«ΔΙΑΒΗΤΙΚΗ ΝΕΦΡΟΠΑΘΕΙΑ: Η ΧΙΟΝΟΣΤΙΒΑΔΑ ΤΗΣ ΝΕΦΡΟΛΟΓΙΑΣ»

Ο έλεγχος της πρωτεϊνουρίας για επιβράδυνση της εξέλιξης της Διαβητικής Νεφροπάθειας

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Disclosure Statement of Financial Interests

Nothing to declare concerning this presentation

Agenda

- The spectrum of Albuminuria
- Diabetic nephropathy progression
- Pathophysiologic mechanism
- Strict glycemic control
- Reduction of the intraglomerular pressure
- RAAS inhibition for primary prevention-agents
- Blood Pressure levels & diabetic nephropathy progression
- Conclusions

The spectrum of Albuminuria

Screening for albuminuria
The past (1892)

ALBUMINURIA

IN

HEALTH AND DISEASE

WITH TWO APPENDICES

(1) A CONTRIBUTION TO THE THEORY OF URINARY SECRETION.

(2) THE HYGIENIC TREATMENT OF ALBUMINURIA.

BY

DR. H. SENATOR,

PROFESSOR EXTRAORDINARY OF MEDICINE; PHYSICIAN TO THE ROYAL CHARITÉ HOSPITAL, AND TO THE AUGUSTA HOSPITAL OF BERLIN.

WITH ONE LITHOGRAPHED ILLUSTRATION.

TRANSLATED BY

DR. T. P. SMITH.

Potential presence of albuminuria even in

perfectly

(or at least seemingly)

healthy individuals

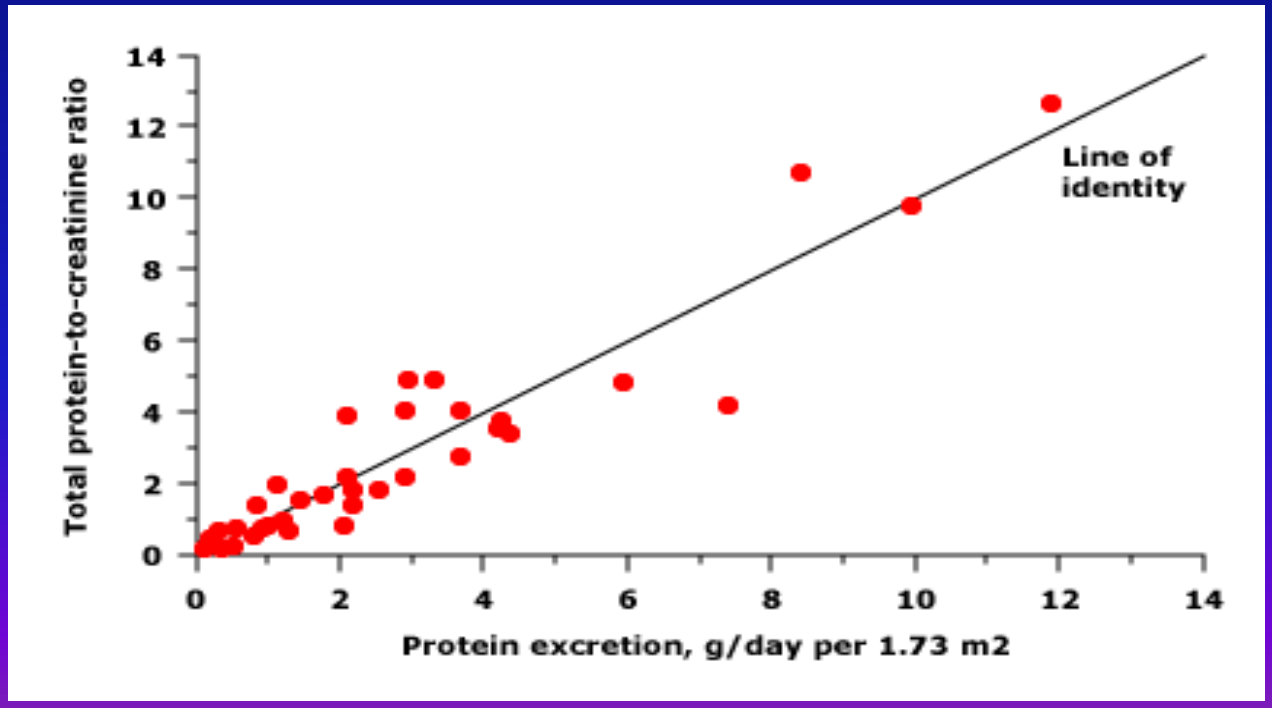
Hermann Senator (1834–1911)

A forgotten pioneer

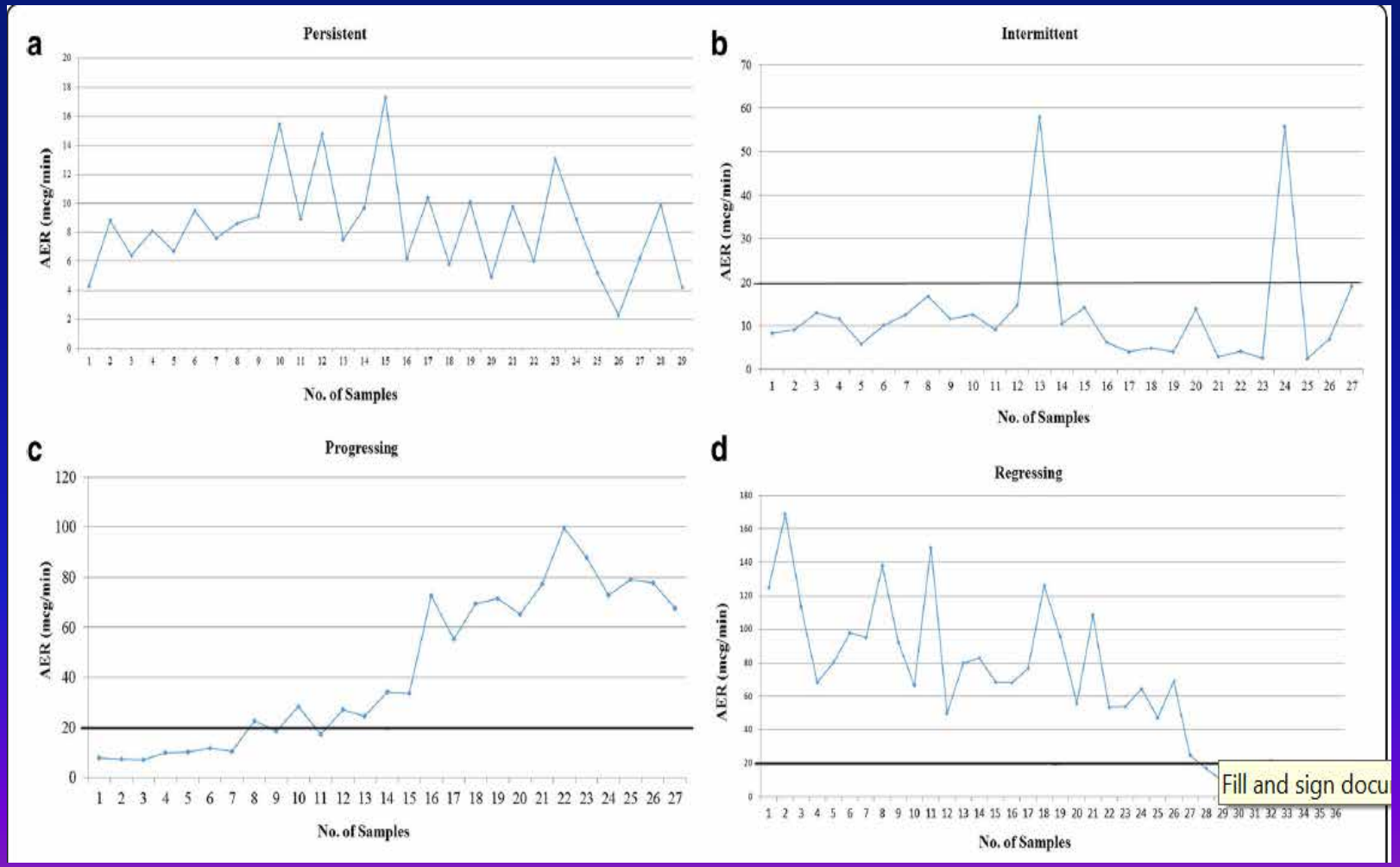
Gansevoort and Ritz, Nephrol Dial Transplant 2008

Proteinuria

- **Ποσοτικός προσδιορισμός**
  - » 24ωρη συλλογή ούρων
  - » Δείγμα ούρων: πρωτεΐνη/κρεατινίνη



The long-term intra-individual coefficient of variation of AER is high, implying that more than **three AER measurements** may be necessary to accurately categorize albuminuria.



Leong et al. BMC Nephrology (2017) 18:355

Changes in Albuminuria/Proteinuria—
A Prognostic Marker of Kidney Disease Progression

Rigas G Kalaitzidis, MD, Madhav Rao, MD and George L Bakris, MD

Table 2: Methods of Albuminuria Measurement with Normal and Abnormal Ranges

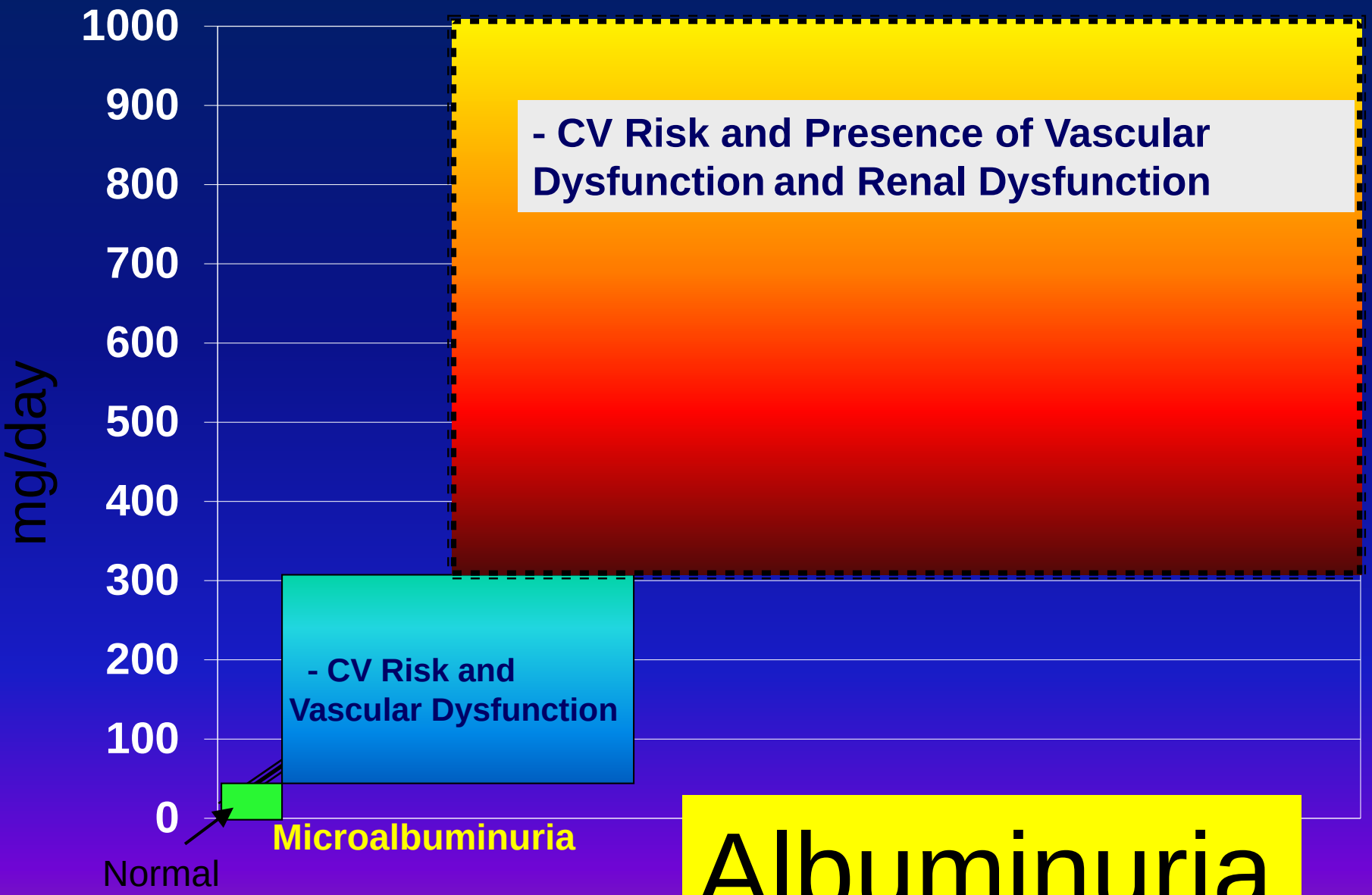
	24-hour Urine Albumin (mg/24hr)	Overnight Urine Albumin (µg/min)	Spot Urine			
			Albumin (mg/l)	Gender	Albumin/Creatinine Ratio (mg/mmol)	(mg/g)
Normal	<15	<10	<10	M	<1.25	<10
				F	<1.75	<15
High/normal	15 to <30	10 to <20	10 to <20	M	1.25 to <2.5	10 to <20
				F	1.75 to <2.5	15 to <30
Microalbuminuria	30 to <300					<200
						<300
Macroalbuminuria	>300					

Moderately increased albuminuria-Μέτρια αύξηση

Severely increased albuminuria-σημαντική αύξηση

J S N E P H R O L O G Y:2009,Volume 4,Issue1: 59--64

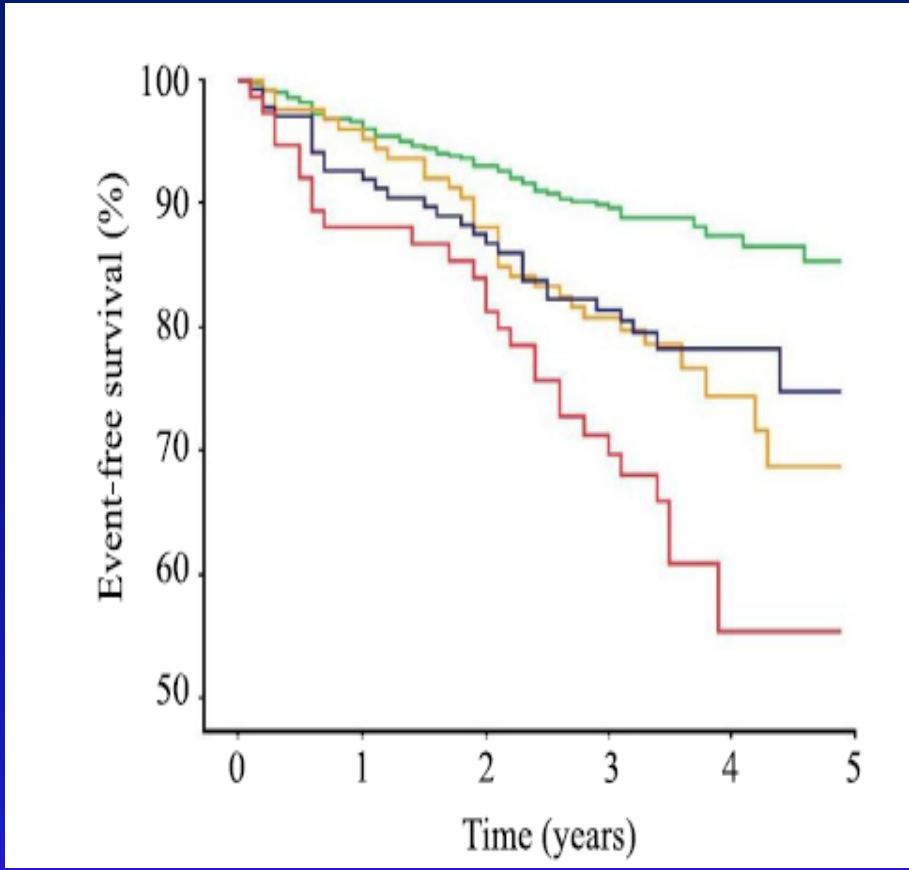
The Spectrum of Albuminuria



Albuminuria

(Proteinuria)

Is albuminuria a myocardial infarction risk equivalent for atherothrombotic events?



Event-free survival with respect to albuminuria and prior MI. Event-free survival in normoalbuminuric patients with no history of prior MI (green line), in patients with albuminuria without prior MI (orange line), in normoalbuminuric patients with a history of prior MI (blue line), and in patients with both, albuminuria and prior MI (red line).

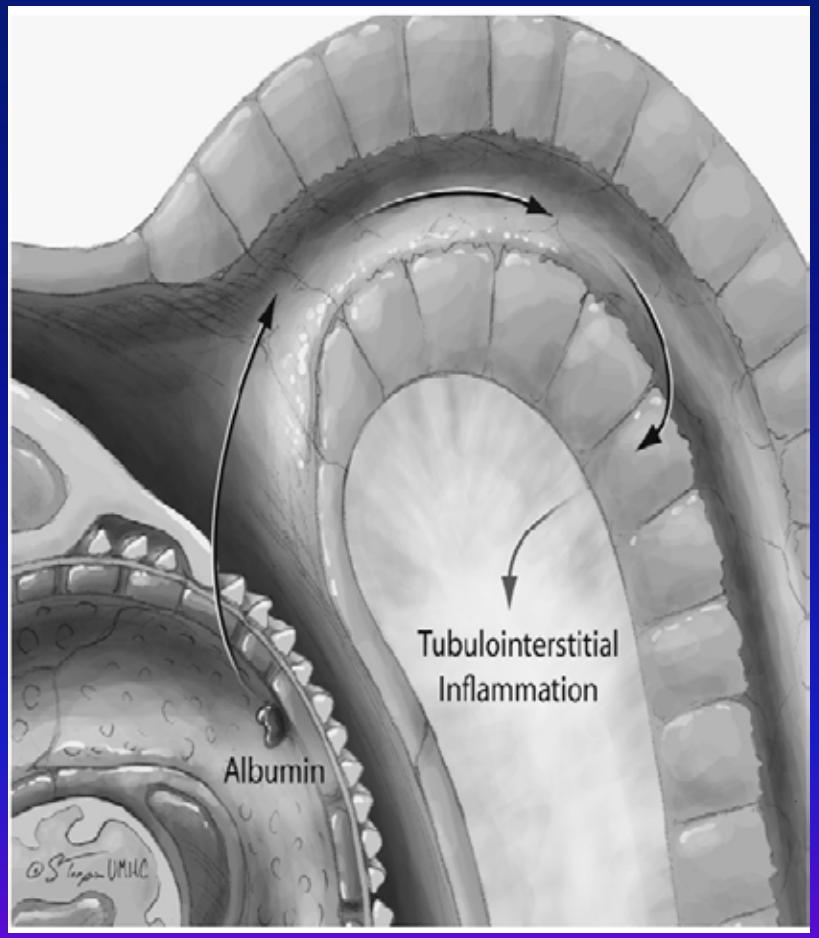
Albuminuria emerges as a CAD risk equivalent: The event rate of patients with albuminuria but no prior MI was almost equal to that of normoalbuminuric patients with prior MI.

Albuminuria is a CAD risk equivalent. Thus, cardiovascular risk factors in albuminuric patients should be treated as aggressively as in patients with prior MI.

Atherosclerosis 240 (2015) 21e25

Ultra filtered proteins in excess **are toxic to the tubular cells**, resulting in tubular damage and interstitial inflammation in the kidney

Albumin Leakage Causes Renal Damage



Regardless of the origin of albumin leakage emerging data show that albuminuria also has a direct toxic effect on renal tissue leading to progressive function loss

Whaley-Connell & Kalaitzidis R, Cardiol Clin 28 (2010) 437–445

Φυσική εξέλιξη της διαβητικής νεφροπάθειας τύπου 2

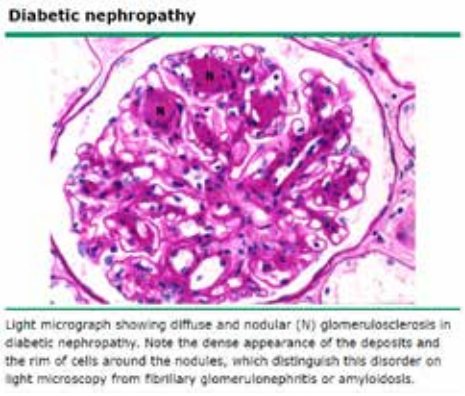
* Μέγεθος νεφρών - , βραχυχρόνια GFR - , μακροχρόνια GFR ¯ .

† Πάχυνση GBM - , Διόγκωση του μέσου πετάλου του έλυτρου Bowmann - , μικροαγγειακές μεταβολές +/-.

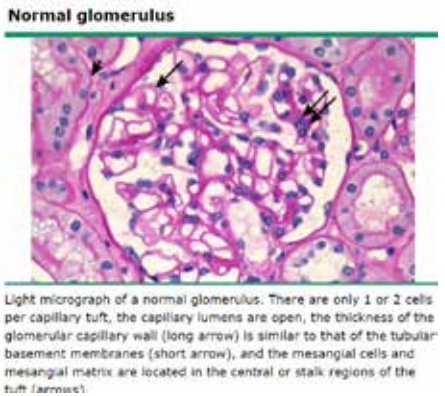
Diabetic nephropathy

Diabetic nephropathy, is most likely to occur in patients who have:

- **Worse glycemic control**
- **Hypertension**
- **Glomerular hyperfiltration**
- **Genetic predisposition**



Light micrograph showing diffuse and nodular (N) glomerulosclerosis in diabetic nephropathy. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis.



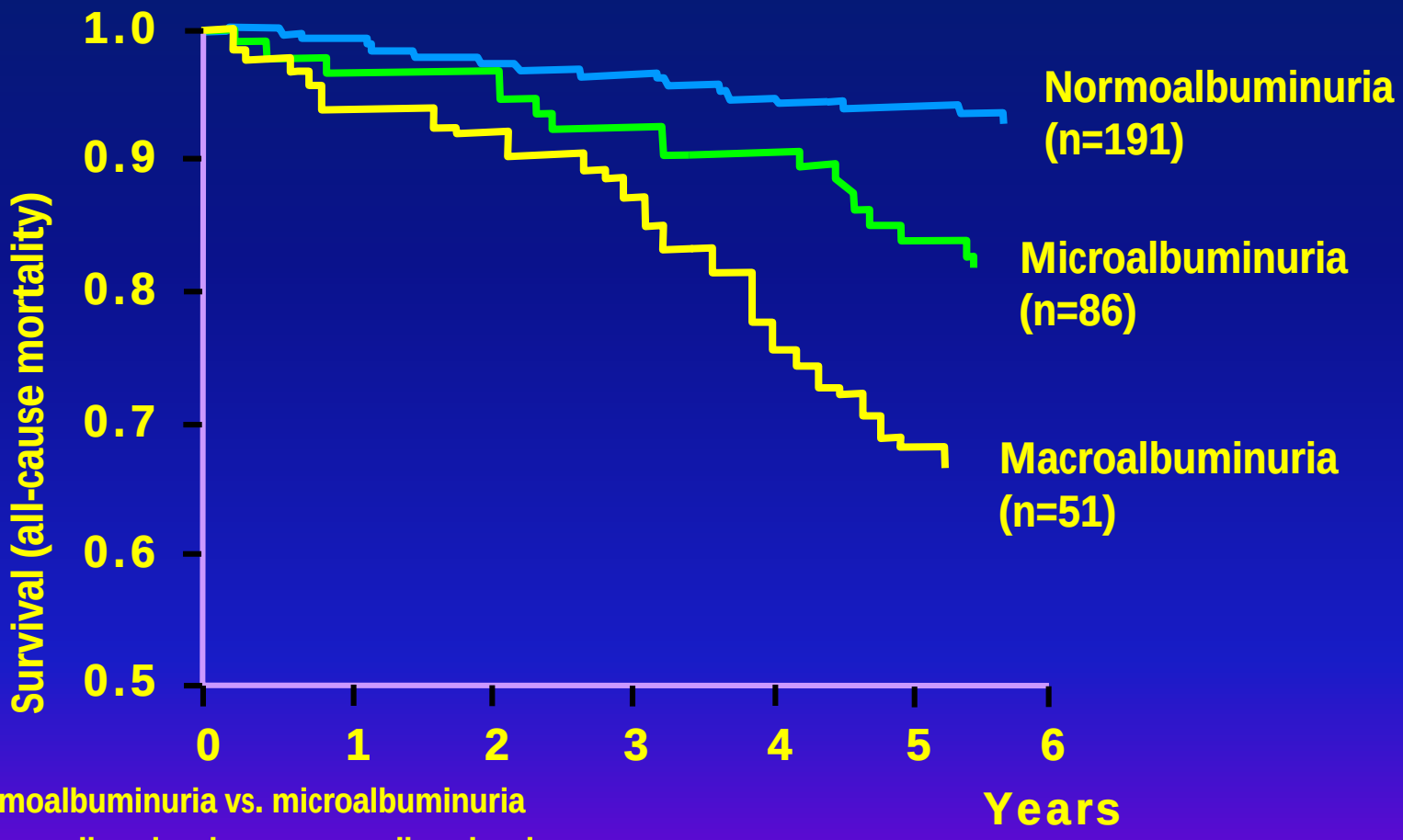
Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).

