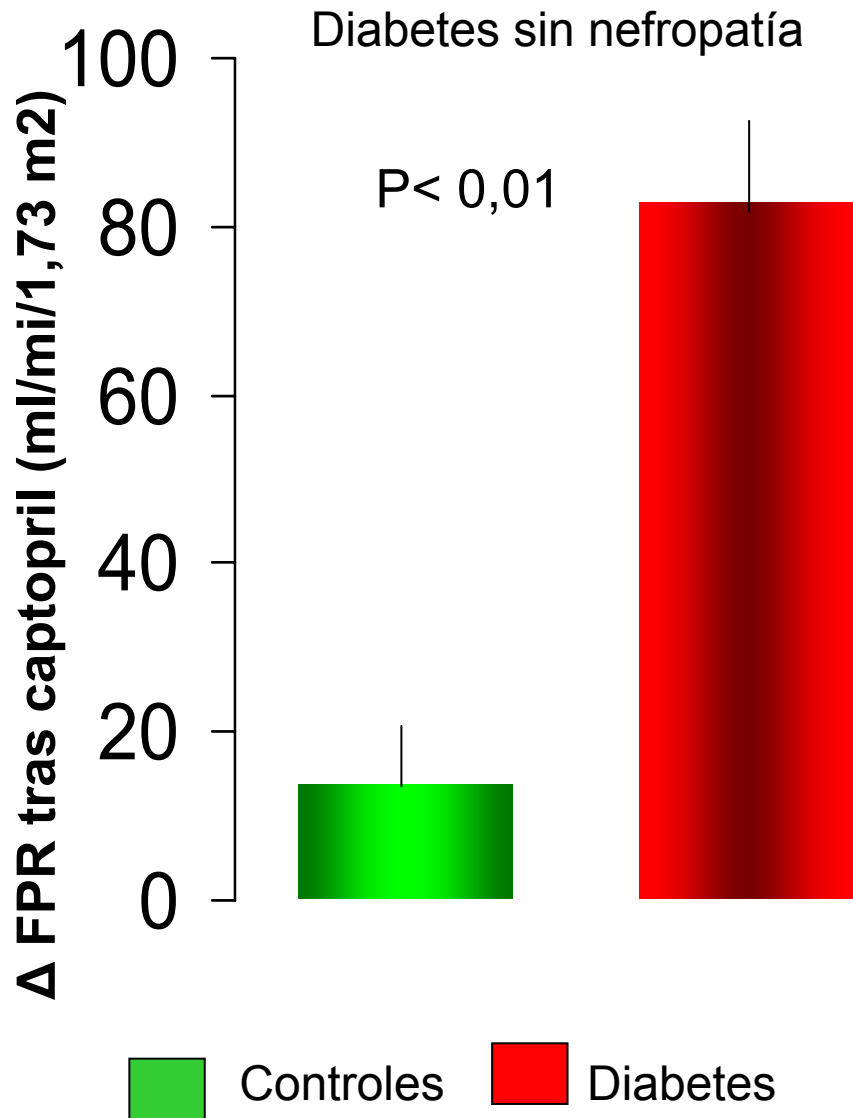# Efectos catalíticos y no catalíticos de la prorrenina activada tras su unión al receptor (pro)renina

SRA circulante , tisular e intracelular

Angiotensina 12
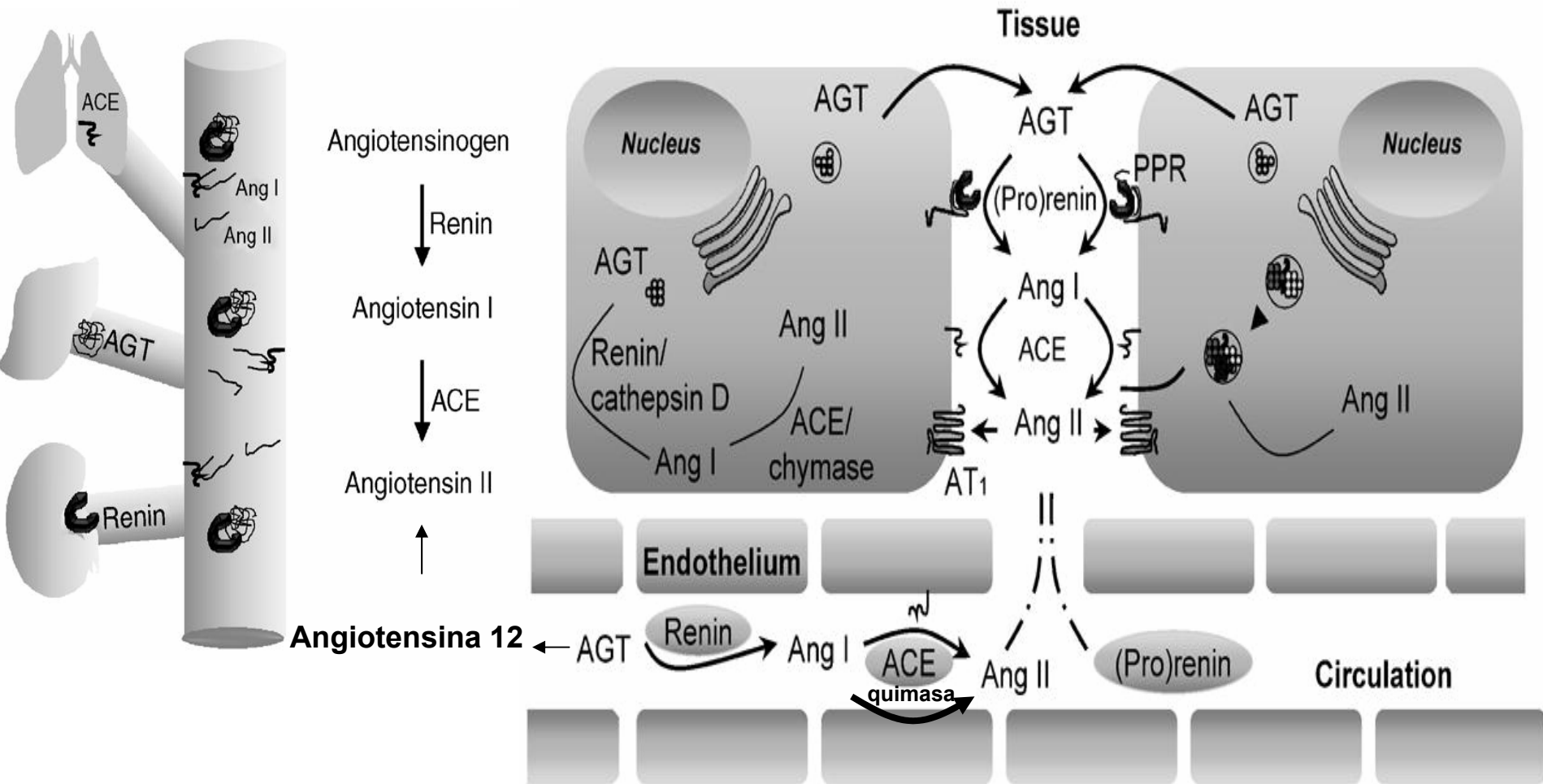
Respuesta hemodinámica renal a IECA y ARA2 en diabetes mellitus

Diabetes sin nefropatía

Diabetes con nefropatía

P< 0,01

Δ FPR tras captopril (ml/mi/1,73 m2)

Dosis de irbesartan (mg)

Controles   Diabetes

Pablo Gómez
Hospital de Jerez

Stankovic et al J Am Soc Nephroll 17:3293,2006

Price et al J Am Soc Nephrol 10:2382-2391, 1999

Efectos de hiperglucemia en RAS intracelular

RAS en miocardiocitos

RAS en podocitos

Disminucion de nefrina
Apoptosis → albuminuria

Singh et al Am J Physiol Heart Circ Physiol 293:H939,2007
Durvasula et al Am J Physiol renal Physiol 294,F830,2007

