

Διαβητική νεφροπάθεια: η σημασία της αναστολής του άξονα ρενίνης αγγειοτενσίνης

ΤΣΟΥΧΝΙΚΑΣ ΙΩΑΝΝΗΣ
ΝΕΦΡΟΛΟΓΟΣ
ΝΕΦΡΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ ΑΠΘ

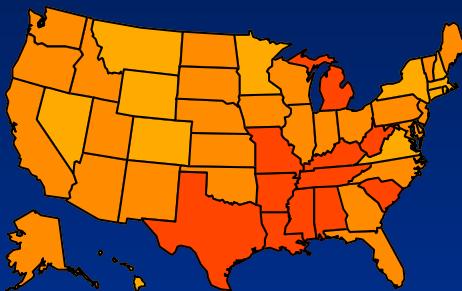
Age-adjusted Percentage of U.S. Adults Who Were Obese or Who Had Diagnosed Diabetes

Obesity (BMI $\geq 30 \text{ kg/m}^2$)

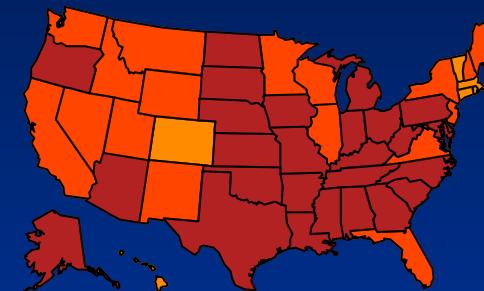
1994



2000



2007



Diabetes

1994



2000



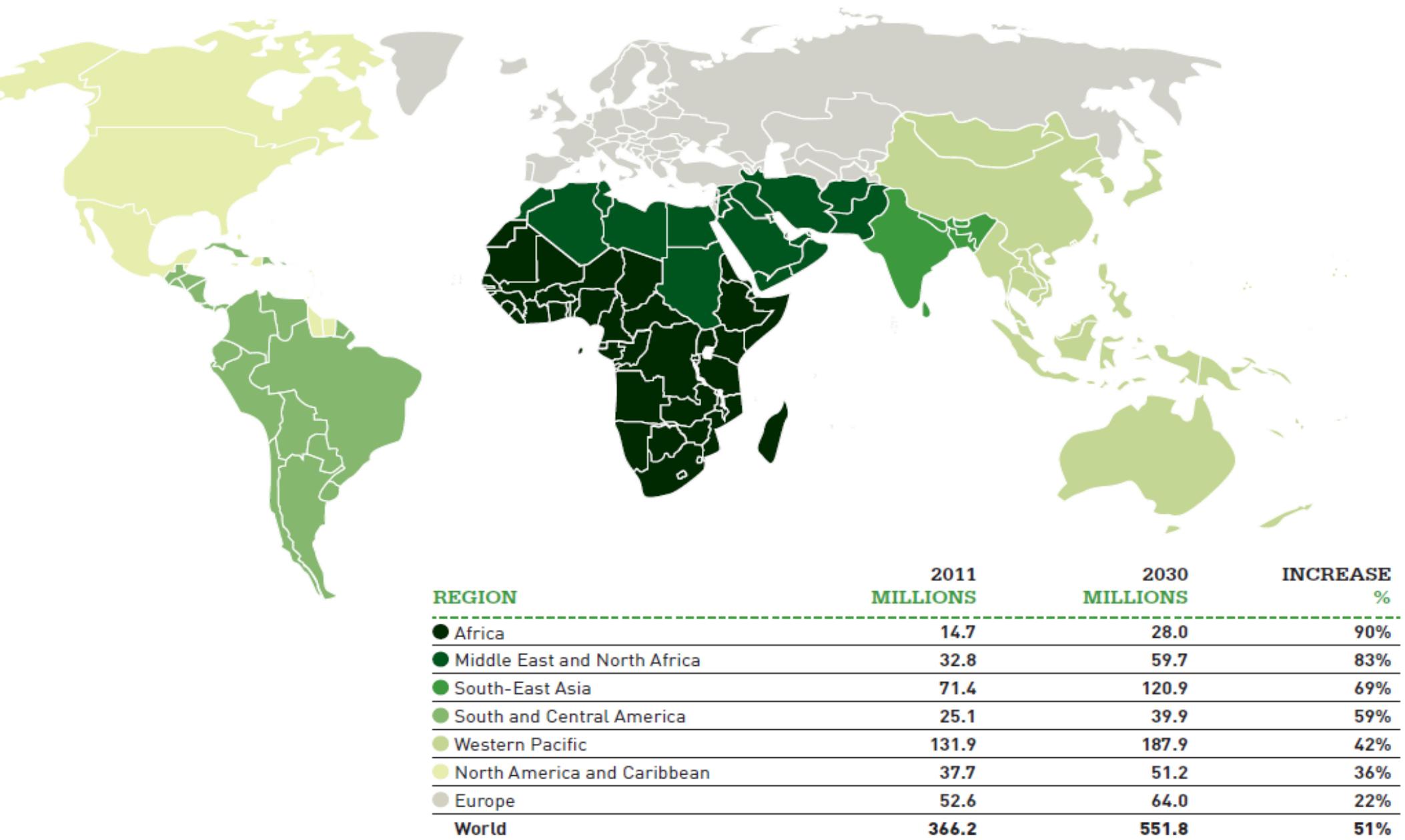
2009



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at
<http://www.cdc.gov/diabetes/statistics>



Map: IDF Regions and global projections of the number of people with diabetes (20-79 years), 2011 and 2030

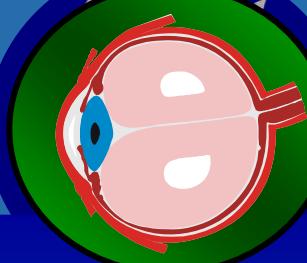


Impact of Diabetes Mellitus

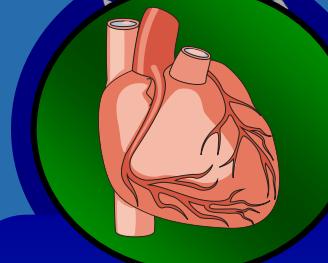
Diabetes



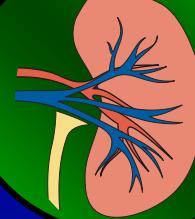
The leading cause of nontraumatic lower extremity amputations



The leading cause of new cases of blindness in working-aged adults

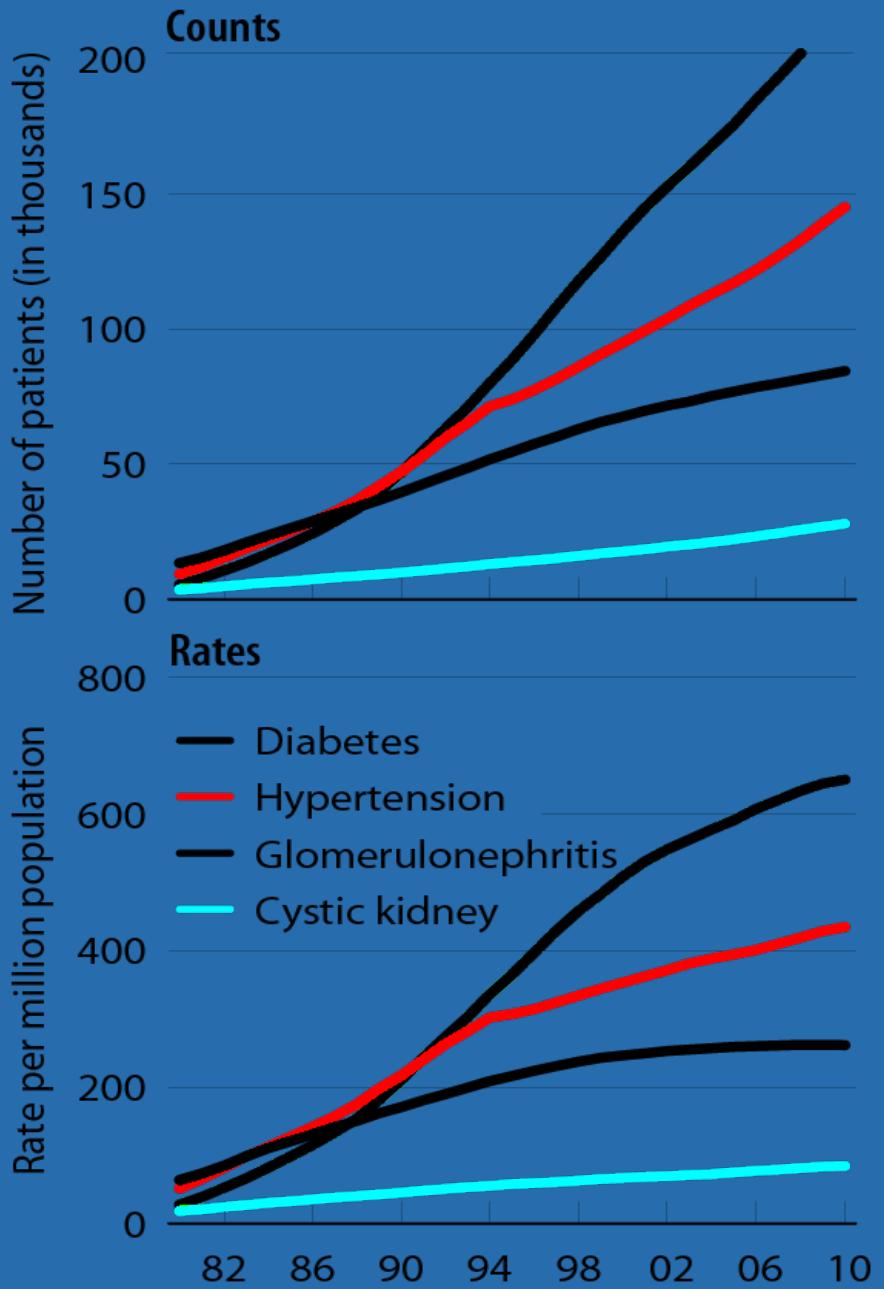


A 2- to 4-fold increase in cardio-vascular mortality



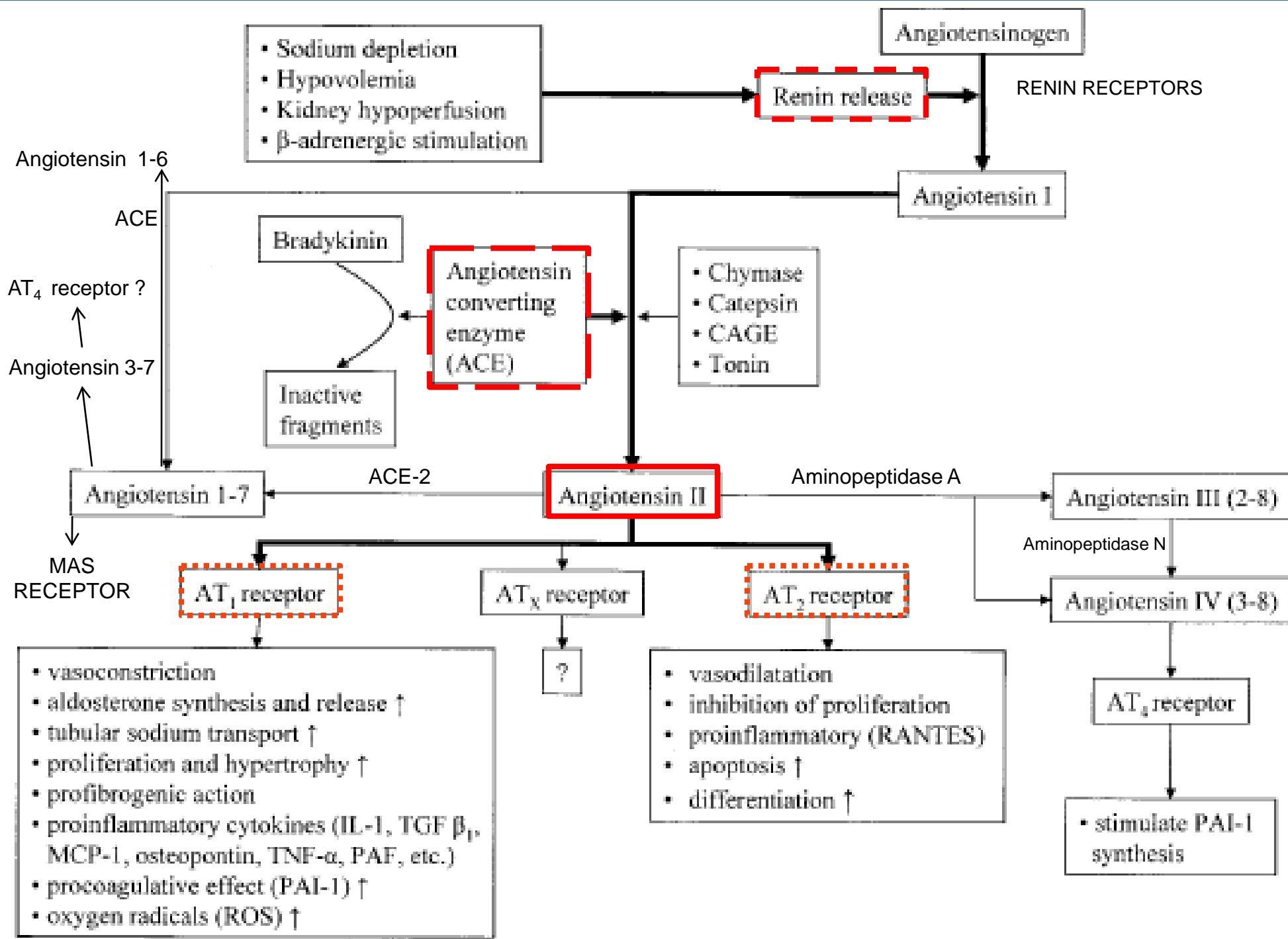
The leading cause of new cases of end stage renal disease

Prevalent counts & adjusted rates of ESRD, by primary diagnosis

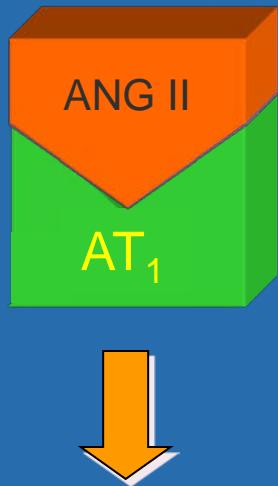


ΣΥΣΤΗΜΑ PENINΗΣ ΑΓΓΕΙΟΤΕΝΣΙΝΗΣ ΑΛΔΟΣΤΕΡΟΝΗΣ

- 1898: Renin (Tigerstedt R, Bergman PG. Niere und Kreislauf. Skand Arch Physiol. 1898;8: 223–271)
- 1940 : Angiotensin
- 1941: Angiotensinogen
- 1956: ACE
- 1971: Saralasin
- 1975: Captopril (First ACEi). FDA approved 1981
- 1986: Losartan. FDA approved 1995



Angiotensin-Receptors



- Vasoconstriction
- Na^+ -retention
- Aldosterone-Release
- Proliferation
- Fibrosis
- Inflammation



- Vasodilation
- Anti-Proliferation
- Anti-Fibrosis
- Anti-Inflammation

LOCAL OR TISSUE RAS SYSTEMS

(Presence of RAS components at tissue level)

- Heart
- Blood vessels
- Kidney
- Adrenal gland
- Pancreas
- Central Nervous System
- Reproductive system
- Adipose tissue

Autocrine

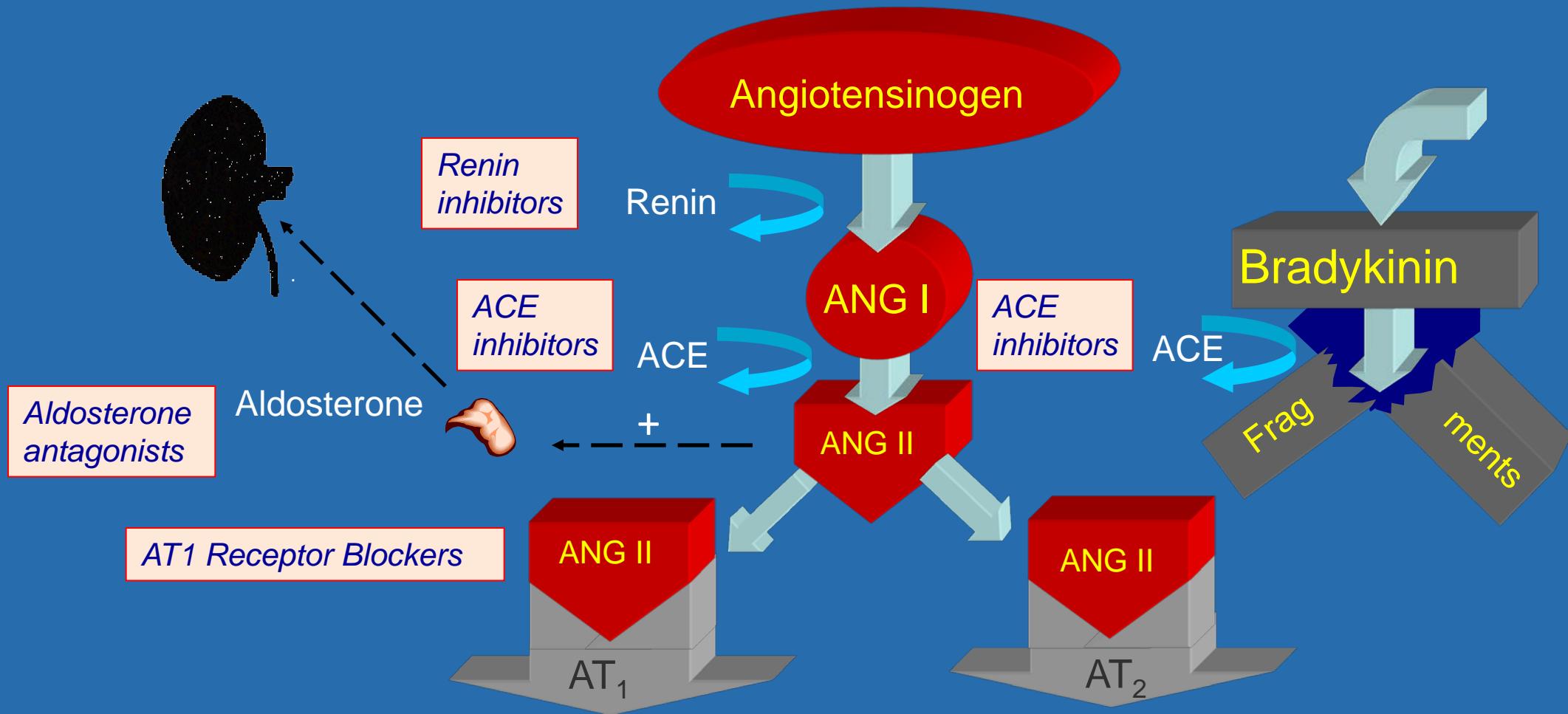
Paracrine

Endocrine

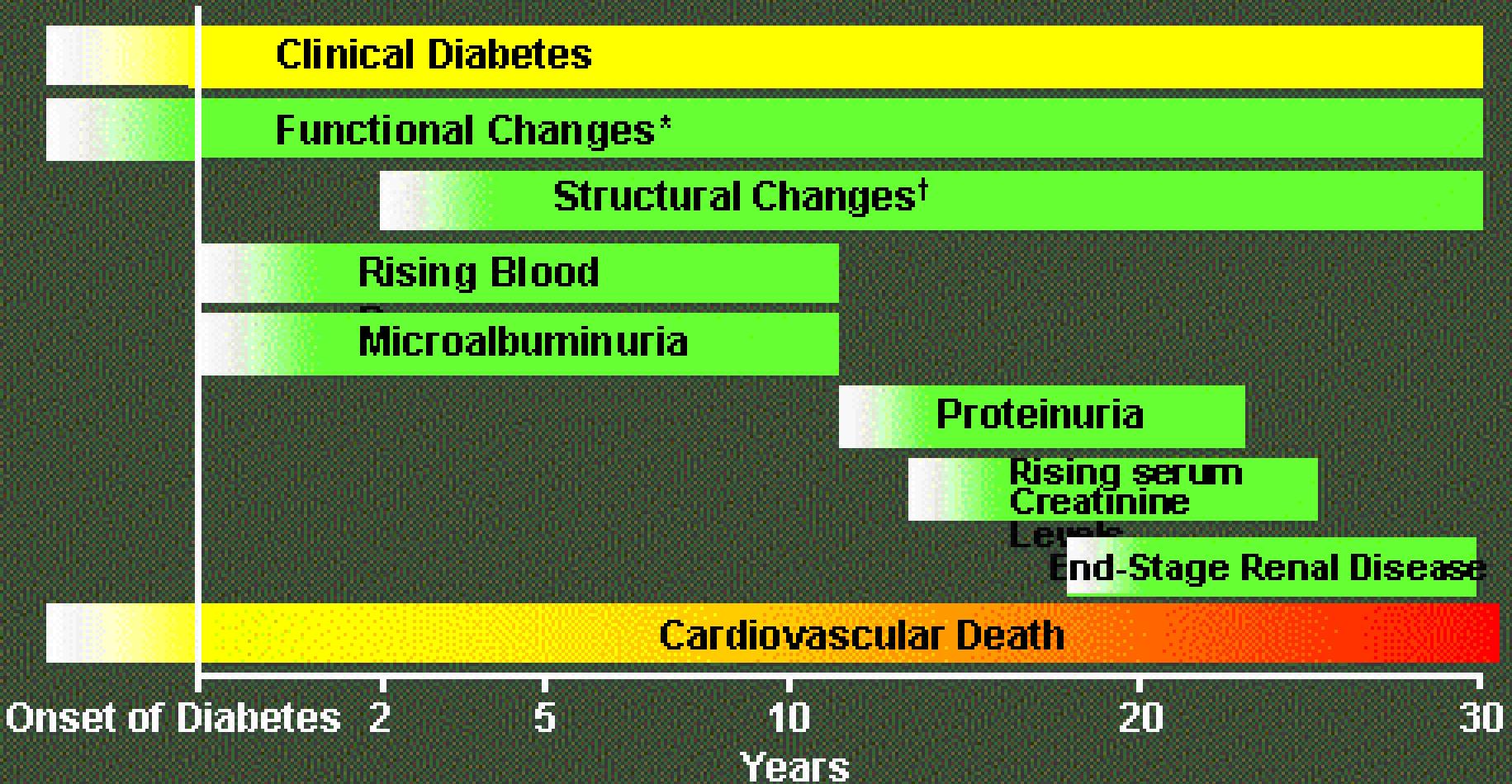
Ο ΡΟΛΟΣ ΤΟΥ RAS ΣΤΗΝ ΠΑΘΟΓΕΝΕΙΑ ΤΗΣ ΔΝ (Angiotensin II, AII)