Albuminuria and disease progression

The degree of albuminuria is not necessarily linked to disease progression in patients with diabetic nephropathy associated with either type 1 or type 2 diabetes

Patients who progressed to severely increased albuminuria had the highest rate of loss of GFR

Proteinuria as a Risk Factor for Mortality in Type 2 Diabetes



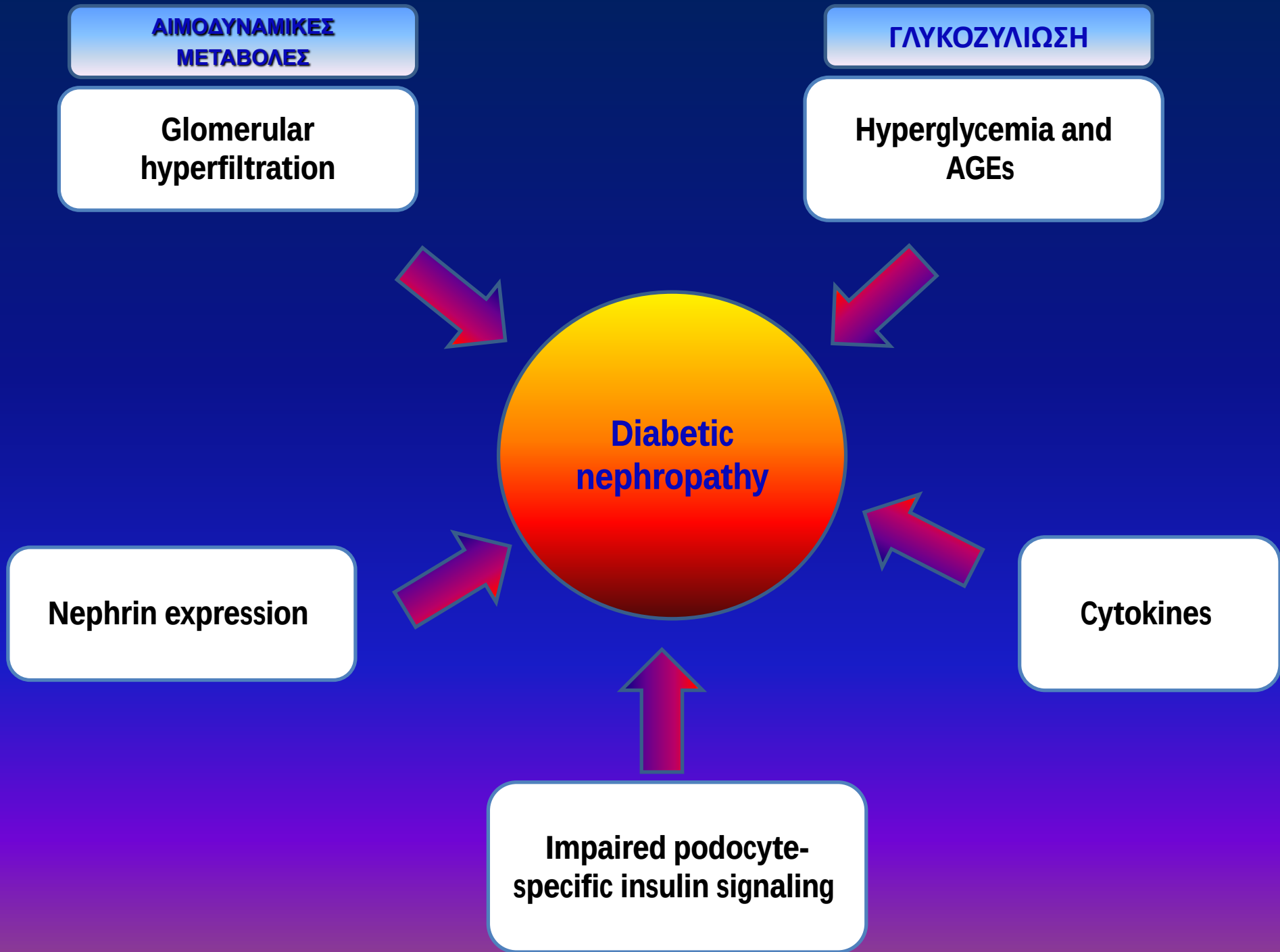
P<0.01 normoalbuminuria vs. microalbuminuria

P<0.001 normoalbuminuria vs. macroalbuminuria

P<0.05 microalbuminuria vs. macroalbuminuria

Gall MA, et al. Diabetes. 1995;44:1303-1309.

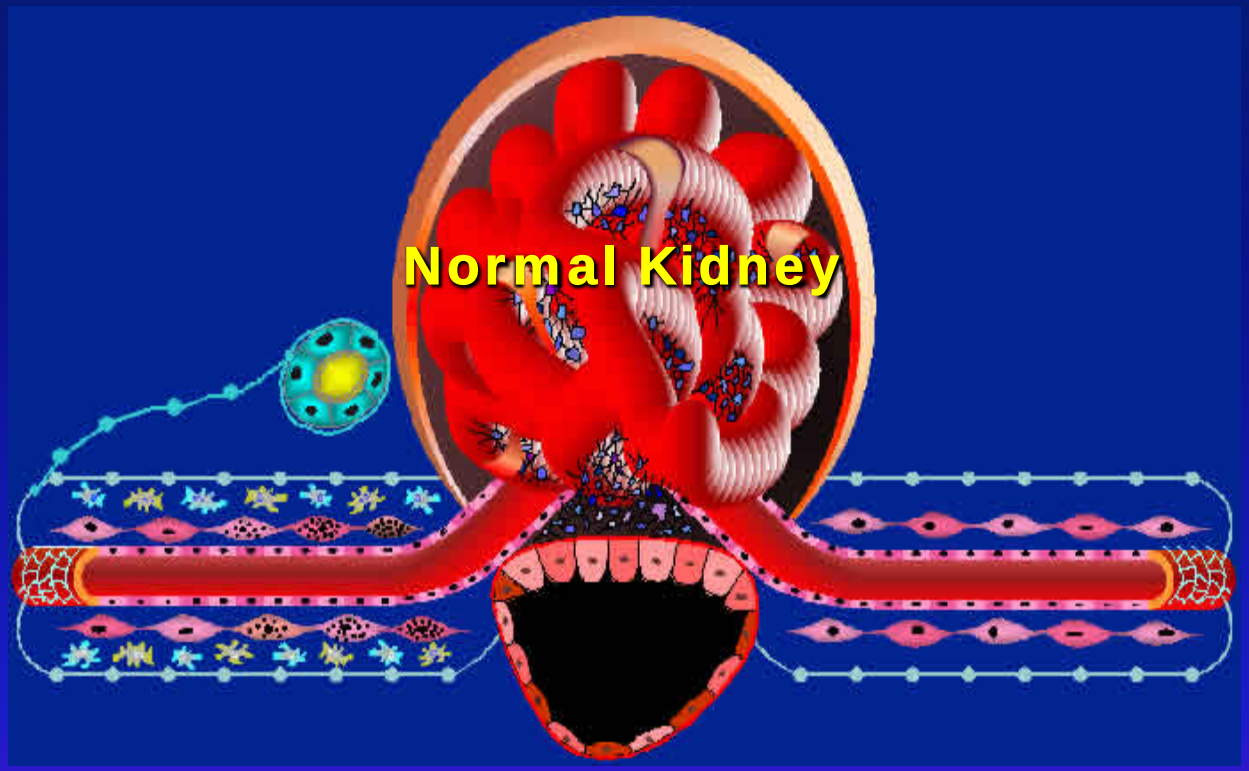
Pathophysiologic mechanism


ΑΙΜΟΔΥΝΑΜΙΚΕΣ ΜΕΤΑΒΟΛΕΣ
Glomerular hyperfiltration
ΓΛΥΚΟΖΥΛΙΩΣΗ
Hyperglycemia and AGEs
Diabetic nephropathy
Nephrin expression
Cytokines
Impaired podocyte-specific insulin signaling

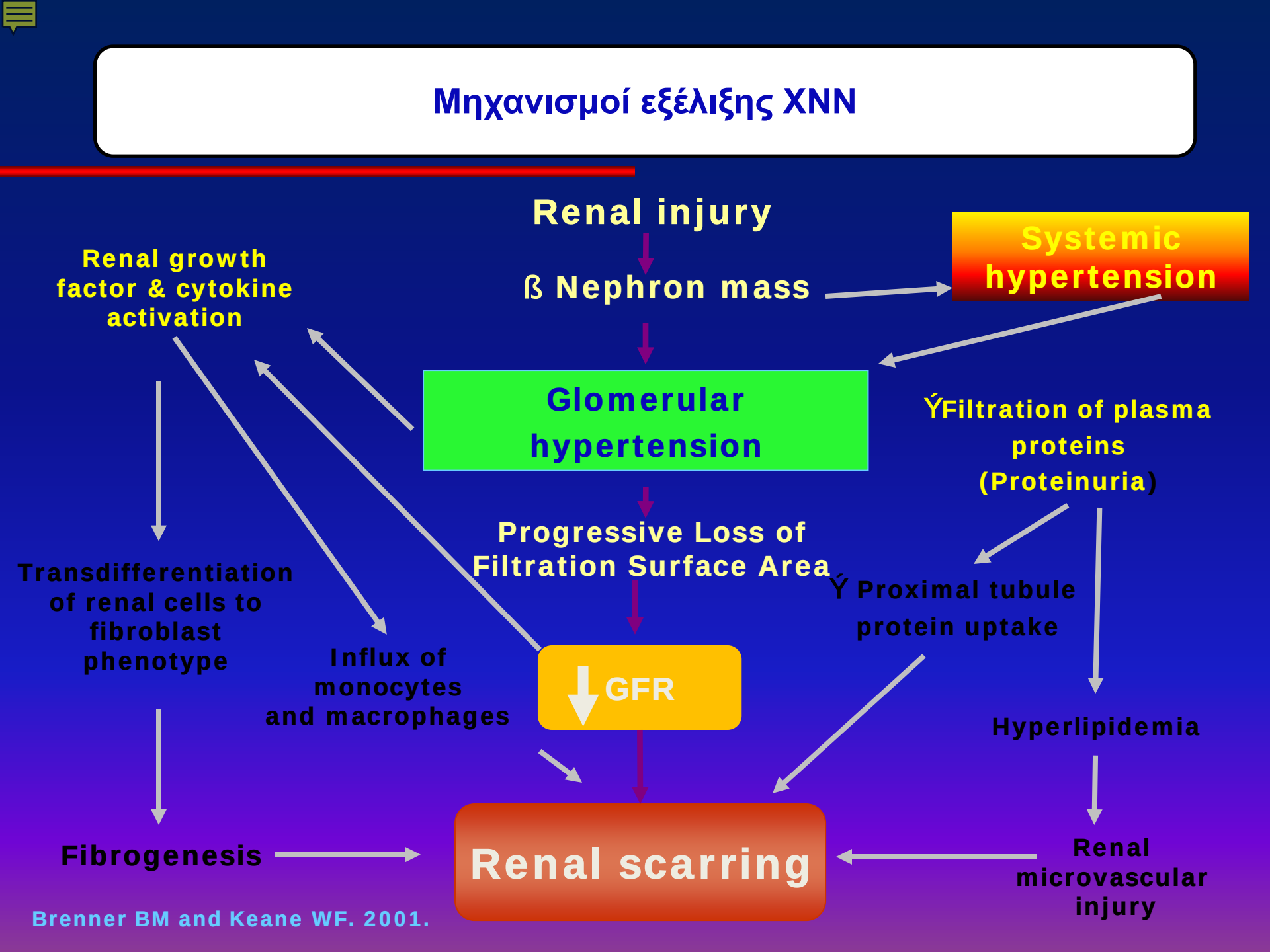
Μηχανισμοί Νεφρικής βλάβης στην ΥΠ

Μηχανισμοί

- Ενδοσπειραματική Υπέρταση
  - Υπερδιήθηση
- Δυσλειτουργία του σπειραματικού φραγμού
  - Πρωτεϊνουρία
- Υπερπλασία μεσαγγειακών κυττάρων
- Ενδονεφρική φλεγμονώδης διαδικασία
- Ενδοθηλιακή δυσλειτουργία
- VSMC υπερπλασία



Μηχανισμοί εξέλιξης ΧΝΝ



Brenner BM and Keane WF. 2001.

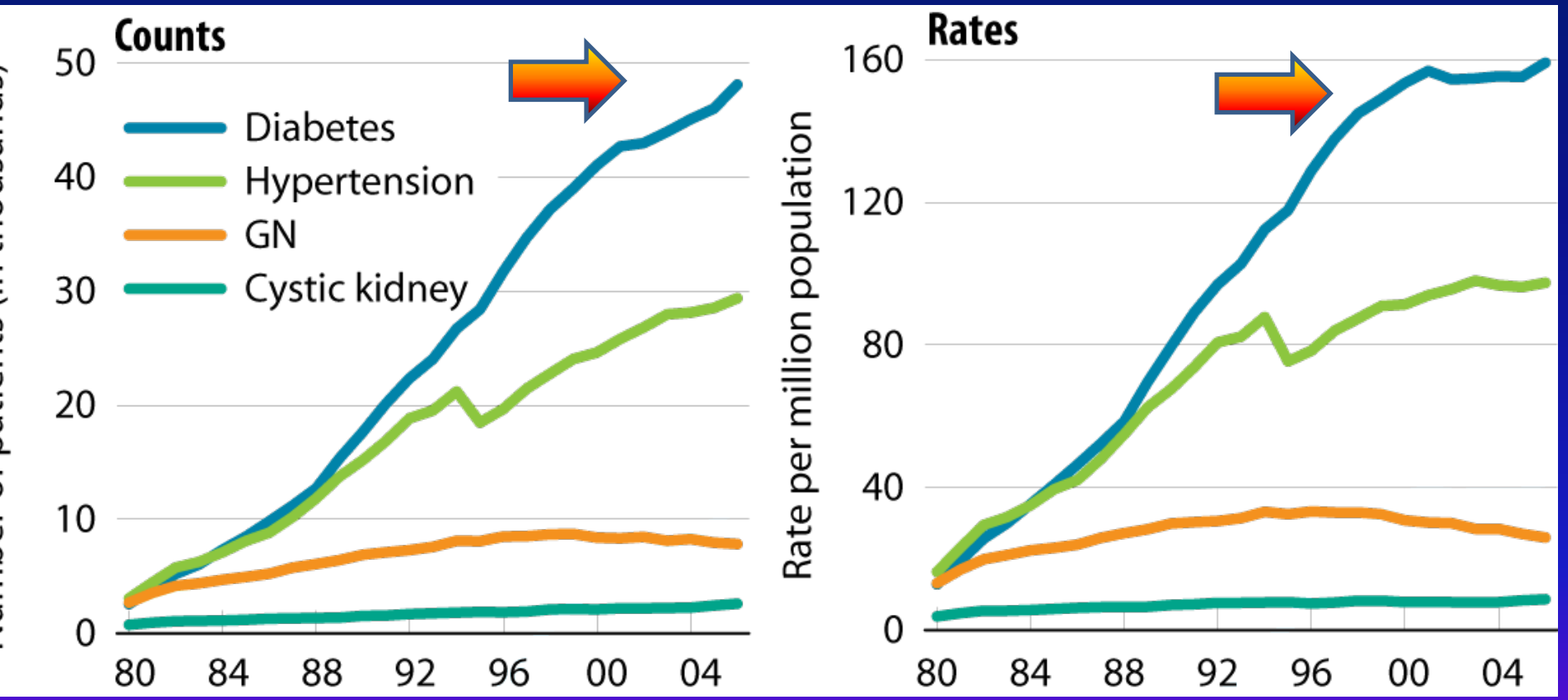
Equivalent renal risk in type 1 % 2 diabetes

TYPE 1: The incidence of overt nephropathy was 25 to 45 percent, The incidence of ESRD was 4 to 17 percent at 20 years and 16 percent at 30 years of being diagnosed with diabetes.

TYPE2: The incidence of diabetic ESRD was noted to have declined significantly from the period 1991-1994 to the period 1999-2002 (32 to 15 cases per 1000 patient-years, respectively)

Data suggest that the renal risk is currently equivalent in the two types of diabetes

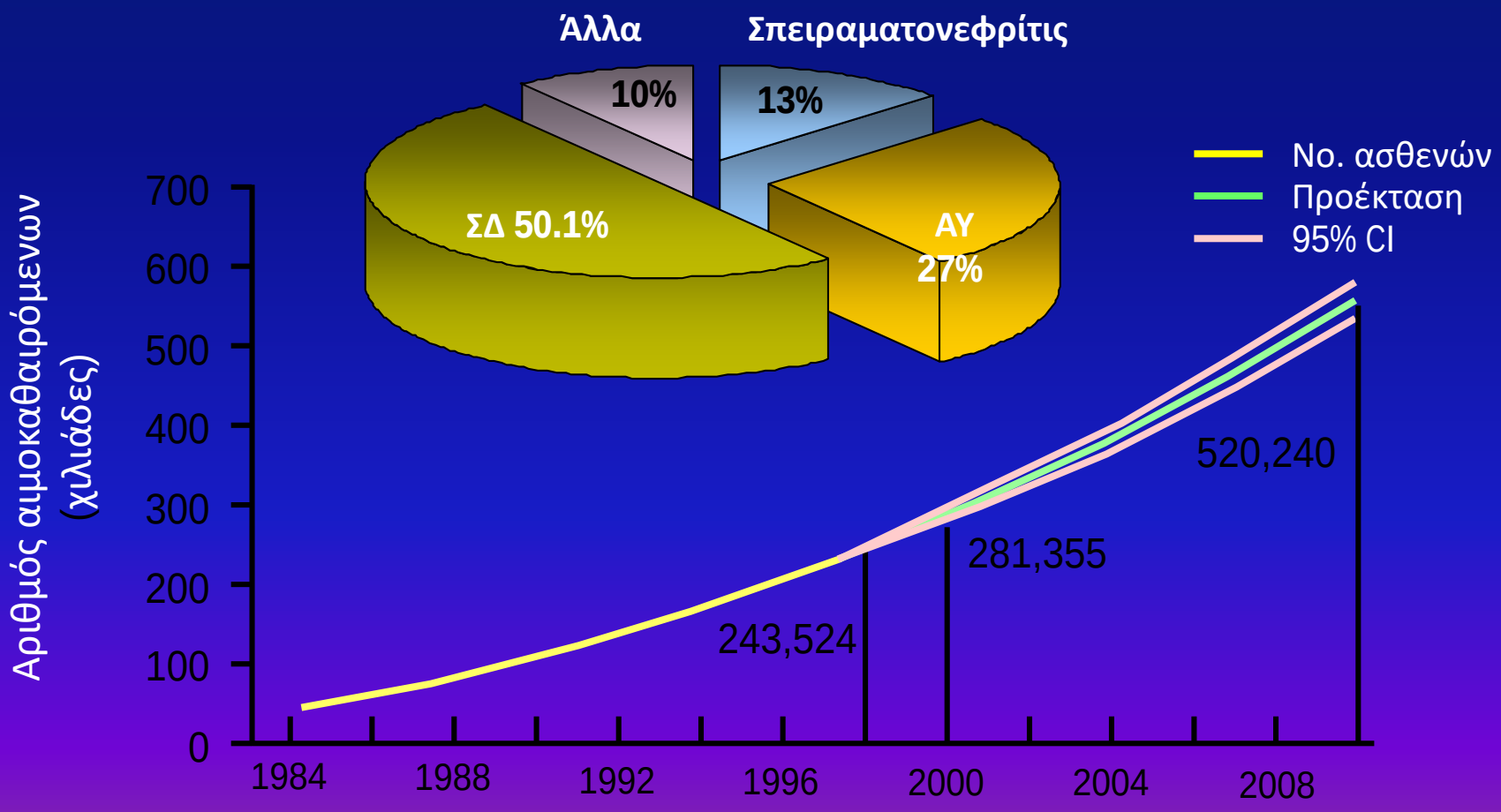
Incident counts & adjusted rates of ESRD by primary diagnosis



Incident ESRD patients; rates adjusted for age, gender, & race.

USRDS 2008, Figure 2.8 (Volume 2)

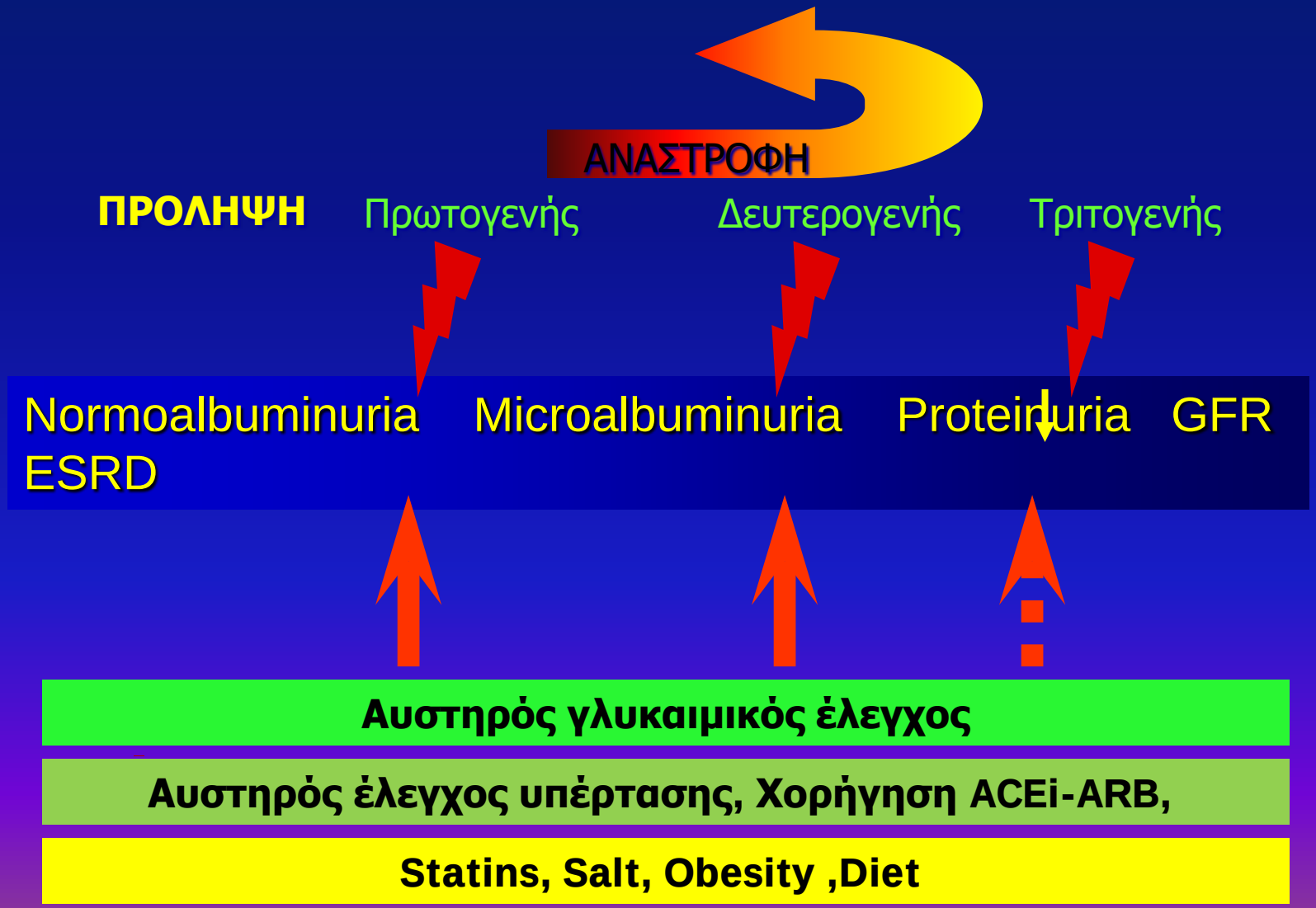
Βασική αιτία ΧΝΝ τελικού σταδίου ασθενών που εντάσσονται σε πρόγραμμα υποκατάστασης της νεφρικής λειτουργίας



United States Renal Data System. Annual data report. 2000.