Pablo Gómez
Hospital de Jerez
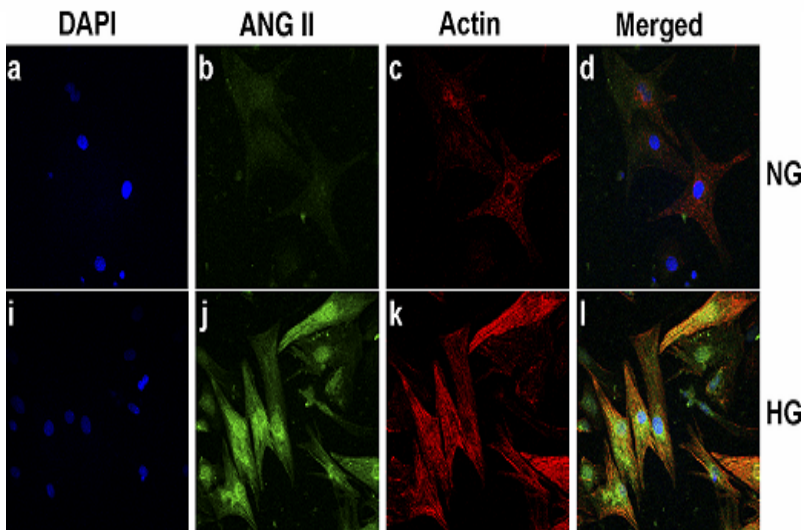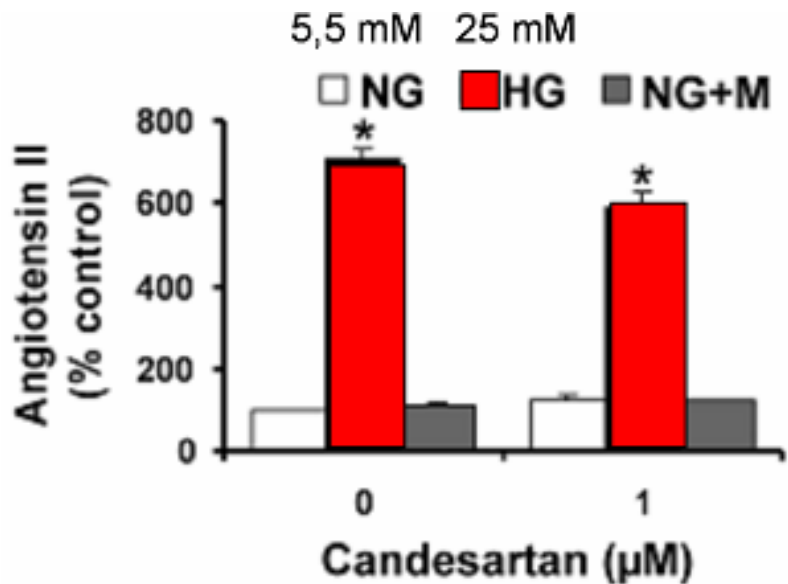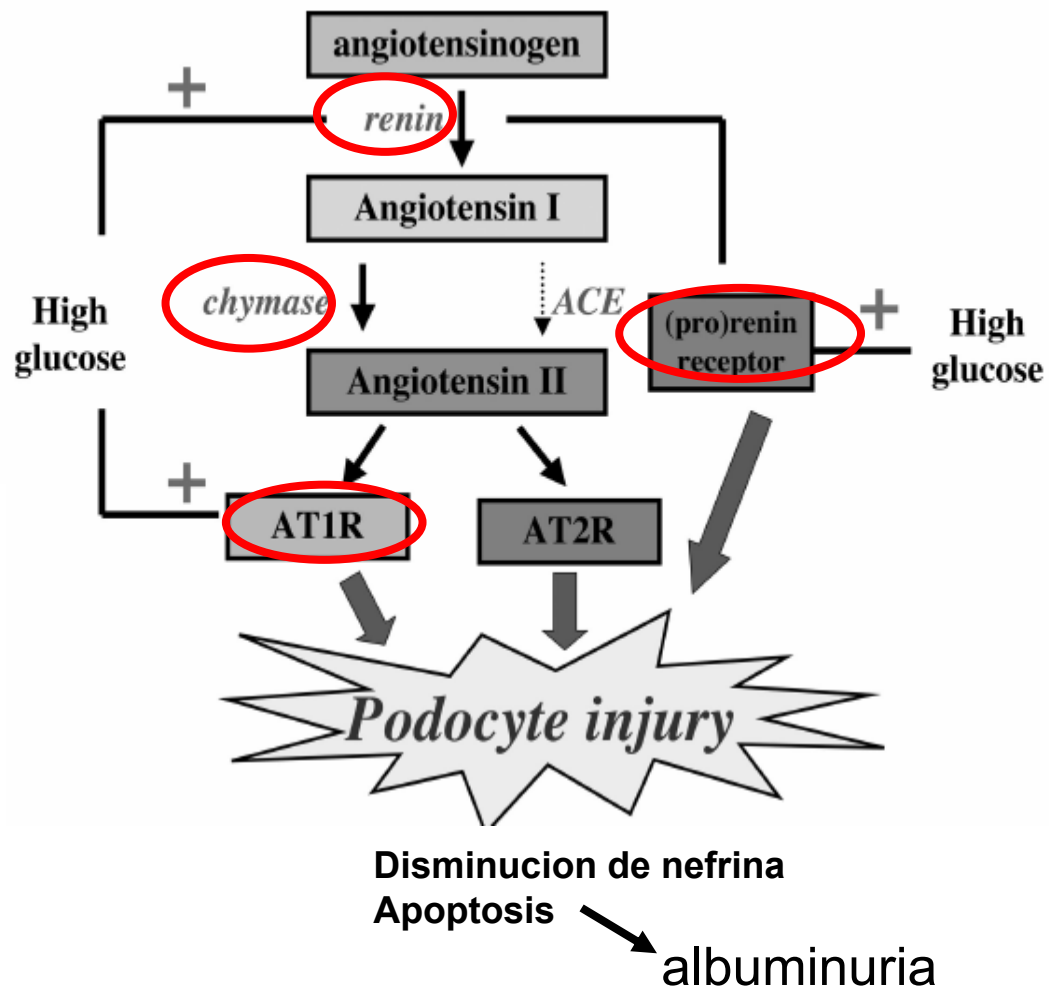
Si hiperglucemia se asocia a un aumento de SRA tisular ,y la A$_{II}$ induce daño vascular ,la terapia con bloqueantes /moduladores del SRA podría ser beneficiosa en todos los diabéticos………………..

Pablo Gómez
Hospital de Jerez

Guión

- Riesgo vascular en diabetes mellitus

- Implicación del SRA en el daño vascular del diabético

- **Evidencias de protección vascular con bloqueantes del SRA en la diabetes mellitus tipo 2**

Pablo Gómez
Hospital de Jerez

Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes

CE Mogensen

Abstract

We studied whether microalbuminuria (30 to 140 micrograms of albumin per milliliter) would predict the later development of increased proteinuria and early mortality in Type II diabetics. During 1973, morning urine specimens of diabetic clinic patients 50 to 75 years of age whose disease had been diagnosed the age of 45 were examined for albumin level by radioimmunoassay. Seventy-six patients with albumin concentrations of 30 to 140 micrograms per milliliter were identified for long-term follow-up. They were compared with normal controls, diabetic patients with lower albumin concentrations (75 patients with concentrations less than 15 micrograms per milliliter and 53 with concentrations of 16 to 29 micrograms per milliliter), and 28 diabetic patients with higher concentrations (greater than 140). Age, duration of diabetes, treatment method, fasting blood glucose level, blood pressure, height, and weight were determined for the four diabetic groups. After nine years the group with albumin concentrations of 30 to 140 micrograms per milliliter was more likely to have clinically detectable proteinuria (greater than 400 micrograms per milliliter) than were the groups with lower concentrations. Mortality was 148 per cent higher in this group than in normal controls--comparable to the increase (116 per cent) in the group with heavy proteinuria (albumin levels greater than 140 micrograms per milliliter). In addition, mortality was increased 76 per cent in the group with albumin levels of 16 to 29 micrograms per milliliter and 37 per cent in the group with levels below 15. We conclude that microalbuminuria in patients with Type II diabetes is predictive of clinical proteinuria and increased mortality
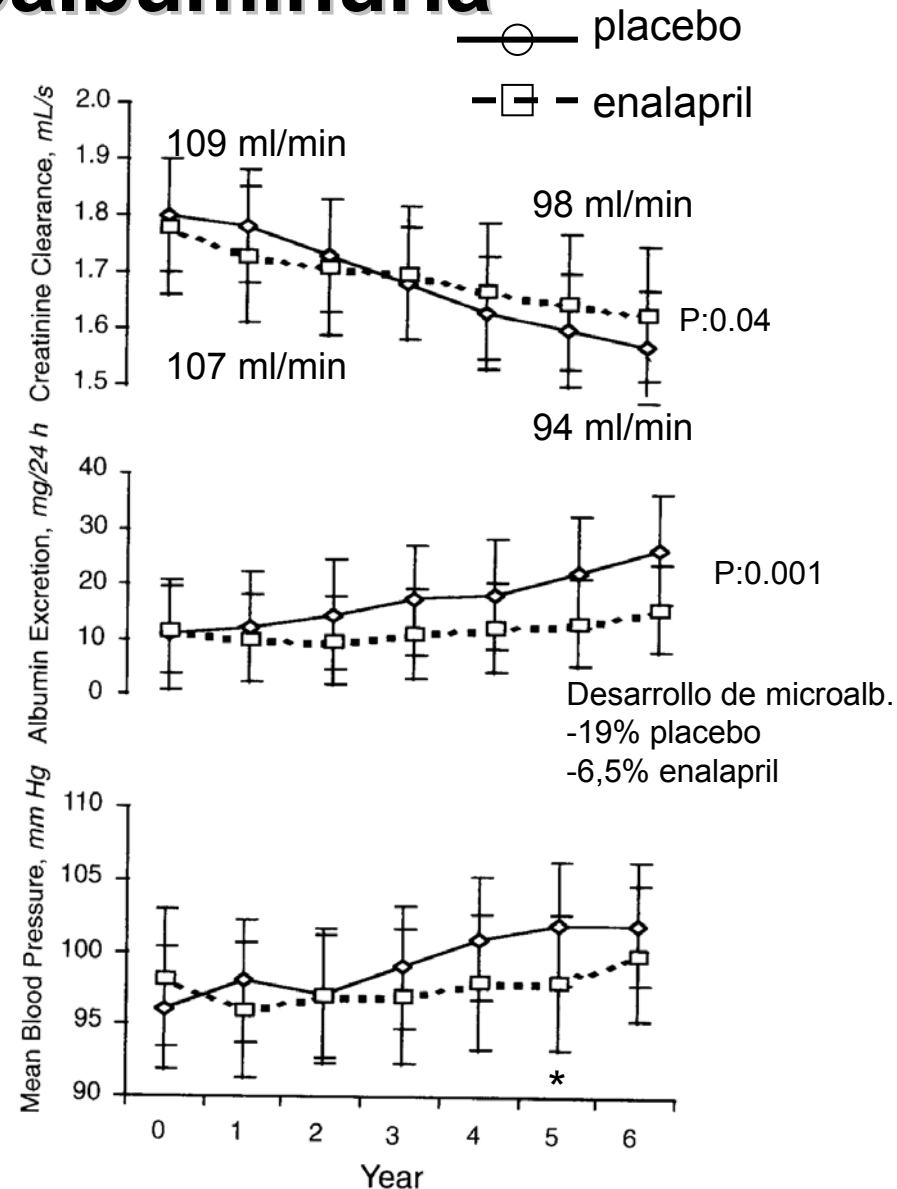
Mortalidad a los 9 años
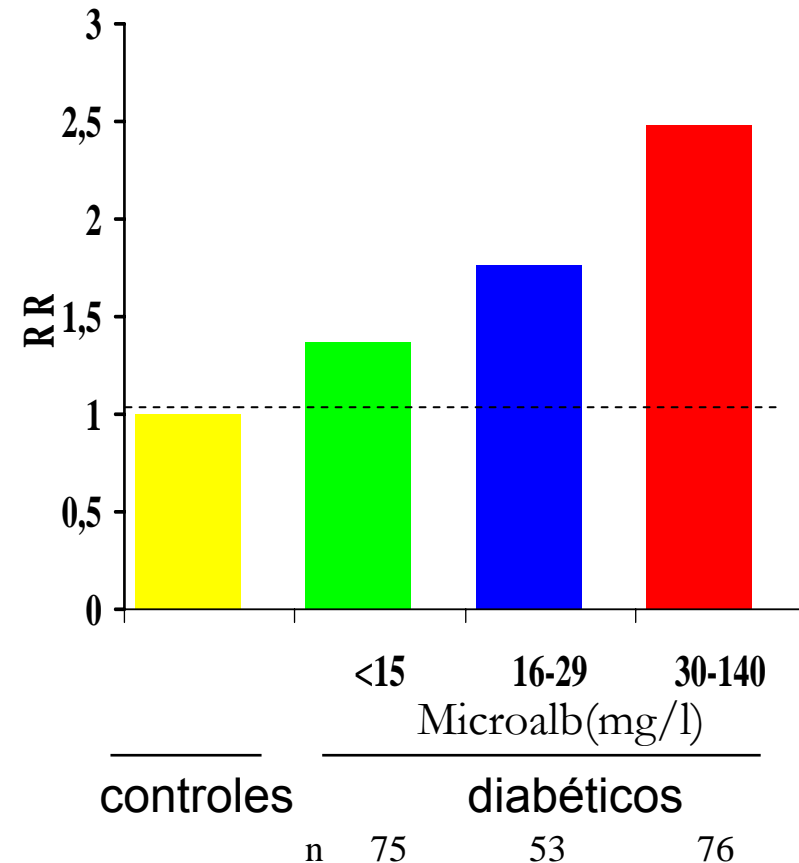
Bloqueo del SRA en la diabetes mellitus tipo 2

Normotensos normoalbuminúricos

-Ravid et al. Use of enalapril to attenuate decline in renal fucntion in normotensive , normoalbuminuric patients with type 2 diabetes mellitus Ann Intern Med 1998

-Schrier R,Estacio R,Esler A,Mehler P.Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes.Kidney Intern. 61:1086-1097,2002

-Bilous et al.Effect of candesartn on microalbumnuria and albumin excretion rate in diabetes . Ann Intern Med 151:11,2009.

