



ΠΡΩΙΜΑ ΣΤΑΔΙΑ ΔΙΑΒΗΤΙΚΗΣ ΝΕΦΡΟΠΑΘΕΙΑΣ ΔΙΑΓΝΩΣΗ ΑΝΤΙΜΕΤΩΠΙΣΗ

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Αναπληρωτής Καθηγητής
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Έρευνας και Διαβητολογικό Κέντρο
Πανεπιστημίου Αθηνών,
Πανεπιστημιακό Γ.Ν. “Αττικόν”**

6-10-2017



Δήλωση σύγκρουσης συμφερόντων

- Η ομιλία εκφράζει τις απόψεις του ομιλητή
- Ο ομιλητής έχει λάβει αμοιβή για διαλέξεις & συμμετοχή σε συμβουλευτικές επιτροπές καθώς και χρηματοδότηση για έρευνα από τις ακόλουθες φαρμακευτικές εταιρείες:

Abbot, Astra Zeneca, Boehringer Ingelheim, Bristol, Chiesi, Menarini, MSD, Novartis, Novo Nordisk, Sanofi, Vianex



ΔΝ – Επιδημιολογία

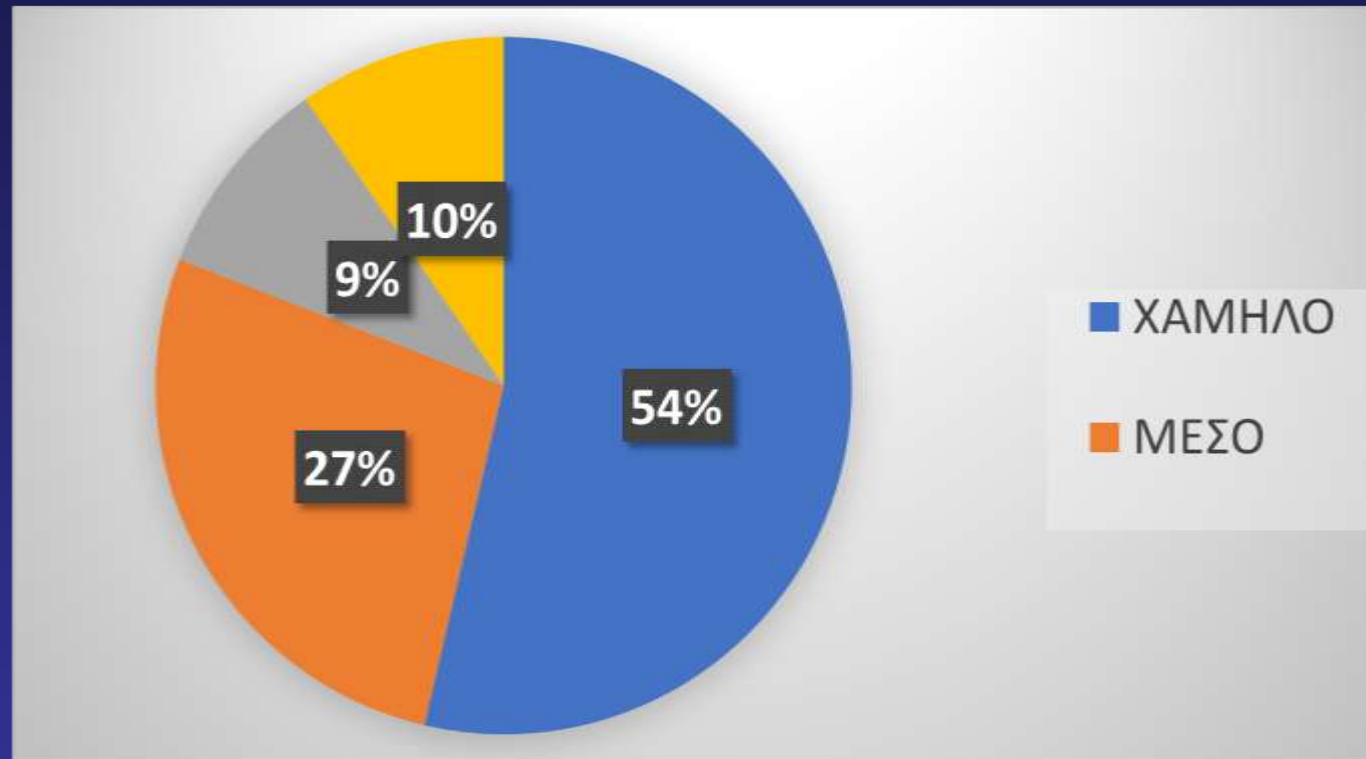
- ΔΝ: 30%-40% ΣΔ 1
10%-20% ΣΔ 2

Πρόσφατα δεδομένα:

- ΔΝ σε ΣΔ 2 (USA): 39,7% (NHANES IV)
*Koro CE et al, Clin Ther 2009;
31: 2608*
- ΔΝ σε ΣΔ 2 (Korea): 32,1%
Yang CW et al, NDT, Mar 3, 2011



ΑΠΟΤΕΛΕΣΜΑΤΑ-ΚΑΤΗΓΟΡΙΕΣ ΚΙΝΔΥΝΟΥ

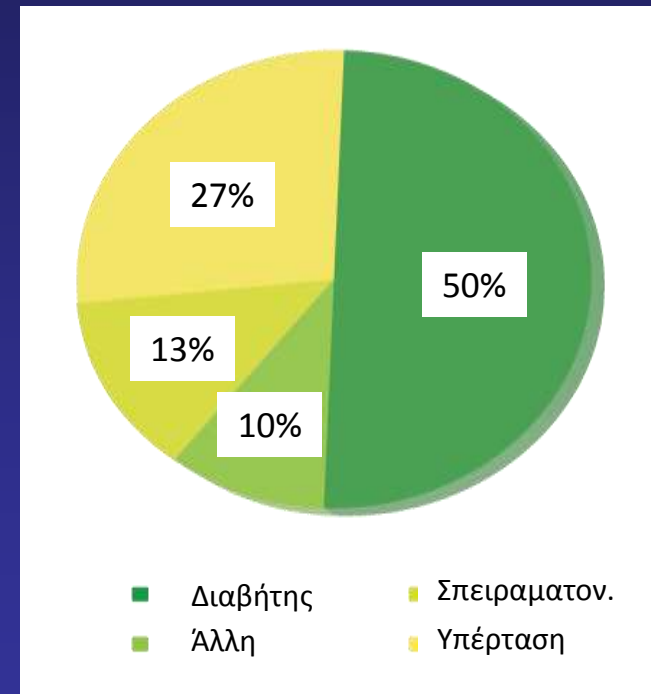
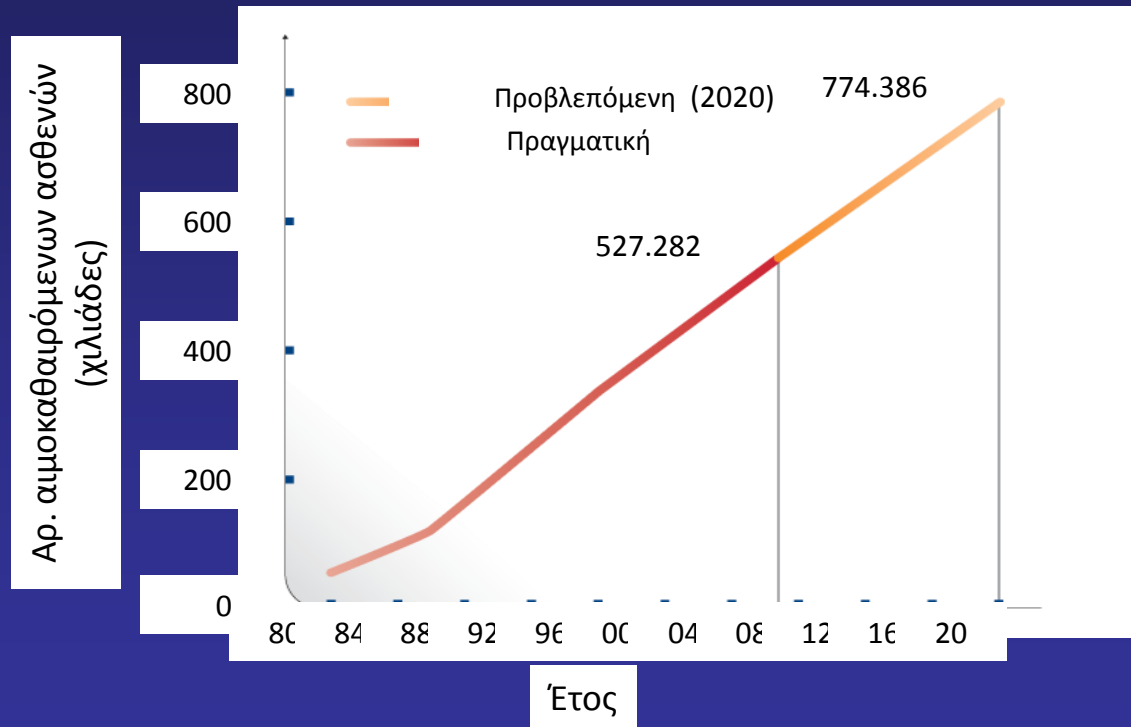


Αν εξαιρεθούν οι ελλιπείς τιμές (71 ασθενείς), τότε το ποσοστό των συμμετεχόντων πάσχει από μέτρια / σοβαρή / πολύ σοβαρή ΧΝΝ τροποποιείται από 46% σε 44.55%



Ο διαβήτης είναι το κύριο αίτιο νεφρικής ανεπάρκειας τελικού σταδίου¹

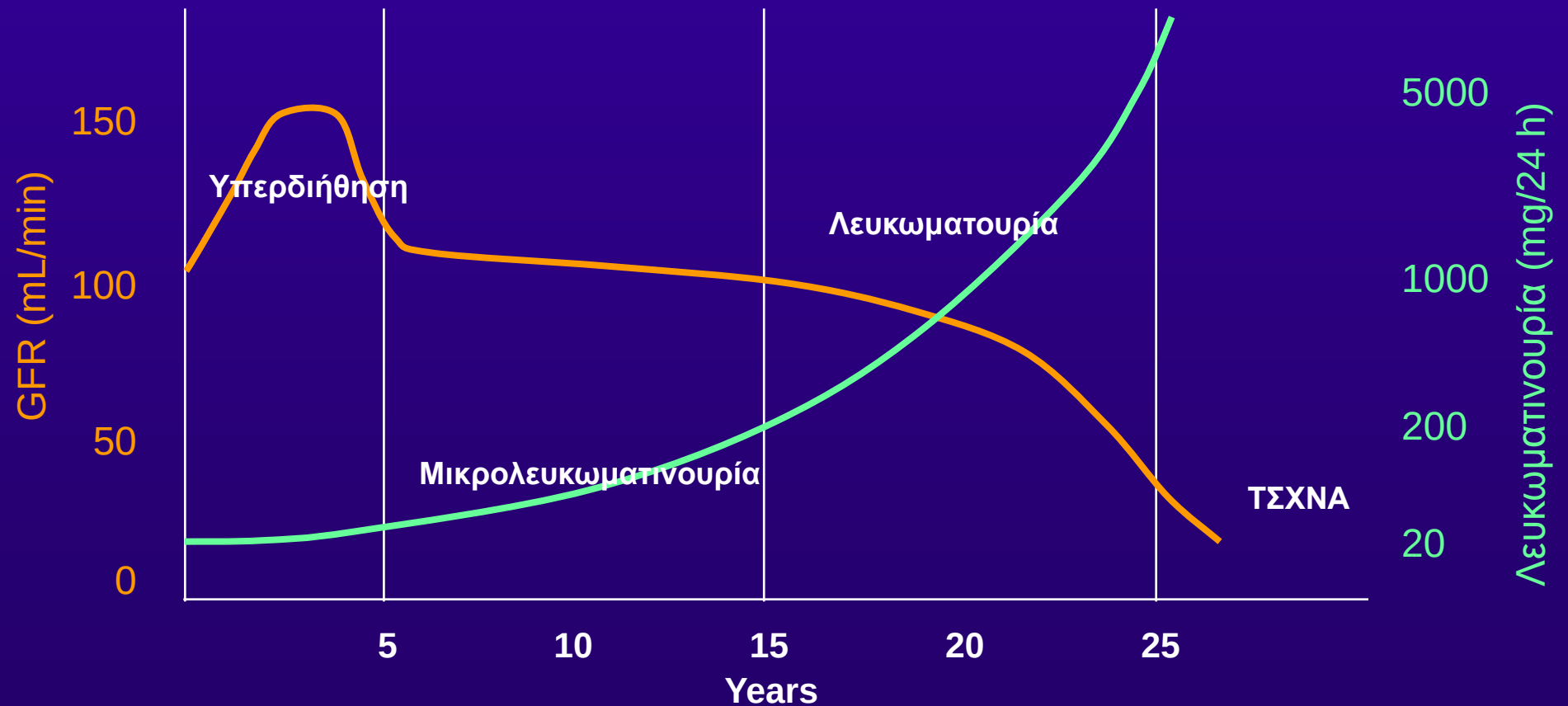
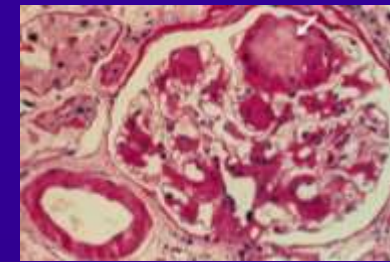
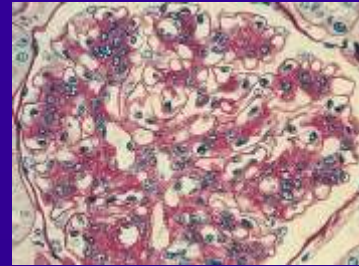
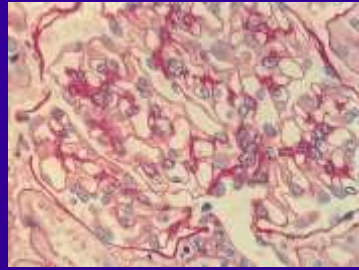
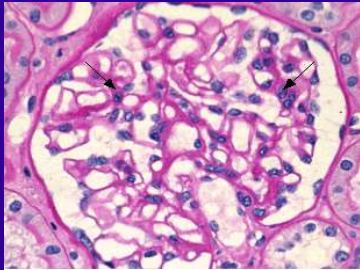
- Η επίπτωση αυξάνεται δραματικά
- Αρχική διάγνωση για ασθενείς που ξεκινούν αιμοδιύλιση



1. United States Renal Data System. Annual data report. 2000, 2007. <http://www.usrds.org/atlas.htm> , http://www.usrds.org/adr_2000.htm. Accessed 10 January 2011.

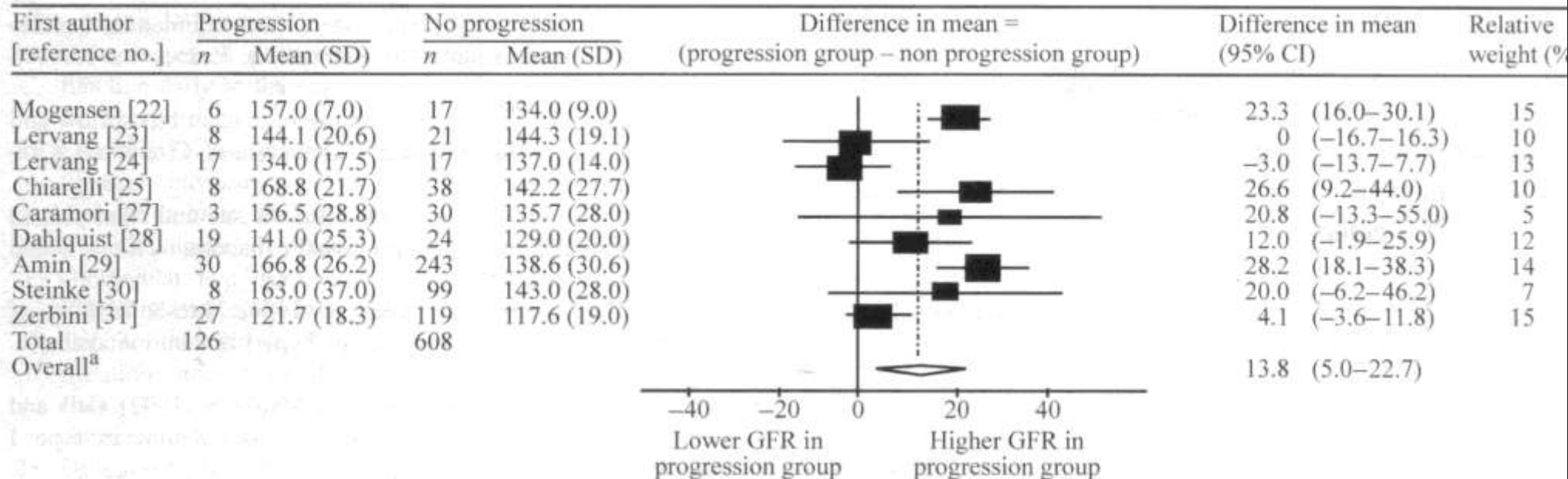


Εξέλιξη της διαβητικής νεφροπάθειας





Υπερδιήθηση και εξέλιξη νεφρικής νόσου Μετανάλυση



Οι πιθανότητες ανάπτυξης ΜΑ σε ασθενείς με υπερδιήθηση ήταν **2,71** φορές περισσότερες σε σχέση με αυτούς με φυσιολογική διήθηση



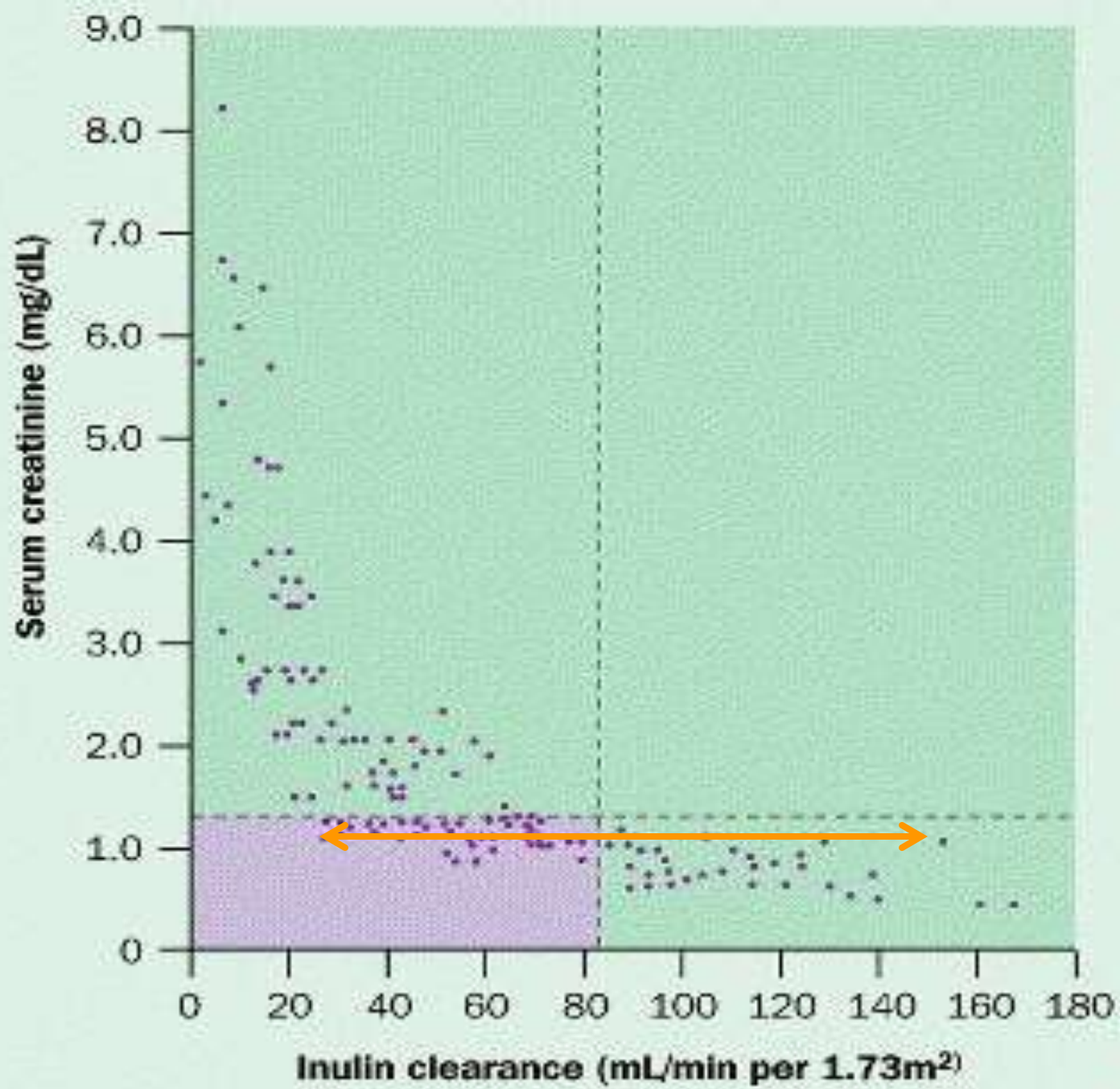
Εκτίμηση Χρόνιας Νεφρικής Νόσου



ΝΕΦΡΟΛΟΓΙΚΗ ΕΚΤΙΜΗΣΗ (1)

- Ρυθμός σπειραματικής διήθησης
Glomerular Filtration Rate







Υπολογισμός πειραματικής διήθησης (ml/min)

MDRD
CKD-EPI

(140 - ηλικία) X ΒΣ (Kg)

(72 ή 85) X κρεατ. (mg%)





ΝΕΦΡΟΛΟΓΙΚΗ ΕΚΤΙΜΗΣΗ (2)

- Απώλεια αλβουμίνης* και λευκωμάτων στα ούρα





Επίπεδα Λευκωματινουρίας

Albuminuria categories in CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent)		Terms
		(mg/mmol)	(mg/g)	
A1	< 30	< 3	< 30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	> 300	> 30	> 300	Severely increased**

9. Microvascular Complications and Foot Care

Diabetes Care 2016;39(Suppl. 1):S72–S80 | DOI: 10.2337/dc16-S012

KDIGO 2012



**Prognosis of CKD by GFR
and Albuminuria Categories:
KDIGO 2012**

				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased <30 mg/g <3 mg/mmol	Moderately increased 30-300 mg/g 3-30 mg/mmol	Severely increased >300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m ²) Description and range	G1	Normal or high	≥90	Green	Yellow	Orange
	G2	Mildly decreased	60-89	Green	Yellow	Orange
	G3a	Mildly to moderately decreased	45-59	Yellow	Orange	Red
	G3b	Moderately to severely decreased	30-44	Orange	Red	Red
	G4	Severely decreased	15-29	Red	Red	Red
	G5	Kidney failure	<15	Red	Red	Red

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.



IGT vs IFG:

Individuals with persistent impaired glucose tolerance have a higher risk to develop kidney disease over ten years than individuals with persistent impaired fasting glucose.

Dep. of Primary Health Care, Institute of Medicine of Sahlgrenska Academy, Gothenburg, Sweden

Background

During the development of type 2 diabetes, the hormones of fasting glucose are not just glucose tolerance hormone or "pancreatic insulin." Metabolic conditions are associated with significant changes [22] and contribute to abnormalities in fasting insulin, insulin-stimulated glucose (IPG), and insulin: glucose tolerance ratio (IGTR), so that insulin resistance does not affect only the basal or fasting of the insulin resistance. When glucose is the number and quality of insulin, there is a need to investigate the metabolic effects of insulin resistance. Insulin resistance has been associated with type 2 diabetes, and it is important to understand the

Figure 1:
Flow chart of study population



Objective

The aim of this study was to explore the development of clinical research training stage 2 in three steps referred to as (1) a first phase, concerned with the use of a role-play exercise over the course of 3 days.

Methods and Materials

[illegible]

Results

Using the above up-bias a decrease in ΔZ^2 was obtained if the total static population (compared to $Z^2 = 1.0$) at time $t = 1.5 \times 10^{-10}$ s at each depth is ~ 0.07 and 0.02 are increased to 0.1 and 0.15 at $t = 1.0$ s. The decrease in ΔZ^2 was greater in materials with increased Z^2 after irradiation to about half (around 4% at $\Delta Z^2 = 0.72$ to 0.4) versus

Thirty individuals with consistent P12. The mean age (SD) of the sample group was 36.6 (10.4) years. All subjects were consistent P12 at follow-up. Data on P12 are in Table 1. These differences were all significant after adjustment for age sex, and were all $p < 0.0001$.

There was no significant difference in the development of skin lesions between individuals with diabetes and individuals with nondiabetic hyperlipidemic abnormalities (Fig. 3). Age, sex, BMI, and HDL-C were



Conclusion

Information will be provided to you at the time you are asked to complete the questionnaire and will be available to you at the time you are asked to complete the questionnaire. The information will be provided to you at the time you are asked to complete the questionnaire and will be available to you at the time you are asked to complete the questionnaire.

Take home message

Figure 2:
Mean difference in temperature in ΔT_{DBT} over two years in
individuals with persistent NGT, IFD and diabetes.



© 1995, University of Toronto Press. Printed in Canada.

2007 ...
2006 ...
2005 ...
2004 ...
2003 ...