- ΑΙΜΟΔΥΝΑΜΙΚΕΣ ΕΠΙΔΡΑΣΕΙΣ ΤΗΣ AII
 - Ενδοσπειραματική Υπέρταση
 - Αύξηση της συστηματικής ΑΠ
- ΜΗ ΑΙΜΟΔΥΝΑΜΙΚΕΣ ΕΠΙΔΡΑΣΕΙΣ ΤΗΣ AII
 - Υπερπλασία μεσαγγείου
 - Αυξημένη σύνθεση κυτταροκινών, TGF-b, ↑ ECM
 - Ενεργοποίηση μακροφάγων (φλεγμονή)
 - Ενεργοποίηση του PAI1 από ενδοθηλιακά κύτταρα
- ΕΠΙΔΡΑΣΕΙΣ ΑΛΔΟΣΤΕΡΟΝΗΣ
 - Κατακράτηση Να / H₂O, Υπέρταση
 - Υπερπλασία κυττάρων και εναπόθεση άμορφης ουσίας στο μεσάγγειο

ΦΑΡΜΑΚΑ ΠΟΥ ΑΝΑΣΤΕΛΛΟΥΝ ΤΟ ΣΥΣΤΗΜΑ ΡΕΝΙΝΗΣ ΑΓΓΕΙΟΤΕΝΣΙΝΗΣ ΑΛΔΟΣΤΕΡΟΝΗΣ



Natural History of Diabetic Nephropathy



* Kidney size ↑, short-term GFR ↑, long-term GFR ↓ † GBM thickening ↑, mesangial expansion ↑, microvascular changes +/-

Kidney Disease and Increased Mortality Risk in Type 2 Diabetes

Afkarian M, JASN 2013; 24: 302-308

NHANES III, n=15672,
9.5% had Diabetes n=1430
42.3% kidney disease n=658

Table 3. Ten-year standardized all-cause and cardiovascular mortality by diabetes and kidney disease status

	Number of Events	Standardized Cumulative Incidence, % (95% CI)	Adjusted Difference in Cumulative Incidence, % (95% CI)	
			Model 1	Model 2
All-cause mortality				
None	1027	7.7 (7.0–8.3)	0 (Reference)	0
Diabetes	168	11.5 (7.9–15.2)	3.9 (0.1–7.7)	3.4 (−0.3 to 7.0)
Kidney disease	750	17.2 (14.6–19.7)	9.5 (7.0–12.0)	9.0 (6.6–11.4)
Diabetes and kidney disease	332	31.1 (24.7–37.5)	23.4 (17.0–29.9)	23.4 (17.2–29.6)
Cardiovascular mortality				
None	347	3.4 (3.1–3.7)	0	0
Diabetes	68	6.7 (4.2–9.1)	3.3 (0.7–5.8)	3.0 (0.3–5.6)
Kidney disease	343	9.9 (7.9–11.9)	6.5 (4.5–8.5)	6.1 (4.0–8.1)
Diabetes and kidney disease	155	19.6 (14.7–24.4)	16.1 (11.2–21.0)	16.0 (11.1–20.9)
Noncardiovascular mortality				
None	663	5.7 (5.2–6.3)	0	0
Diabetes	97	7.2 (3.9–10.5)	1.5 (−2.0 to 4.9)	1.1 (−2.1 to 4.2)
Kidney disease	404	11.7 (9.5–13.9)	6.0 (3.9–8.1)	6.0 (4.0–7.9)
Diabetes and kidney disease	174	23.2 (16.5–29.9)	17.5 (10.6–24.3)	18.1 (11.4–24.8)

Absolute differences in mortality risk were estimated using linear regression and were adjusted for age, sex, and race (model 1) or additionally adjusted for smoking, BP, and cholesterol (model 2). Standardized 10-year all-cause cumulative incidences were estimated from model 1 for the mean levels of the covariates in the study population. In the two columns to the right, adjusted cumulative incidence of mortality in each of the three other subgroups is compared with that of the no-diabetes, no-kidney disease subgroup. Cause of death was unknown for 1.1% of study participants.

Αυξημένη αποβολή αλβουμίνης στα ούρα (increased urinary albumin excretion)

Table 3. Definitions of Abnormalities in Albumin Excretion

Category	Spot Collection (mg/g creatinine)	24-Hour Collection (mg/24 h)	Timed Collection (µg/min)
Normoalbuminuria	<30	<30	<20
Microalbuminuria	30-300	30-300	20-200
Macroalbuminuria	>300	>300	>200

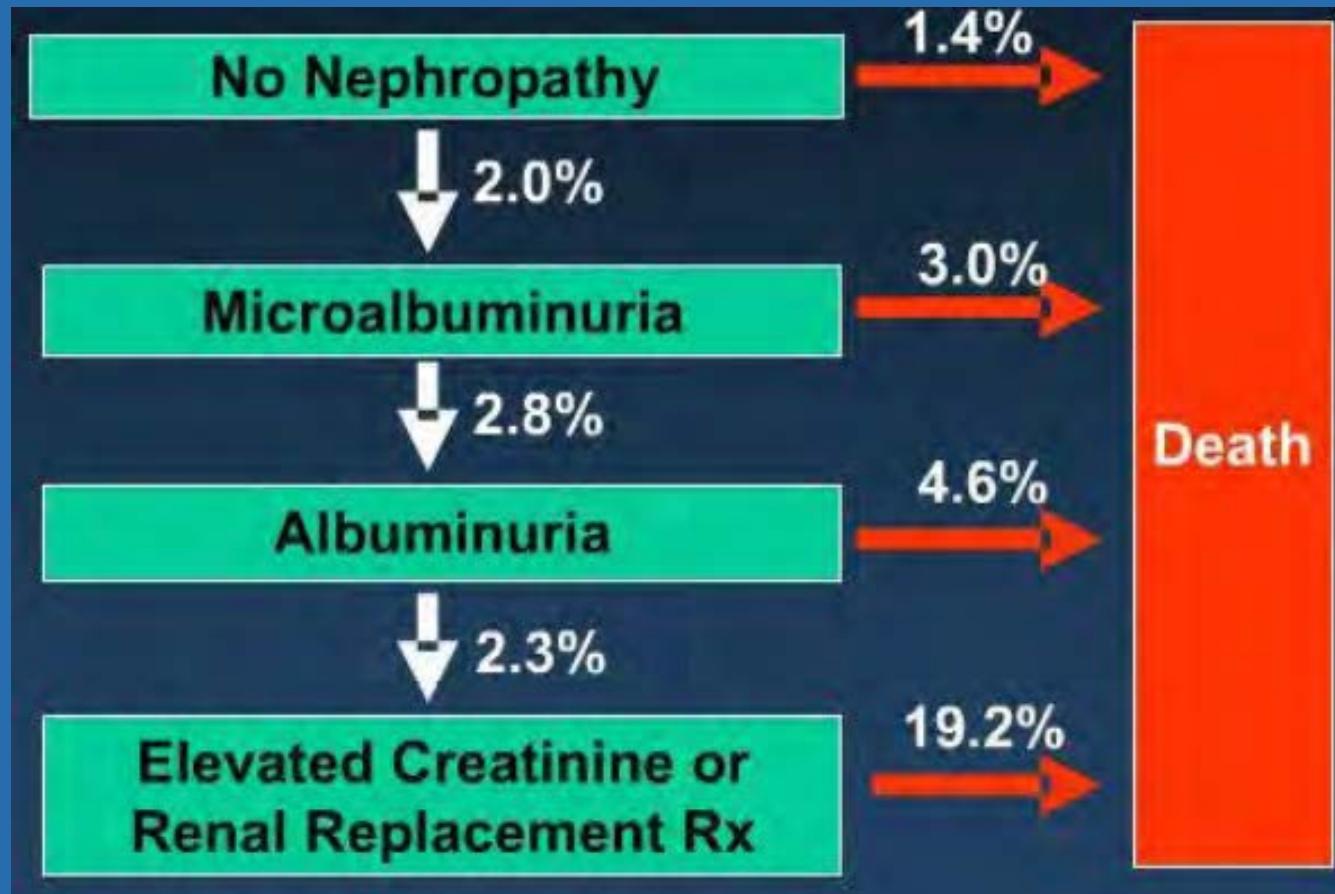
Because of variability in urinary albumin excretion, at least 2 specimens, preferably first morning void, collected within a 3- to 6-month period should be abnormal before considering a patient to have crossed 1 of these diagnostic thresholds. Exercise within 24 hours, infection, fever, congestive heart failure, marked hyperglycemia, pregnancy, marked hypertension, urinary tract infection, and hematuria may increase urinary albumin over baseline values.

American Journal of Kidney Diseases, Vol 49, No 2, Suppl 2 (February), 2007: pp S42-S61

ΛΕΥΚΩΜΑΤΟΥΠΙΑ ΚΑΙ ΘΝΗΤΟΤΗΤΑ UKPDS

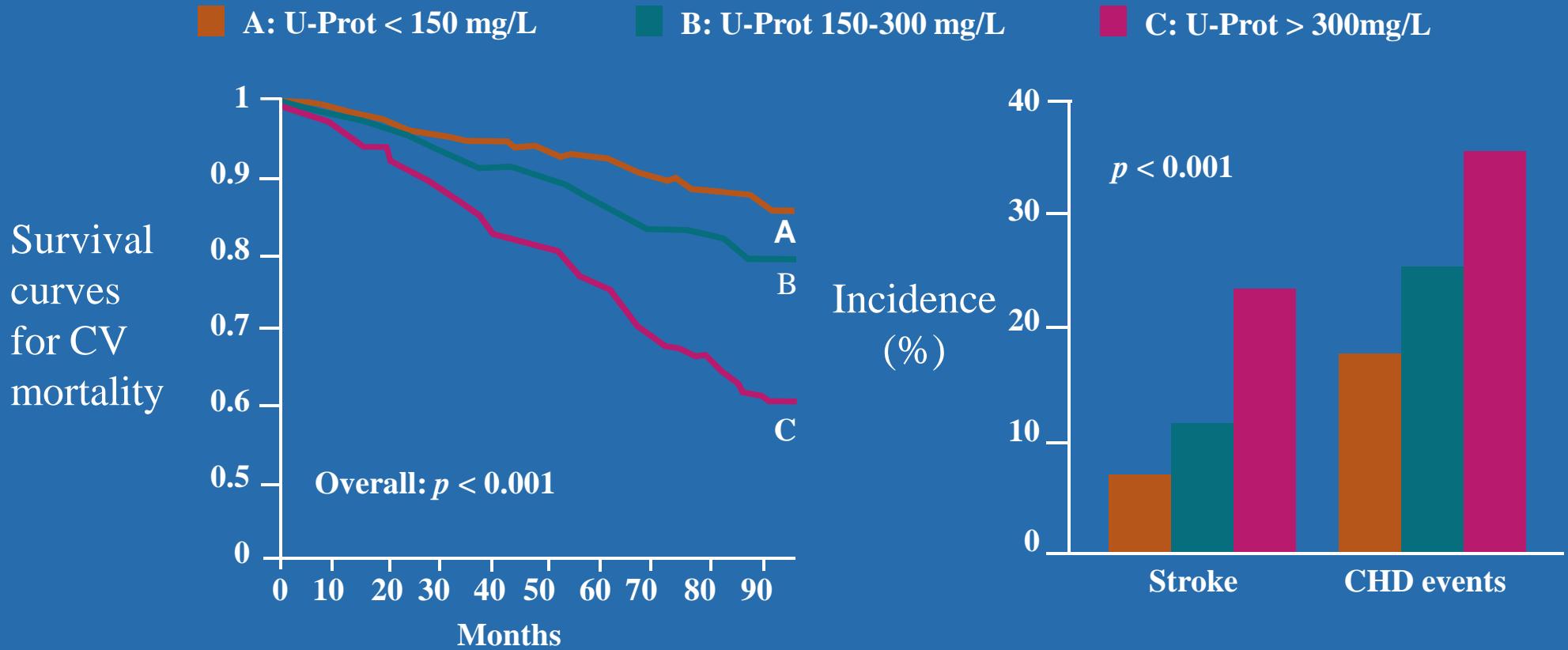
5097 DM TYPE II

Annual transition rates



Adler AI, KI 2003; 63: 225-232

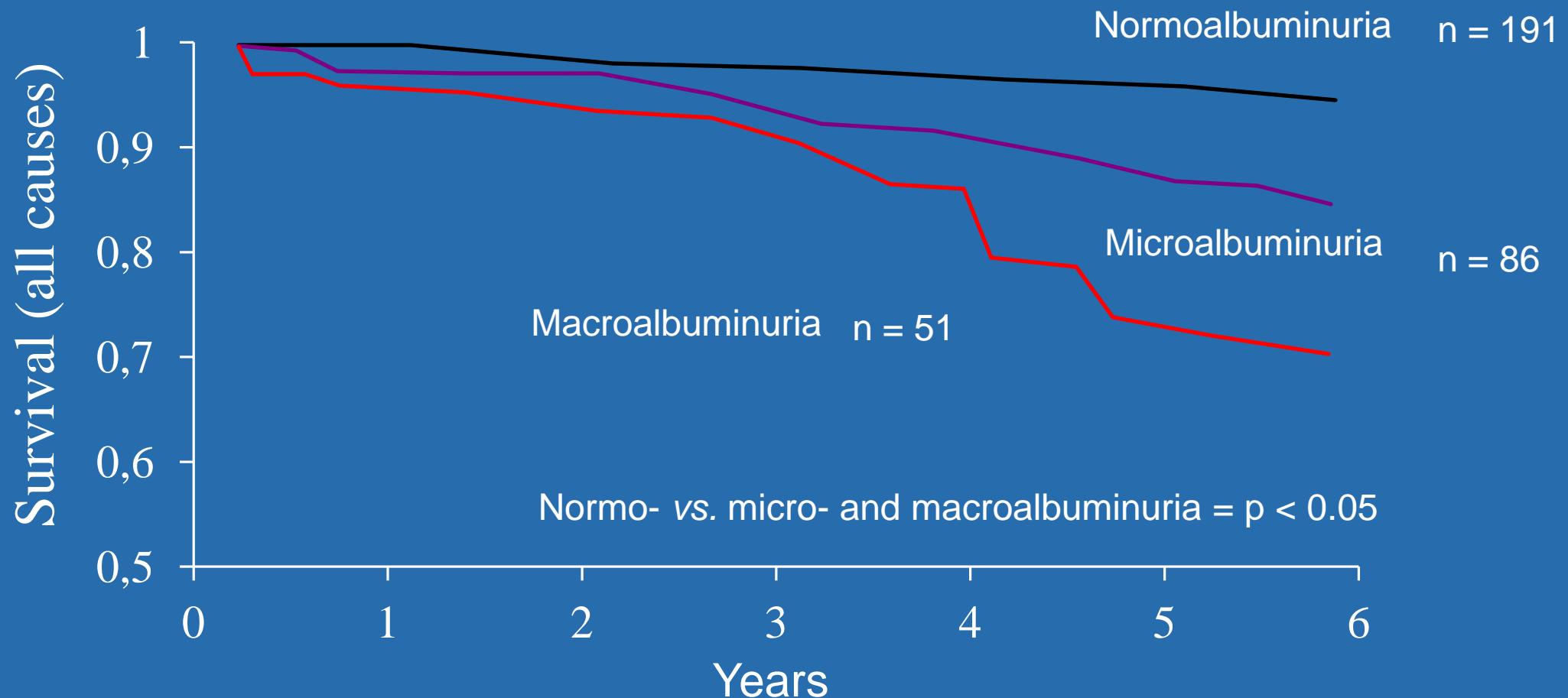
Proteinuria predicts stroke and CHD events in type II diabetes (7-year follow-up, 1056 patients)



U-Prot = Urinary protein concentration.

1. Miettinen H et al, 1996.
2. Wang et al, 1996.
3. Dinneen SF et al, 1997.

Proteinuria and Mortality in NIDDM



Gall MA, Diabetes 1995; 44: 1303-1309

ALBUMINURIA

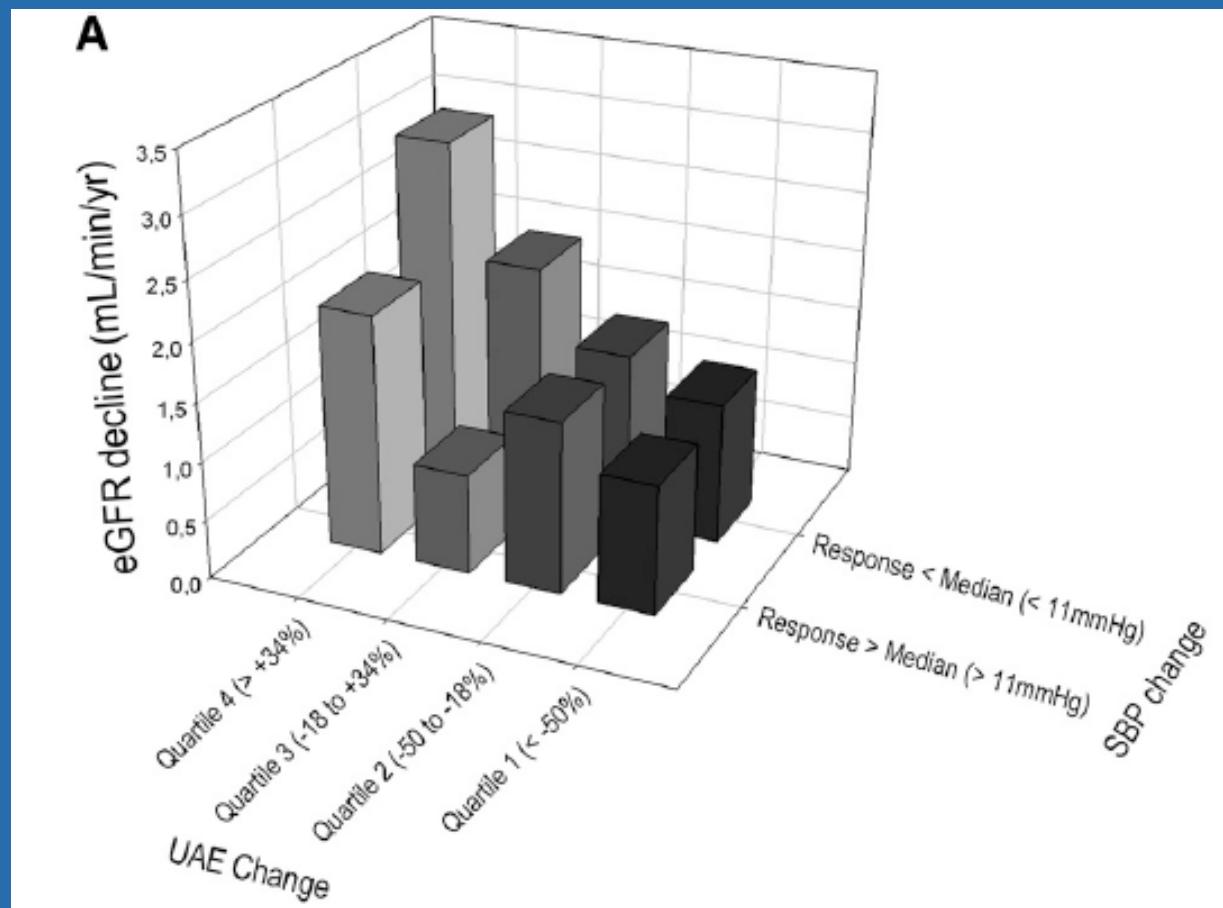
as a target for treatment efficacy

Initial AR blockade-induced decrease in albuminuria is associated with long-term renal outcome in type 2 diabetic pts with microalbuminuria

Hellemons ME, Diabetes Care 2011, 34, 2078-83

A post-hoc analysis of IRMA -2

590 hypertensive patients with type 2 diabetes and persistent microalbuminuria

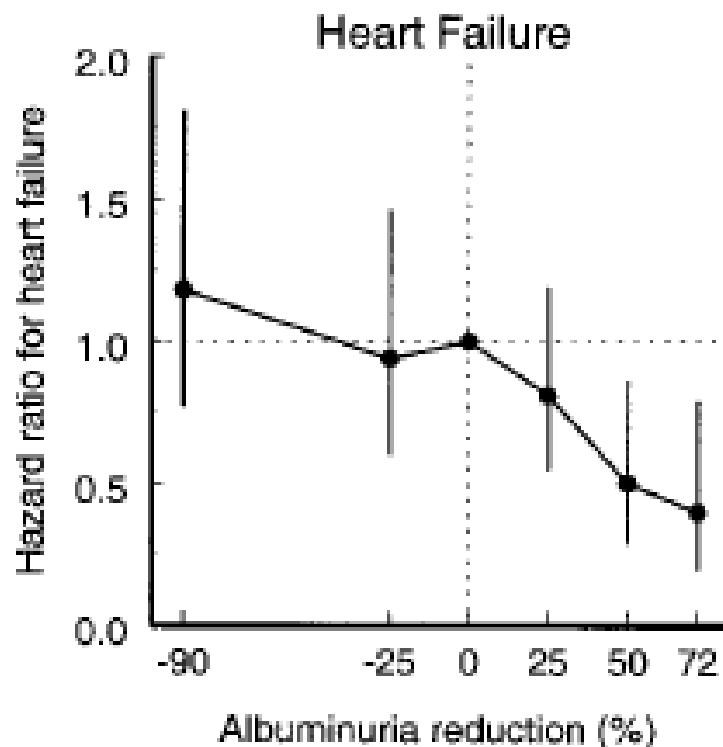
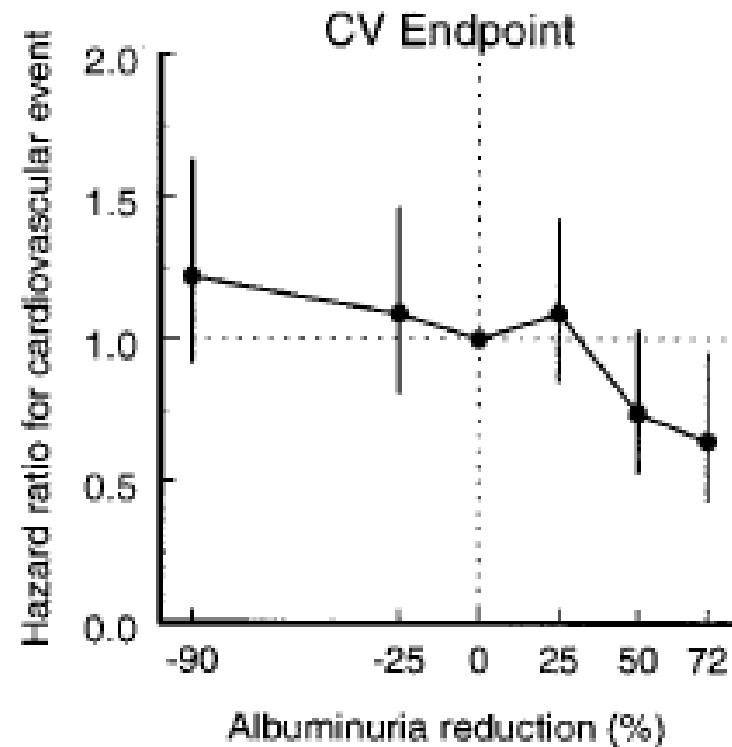