Albuminuria as a Appropriate Therapeutic Target in diabetic nephropathy

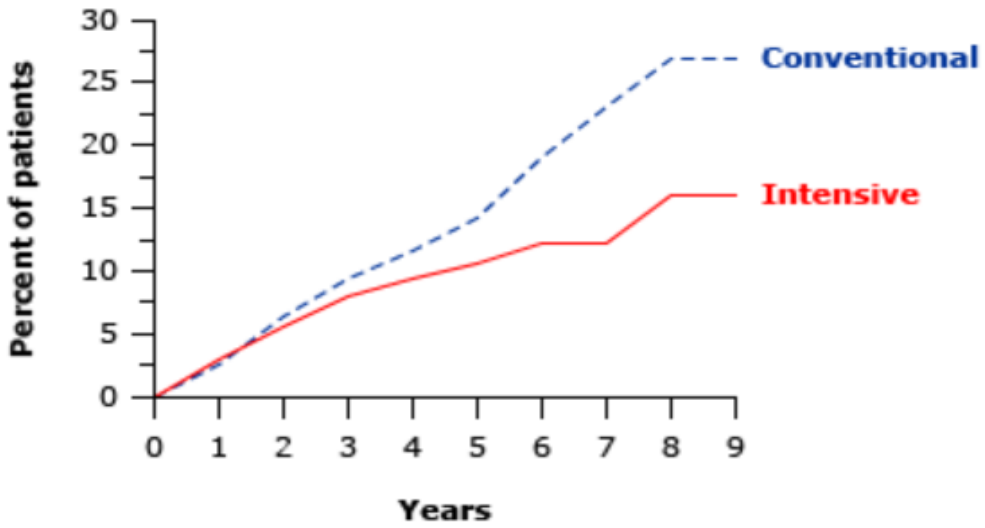
Παρεμβάσεις για την πρόληψη της εξέλιξης της νεφρικής νόσου σε διαβητικούς ασθενείς



The importance of glycemic control

Cumulative incidence of moderately increased albuminuria () in patients with type 1 diabetes treated with either conventional or intensive insulin therapy for up to nine years. There was an increasing benefit of intensive therapy over time (p<0.04)

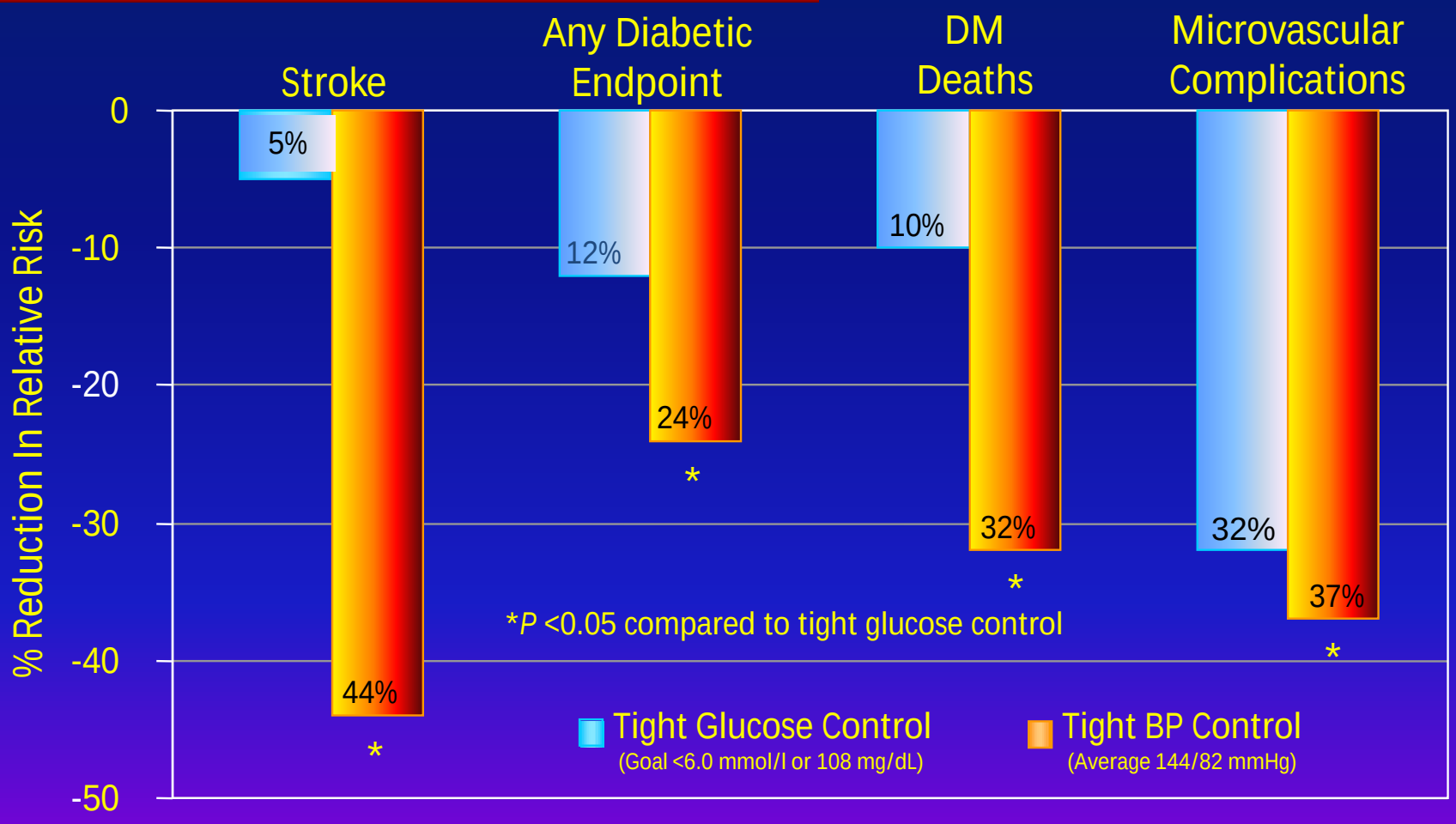
Strict glycemic control prevents moderately increased albuminuria (formerly called microalbuminuria) in patients with type 1 diabetes mellitus



The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329:977.

Reducing the intraglomerular pressure
AND/OR
Prevention of intraglomerular hypertension

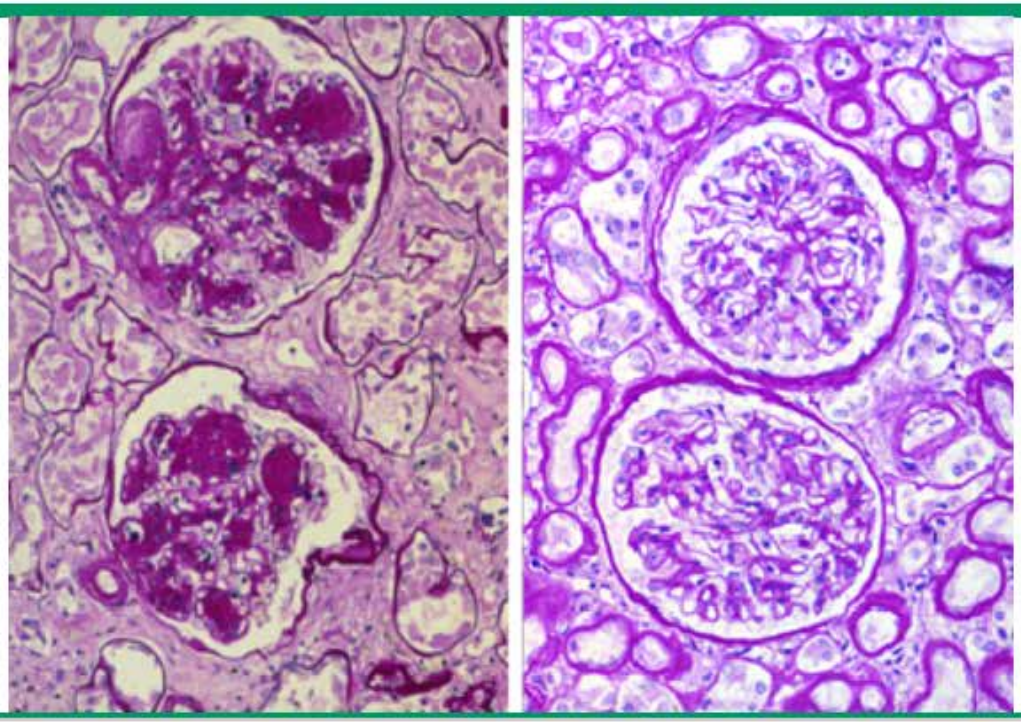
Ρύθμιση σακχάρου έναντι ρύθμισης ΑΠ στην έκβαση καρδιαγγειακών επιπλοκών σε ασθενείς με ΣΔ τύπου 2



Bakris GL, et al. Am J Kidney Dis. 2000;36(3):646-661.
Reprinted by permission from WB Saunders.

Intraglomerular pressure and diabetic nephropathy

Unilateral diabetic glomerulosclerosis



Light micrographs from a postmortem examination of a diabetic patient with unilateral renal artery stenosis on the right side. Classic Kimmelstiel-Wilson nodules are seen in the glomeruli in the left kidney

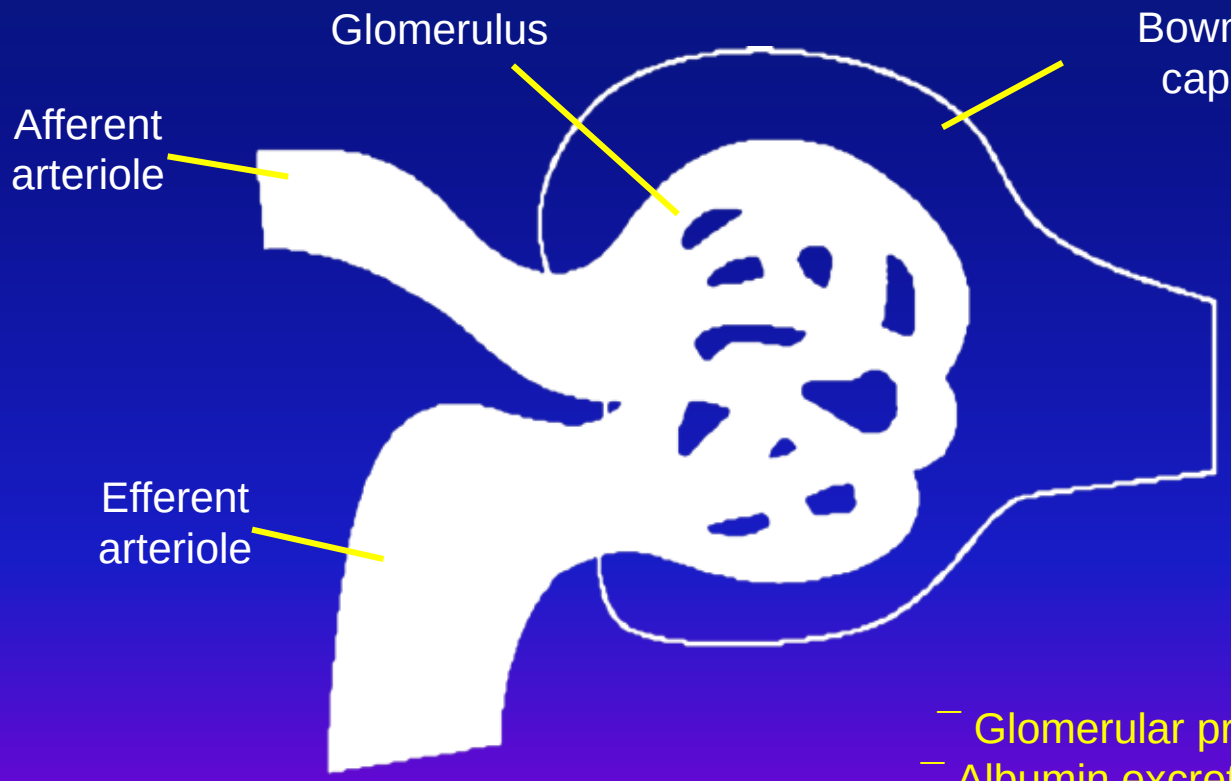
Reducing the intraglomerular pressure with **dietary protein restriction** or **antihypertensive therapy** with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) or the prevention of intraglomerular hypertension because of **concurrent renal artery stenosis** can minimize progression of or even prevent glomerular disease in the absence of glycemic control

G Bakris Uptodate 2018

Antihypertensive therapy with emphasis on the use of ACE inhibitors or ARBs

Mechanistic rationale for ACE inhibitors and ARBs in diabetes

Dilation of Efferent Arteriole Only

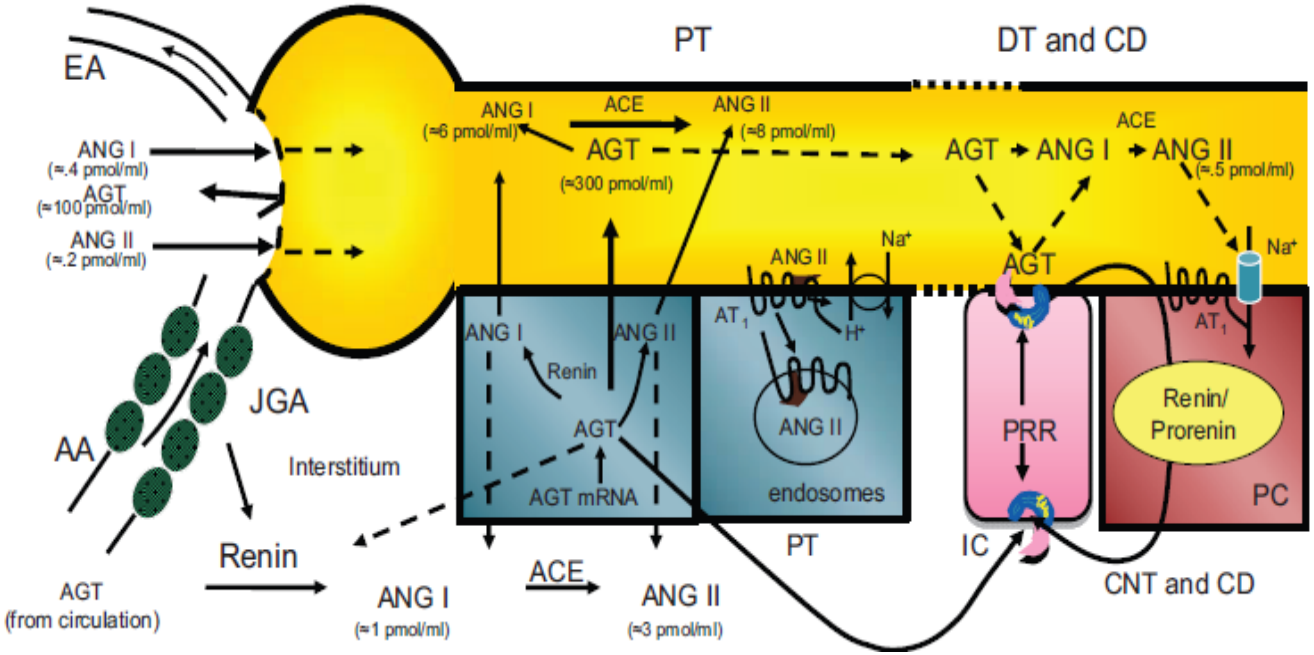


– Glomerular pressure
– Albumin excretion rate

Valentino VA et al. *Arch Intern Med* 1991;151:2367-2372.

Intratubular Renin-Angiotensin System in Hypertension

L. Gabriel Navar, Hiroyuki Kobori, Minolfa C. Prieto, Romer A. Gonzalez-Villalobos



Cascade of intratubular RAS in Ang II–dependent hypertension. In Ang II–dependent hypertension, the kidney maintains intrarenal Ang II formation, enhanced proximal tubule AGT formation and spillover into distal nephron segments coupled with enhancement of CD renin and stimulation of tubular ACE.

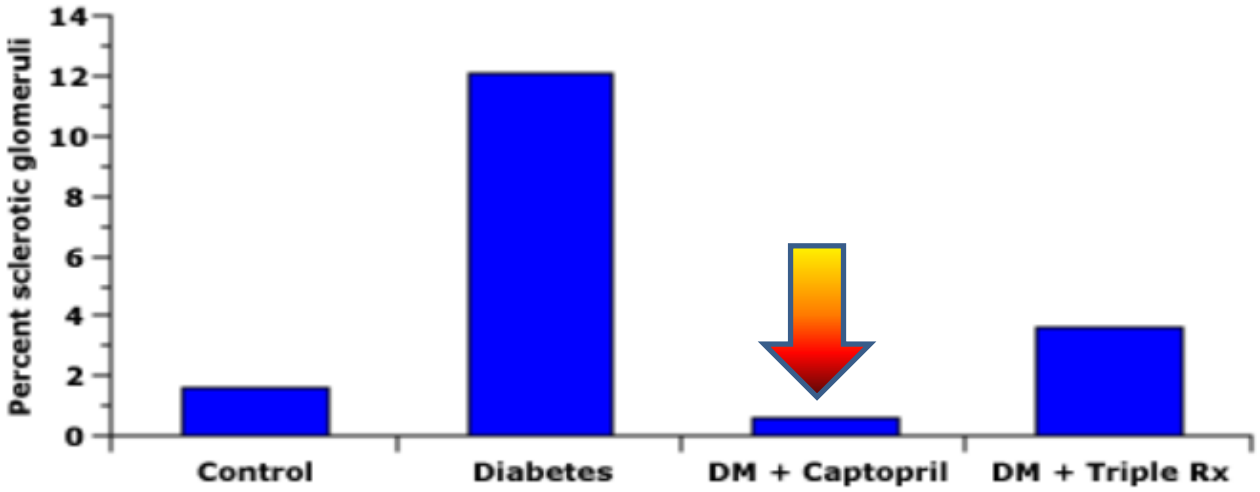
PT indicates proximal tubule; IC, intercalated cell; PC, principal cell; AA, afferent arteriole; EA, efferent arteriole.

Type 1 diabetes

Renal protection with ACEIs

ACE inhibitor vs triple therapy

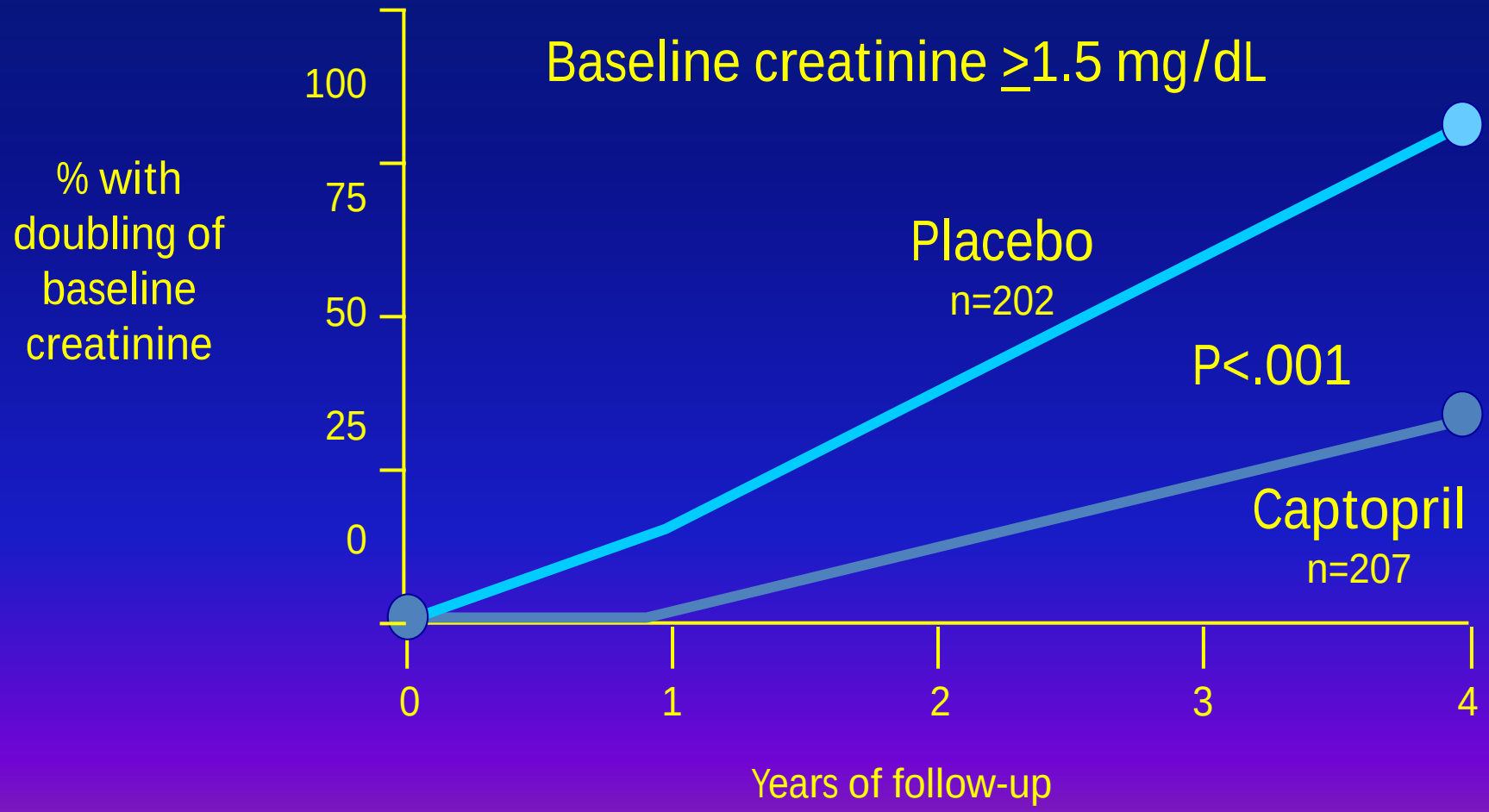
ACE inhibitor is more effective than triple therapy in protecting against experimental diabetic nephropathy



Efficacy **of antihypertensive therapy** in diabetic rats in reducing the number of sclerotic glomeruli at 70 weeks. Triple therapy with hydrochlorothiazide, hydralazine, and reserpine was partially protective, but captopril was completely protective, with the degree of glomerulosclerosis being less than that in control (normal) rats (left column). Captopril also normalized the intraglomerular pressure (46 mmHg) versus 64 mmHg in untreated diabetic animals and 56 mmHg with triple therapy.

Kidney Int 1989; 36:526.

The effect of the administration of placebo or captopril to patients with type 1 diabetes with overt proteinuria and a Pcr equal to or greater than 1.5 mg/dL (132 µmol/L).
The likelihood of a doubling of the Pcr was reduced by more than 50 percent in the captopril group.

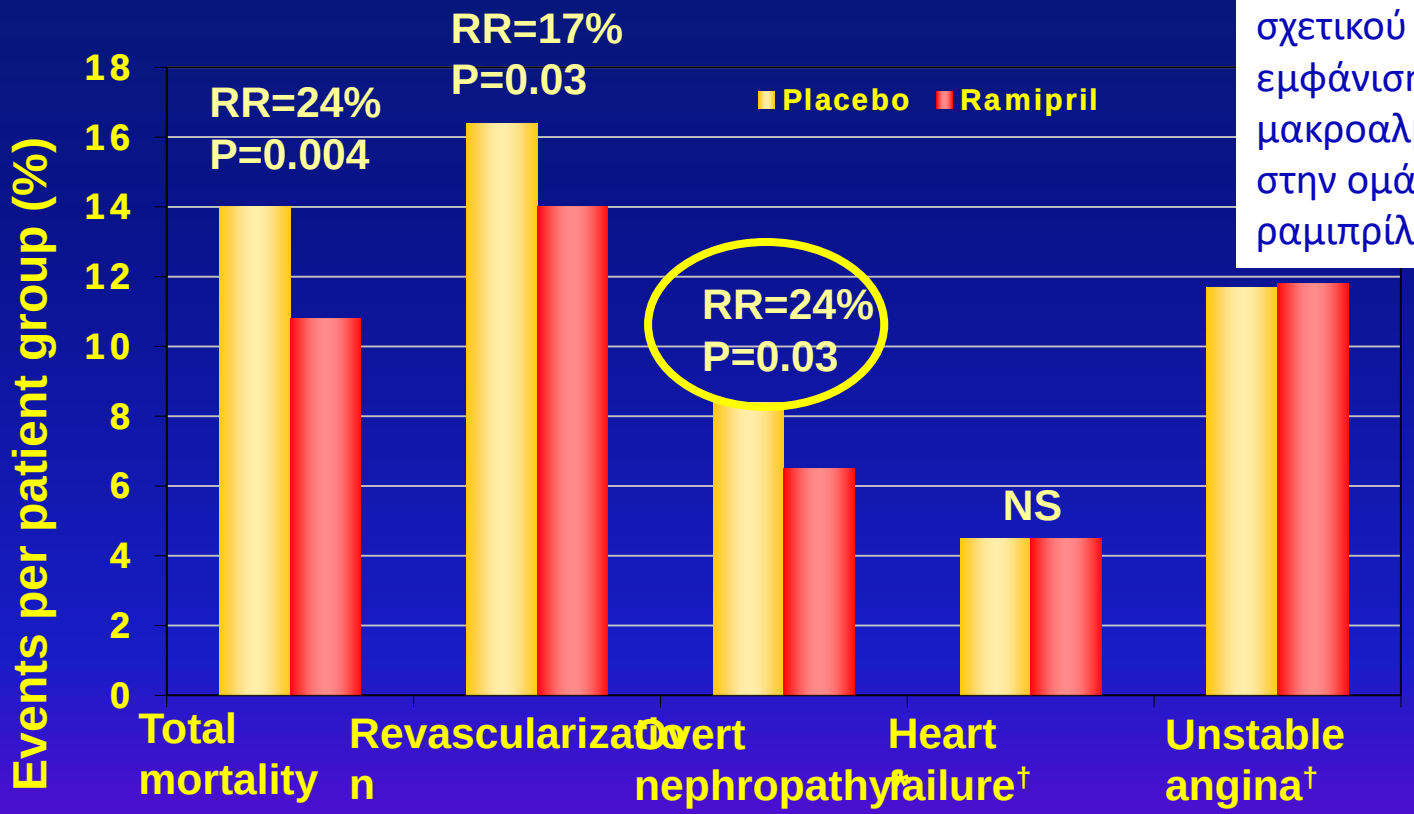


Lewis EJ, et al. N Engl J Med. 1993;329(20):1456-1462.