Table 1.
Total weight for each persistent state at baseline and at follow-up

	2007-2008		2008-2009		2009-2010	
2007-2008	100	100	100	100	100	100
2008-2009	90.5	90.5	90.5	90.5	90.5	90.5
2009-2010	80.5	80.5	80.5	80.5	80.5	80.5
2010-2011	70.5	70.5	70.5	70.5	70.5	70.5
2011-2012	60.5	60.5	60.5	60.5	60.5	60.5

© 2005 Blackwell Publishing Ltd *Journal of Internal Medicine* 258: 103–110

[illegible]

Table 2:
Mean difference in detrital
nutrition over two years, before
with normal and abnormal

[illegible]

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- 42200 *Intermediate Algebra* (3 credits)
- 42210 *Advanced Algebra* (3 credits)
- 42220 *Calculus* (3 credits)
- 42230 *Calculus* (3 credits)
- 42240 *Calculus* (3 credits)
- 42250 *Calculus* (3 credits)
- 42260 *Calculus* (3 credits)
- 42270 *Calculus* (3 credits)
- 42280 *Calculus* (3 credits)
- 42290 *Calculus* (3 credits)



Figure 1:
Flow chart of study population

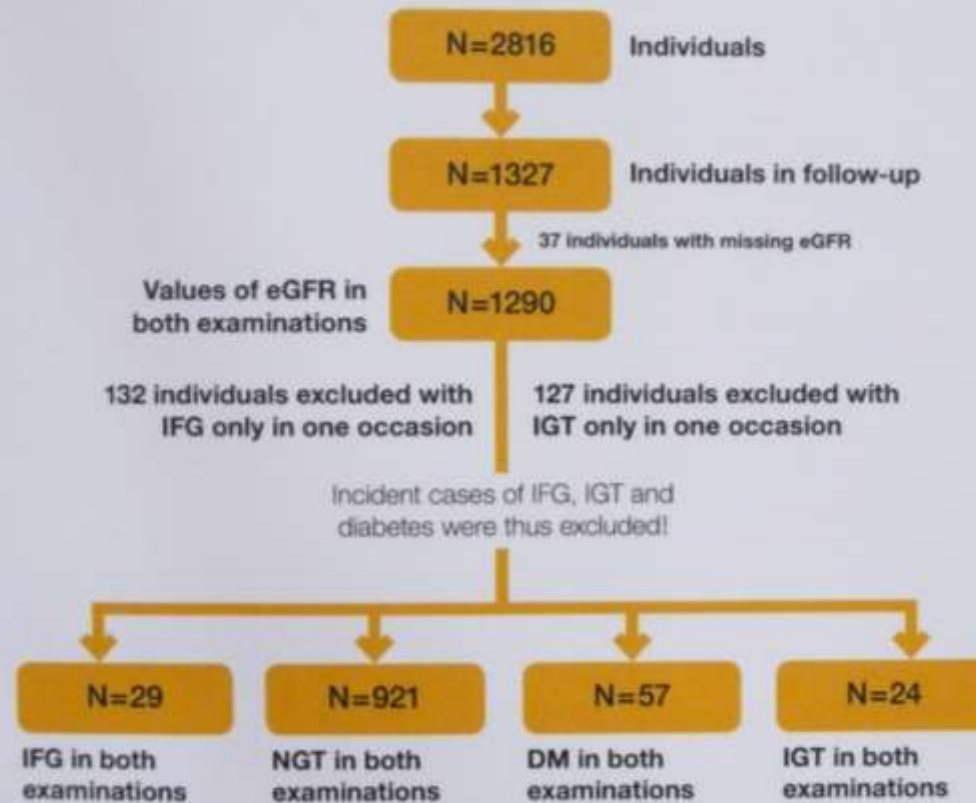
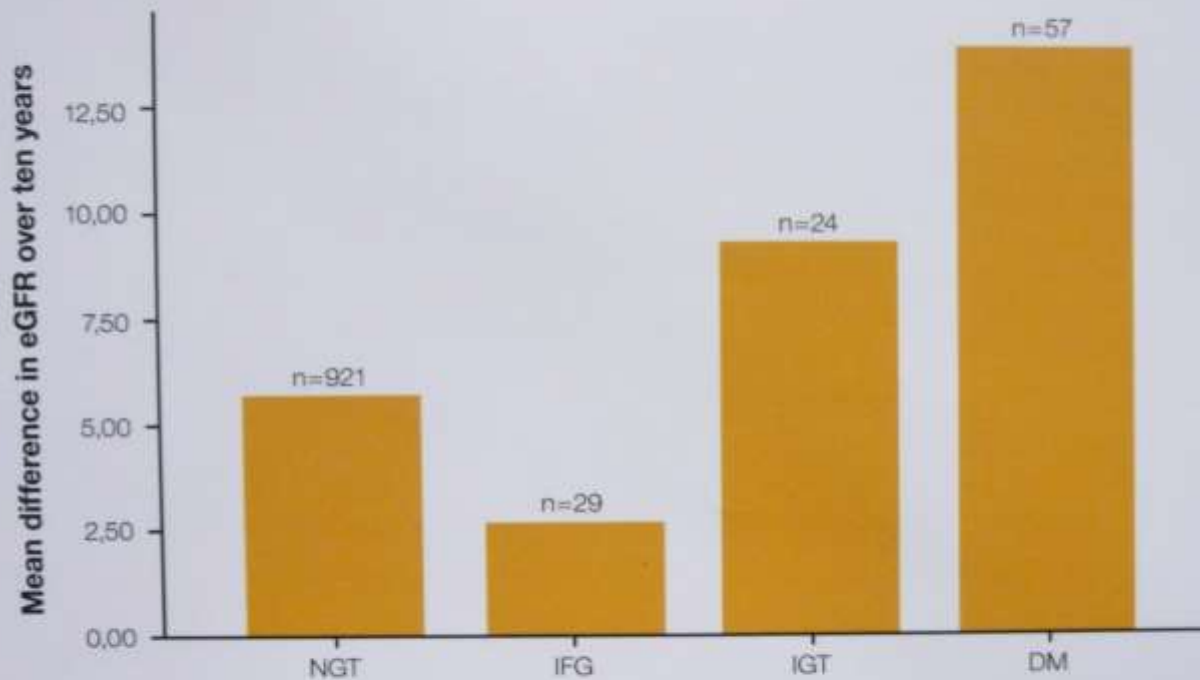




Figure 2:

Mean difference in deterioration in eGFR over ten years in individuals with persistent NGT, IFG and diabetes.



eGFR: Estimated glomerular filtration rate in ml/min /1.73m² .

NGT: Normal Glucose Tolerance

IFG: Impaired fasting Glucose

IGT: Impaired Glucose Tolerance

DM: Diabetes Mellitus type 2

Analysed states persistent in both examinations



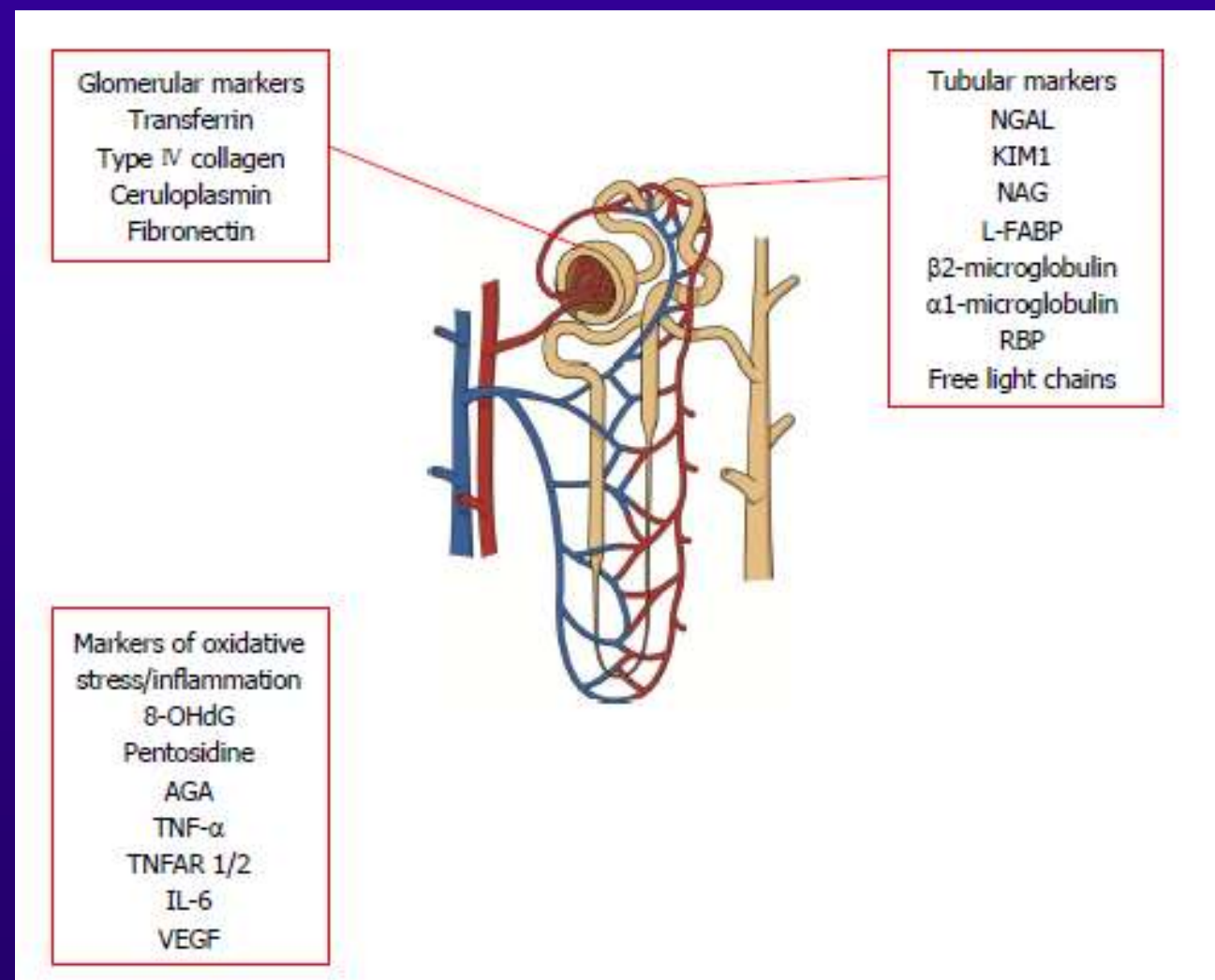
Conclusion

Individuals with persistent IGT are at higher risk to develop nephropathy when compared with individuals with persistent IFG and NGT. Thus, it is particularly important to identify individuals with persistent IGT to implement lifestyle interventions and when indicated also treatment with pharmaceuticals to prevent the development of CKD.



Biomarkers in diabetic nephropathy: Present and future

Gemma Currie, Gerard McKay, Christian Delles





Biomarkers in diabetic nephropathy: Present and future

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Table 1 Summary of biomarkers with potential utility in diagnosis of diabetic nephropathy

Biomarker	Serum/plasma or urine	Type of marker	Status in DN	Potential for additional information beyond UAE	Ref.
Transferrin	Urine	Glomerular	Elevated	Predicts MA	[30-35]
Type IV collagen	Urine	Glomerular	Elevated	Rises in parallel with UAE, even in nonalbuminuric stage	[36-41]
Ceruloplasmin	Urine	Glomerular	Elevated	Predicts MA	[33,42-44]
Fibronectin	Plasma/urine	Glomerular	Both elevated	No	[32,45]
NGAL	Urine	Tubular	Elevated	Marker of glomerular hyperfiltration	[46-53]
KIM1	Urine	Tubular	Elevated	Marker of glomerular hyperfiltration	[49,50,53-57]
NAG	Urine	Tubular	Elevated	Comparable to UAE	[30,58-64]
L-FABP	Urine	Tubular	Elevated	No	[52,65-66]
AIM	Urine	Tubular	Elevated	No	[30,39,63,69-74]
RBP	Urine	Tubular	Elevated	No	[17,30,69,72-75]
FLCs	Urine	Tubular	Elevated	No	[17,63,69,72-75]
8-OHdG	Urine	Oxidative stress	Elevated	Predicts DN but value in comparison to MA remains unclear	[77-80]
Pentosidine	Urine/serum	Oxidative stress	Both elevated	No	[61,81-86]
AGA	Urine	Oxidative stress	Elevated	Urinary excretion predicts MA	[91-97]
TNF- α	Urine/serum	Inflammatory	Both elevated	No	[88,92,98-100]
TNFR 1/2	Serum	Inflammatory	Elevated	Predictive of onset of stage 3-5 CKD independent of albuminuria status	[99-101]
IL-6	Urine/serum	Inflammatory	Serum levels elevated	No	[99,101-103]
VEGF	Urine/serum	Inflammatory	Urinary levels elevated	No	[104-108]

DN: Diabetic nephropathy; NGAL: Neutrophil gelatinase associated lipocalin; KIM1: Kidney injury molecule 1; NAG: N-acetyl-b-d-glucosaminidase; AIM: α -1-microglobulin; L-FABP: Liver type fatty acid binding protein; RBP: Retinol binding protein; FLCs: Free light chains; 8-OHdG: 8-oxo-7,8-dihydro-2'-deoxyguanosine; AGA: α -1-acid glycoprotein; TNF- α : Tumour necrosis factor α ; TNFR 1/2: Tumour necrosis factor α receptors 1 and 2; IL-6: Interleukin-6; VEGF: Vascular endothelial growth factor; CKD: Chronic kidney disease; UAE: Urinary albumin excretion; MA: Microalbuminuria.



Biomarker	Source	Cohort (size)	Key points	Reference
KIM-1	Blood	Type 1 (124)	Baseline KIM-1 in proteinuric (>500 mg/day) patients predicted rate of eGFR loss and ESRD during 5–15 years of follow-up.	Sabbiseti et al ²⁰⁸
	Urine	Type 1 (63)	KIM-1 associated with decline in GFR but not independent of albuminuria.	Nielsen et al ²⁰⁹
	Urine	Type 2 (978)	Urine KIM-1/Cr associated with faster decline in GFR during 4 years follow-up but offered no additional prognostic information to albumin/Cr ratio.	Conway et al ²¹⁰
NGAL	Serum/urine	Type 1 (50)	Elevated before microalbuminuria. Serum NGAL correlated with HbA _{1c} and urine NGAL correlated with albuminuria.	Lacquaniti et al ²¹¹
	Urine	Type 1 (63)	NGAL associated with decline in GFR but not independent of albuminuria.	Nielsen et al ²⁰⁹
	Serum/urine	Type 2 (140)	No correlation with eGFR.	Chou et al ²¹²
L-FABP	Urine	Type 1 (1,549)	Patients ranged from normoalbuminuria to macroalbuminuria. Urine L-FABP/Cr ratio at baseline predicted progression of DN but adding L-FABP to albumin excretion did not improve prediction model.	Panduru et al ²¹³
	Urine	Type 1 (277)	Urine L-FABP predicted progression of albuminuria or death.	Nielsen et al ²¹⁴
	Urine	Type 1 (63)	L-FABP not related to decline in GFR.	Nielsen et al ²⁰⁹
	Serum/urine	Type 2 (140)	Serum L-FABP correlated with baseline eGFR but did not predict decline in eGFR.	Chou et al ²¹²
	Urine	Type 2 (618)	Japanese patients without overt proteinuria and serum creatinine ≤1.0 mg/dL followed for median of 12 years. Urine L-FABP in the highest tertile was associated with 50% decline in eGFR or progression to eGFR < 30 mL/minute/m ² .	Araki et al ²¹⁵
	Urine	Type 2 (140)	High L-FABP associated with progressive albuminuria, ESRD, or hemodialysis.	Kamijo-Ikemori et al ²¹⁶
	Urine	Type 2 (237)	Urine cystatin C/Cr ratio associated with decline in eGFR, with the upper tertile of levels associated with progression to stage 3 CKD or higher after 20 months follow-up.	Kim et al ²¹⁷
Abbreviations: CKD, chronic kidney disease; Cr, creatine; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GFR, global filtration rate; HbA _{1c} , hemoglobin A _{1c} .				

KIM 1 : Kidney injury molecule 1

NGAL : Neutrophil gelatinase-associated lipocalin

L-FABP : Liver-fatty acid –binding protein



Biomarkers associated with progression of renal disease in Type 1 Diabetes

M. Colombo¹, E. Valo², S. McGurnaghan³, L. Blackburn⁴, R. Neil Dalton⁵, D. Dunger⁶, P.-H. Groop⁷, P.M. McKelvie⁸, C. Forsblom⁹, H.M. Colhoun¹⁰

on behalf of the Scottish Diabetes Research Network Type 1 Bioresource and FinnDiane Study Group

¹Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, UK ²Folkhälsan Institute of Genetics, Folkhälsan Research Center, Helsinki, Finland

³Institute of Genetics and Molecular Medicine, University of Edinburgh, UK ⁴WellChild Laboratory, King's College London, UK ⁵Department of Paediatrics, University of Cambridge, UK



Background and aims

Most renal failure in type 1 diabetes mellitus (T1DM) is due to diabetic-specific kidney disease (DKD). Given the lack of effective therapies and repeated drug trial failures, improved insights into pathogenesis and prediction of renal function decline are needed.

We aimed to identify biomarkers that predict progression of renal disease in subjects with T1DM and assessed their prediction on top of clinical covariates.

Materials and methods

From the Scottish Diabetes Research Network Type 1 Bioresource (SDRNT1BIO) of 5127 people with T1DM representative of all adults with T1DM nationally, we selected those 325 patients with eGFR < 70 ml/min/1.73m² at baseline. A comparison sample of 315 patients from the FinnDiane project with eGFR < 70 ml/min/1.73m² and microalbuminuria at baseline date was also examined. Progression of renal disease was estimated by approximating prospective eGFR trajectories for each patient by a linear slope and by defining as rapid progressors those with a loss of more than 3 ml/min/1.73m²/year.

Table 1. Patient characteristics at study day (Median (IQR) or %)

Variable	SDRNT1BIO (N = 325)	FinnDiane (N = 315)
Female	56%	45%
Age (years)	56 (46, 55)	46 (36, 52)
Diabetes duration (years)	26 (17, 38)	32 (25, 38)
eGFR (ml/min/1.73m ²)	71 (63, 82)*	55 (48, 66)
HbA1c (mmol/mol)	68 (60, 79)	72 (63, 83)
HDL (mmol/l)	1.5 (1.3, 1.9)	0.9 (0.7, 1.0)
LDL (mmol/l)	2.3 (1.8, 2.8)	3.2 (2.6, 3.8)
SBP (mmHg)	134 (122, 146)	145 (131, 158)
ACR category (Normo/Micro/Macro)	83% / 11% / 6%	72% / 27% / 1%
Follow-up (years)	4.0 (3.2, 4.8)	8.5 (5.9, 12.0)
Slope (ml/min/1.73m ² /year)	-1.7 (-3.1, 0.6)	-2.3 (-4.4, -0.9)
Rapid progressors (slope < -3)	23%	40%

* Some only eGFRs were adjusted for creatinine variation.

We measured 124 biomarkers in non-fasting serum samples using the Luminex platform (30 proteins) and mass spectrometry (94 metabolites). We evaluated them independently in linear/logistic regression models adjusted for age, sex, diabetes duration and eGFR (basic covariates). We further adjusted models for SBP, SBP/DBP, HbA1c, HDL, total cholesterol, smoking status and ACR category (full covariates). Associations were declared significant at $p < 0.05$ / 124 = 40.4.

We created sparse panels of biomarkers by cross-validated forward selection, and evaluated their performance in predicting rapid progression through AUROCs.

Results

Five biomarkers were significantly associated with rapid progression in both studies (in bold in Figure 1) in univariate analyses. Apart from Serum KIM-1, Microglobulin, the same biomarkers were also associated with slopes.

Fig 1. Volcano plots of associations with rapid progression

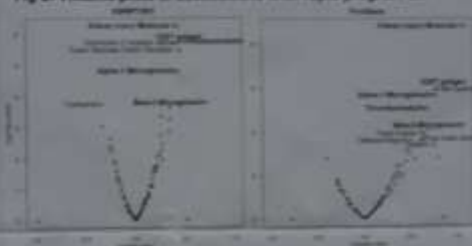


Table 2 shows the ranking of the biomarkers chosen by forward selection for prediction of rapid progression of renal decline, as well as the change in log-likelihood by adding each marker to the initial set of covariates. The FinnDiane panel was consistent with results shown above; the SDRNT1BIO panel was less so, presumably due to the much shorter follow-up.

Table 2. Panels of biomarkers chosen by forward selection

Biomarker	Basic covariates		Full covariates	
	Rank	Diff. loglik.	Rank	Diff. loglik.
SDRNT1BIO				
Tumor Necrosis Factor Receptor 1	1	11.0	—	—
Interleukin-2 receptor alpha	—	—	1	6.3
Uric Acid	—	—	2	2.0
FinnDiane				
Thrombomodulin	1	10.6	—	—
Kidney Injury Molecule-1	2	10.0	1	9.4

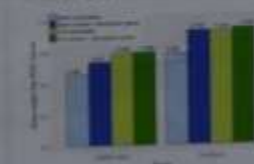


Fig 2. Performance of panels of biomarkers

The sparse panels of biomarkers express the predictive performance of models with basic covariates, maximal change can be achieved when a richer set of covariates is available.

Adding just KIM-1 to models adjusted for basic covariates (age, sex, diabetes duration and eGFR) produces a model that performs similarly to a model with ACR added to the same covariates.

Such model gave similar prediction to a model with the full set of covariates including categorical ACR. However, serum KIM-1 did not increment prediction beyond these full covariates if continuous ACR was used instead.

Fig 3. ROC curves for predicting rapid progression



Conclusions

Serum KIM-1, Thrombomodulin and CD27 antigen are consistently among the best performing markers in predicting progression of renal disease.

Using clinical data to its fullest extent achieves very good predictions. However, KIM-1 and a basic set of covariates performs similarly to a rich set of clinical covariates in predicting rapid progression. In this setting, serum KIM-1 performs similarly to ACR.

Whether a more sensitive serum KIM-1 assay could be more useful than albumin excretion rate at the early stages of renal function decline deserves more attention.

Acknowledgements

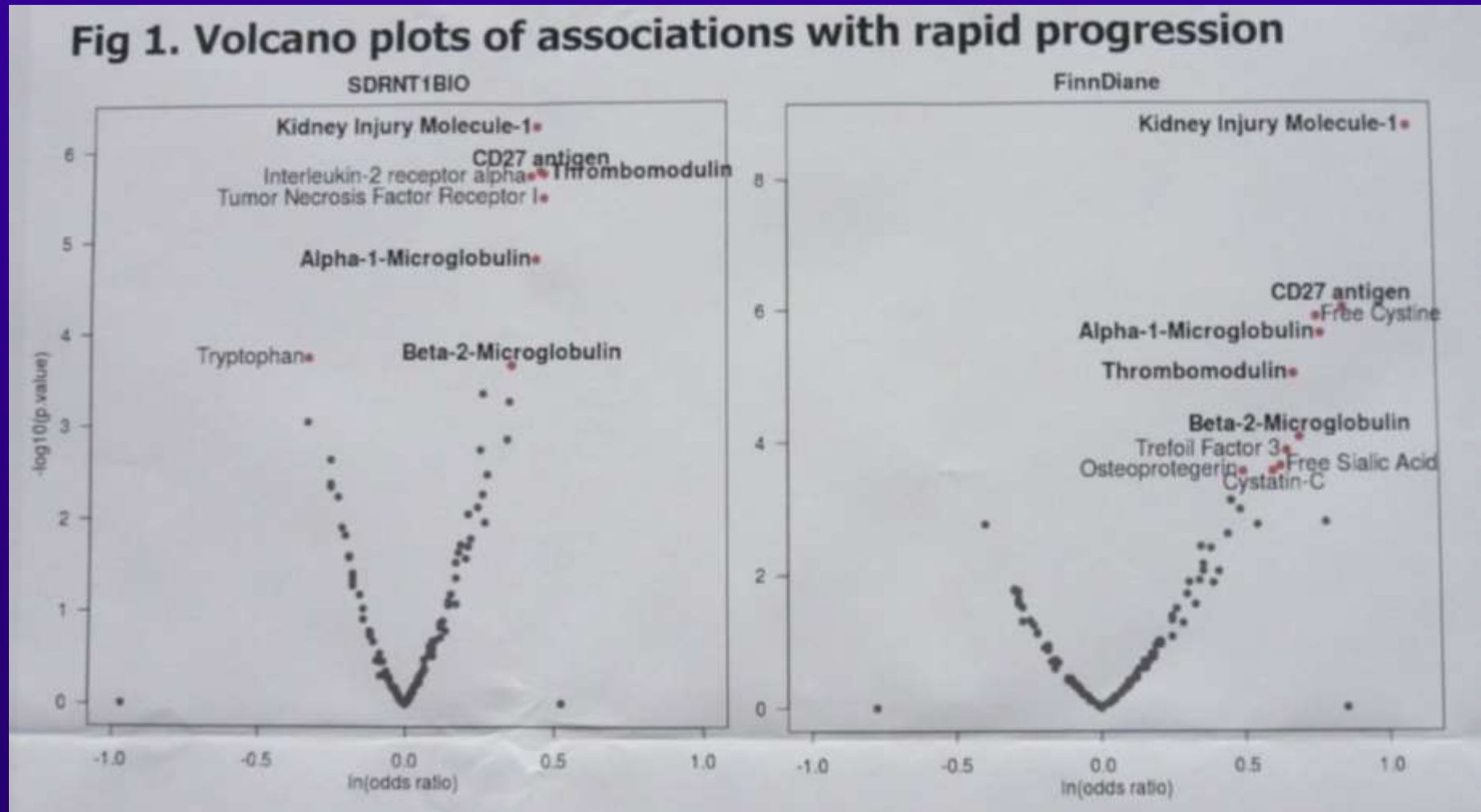
SDRNT1BIO Funding: Juvenile Diabetes Research Foundation, Chief Scientist Office, Diabetes UK, in-kind contributions from Scottish Diabetes Research Network to facilitate recruitment.



$\Sigma\Delta\tau 1$

926 ασθενείς

315 ασθενείς



Luminex platform (30 protein biomarkers)
Mass spectrometry (94 metabolites)



Conclusions

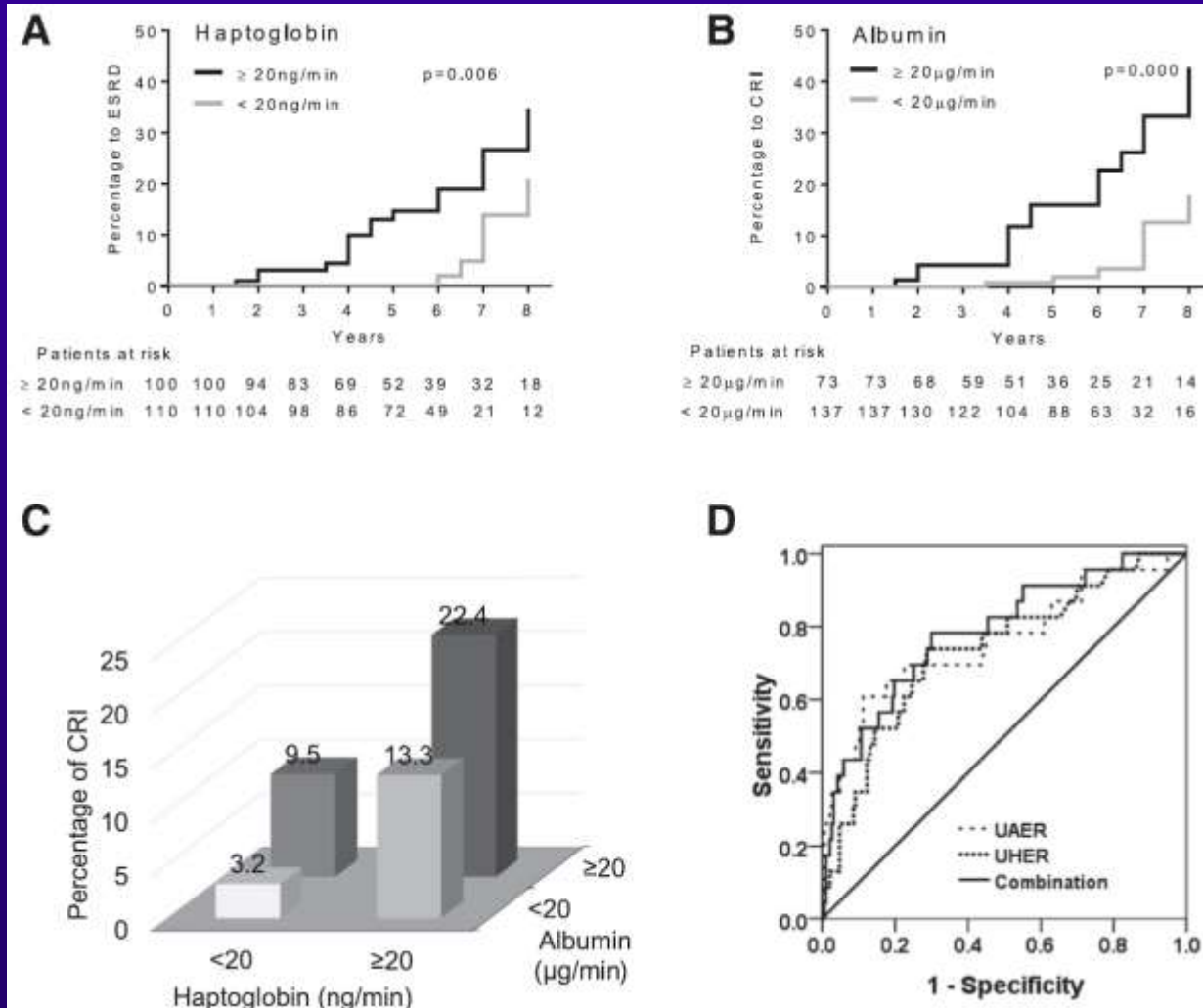
Serum KIM-1, Thrombomodulin and CD27 antigen are consistently among the best performing markers in predicting progression of renal disease.

Using clinical data to its fullest extent achieves very good predictions. However, KIM-1 and a basic set of covariates performs similarly to a rich set of clinical covariates in predicting rapid progression. In this setting, serum KIM-1 performs similarly to ACR.

Whether a more sensitive serum KIM-1 assay could be more useful than albumin creatinine ratio at the early stages of renal function decline deserves more attention.