Albuminuria, a Therapeutic Target for Cardiovascular Protection in Type 2 Diabetic Patients With Nephropathy

De Zeeuw D, Circulation 2004; 110: 921-927

RENAAL Losartan 100

Albuminuria reduction the first 6 months



ΣΤΟΧΟΙ ΘΕΡΑΠΕΥΤΙΚΗΣ ΠΑΡΕΜΒΑΣΗΣ ΣΤΗΝ ΕΠΙΒΡΑΔΥΝΣΗ ΤΗΣ ΕΞΕΛΙΞΗΣ ΤΗΣ ΔΝ

ΠΡΩΤΟΓΕΝΗΣ



ΔΕΥΤΕΡΟΓΕΝΗΣ

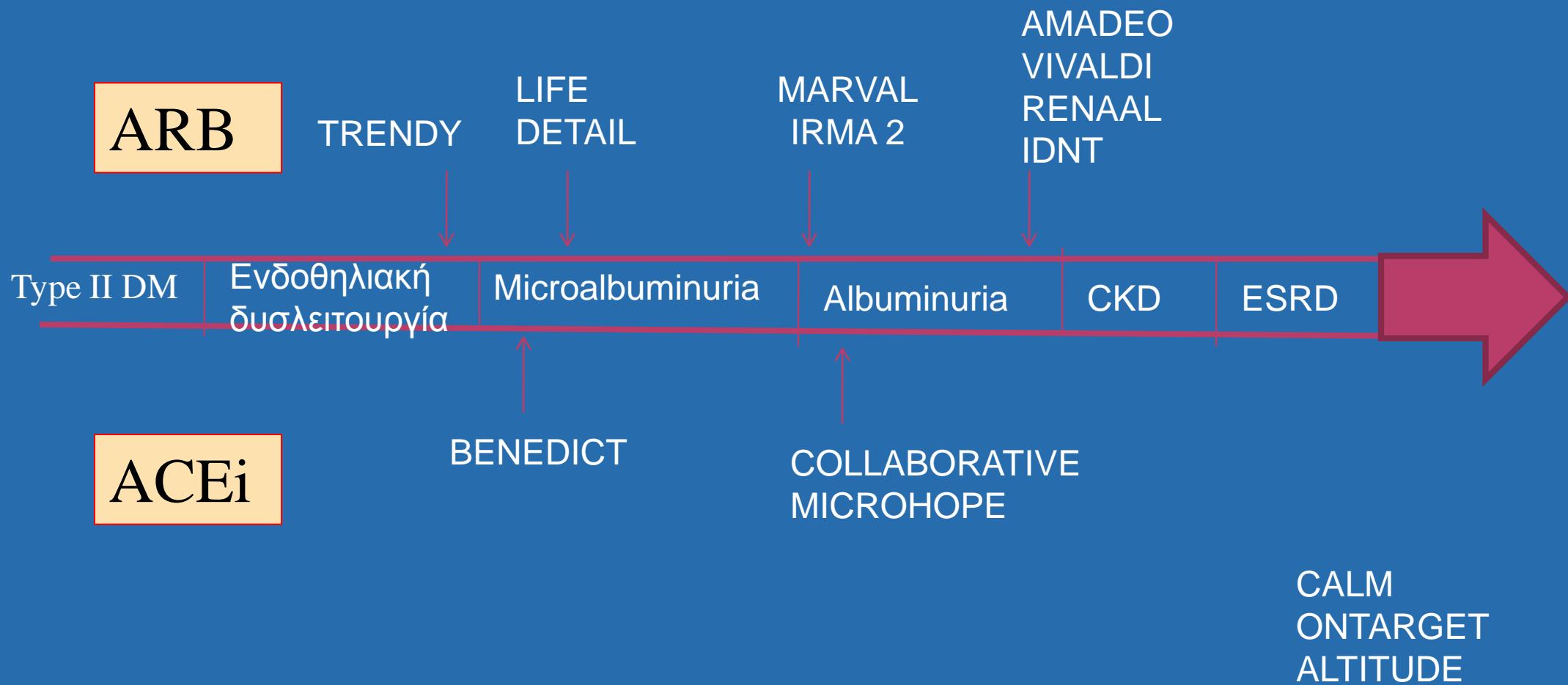


ΤΡΙΤΟΓΕΝΗΣ



Σ/Δ ΝΟΡΜΟΛΕΥΚΩΜΑΤΙΝΟΥΡΙΑ ΜΙΚΡΟΛΕΥΚΩΜΑΤΙΝΟΥΡΙΑ ΛΕΥΚΩΜΑΤΟΥΡΙΑ XNA

ΑΝΑΣΤΟΛΗ ΤΗΣ ΕΞΕΛΙΞΗΣ ΤΗΣ ΔΙΑΒΗΤΙΚΗΣ ΝΕΦΡΟΠΑΘΕΙΑΣ ΜΕΣΩ ΑΠΟΚΛΕΙΣΜΟΥ ΤΟΥ RAS



ΧΡΟΝΟΣ ΕΞΕΛΙΞΗΣ 25 ΕΤΗ

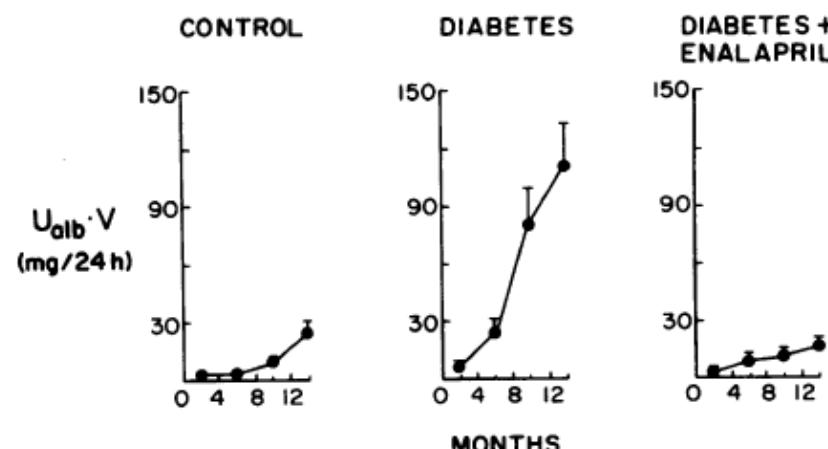
Prevention of Diabetic Glomerulopathy by Pharmacological Amelioration of Glomerular Capillary Hypertension

Zats RJ, Clin Invest 1986; 77: 1925-1930

Table II. Glomerular Hemodynamics after 4-6 Wk of Diabetes

Group	SNGFR	Q_A	SNFF	R_A	R_E	R_T	R_A/R_T	\bar{P}_{GC}	P_T	P_E	ΔP	C_A	C_E	π_A	π_E	K_f
	nl/min	nl/min			$\times 10^{10} \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$			$mmHg$	$mmHg$	$mmHg$	$mmHg$	g/dl	g/dl	$mmHg$	$mmHg$	$nl/(s \cdot mmHg)$
C (n = 7 rats)	45.9 ± 3.8	154 ± 18	0.31 ± 0.02	2.13 ± 0.40	1.41 ± 0.21	3.54 ± 0.61	0.59 ± 0.02	53 ± 1	13 ± 0.2	15 ± 0.6	39 ± 1	5.6 ± 0.2	8.2 ± 0.3	18.5 ± 0.8	33.3 ± 1.8	0.070 ± 0.018
DM (n = 8)	81.6 $\pm 5.7^*$	269 $\pm 26^*$	0.31 ± 0.02	0.89 $\pm 0.13^*$	1.00 ± 0.12	1.90 $\pm 0.21^*$	0.47 $\pm 0.03^*$	63 $\pm 2^*$	11 $\pm 0.4^*$	15 ± 1	52 $\pm 2^*$	5.9 ± 0.1	8.6 ± 0.3	19.7 ± 0.4	36.0 ± 1.8	0.057 ± 0.005
DM + E (n = 8)	71.9 $\pm 7.2^*$	227 $\pm 14^*$	0.31 ± 0.01	0.92 $\pm 0.07^*$	0.76 $\pm 0.04^*$	1.68 $\pm 0.10^*$	0.55 $\pm 0.02^{\ddagger}$	50 $\pm 1^{\ddagger}$	12 $\pm 0.3^{\ddagger}$	17 ± 0.6	37 $\pm 1^{\ddagger}$	5.3 $\pm 0.1^{\ddagger}$	7.8 ± 0.2	17.1 $\pm 0.3^{\ddagger}$	30.7 ± 1.2	0.101 ± 0.017

Abbreviations used in this table: P_T , proximal tubule hydraulic pressure; P_E , efferent arteriolar hydraulic pressure; C_A , afferent (systemic) arteriolar total plasma protein concentration; C_E , efferent arteriolar total plasma protein concentration; π_E , efferent arteriolar plasma colloid osmotic pressure. Values given as mean ± 1 SEM. * $P < 0.05$ vs. C; $\ddagger P < 0.05$ vs. DM.



Role of ACEi to treat DN

Type I DM (207 captopril and 202 placebo)

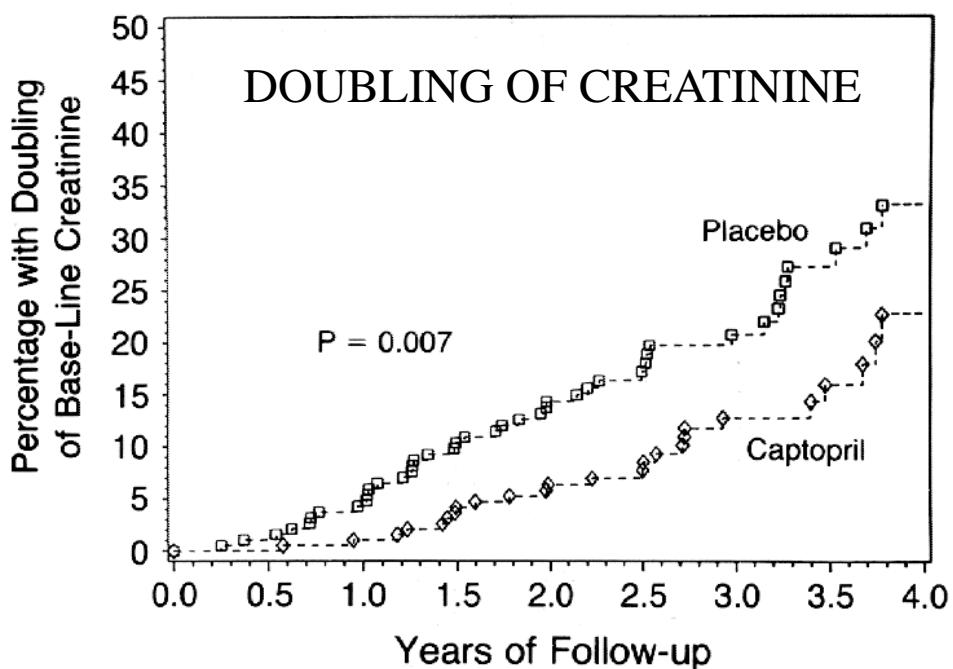
Proteinuria > 500 mg/24 h

Creat < 2.5 mg/dl

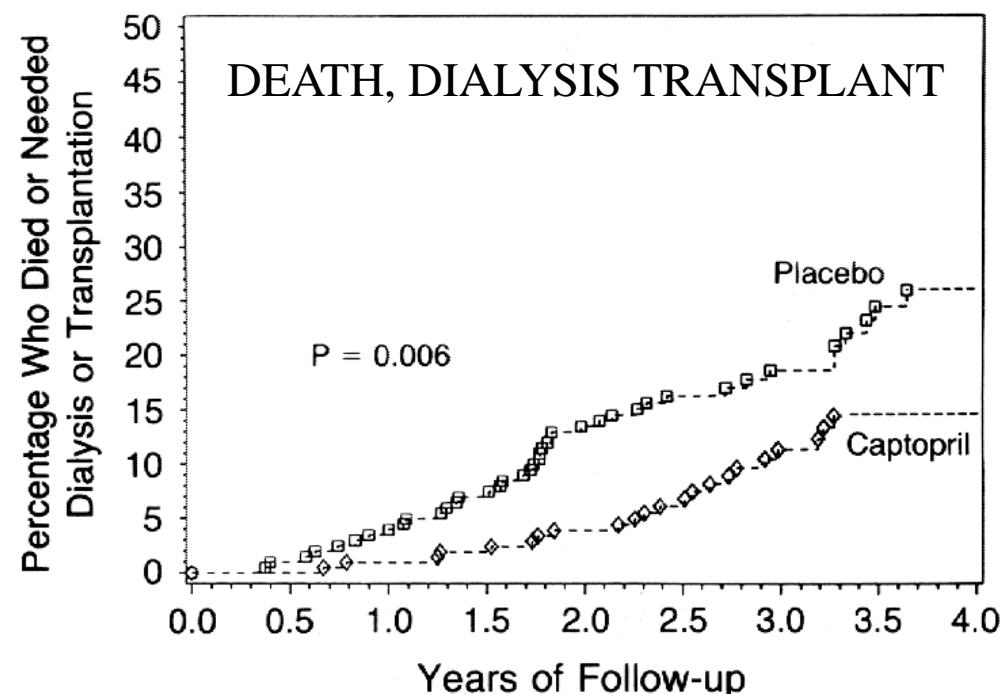
FU: 3y

Significant effect of captopril on blood pressure

A



B



EFFECTS OF LOSARTAN ON RENAL AND CV OUTCOMES IN PTS WITH TYPE 2 DIABETES AND NEPHROPATHY

Brenner BM, NEJM 2001; 345: 861-869

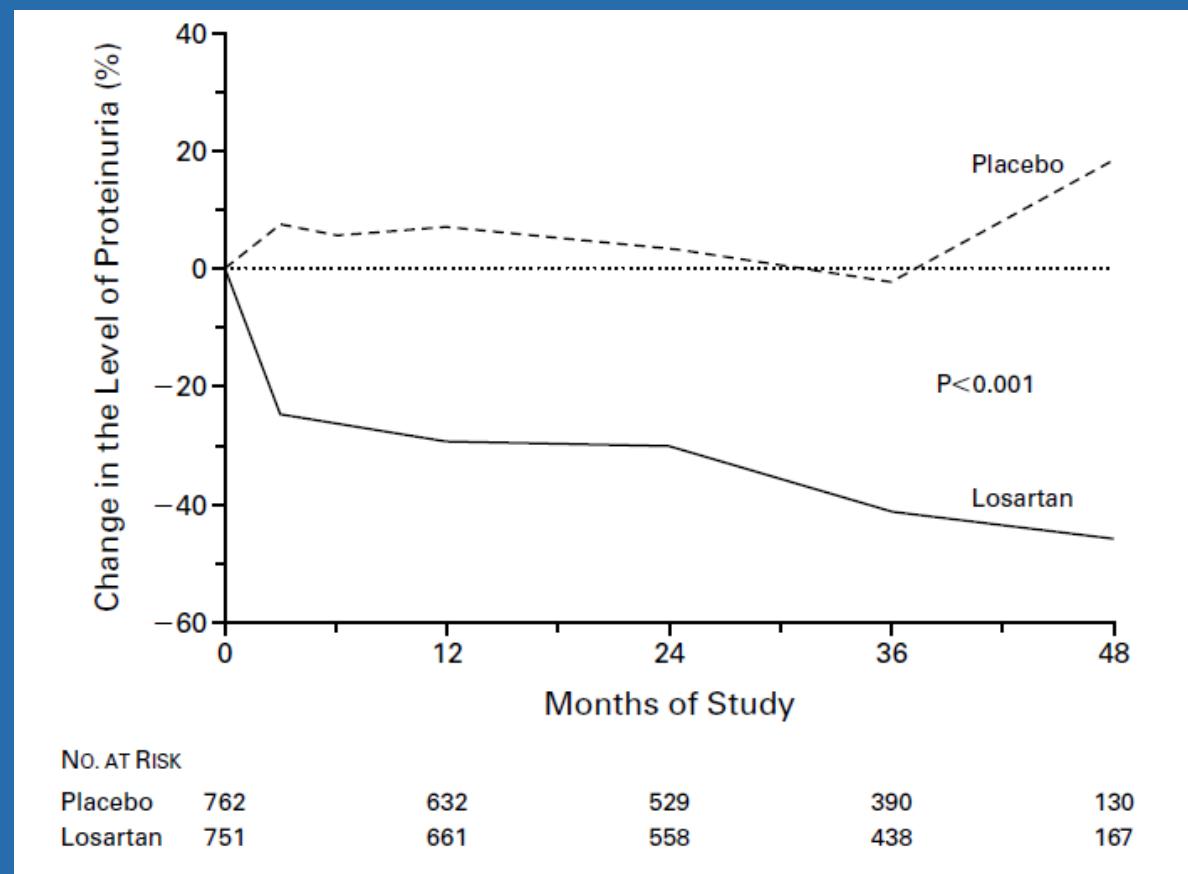
RENAAL

LOSARTAN 100 mg

Placebo

40% reduction of proteinuria
with Losartan

PROTEINURIA



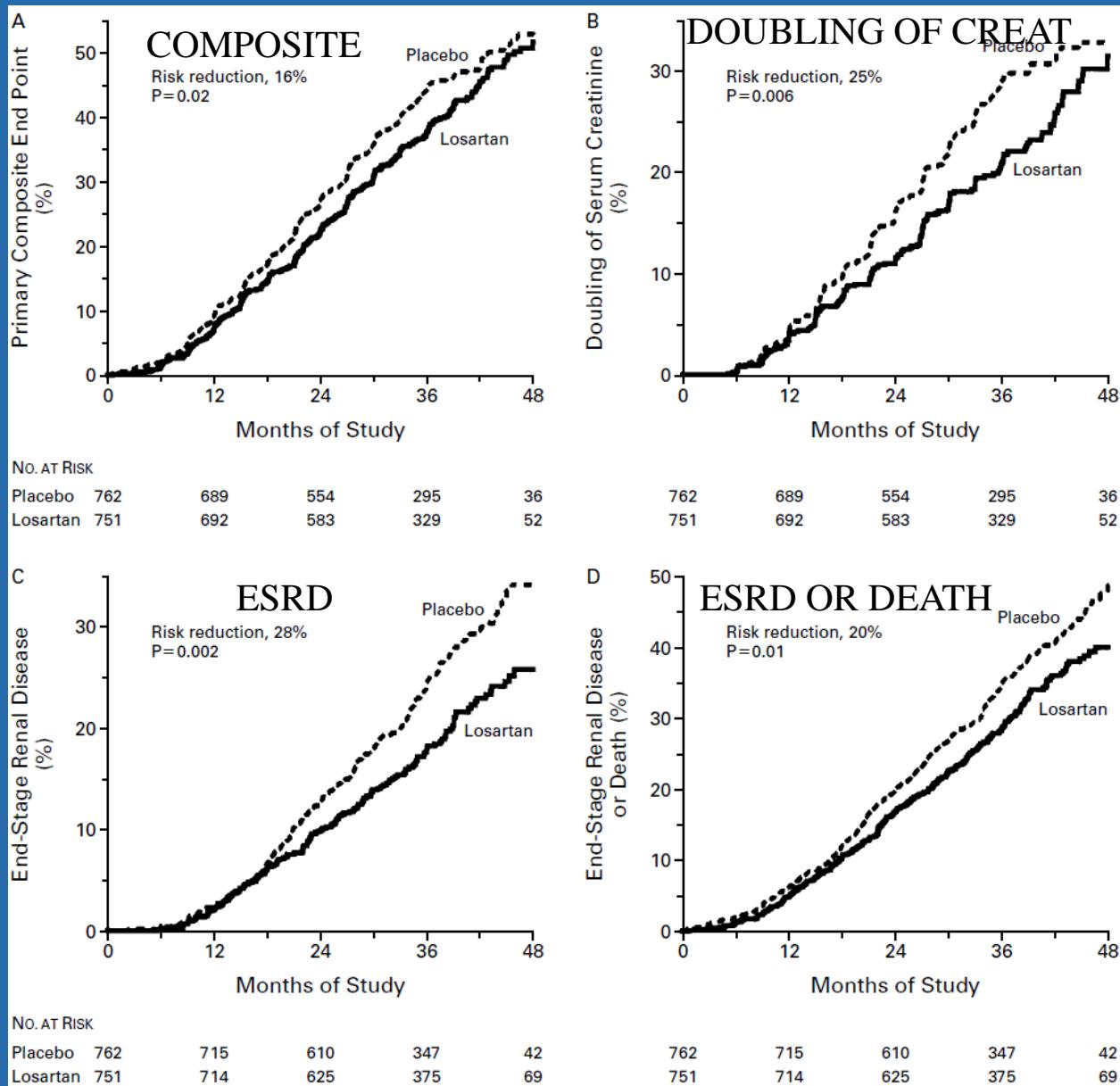
EFFECTS OF LOSARTAN ON RENAL AND CV OUTCOMES IN PTS WITH TYPE 2 DIABETES AND NEPHROPATHY

Brenner BM, NEJM 2001; 345: 861-869

RENAAL

LOSARTAN 100 mg
Placebo

Primary Composite :
(Renal Outcome)
doubling of the base creatinine,
end-stage renal disease,
death



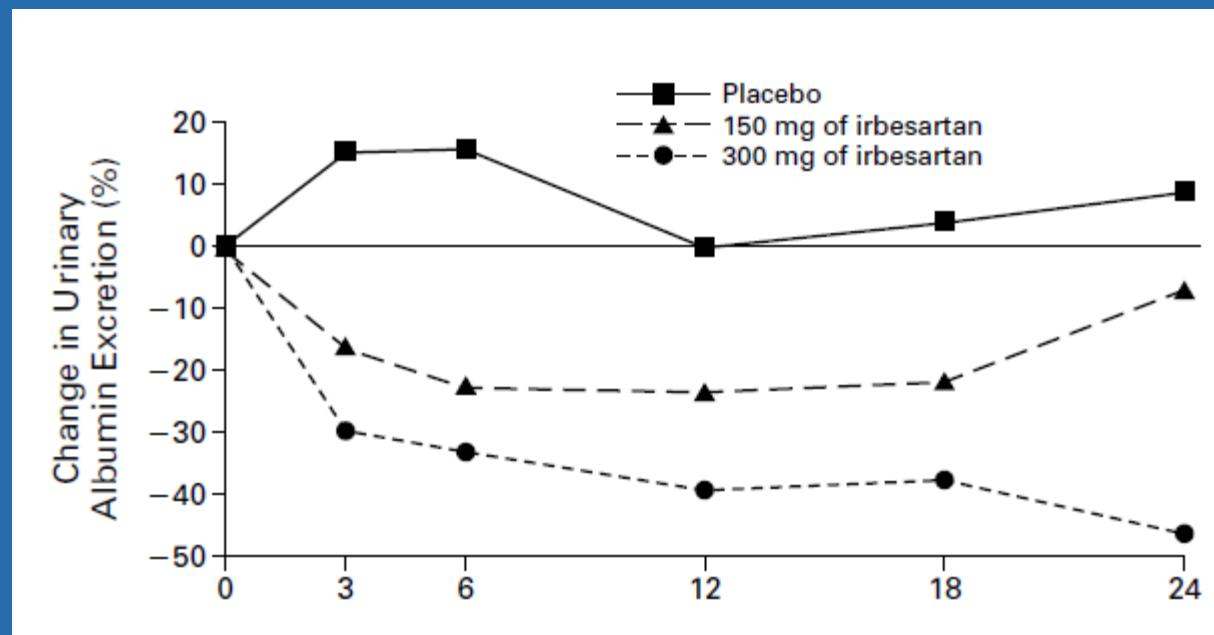
THE EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PTS WITH TYPE 2 DIABETES