MICRO-HOPE Events Per Patient Group for Secondary Endpoints

3557 ασθενείς

↓ κατά 24% του σχετικού κινδύνου εμφάνισης μακροαλβουμινουρίας στην ομάδα της ραμιπρίλης vs placebo



*Based on positive 24h urine collection or albumin/creatinine ratio ³ 36 mg/mmol

†Requiring hospital admission NS ³ 0.05

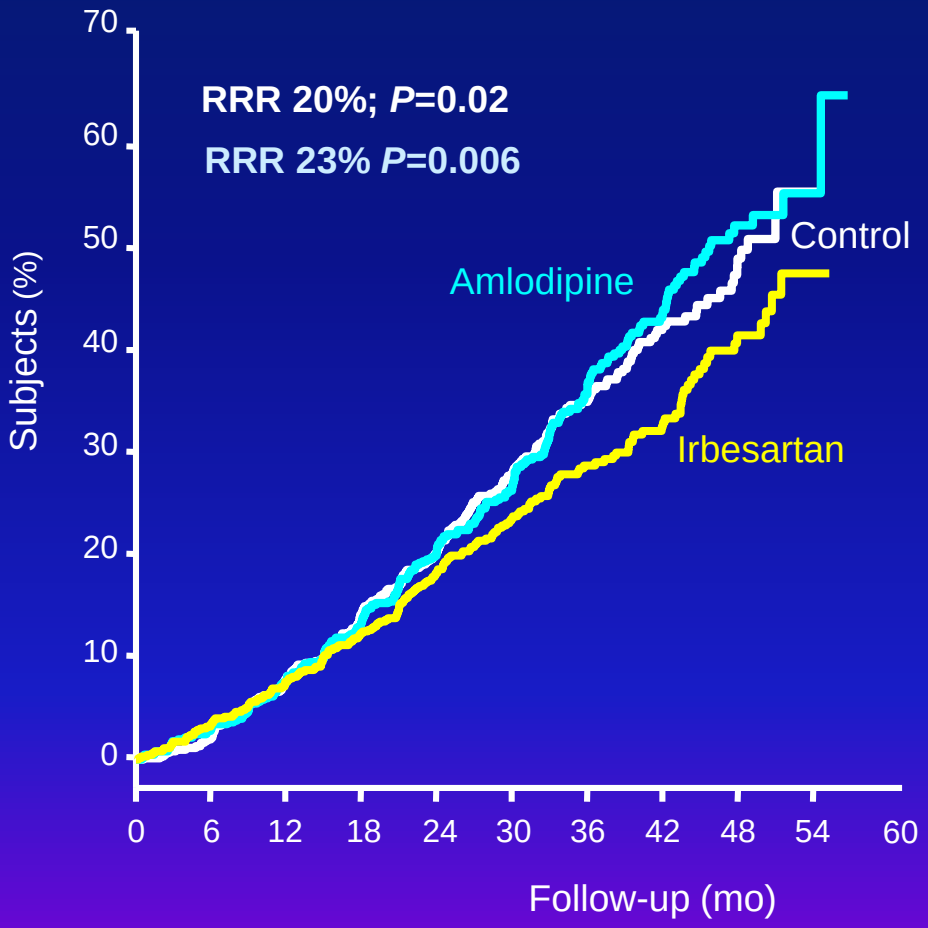
RR=Relative risk reduction

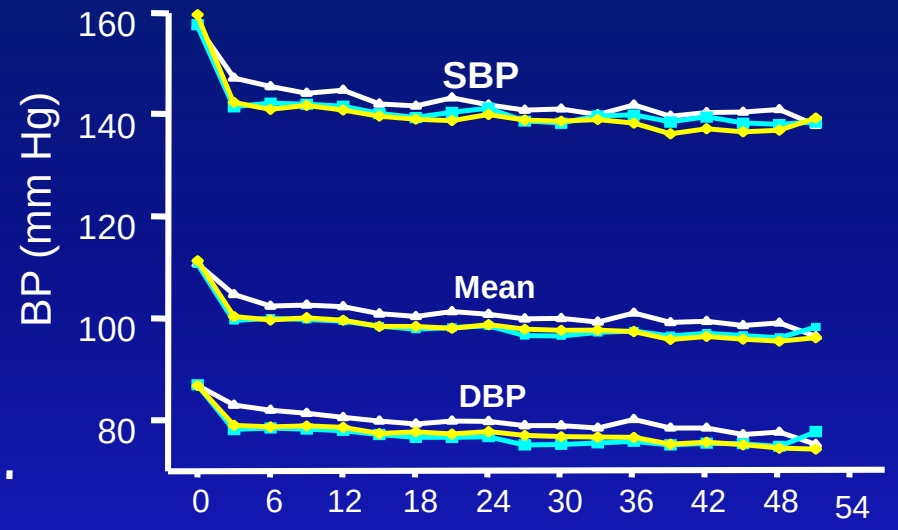
HOPE Study Investigators. Lancet. 2000;355:253-259.

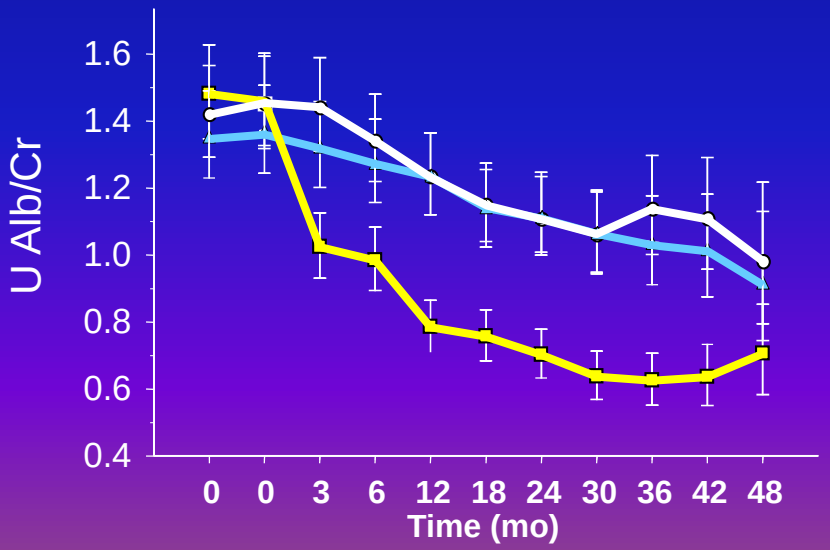
Type 2 diabetes

Renal protection with ARBs

Irbesartan slows progression of nephropathy in type 2 diabetes

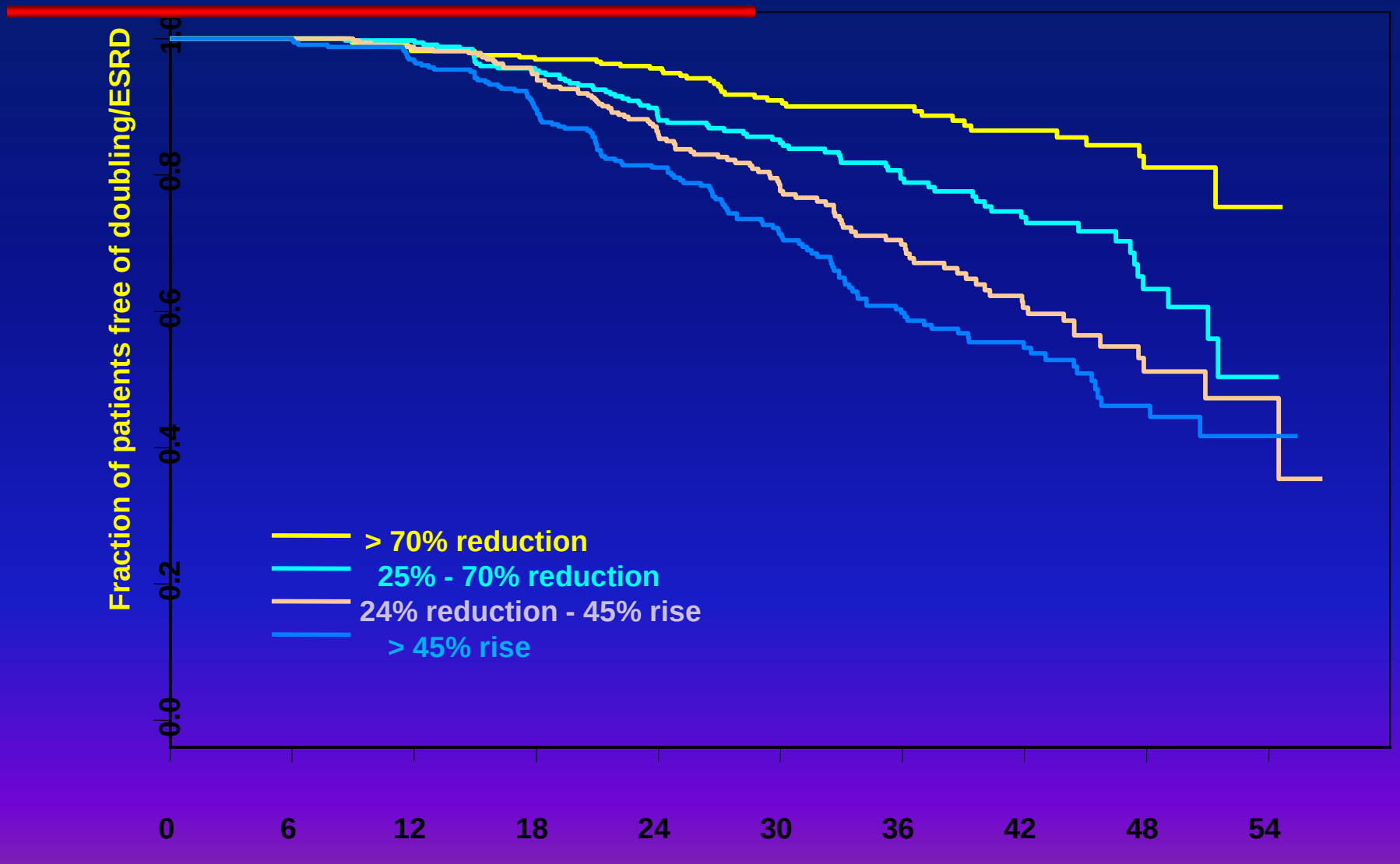






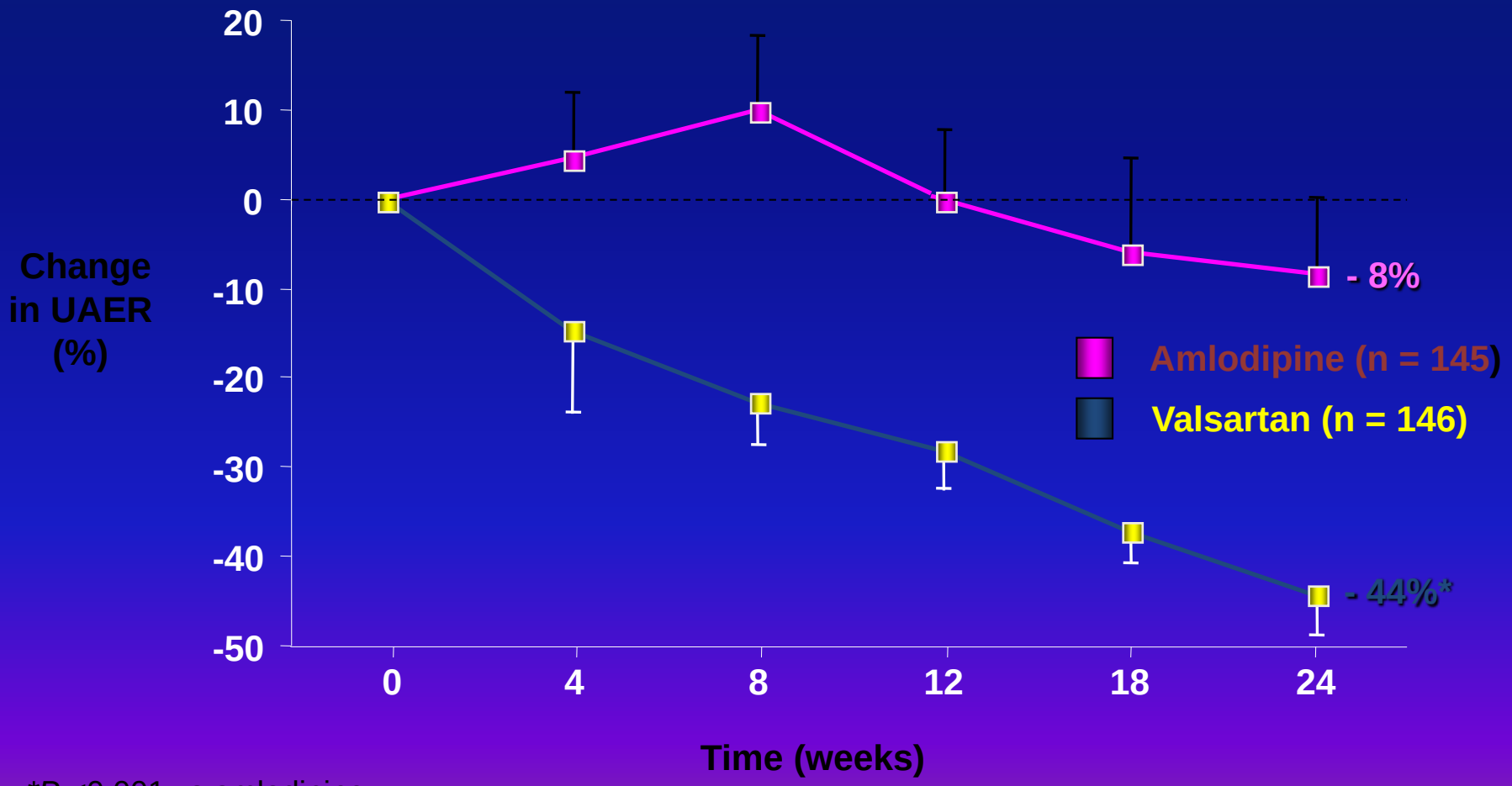
Lewis EJ et al. N Engl J Med 2001;345:851-860.

A dose-response relationship, with a greater reduction in proteinuria associated with greater reduction in risk of renal failure



Atkins R et.al Am J Kidney Dis 2005;45:281-287

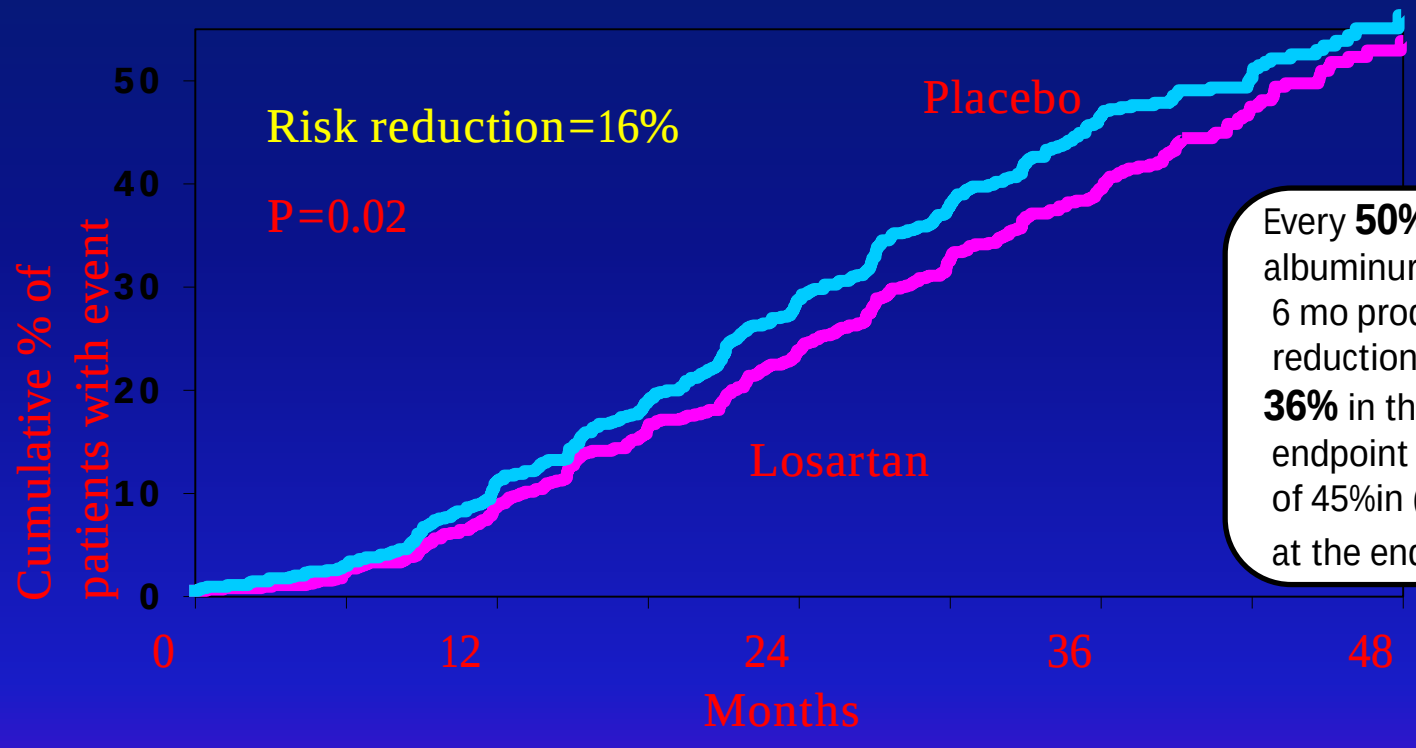
MARVAL: Valsartan Significantly Lowers Urinary Albumin Excretion Rate



**P* <0.001 vs amlodipine.

Viberti G et al. *Circulation.* 2002;106:672-678.

RENAAL:Losartan reduced the incidence of a doubling of the plasma Creatinine by 25 % & ESRD by 28 percent;



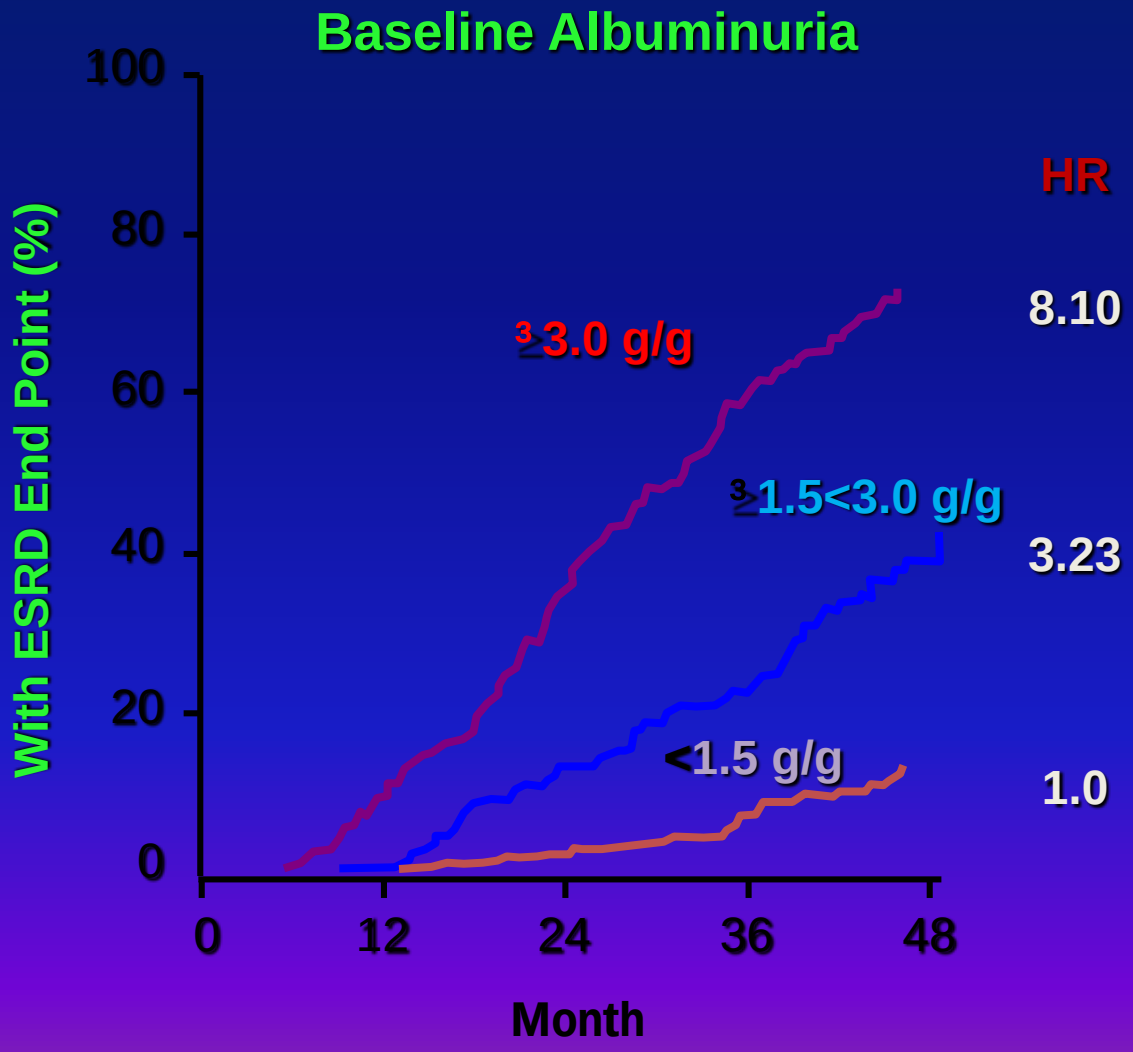
Every **50%** reduction in albuminuria in the first 6 mo produced a reduction of **36%** in the primary endpoint and a reduction of 45%in (ESRD) at the end of study.

†In combination with open-label diuretic, calcium channel blocker, beta-blocker, alpha-blocker, and/or centrally acting agent

*doubling of serum creatinine, end stage renal disease, death

Brenner BM, et al. *N Engl J Med.* 2001;345(12):861-869.

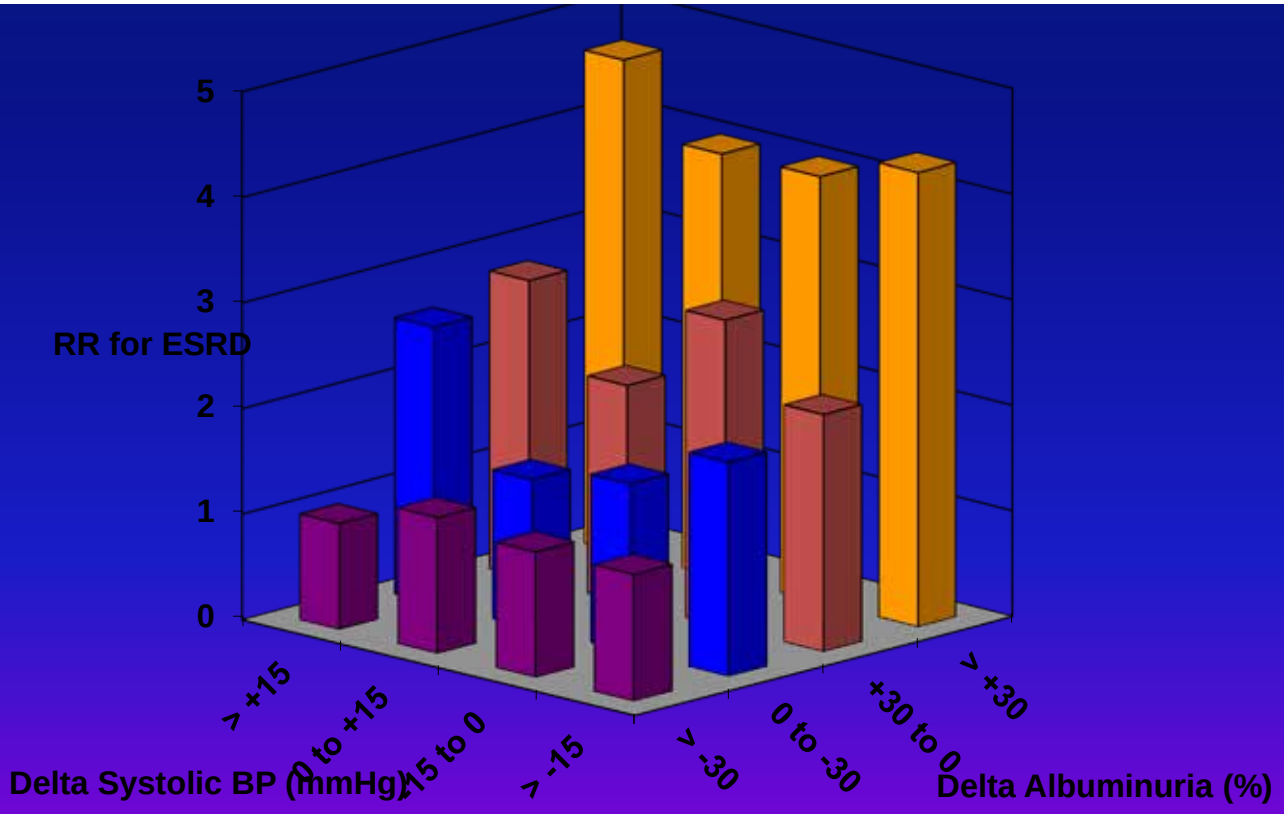
RENAAL; Albuminuria at Baseline Predicts ESRD in Type 2 Diabetics With Nephropathy (N=1513)



de Zeeuw et al. *Kidney Int.* 2004;65:2309-2320.