Urine Proteome Specific for Eye Damage Can Predict Kidney Damage in Patients With Type 2 Diabetes: A Case-Control and a 5.3-Year Prospective Cohort Study





Τι είναι ΧΝΝ;

Στάδιο ΧΝΝ	eGFR (mL/min)
Χωρίς ΧΝΝ	≥90*
1	≥90**
2	60–89
3α	45–59
3β	30–44
4	15–29
5	<15 ή ΕΝΥ

Νεφρική βλάβη

Νεφρική νόσος

* Χωρίς σημεία νεφρικής βλάβης

** Λευκωματινουρία – νεφρική βλάβη



**Τι συμβαίνει εάν προσδιορίσουμε νεφρική
λειτουργία και λευκωματουρία ταυτόχρονα;**

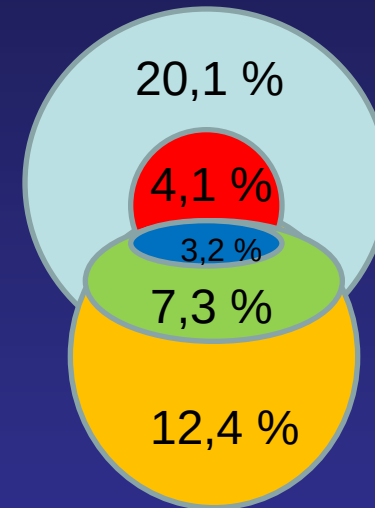


Μελέτη NEFRON

Κατανομή λευκωματινουρίας
και $eGFR < 60 \text{ ml/min/1.73m}^2$
σε ασθενείς με ΣΔτ2 στην
Αυστραλία (n=3.893)

1 στους 2
Νεφρική δυσλειτουργία

52,9%



- Μικρολευκωματινουρία
- Μακρολευκωματινουρία
- $eGFR < 60 \text{ ml/min/1.73m}^2$



Γλυκαιμικός έλεγχος και επιπλοκές σε άτομα με ΣΔτ2 στις ΗΠΑ

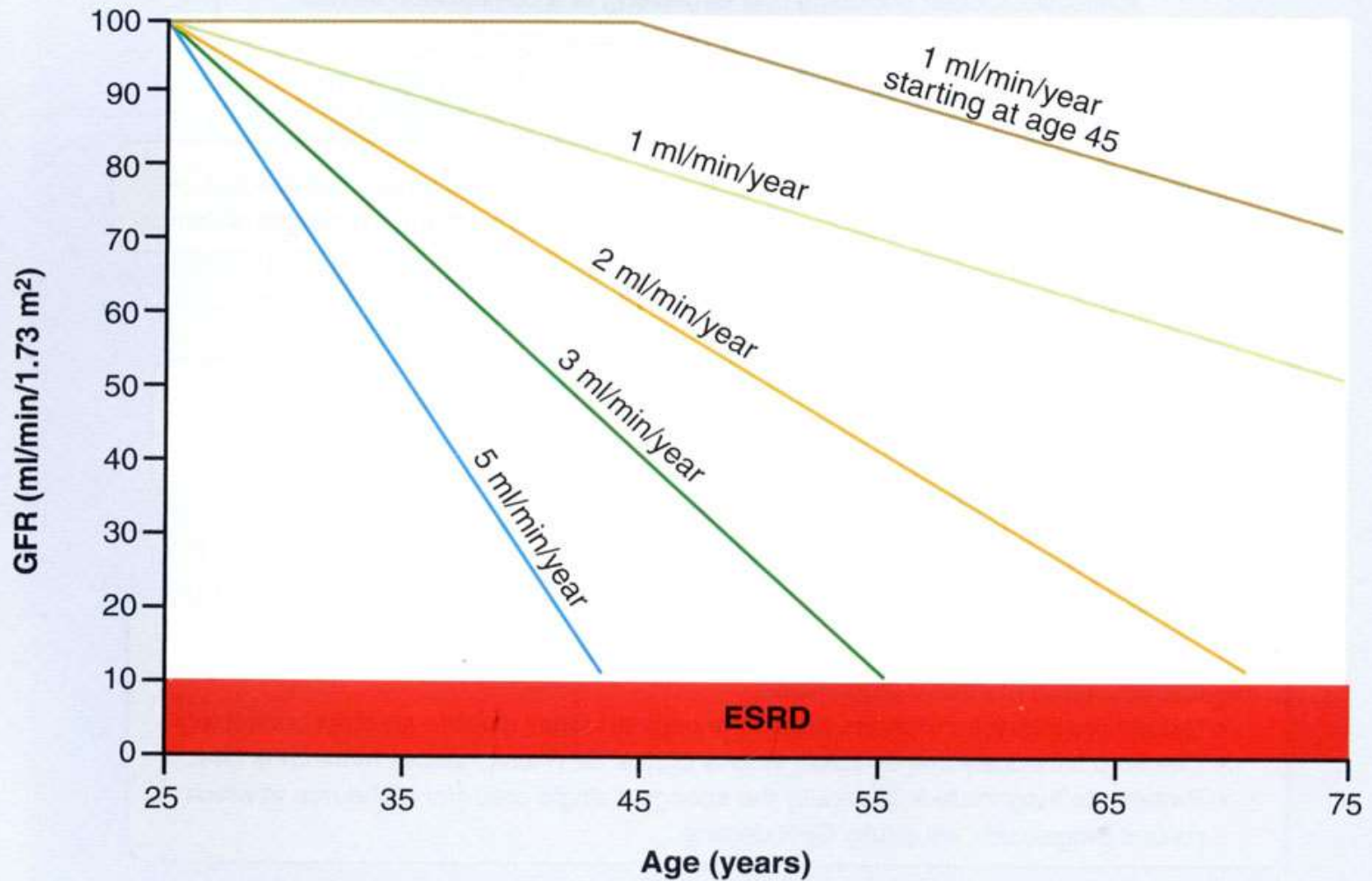
Στάδιο ΧΝΝ	eGFR	%	Αριθμός
1	> 90	9.1	6.444
2	60-89	46.0	32.674
3	30-59	32.0	22.754
4	15-29	2.5	1.770
5	< 15	0.3	194
Ελλιπή δεδομένα		10.2	7.256

78

Αναδρομική μελέτη (2004-2008) σε 71.092 άτομα με ΣΔτ2, ηλικίας > 60 έτη

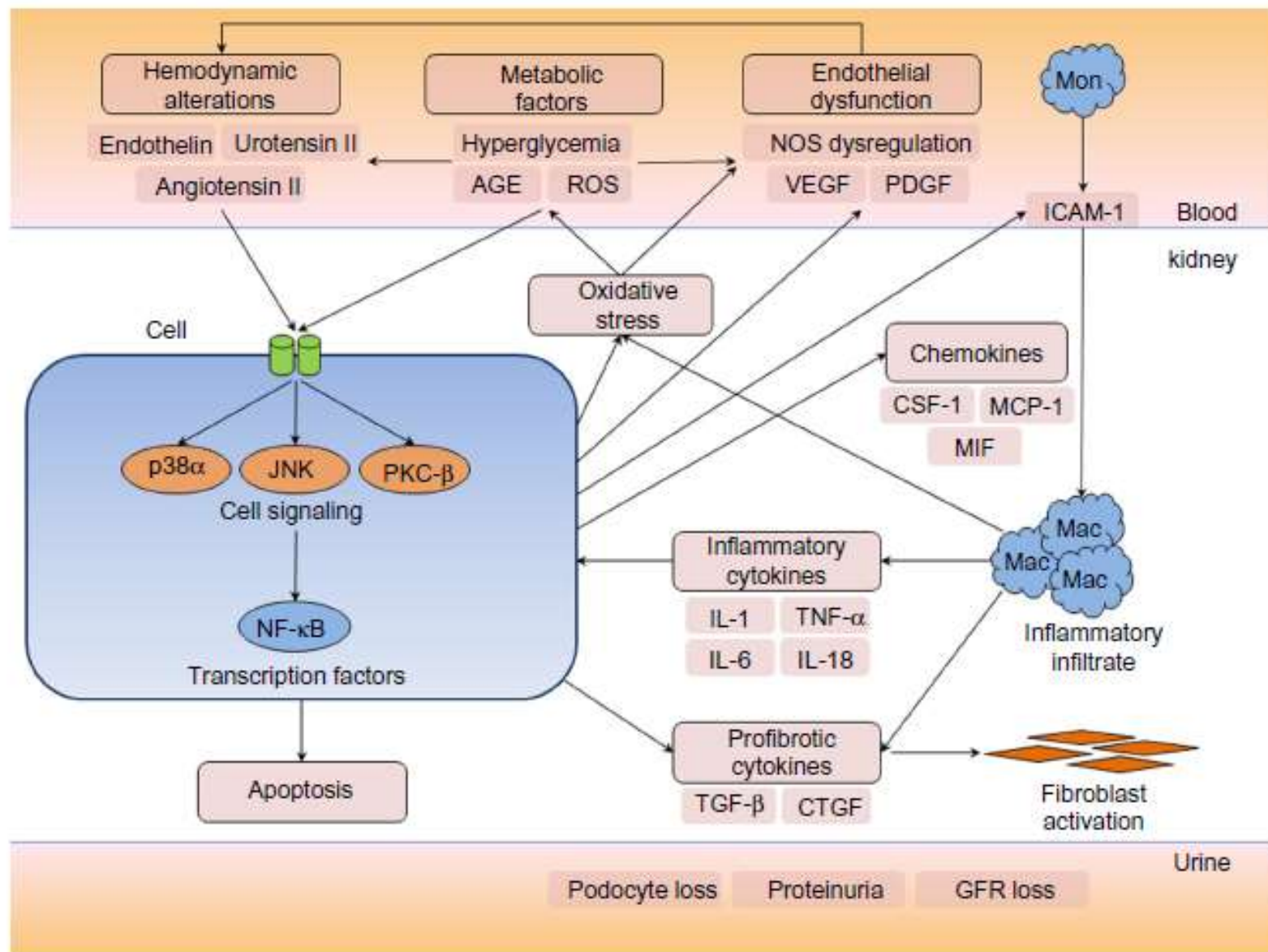


Average rate of GFR decline due to aging





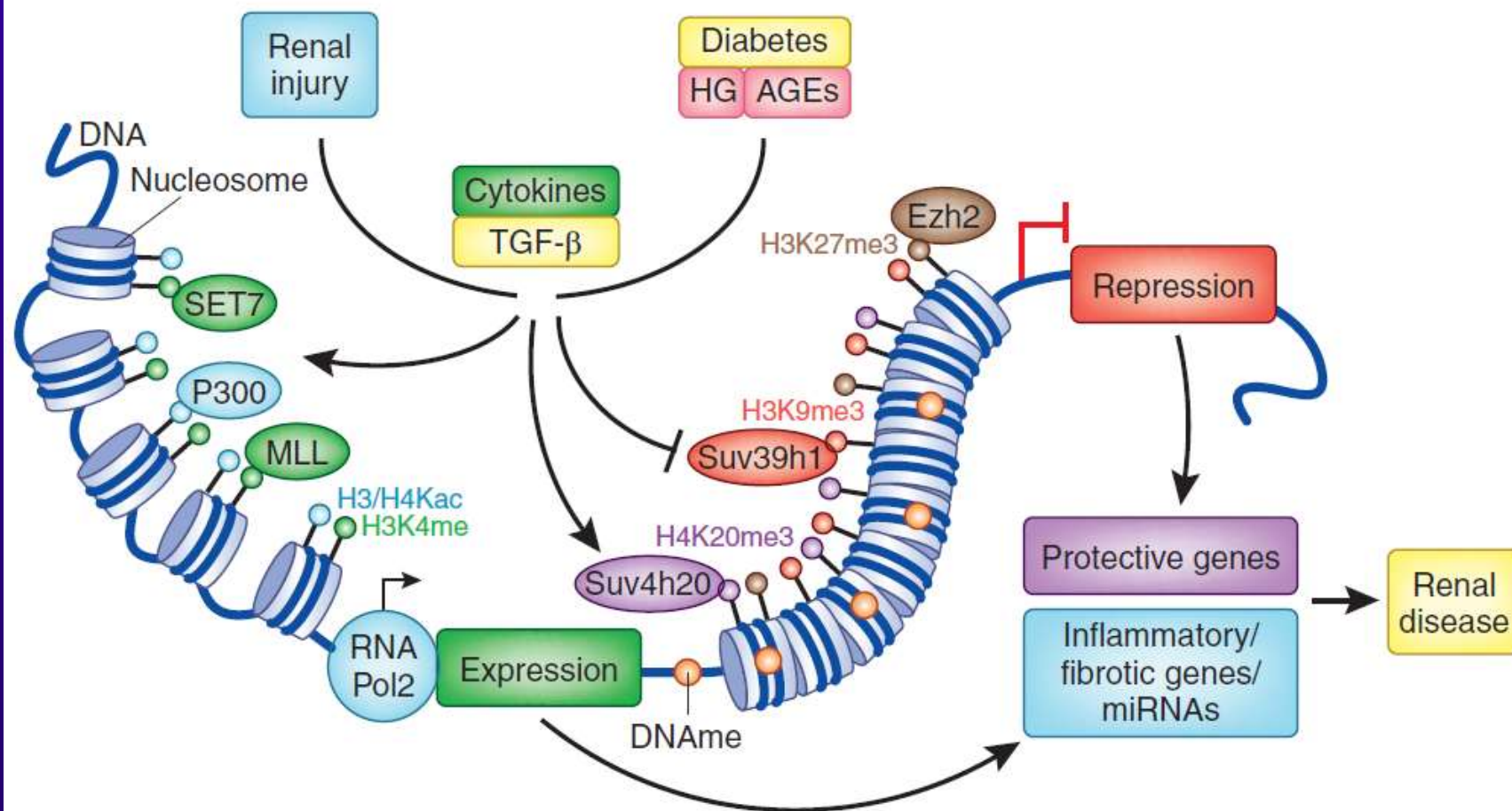
Παθογενετικοί μηχανισμοί





Epigenetics in Diabetic Kidney Disease

Marpadga A. Reddy and Rama Natarajan



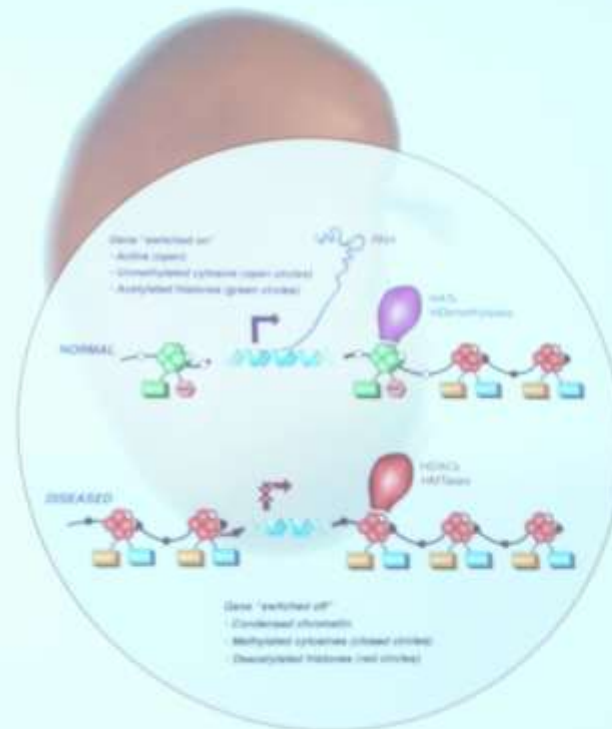


Epigenetics of Diabetic Nephropathy

Dominic Raj MD
Professor and Chief
Division of Renal Disease and
Hypertension
The George Washington
University
Washington DC, USA



13th Annual Meeting of the
European Association for the
Study of Diabetes
19 - 24 September 2017





Summary

- Considerable evidence indicate that diabetic nephropathy has a strong genetic basis
- Traditional genetics has not been able to completely explain the heritability of diabetic nephropathy
- Metabolic memory and gene-environmental interaction in diabetic complications may be explained by epigenetics
- Intra-renal inflammation, epithelial-mesenchymal transition and progressive fibrosis in diabetic kidney disease is epigenetically regulated
- Reversibility of epigenetic modifications offer an unique opportunity for targeted interventions in slowing or reversing the progression of diabetic kidney disease

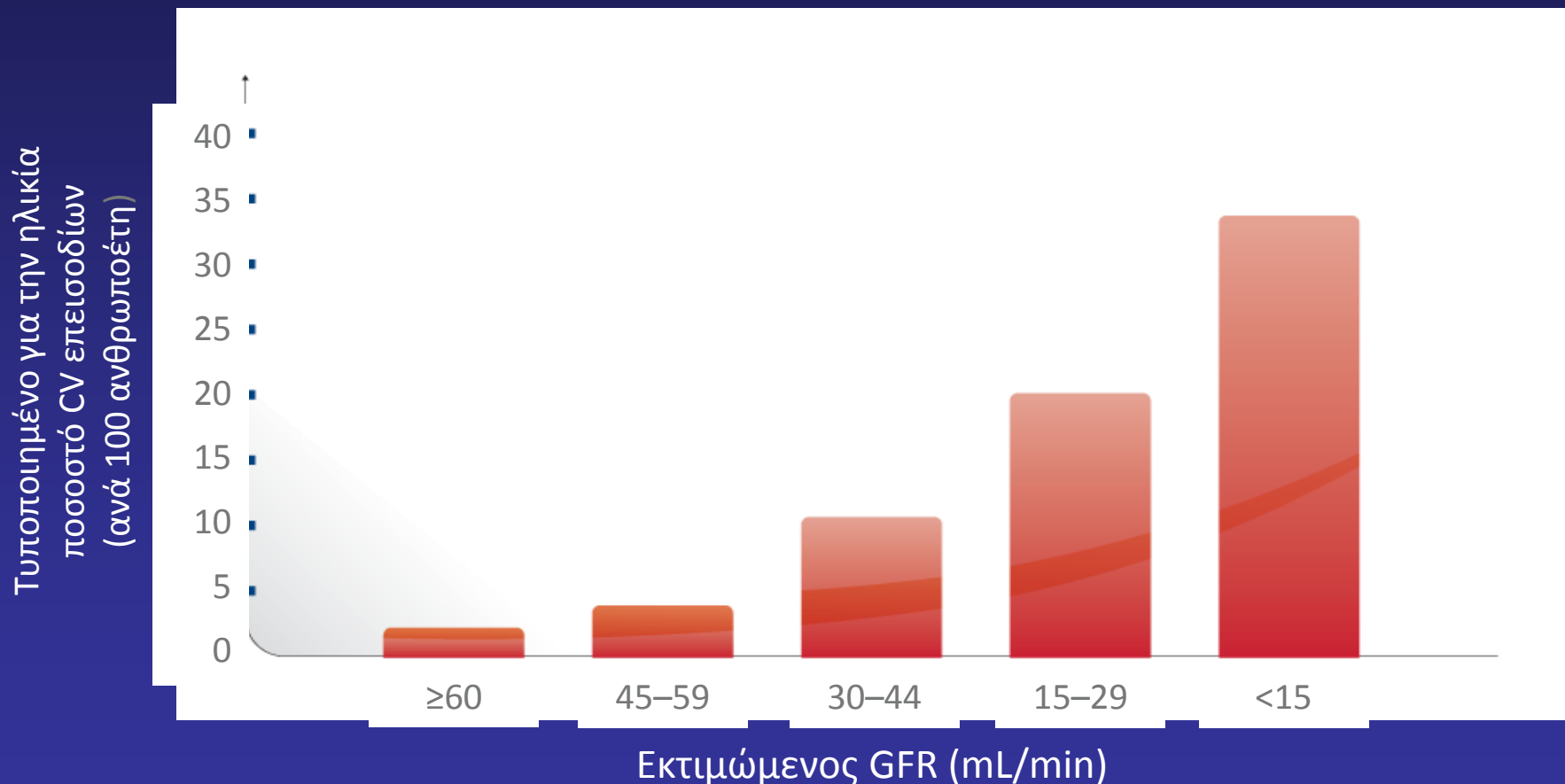


**Η μείωση της νεφρικής λειτουργίας
συχετίζεται με αυξημένο καρδιαγγειακό
κίνδυνο**



Νεφρική Λειτουργία: ο πιο σημαντικός προγνωστικός παράγοντας μακροαγγειακής νόσου

Τυποποιημένα για την ηλικία ποσοστά θανάτου από καρδιαγγειακά (CV) επεισόδια ανάλογα με τον εκτιμώμενο GFR¹



Ως CV επεισόδιο ορίσθηκε η νοσηλεία για στεφανιαία νόσο, καρδιακή ανεπάρκεια, ισχαιμικό εγκεφαλικό επεισόδιο και περιφερική αρτηριοπάθεια

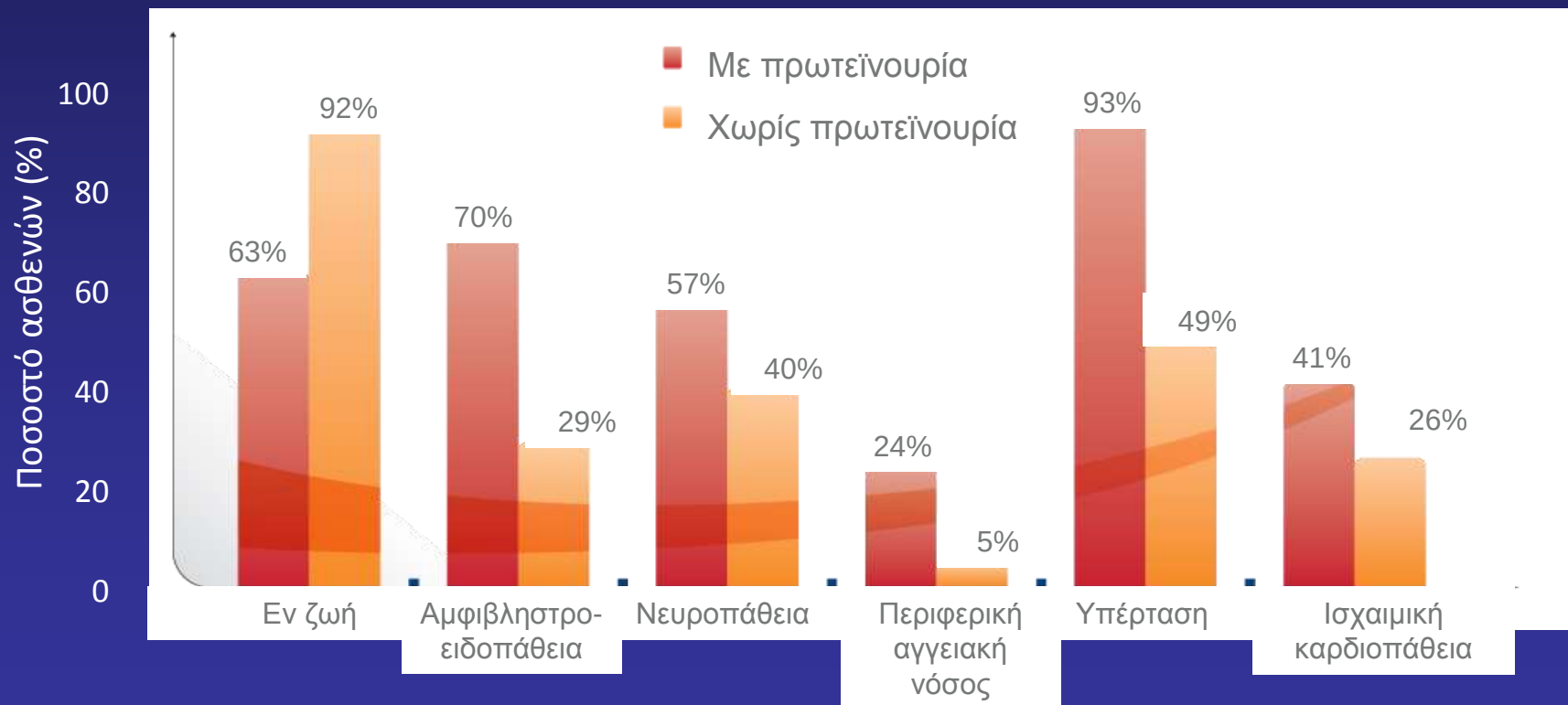
1. Go AS, et al. *N Engl J Med* 2004;351:1296–305.