- ROADMAP (incluye normo e hipertensos) (San Diego 2010)

Pablo Gómez
Hospital de Jerez

Bloqueo del SRA en diabetes normotensión y normoalbuminuria

- 156 sujetos con diabetes mellitus, normotension (<140 / 90 mmHg) y normoalbuminuria (< 30 mg /24 h)
- Edad: 55.
- Duración de diabetes : 6 años
- Randomización a Enalapril 10 mg/d vs placebo
- Seguimiento 6 años
- Modificación de Ccreat y albuminuria

placebo
enalapril

109 ml/min
98 ml/min
107 ml/min
94 ml/min
P:0.04

P:0.001

Desarrollo de microalb.
-19% placebo
-6,5% enalapril

Pablo Gómez
Hospital de Jerez

Ravid et al Ann Intern Med 128,1998

Proporción acumulativa de microalbuminuria
(Programa DIRECT)

DIRECT-2(n:1.905)
PAS: 123±9 mmHg
PAD: 75±6 mmHg

P = 0.60
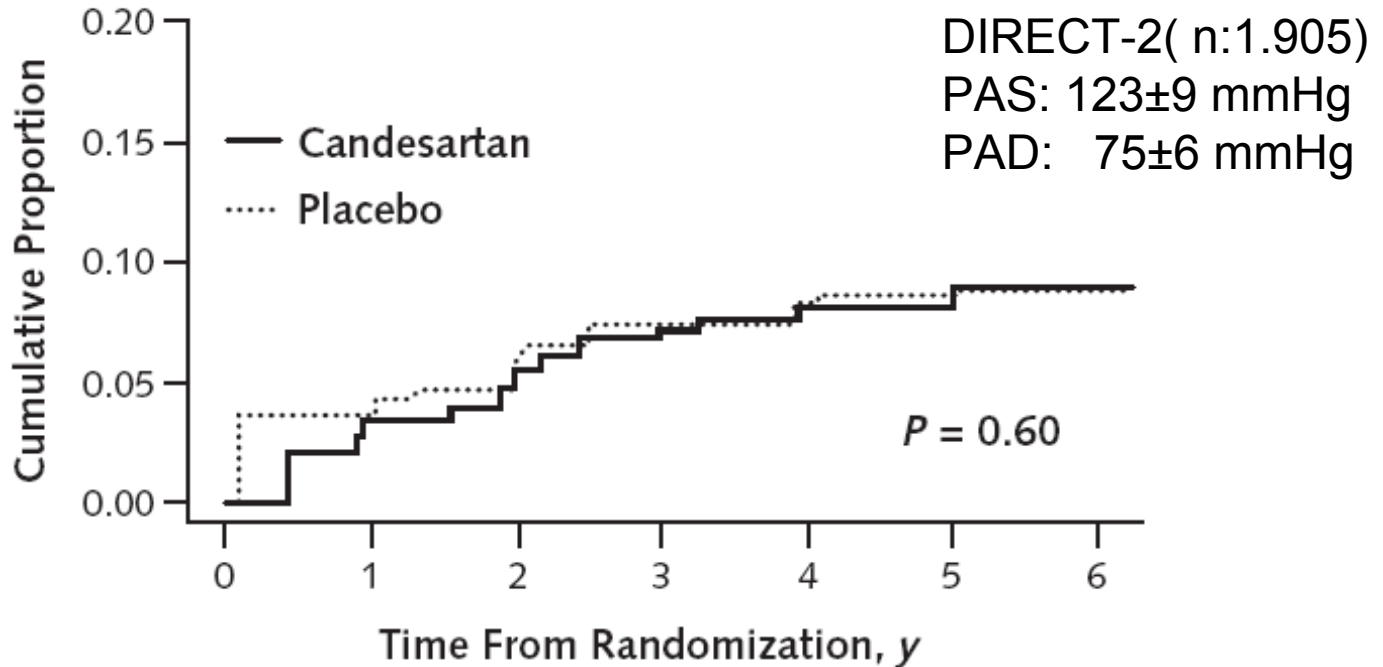
At risk, *n*

Placebo	2618	2410	2247	2092	1754	526	15
Candesartan	2613	2426	2278	2150	1793	540	13

DIRECT-Protect 2

Antihypertensive use at baseline

Incidence of microalbuminuria per 1000 patient-years (95% CI)	36 (28.7–44.7)	36 (28.4–44.5)	1.01 (0.74–1.39)
Least-squares mean of annual rate of change in UAER (95% CI), μg/min	0.68 (0.60–0.76)	0.73 (0.66–0.81)	0.95 (0.85–1.06)

Normotensive at baseline

Incidence of microalbuminuria per 1000 patient-years (95% CI)	29 (21.2–39.4)	40 (30.5–52.6)	0.73 (0.48–1.10)
Least-squares mean of annual rate of change in UAER (95% CI), μg/min	0.62 (0.57–0.67)	0.69 (0.65–0.74)	0.93 (0.87–0.99)

Desarrollo de microalbuminuria en normotensos:
-Candesartan …..14%   ns
-Placebo…………..17%

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Hospital de Jerez

Bilous et al Ann Intern Med 151:11,2009.

Normotensos normoalbumínuricos

GUIAS

No se contempla en las guías la prevención de la microalbuminuria en Diabéticos tipo 2 normotensos

Pablo Gómez
Hospital de Jerez

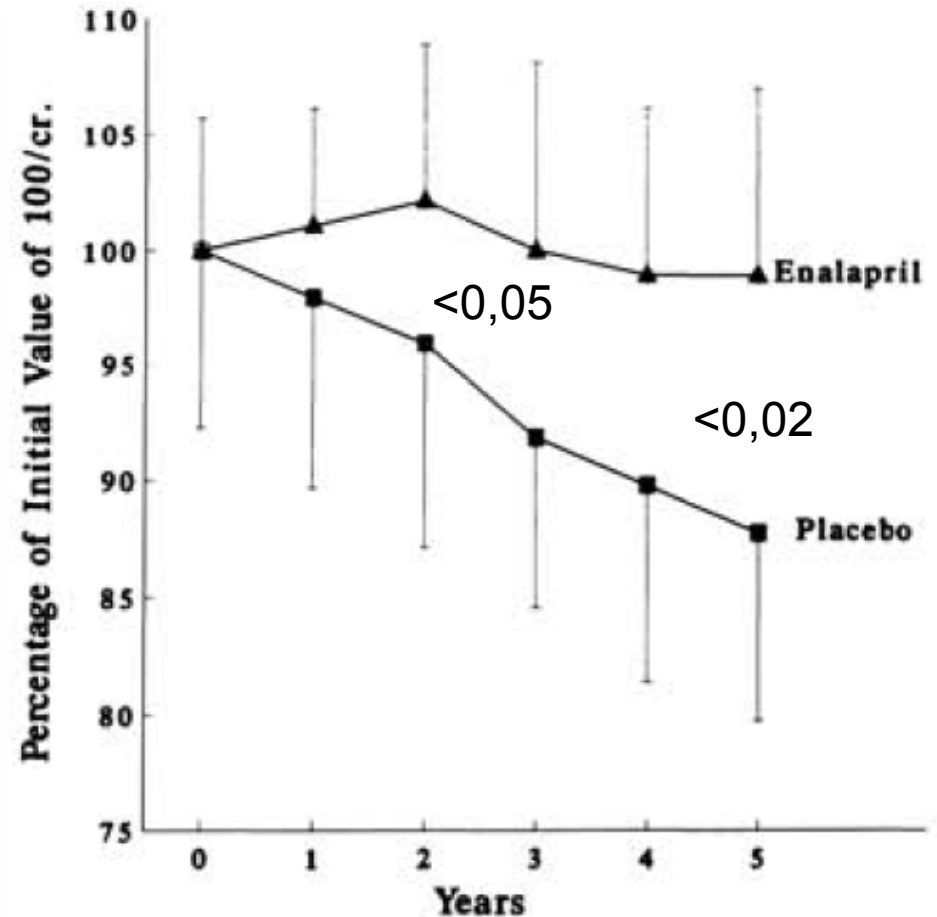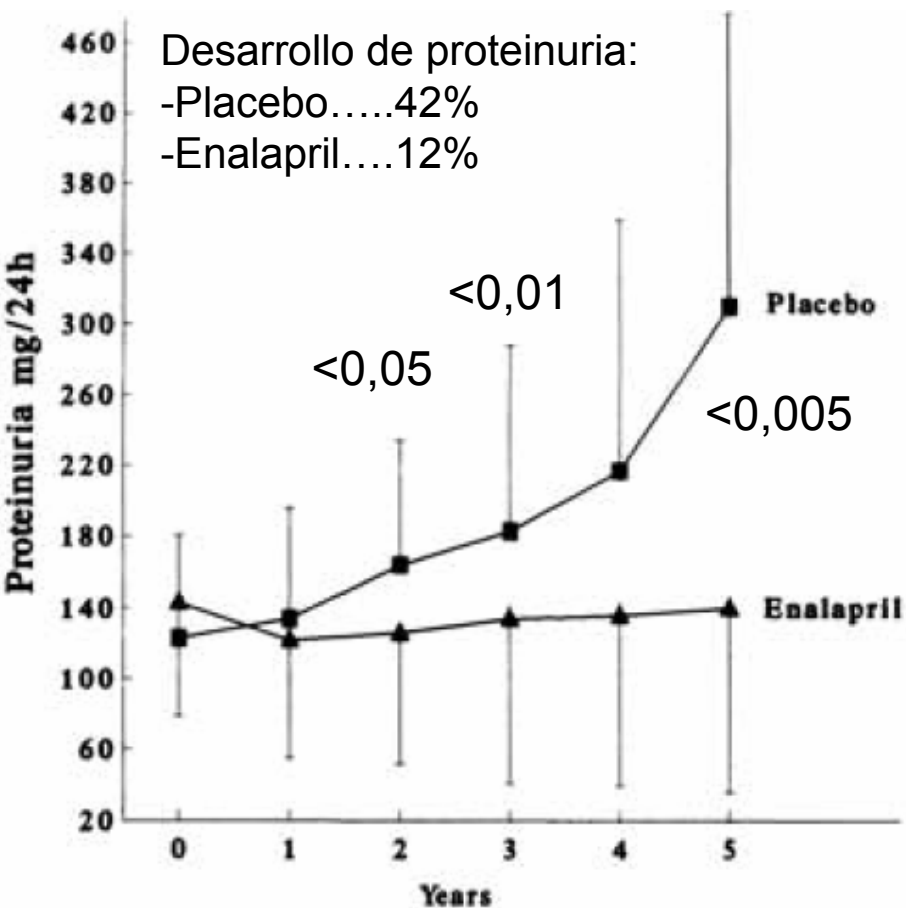# Bloqueo del SRA en la diabetes mellitus tipo 2