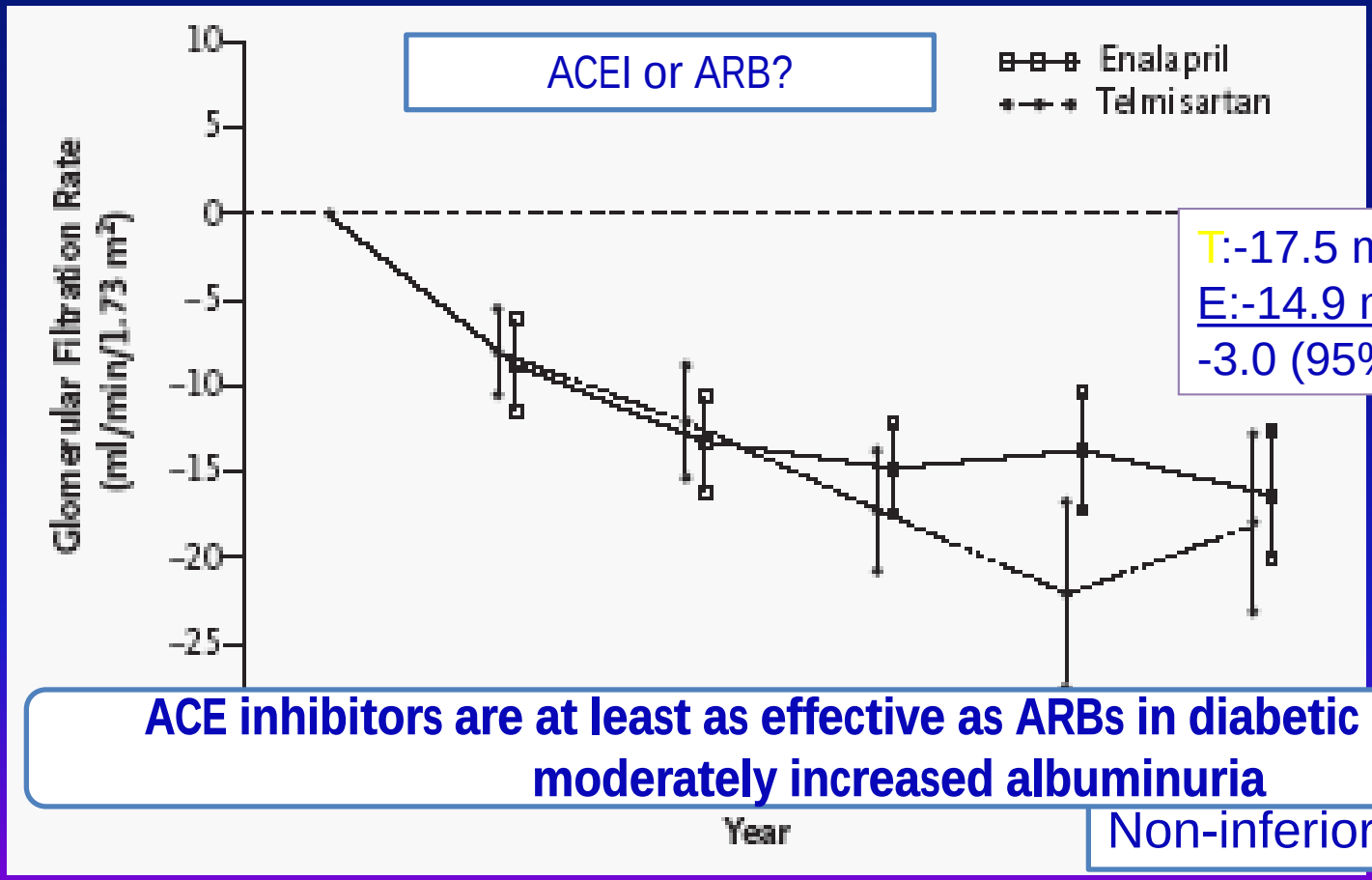
RENAAL: Dominant Role of Altered Proteinuria in Reducing Risk of ESRD

Increase in albuminuria constitutes higher risk for ESRD than increase in BP



Eijkelkamp W et al. J Am Soc Nephrol 2007:18;1540–6

DETAIL was a randomized controlled trial that compared enalapril to the ARB telmisartan



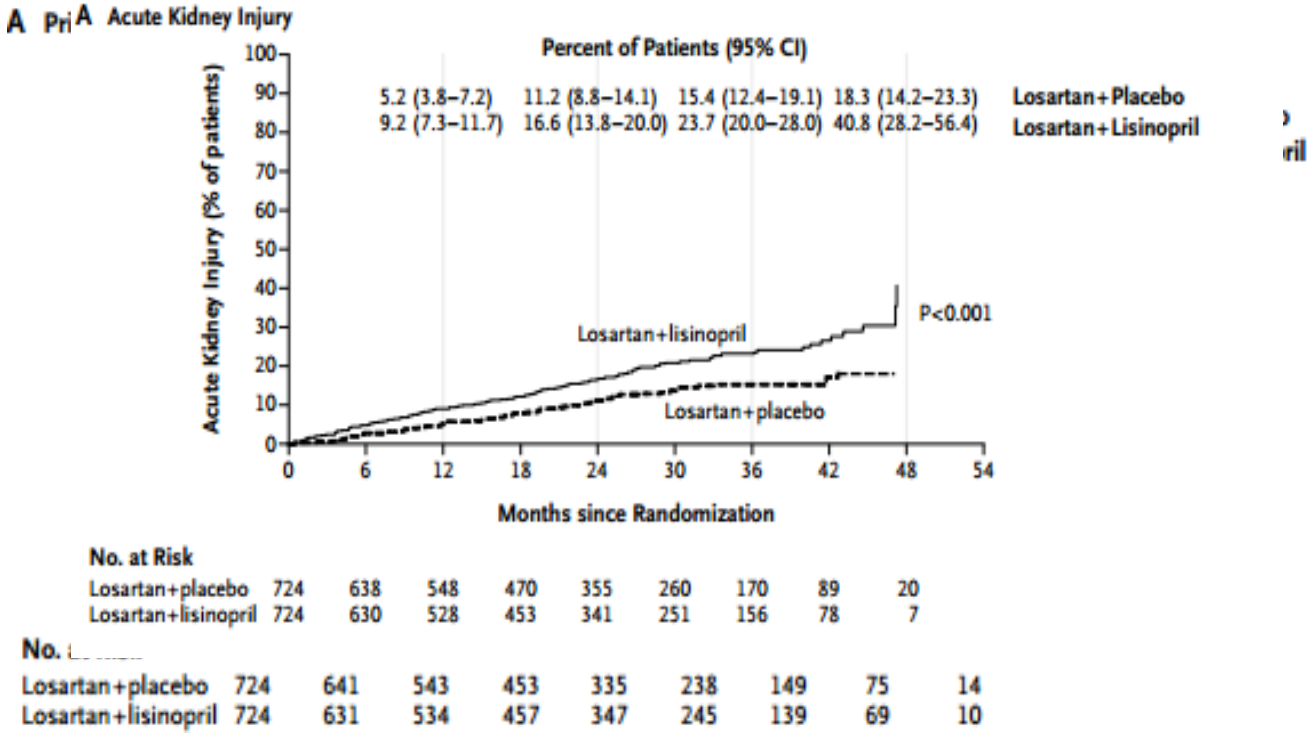
T:-17.5 ml/min/1.73 m^2
E:-14.9 ml/min/1.73 m^2
-3.0 (95% CI: -7.6 to 1.6)

ACE inhibitors are at least as effective as ARBs in diabetic patients with moderately increased albuminuria

Non-inferiority of ARB

Barnett AH et al. New Engl J Med 2004; 351:1952-61

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy



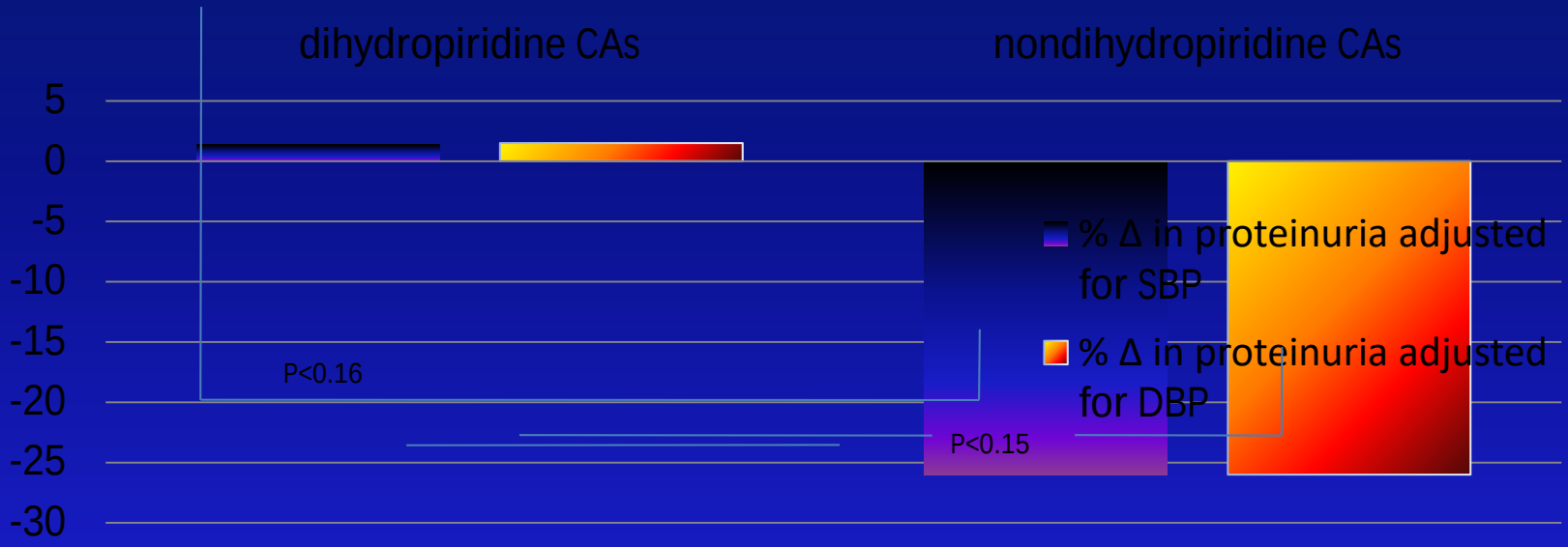
The primary end point was the first occurrence of a change in the estimated GFR (a decline of ≥30 ml per minute per 1.73 m2 if the initial estimated GFR was ≥60 ml per minute per 1.73 m2 or a decline of ≥50% if the initial estimated GFR was <60 ml per minute per 1.73 m2), end-stage renal disease (ESRD), or deat

VA-NEFRON-D

Other antihypertensive drugs and combinations

Diltiazem and verapamil appear to be as consistently effective as an ACE inhibitor or ARB in lowering protein excretion in diabetic patients

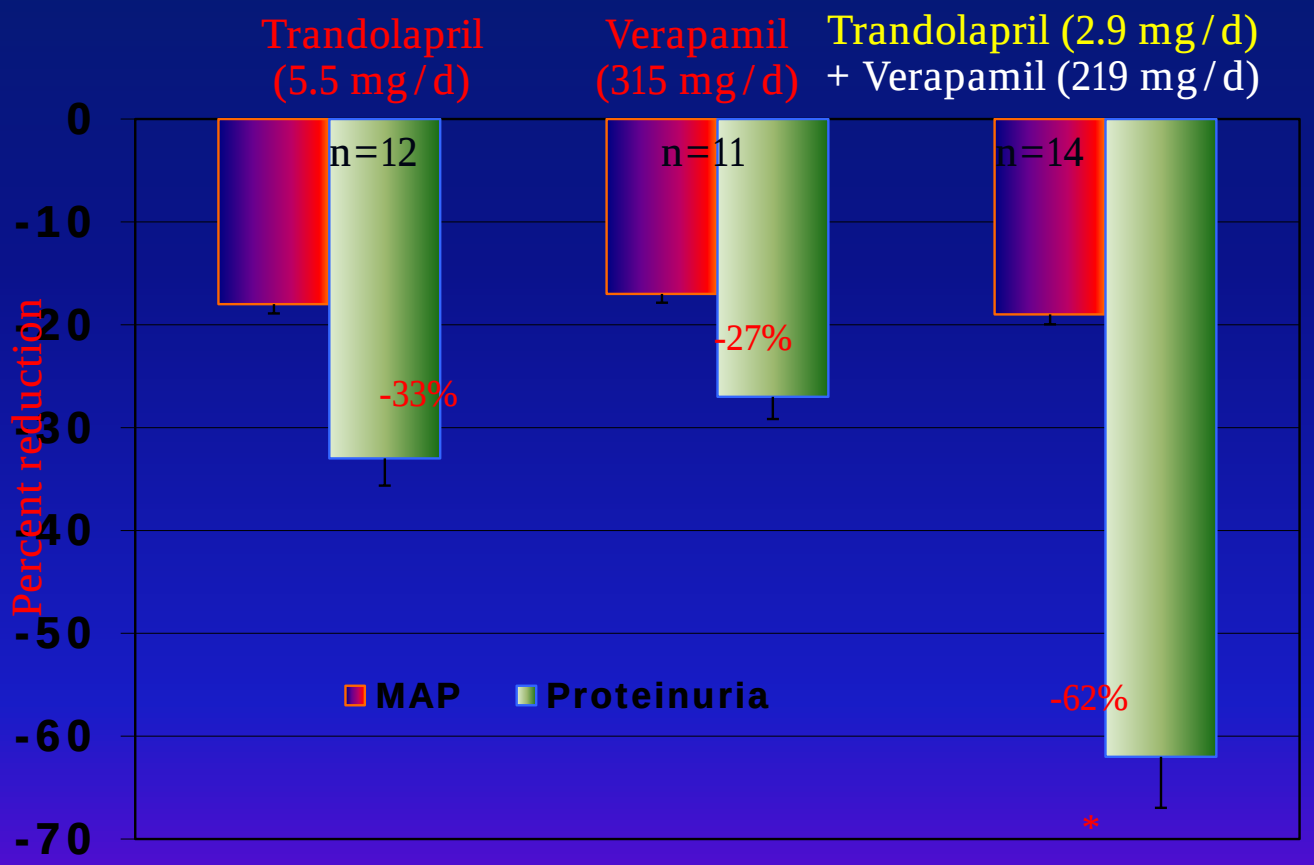
Nondihydropiride CAs VS Dihydropiridine Cas in proteinuria reduction



The percentage change in proteinuria among patients treated with dihydropiridine CAs or nondihydropiride CAs adjusted for change in SBP and DBP

Kalaitzidis R & Bakris G , Arch Med Sci 2009

ACE-I + Verapamil: Additive Reduction of Proteinuria in Type 2 Diabetes at 1 Year



*p <0.001 combination vs either monotherapy

Bakris GL, et al. Kidney Int. 1998;54:1283-1289.
Reprinted by permission, Blackwell Science, Inc.

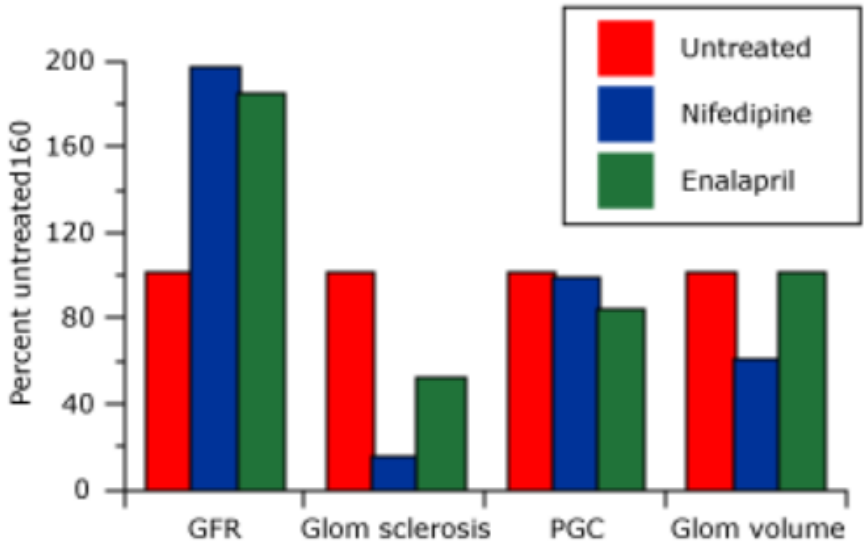
Dihydropyridine CCBs only when used in combination with a RAAS blocker

Can reduce proteinuria among patients with advanced proteinuric nephropathy

Am J Kidney Dis 2013, **62:**201-213.
Kalaitzidis R & Bakris G Curr.Cardiol.Rep. 2009, *11:436-442.*

ACE Inhibitor & CCB nephroprotection

ACE inhibitor and calcium blocker therapy protect against progressive glomerulosclerosis in rats by different mechanisms

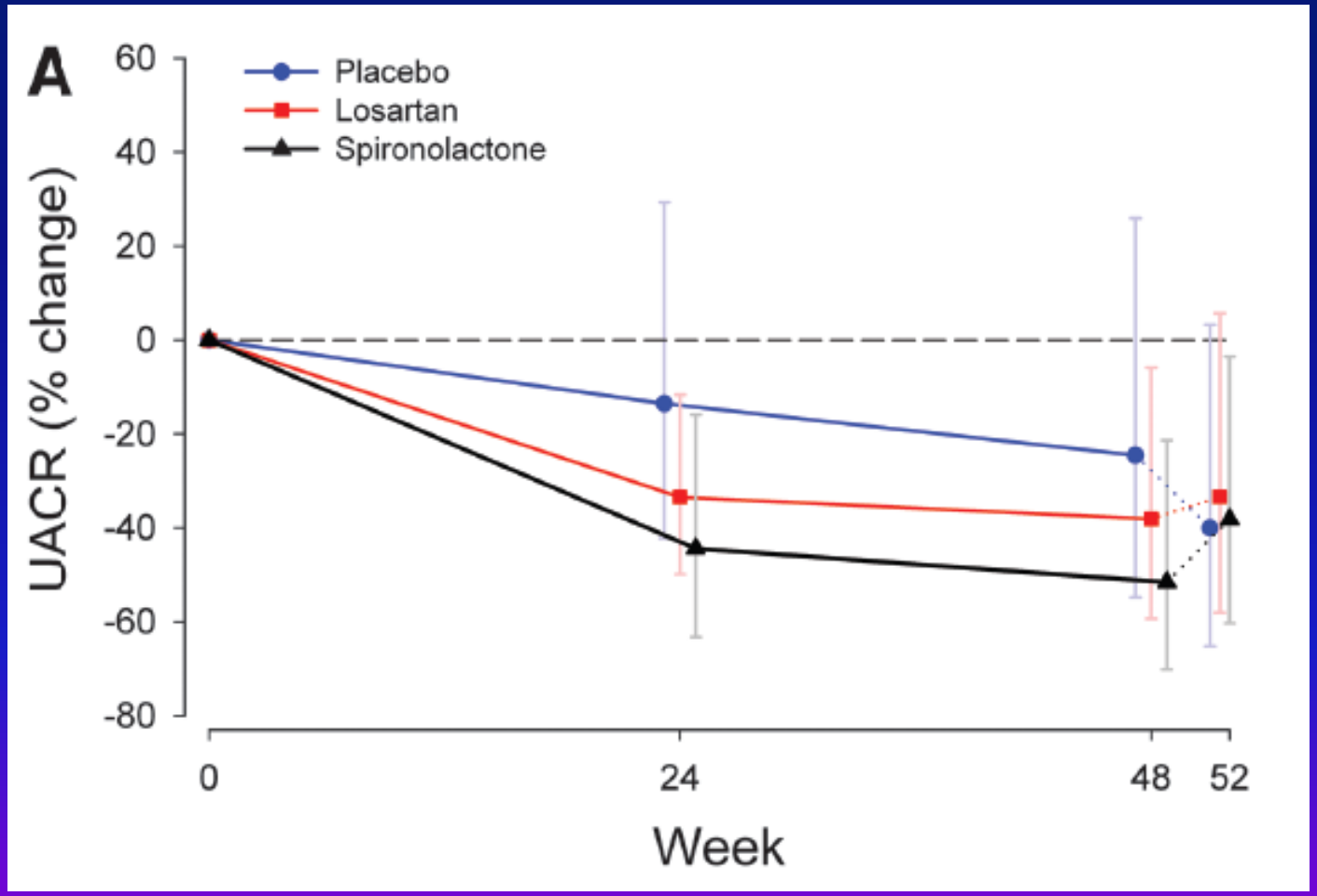


The mechanism of protection appeared to be different: enalapril lowered the glomerular capillary pressure (PGC),
while nifedipine minimized glomerular hypertrophy
as manifested by a reduction in glomerular volume.

Dworkin LD, Burstein JA, Parker M, et al. Kidney Int 1993; 43:808.

Mineralocorticoid receptor antagonists

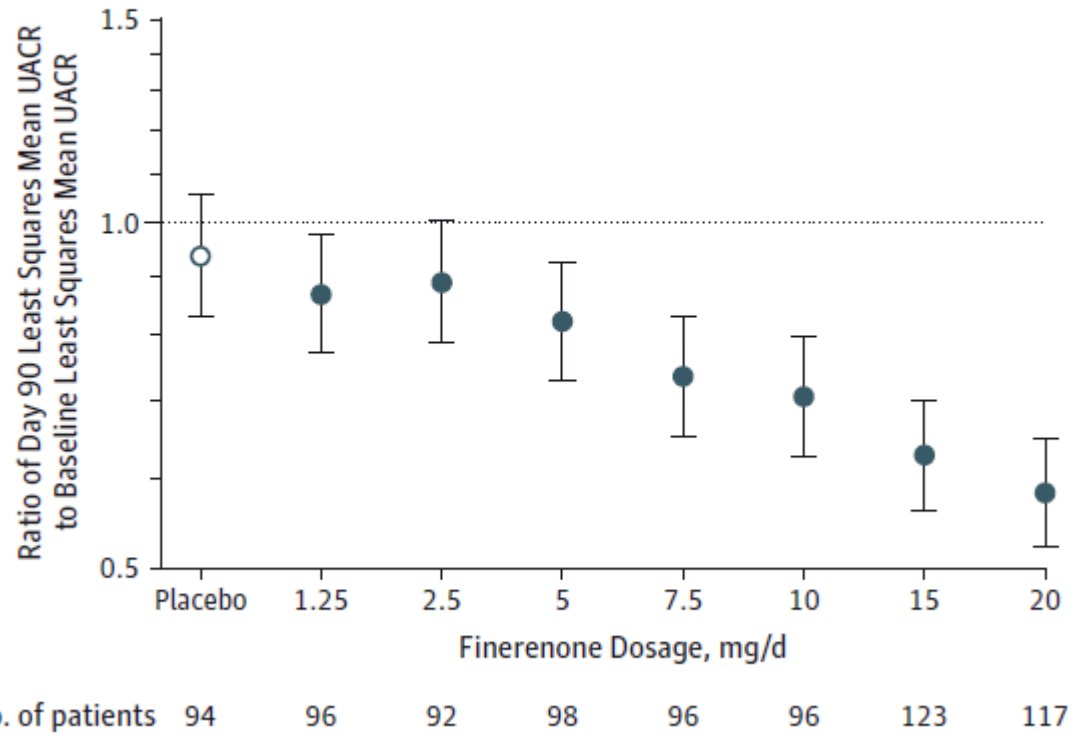
Aldosterone Blockade in Diabetic Nephropathy with Proteinuria



Mehdi et al, J Am Soc Nephrol 2009

Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy

Figure 2. Change in Least Squares Mean UACR at Day 90 Relative to Baseline in Patients Treated With Finerenone, 1.25-20 mg/d, or Placebo



Among patients with diabetic nephropathy, **most receiving an ACE inhibitor or an angiotensin receptor blocker,** the addition of finerenone compared with placebo resulted in improvement in the UACR

A dose-dependent effect was observed, with albuminuria reductions ranging from 21 to 38 percent with doses ranging from 7.5 mg/day to 20 mg/day.

Bakris GL J AMA. 2015 Sep;314(9):884-94.

Sodium-glucose cotransporter 2 inhibitors

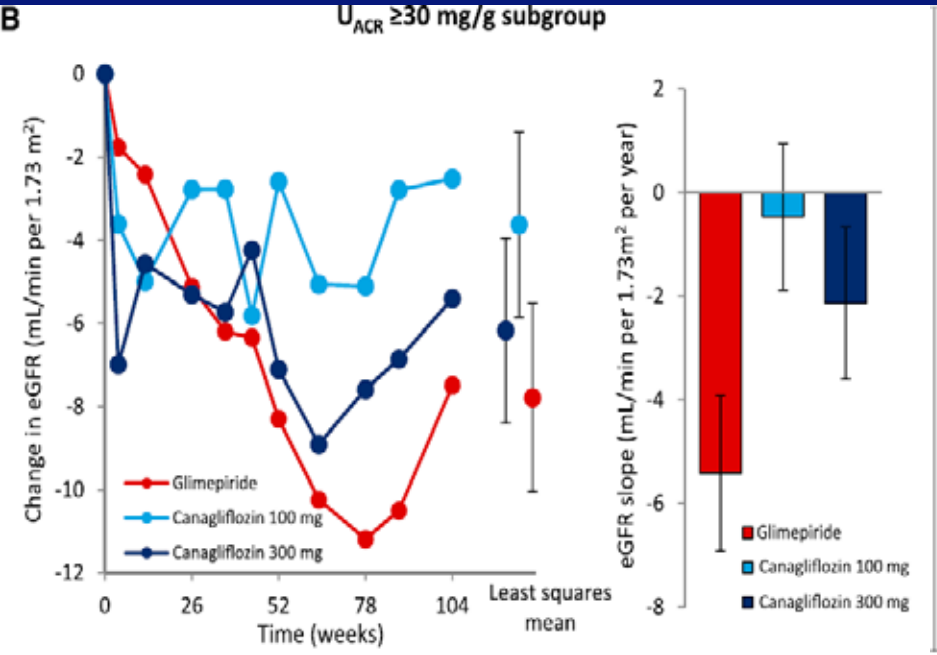
Sodium-glucose cotransporter 2 inhibitors

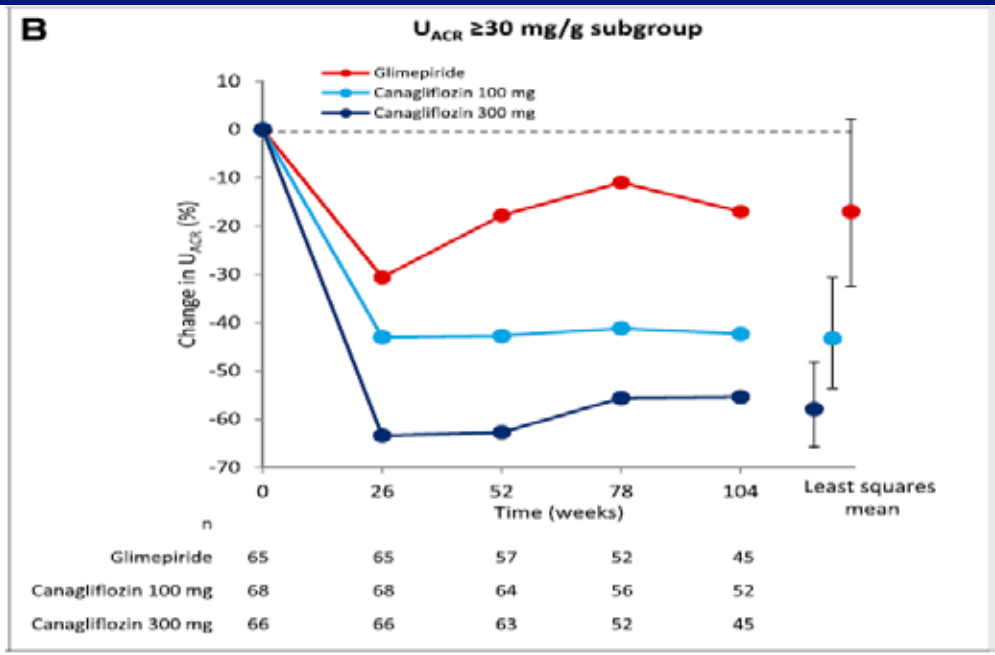
The use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, such as canagliflozin and empagliflozin in patients with type 2 diabetes

Reduced the risk of kidney disease progression and of renal endpoints in some trials

J Am Soc Nephrol. 2017 Jan;28(1):368-375.
N Engl J Med. 2016;375(4):323. Epub 2016 Jun 14.