Η πρωτεΐνουρία συνδέεται με υψηλό κίνδυνο αγγειακής νόσου και θανάτου¹

Πενταετείς εκβάσεις σε ασθενείς με ΣΔΤ2 με και χωρίς πρωτεΐνουρία

Η πρωτεΐνουρία συνδέεται με $\approx$ πενταπλάσια πιθανότητα θανάτου σε ασθενείς με ΣΔΤ2
(37% έναντι 8%, $P < 0,0001$)





Θεραπευτικές παρεμβάσεις



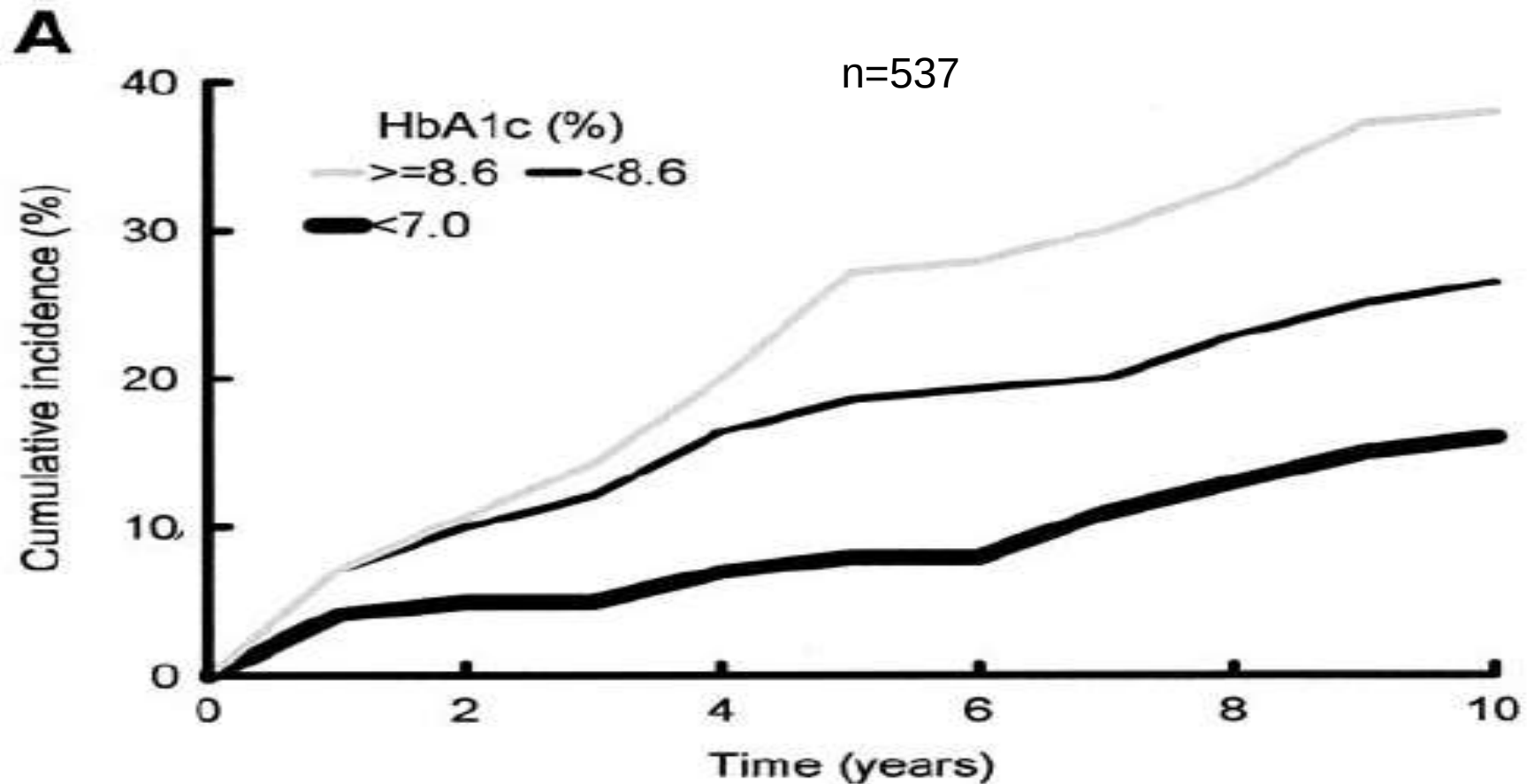
Παθολογία Διαβητικής Νεφροπάθειας





Risk Factors for Development of Incipient and Overt Diabetic Nephropathy in Type 1 Diabetic Patients

A 10-year prospective observational study





Μελέτη DCCT

ΣΔ τύπου 1:

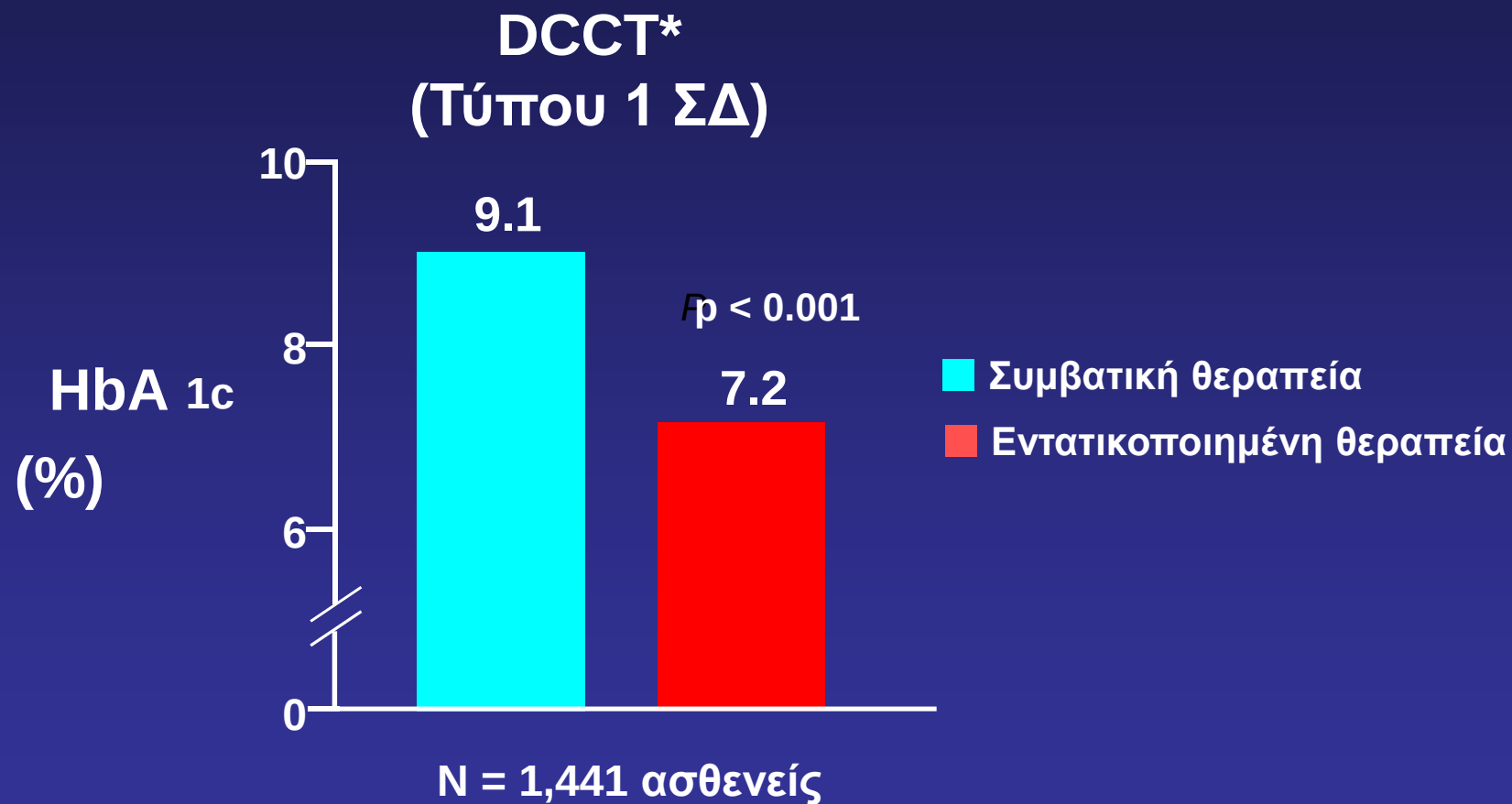
Εντατικοποιημένος έλεγχος σακχάρου

VS.

Συμβατικός έλεγχος σακχάρου



Παρέμβαση - Γλυκαιμικός έλεγχος

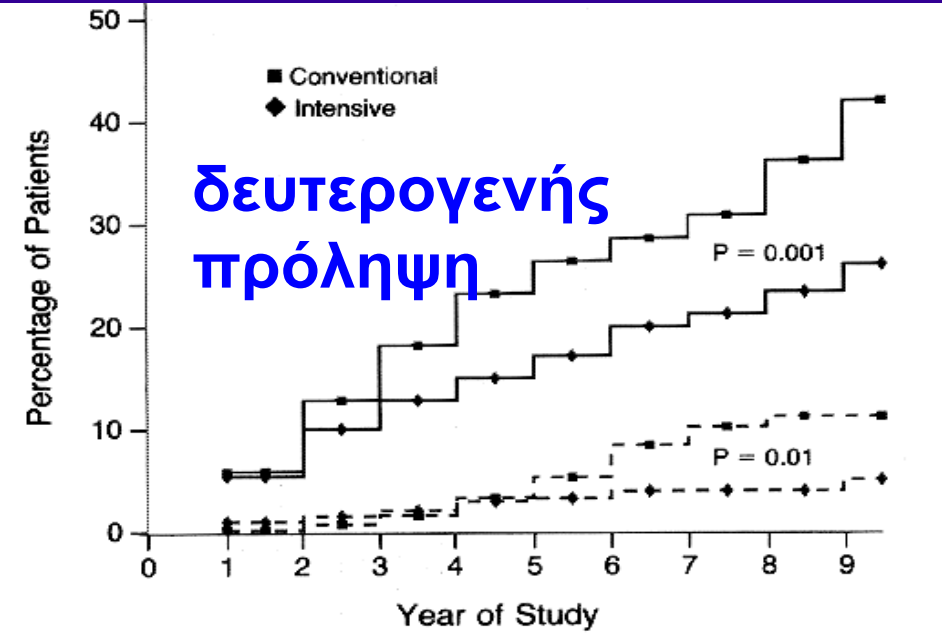
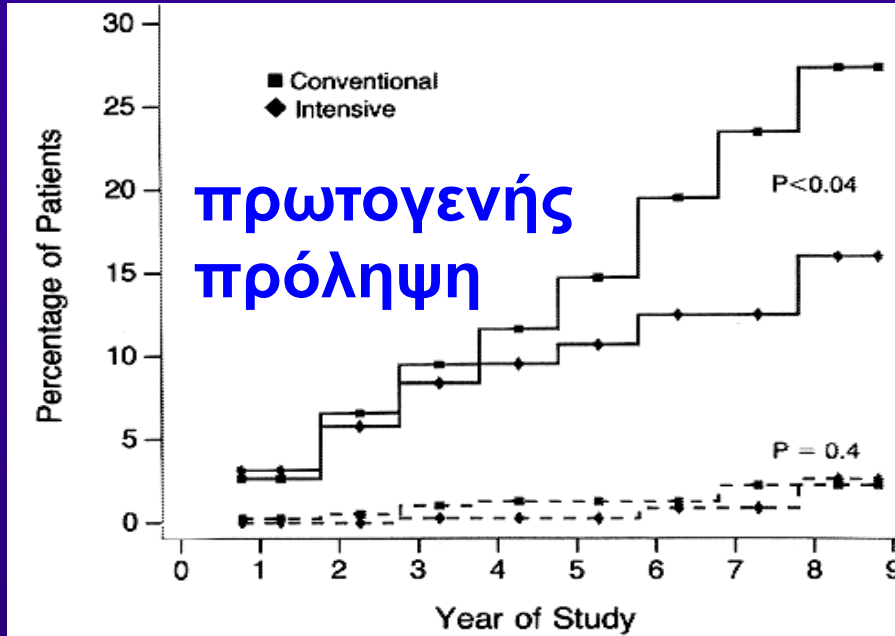


*After 6.5 years

DCCT Research Group. *N Engl J Med.* 1993;329:977-986.



Διαβητική Νεφροπάθεια και ΣΔ Τύπου 1



- DCCT: 1441 ασθενείς με ΣΔ τύπου 1 τυχαιοποιημένοι σε εντατική και συμβατική ινσουλινοθεραπεία.
- Η αυστηρή ρύθμιση του σακχάρου βελτιώνει τη μικρολευκωματινουρία (κατά 39%) και την λευκωματινουρία (κατά 54%).
- Δρα δηλαδή και στην πρωτογενή και στη δευτερογενή πρόληψη.



Επίπτωση ΜΑ στη μελέτη DCCT/EDIC

- 38% μετά 30 έτη στην ομάδα με την συμβατική θεραπεία
- 25% στην εντατικοποιημένη

De Boer IH et al., Arch Intern Med 171,412, 2011



Μελέτη UKPDS

ΣΔ τύπου 2 :

Εντατικοποιημένος έλεγχος σακχάρου

VS.

Συμβατικός έλεγχος σακχάρου

- ✓ 5102 νεοδιαγνωσθέντες διαβητικοί τύπου 2
- ✓ Μέση διάρκεια παρακολούθησης 11 έτη



UKPDS: Αποτελέσματα γλυκαιμικού ελέγχου

- Εντατικοποιημένη θεραπεία μείωσε την HbA_{1c} κατά 0.9% εντός 11 ετών, με αποτέλεσμα την μείωση των επιπλοκών (κυρίως των μικροαγγειακών)

Μεταβολές
στον κίνδυνο*

P value

Μικρολευκωματινουρία στα 12 έτη

↓ 33%

<0.001



Reversal of diabetic nephropathy: lessons from pancreas transplantation

J Nephrol 2012; 25(1): 13 - 18
DOI:10.5301/jn.5000061

Authors

Paola **Fioretto**, Michael **Mauer**

Abstract

Pancreas transplantation is the only therapeutic intervention able to achieve and maintain long-term euglycemia, without risks of hypoglycemia; this makes it possible to test the impact of normoglycemia in the different stages of diabetic nephropathy. Pancreas and islet transplantation in animal models prevent the development of diabetic nephropathy lesions and ameliorate or reverse established glomerular lesions. In type 1 diabetic patients, pancreas transplantation, performed simultaneously or after kidney transplantation, has been shown to prevent the recurrence of diabetic glomerulopathy lesions. The established lesions of diabetic nephropathy have been considered to be irreversible; pancreas transplantation alone allows us to test whether this is true. To this end, we studied renal structure before and 5 and 10 years after pancreas transplantation in 8 nonuremic type 1 diabetic patients. These patients, with a long diabetes duration, had established diabetic nephropathy lesions at the time of transplantation. We report that diabetic glomerulopathy lesions, unchanged at 5 years post pancreas transplantation, significantly improved after 10 years, with complete normalization of glomerular structure in most patients. Thus this study demonstrates that the lesions of diabetic nephropathy are reversed by long-term normoglycemia and that the human kidney has the potential in humans to obtain a substantial architectural remodeling of the glomerular and tubular structures toward healing.



REVERSAL OF LESIONS OF DIABETIC NEPHROPATHY AFTER PANCREAS TRANSPLANTATION

PAOLA FIORETTO, M.D., PH.D., MICHAEL W. STEFFES, M.D., PH.D., DAVID E.R. SUTHERLAND, M.D., PH.D.,
FREDERICK C. GOETZ, M.D., AND MICHAEL MAUER, M.D.

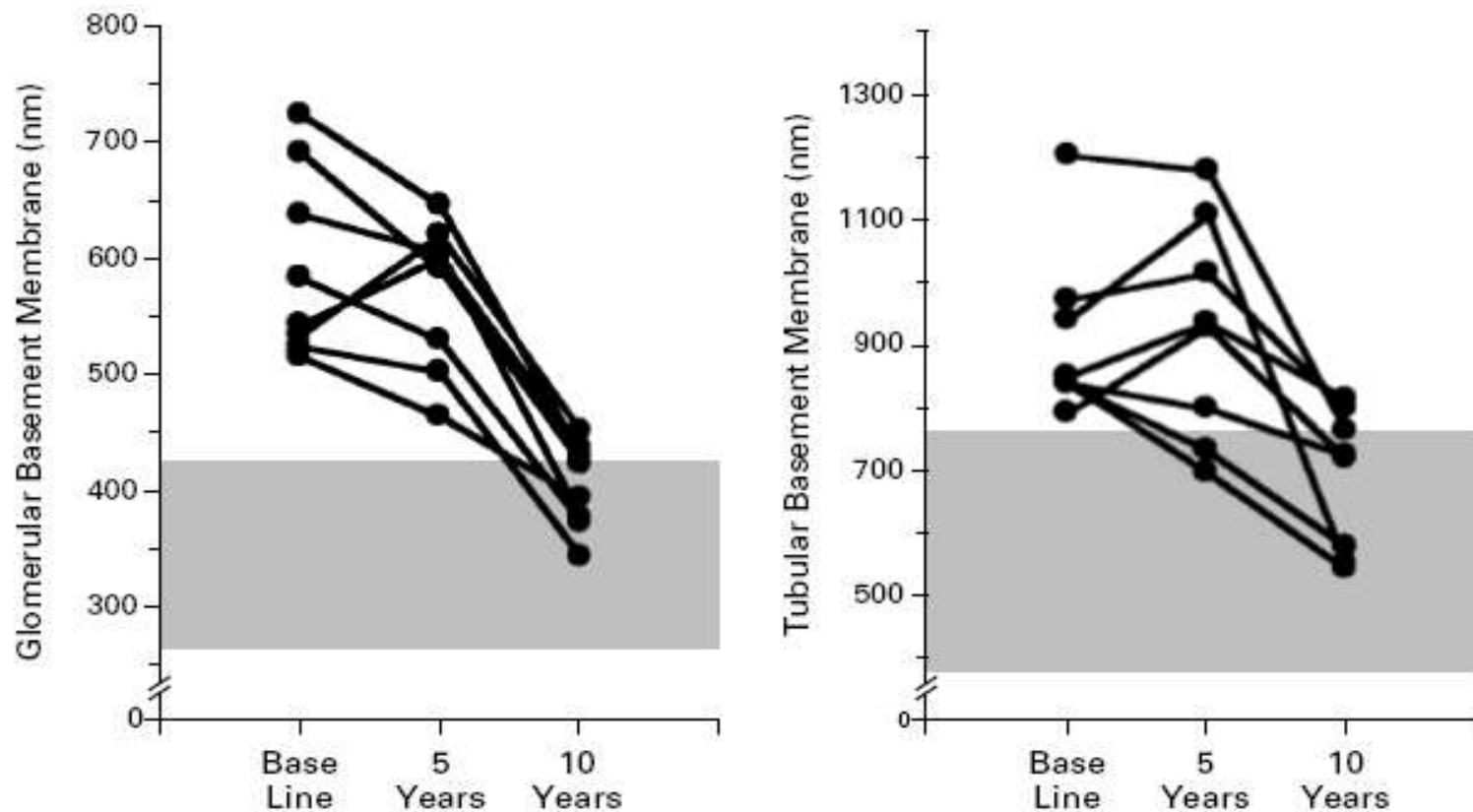
TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND MEASURES OF RENAL FUNCTION AT BASE LINE AND 1, 5, AND 10 YEARS AFTER PANCREAS TRANSPLANTATION IN PATIENTS WITH TYPE 1 DIABETES.

PATIENT NO. AND SEX	AGE AT BASE LINE	DURATION OF DIABETES AT BASE LINE	URINARY ALBUMIN EXCRETION			CREATININE CLEARANCE			
			BASE LINE	5 YR	10 YR	BASE LINE	1 YR	5 YR	10 YR
		yr	mg/24 hr			ml/min/1.73 m ²			
1/M	33	20	7	2	6	138	75	82	83
2/F	31	15	8	4	23	113	71	63	68
3/F	33	24	12	21	43	101	61	86	91
4/F	35	22	86	6	6	116	86	91	78
5/M	30	23	120	80	48	128	61	90	89
6/F	33	17	127	155	18	84	49	44	50
7/F	31	27	278	126	20	110	54	72	67
8/F	38	29	1276	40	176	78	65	68	67
Mean ±SD	33±3	22±5	103*	30*†	20*‡	108±20	65±12§	74±16§	74±14§



REVERSAL OF LESIONS OF DIABETIC NEPHROPATHY AFTER PANCREAS TRANSPLANTATION

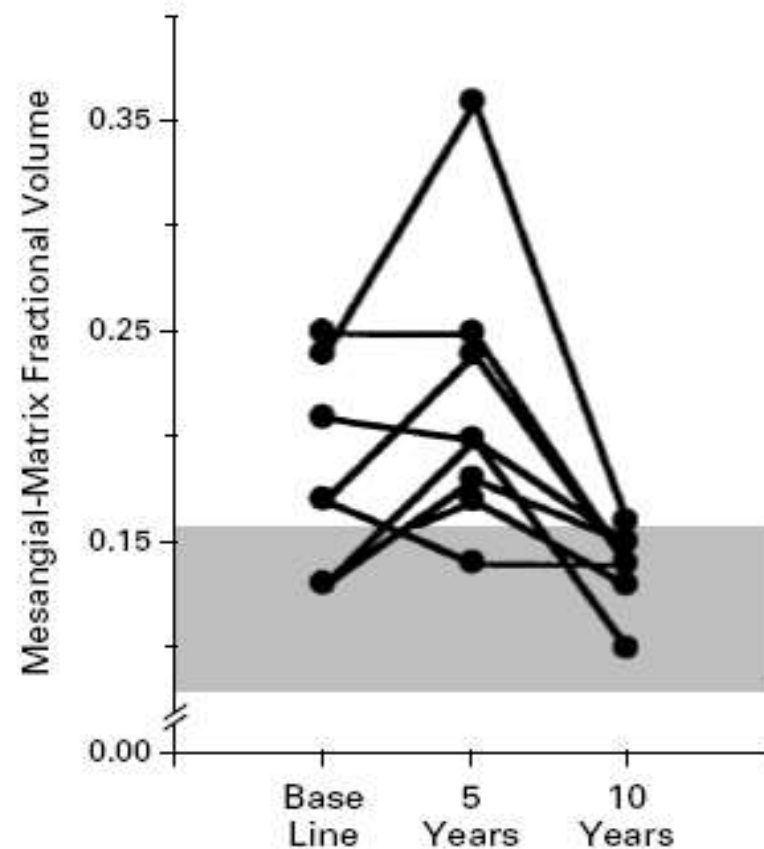
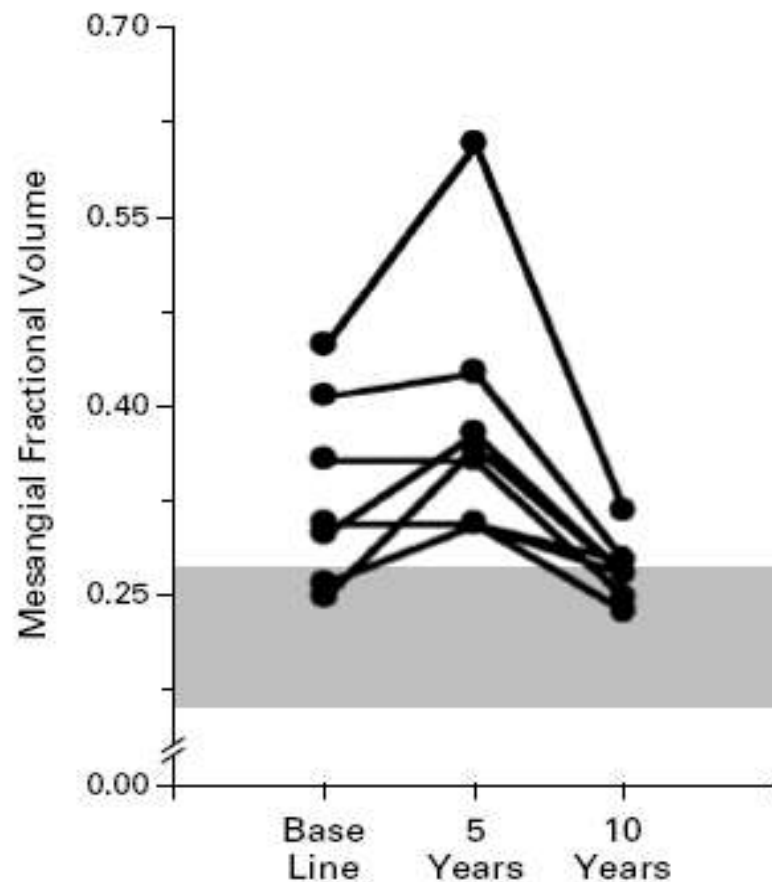
PAOLA FIORETTO, M.D., PH.D., MICHAEL W. STEFFES, M.D., PH.D., DAVID E.R. SUTHERLAND, M.D., PH.D.,
FREDERICK C. GOETZ, M.D., AND MICHAEL MAUER, M.D.





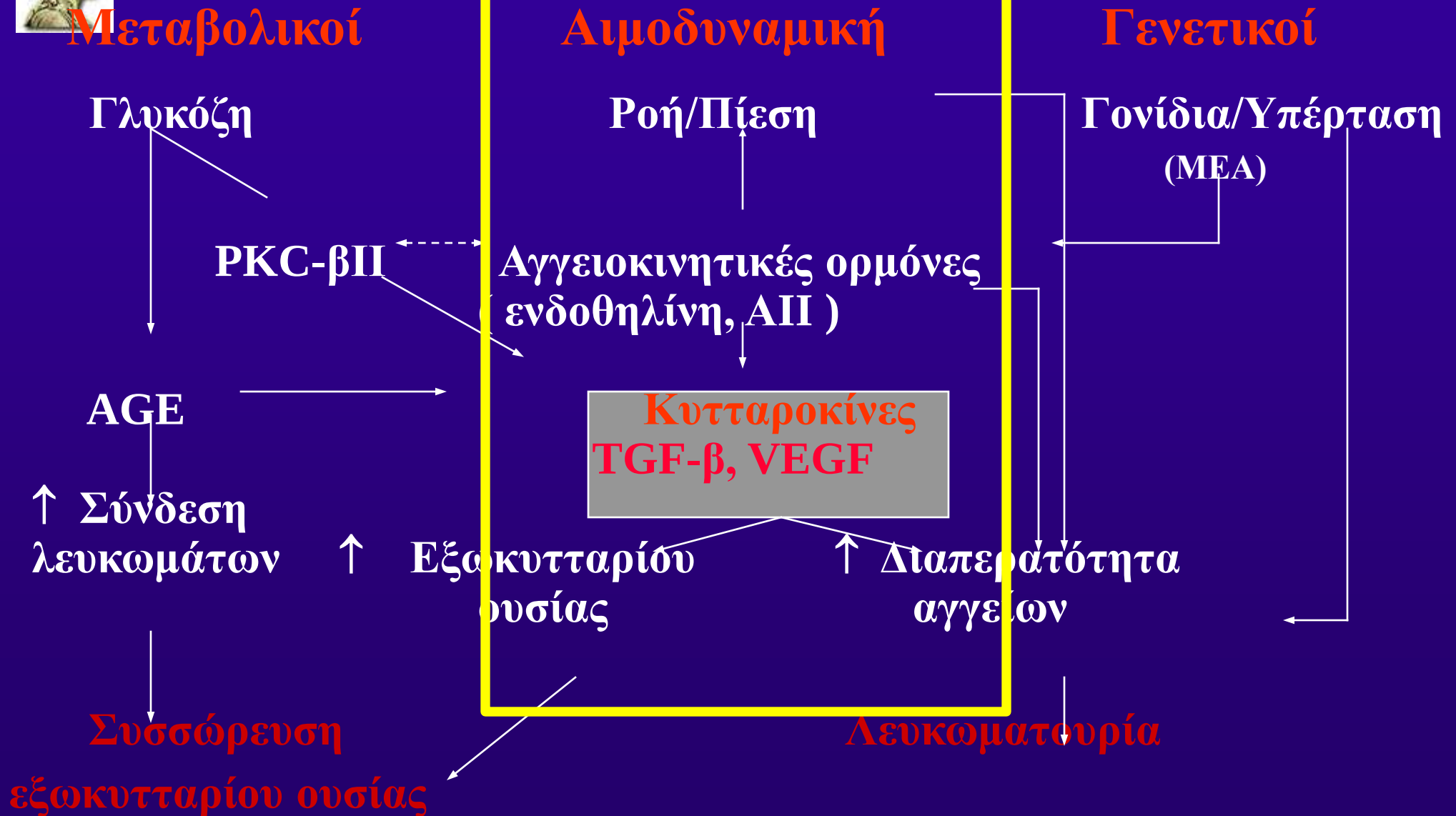
REVERSAL OF LESIONS OF DIABETIC NEPHROPATHY AFTER PANCREAS TRANSPLANTATION

PAOLA FIORETTO, M.D., PH.D., MICHAEL W. STEFFES, M.D., PH.D., DAVID E.R. SUTHERLAND, M.D., PH.D.,
FREDERICK C. GOETZ, M.D., AND MICHAEL MAUER, M.D.