Normotensos microalbuminúricos

-Ravid M, et al.Long term stabilizing effect of angiotensin converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type 2 diabetic patients.Ann Intern Med 118,577-581,1993

-Sano T, Hotta N, Kawamura T, et al: Effects of long-term enalapril treatment on persistent microalbuminuria in normotensive type 2 diabetic patients: Results of a 4-year, prospective, randomized study . Diabet Med 13:120-124,1996.

-Zandbergen et al Effect of losartan on microalbuminria in normotensive patientswith type 2 diabetes melitus.A randomized clnical trial Ann Intern Med 130:90,2003.

Pablo Gómez
Hospital de Jerez

Efecto de IECA en diabetes tipo 2 con normotensión y microalbuminuria

-n :94
-Edad 44 años
-Duracion de diabetes :6,5 años
-PAM: 99 mmHg
-HbA1C 10,4%
-Randomización a Enalapril 10 mg /placebo

Desarrollo de proteinuria:
-Placebo…..42%
-Enalapril….12%

Pablo Gómez
Hospital de Jerez

Ravid et al Ann Intern Med 118,577,1993

Bloqueo del SRA en la diabetes mellitus tipo 2

Normotensos microalbuminúricos GUIAS

2007 Guidelines for the Management of Arterial Hypertension

The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

Microalbuminuria should prompt the use of antihypertensive drug treatment also when initial BP is in the high normal range. Blockers of the renin-angiotensin system have a pronounced antiproteinuric effect and their use should be preferred.

NKF KDOQI GUIDELINES
Published KDOQI Guidelines Are Available Online
www.kdoqi.org

© 2007 National Kidney Foundation, Inc.

Treatment with an ACE inhibitor or an ARB may be considered in normotensive people with diabetes and microalbuminuria. (C)

Standards of Medical Care in Diabetes—2011

AMERICAN DIABETES ASSOCIATION

No se contempla

Pablo Gómez
Hospital de Jerez

Bloqueo del SRA en la diabetes mellitus tipo 2

Diabetes + HTA

-Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39 UK Prospective Diabetes Study Group.BMJ 317,713,1998

-Estacio R,et al.The effect of nisoldipine comapred with enlapril on cardiovascuolar outcomes in patienst with non insulin.ddependent diabetes and hypertension N Engl J Med.338:645,1998**.**

-Hansson Let al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial .Lancet 353: 611–16,1999

-Tatti P,et al Outcome Results of the Fosinopril Ve r s u s Amlodipine Cardiovascular Events Randomized Trial (FACET) in Patients.With Hypertension and NIDDM. Diab Care 21,597,1998

-Lindholm et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol Lancet 359,1004,2002.
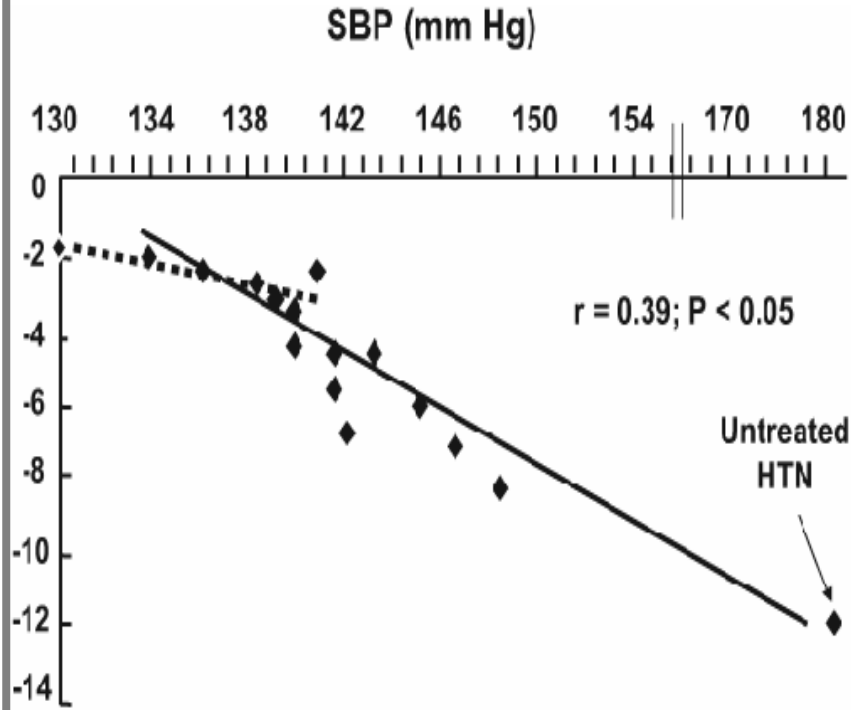
-Ruggenenti et al.Preventing Microalbuminuria in Type 2 Diabetes N Eng J Med 351,2004

Pablo Gómez
Hospital de Jerez

El descenso de la PA reduce eventos vasculares y la disminución del FG

RR de eventos y diferencia de PA
Metaanálisis ;30 ensayos,n:221.024
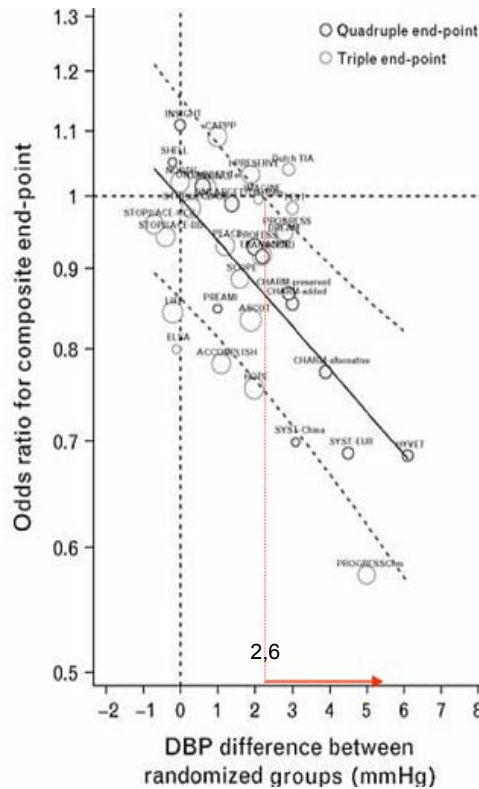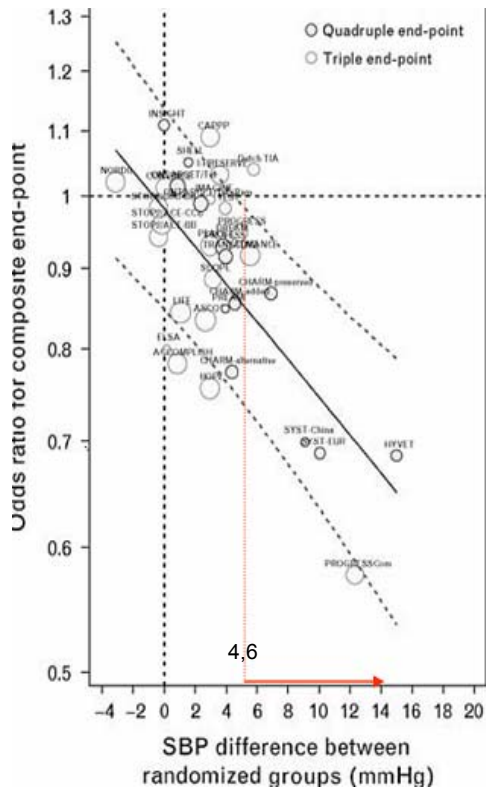
Relación entre PAS conseguida y FG en ensayos controlados

o :ICTUS, IM, muerte CV

O :ICTUS, IM. muerte CV,IC

↓ 5 mmHg de PAS → RRR 13%

↓ 2 mmHg de PAD → RRR 12%

-Parving HH et al. *Br Med J*, 1989
-Viberti GC et al. *JAMA*, 1993
-Lewis EJ et al. *N Engl J Med*, 1993
-Lebovitz H et al. *Kidney Int*. 1994
-Bakris GL et al. *Kidney Int*, 1996
-Bakris GL *Hypertension*. 1997
-Estacio R et al. *Diabetes Care*, 2000
-Lewis EJ et al. *N Engl J Med*, 2001
-Bakris, GL et al. *Arch Intern Med*, 2003