Canagliflozin Slows Progression of Renal Function Decline Independently of Glycemic Effects

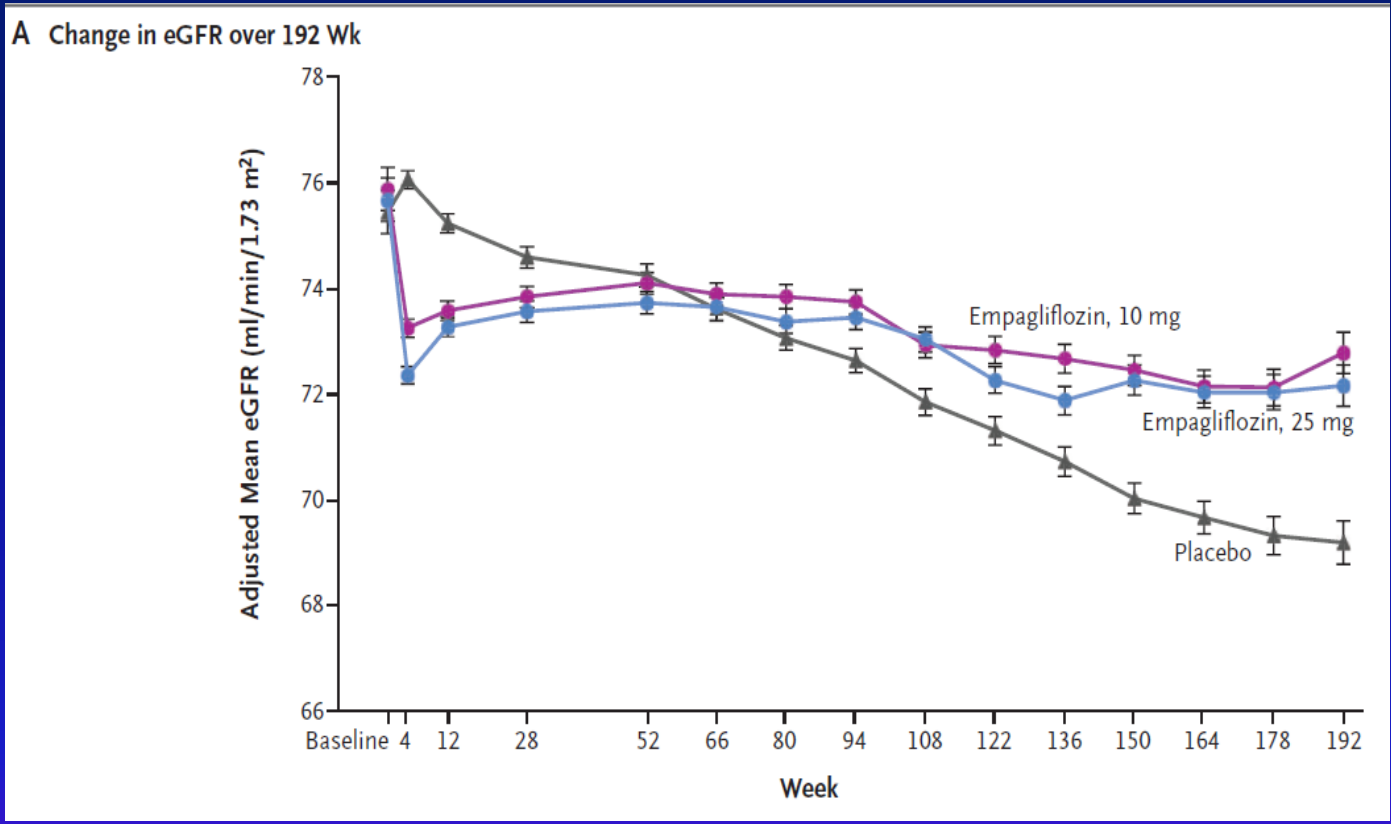




Canagliflozin 100 or 300 mg/d, compared with glimepiride, slowed the progression of renal disease over 2 years in patients with type 2 diabetes. Changes in UACR in a subgroup ofpatients with UACR$30 mg/g at baseline
, and canagliflozin may confer renoprotective effects independently of its glycemic effects

Am Soc Nephrol 28: 368–375, 2017

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

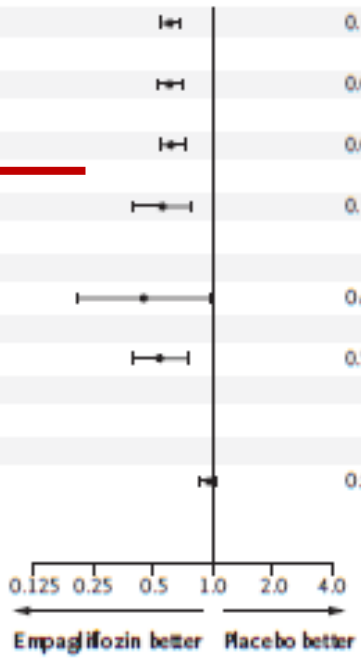


In patients with type 2 diabetes at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events

N Engl J Med 2016;375:323-34.

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

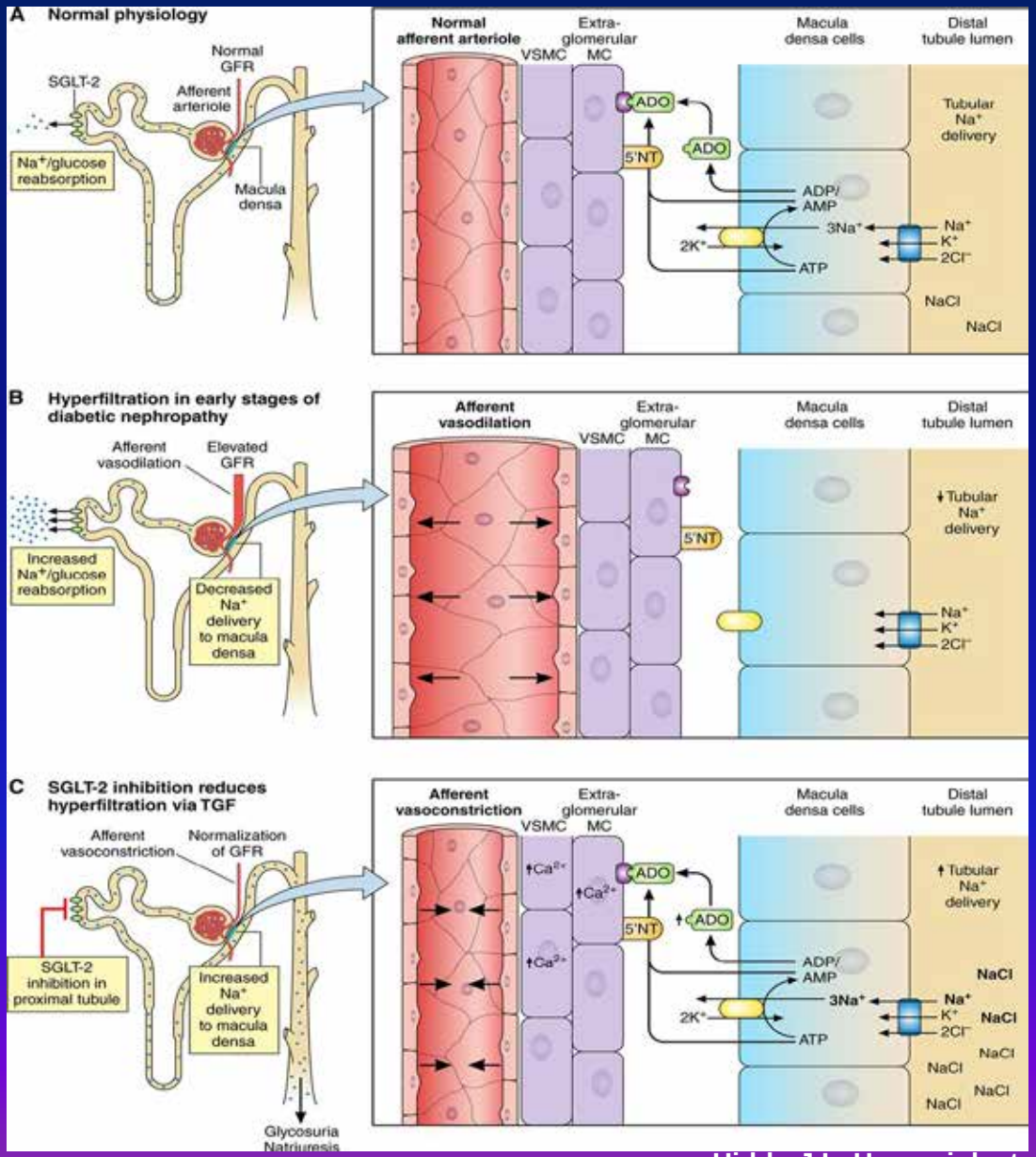
Renal Outcome Measure	Empagliflozin: no. with event/ no. analyzed (%)	Empagliflozin: rate/1000 patient-yr	Placebo: no. with event/ no. analyzed (%)	Placebo: rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2083 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m²	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



Risk Comparison for Seven Renal Outcomes

N Engl J Med 2016;375:323-34.

Putative mechanism for sodium-mediated changes in adenosine bioactivity at the afferent arteriole. During normal conditions (A), sodium-glucose cotransport leads to minimal glycosuria.

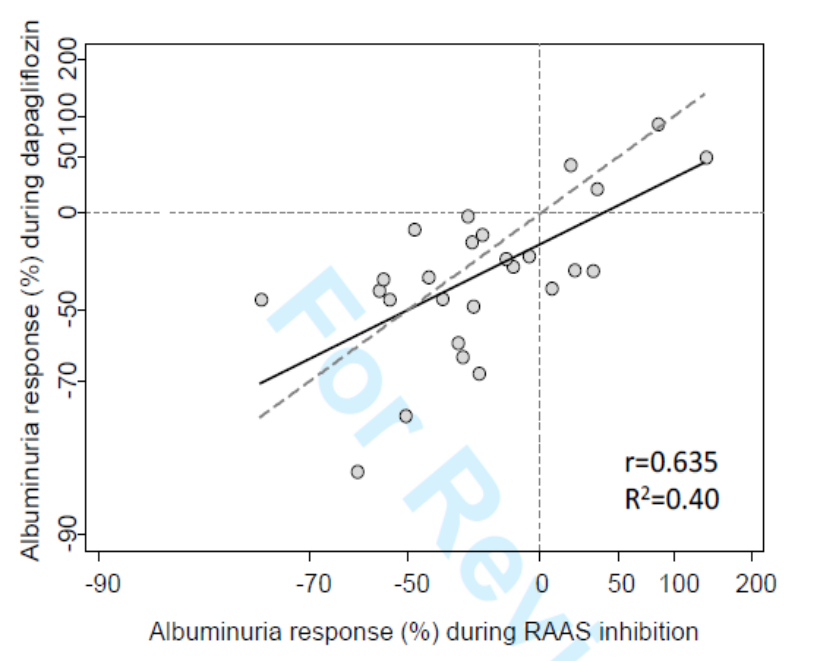


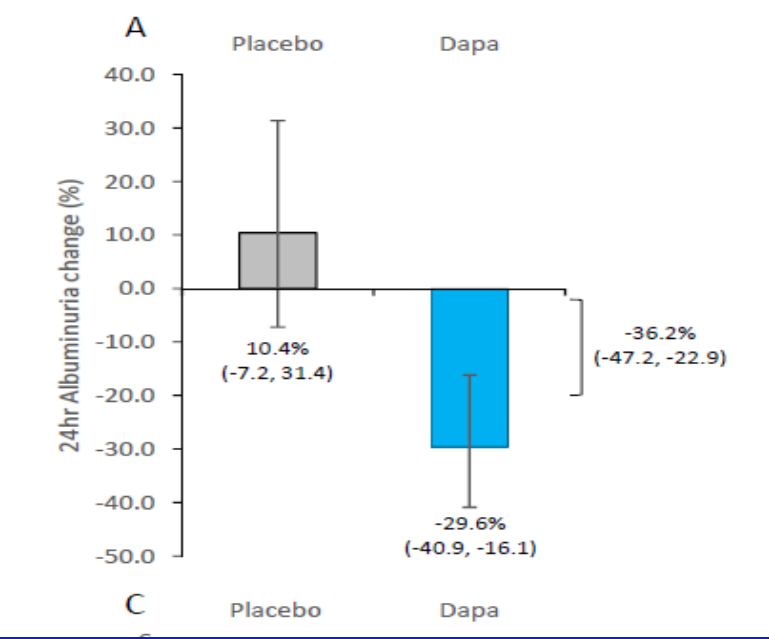
American Heart Association

Hiddo J.L. Heerspink et al. Circulation. 2016;134:752-772

Does SGLT2 inhibition with dapagliflozin overcome individual therapy resistance to RAAS inhibition?

The albuminuria response to RAASi significantly correlated with response to dapagliflozin





Individual therapy resistance to RAASi cannot be overcome with the addition of a completely different class of drugs, SGLT2 inhibitors. These data suggest that the individual drug response is an intrinsic individual characteristic possibly unrelated to the type of intervention, unless the mode of action of dapagliflozin on albuminuria is through the RAAS.

Diabetes, Obesity and Metabolism, doi: 10.1111/dom.12936 doi: 10.1111/dom.13057

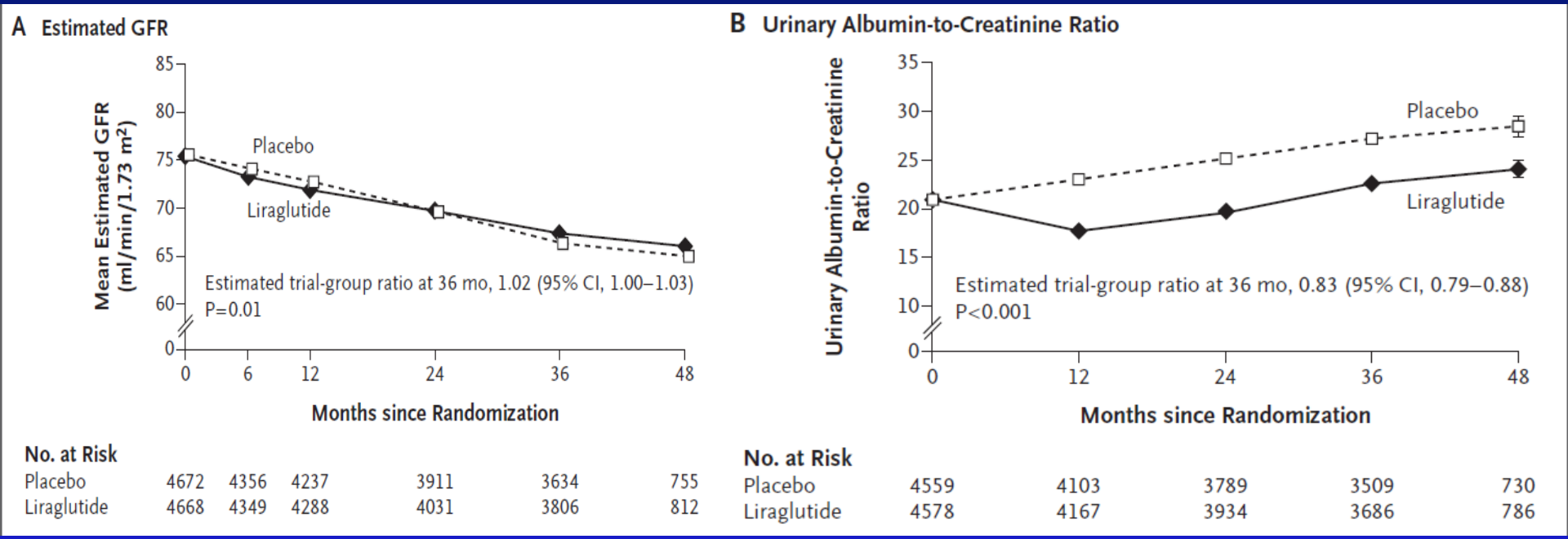
Glucagon-like peptide-1 receptor agonists

The glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide in a large trial of patients with type 2 diabetes

Reduced the incidence of a composite renal endpoint
(consisting of new onset of albuminuria >300 mg/day, doubling of serum creatinine, end-stage renal disease, or renal death)

N Engl J Med. 2017;377(9):839.

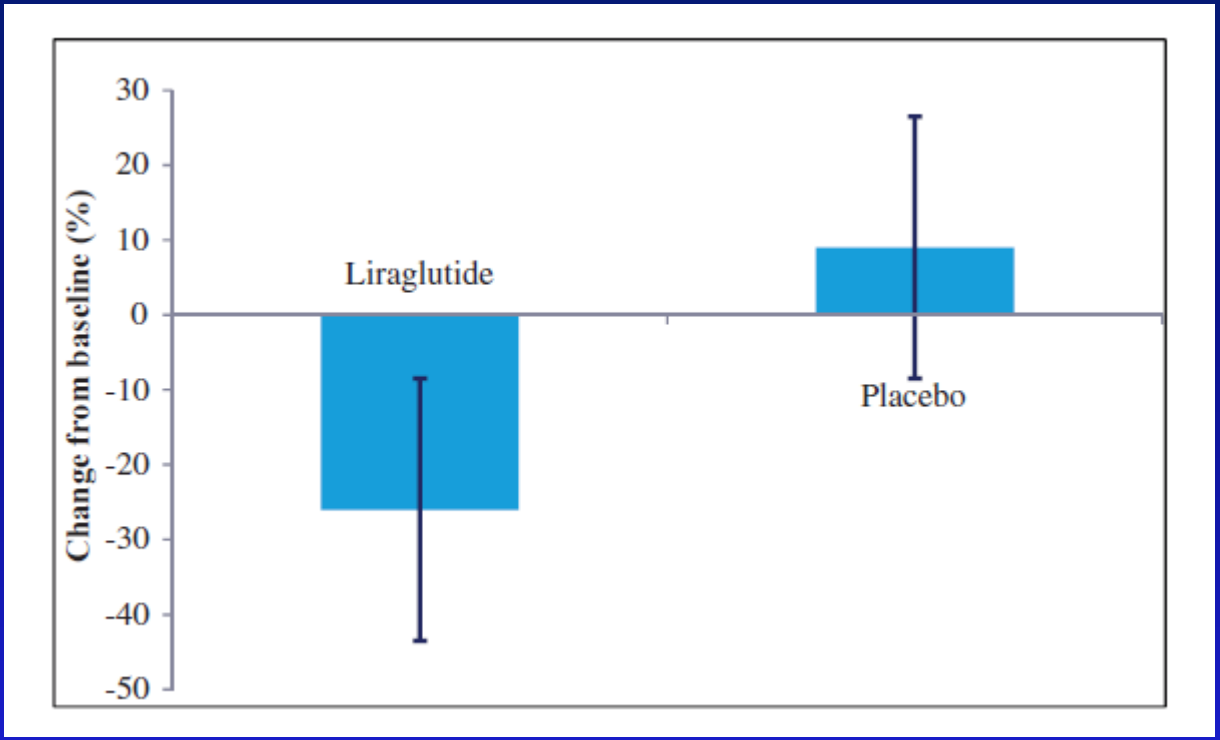
Liraglutide and Renal Outcomes in Type 2 Diabetes



When added to usual care, liraglutide resulted in lower rates of the development and progression of diabetic kidney disease than placebo

N Engl J Med 2017;377:839-48.

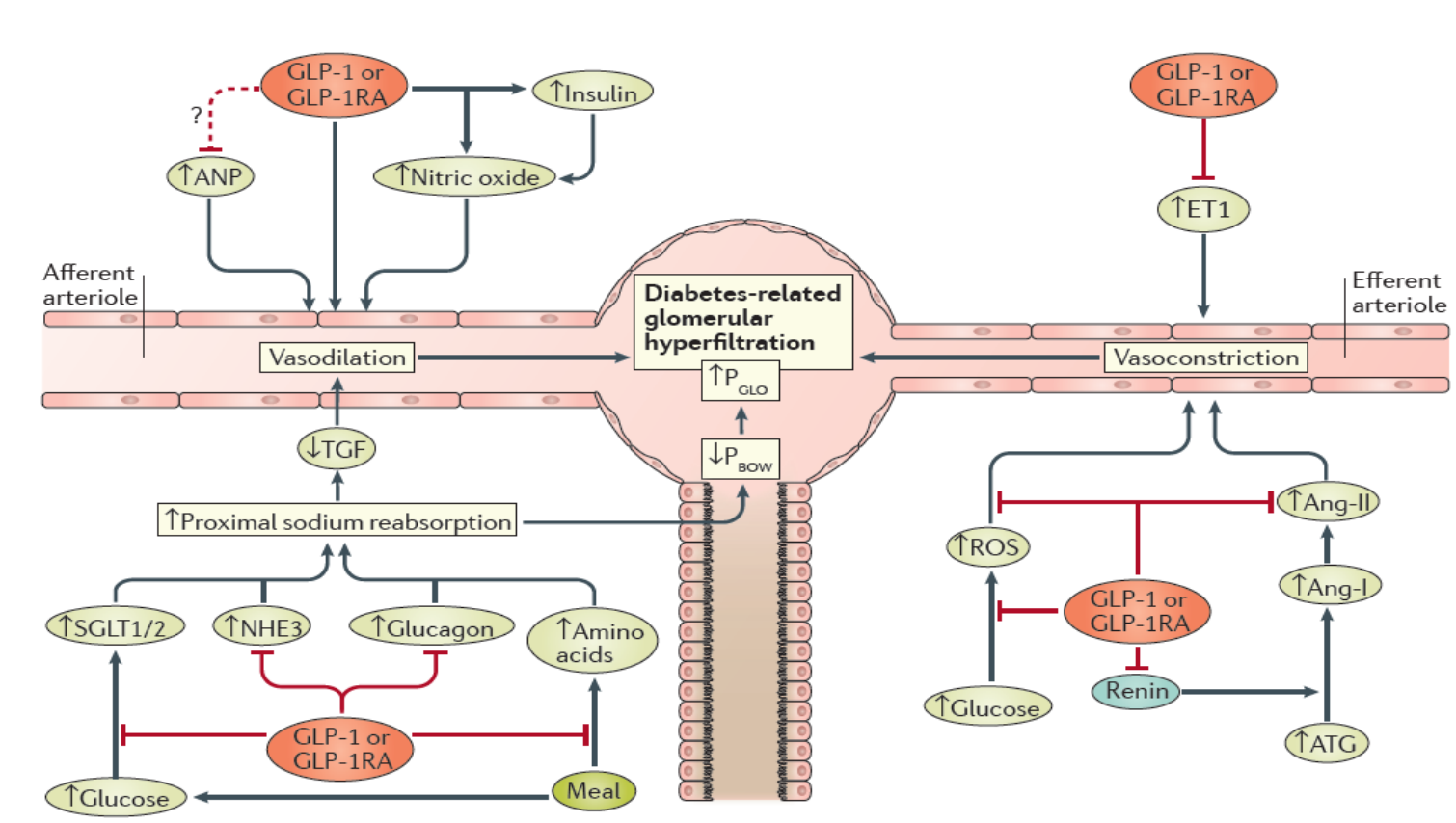
The effect of liraglutide on renal function: A randomized clinical trial



Changes in urinary albumin excretion rate. Change in urinary albumin excretion rate (UAER) from baseline to end of treatment. UAER was reduced by 26 (95% CI: 5; 43)% during liraglutide treatment and increased by 9 (95% CI: −6; 22)% during placebo treatment.

Diabetes Obes Metab 2017; ***19(2):239–247***

GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes



GLP-1RAs are associated with direct GLP-1R-mediated and, at least in part, nitric oxide-dependent vasodilation of the afferent renal arteriole, as well as indirect inhibition of vascular and tubular factors that are putative mediators of glomerular hyperfiltration in diabetes. The integrated effect of incretin-based therapy on renal haemodynamics seems to be the result of direct vasodilative actions and inhibition of pathways of glomerular hyperfiltration.