Parving, NEJM 2001; 345: 870-878

IRMA

590 hypertensive patients with type 2 diabetes and persistent microalbuminuria

RENAL OUTCOME PROTEINURIA



ARBs in DIABETIC NEPHROPATHY TYPE II

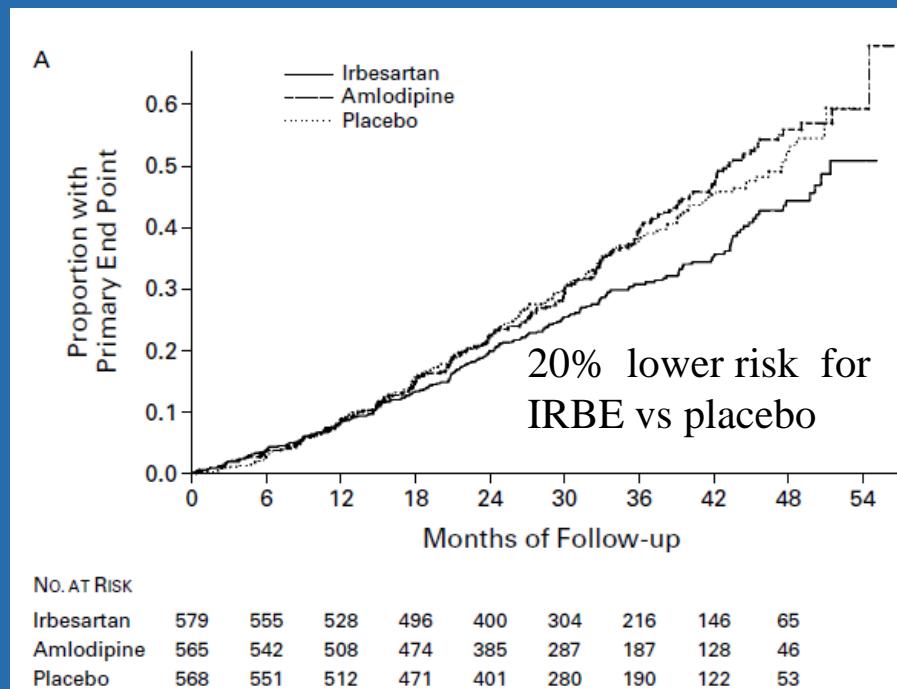
RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES

LEWIS EJ, NEJM 2001; 345: 851-860

IDNT

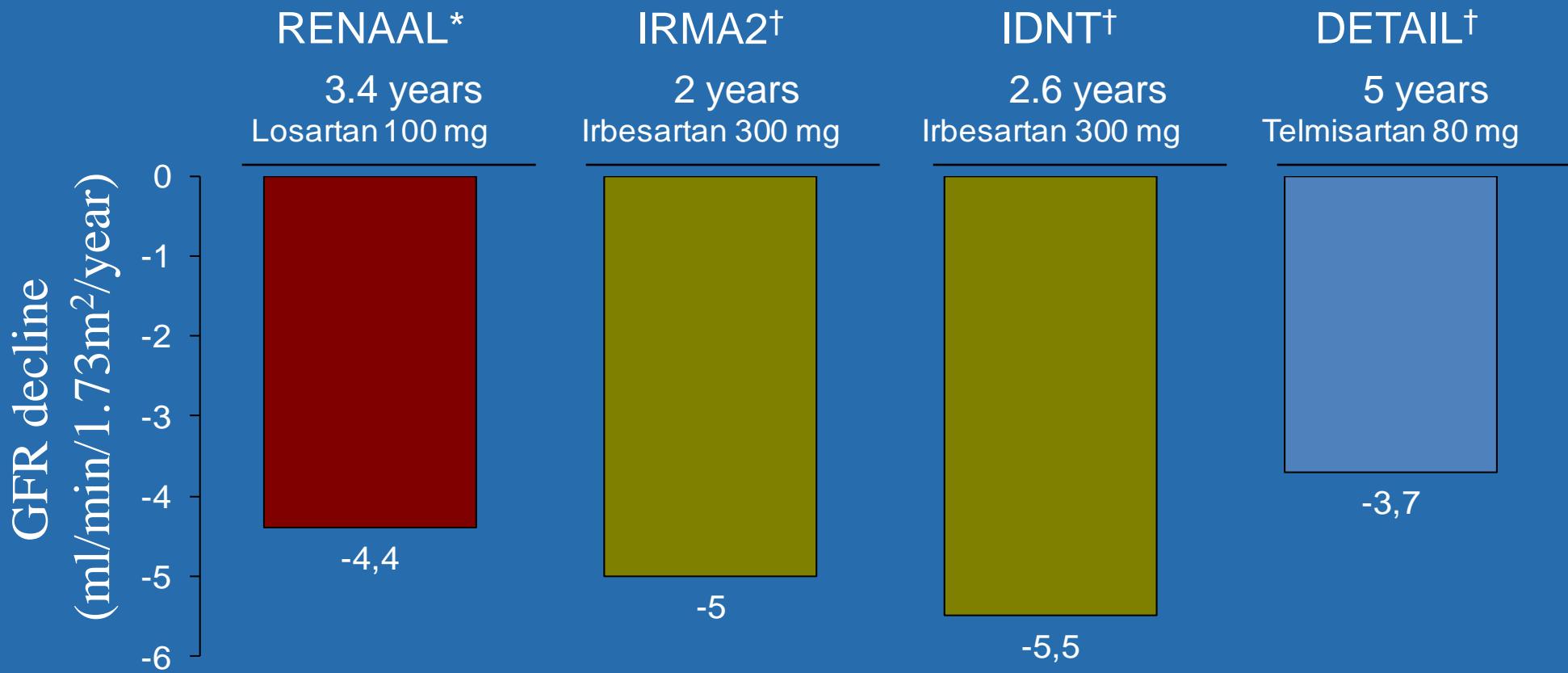
RENAL OUTCOME

- Irbesartan 300
- Amlodipine 10
- Placebo



The primary end point was the composite of a doubling of the base creatinine , the onset of ESRD (as indicated by the initiation of dialysis, renal transplantation, or a serum creatinine of at least 6.0 mg/d), or death from any cause

Renoprotective effects of ARBs: GFR decline in DETAILED, IRMA 2, IDNT and RENAAL

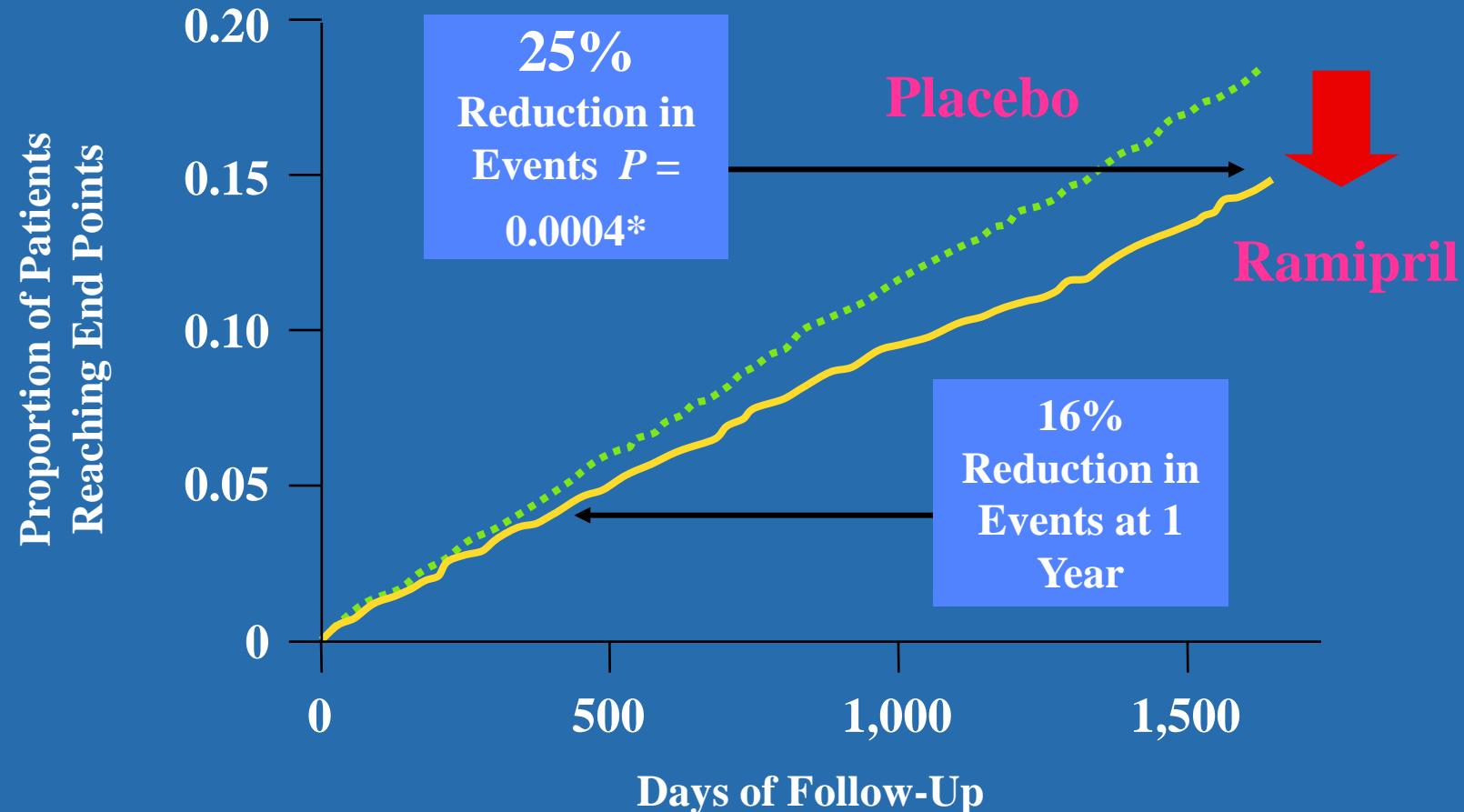


* Median

† Mean

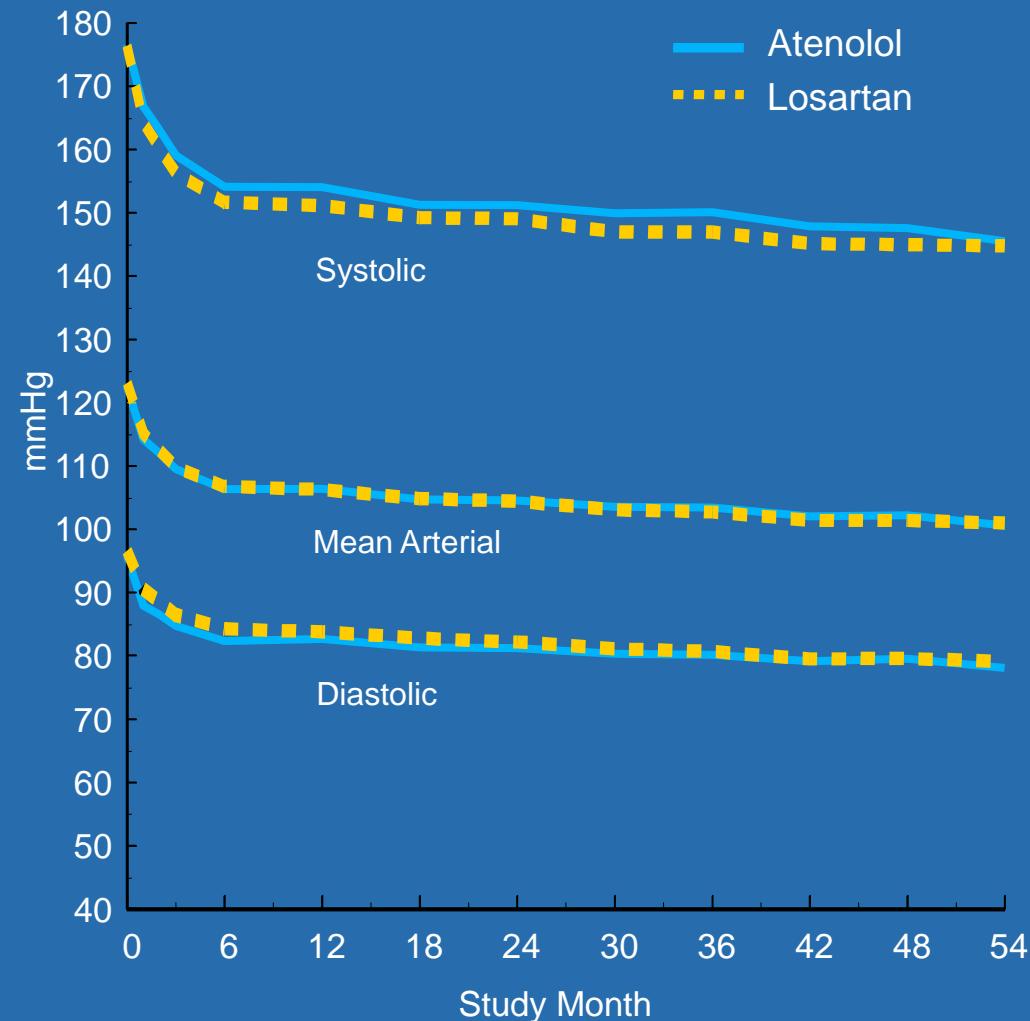
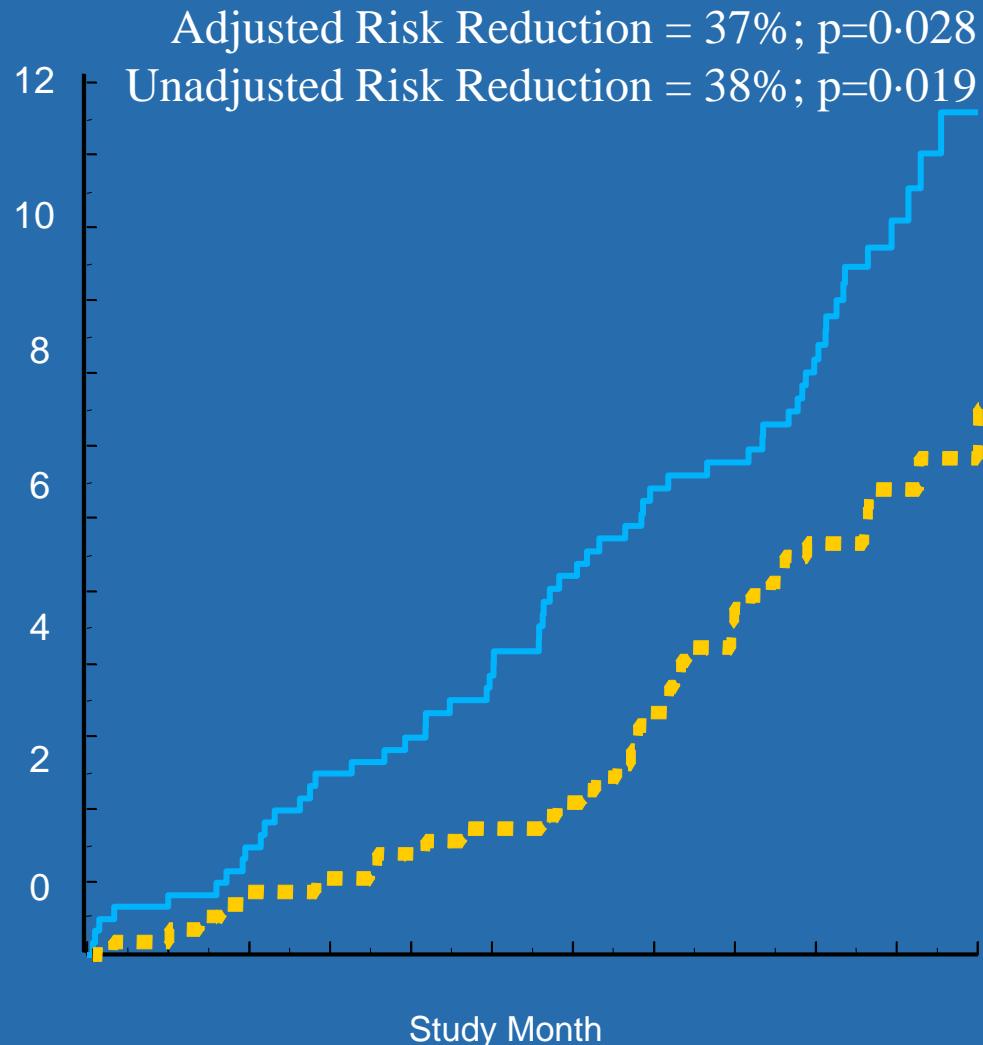
Parving et al. N Engl J Med 2001; Brenner et al. N Engl J Med 2001
Lewis et al. N Engl J Med 2001; Barnett et al. N Engl J Med 2004; 351:1952–1961

MICRO-HOPE*: Primary Outcome Reductions in Stroke, MI, and CV Death



Trial halted early because of the highly significant risk reductions seen with ramipril
HOPE Study Investigators. Lancet 2000; 355: 253-259.

LIFE: Hypertensive diabetic with LVH; Cardiovascular mortality comparing RAAS-i and beta-blockade



ARBs in DIABETIC NEPHROPATHY TYPE II CV OUTCOMES

RENAAL: Losartan 100 vs placebo

IDNT: Irbesartan 300 vs amlodipine 10 vs placebo

IRMA: Irbesartan 300 vs irbesartan 150 vs placebo

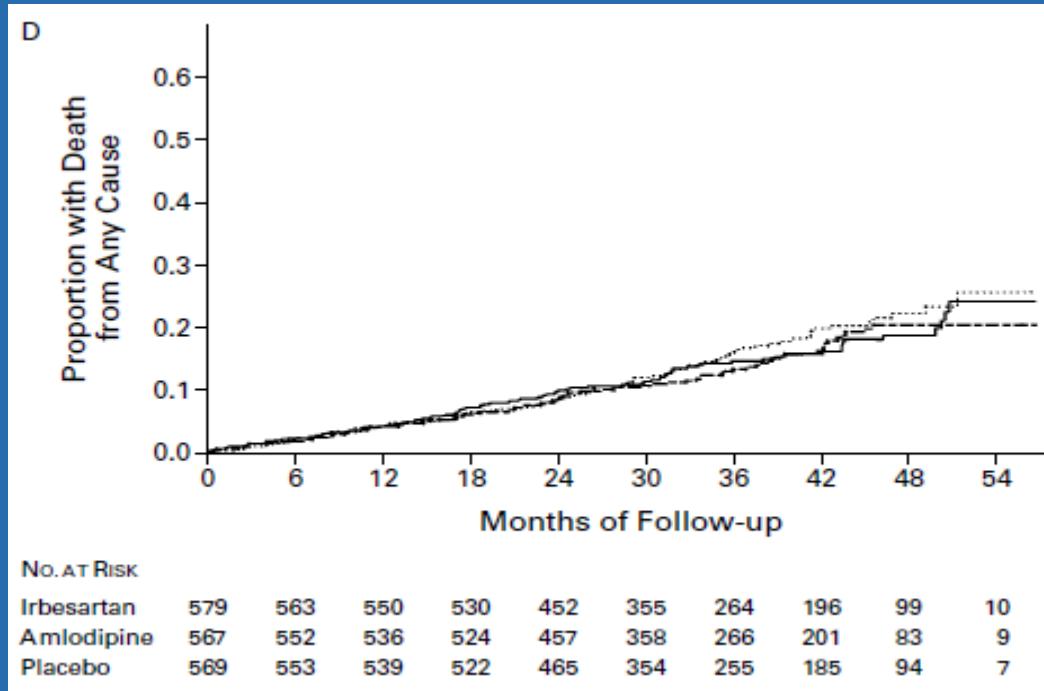
NO DIFFERENCE ON CV OUTCOMES

ARBs in DIABETIC NEPHROPATHY TYPE II MORTALITY OUTCOME

RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST
IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES
LEWIS EJ, NEJM 2001; 345: 851-860

IDNT

- Irbesartan 300
- Amlodipine 10
- Placebo



no significant difference among the three groups in the unadjusted risk of death from any cause

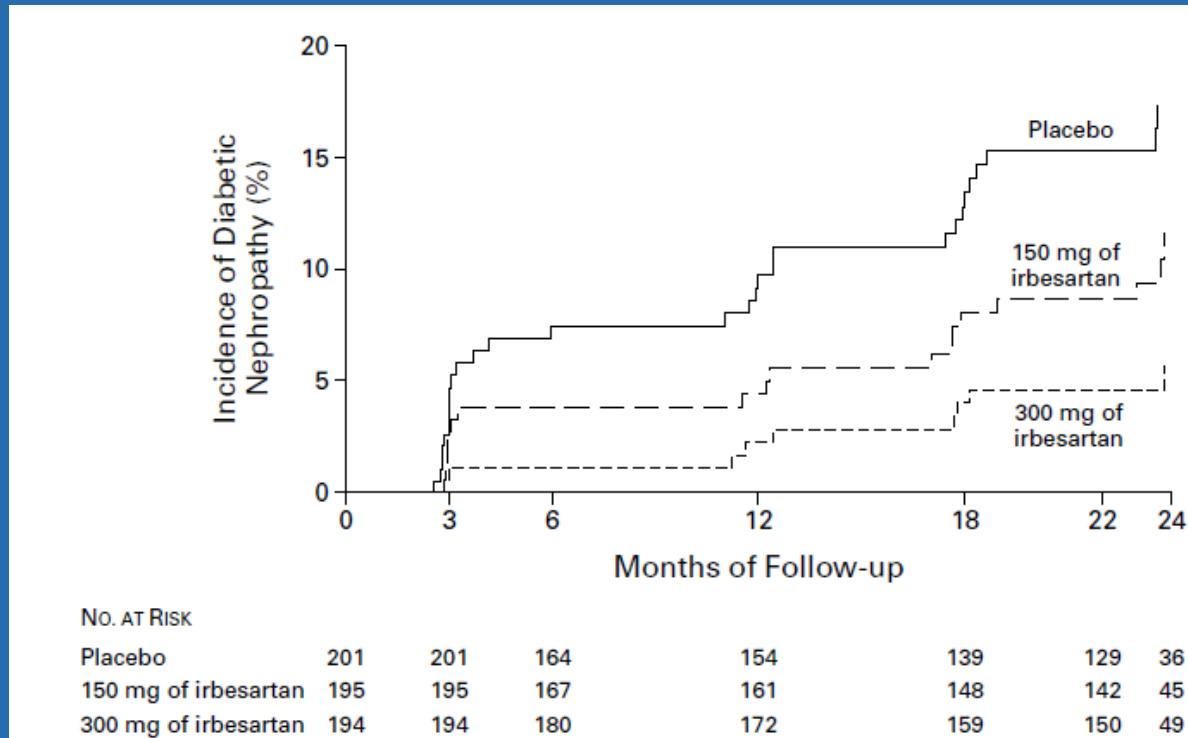
ARBs PREVENT THE PROGRESSION FROM MICRO ALBUMINURIA TO PROTEINURIA