Pablo Gómez
Hospital de Jerez

Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39

-N: 758;edad 56 años

-Duración diabetes : 2,6 años

-PA inicio 159/94 mmHg

-Microalb 16%;proteinuria 2%

-Segui. 9 años

-Objetivo de PA :<150/85
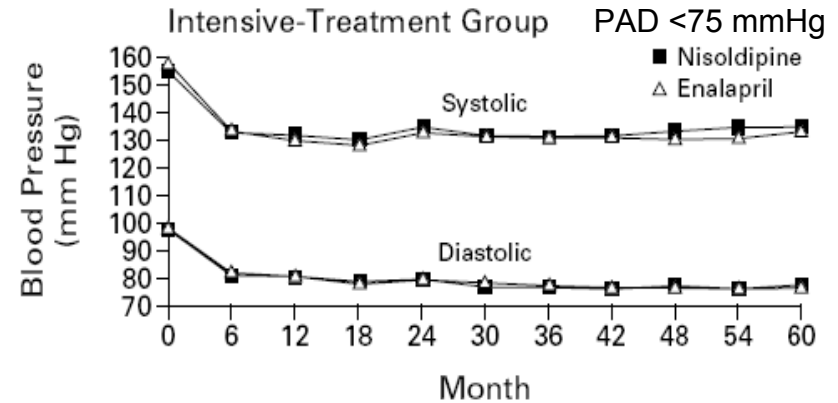
-PA final : Capt. 144/83

         Aten .143/81

Variables : -Eventos relacionados con diabetes
- Muertes relacionadas con diabetes
- Muerte de cualquier causa
- Eventos CV
- Complicaciones microvasculares

Clinical end point	Patients with aggregate end points		Absolute risk (events per 1000 patient years)		P value	Relative risk for captopril (95% CI)
	Captopril (n=400)	Atenolol (n=358)	Captopril	Atenolol		
Any diabetes related end point	141	118	53.3	48.4	0.43	1.10 (0.86 to 1.41)
Deaths related to diabetes	48	34	15.2	12.0	0.28	1.27 (0.82 to 1.97)
All cause mortality	75	59	23.8	20.8	0.44	1.14 (0.81 to 1.61)
Myocardial infarction	61	46	20.2	16.9	0.35	1.20 (0.82 to 1.76)
Stroke	21	17	6.8	6.1	0.74	1.12 (0.59 to 2.12)
Peripheral vascular disease	5	3	1.6	1.1	0.59	1.48 (0.35 to 6.19)
Microvascular disease	40	28	13.5	10.4	0.30	1.29 (0.80 to 2.10)

0.1   1   10
Favours captopril   Favours atenolol

Pablo Gómez
Hospital de Jerez
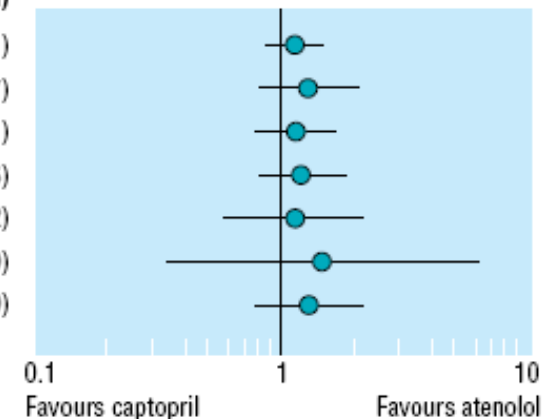
Appropriate Blood Pressure Control in diabetes (ABCD study) (Hypertensive patients)

- N:470
- PAD≥90 mmH.(155/98mmHg)
- Duración diabetes: 9 años
- Edad:59 años
- ECV 51%;HVI 30%,proteinuria 18%.
- Objetivo 1º: Cambio de Clcreat
- Objetivo 2º: Eventos CV; retinopatia albuminuria, neuropatía, HVI

Intensivo — Enalapril / Nisoldipino

Moderado — Enalapril / Nisoldipino

Intensive-Treatment Group   PAD <75 mmHg
- ■ Nisoldipine
- △ Enalapril

No. of patients 237   189   199   176   166   137

Moderate-Treatment Group   PAD 80-89 mmHg
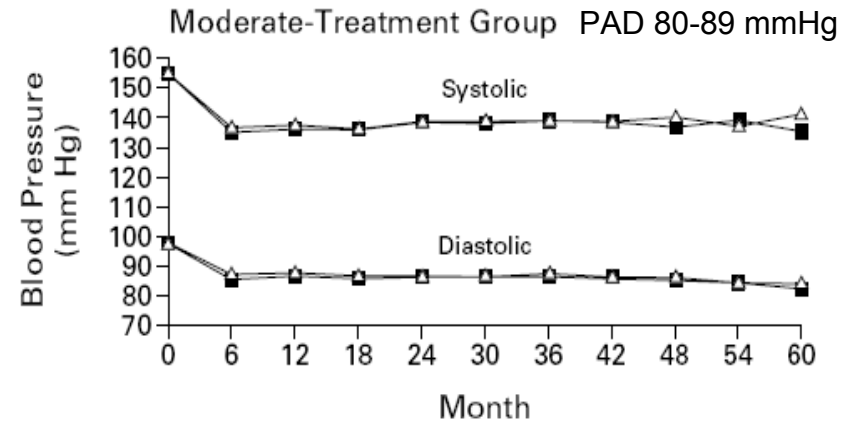
No. of patients 233   178   183   161   161   114

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Hospital de Jerez

Estacio et al N Engl J Med 338:645,1998
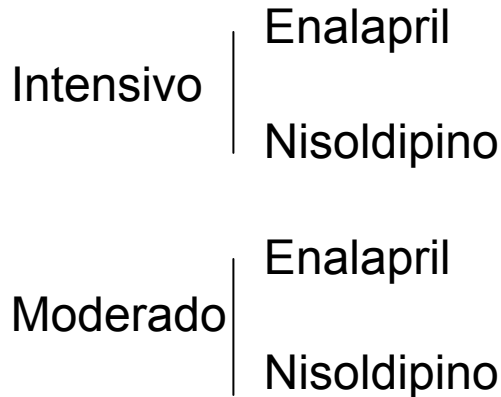
Appropriate Blood Pressure Control in diabetes (ABCD study)

LOGISTIC-REGRESSION ANALYSES OF CARDIOVASCULAR OUTCOMES AND TOTAL DEATHS, ACCORDING TO TREATMENT GROUP.*

OUTCOME	NISOLDIPINE (N = 235)	ENALAPRIL (N = 235)	RISK RATIO (95% CI)	ADJUSTED RISK RATIO (95% CI)†
Fatal or nonfatal myocardial infarction	25	5	5.5 (2.1–14.6)	7.0 (2.3–21.4)
Nonfatal myocardial infarction	22	5	4.8 (1.8–12.8)	5.9 (1.9–18.2)
Cerebrovascular accident	11	7	1.6 (0.6–4.2)	2.2 (0.7–7.1)
Congestive heart failure	6	5	1.2 (0.4–4.0)	1.3 (0.3–5.9)‡
Death from cardiovascular causes	10	5	2.0 (0.7–6.1)	1.4 (0.4–5.1)
Death from any cause	17	13	1.3 (0.6–2.8)	1.0 (0.4–2.3)

Pablo Gómez
Hospital de Jerez

Bloqueantes del SRA en diabéticos con HTA e HVI
Estudio LIFE, n 1.195

-Edad: 68 años
-ECV 35%
-PA inicio 177/96 mmHg
-PA final: Losartan: 146/79 mmHg
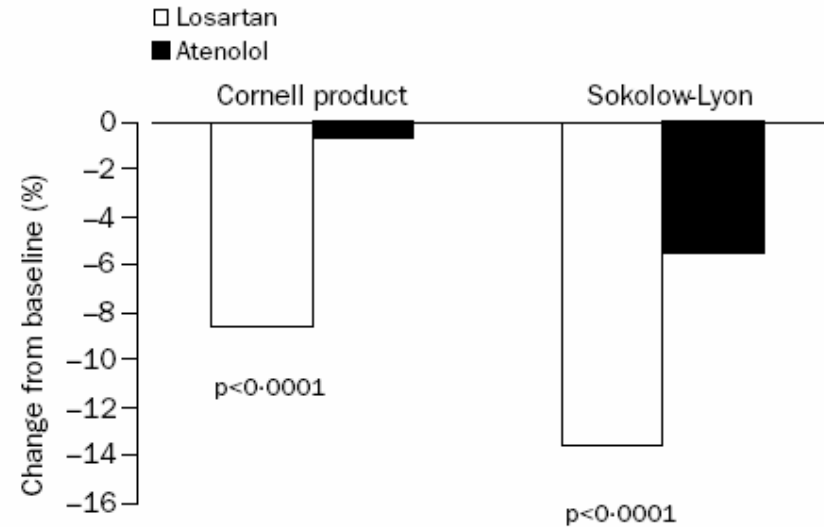   Atenolol : 148/79 mmHg

% reducción índices de HVI

-Muerte CV
-IM
-ICTUS

Primary composite endpoint

— Atenolol
--- Losartan

Proportion of patients with first event (%)

* ARR: 24·5%, p=0·031
URR: 26·7%, p=0·017

Time (months)
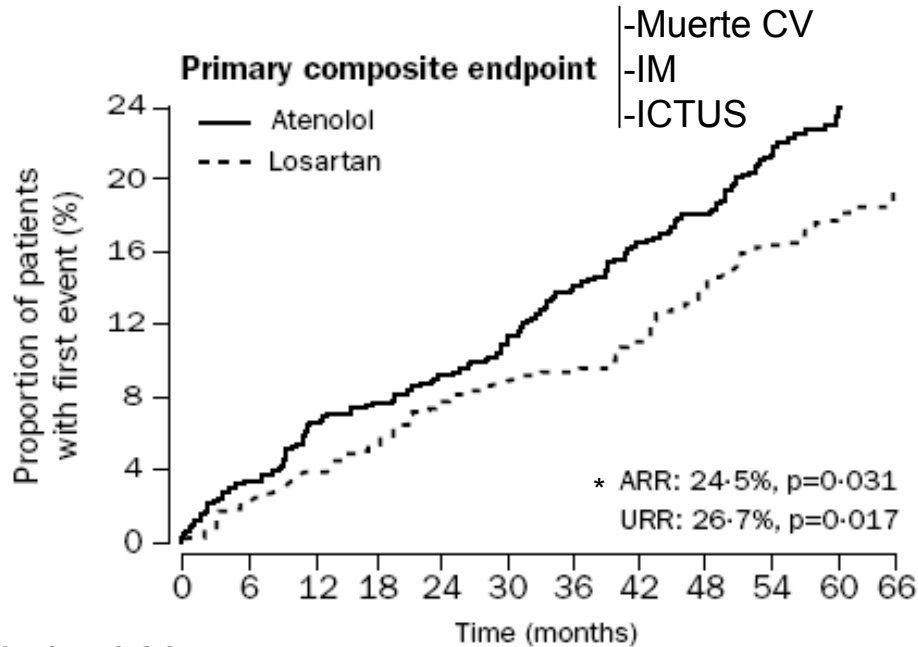
Number at risk

	0	6	12	18	24	30	36	42	48	54	60	66
Losartan	586	569	558	548	532	520	513	501	484	459	237	127
Atenolol	609	588	562	552	540	527	507	486	472	434	204	99