Nature Reviews Nephrology **volume 13**, pages 605–628 (2017)

Data from clinical trials suggest that GLP-1R agonists and, to a lesser extent, DPP-4 inhibitors

Marginally improve surrogate renal end points, plausibly beyond the effects of improved glycaemic control

Nature Reviews Nephrology **volume 13**, pages 605–628 (2017)

Salt intake and proteinuria

Salt intake and proteinuria

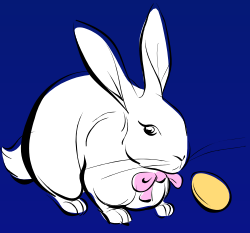
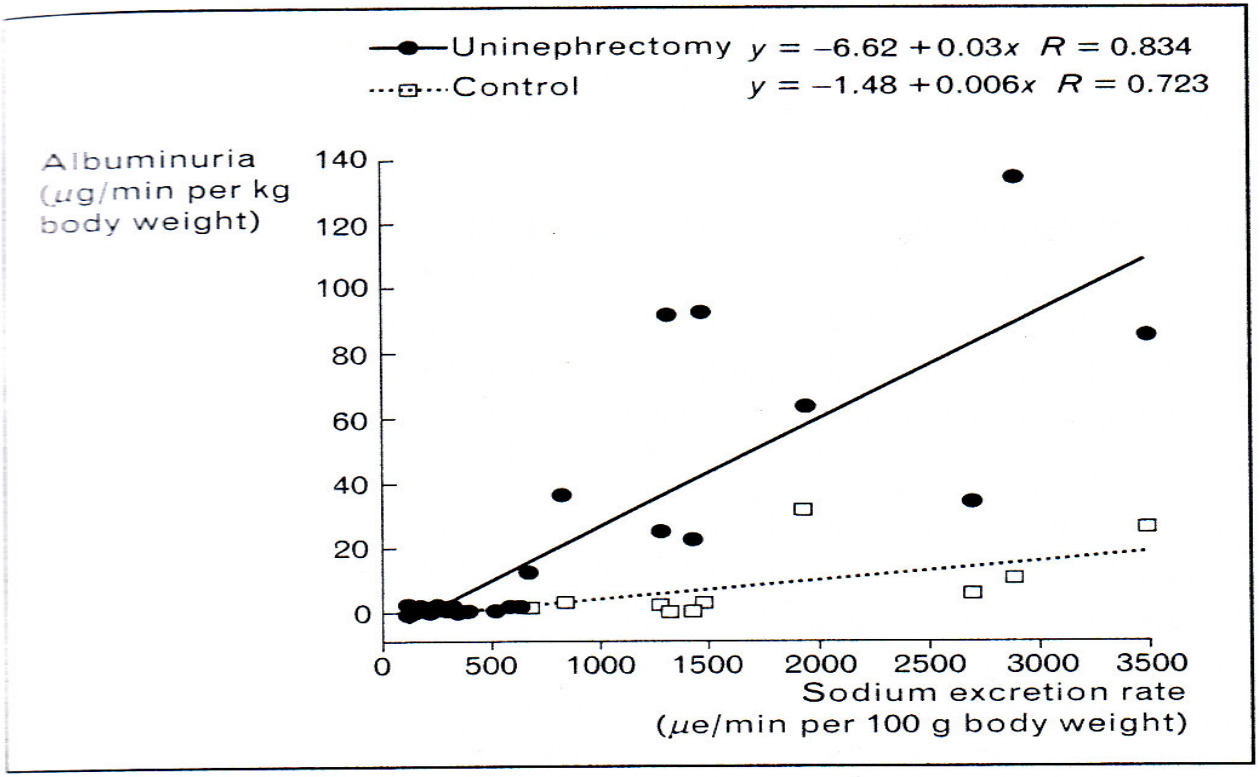
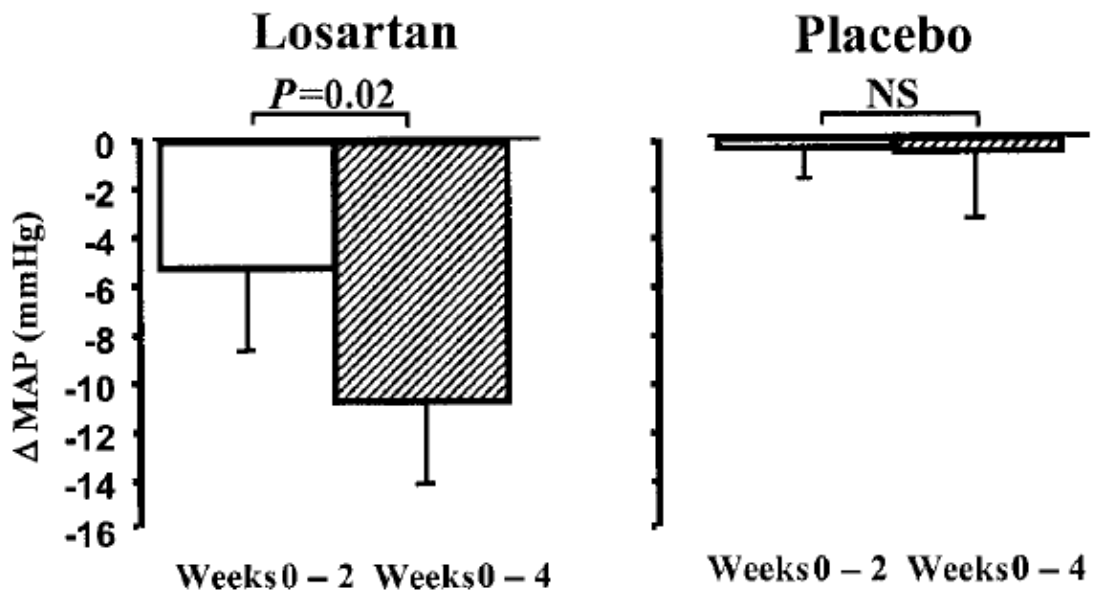


Figure 3 Relationship between dietary salt intake and albuminuria in normal (control) rats and uninephrectomized Lewis rats



A direct correlation between degree of salt intake and albumin excretion rate was identified in both groups, although the slope of the line was increased in those rats that had undergone unilateral nephrectomy. Data were obtained from Sanders *et al.* [41].

A Low-Sodium Diet Potentiates the Effects of Losartan in Type 2 Diabetes



Salt restriction and/or diuretics enhance the effect of renin-angiotensin blockade on proteinuria in these patients.

Diabetes Care. 2002;25(4):663.

Protein restriction for diabetic renal disease (Review)

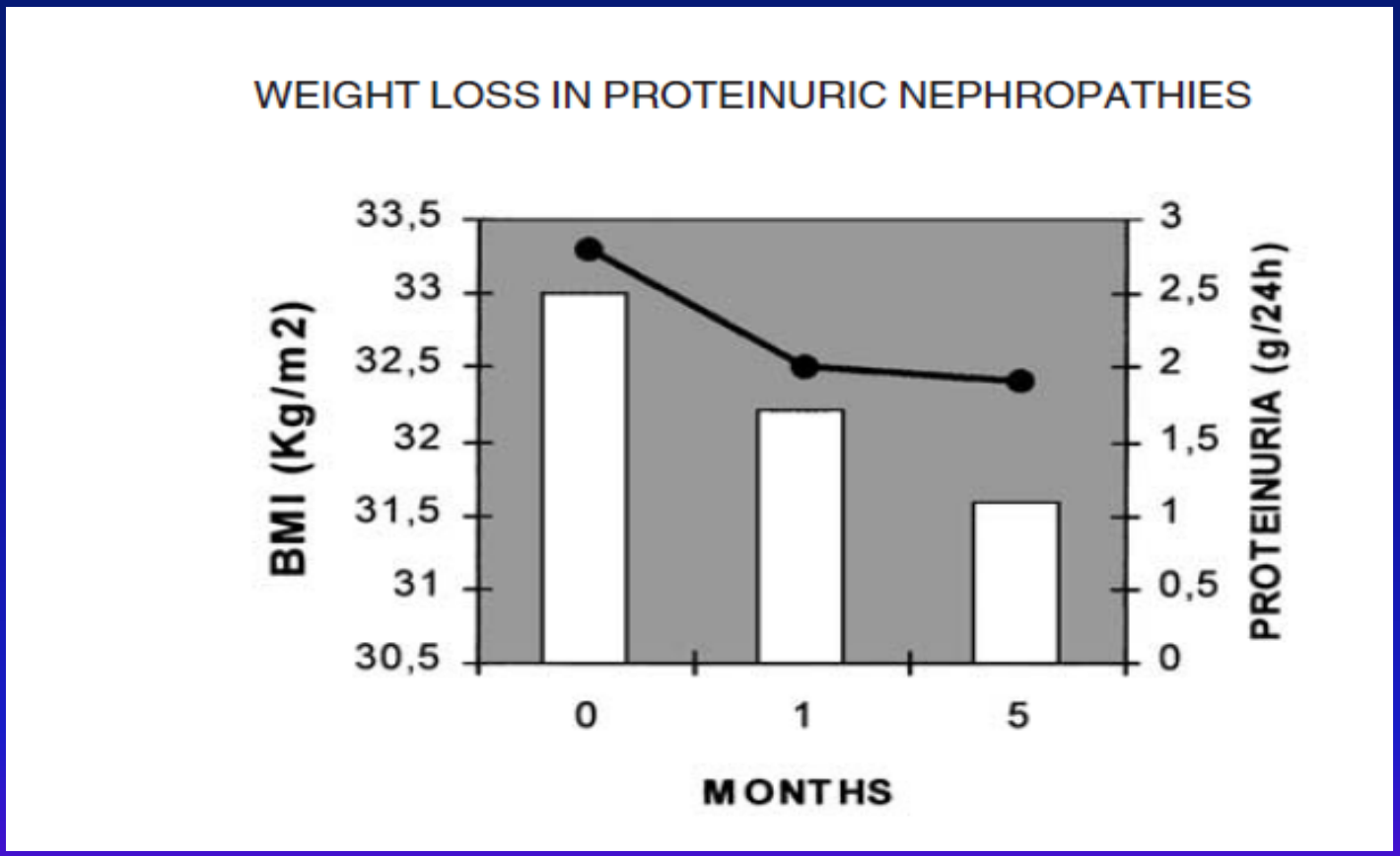
- **12 μελέτες** (9 RCT, 3 before and after)
- **Σκοπός:** πιθανή επίδραση του περιορισμού της πρωτεϊνικής πρόσληψης (0.7-1.1g/kg/d) στη νεφρική λειτουργία ασθενών με ΣΔ τύπου I & II
- **ΣΔ I:** μεταβολή του GFR κατά 0.1ml/min/m (μη σημαντική)
- **ΣΔ II:** παρόμοια – μη σημαντική μεταβολή του GFR

Η μειωμένη πρωτεϊνική πρόσληψη επιβραδύνει ελάχιστα και μη στατιστικά σημαντικά την εξέλιξη της διαβητικής ΧΝΝ

- Προτεινόμενη ημερήσια πρόσληψη πρωτεΐνης: **0.8-1 g/kg**

The Cochrane Collaboration, Robertson LM, et al. The Cochrane Library 2009

Weight reduction



Marked decreases in proteinuria may be observed in obese diabetics who lose weight

Morales , Am J Kidney Dis. 2003;41(2):319.

Hyperlipidemia

Lipid lowering (at least with statins) may slow the rate of progression of chronic kidney disease, including diabetic nephropathy

Kidney Int. 2006;70(1):177

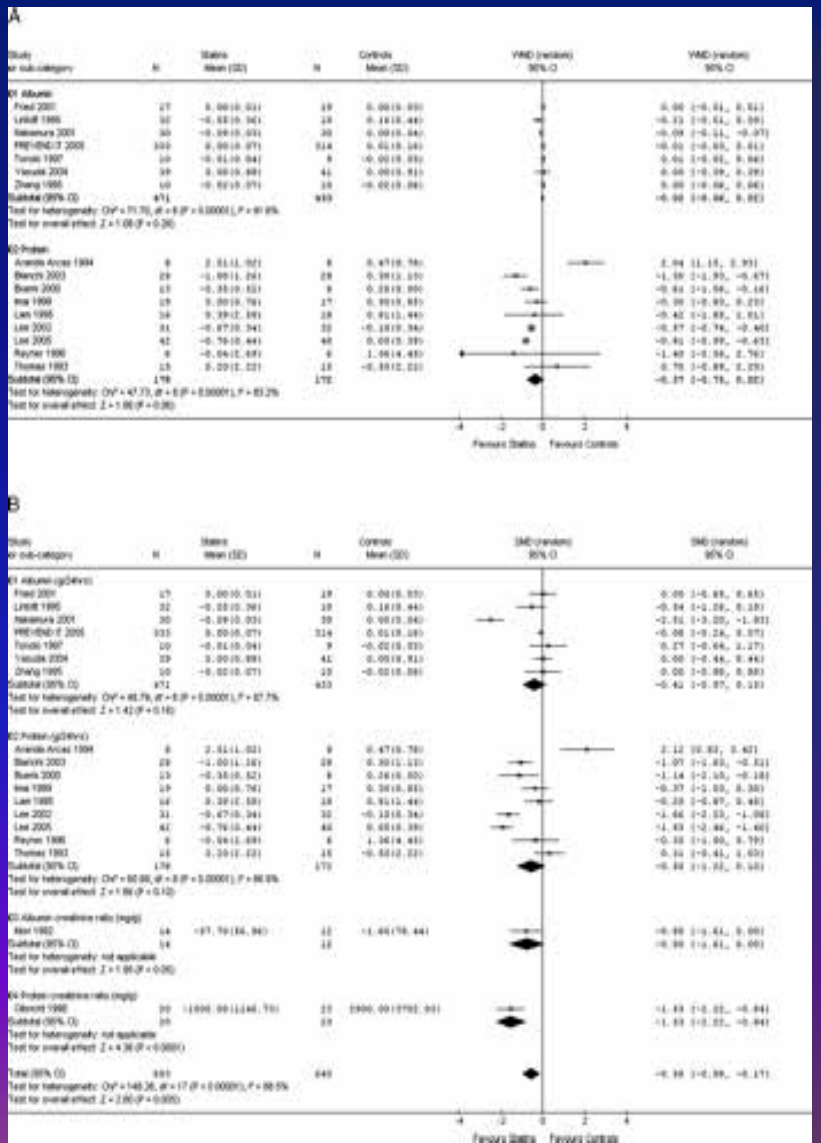
The Role of Statins in Chronic Kidney Disease

Table 1. Statins and CKD progression

Study		Subjects in the study, n	Follow-up	Treatment	Outcome	Results
HPS [36]	retrospective analysis	5,963 patients with DM2	4–6 years	simvastatin 40 mg/day of placebo	rate of kidney function decline	GFR decline (5.9 vs. 6.9 ml/min; p = 0.003) in the simvastatin group vs. placebo
GREACE [32]	post-hoc subgroup analysis	1,600 patients with dylipidemia and CHD	3 years	atorvastatin 10–80 mg/day or usual medical care	rate of kidney function decline	CrCl had a 12% increase in atorvastatin group (p < 0.0001); CrCl had a 5.2% decrease in patients not treated with statins (p < 0.0001); CrCl had a 4.9% increase in the usual care group on various statins; HR 0.84 (CI: 0.73–0.95; p = 0.003) with every 5% increase in CrCl
ALLIANCE [54]	post-hoc subgroup analysis	2,442 patients with dyslipidemia	4 years	atorvastatin 10–80 mg/day or usual medical care	rate of kidney function decline	CrCl did not change in the atorvastatin group (p < 0.0001) vs. baseline; CrCl declined by 4.4% in the usual care group (p = 0.0001 vs. baseline)
CARE [33]	post-hoc subgroup analysis	3,402 CKD patients with or at risk for CVD	5 years	pravastatin 40 mg/day vs. placebo	change in eGFR	in patients with GFR of 30–59.9 ml/min per 1.73 m², pravastatin reduced the adjusted rate of kidney function loss by approximately 34%; the absolute reduction in the rate of loss was small (0.22 ml/min per 1.73 m²/year; 95% CI: 0.07–0.37)
CARE [35]	post-hoc subgroup analysis	3,384 individuals, of whom 690 (20.4%) had eGFR <60 ml/min per 1.73 m²	4 years	pravastatin 40 mg/day vs. placebo	change in eGFR	the decline in the pravastatin group vs. placebo group was NS (0.1 ml/min per 1.73 m²/year slower; 95% CI: −0.2 to 0.4; p = 0.49); in patients with eGFR <40 ml/min per 1.73 m²/year, the rate of change in the pravastatin vs. placebo group was 2.5 ml/min per 1.73 m²/year slower (95% CI: 1.4–3.6; p = 0.0001)
TNT [55]	post-hoc subgroup analysis	9,656 participants with CHD	59.5 months	atorvastatin 10 vs. 80 mg	change in eGFR	mean change in eGFR showed an increase of 3.5 ± 0.14 ml/min per 1.73 m² with atorvastatin 10 mg and 5.2 ± 0.14 ml/min per 1.73 m² with atorvastatin 80 mg, respectively (p < 0.0001)
PREVEND-IT [26]	randomized controlled trial	of the 3,440 patients 469 used statins	4 years	pravastatin 40 mg/day or placebo or fosinopril or placebo (2 × 2 factorial)	change in eGFR	GFR fell in both statin users and nonusers (4.6 ± 13.5 and 2.4 ± 11.2, respectively); statin treatment was not associated with a significant change in GFR with only modestly impaired GFR (p = 0.11)

Kalaitzidis R et at al AJ Nephrology 2011

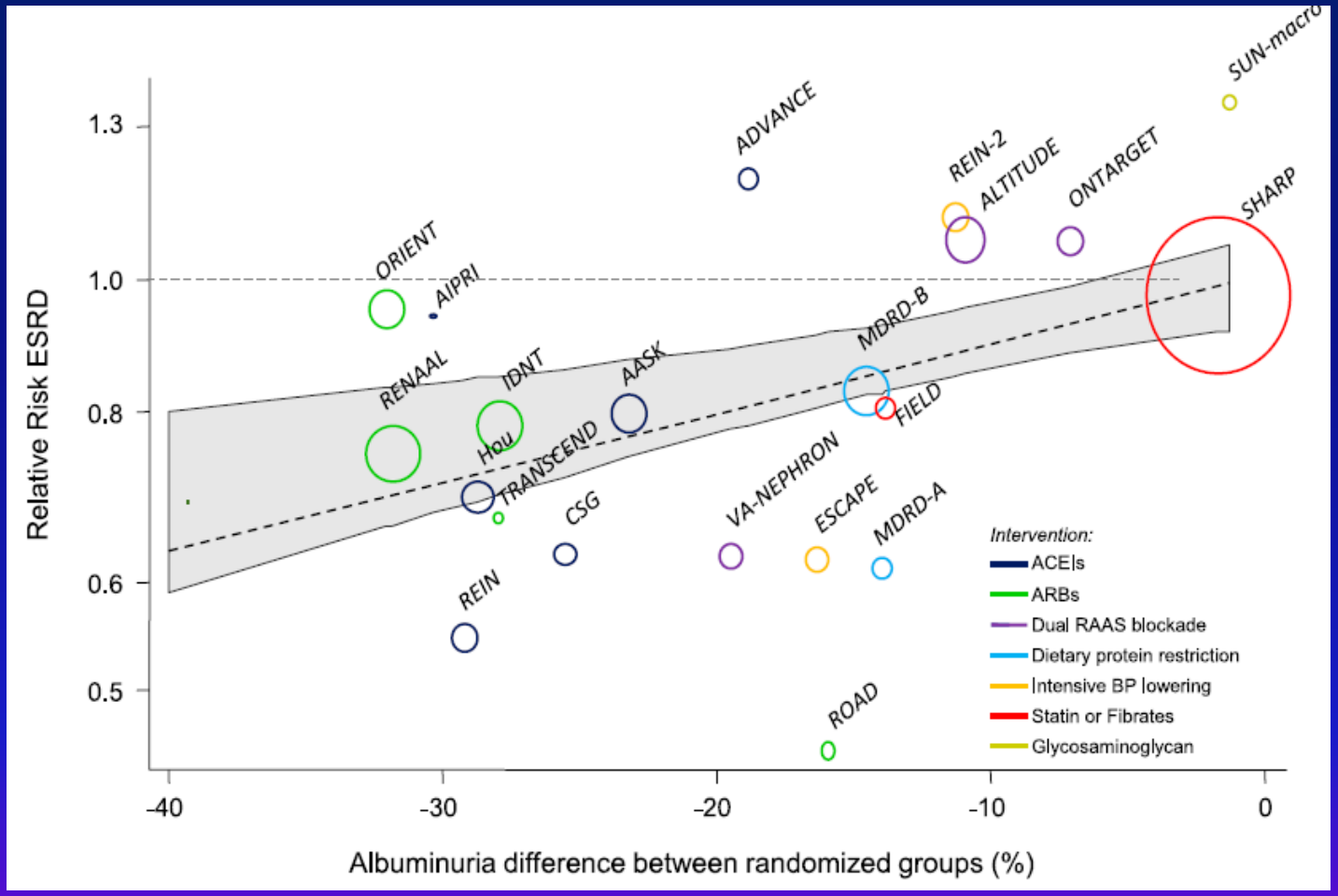
Βελτίωση λευκωματουρίας με την χορήγηση στατινών



(A) Change in urinary protein excretion (g/24 h)
(B) for statins *versus* controls, expressed as
(C) weighted mean difference (WMD).
(D) (B) Change in urinary protein excretion
(E) for statins *versus* controls, expressed as
(F) standardized mean difference (SMD).
(G) Negative differences in changes from
(H) baseline indicate greater decreases in
(I) proteinuria or albuminuria in the statin
(J) group as compared with the placebo group.

Drug-Induced Reduction in Albuminuria Is Associated with Subsequent Renoprotection

Drug-Induced Reduction in Albuminuria Is Associated with Subsequent Renoprotection: A Meta-Analysis



Statistically significant association between drug effects on albuminuria and ESRD. The associations appear to be consistent across a range of drug classes used in the included studies and various patient characteristics.

J Am Soc Nephrol 26: 2055–2064, 2015

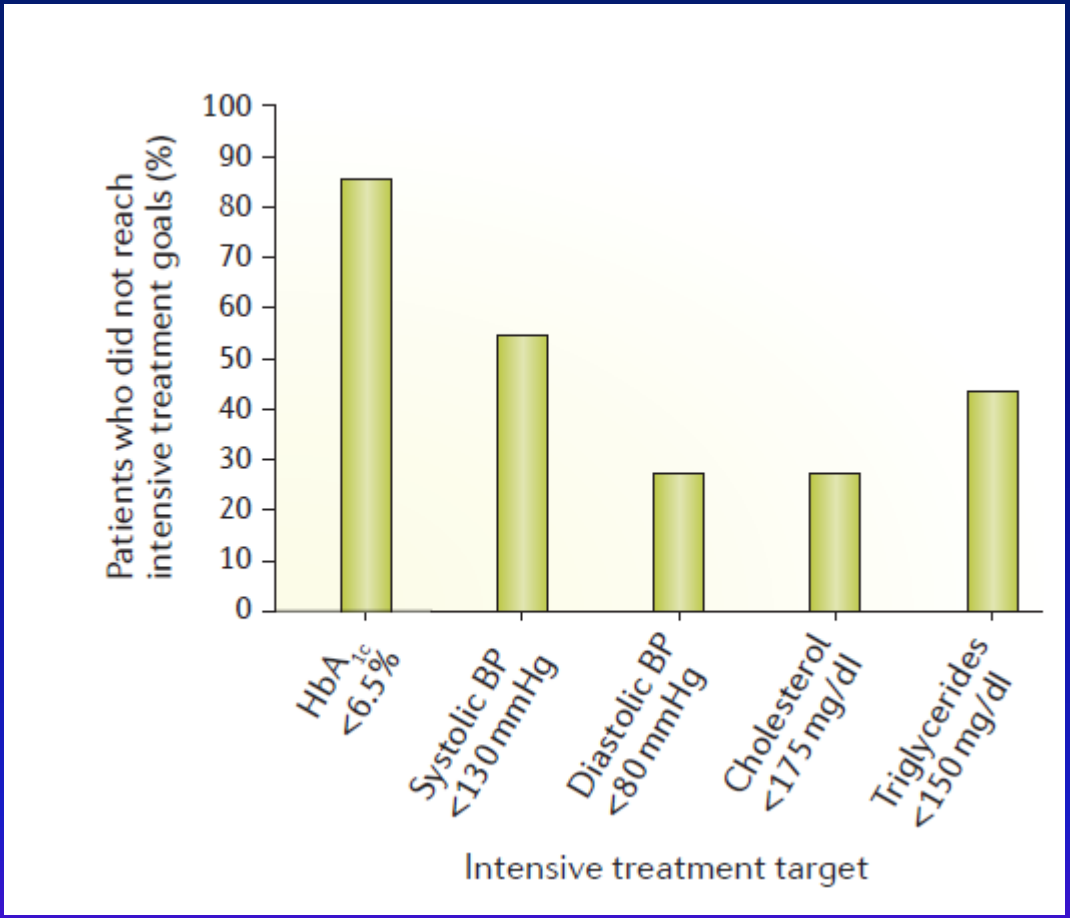
Multiple Risk Factors Intervention In diabetic nephropathy

Steno-2: Multiple Risk Factor Intervention Improves Outcomes in Type 2 Diabetics With Microalbuminuria

- Randomized, open-label, target-driven, long-term intensified intervention trial aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria
  - BP <130/80 mm Hg, (all treated with an ACEI or ARB)
  - A1c <6.5%
  - Total cholesterol <175 mg/dL
  - Total triglyceride 150 mg/dL
- Significant reductions in
  - Primary outcome by 53%
  - Nephropathy 61%
  - Retinopathy 58%

Gaede et al. *N Engl J Med.* 2003;348:383-393.