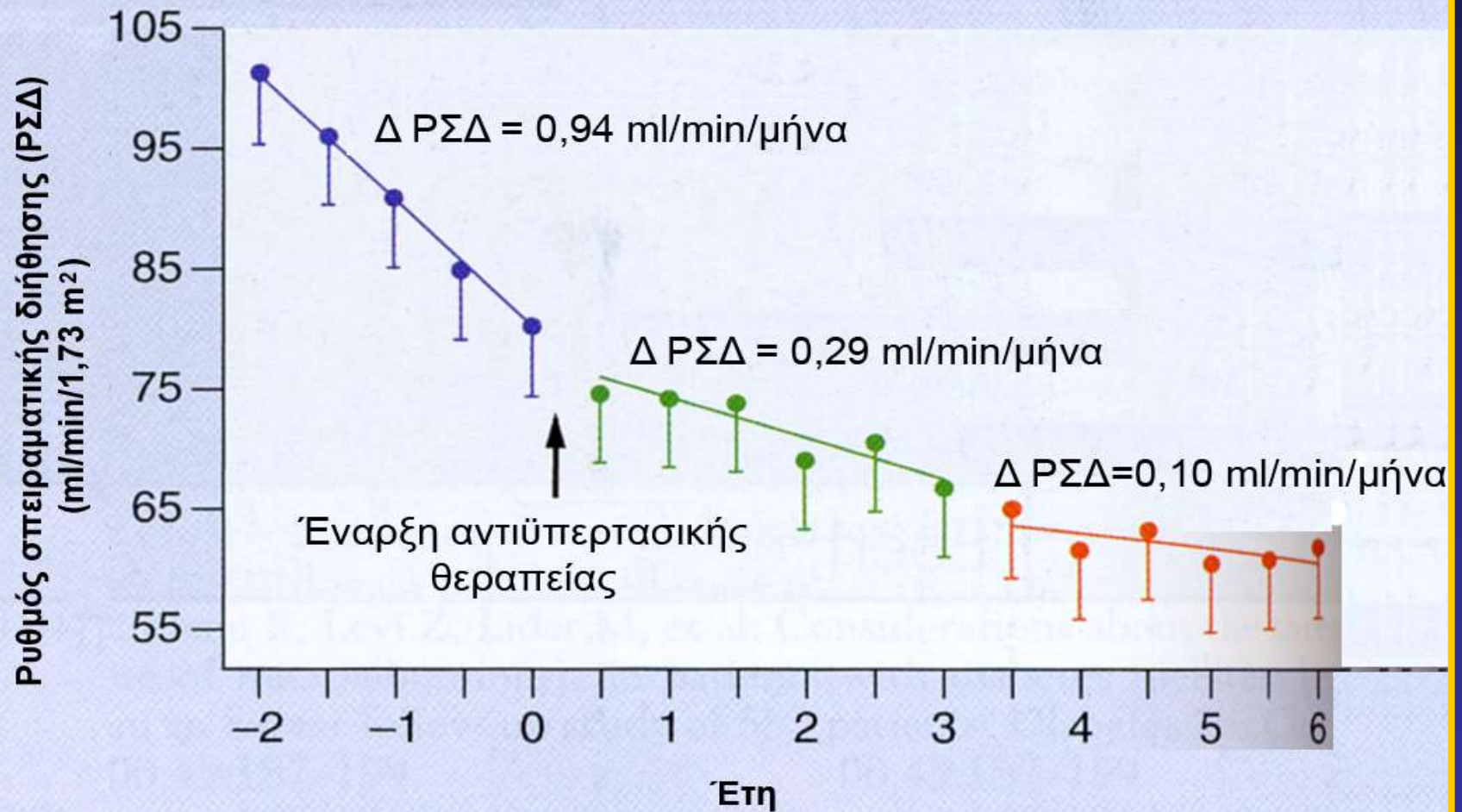


Παθολογία Διαβητικής Νεφροπάθειας





Ο έλεγχος της αρτηριακής πίεσης επιβραδύνει την εξέλιξη της διαβητικής νεφροπάθειας τύπου 1





Όρια αρτηριακής πίεσης σε άτομα με ΣΔ

Υπέρταση

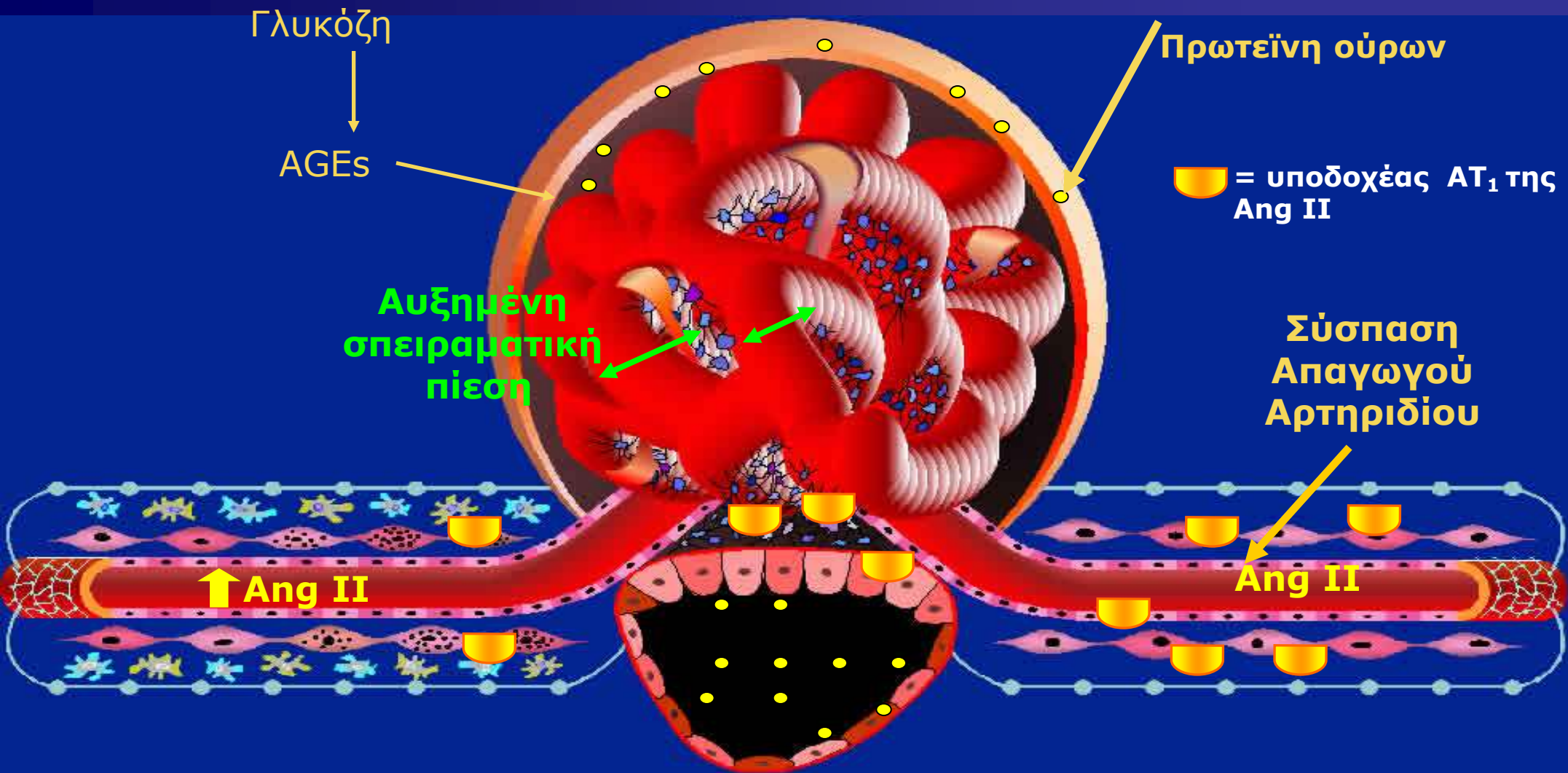
>140 και / ή 90 (ADA)

>140 και / ή 85 (ESC)

>140 και / ή 90 (JNC 8)



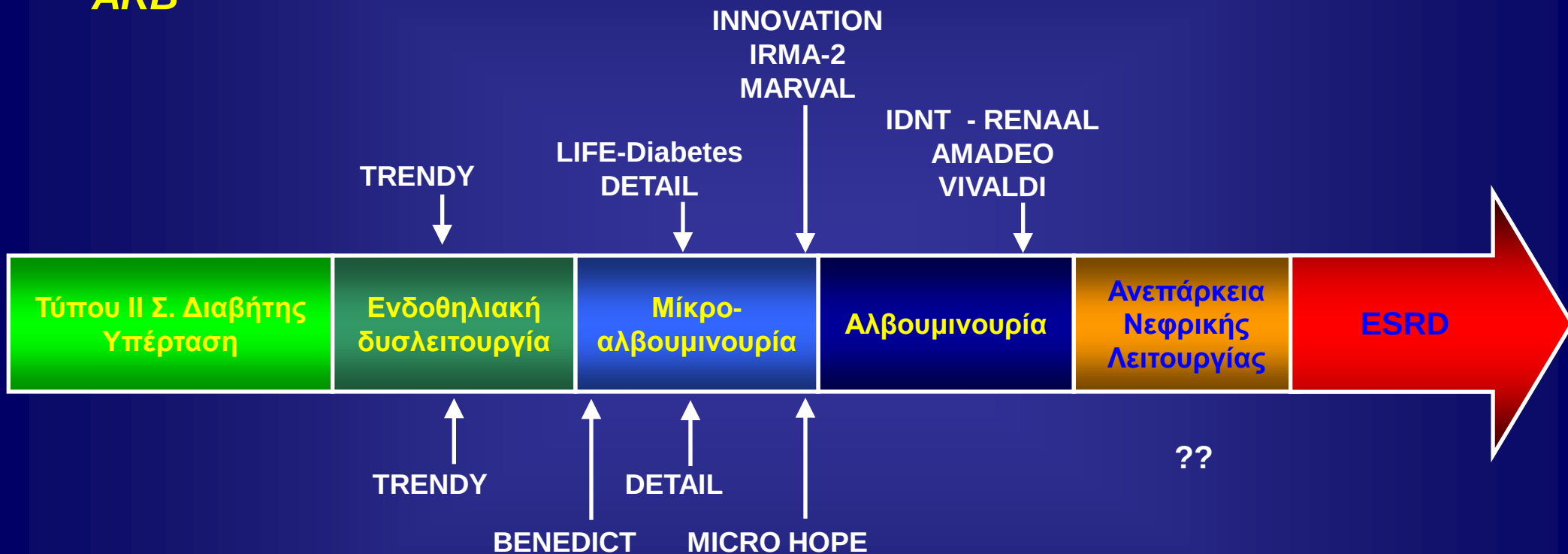
Παθογενετικοί μηχανισμοί που οδηγούν σε βλάβη του σπειράματος και πρωτεϊνουρία





Αναστολή της εξέλιξης της διαβητικής νεφροπάθειας μέσω του αποκλεισμού του RAS

ARB



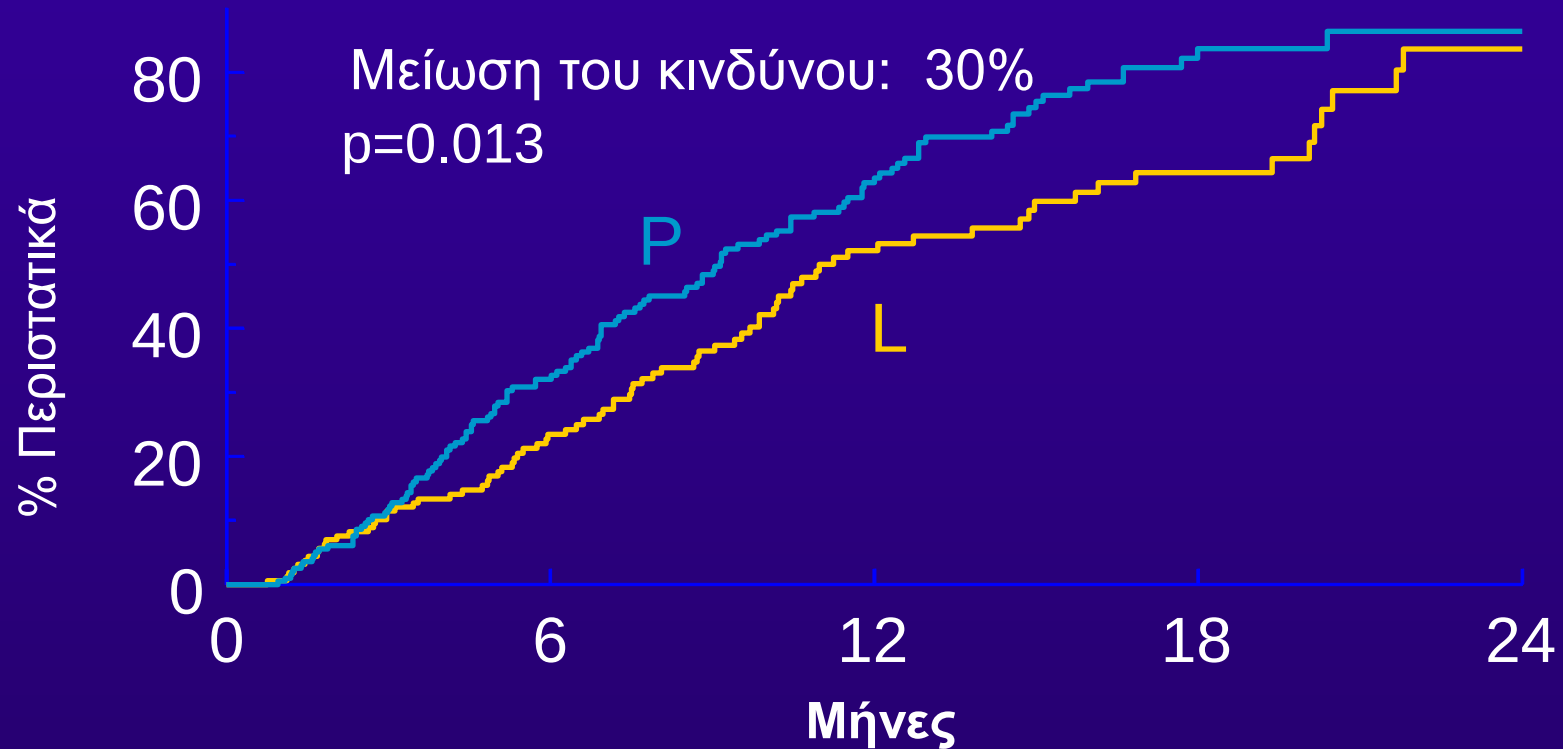
α-MEA



RENAAL

Χρόνος από το Διπλασιασμό της Κρεατινίνης του Ορού μέχρι
το Τελικό Στάδιο Νεφρικής Νόσου

n=1513

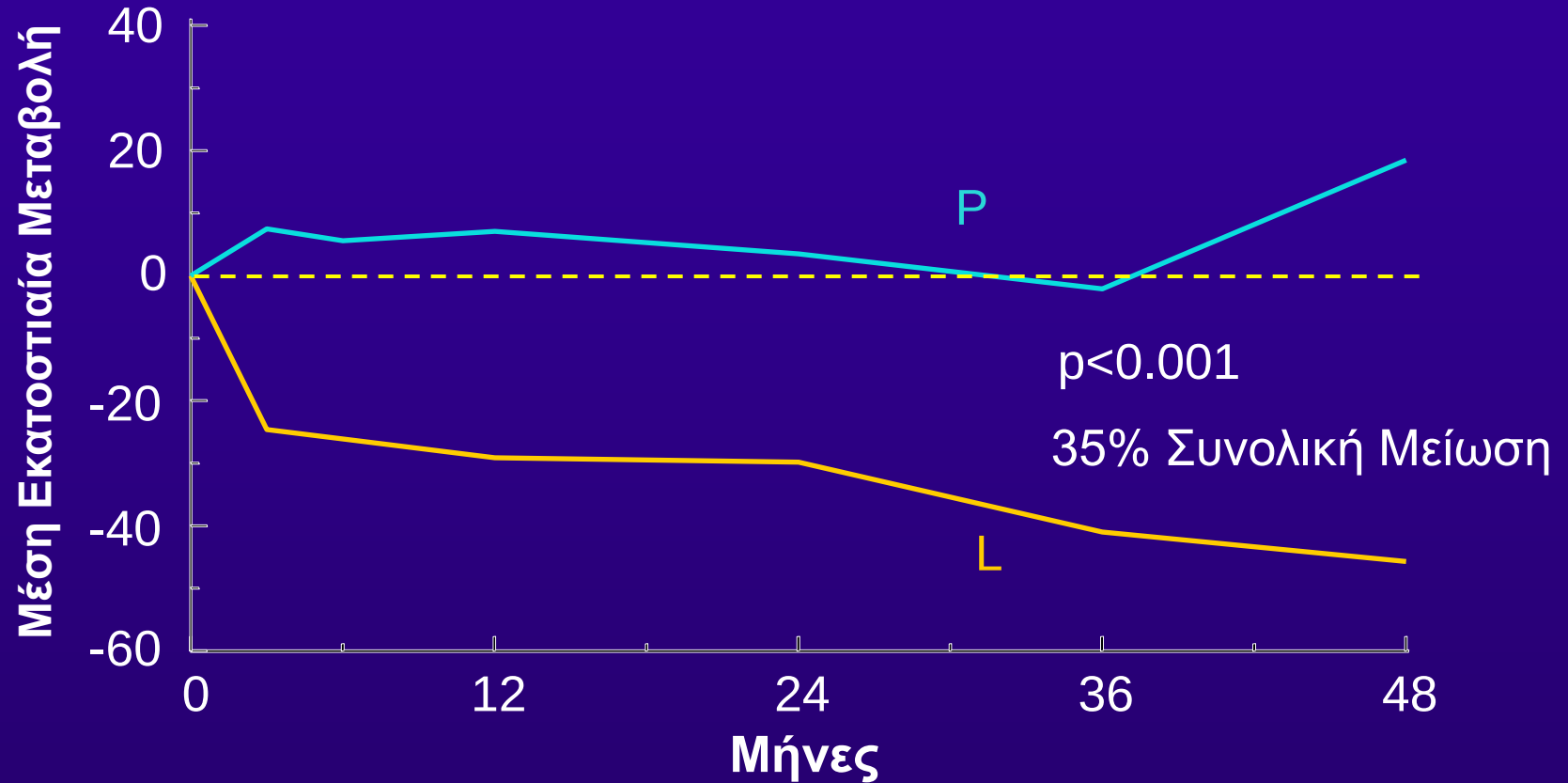


— P (+CT)	198	111	48	11	4
— L (+CT)	162	104	43	19	3



RENAAL

Μεταβολή της Πρωτεϊνουρίας από τις Αρχικές Τιμές



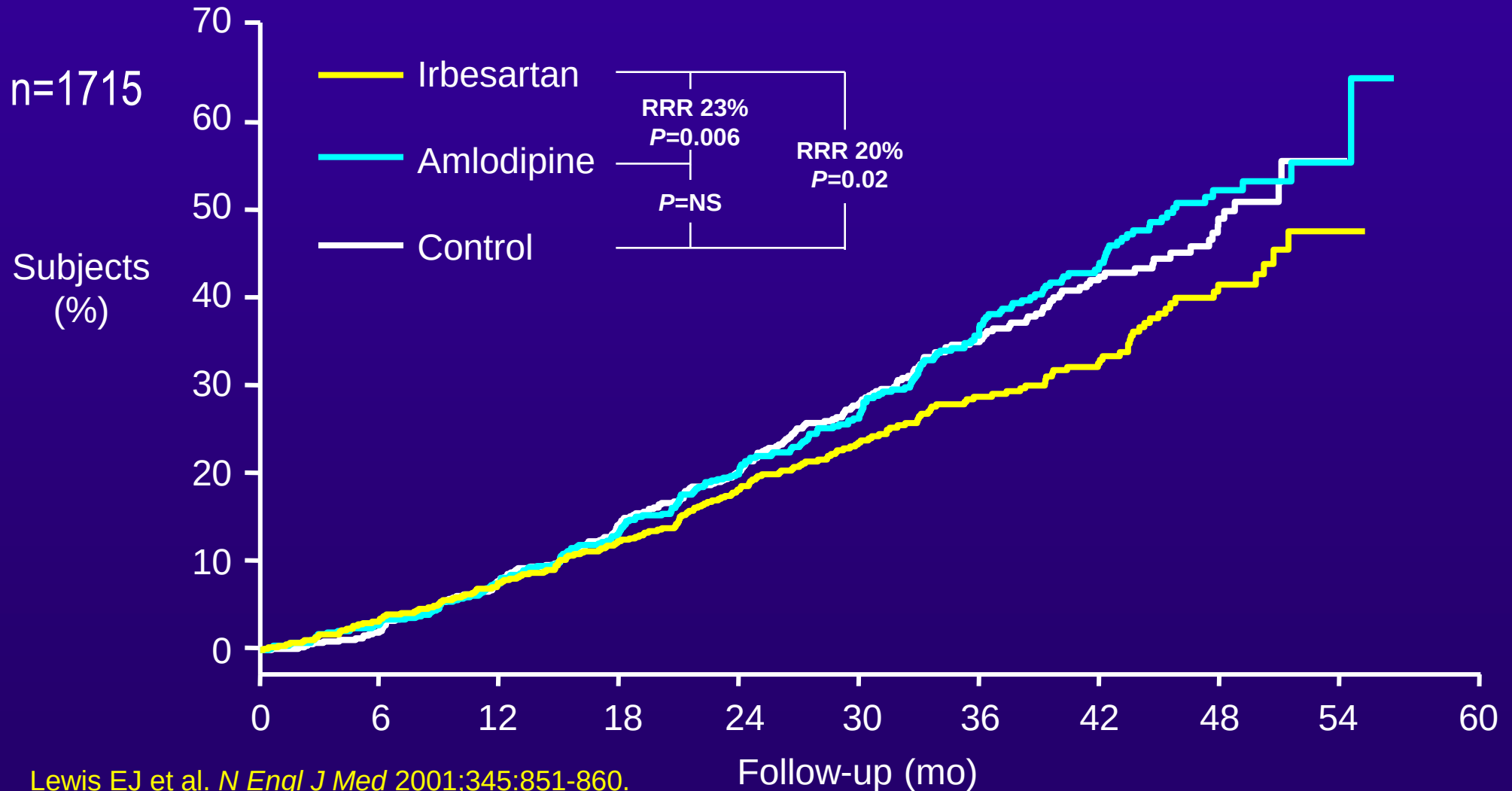
— P (+CT)	762	632	529	390	130
— L (+CT)	751	661	558	438	167

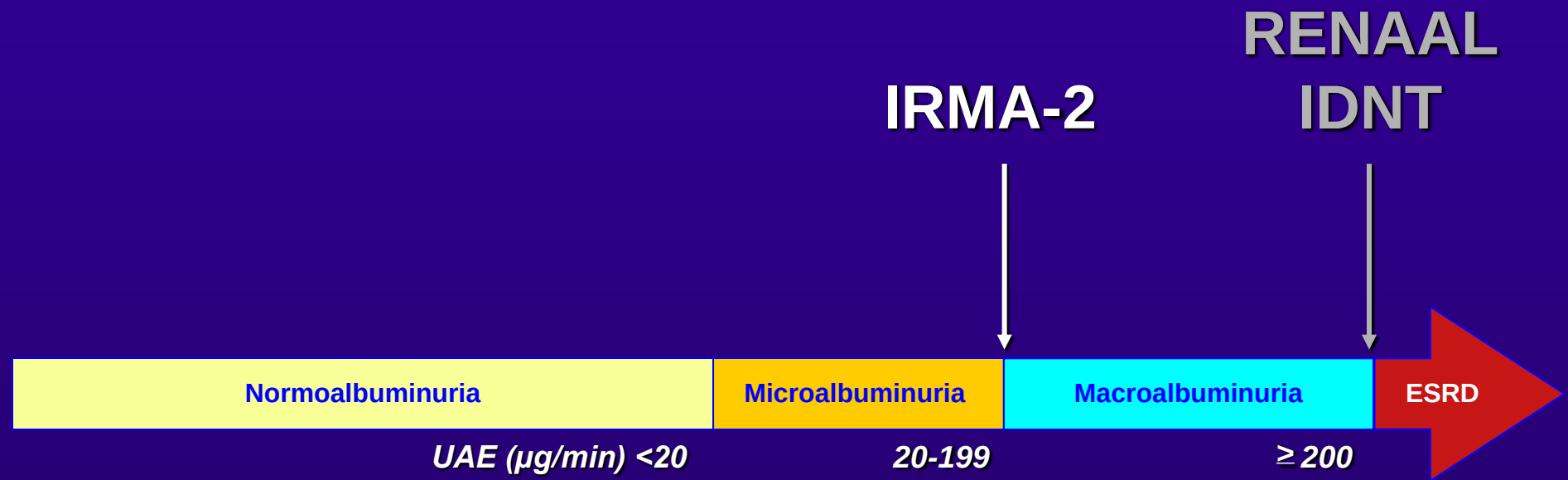
Η πρωτεϊνουρία μετρήθηκε με βάση την αναλογία λευκώματος ούρων/κρεατινίνης στα πρώτα πρωινά ούρα



IDNT

Χρόνος μέχρι το Διπλασιασμό της Κρεατινίνης του Ορού, το ΤΣΧΝΑ ή θάνατο



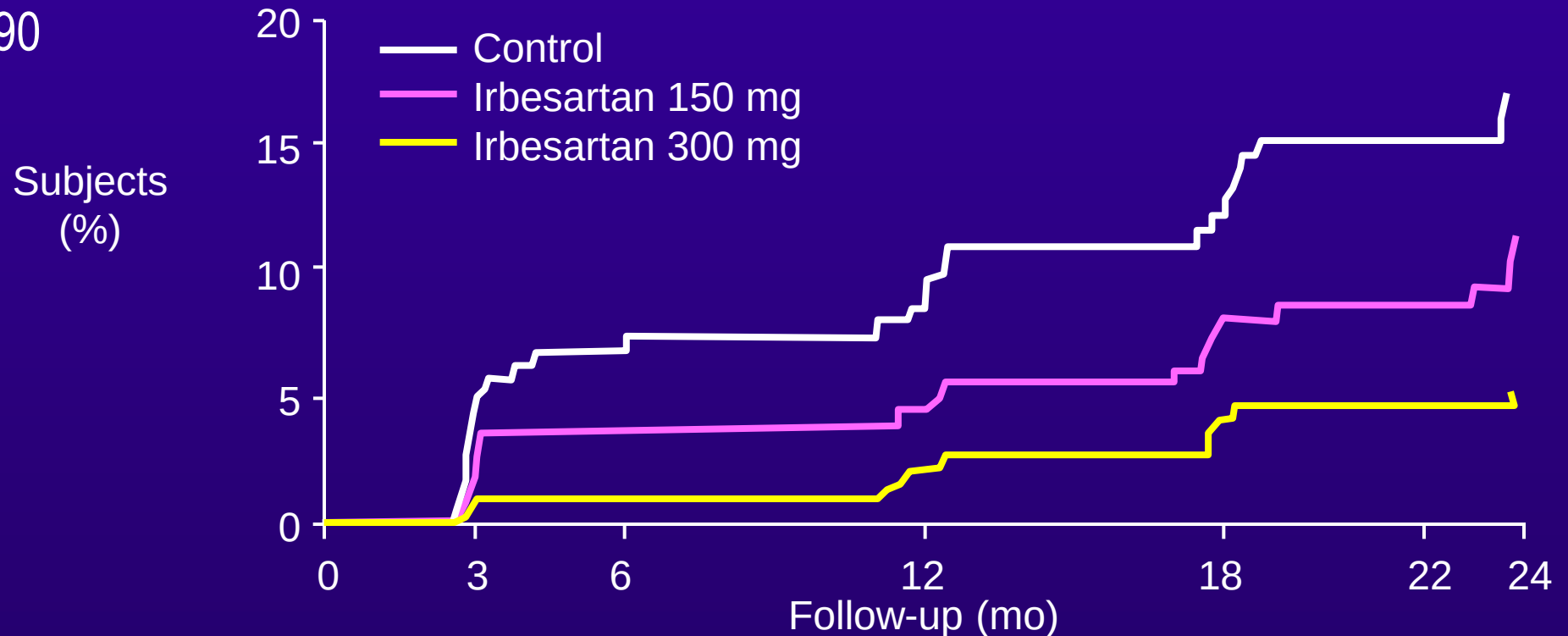




IRMA 2

Χρόνος μέχρι την έκδηλη πρωτεϊνουρία

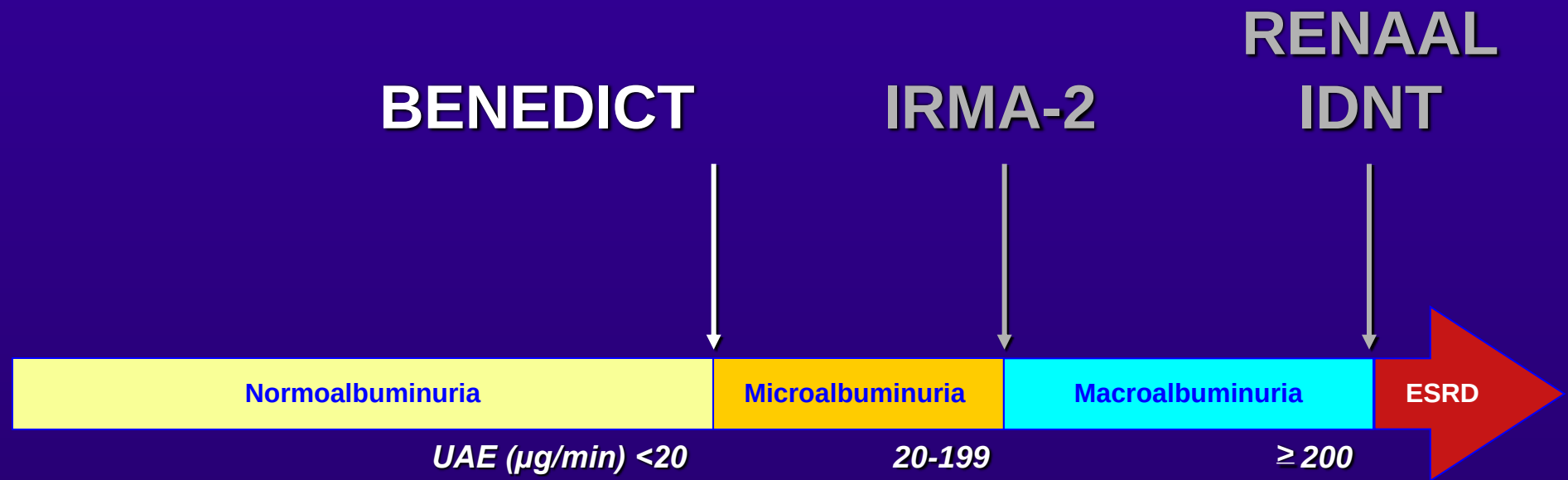
n=590





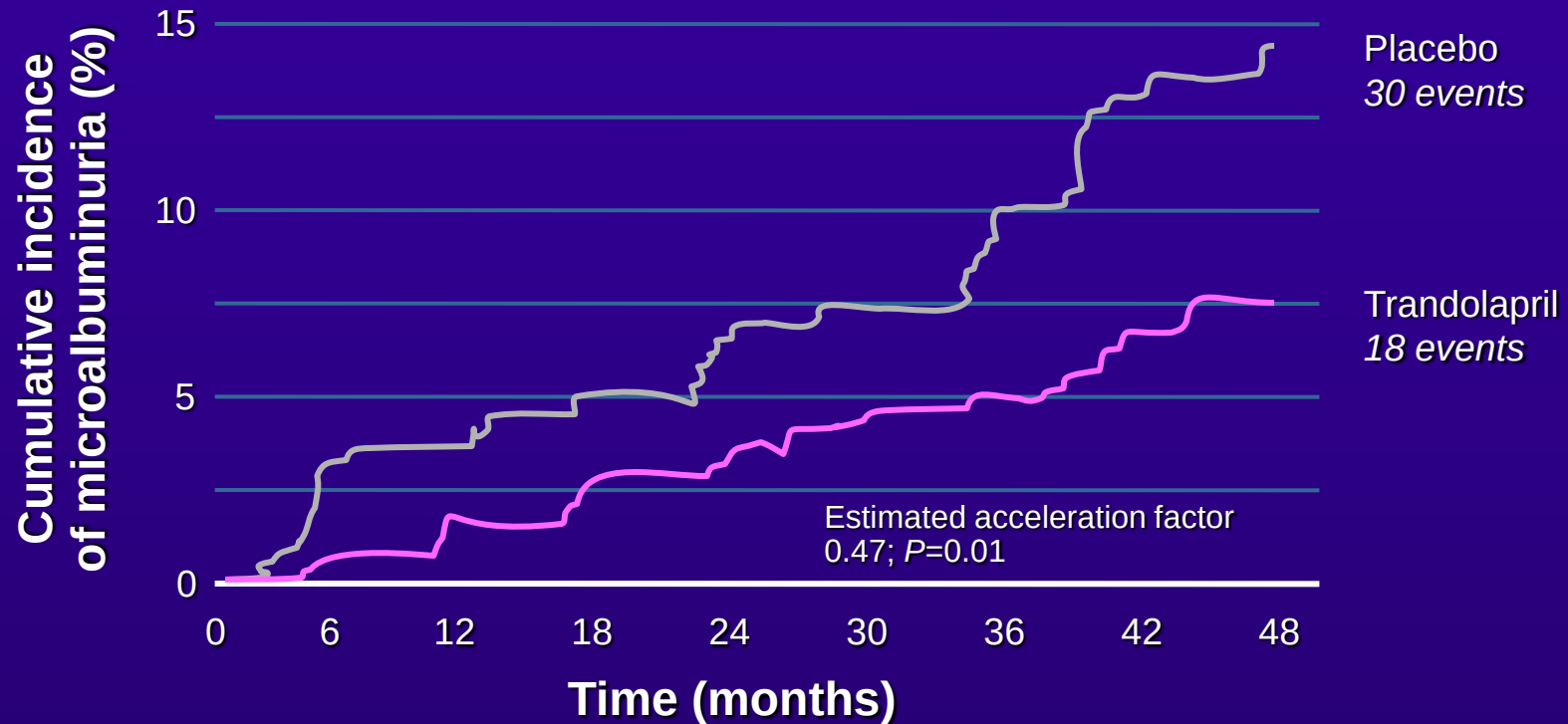
IRMA 2

- Μείωση του κινδύνου για εξέλιξη σε έκδηλο λευκωματουρία κατά 70%
- Μείωση της ΜΑ κατά 38%
- Υποστροφή σε νόρμο κατά 34%