*Ajustado a riesgo Framingham

□ Losartan
■ Atenolol

Cornell product   Sokolow-Lyon

Change from baseline (%)

p<0·0001   p<0·0001

% sujetos con proteinuria

■ **Losartan**
■ **Atenolol**

<0,002

basal   1   2   3   4   5

año

Pablo Gómez
Hospital de Jerez

Lindholm et al Lancet 359:1004,2002
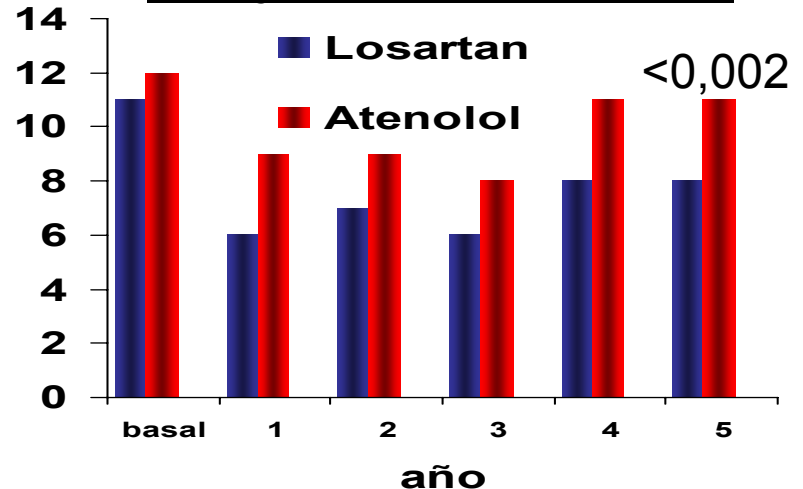
Efecto de IECA en desarrollo de microalbuminuria en diabetes Tipo 2 con HTA* (BENEDICT)

* PA ≥130/85 o en terapia antiHTA

- n:1.204
- Edad 62 años
- Duración diabetes 8 años
- Rand. Tran-Ver; Tran;Placeb
- Seg. 3,6 años (mediana)
- PA inicio 151/87 mmHg
- PA final   139/81 mmHg
- Variable 1ª:

  Desarrollo de microalb persistente

Ruggenenti et al N Eng J Med 351:1941,2004
Sharma et al Vas Health and Risk maneg 2007

Pablo Gómez
Hospital de Jerez
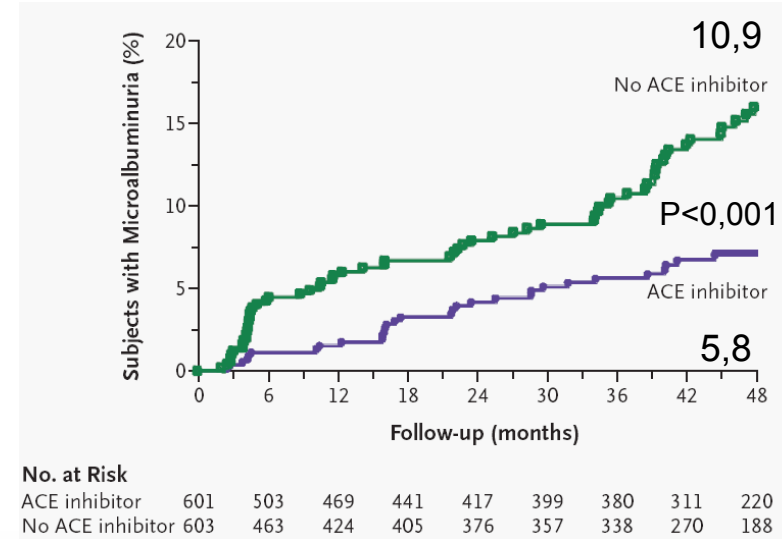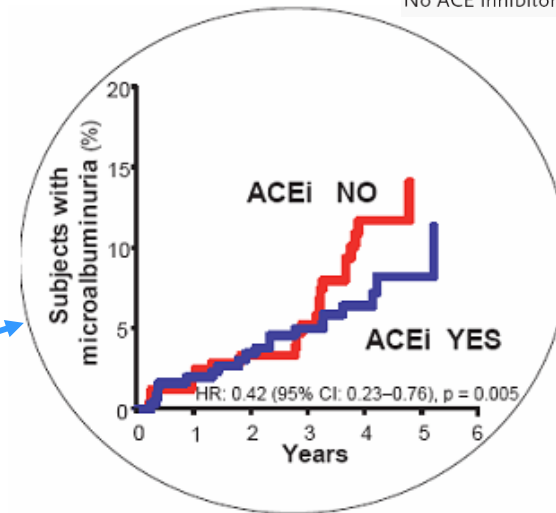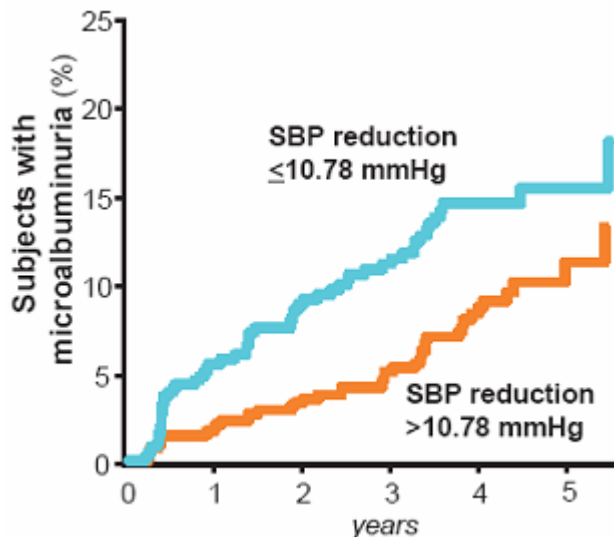
Bloqueo del SRA en la diabetes mellitus tipo 2

Diabetes + HTA
GUIAS

2007 Guidelines for the Management of Arterial Hypertension

The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

Box 14 Antihypertensive treatment in diabetics

-To lower BP, all effective and well tolerated drugs can be used. A combination of two or more drugs is frequently needed.

-Available evidence indicates that lowering BP also exerts a protective effect on appearance and progression of renal damage. Some additional protection can be obtained by the use of a blocker of the renin-angiotensin system (either an angiotensin receptor antagonist or an ACE inhibitor).

- A blocker of the renin-angiotensin system should be a regular component of combination treatment and the one preferred when monotherapy is sufficient.

Standards of Medical Care in Diabetes—2011

AMERICAN DIABETES ASSOCIATION

1. Hypertension/blood pressure control

-Patients with more severe hypertension (systolic blood pressure 140 or diastolic blood pressure 90 mmHg) at diagnosis or follow-up should receive pharmacologic therapy in addition to lifestyle therapy. (A)

-Pharmacologic therapy for patients with diabetes and hypertension should be with a regimen that includes either an ACE inhibitor or an ARB. If one class is not tolerated, the other should be substituted. If needed to achieve blood pressure targets, a thiazide diuretic should be added to those with an estimated GFR (eGFR) > 30 ml/min/1.73 m2 and a loop diuretic for those with an eGFR ≤30 ml/min/1.73 m2. (C)

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Bloqueo del SRA en la diabetes mellitus tipo 2

Diabetes + HTA+Afectación renal

-Parving et al . The effect of irbesartan on the development of diabetic nephropathy n patients with type 2 diabetes. N Eng J Med 345,870,2001

-Lewis et al Renoprotective effects of the angiotensin –receptor antagonist irbesartan inpatients with nephropathy due to type 2 diabetes .N Engl J Med 345,851,2001

-Brenner et al .Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Eng J Med 345,869,2001

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En diabetes tipo 2 con HTA* y microalbuminuria, irbesartan disminuye la aparición de proteinuria .

*>135/85 mmHg

RRR=70%
P=0,0004

RRR=39%
P=0,085

- N: 590;edad:58
- Duración diabetes:10 años
- Enf CV :23%
- Retinopatía: 45%
- PA 153/90 mmHg
- Creat. 1,1 mg/dl
- Seg. 2 años

Pacientes (%)

14,9

9,7

5,2

18
16
14
12
10
8
6
4
2
0

Control
(n=201)

150 mg
(n=195)

300 mg
(n=194)