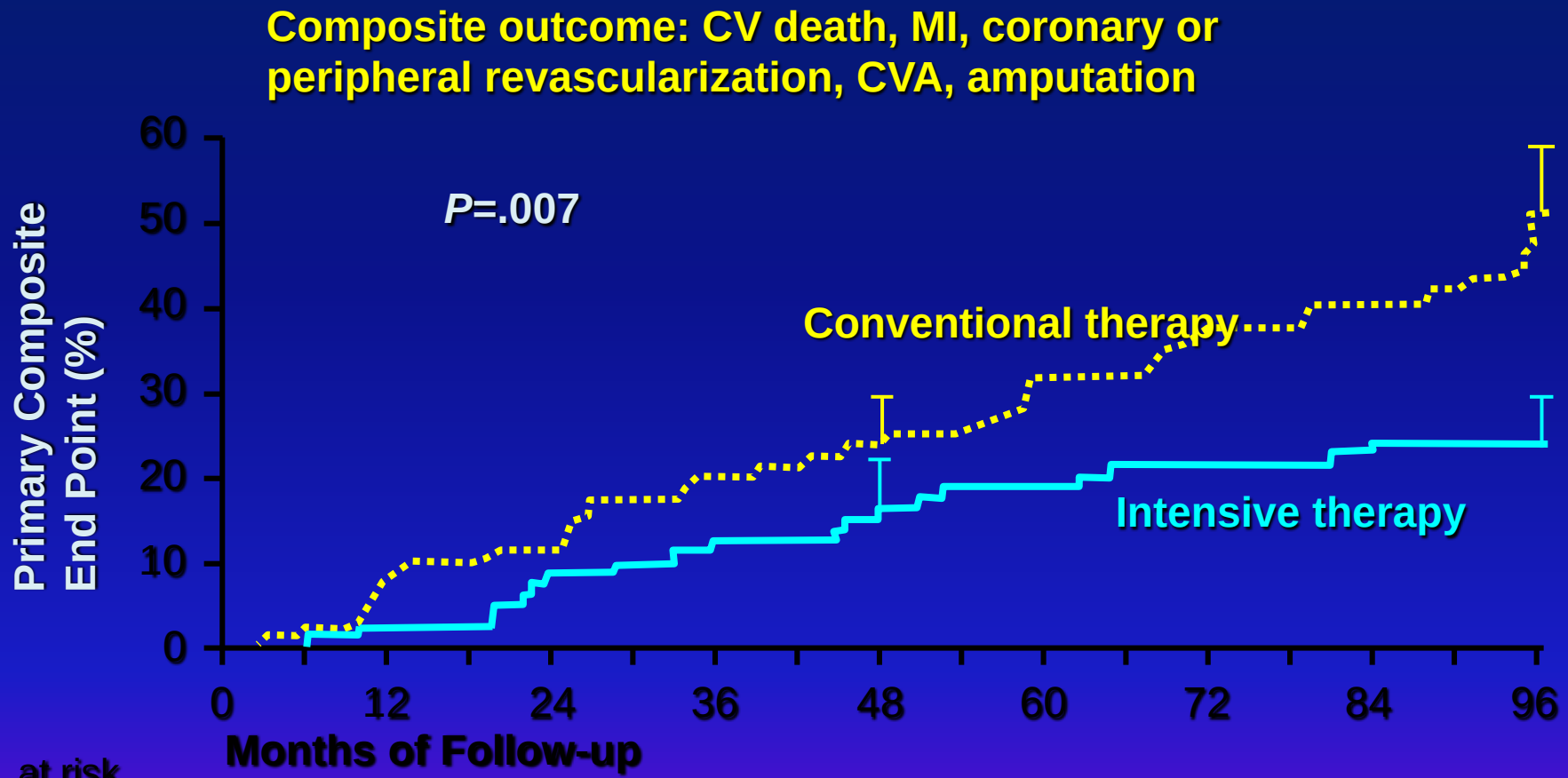
COMBINED THERAPY-the Steno trial



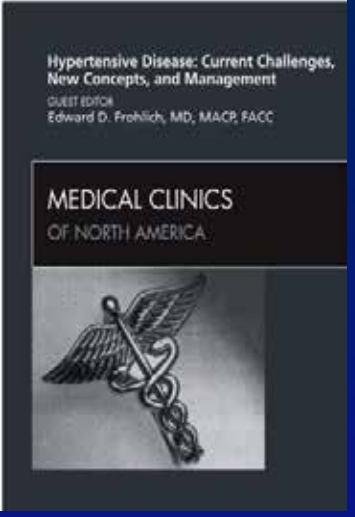
Risk factor control in the intensive treatment group of the Steno-2 trial in patients with type 2 diabetes mellitus and microalbuminuria

Gaede et al. *N Engl J Med.* 2003;348:383-393

Intensive Multiple Risk Factor Intervention Improves Outcomes in Type 2 Diabetes



Gaede et al. *N Engl J Med.* 2003;348:383-393.



The Kidney, Hypertension and remaining challenges

Άμεση συσχέτιση μεταξύ του βαθμού της πρωτεϊνουρίας και εξέλιξης σε τελικό στάδιο ΧΝΝ

Μείωση της πρωτεινουρίας >30%, μείωση του κινδύνου για ΑΜΚ κατά 39-72% (3-5έτη)

Table 1
Outcomes studies with primary CKD progression endpoint

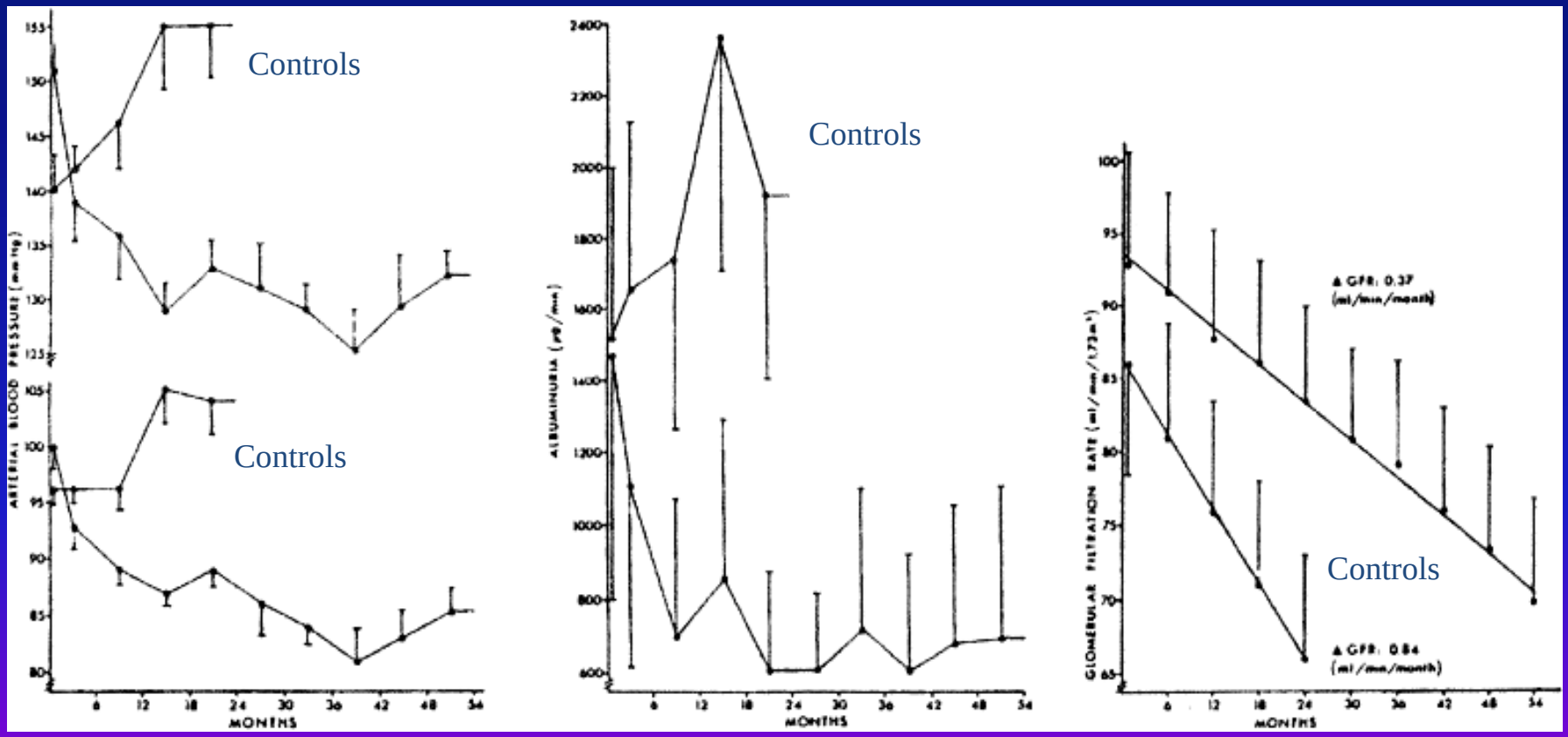
Study	Treatment Groups	Follow up (Mean in Years)	Achieved BP (mm Hg)	Change in Proteinuria	Relevant Outcomes
Captopril trial	Captopril or placebo	3 (median)	MAP 96 MAP 100	−30%	Captopril delays the progression of diabetic nephropathy
AASK[a]	Metoprolol, ramipril, or amlodipine and conventional or intensive blood pressure targets	4	128/78 for lowergroup 141/85 for usual group	−14% for metoprolol−20% for ramipril+58% for amlodipine at 6 months	Ramipril slowed the progression of renal disease when compared with the other groups
RENAAL[a]	Losartan or placebo	3.4	140/74 142/74	−35%	Losartan delayed the need for dialysis by 2 years when compared with placebo
IDNT[a]	Irbesartan or amlodipine or placebo	2.6	140/77 141/77 144/80	−33% −6% −10%	Irbesartan reduced proteinuria to a greater extent and lead to slower progression of renal disease when compared with the other groups

Kosla , Kalaitzidis Bakris 2009

Επίπεδα ΑΠ
&
εξέλιξη διαβητικής Νεφροπάθειας

Relationship between BP and progression of diabetic nephropathy.

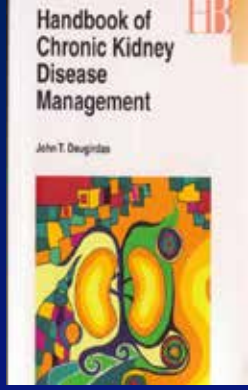
BP, albumin excretion rate, and GFR in patients with type 1 DMs randomly assigned to a reduction in MAP of 10 mm Hg using metoprolol at 100 to 400 mg/d, hydralazine at 50 to 200 mg/d, and furosemide at 80 to 500 mg/d versus no antihypertensive therapy. Solid circles represent the treated group. Open circles represent the control group. Vertical lines represent standard error. Study was stopped earlier in the control group because of faster decline in GFR. Reprinted with permission.[253]



BP vs. Time

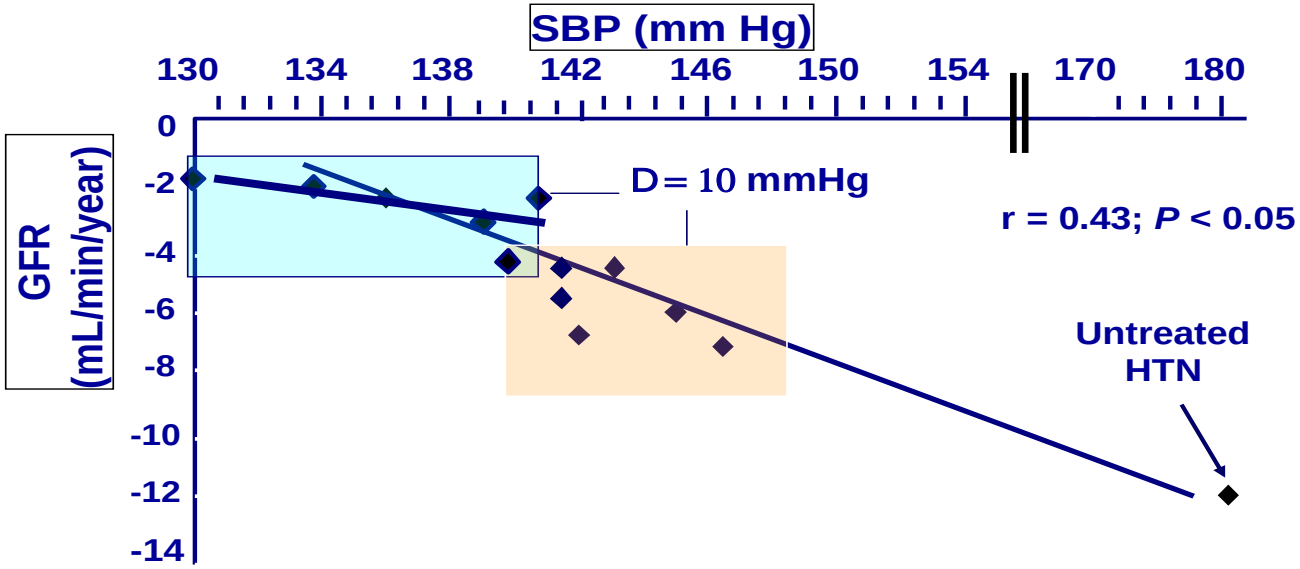
AER vs. Time

GFR vs. Time



18 Optimizing Blood Pressure and Reducing Proteinuria

Rigas Kalaitzidis and George L. Bakris



Major Recommendations of Treatment Guidelines Related to Management of Hypertension in Patients with CKD and Albuminuria

	2017 ACC/AHA[13]	2013 ESH/ESC[14]	2018 ADA[16]	2012 NKF KDOQI[3,7]
Type of CKD considered	Albuminuria ≥300 mg/d or ≥300 mg/g creatinine	Overt proteinuria	Urinary albumin-to-creatinine ratio ≥300 mg/g creatinine or 30–299 mg/g creatinine	Urine albumin excretion of 30 to 300 mg or >300 mg per 24 hours
Recommended BP target (mm Hg)	Lowering <130/80	Lowering SBP to <140 Lowering <130/80 mmHg in individuals with overt proteinuria	Lowering <140/90 Lowering <130/80 mmHg, for individuals at high risk of cardiovascular disease	Lowering ≤130/ 80
Recommended initial antihypertensive treatment	ACE inhibitor or ARB if ACE inhibitor is not tolerated	ACE inhibitor or ARB	ACE inhibitor or ARB If one class is not tolerated, the other should be substituted	ACE inhibitor or ARB
Other comments	A 10% to 25% increase in serum creatinine may occur in some patients with CKD as a result of RAAS therapy	RAS blockade is more effective in reducing albuminuria than other antihypertensive agents and is also effective in preventing incident microalbuminuria	Patients and clinicians should engage in a shared decision-making process to determine individual BP targets Bedtime dosing: moving at least one antihypertensive medication to bedtime ,	The antihypertensive and antialbuminuric effects ACE inhibitor or ARB are complemented by dietary sodium restriction or administration of diuretics.

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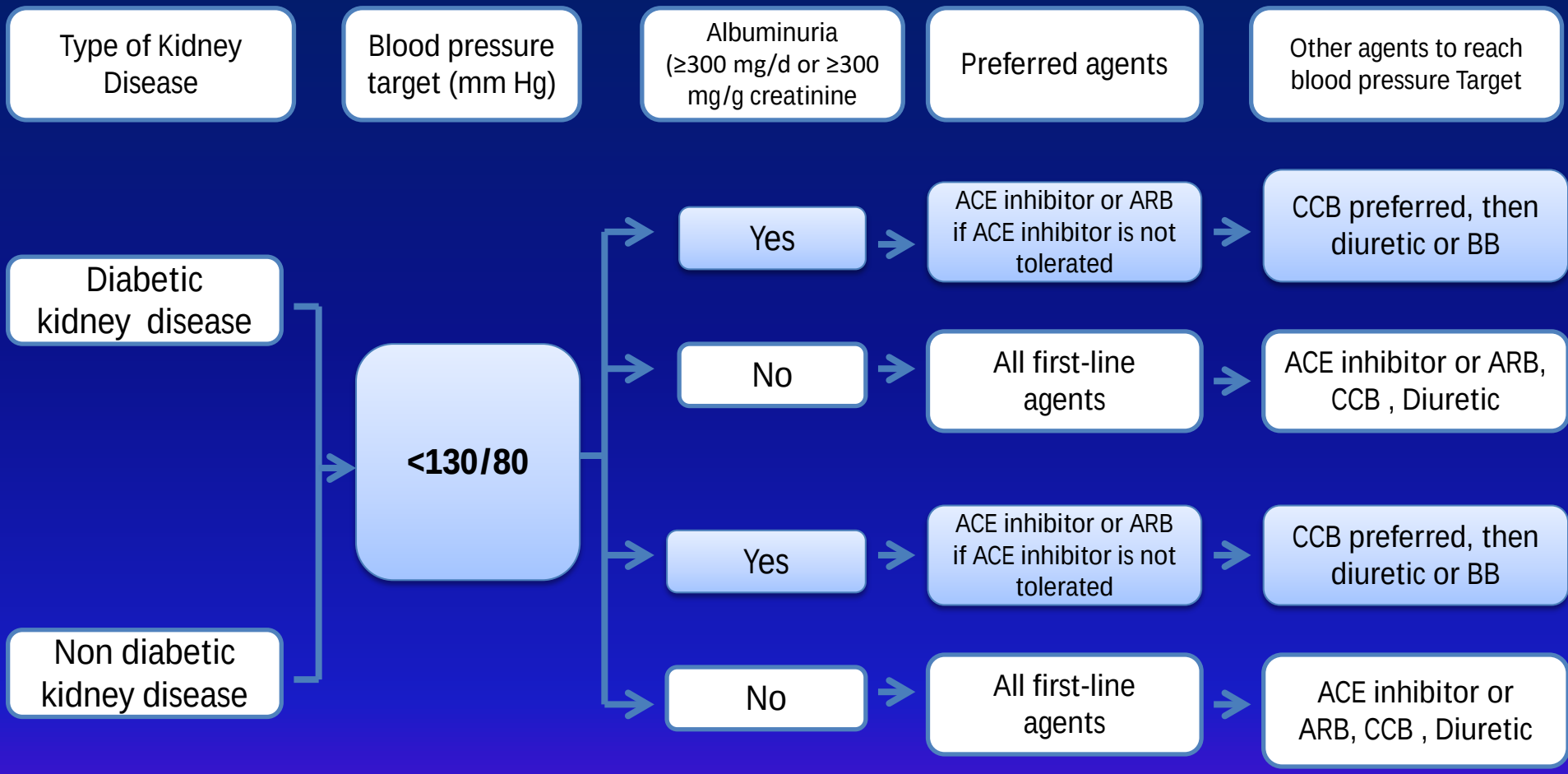
Accepted combinations of antihypertensive agents in BP treatment in CKD patients



BP, blood pressure; CKD, chronic kidney disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BB, beta-blocker

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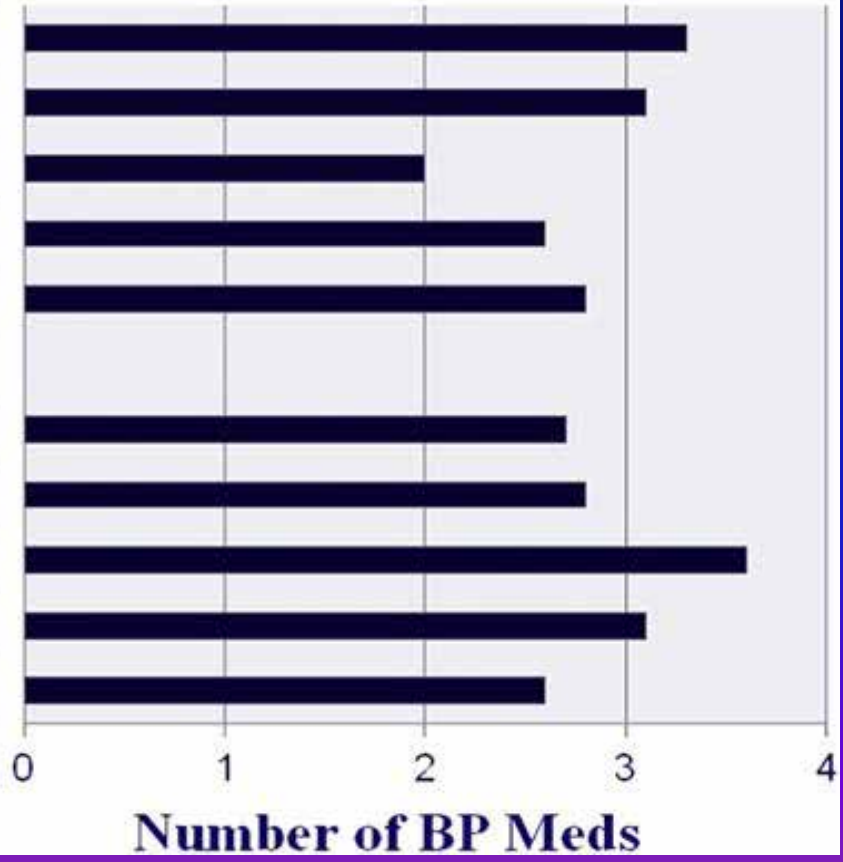
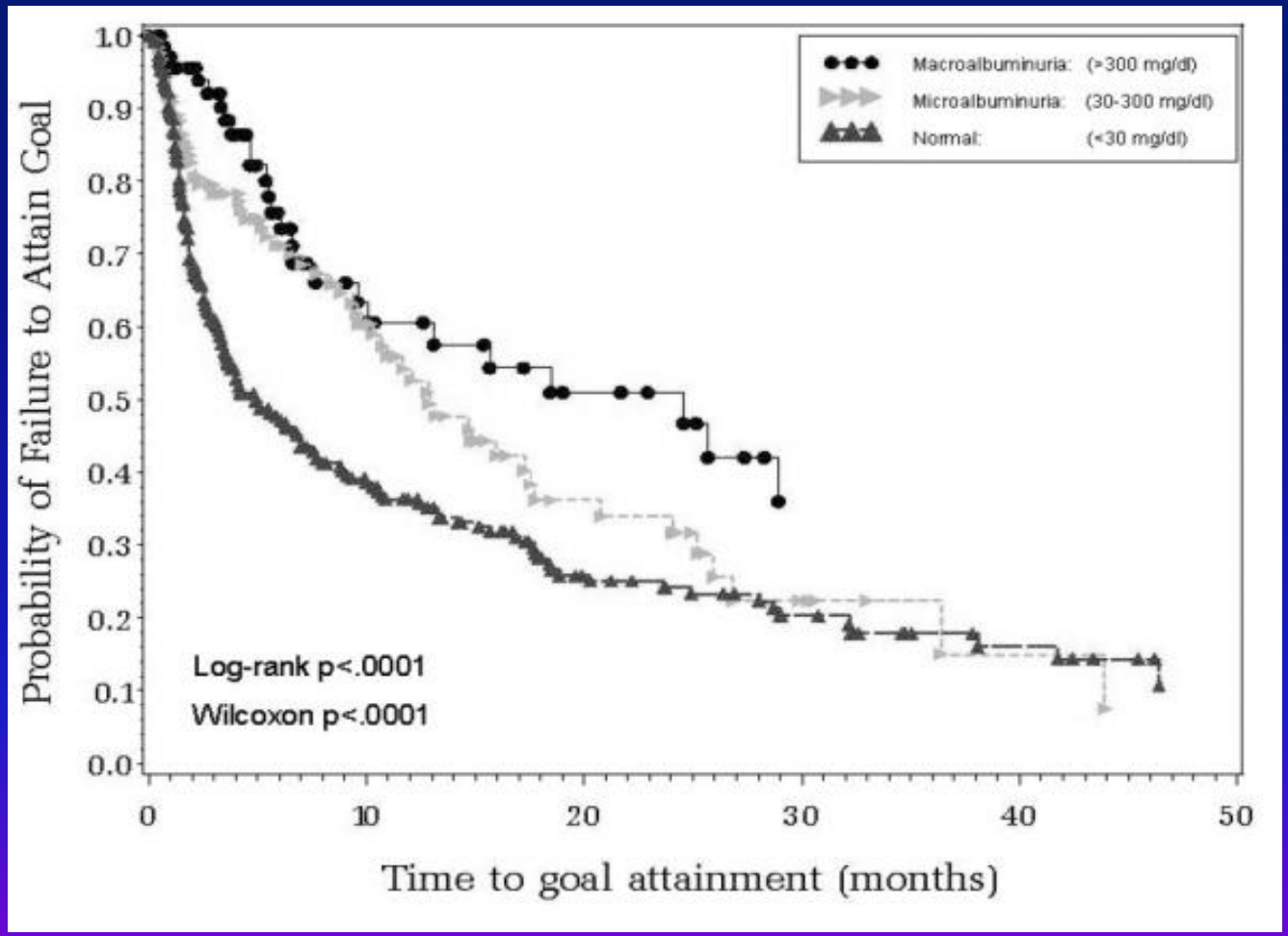
Number of antihypertensive medications required to achieve BP goals in major clinical trials over the past decade

Trial	SBP (mmHg) achieved
Cardiovascular	
INVEST	136
CONVINCE	137
ALLHAT	138
UKPDS	144
HOT	138
CKD Progression	
RENAAL	141
IDNT	138
MDRD	132
AASK	128
ABCD	132



Khosla N, Kalaitzidis R ,Bakris GL Med Clin North Am 2009

Influence of albuminuria on bllod pressure response to antihypertensive therapy



Flack, Vasc Risk Manag 2007

Conclusions

The optimal therapy of diabetic nephropathy continues to evolve

Albuminuria can be considered a modifiable risk factor for renoprotection in diabetic nephropathy

The larger the initial reduction in albuminuria renoprotection in diabetic nephropathy the lower the risk of ESRD during treatment

Conclusions

Most important is maintenance **of strict blood pressure and glycemic control early in the course of the disease with agents that reduce intraglomerular pressure**

The agents slow the rate of progression, but do not stop progression

Combined Intensive therapy for multiple risk factor Intervention Improves outcomes

Thank you