Επίπτωση μικρολευκωματινουρίας: trandolapril vs placebo



No. at risk

Trandolapril	301	254	237	224	207	198	188	149	104
Placebo	300	229	214	203	187	176	164	136	89



Επίδραση της φαρμακευτικής αγωγής στην εξέλιξη της ΔΝ

ADVANCE :

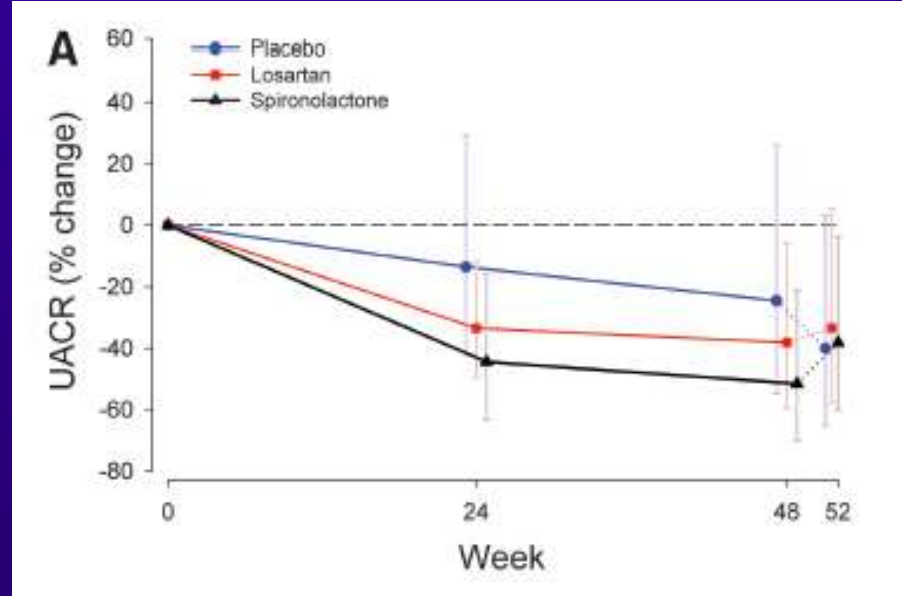
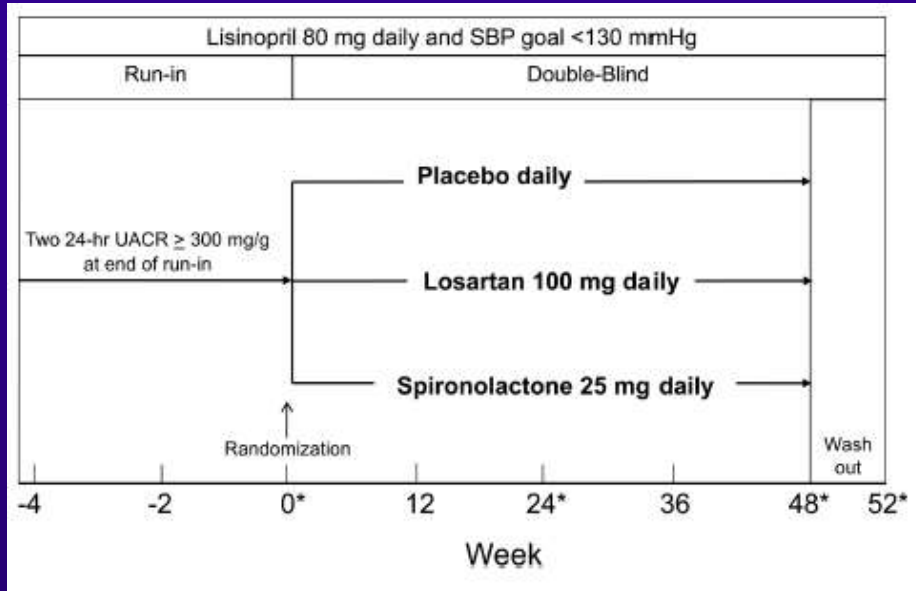
5χροnia παρακολούθηση 11.140 ασθενείς

HbA1c : εντατικοποιημένο 6,5%
 συμβατική 7,5%

στο εντατικοποιημένο σκέλος μείωση του κινδύνου :
65% για ΤΣΧΝΑ
9% για ΜΑ
30% για λευκωματουρία



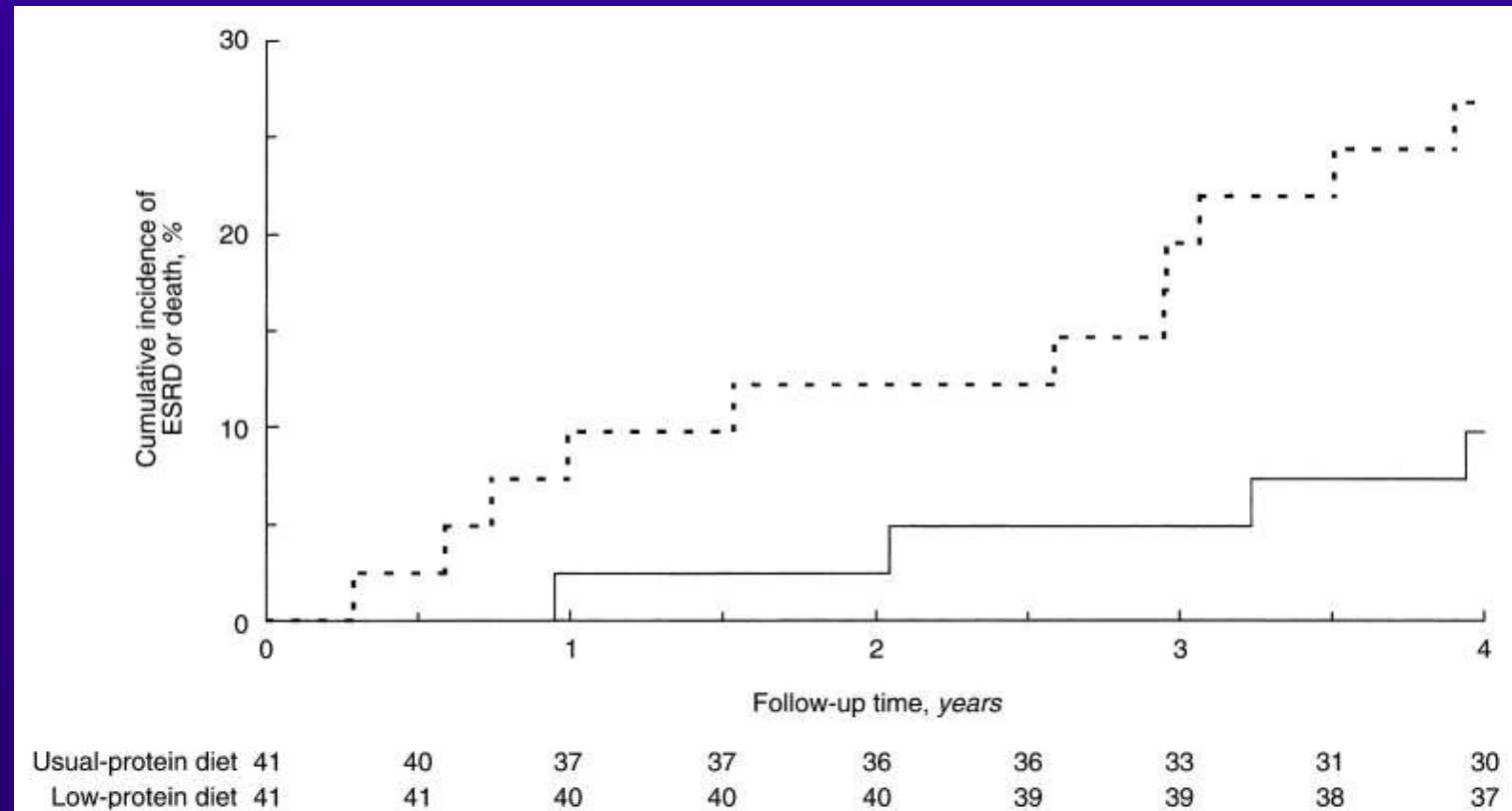
Addition of Angiotensin Receptor Blockade or Mineralocorticoid Antagonism to Maximal Angiotensin-Converting Enzyme Inhibition in Diabetic Nephropathy

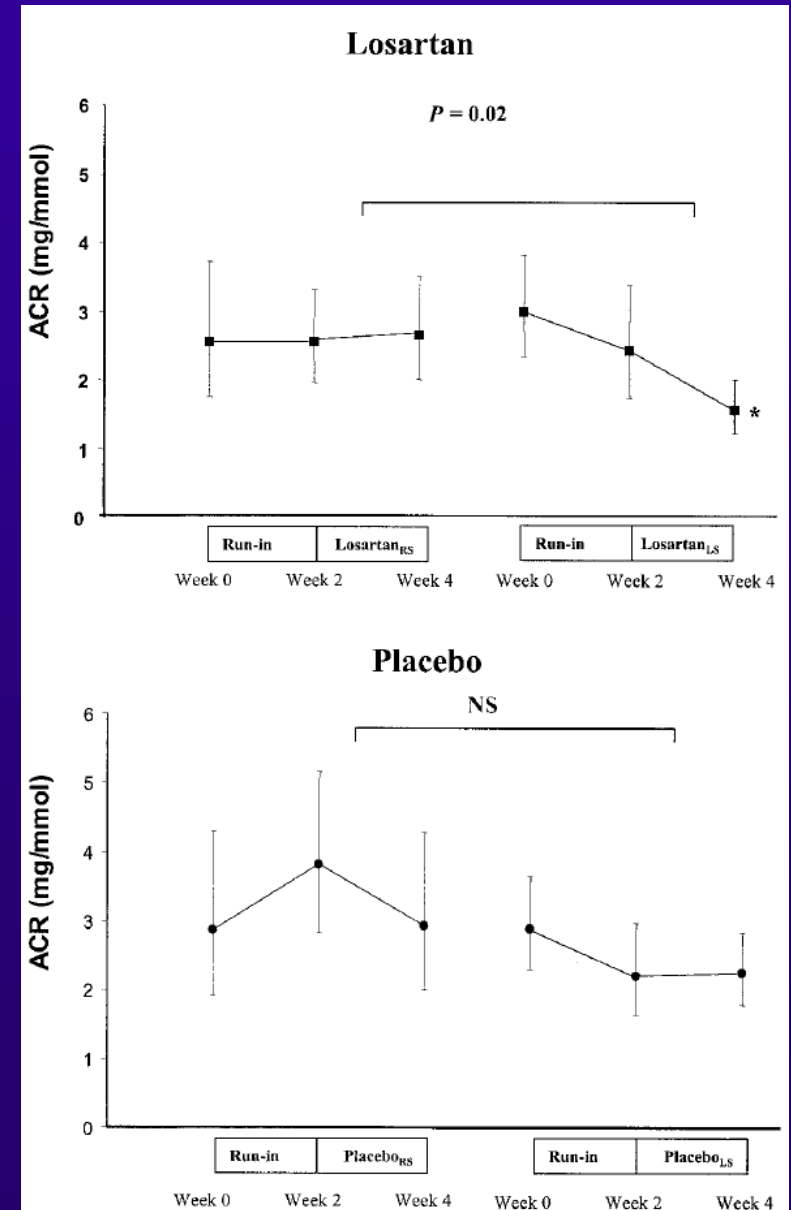




Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy

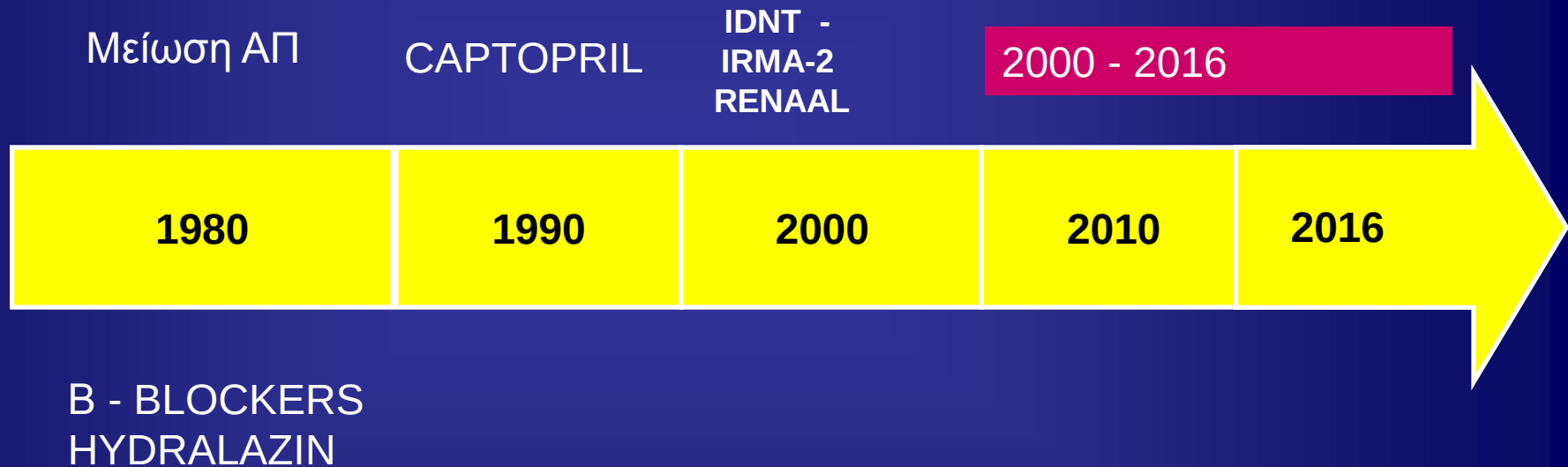
HENRIK P. HANSEN, ELLIS TAUBER-LASSEN, BERIT R. JENSEN, and HANS-HENRIK PARVING







Δεν υπάρχουν νέες θεραπείες για την αντιμετώπιση της ΧΝΝ τα τελευταία 16 χρόνια ...





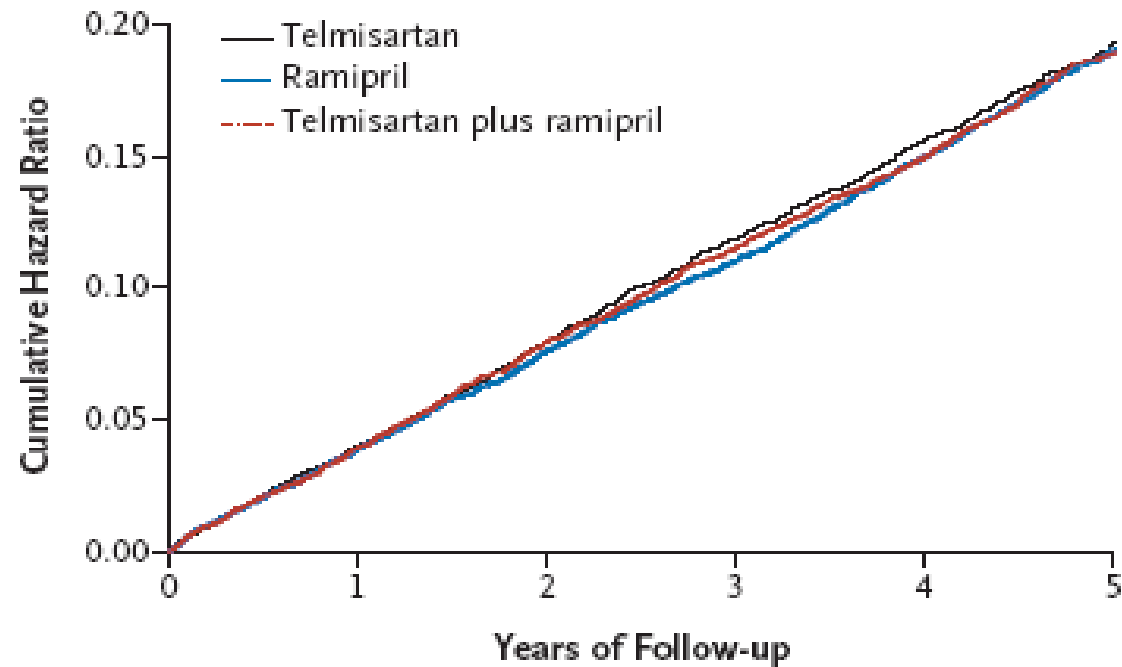
Δεν μπορούμε όμως να πούμε ότι δεν έγιναν προσπάθειες για την αντιμετώπιση της ΔΝ τα χρόνια αυτά

- Διπλή καταστολή του άξονα : ONTARGET, ALTITUDE, NEFRON D, ORIENT
- Αναστολή ενδοθηλίνης : ASCEND, SONAR
- Στατίνες : CARDS
- Βιαταμίνη D : PRIMO, VITAL
- Βιταμίνη B : DIVINE
- Αντιοξειδωτικά : BEACON
- Ερυθροποιητίνη : TREAT
- Soludexine : SUN - MACRO



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

The ONTARGET Investigators*



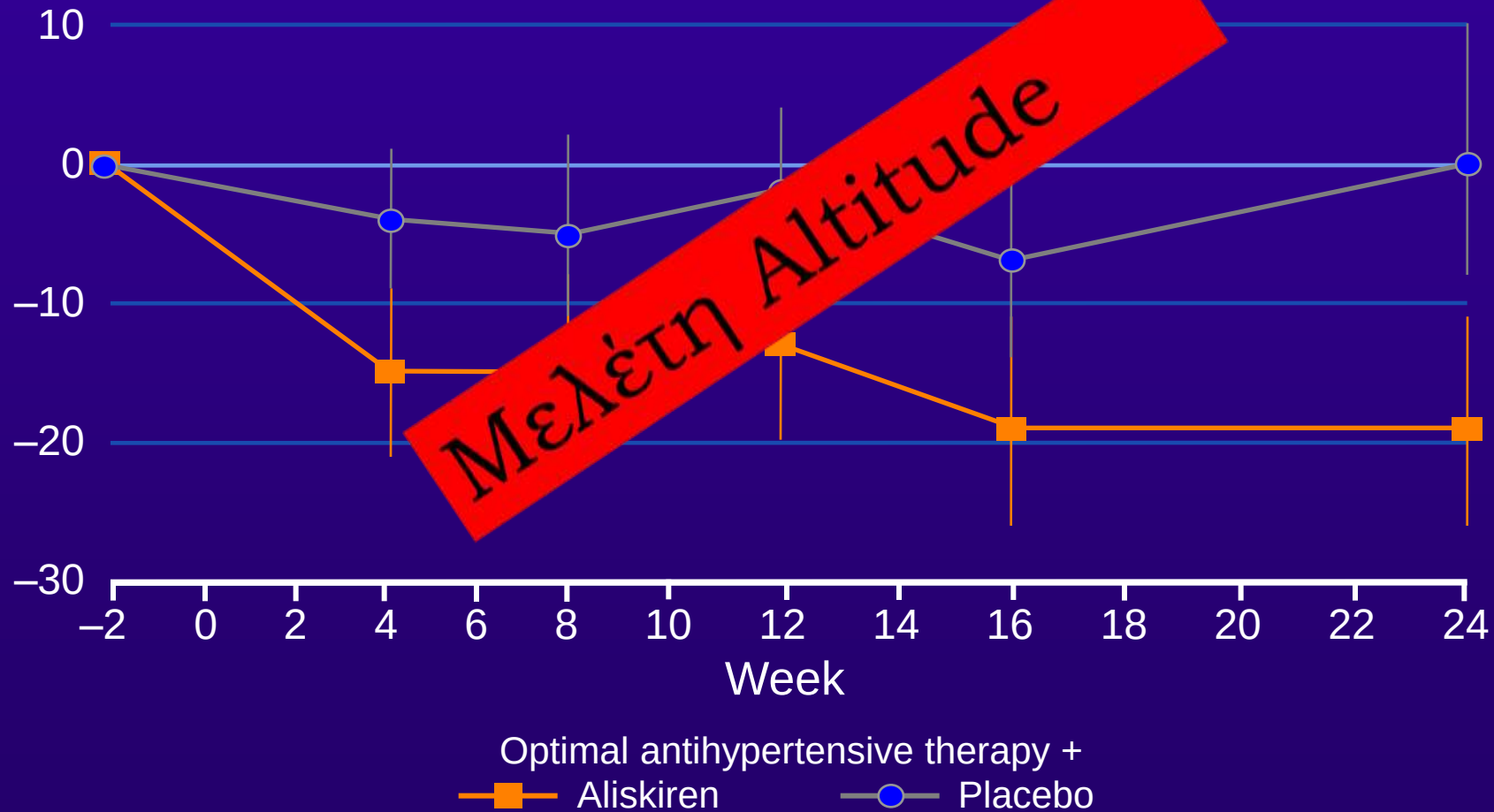
No. at Risk

Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718



Αποτελεσματικότητα της Aliskiren στο ΡΑΛ σε σχέση με το εικονικό φάρμακο

Geometric mean change from baseline in UACR (%)



Baseline was the Week -2 value

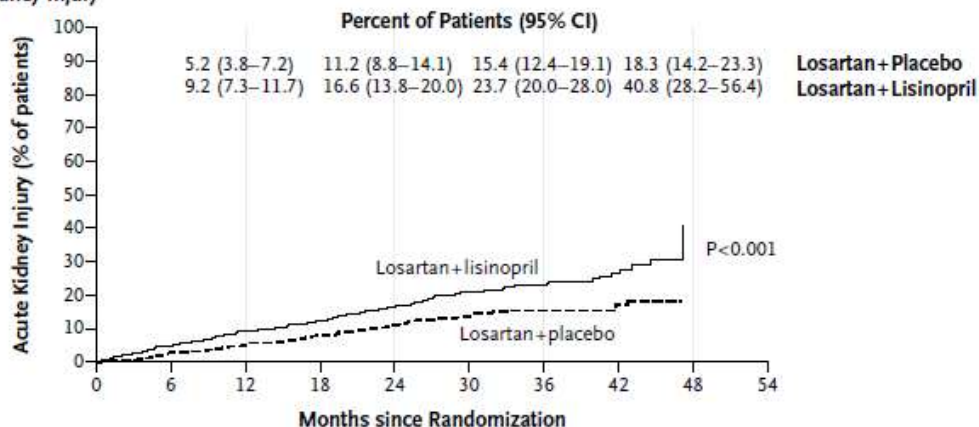
Data are shown as change from baseline in geometric mean (95% CI)

Parving *et al.* 2007



Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

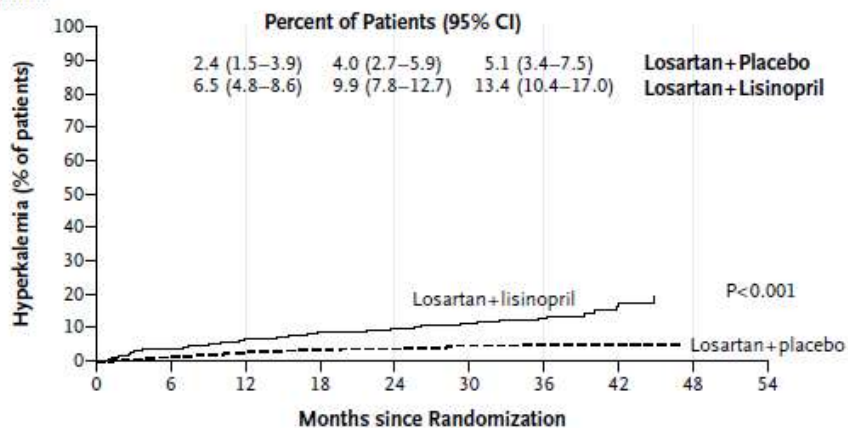
A Acute Kidney Injury



No. at Risk

Losartan+placebo	724	638	548	470	355	260	170	89	20
Losartan+lisinopril	724	630	528	453	341	251	156	78	7

B Hyperkalemia



No. at Risk

Losartan+placebo	724	648	563	487	379	271	174	90	20
Losartan+lisinopril	724	631	535	458	347	258	154	71	10

NEFRON – D TRIAL

- 1448 ΣΔτ2 με ΔΝ
- Διακοπή στα 2,2 χρόνια
- Αύξηση ΟΝΑ και υπερκαλιαιμίας



Αναστολή ενδοθηλίνης

ASCEND (Avosentan)

Διακοπή λόγω οιδημάτων και καρδιακή ανεπάρκεια

SONAR (Atrasentan ET-α)