Irbesartan

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Parving H-H, et al. N Engl J Med 2001; 345: 870-878.
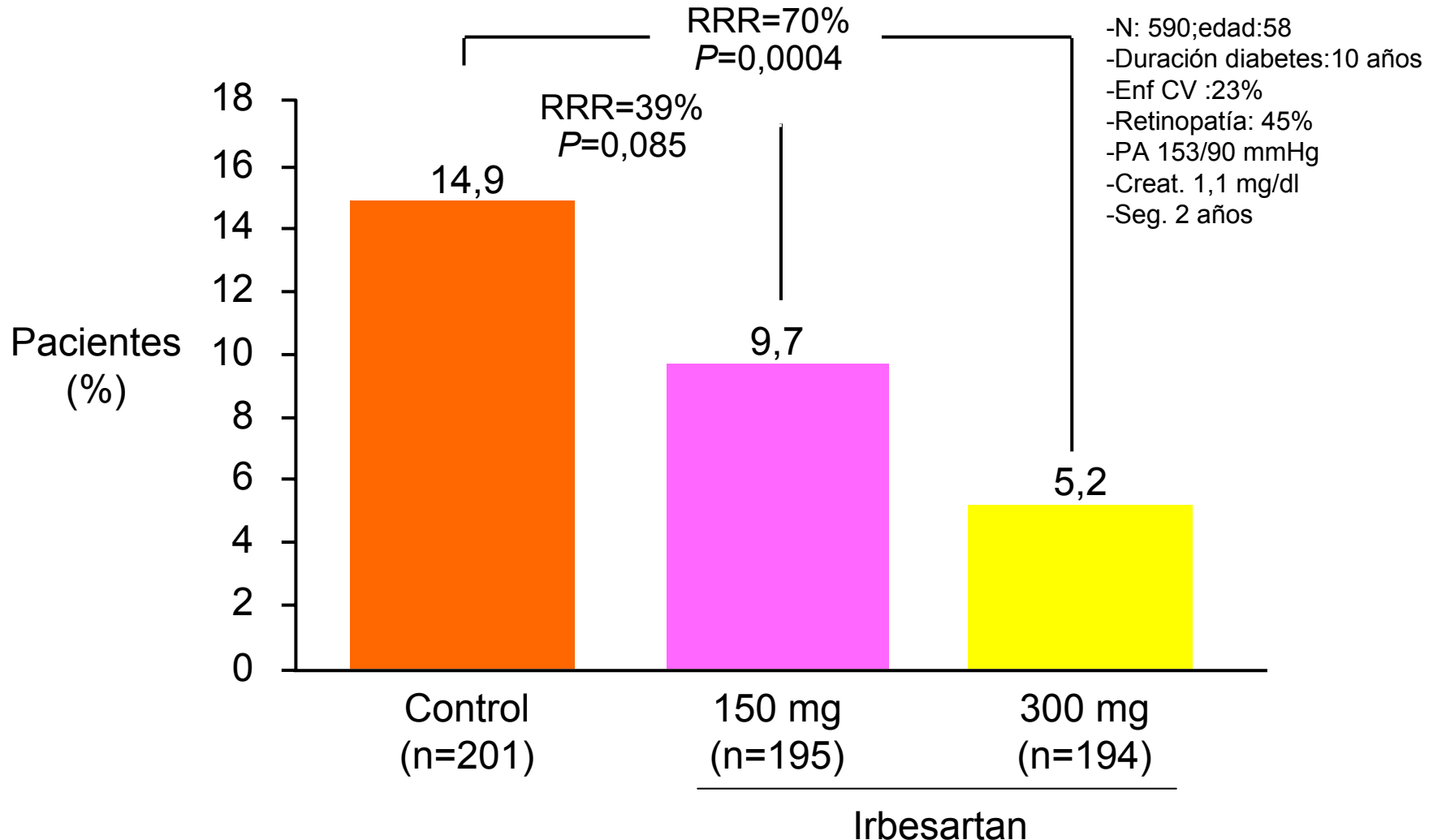
Eficacia renoprotectora de terapia con ARA 2 en diabetes con HTA y nefropatía

-N:1.715;Edad:59
-PA:160 / 87 mmHg
-Retinopatía 69%
-Enf CV 27%
-Creat. 1,67 mg/dl
-Albuminuria 1,9 g/24 h
-Seg 2,6 años

-N:1.513;;Edad:60
-PA:152 / 82 mmHg
-Retinopatía 66%
-Enf CV 27%
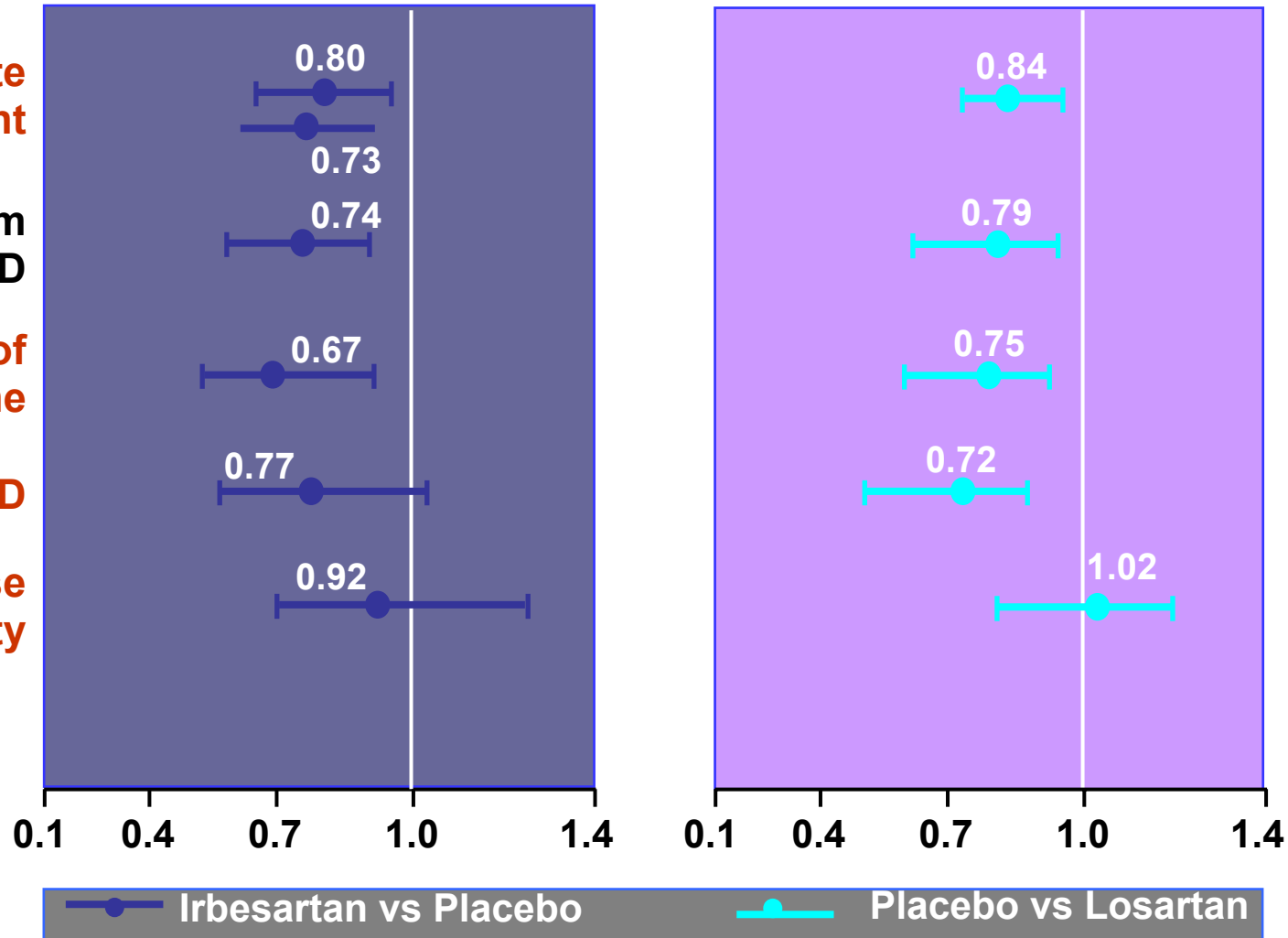-Creat. 1,9 mg/dl
-Albuminuria 1,2 g/g
-Seg 3.4 años

IDNT

RENAAL

Primary composite endpoint — 0.80 / 0.73 | 0.84

Doubling of serum creatinine / ESRD — 0.74 | 0.79

Doubling of serum creatinine — 0.67 | 0.75

ESRD — 0.77 | 0.72

All-cause mortality — 0.92 | 1.02

0.1 0.4 0.7 1.0 1.4   0.1 0.4 0.7 1.0 1.4

— Irbesartan vs Placebo   ▲ Placebo vs Losartan

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Lewis EJ et al. N Engl J Med 2001;345:851-860 Brenner BM et al. N Engl J Med 2001;345:861-869.

Bloqueo del SRA en la diabetes mellitus tipo 2

Diabetes + HTA+Afectación renal GUIAS

2007 Guidelines for the Management of Arterial Hypertension

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-Available evidence indicates that lowering BP also exerts a protective effect on appearance and progression of renal damage. Some additional protection can be obtained by the use of a blocker of the renin-angiotensin system (either an angiotensin receptor antagonist or an ACE inhibitor).

Standards of Medical Care in Diabetes—2011

AMERICAN DIABETES ASSOCIATION

-In the treatment of the nonpregnant patient with micro- or macroalbuminuria,either ACE inhibitors or ARBs should be used. (A)

-In patients with type 2 diabetes, hypertension,and microalbuminuria,both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. (A)

NKF KDOQI GUIDELINES

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Hypertesive people with diabetes And CKD stages 1-4 should be Treated with a ACE inhibitor or an ARB ,usually in combination with Diuretic (A)

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Bloqueo del SRA en la diabetes mellitus tipo 2

Diabetes con muy elevado riesgo vascular

-Effects of ramipril on cardoascular and microvascular outcomes in people with diabetes mellitus:results of the HOPE study and MICRO_HOPE substudy. Lancet 355:253,2000

-The effect of perindopril on cardiovascular morbidity and mortality in patients wit diabetes in the EUROPA study: results from de PERSUADE study. Eur Heart J. 26:1369,2005

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HOPE/MICROHOPE EN DIABETES
(n: 3.577)

Criterios de inclusión

- Edad ≥ 55 años+Diabetes + (al menos 1):