THE EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

Parving, NEJM 2001; 345: 870-878

IRMA 2

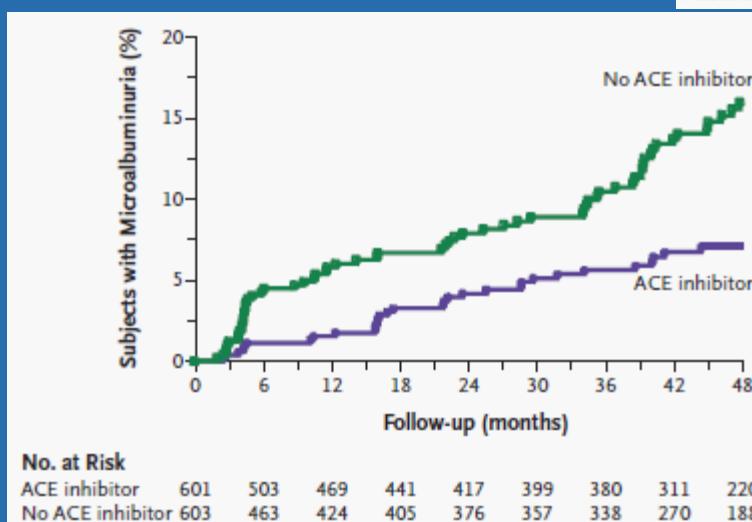
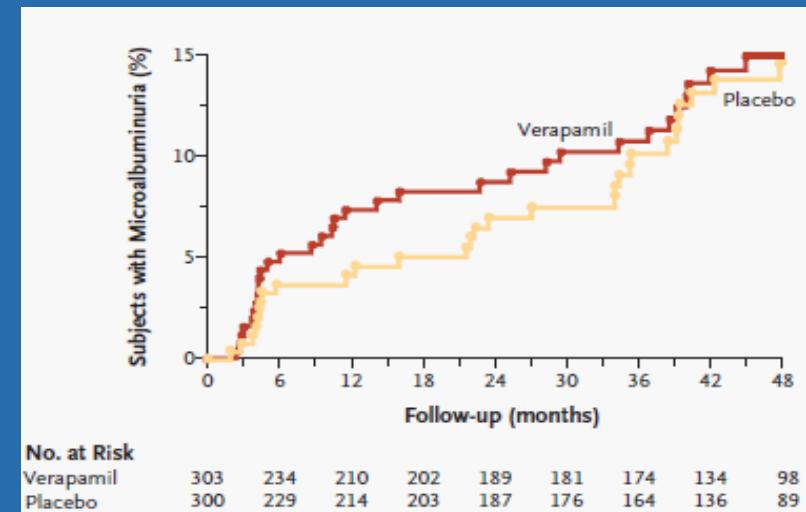
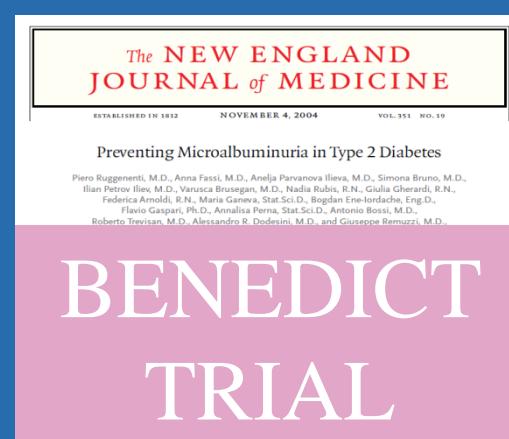
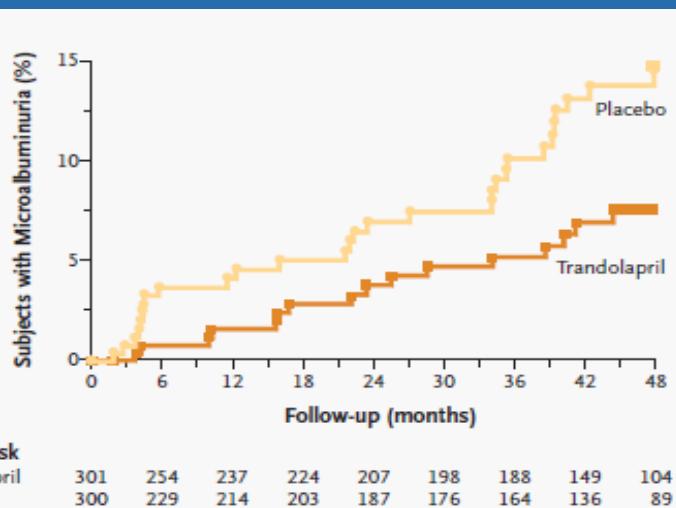
590 hypertensive patients with type 2 diabetes and persistent microalbuminuria



ACE ΚΑΙ ΕΜΦΑΝΙΣΗ ΜΙΚΡΟΛΕΥΚΩΜΑΤΙΝΟΥΡΙΑΣ ΣΕ ΣΔ II ΚΑΙ AY

type 2 DM not exceeding 25 years, >40 y and HTN
urinary albumin excretion rate < 20 µg/min ,
serum creatinine <1.5 mg/dL.

N=1204



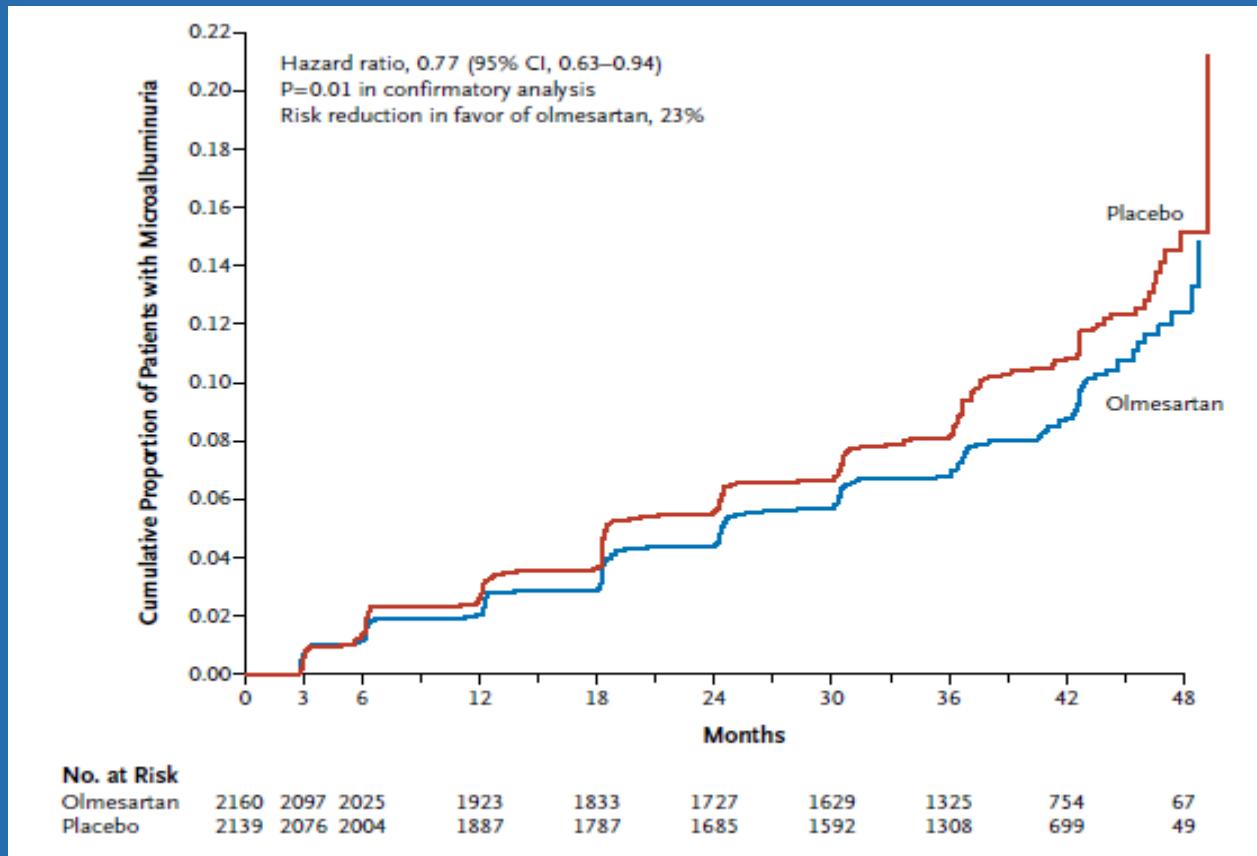
Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes

Haller H, NEJM 2011;364:907-17

N=4300

FU: 4y

ROADMAP



Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes

Haller H, NEJM 2011;364:907-17

ROADMAP

Table 2. Secondary Efficacy End Points during the Double-Blind Treatment Period.*

End Point	Olmesartan (N=2232)	Placebo (N=2215)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Composite of cardiovascular complications or death from cardiovascular causes	96 (4.3)	94 (4.2)	1.00 (0.75–1.33)	0.99
Composite of death from any cause	26 (1.2)	15 (0.7)	1.70 (0.90–3.22)	0.10
Death from cardiovascular causes	15 (0.7)	3 (0.1)		
Death not related to cardiovascular causes	8 (0.4)	10 (0.5)		
Death from unknown cause	3 (0.1)	2 (0.1)		
Composite of death from cardiovascular causes	15 (0.7)	3 (0.1)	4.94 (1.43–17.06)	0.01
Sudden cardiac death	7 (0.3)	1 (<0.1)		
Death due to fatal myocardial infarction	5 (0.2)	0		
Evidence of recent myocardial infarction on autopsy	0	0		
Death due to congestive heart failure	0	0		
Death during or after percutaneous transluminal coronary angioplasty or CABG	1 (<0.1)	0		
Death due to fatal stroke	2 (0.1)	2 (0.1)		
Composite of cardiovascular complications, excluding new-onset atrial fibrillation and transient ischemic attack	63 (2.8)	71 (3.2)	0.87 (0.62–1.22)	0.42
Composite of new-onset atrial fibrillation or transient ischemic attack	19 (0.9)	28 (1.3)	0.67 (0.37–1.19)	0.17
Composite of all cardiovascular complications	81 (3.6)	91 (4.1)	0.87 (0.65–1.18)	0.37

* All results were based on adjudicated end points. The composite secondary efficacy end points were analyzed with the use of a Cox proportional-hazards regression model with study treatment as the fixed effect. For composite end points, the time to the onset of an event was defined as the time from randomization (date of visit 1) to the first occurrence of any component of the composite end point. CABG denotes coronary-artery bypass grafting.

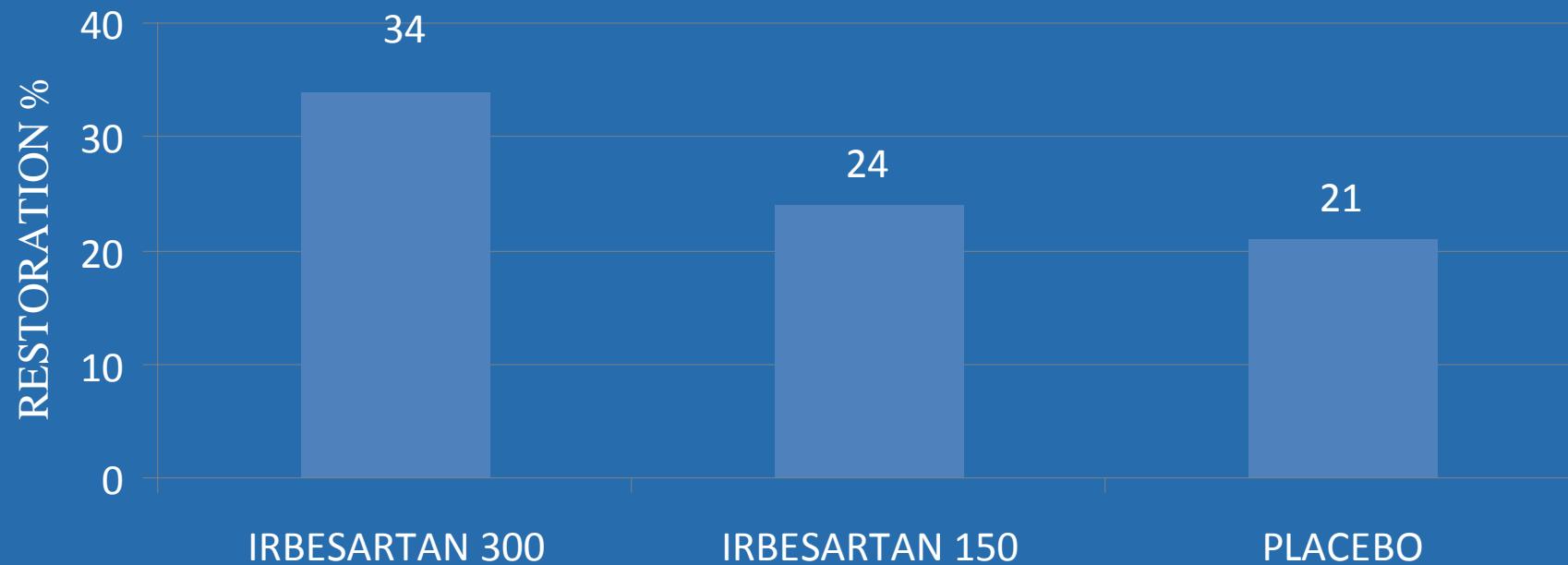
RESTORATION OF NORMOALBUMINURIA IN ARBs TREATED TYPE II DIABETICS WITH MICRO ALBUMINURIA

THE EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF
DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

Parving, NEJM 2001; 345: 870-878

IRMA 2

590 hypertensive patients with type 2 diabetes and persistent microalbuminuria



ΑΝΑΣΤΟΛΗ ΤΟΥ RAS ΚΑΙ ΕΜΦΑΝΙΣΗ ΜΙΚΡΟΛΕΥΚΩΜΑΤΙΝΟΥΡΙΑΣ ΣΕ ΣΔ Ι ΧΩΡΙΣ ΥΠΕΡΤΑΣΗ

Renal and Retinal Effects of Enalapril and Losartan in Type 1 Diabetes
Mauer M, NEJM 2009; 361: 40-51

N=285
FU: 5y
Losartan 100
Enalapril 20
Placebo

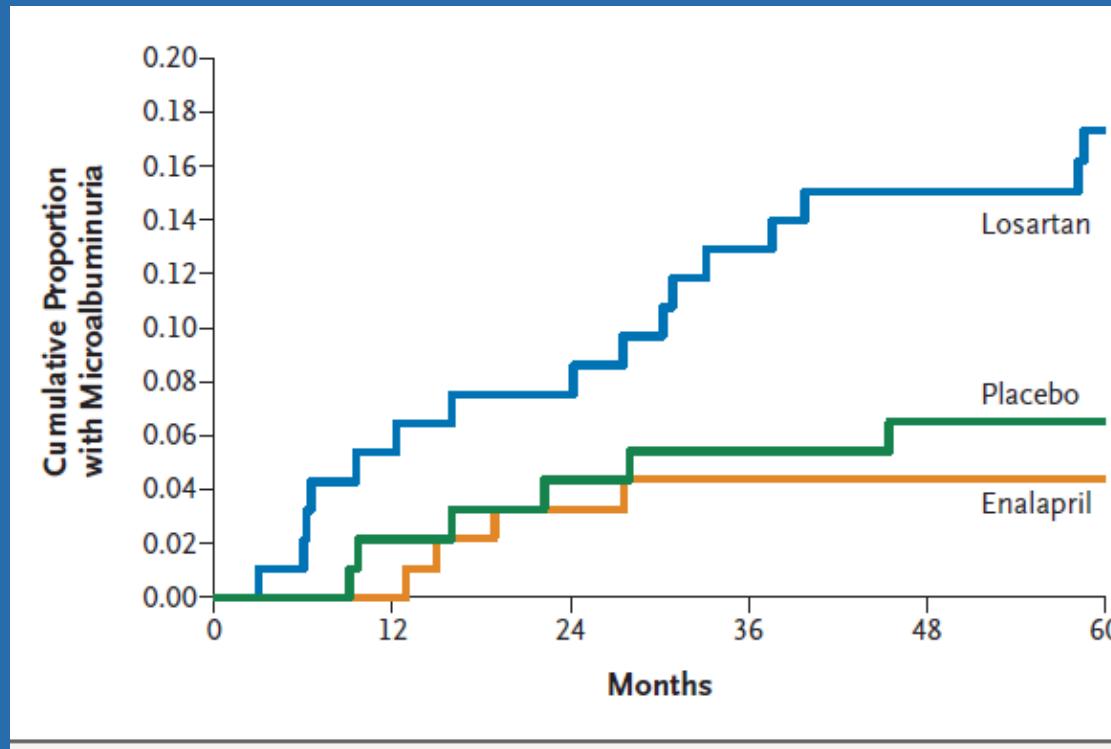
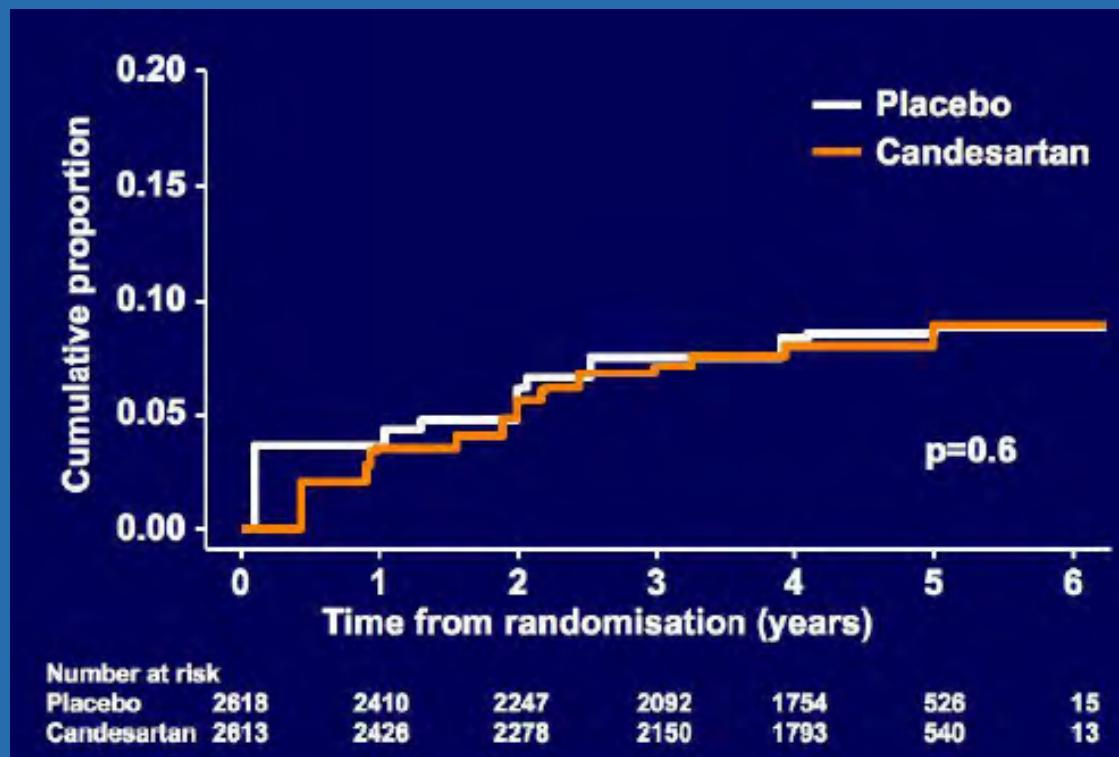


Figure 2. Kaplan–Meier Estimates of Time to Microalbuminuria.