Πληθυσμός 4148 ΣΔτ2

Έναρξη Μάιος 2013

Τέλος Νοέμβριος 2018



Vitamin D & its analogues in type 2 diabetic nephropathy: a systematic review

Mrunalini K Chokhandre^{1*}, Mahmoud I Mahmoud¹, Tahir Hakami¹, Mohammed Jafer² and Aadil S Inamdar²

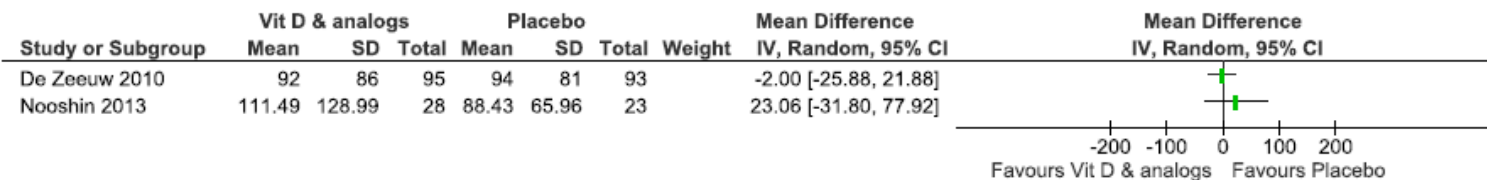


Fig. 2 Forest Plot - Vit D & analogs in Kidney functions in DN - UACR

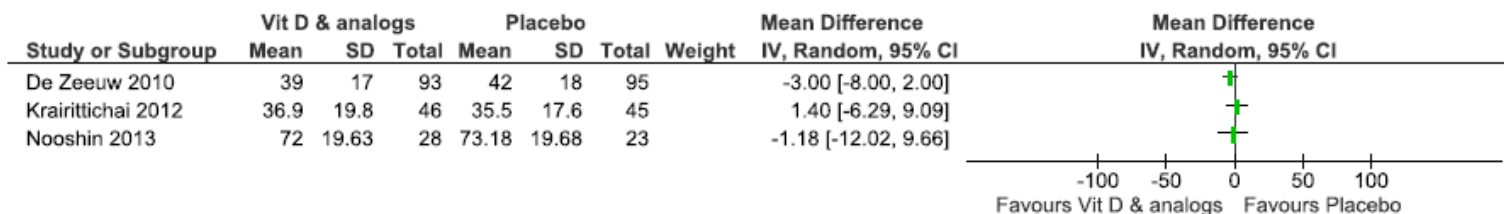
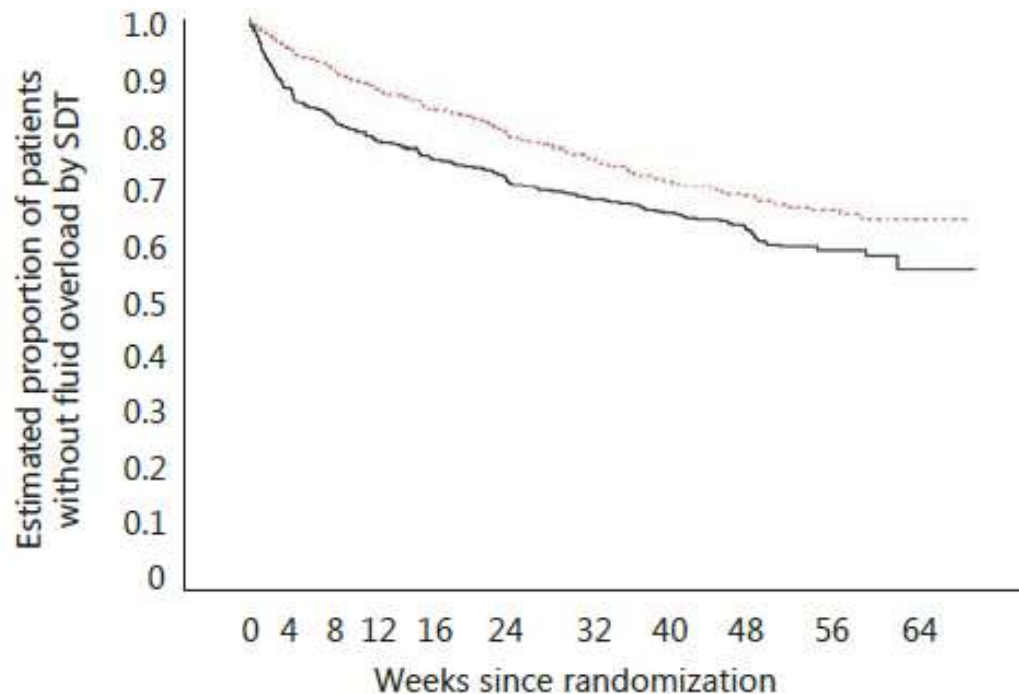


Fig. 3 Forest Plot - Vit D & analogs in Kidney functions in DN - eGFR



Mechanisms Contributing to Adverse Cardiovascular Events in Patients with Type 2 Diabetes Mellitus and Stage 4 Chronic Kidney Disease Treated with Bardoxolone Methyl



BEACON TRIAL

Αύξηση ΚΑ συμβαμάτων :

- ΚΑ θάνατοι
- Νοσηλεία για ΚΑ
- Μη θανατηφόρα ΑΕΕ
- Μη θανατηφόρα ΕΜ

Αύξηση eGFR και ΑΠ



Δράση του SULODEXIDE στο AER

(glycosaminoglycan mixture of 80% heparan sulfate and 20% dermatan sulfate)

Albuminuria	Parameter	Sulodexide Group	Control Group
Macro-	AER0 (mg/24hours)	1620	1534
	AER6 (mg/24hours)	1083	1544
	%AER6 (°)	66.9 (60.2 - 74.4)	100.6 (91.2 - 111.1)
	%AER6 ratio between groups (^)	0.665 (0.575 - 0.768) (*)	
Micro-	AER6 (mg/24hours)	117	367
	%AER6 (°)	58.0 (52.8 - 63.9)	139.4 (126.8 - 153.4)
	%AER6 ratio between groups (^)	0.416 (0.364 - 0.476) (*)	
	AER12 (mg/24hours)	77	458
	%AER12 (°)	38.1 (34.5 - 42.1)	173.9 (157.4 - 192.1)
	%AER12 ratio between groups (^)	0.219 (0.190 - 0.253) (*)	

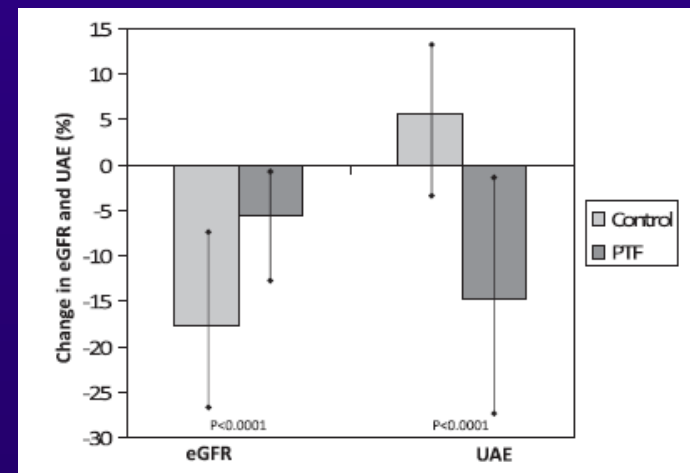
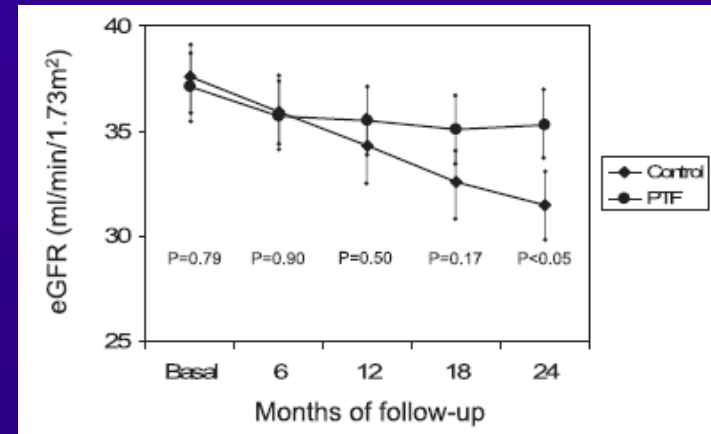
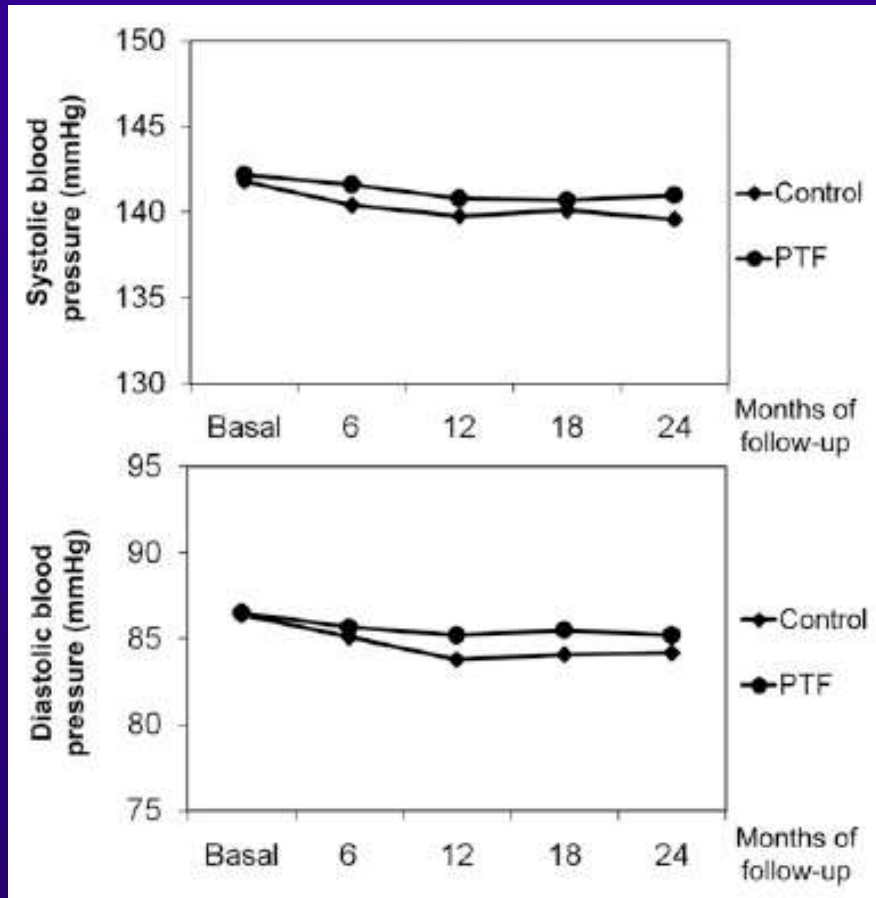
Μελέτη SUN-MACRO απέτυχε να δείξει σταθεροποίηση ή μη εξέλιξη σε έκδηλο λευκωματουρία

Pckham D et al., J Am Soc Nephrol 2012

°) AER as % of baseline (AER6 / AER0 x100 or AER12 / AER0 x100).
^) Sulodexide / Control.
*) p = 0.0001.



Effect of Pentoxifylline on Renal Function and Urinary Albumin Excretion in Patients with Diabetic Kidney Disease: The PREDIAN Trial





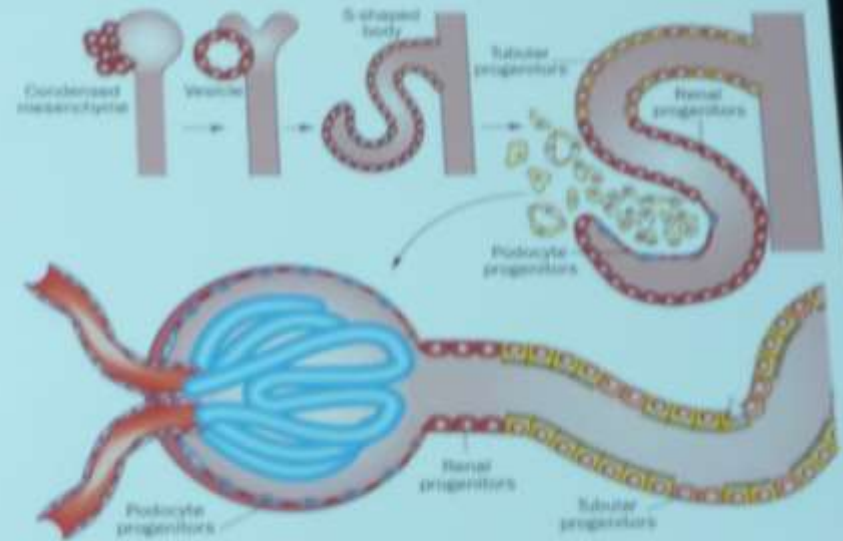
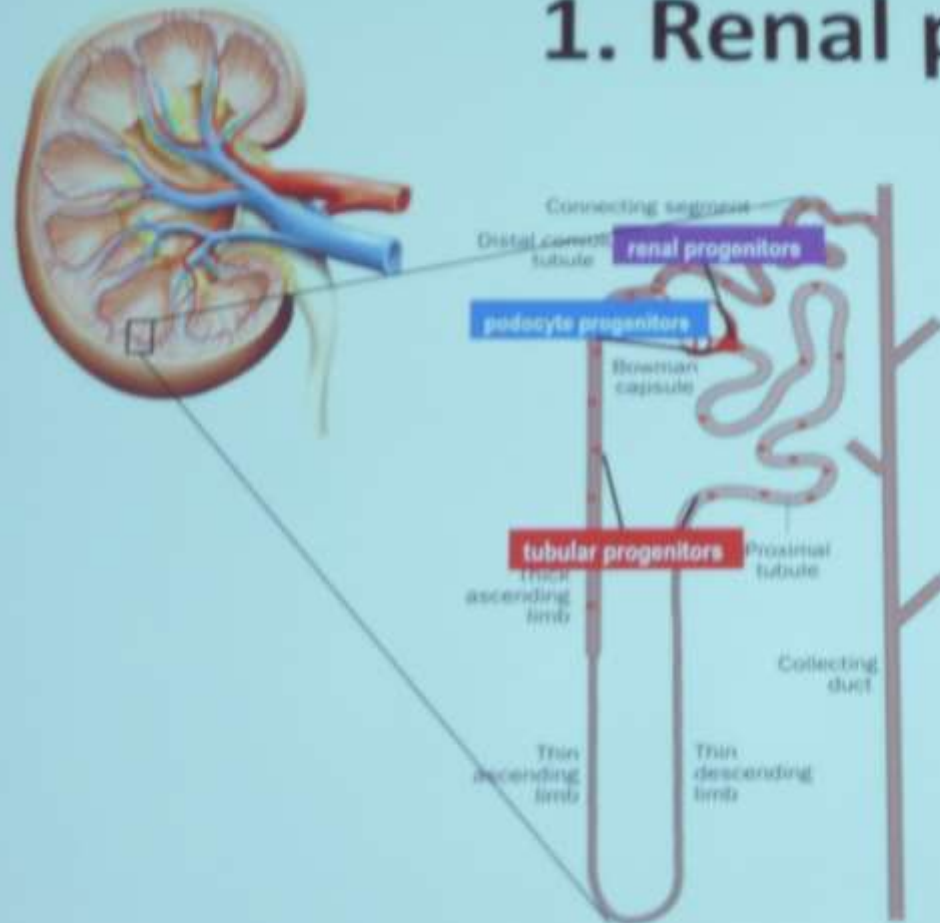
New Therapies for Diabetic Kidney Disease

Unfortunately, the failure rate of new drug therapies in clinical trials is extraordinarily high, exceeding **90%** overall; even in phase 3 trials, it is still approximately **50%**

Himmelfard J and Tuttle K, NEJM, Dec 26, 2013

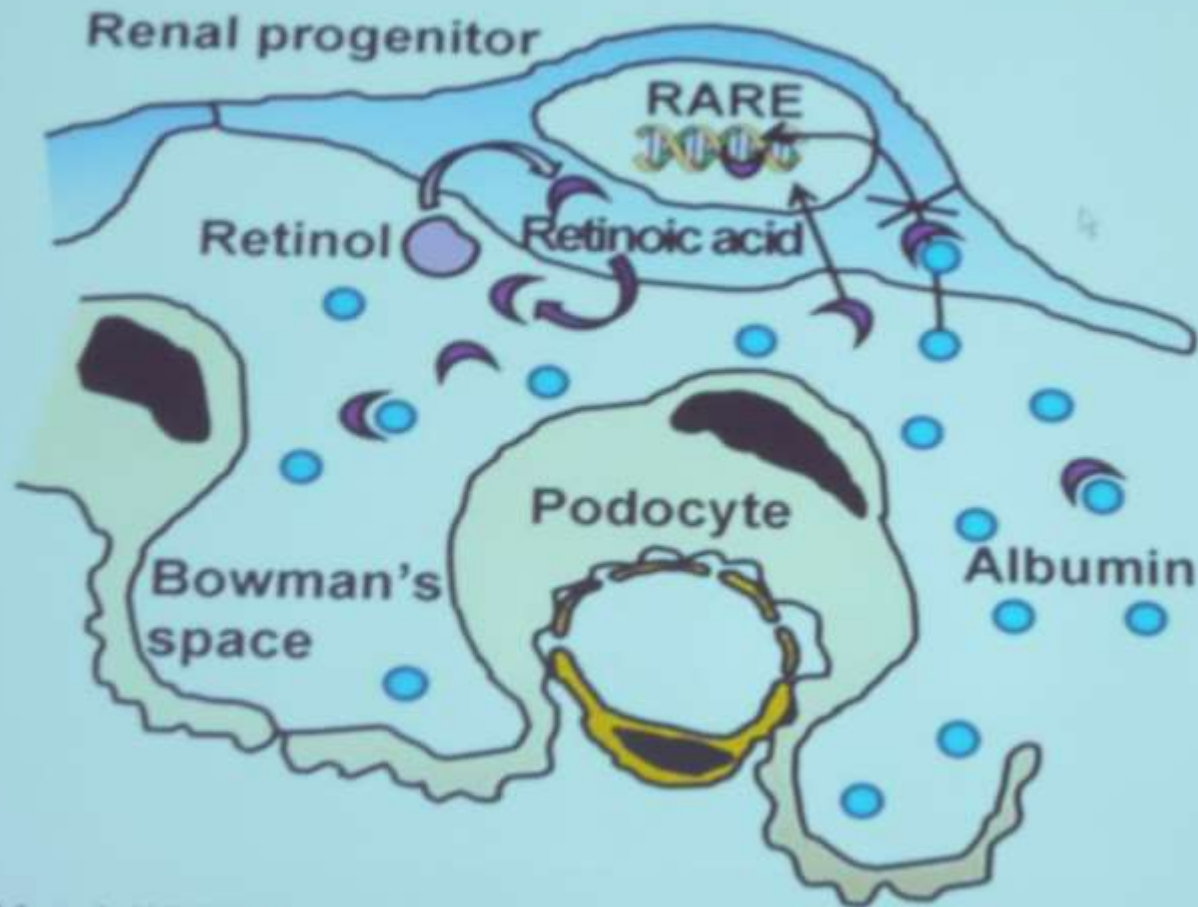


1. Renal progenitors



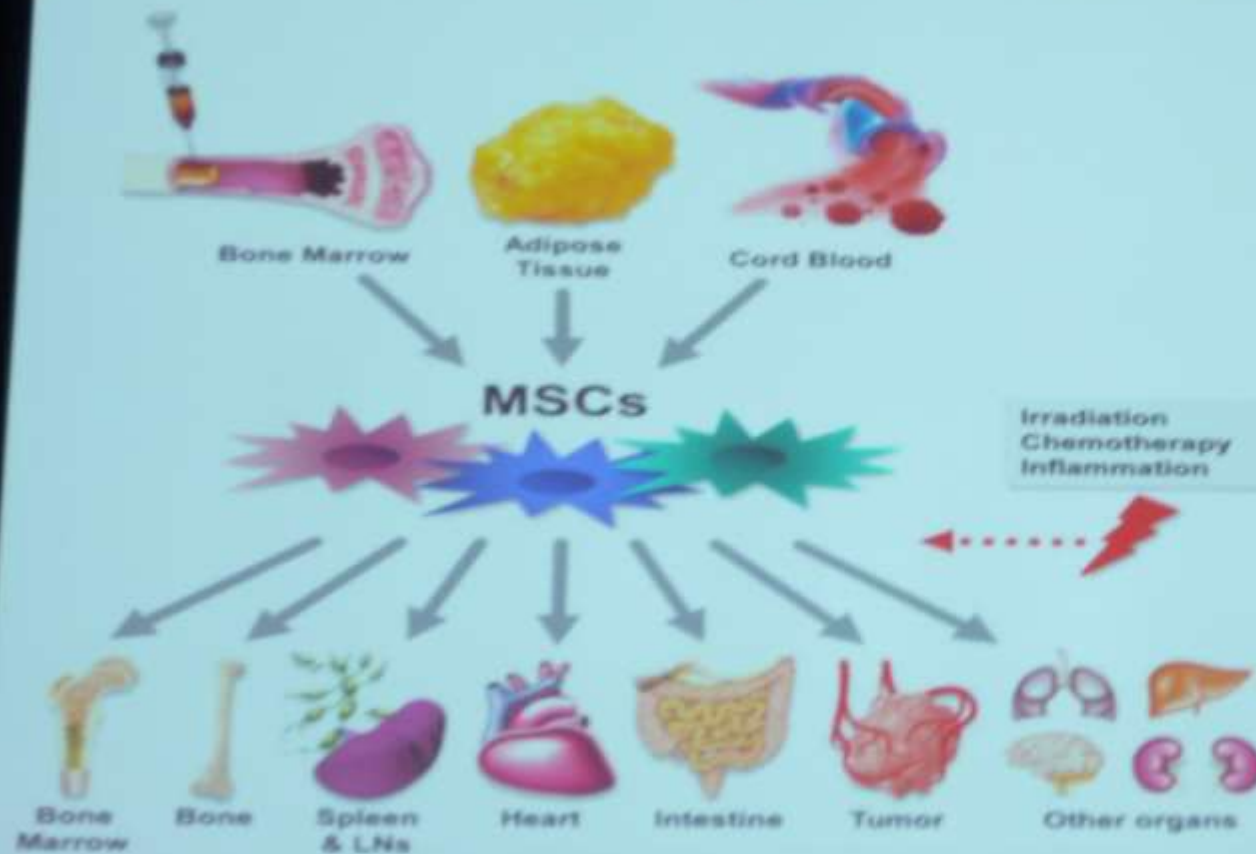


Proteinuria impairs renal progenitors differentiation into podocytes





2. Mesenchymal stromal cells (MSC)



Anders HJ et al. NEPHSTROM Consortium in preparation



Strategies for stem cell-based therapy for kidney disorders

1. *Renal progenitors*
 - Cell therapy
 - Modeling
 - Drug-mediated kidney regeneration
2. *Mesenchymal stromal cells*
 - Cell therapy
 - Anti-inflammatory
 - Kidney regeneration by enhancing renal progenitor activity
3. *iPSC and kidney organoids* ——— Disease modeling



Επίδραση της φαρμακευτικής αγωγής στην εξέλιξη της ΔΝ

Γλιταζόνες: ευεργετική δράση στη ΔΝ ανεξάρτητα από το υπογλυκαιμικό αποτέλεσμα

Yang J. et al., Clin. Sci, 116,2009
Thomas M et al., PPAR Res. 2012

Αναστολείς DPP-4: Λιναγλιπτίνη : μειώνει την απέκκριση λευκωματίνης

Groop PH et al., Diabetes Care 36 (11),Nov, 2013

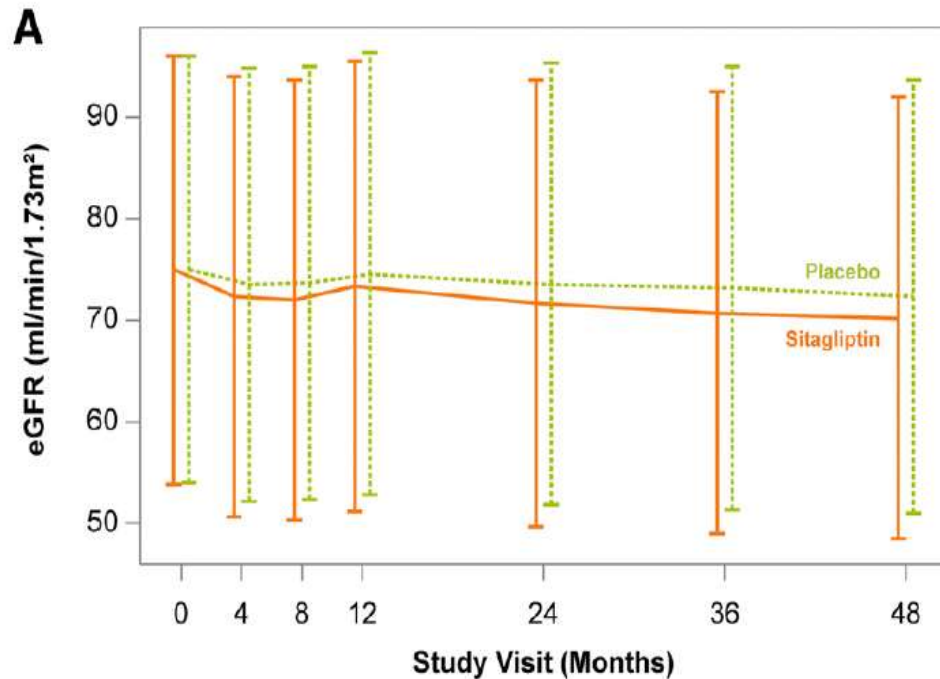


Effect of Sitagliptin on Kidney Function and Respective Cardiovascular Outcomes in Type 2 Diabetes: Outcomes From TECOS

DOI: 10.2337/dc16-1415

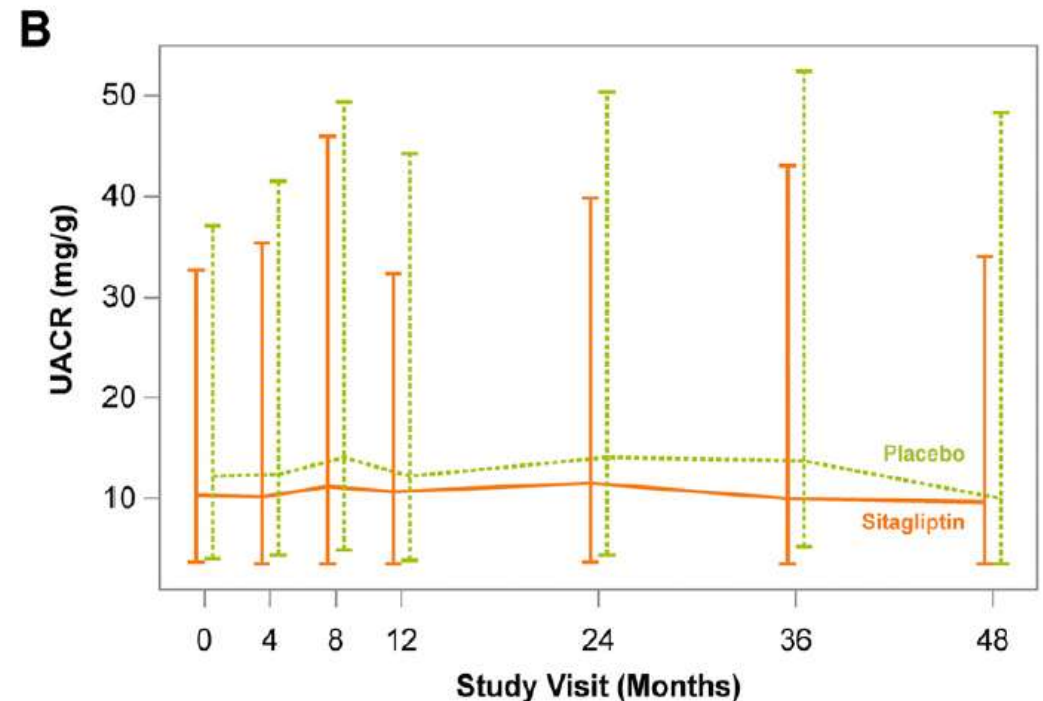


Jan H. Cornel,¹ George L. Bakris,²
 Susanna R. Stevens,³ Michael Alvarsson,⁴
 Willem A. Bax,¹ Lee-Ming Chuang,⁵
 Samuel S. Engel,⁶ Renato D. Lopes,⁷
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 Helena Wachslicht Radbard,⁹
 Isaac Sinay,¹⁰ Tsvetelina Tankova,¹¹
 Julia Walinstein,¹² Eric D. Peterson,³ and
 Rury R. Holman,^{1,3} on behalf of the TECOS
 Study Group