-Hipercolesterolemia
-Disminución HDL-c
-HTA*
-Microalbuminuria
-Tabaquismo

*Terapia antiHTA o >160/90 mmHg

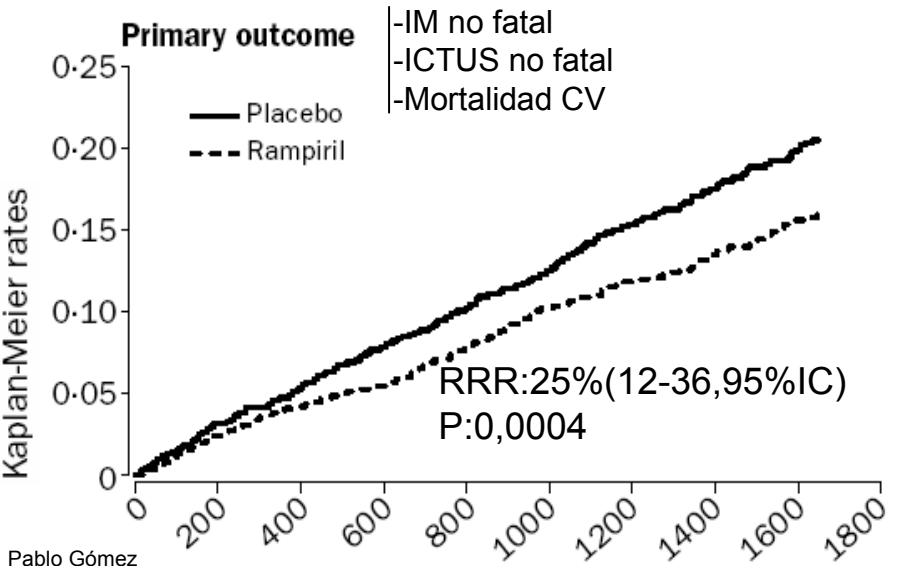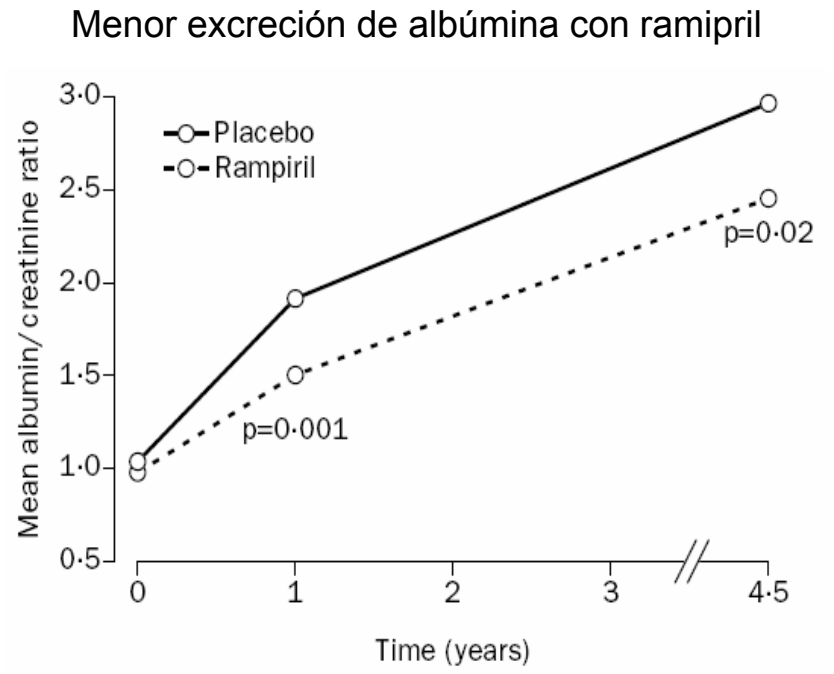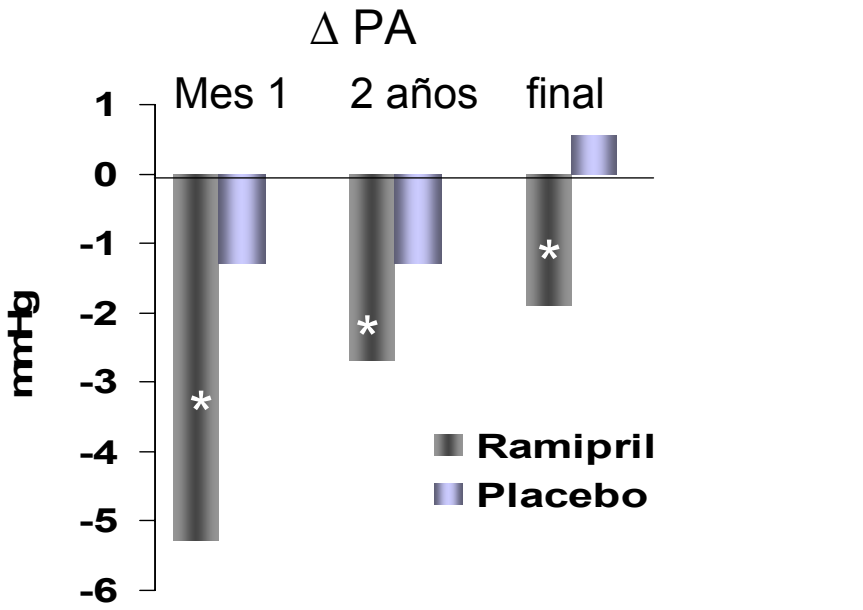## Características de los sujetos

- Edad   65 años
- Duración diabetes   11 años
- Hª HTA   58%
- PA:142/80 mmHg
- Enf CV previa   67%
- Microalbuminuria   31%

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HOPE/MICROHOPE EN DIABETES
Protección cardio-renal

Δ PA

Mes 1   2 años   final

mmHg

- Ramipril
- Placebo

Menor excreción de albúmina con ramipril

Mean albumin/creatinine ratio
- Placebo
- Rampiril

p=0·02

p=0·001

Time (years)

Primary outcome

-IM no fatal
-ICTUS no fatal
-Mortalidad CV

Kaplan-Meier rates

- Placebo
- Rampiril

RRR:25%(12-36,95%IC)
P:0,0004

Días seguimiento

-RRR desarrollo de nefropatía
diabética: 24%(3-40,95% IC,p:0,027)

-Ramipril no reduce el riesgo de desarrollo
de microalb, en los sujetos normoalbuminúricos

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Lancet 355:253,2000

Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease

The Task Force on ACE-inhibitors of the European Society of Cardiology

Task Force Members, José López-Sendón, Chairperson* (Spain), Karl Swedberg (Sweden), John McMurray (UK), Juan Tamargo (Spain), Aldo P. Maggioni (Italy), Henry Dargie (UK), Michal Tendera (Poland), Finn Waagstein (Sweden), Jan Kjekshus (Norway), Philippe Lechat (France), Christian Torp-Pedersen (Denmark)

Table 6 Use of ACE-I in hypertension: guidelines

Setting/indication	Class	Level
To control blood pressure	I	A
Patients with heart failure, systolic left ventricular dysfunction, diabetics, previous MI or stroke, high coronary disease risk	I	A

Table 7 Use of ACE-I in secondary prevention: guidelines

Setting/indication	Class	Level
High-risk patients (evidence of cardiovascular disease or diabetes and one other risk factor)	I	A

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Bloqueo del SRA en la diabetes mellitus tipo 2

Mayor eficacia del bloqueo del SRA para disminuir el riesgo cardio-renal cuando se asocia a otras terapias
(Terapia multi-factorial)

-Gaede et al. Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes N Eng J Med 348,2003

-Tu et al.Prevention of Diabetic Nephropathy by Tight Target Control in an Asian Population With Type 2 Diabetes Mellitus A 4-Year Prospective Analysis. Arch Intern Med 170:155,2010.

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Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study

	Start of study period		End of study period	
	Standard group (n=80)	Intensive group (n=80)	Standard group (n=76)	Intensive group (n=73)
Glucose lowering				
Diet alone	21	28	6	4
Oral hypoglycaemic agent	48	47	38	29
Insulin and oral hypoglycaemic agent	1	0	4	28
Insulin alone	10	5	28	12
Median (IQR) insulin dose (units)	30 (22–70)	42 (10–50)	48 (34–60)	48 (33–68)
Antihypertensive (includes ACE inhibitors)	33	33	48	71
ACE inhibitors	16	15	36	69
Lipid lowering				
Statin	0	2	2	33
Fibrate	1	1	3	1
Both statin and fibrate	0	0	1	1
Aspirin	11	10	17	31
Antioxidants	—	—	—	48
Hormone replacement therapy	3	2	3	2

	Start of Study Period		End of Study Period		P Value*
	Conventional Therapy (N=80)	Intensive Therapy (N=80)	Conventional Therapy (N=63)	Intensive Therapy (N=67)	
ACE inhibitor†	16	15	32	53	0.002
Angiotensin II–receptor antagonist	0	0	12	31	0.002
Both	0	0	0	19	<0.001
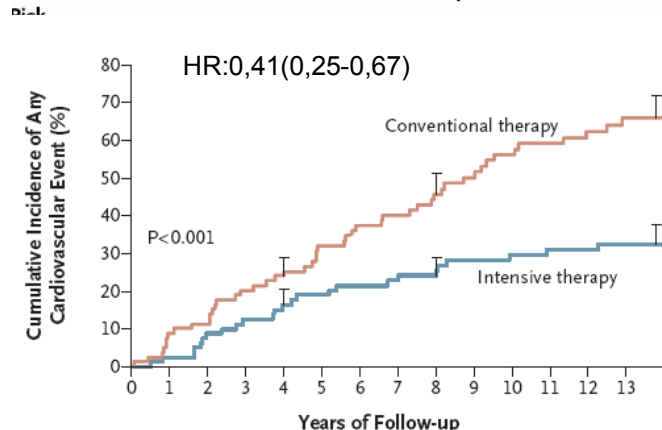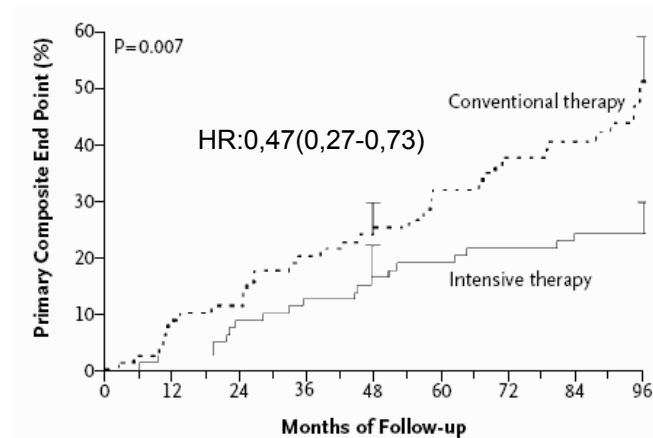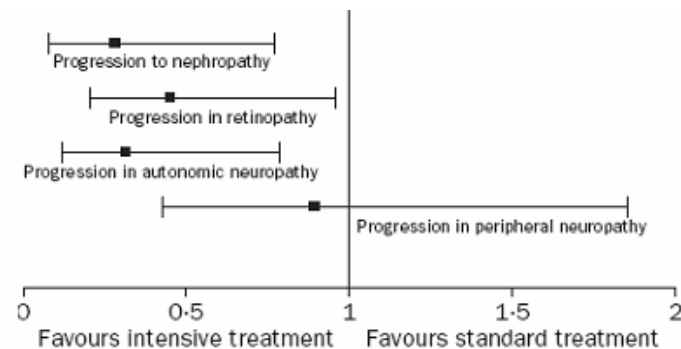
Gaede et al Lancet 353,1999
Gaede et al N Eng J Med ,348,2003
Gaede et al N Engl J Med 358,2008

3,8 años

8 años

13 años

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CONCLUSIONES

Bloqueo del sistema renina-angioten-sina en el paciente diabético tipo 2

A quién?

A quién no?

Actualmente no hay evidencias consistentes de beneficios de bloqueo del SRA en diabéticos tipo 2 normotensos de bajo riesgo .
¿Existen estos enfermos?