ΑΝΑΣΤΟΛΗ ΤΟΥ RAS ΚΑΙ ΕΜΦΑΝΙΣΗ ΜΙΚΡΟΛΕΥΚΩΜΑΤΙΝΟΥΡΙΑΣ ΣΕ ΣΔ ΧΩΡΙΣ ΥΠΕΡΤΑΣΗ

DIRECT



Type 1 (n=3326) / Type 2 diabetics (n=1905)

Normotensive with normoalbuminuria

FU: 4.7 y

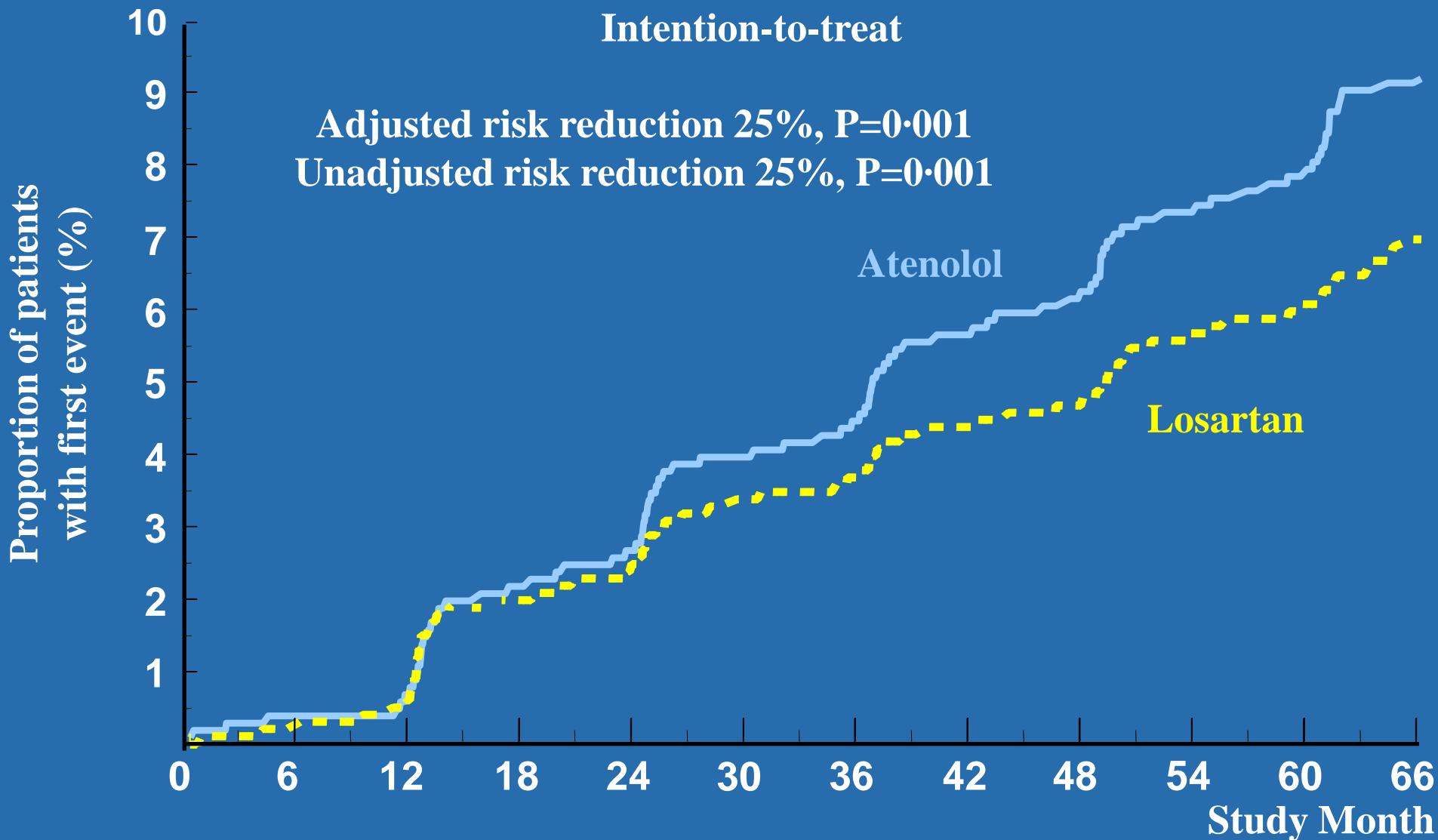
RAS BLOCKADE REDUCE THE INCIDENCE OF NEW-ONSET DIABETES

RAS BLOCKADE REDUCE THE INCIDENCE OF NEW-ONSET DIABETES

Table 3 Effects of inhibition of the renin–angiotensin system on risk of new-onset diabetes in select key randomised controlled trials

Study	Comparators	Duration (years)*	Patient population	Relative risk (95% CI)	p-Value	Prespecified end-point?
ACE inhibitors						
CAPP (41)	Captopril vs. β-blocker/diuretic	6.1	10,985 hypertensive patients	0.79 (0.67–0.94)	0.007	Yes
HOPE (42)	Ramipril vs. placebo	5	9297 patients with history of CAD, stroke, PVD, for diabetes and ≥ 1 other CVD risk factor	0.66 (0.51–0.85)	< 0.001	Yes
ALLHAT (43)	Lisinopril vs. diuretic	4.9	33,357 hypertensive patients with ≥ 1 other CVD risk factor	0.70 (0.56–0.86)	< 0.001	No
PEACE (44)	Trandolapril vs. placebo	4.8 (median)	8290 with stable CAD	0.83 (0.72–0.96)	0.001	No
ASCOT-BPLA (39)	Amlodipine (±perindopril) vs. atenolol (+diuretic)	5.5 (median)	19,257 hypertensive patients with ≥ 3 other CVD risk factors	0.70 (0.63–0.78)	< 0.0001	Yes
DREAM (51)	Ramipril vs. placebo	3.0 (median)	5269 patients with IFG and/or IGT but without CVD or renal disease	0.91 (0.80–1.03)	ns	Yes
ARBs						
LIFE (45)	Losartan vs. atenolol	4.8	9193 hypertensive patients with LVH	0.75 (0.63–0.86)	0.001	Yes
SCOPE (46)	Candesartan vs. placebo/other drugs	3.7	4964 hypertensive patients aged 70–89 years	0.81 (0.61–1.02)	0.09	No
CHARM (47)	Candesartan vs. placebo	3.1	7599 patients with HF	0.78 (0.64–0.96)	0.02	Yes
VALUE (48)	Valsartan vs. amlodipine	4.2	15,245 hypertensive patients with high risk of CVD events	0.77 (0.69–0.86)	< 0.0001	Yes
TRANSCEND (57)	Telmisartan vs. placebo	4.7 (median)	5926 patients intolerant to ACE inhibitors with CAD, PVD, CBVD or diabetes with end-organ damage	0.85 (0.71–1.02)	0.081	Yes
ACE inhibitor/ARB combination						
ONTARGET (56)	Telmisartan vs. ramipril; telmisartan + ramipril vs. ramipril	4.7 (median)	25,620 patients with CAD, PVD, CBVD or diabetes with end-organ damage	1.12 (0.97–1.29)	ns	Yes
				0.91 (0.78–1.06)	ns	

LIFE Study New-Onset Diabetes



DREAM STUDY

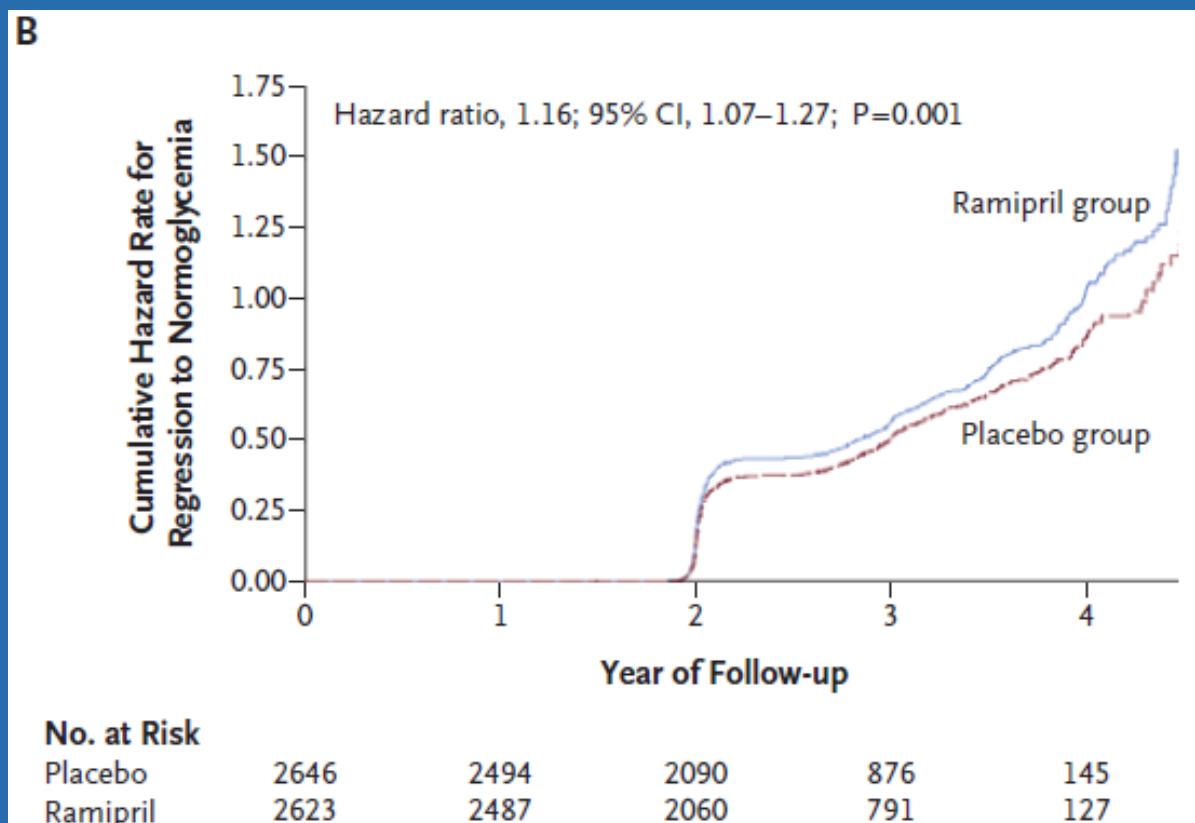
Effect of Ramipril on the Incidence of Diabetes

NEJM 2006; 355: 1551-1562

Pts with CV disease with impaired FGL (110-126) or impaired glucose tolerance (140-200)

N=5269

Regression to normoglycemia



RAS BLOCKADE REDUCE THE INCIDENCE OF NEW-ONSET DIABETES

Βελτιώνει τον μεταβολισμό της γλυκόζης

αυξάνει την ευαισθησία του υποδοχέα της ινσουλίνης στα μυϊκά και λιπώδη κύτταρα
αυξάνει τη μεταφορά των GLUT4 στην κυτταρική μεμβράνη

↑ ροή αίματος στους μύες

↑ ροής αίματος στα νησίδια του παγκρέατος που οδηγεί σε αυξημένη παραγωγή ινσουλίνης

Μειώνει την απόπτωση των β-κυττάρων

Μειώνουν την απώλεια K+

αυξάνει η έκκριση ινσουλίνης από τα β-κύτταρα

Αυξάνει τα επίπεδα της αδιπονεκτίνης

η αδιπονεκτίνη αυξάνει την ευαισθησία στην ινσουλίνη

ACEi or ARB on diabetic nephropathy ?

ACEi or ARB on Diabetic Nephropathy?

DETAIL STUDY

RENAL OUTCOME

Barnett AH, NEJM 2004; 351:1952-1961

Table 3. Secondary Renal End Points after Five Years of Treatment, According to Analysis of the Last Observation Carried Forward.*

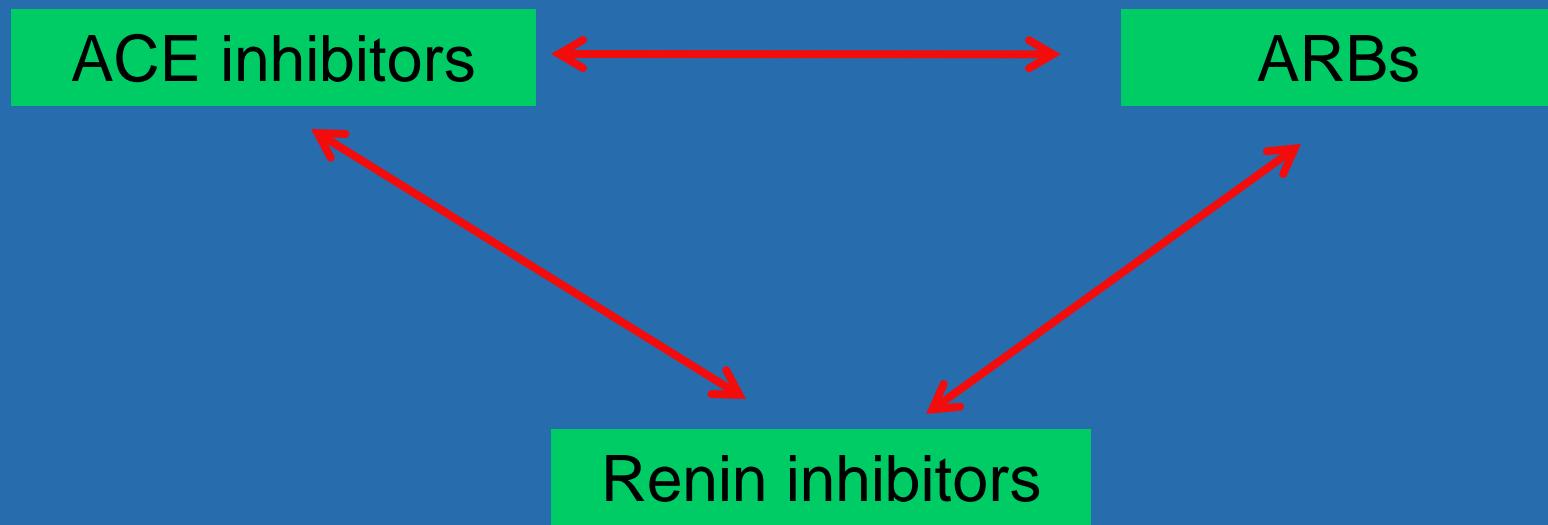
End Point	Change from Baseline		Difference between Groups (95% CI)
	Telmisartan Group	Enalapril Group	
Serum creatinine (mg/dl)	0.10	0.10	0 (-0.66 to 0.65)
Urinary albumin excretion (ratio)†	1.03	0.99	1.04 (0.71 to 1.51)‡

* One hundred sixteen subjects (35 with the last observation carried forward) in the telmisartan group and 128 (44 with the last observation carried forward) in the enalapril group were included in the analysis of serum creatinine, and 115 (35 with the last observation carried forward) and 125 (42 with the last observation carried forward), respectively, were included in the analysis of urinary albumin excretion.

† Urinary albumin excretion rates were determined as the ratio of the final value to the baseline value.

‡ The ratio of the difference between treatment groups is shown. Because of the skewed distribution of the albumin excretion rate, the log analysis (when log values are converted back to nonlog values, or "anti-logged") yields treatment ratios, both for treatment means (ratio of year 5 value to baseline value) and treatment differences (ratio of telmisartan to enalapril).

- Prospective, multicentered, double-blind study
- 250 patients with type 2 DM and DN (micro or macroalbuminuria)
- Telmisartan 80 mg vs enalapril 20 mg
- Follow-up: 5y
- Primary end-point: change in iohexol GFR
- Secondary end-points: creat, UAE, BP no difference!



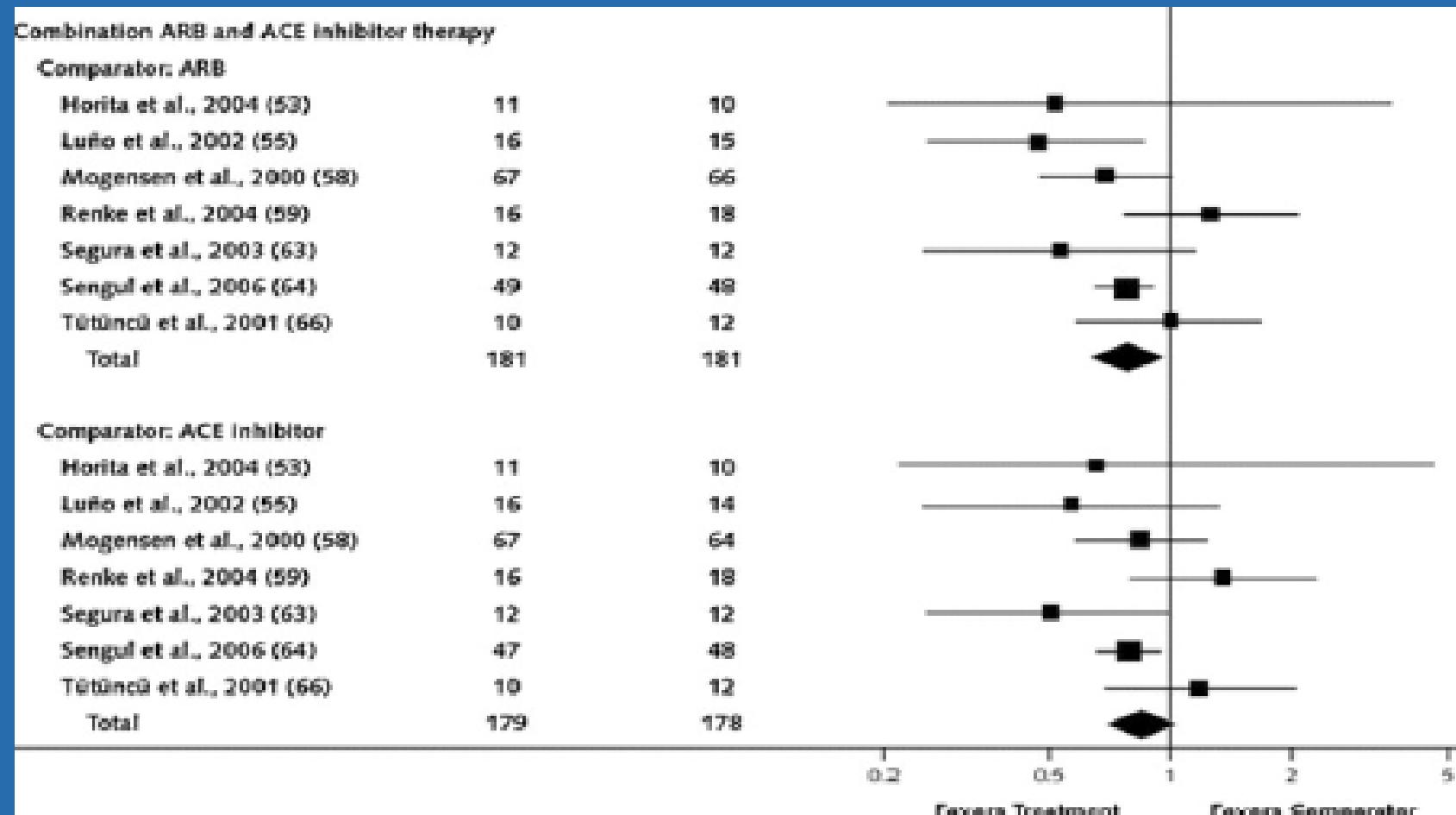
Mineralocorticoid Antagonism

Γιατί διπλή ή ίσως και τριπλή αναστολή του άξονα;

1. Κάθε ουσία μπλοκάρει ένα μόνο κομμάτι του καταράκτη του άξονα
2. Aldosterone escape
3. Εναπομείνουσα λευκωματουρία (RENAAL)

Meta-analysis: Effect of Monotherapy and Combination Therapy with Inhibitors of the Renin–Angiotensin System on Proteinuria in Renal Disease

Kunz R, Ann Intern Med 2008; 148(1): 30-48



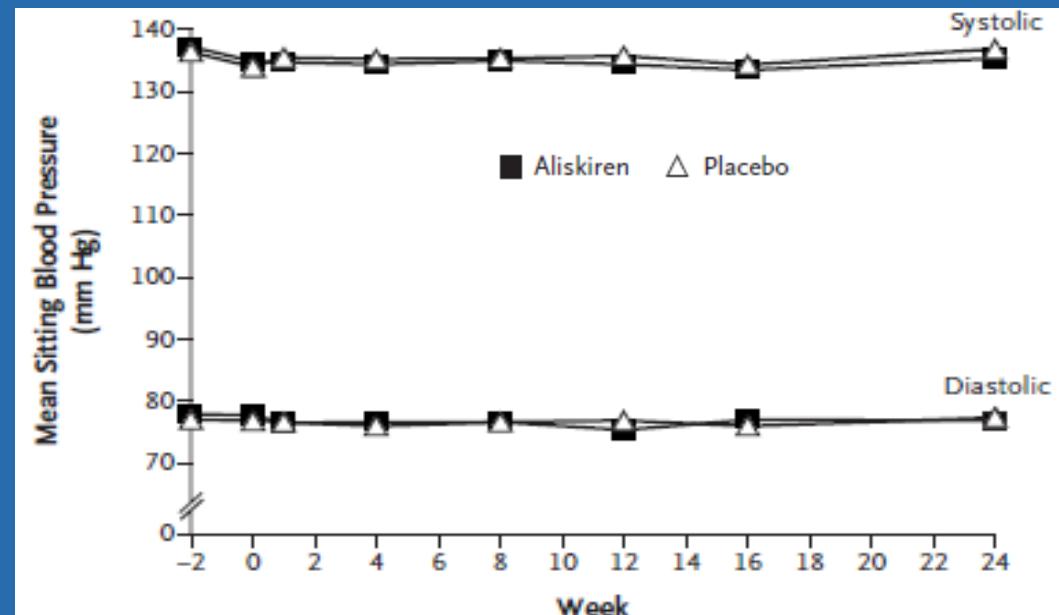
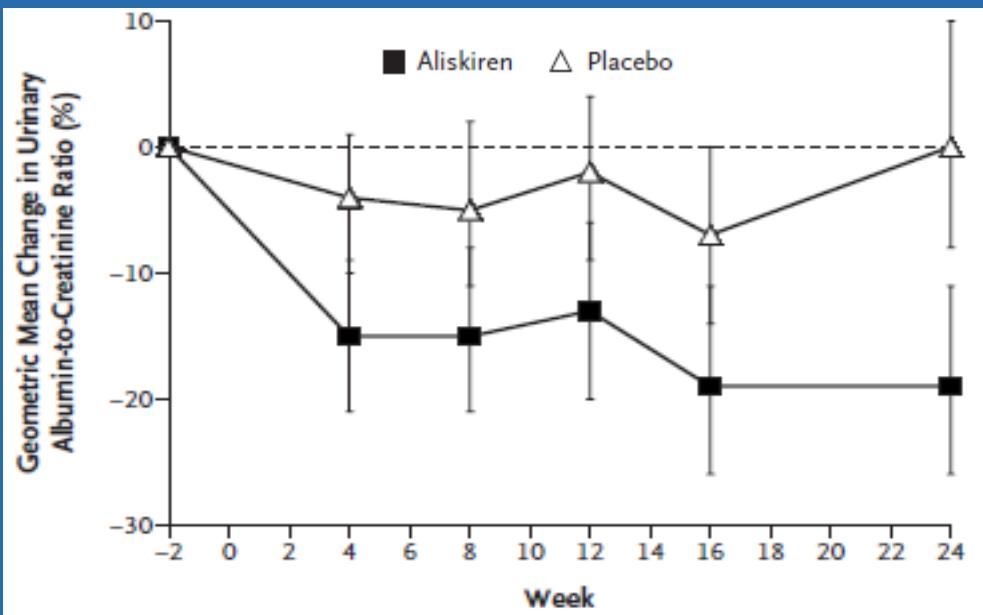
Aliskiren Combined with Losartan in Type 2 Diabetes & Nephropathy

Parving H-H, NEJM 2008; 358: 2433-2446

AVOID TRIAL

Hypertensive Type 2 Diabetics with Albuminuria

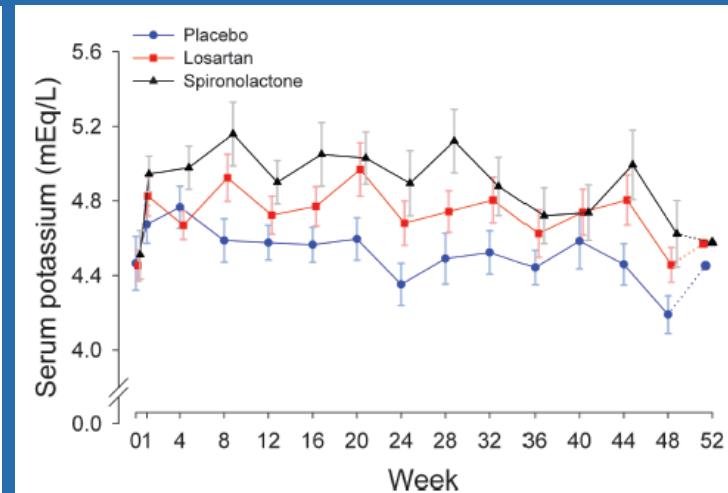
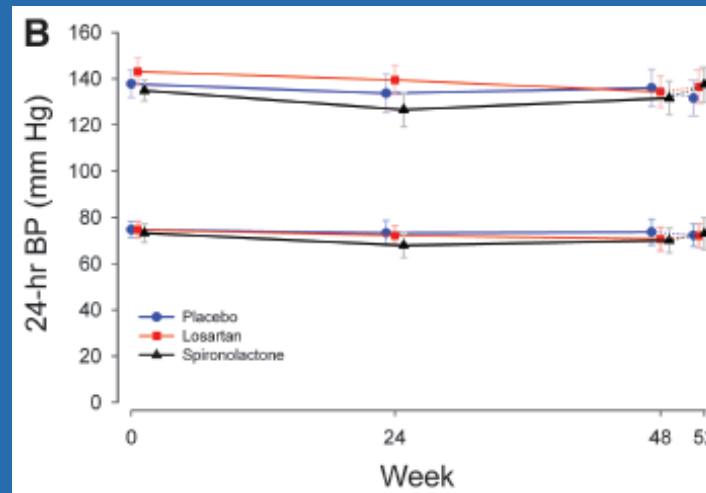
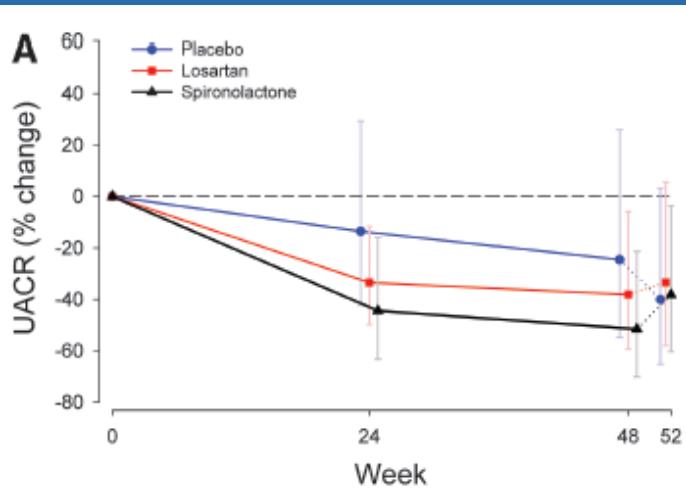
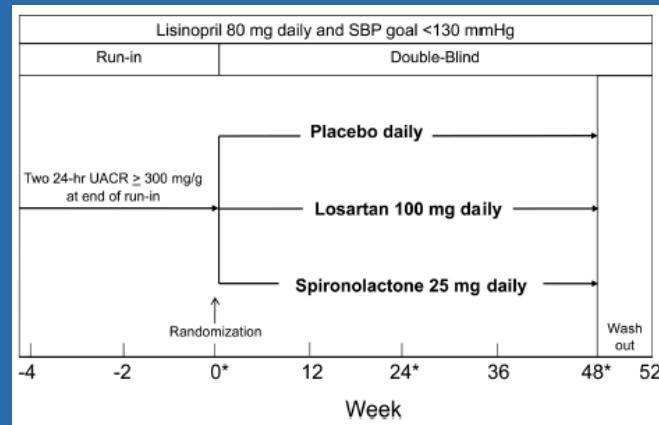
Aliskiren 300 mg (**N = 301**) or placebo (**N = 298**) added on Losartan 100mg



Aliskiren reduced albuminuria by 20%

Addition of ARB or Mineralocorticoid Antagonism to Maximal ACE Inhibition in Diabetic Nephropathy

Mehdi UF, JASN 2009; 20: 2641-2650



Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

ONTARGET

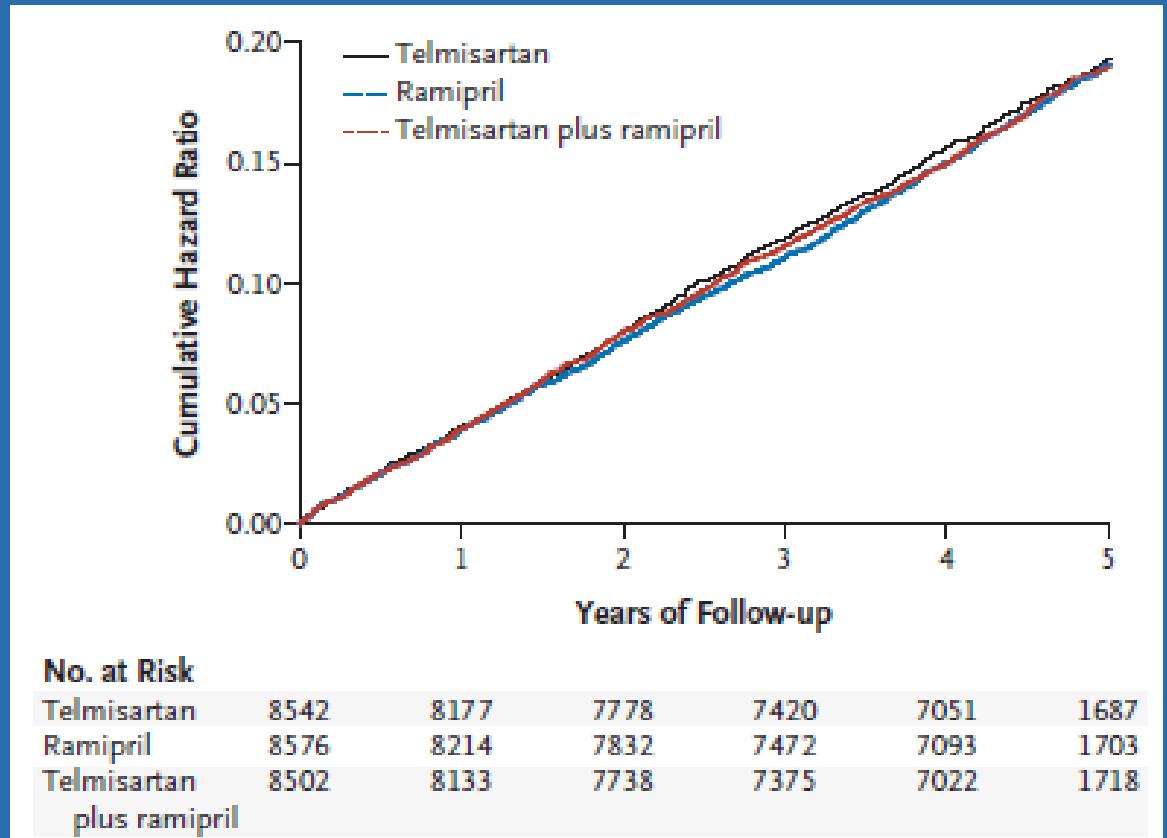
Ramipril
(N = 8576)

Telmisartan
(N = 8542)

Combination Therapy
(N = 8502)

69% had hypertension, and 38% had diabetes

Composite primary outcome :
death from cardiovascular
myocardial infarction
stroke
hospitalization for heart failure



Kaplan–Meier Curves for the Primary Outcome in the Three Study Groups

ONTARGET: RENAL OUTCOMES

	Ramipril n (%)	Telmisartan n (%)	Ramipril+ telmisartan n (%)	Telmisartan vs ramipril HR (95% CI)	p	Ramipril+ telmisartan vs ramipril HR (95% CI)	p
All dialysis, doubling, death	1150 (13.4)	1147 (13.4)	1233 (14.5)	1.00 (0.92-1.09)	0.968	1.09 (1.01-1.18)	0.037
All dialysis and doubling	174 (2.03)	189 (2.21)	212 (2.49)	1.09 (0.89-1.34)	0.420	1.24 (1.01-1.51)	0.038
All dialysis	48 (0.56)	51 (0.60)	63 (0.74)	1.07 (0.72-1.58)	0.747	1.33 (0.92-1.94)	0.133
All death	1014 (11.8)	989 (11.6)	1065 (12.5)	0.98 (0.90-1.07)	0.641	1.07 (0.98-1.16)	0.144
Doubling	140 (1.63)	155 (1.81)	166 (1.95)	1.11 (0.88-1.30)	0.378	1.20 (0.96-1.50)	0.110
Acute dialysis	13 (0.15)	20 (0.23)	28 (0.33)	1.55 (0.77-3.11)	0.221	2.19 (1.13-4.22)	0.020
Chronic dialysis	35 (0.39)	31 (0.36)	34 (0.40)	0.94 (0.58-1.54)	0.817	1.05 (0.65-1.69)	0.854

Dialysis=at least one dialysis. Chronic dialysis=more than 2 months. Acute dialysis=2 months or less. Doubling=doubling of serum creatinine from baseline values. HR=hazard ratio. Reasons for acute dialysis were reported as severe infection (n=22), volume depletion (n=9), post-surgery (n=7), drugs (n=5), specific renal diseases (n=5), and other reasons (n=23). In three of 165 originally reported cases of dialysis,* detailed analysis revealed that no dialysis took place. In three of the 162 cases of dialysis, we got no information on duration of dialysis. Investigators could report several reasons for acute dialysis.

Table 2: Incidence of primary and secondary renal outcomes and of its components

Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes

ALTITUDE STUDY

Type 2 diabetes at high risk for CV who were already taking a renin–angiotensin system blocker

PLACEBO

ALISKIREN

Table 2. Prespecified Primary and Secondary Composite Outcomes and Deaths.*

Outcome	Aliskiren (N=4274)	Placebo (N=4287)	Hazard Ratio (95% CI)	P Value†
	no. of patients (%)			
Primary composite outcome	783 (18.3)	732 (17.1)	1.08 (0.98–1.20)	0.12
Death from cardiovascular causes	246 (5.8)	215 (5.0)	1.16 (0.96–1.39)	0.12
Cardiac arrest with resuscitation	19 (0.4)	8 (0.2)	2.40 (1.05–5.48)	0.04
Myocardial infarction (fatal or nonfatal)	147 (3.4)	142 (3.3)	1.04 (0.83–1.31)	0.72
Stroke (fatal or nonfatal)	147 (3.4)	122 (2.8)	1.22 (0.96–1.55)	0.11
Unplanned hospitalization for heart failure	205 (4.8)	219 (5.1)	0.95 (0.78–1.14)	0.56
ESRD, death attributable to kidney failure, or loss of kidney function‡	121 (2.8)	113 (2.6)	1.08 (0.84–1.40)	0.56
Doubling of baseline serum creatinine	210 (4.9)	217 (5.1)	0.97 (0.80–1.17)	0.75
Cardiovascular composite outcome	590 (13.8)	539 (12.6)	1.11 (0.99–1.25)	0.09
Renal composite outcome	257 (6.0)	251 (5.9)	1.03 (0.87–1.23)	0.74
Death from any cause	376 (8.8)	358 (8.4)	1.06 (0.92–1.23)	0.42

* A patient may have had multiple cardiovascular and renal events of different types. All composite outcomes reflect only the first occurrence of any of the components.

† P values have not been adjusted for multiple comparisons.

‡ Loss of kidney function was defined by the need for renal-replacement therapy with no dialysis or transplantation available or initiated. ESRD denotes end-stage renal disease.

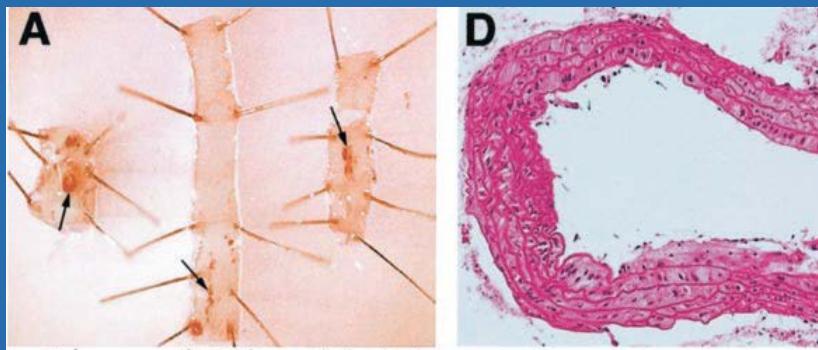
Ο ΡΟΛΟΣ ΤΟΥ ΑΛΑΤΙΟΥ

Prevention of Accelerated Atherosclerosis by ACE Inhibition in Diabetic Apolipoprotein E -Deficient Mice

Candido R, Circulation 2002;106:246-253

ApoE-Deficient Mice

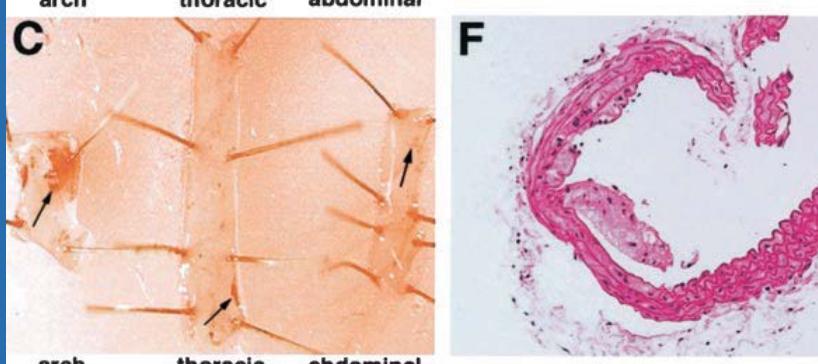
Control



Diabetic



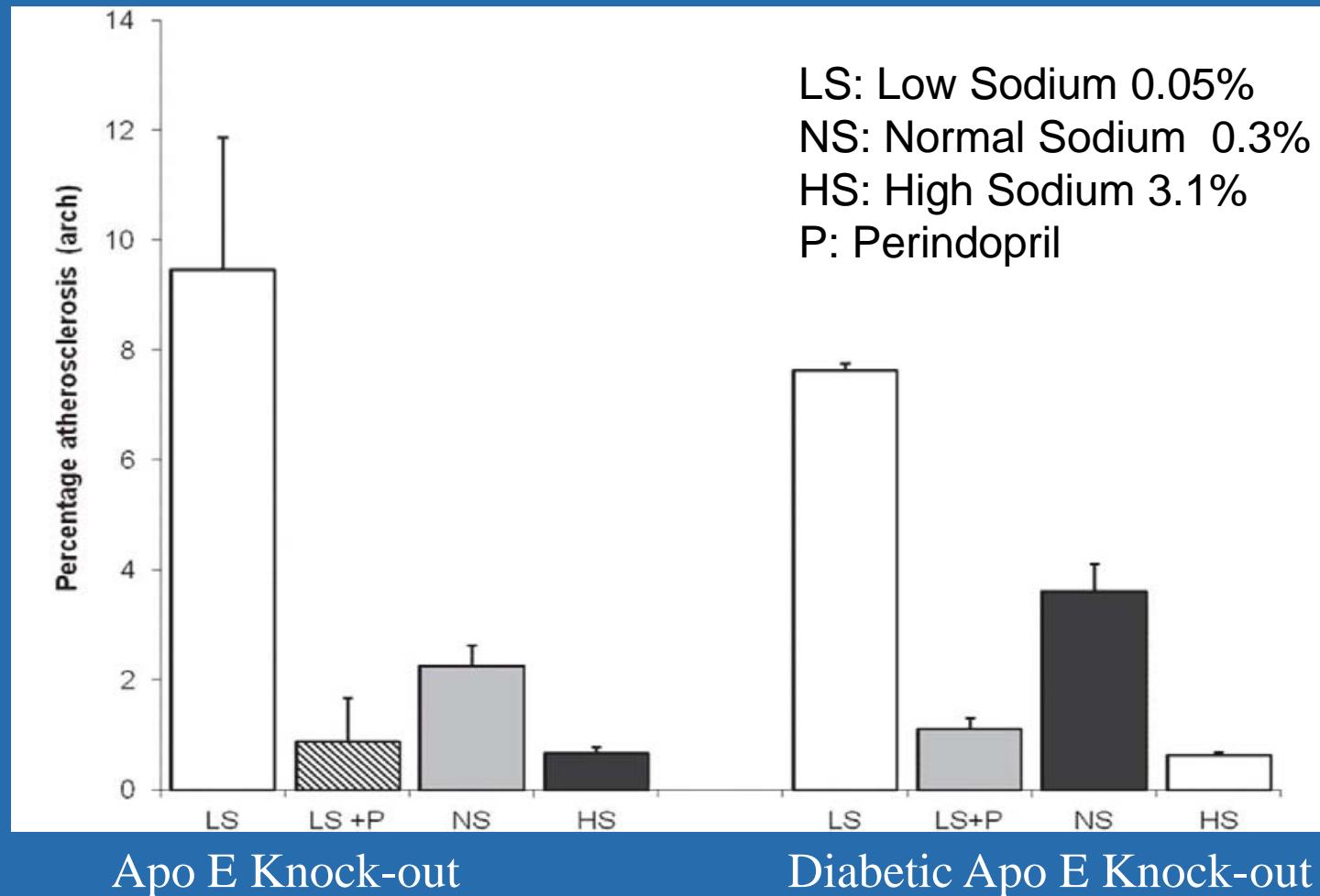
Diabetic + perindopril



Aortic arch and thoracic and abdominal aorta showing atherosclerotic lesions

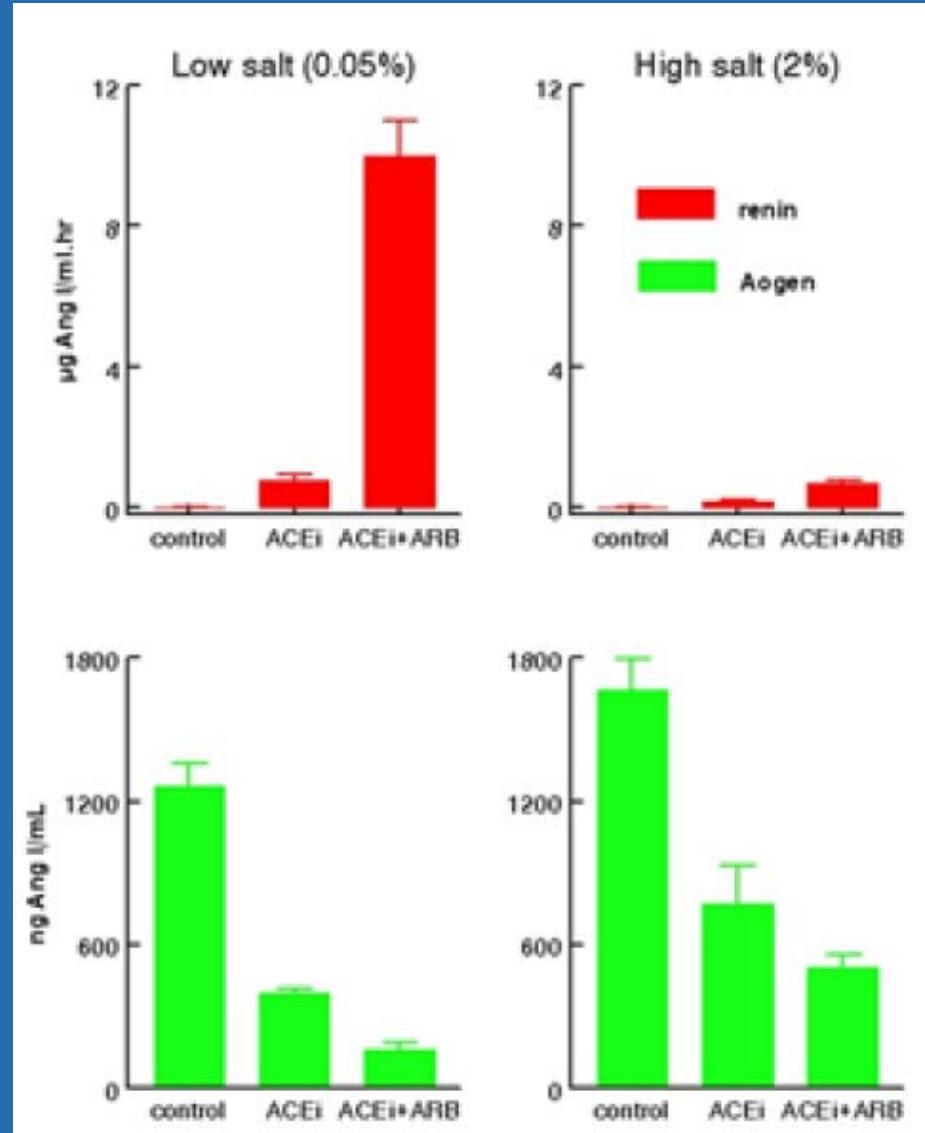
The association of dietary sodium intake with atherogenesis in experimental diabetes

Ticellis C, Clin Sci (Lond) 2013 May 1;124(10):617-26



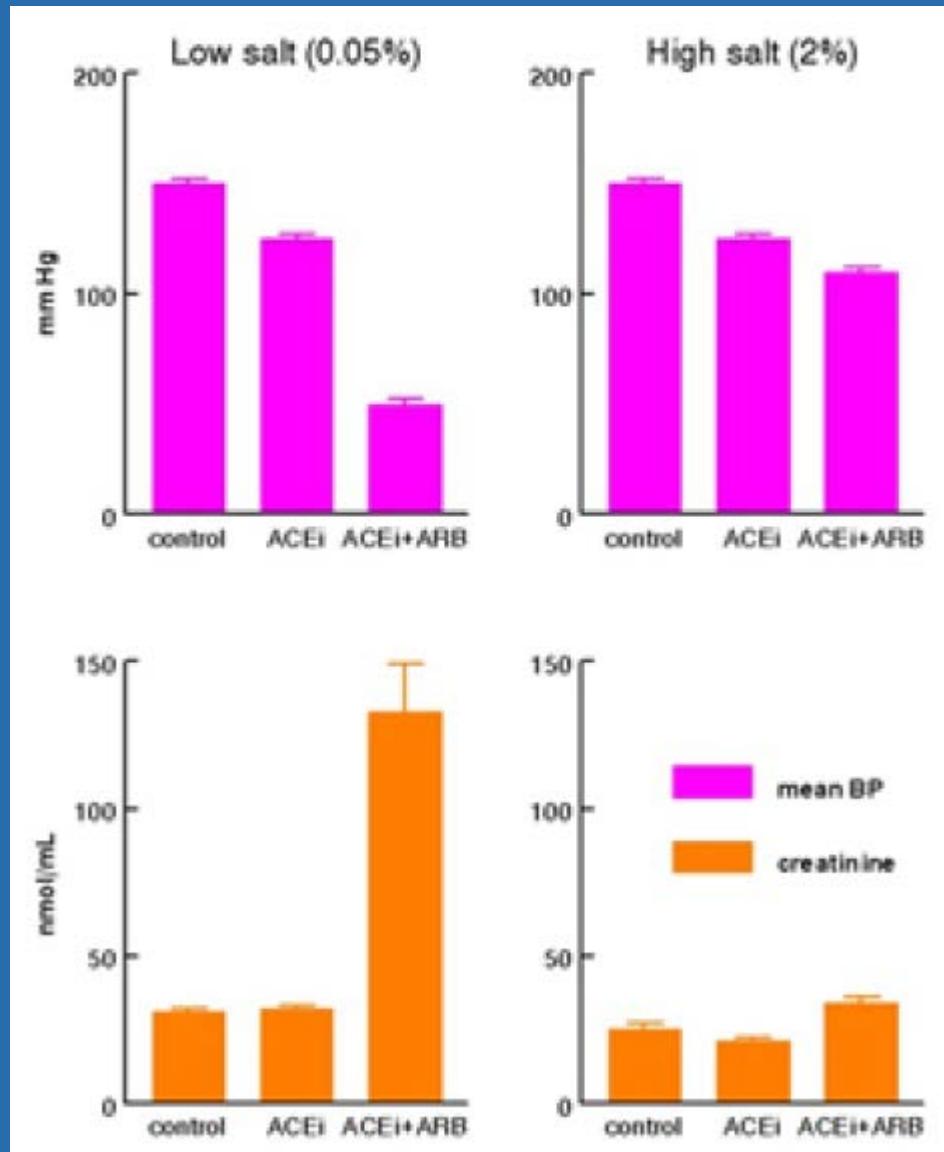
DUAL RAS BLOCKADE: THE IMPORTANCE OF SALT

Spontaneously
Hypertensive Rats



DUAL RAS BLOCKADE: THE IMPORTANCE OF SALT

Spontaneously
Hypertensive Rats



Urinary Sodium and Potassium Excretion and Risk of CV Events

O' Donnell MJ, JAMA 2011; 306(20): 2229-2238

ONTARGET and TRANSCEND trials N=28880

Main Outcome: CV death, MI, stroke, and hospitalization for CHF

Table 1. Baseline Patient Characteristics by 24-Hour Sodium Excretion Range^a

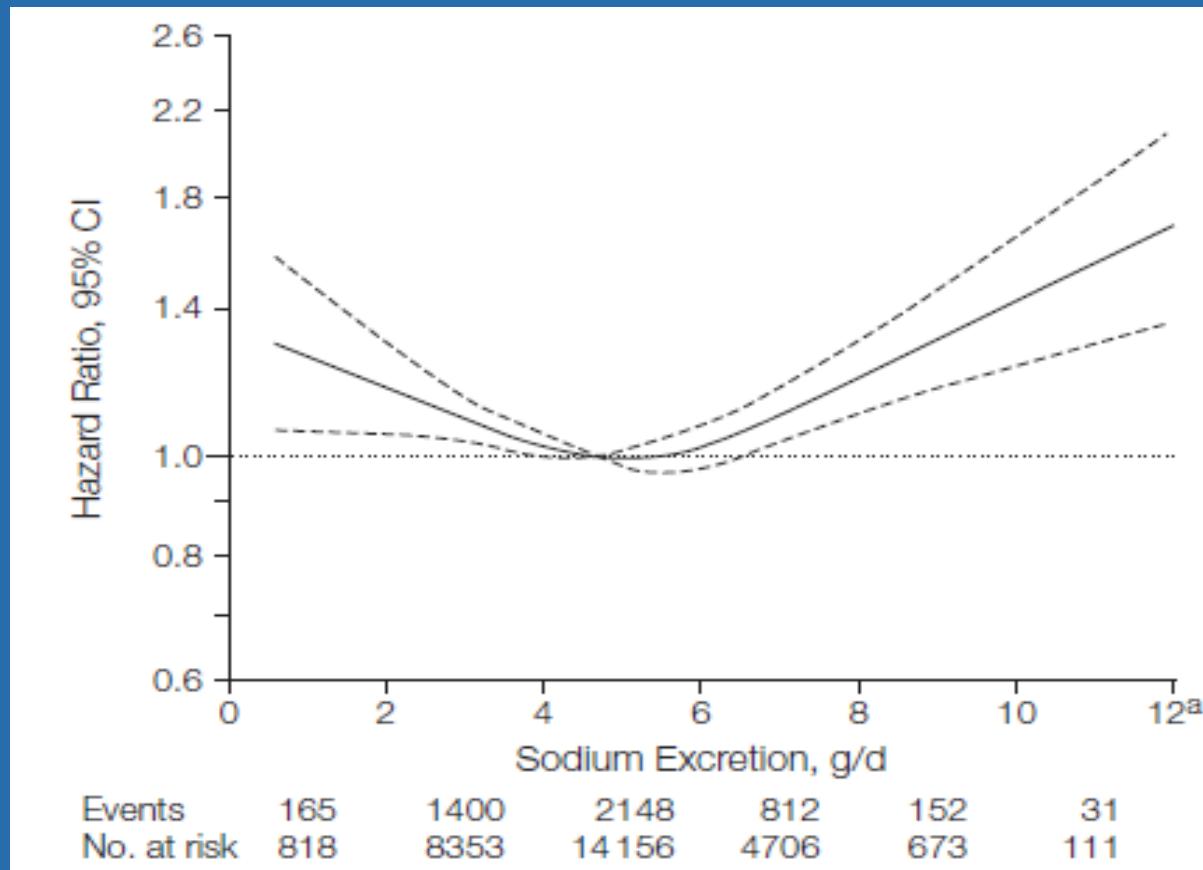
Variable	Overall (N = 28 880)	Sodium Excretion, g/d ^b					P Value
		<2 (n = 818)	2-3.99 (n = 8353)	4-5.99 (n = 14 156)	6-8 (n = 4706)	>8 (n = 847)	
Sodium excretion, mean (SD), g/d	4.77 (1.61)	1.55 (0.35)	3.24 (0.53)	4.93 (0.56)	6.71 (0.53)	9.40 (1.81)	<.001
Creatinine, µmol/L	93.92 (24.41)	95.55 (27.47)	94.15 (25.18)	93.82 (23.80)	93.54 (24.05)	93.75 (25.72)	.22
Medications							
β-Blocker	16 529 (57.2)	476 (58.2)	4857 (58.1)	8074 (57.0)	2647 (56.2)	475 (56.1)	.22
Diuretic	8299 (28.7)	335 (41.0)	2568 (30.7)	3663 (25.9)	1366 (29.0)	367 (43.3)	<.001
Calcium antagonist	9986 (34.6)	363 (44.4)	2700 (32.3)	4572 (32.3)	1921 (40.8)	430 (50.8)	<.001
Ramipril	7851 (27.2)	210 (25.7)	2278 (27.3)	3859 (27.3)	1291 (27.4)	213 (25.1)	.57
Telmisartan	10 518 (36.4)	296 (36.2)	3082 (36.9)	5090 (36.0)	1750 (37.2)	300 (35.4)	.45
Ramipril plus telmisartan	7792 (27.0)	206 (25.2)	2215 (26.5)	3889 (27.5)	1247 (26.5)	235 (27.7)	.31
Diabetes mellitus	10 717 (37.1)	320 (39.1)	2691 (32.2)	5128 (36.2)	2141 (45.5)	437 (51.6)	<.001

24-hour urinary sodium and potassium excretion were estimated from a morning fasting urine sample

Urinary Sodium and Potassium Excretion and Risk of CV Events

O' Donnell MJ, JAMA 2011; 306(20): 2229-2238

ONTARGET and TRANSCEND trials N=28880



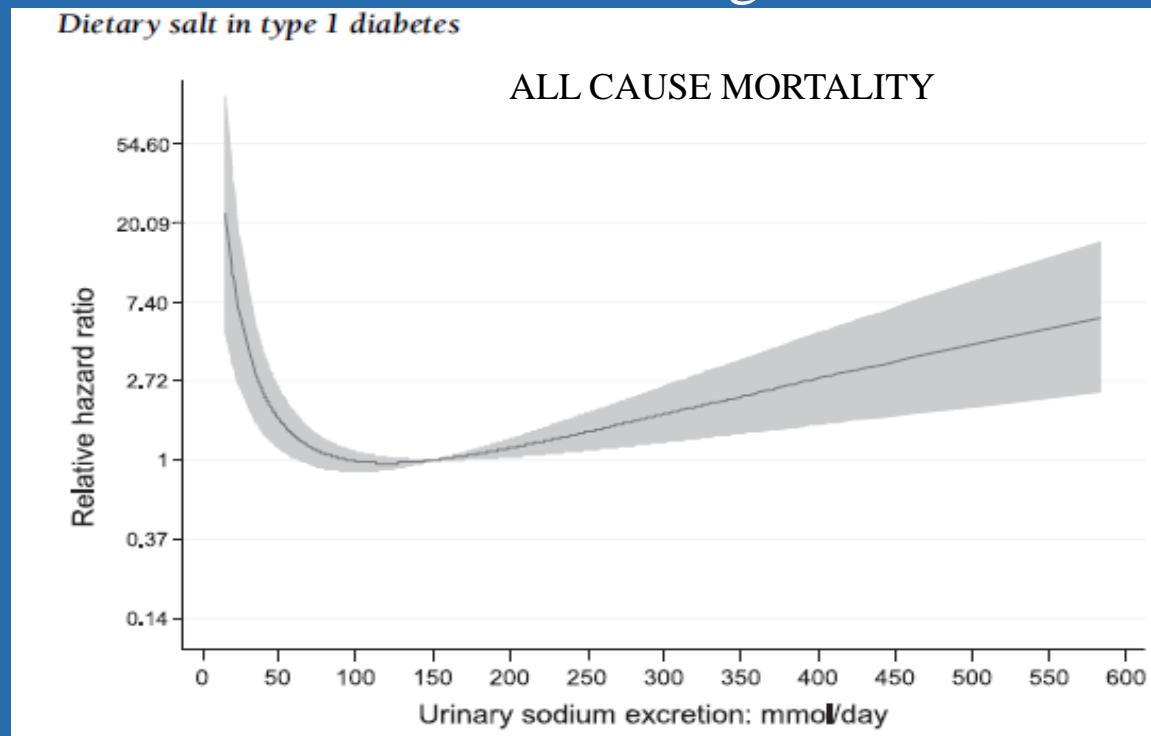
Estimated 24-Hour Urinary Excretion of Sodium and Composite of
CV Death, Stroke, MI, and Hospitalization for CHF

The Association Between Dietary Sodium Intake, ESRD, and All-Cause Mortality in Patients With Type 1 Diabetes

Diabetes Care 34:861–866, 2011

The association between 24-h UNa and all-cause mortality modeled within the conventional Cox model as a cubic regression

Part of the ongoing Finn Diane Study
2807 pts
Age: 39y
HTN:47%
FU:10y
One single urinary measurement
Mean 24-h Una: 150 mmol
217 deaths



24-h UNa was nonlinear significantly associated with all-cause mortality.
Individuals with the highest daily UNa, as well as the lowest excretion, had reduced cumulative survival.

The Association Between Dietary Sodium Intake, ESRD, and All-Cause Mortality in Patients With Type 1 Diabetes

Diabetes Care 34:861–866, 2011

Individuals with the lowest 24-h UNa had the highest cumulative incidence of ESRD.

Part of the ongoing Finn Diane
2807 pts

Age: 39y

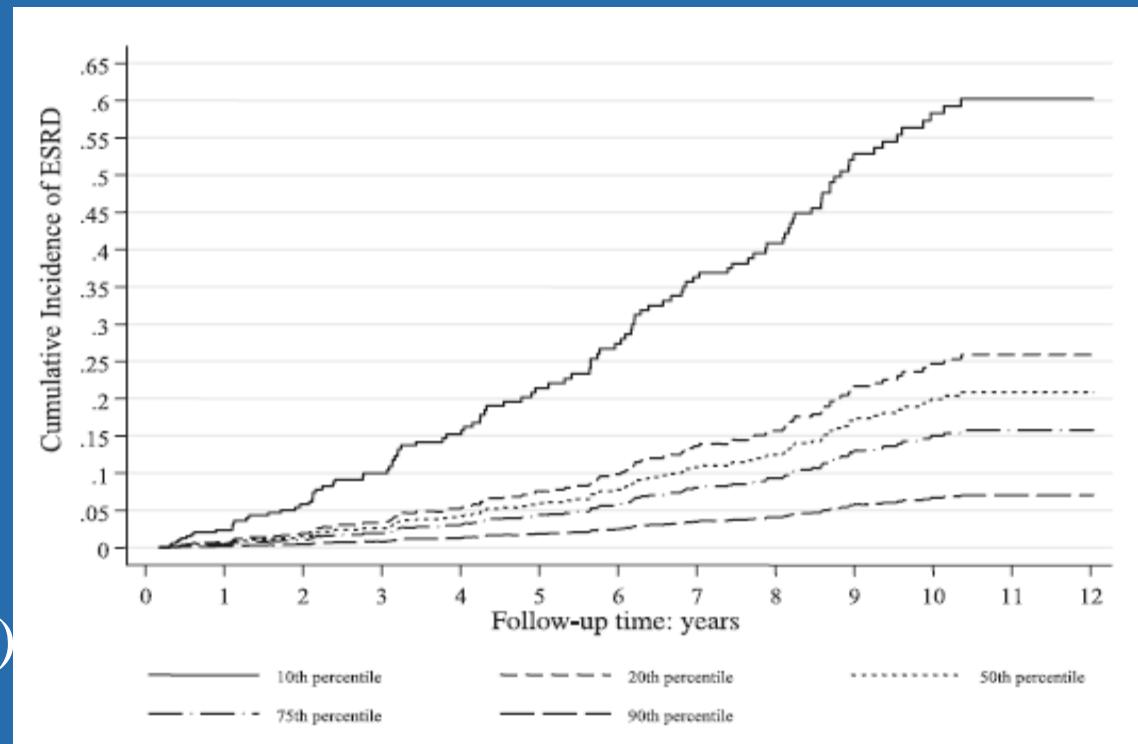
HTN:47%

FU:10y

One single urinary measurement

424 pts macroalbuminuria

122 ESRD (120 macroalbuminuria)



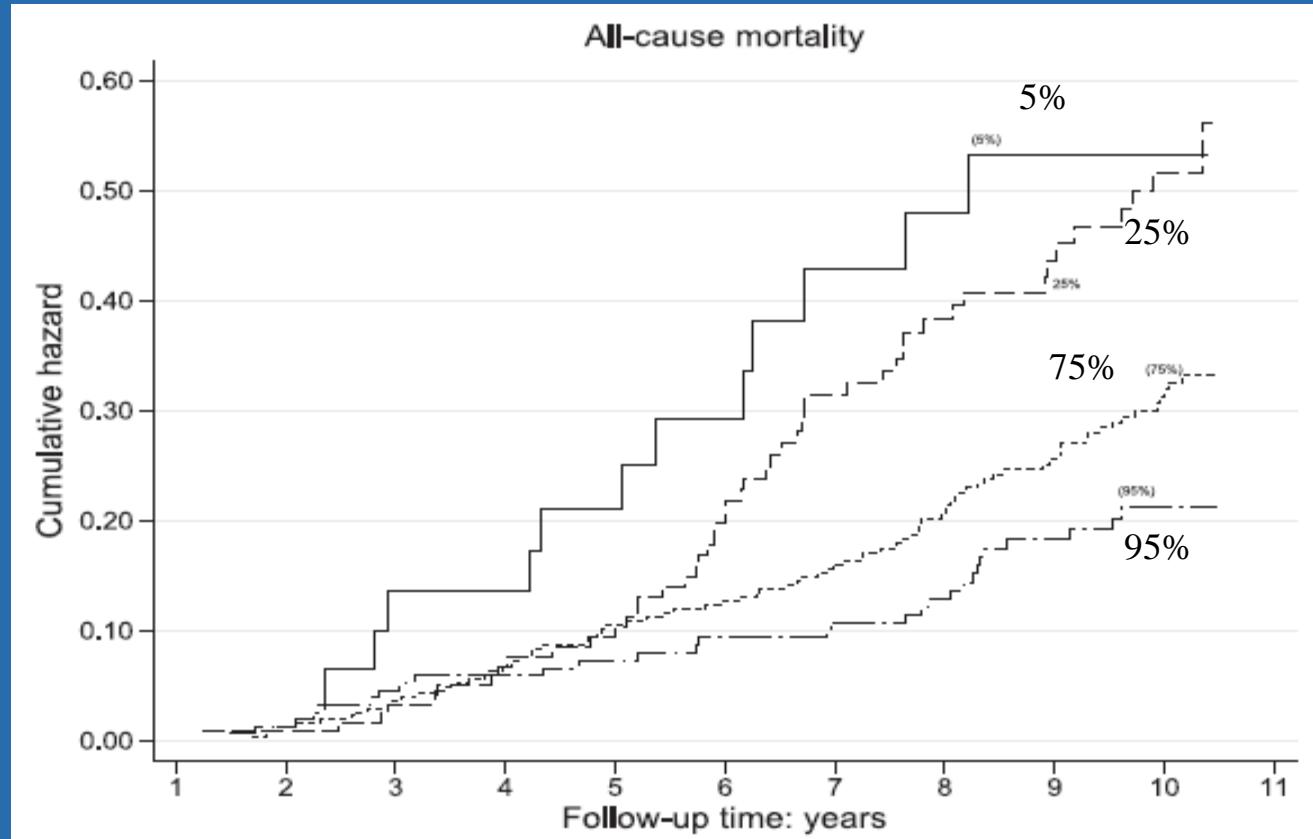
The cumulative incidence of ESRD over the 10th, 25th, 50th, 75th, and 90th percentiles of 24-h UNa, adjusted for other covariate predictors and accounting for pre-ESRD mortality as the competing risk.

Dietary Salt Intake and Mortality in Patients With Type 2 Diabetes

Diabetes Care 2011; 34:703–709

All-cause mortality was inversely associated with 24-h UNa

638 pts
HTN 85%
175 deaths
24hUNa yearly
Mean 24hUNa
184 mmol Na



Cumulative hazard of all-cause mortality, stratified by percentiles (5th, 25th, 75th, and 95th) of 24-h UNa

Dietary Salt Intake and Mortality in Patients With Type 2 Diabetes

Diabetes Care 2011; 34:703–709

638 pts
 HTN 85%
 175 deaths
 24hUNa yearly
 Mean 24hUNa
 184 mmol Na

All-cause mortality			
Baseline parameter	Hazard ratio	P	95% CI
24-h urinary sodium excretion (per 100 mmol/day)	0.72	0.017	0.55–0.94
Age (per decade)	1.05	<0.001	1.03–1.07
Male sex (yes/no)	1.51	0.013	1.09–2.09
Pre-existing CVD (yes/no)	1.85	0.001	1.30–2.64
eGFR (per 10 mL/min/1.73 m ²)	0.988	0.002	0.980–0.996
Atrial fibrillation (yes/no)	1.97	<0.001	1.39–2.81
Log ₁₀ AER	1.71	<0.001	1.38–2.12
Systolic blood pressure (mmHg)	0.986	0.015	0.974–0.997
Diabetes duration (decades)	1.02	0.010	1.01–1.04
Cardiovascular mortality			
Baseline parameter	Sub-hazard ratio	P	95% CI
24-h urinary sodium excretion (per 100 mmol/day)	0.65	0.026	0.44–0.95
Male sex (yes/no)	1.93	0.011	1.17–3.20
Pre-existing CVD (yes/no)	1.88	0.014	1.14–3.11
eGFR (per 10 mL/min/1.73 m ²)	0.985	0.001	0.98–0.99
Atrial fibrillation (yes/no)	2.78	<0.001	1.71–4.53
Log ₁₀ AER	1.76	<0.001	1.28–2.42
Systolic blood pressure (mmHg)	0.97	<0.001	0.96–0.99
Diabetes duration (decades)	1.05	<0.001	1.02–1.08

For every 100 mmol rise in 24hUNa, all-cause mortality was 28% lower
 (95% CI 6–45%, P = 0.02)

Standards of Medical Care in Diabetes 2013

Clinical Practice Recommendations

AMERICAN DIABETES ASSOCIATION
DIABETES CARE, 2013; 36 (Suppl 1)

PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS

Pharmacological therapy for patients with diabetes and hypertension should be with a regimen that includes either an ACE inhibitor or an angiotensin receptor blocker (ARB). If one class is not tolerated, the other should be substituted. (C)

In the treatment of the non pregnant patient with modestly elevated (30–299 mg/day) (C) or higher levels (>300 mg/day) of urinary albumin excretion (A), either ACE inhibitors or ARBs are recommended.

Standards of Medical Care in Diabetes 2013

Clinical Practice Recommendations

AMERICAN DIABETES ASSOCIATION
DIABETES CARE, 2013; 36 (Suppl 1)

Lifestyle therapy for elevated blood pressure consists of weight loss, if overweight; Dietary Approaches to Stop Hypertension (DASH)-style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. (B)

Lifestyle therapy consists of reducing sodium intake (to below 1,500 mg/day) and excess body weight;

KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update.

Am J Kidney Dis. 2012;60(5):850-886

G 6: Management of Albuminuria in Normotensive Patients with Diabetes

6.1: We recommend **not using** an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) for the primary prevention of DKD in normotensive normoalbuminuric patients with diabetes. (1A)

6.2: We suggest **using** an ACE-I or an ARB in normotensive patients with diabetes and albuminuria levels >30 mg/g who are at high risk of DKD or its progression. (2C)

Dietary sodium reduction to 2.3 g/d (100 mmol/d) is recommended based on the DASH and DASH-Sodium diets

CURRENT GUIDELINES FOR USING ACEI AND ARBS IN CKD IS THE EVIDENCE BASE RELEVANT TO OLDER ADULTS?

ANN M O' HARE ANN INTERN MEDICINE 2009; 150(10): 717-724

'current guidelines for the use of angiotensin converting enzyme inhibitor and angiotensin receptor blocker in chronic kidney disease are based on evidence with limited relevance to most persons older than 70 years with this condition'.

ΣΥΜΠΕΡΑΣΜΑΤΑ

1. Η αναστολή του συστήματος ρενίνης αγγειοτενσίνης συνιστάται σε διαβητικούς με αυξημένες τιμές λευκωματίνης στα ούρα
2. Η αναστολή του συστήματος ρενίνης αγγειοτενσίνης αναστέλλει μακροπρόθεσμα την απώλεια του GFR.
3. Η αναστολή του συστήματος δεν έχει αποδείξει τη μείωση της συνολικής θνητότητας
4. Η ένταση της αναστολής του συστήματος θα πρέπει μάλλον να είναι ήπια
5. Ο ρόλος του άλατος αλλά και του καλίου μένει να διευκρινισθεί.

ΣΥΜΠΕΡΑΣΜΑΤΑ

‘ΜΕΤΡΟΝ ΑΡΙΣΤΟΝ’

ΕΥΧΑΡΙΣΤΩ