Number of Patients:

Sitagliptin	6,809	4,135	3,809	5,263	5,553	3,291	1,360
Placebo	6,795	4,169	3,772	5,197	5,482	3,165	1,335



Number of Patients:

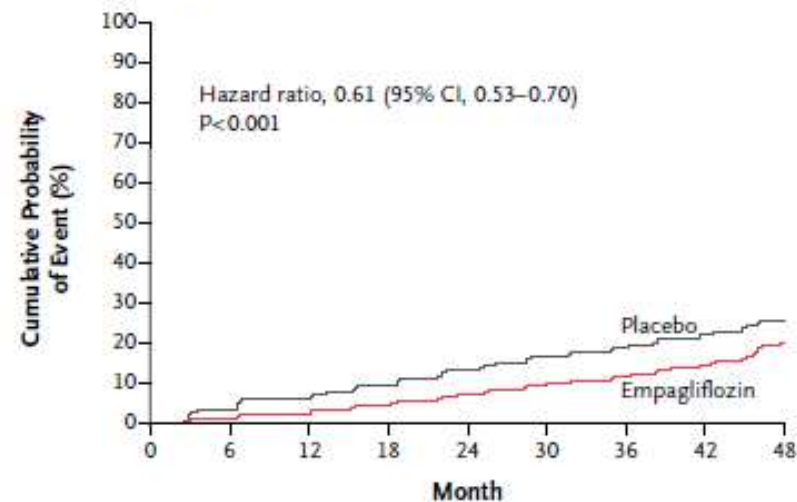
Sitagliptin	1,949	687	664	1,171	1,054	562	276
Placebo	1,883	730	640	1,129	1,006	580	273

A: eGFR over 4 years (N = 13,604). B: UACR over 4 years (N = 3,832)



Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

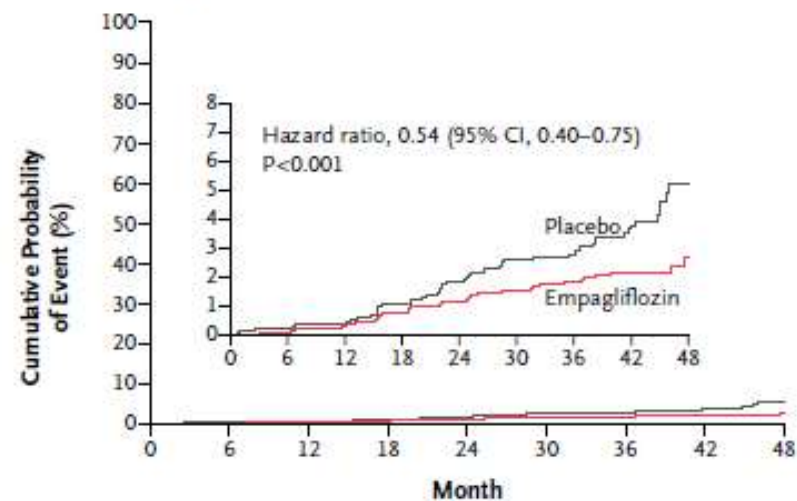
A Incident or Worsening Nephropathy



No. at Risk

Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

B Post Hoc Renal Composite Outcome



No. at Risk

Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

The New England Journal of Medicine

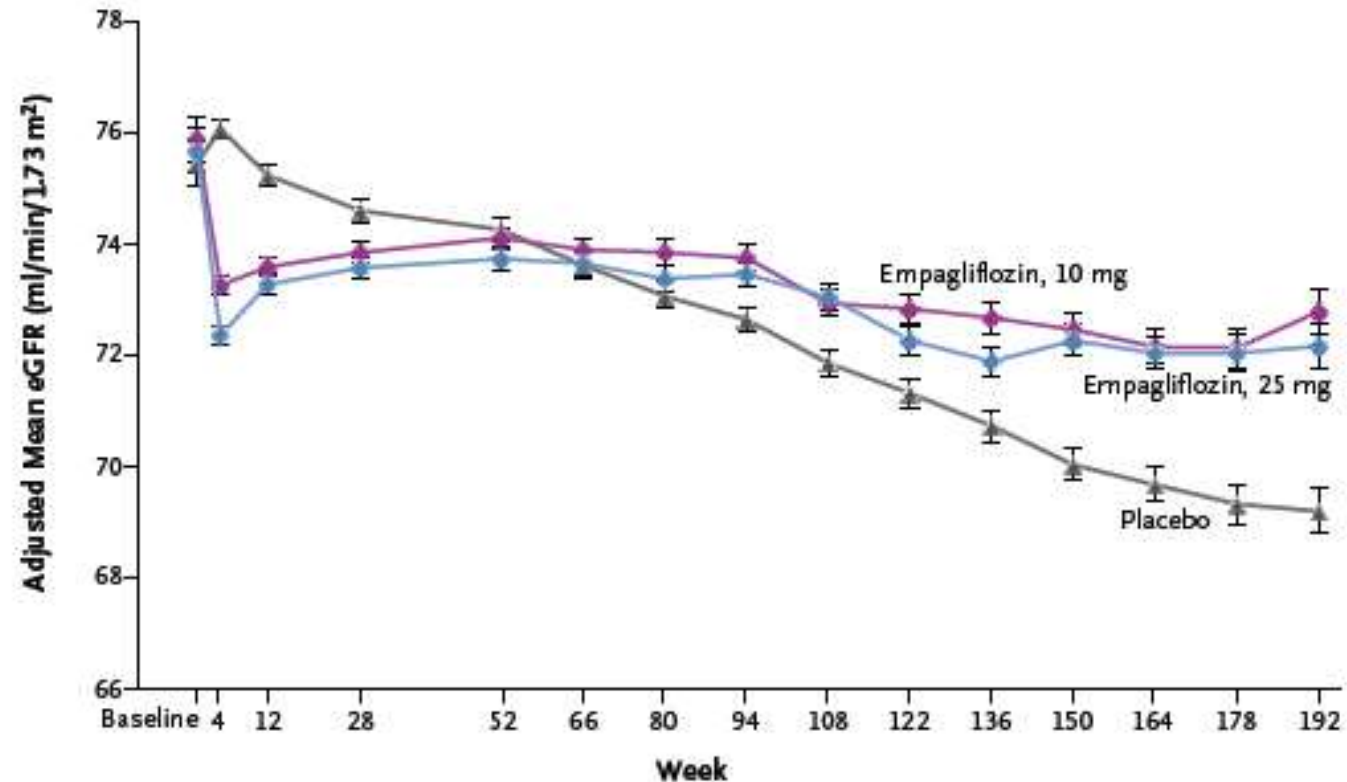
Downloaded from nejm.org on June 18, 2016. For personal use only. No other uses without permission.

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Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

A Change in eGFR over 192 Wk



Most at Risk



The NEW ENGLAND JOURNAL *of* MEDICINE

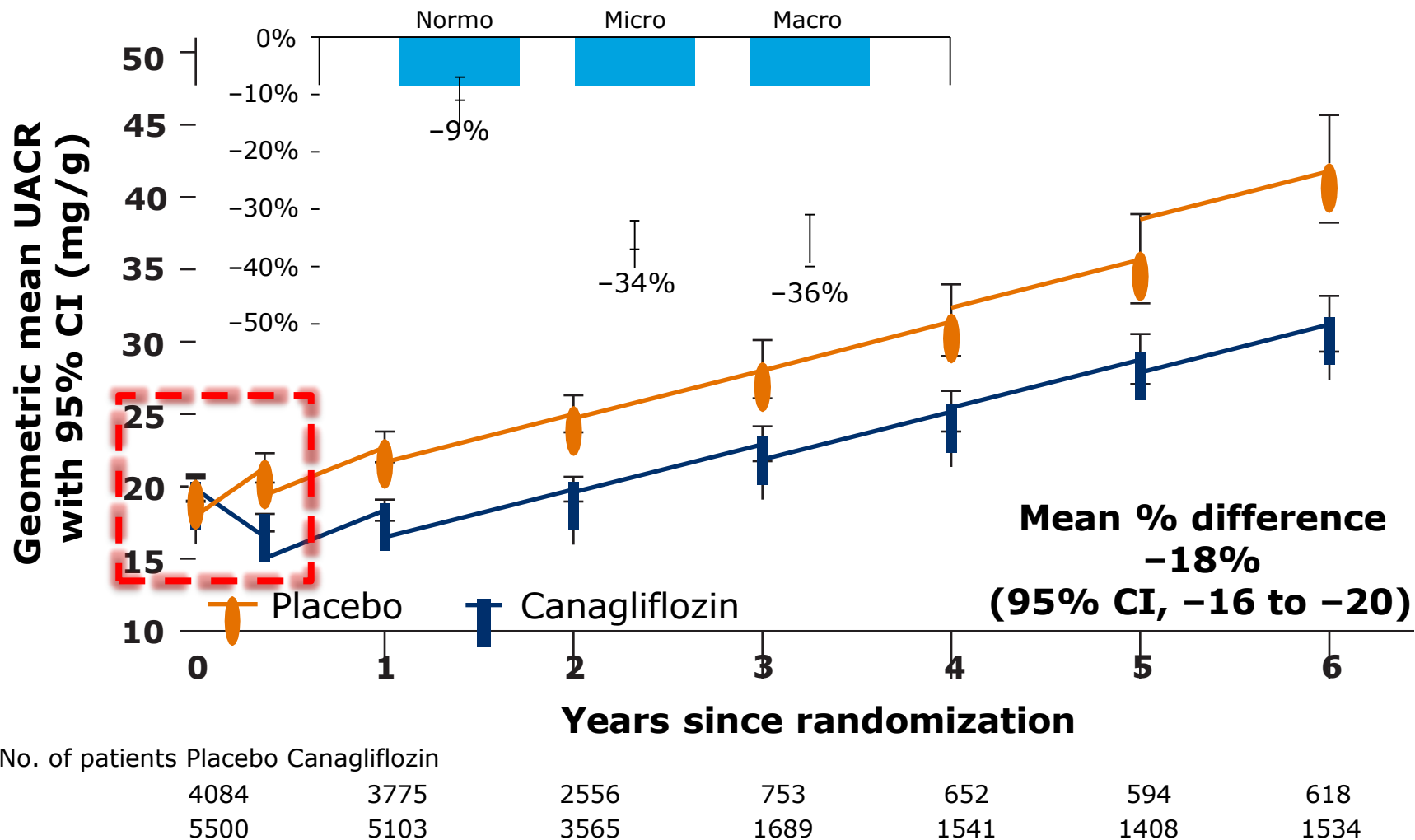
ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

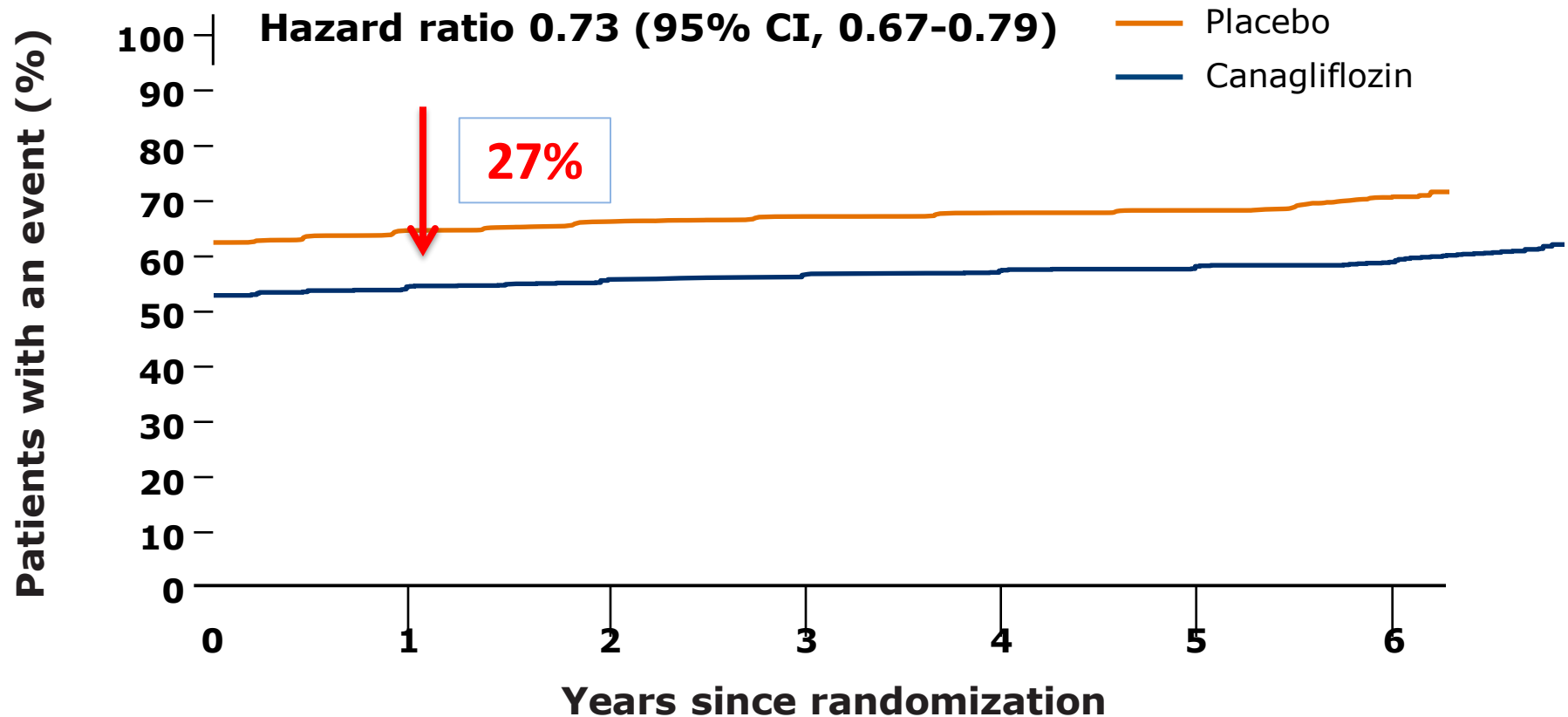
Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D.,
Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D.,
Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D.,
Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch.,
for the CANVAS Program Collaborative Group*

Μεταβολή του λόγου Αλβουμίνης/Κρεατινίνης (UACR)

Percent Change in UACR per Albuminuria Class (inset)



Εξέλιξη/Επιδείνωση της Αλβουμινουρίας

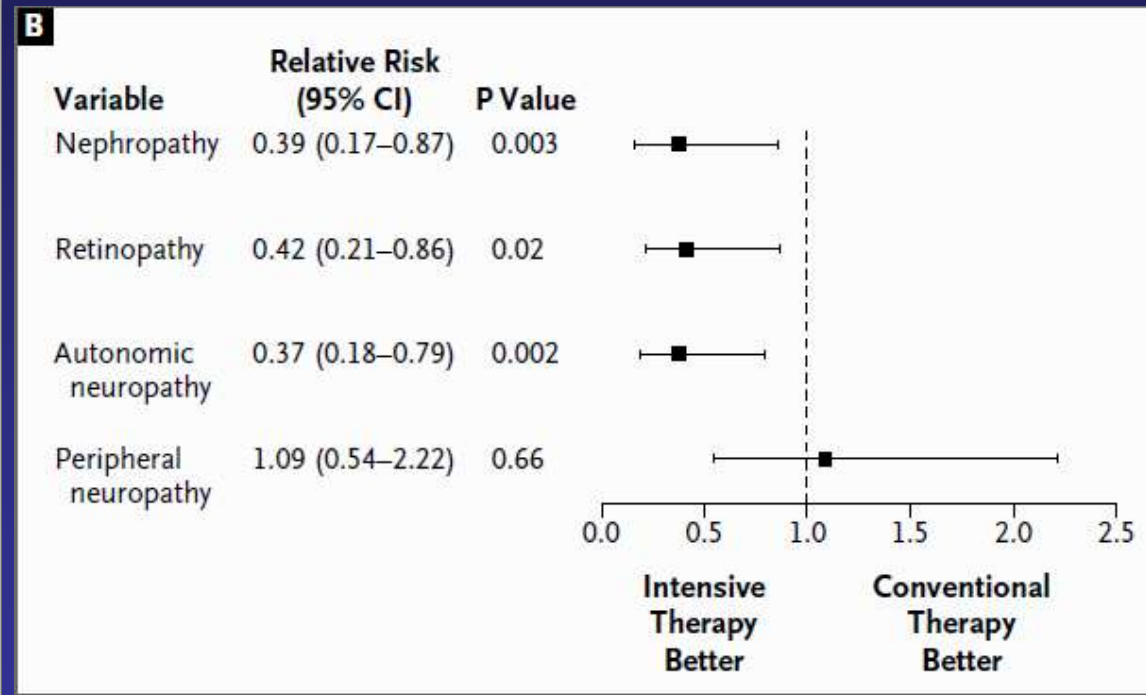
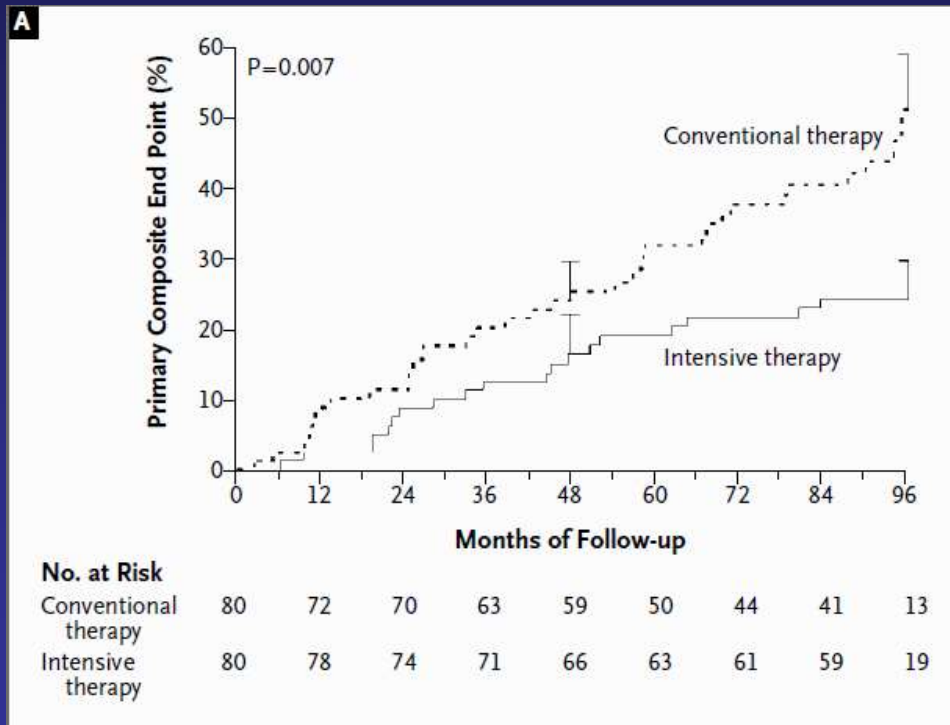


No. of patients Placebo

Canagliflozin	3819	3096	1690	724	626	548	303
	5196	4475	2968	1730	1528	1354	775



Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes





Θεραπευτική προσέγγιση σε διαβητικό με ΧΝΝ

1. Ρύθμιση σακχάρου αίματος
2. Ρύθμιση αρτηριακής πίεσης
3. Αναστολή συστήματος ΡΑΑ
4. Πολυπαραγοντική παρέμβαση (Δίαιτα, άσκηση, κάπνισμα)

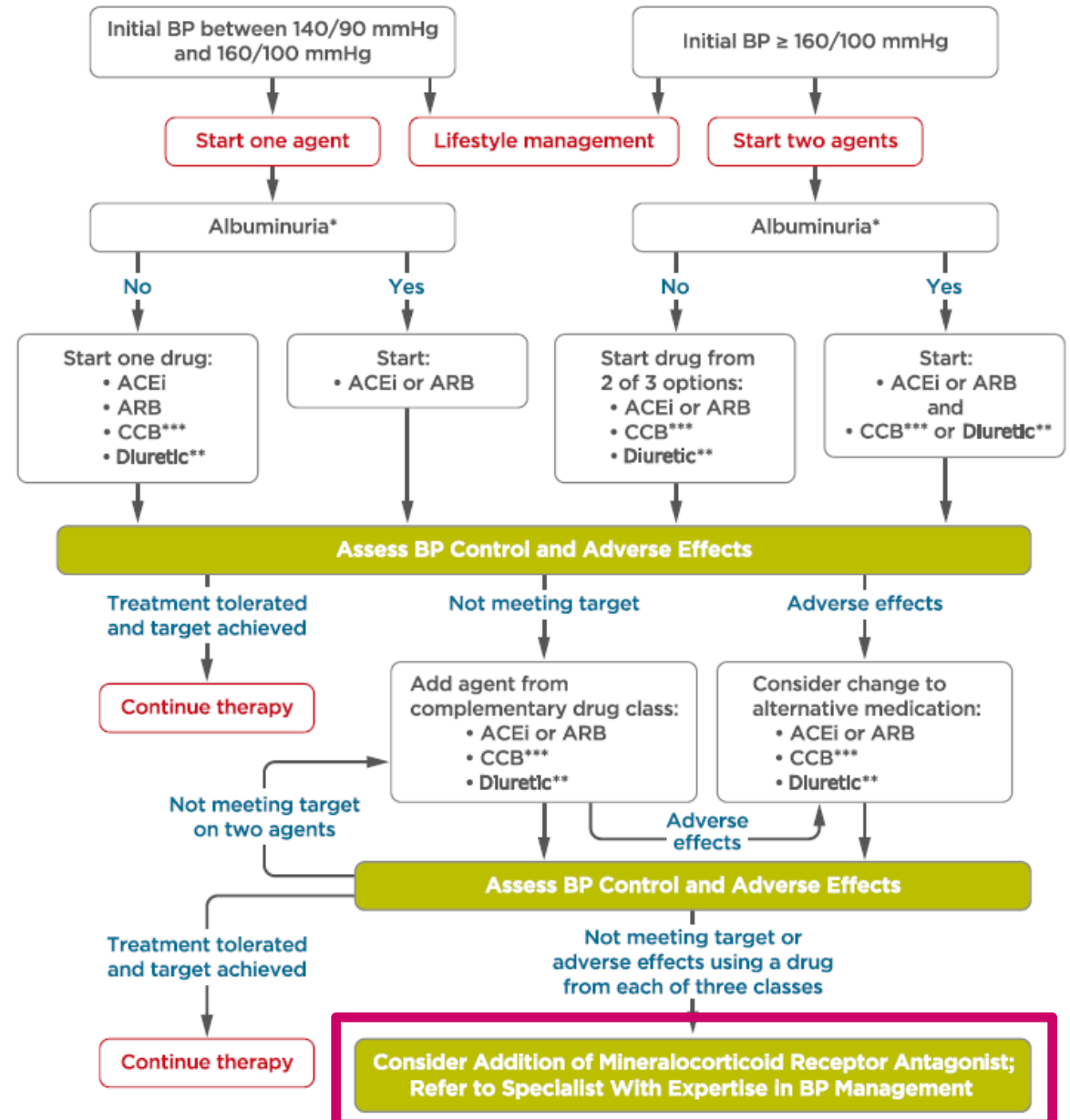


Diabetes and Hypertension: A Position Statement by the American Diabetes Association

Diabetes Care 2017;40:1273–1284 | <https://doi.org/10.2337/dc17-0026>

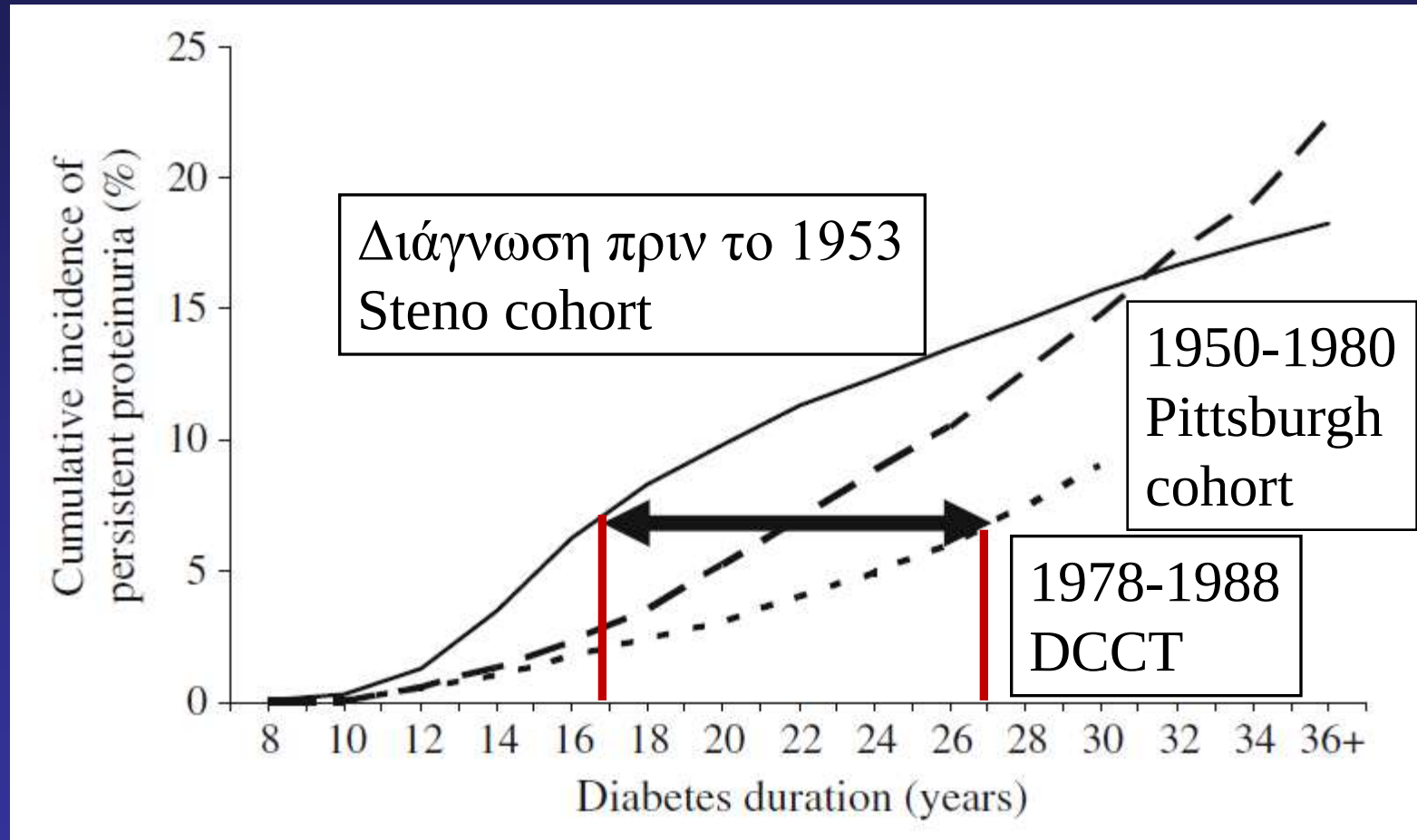
Kim H. de Boer,¹ Sripal Bangalore,²
Athanasios Benetos,³ Andrew M. Davis,⁴
Erin D. Michos,⁵ Paul Muntner,⁶
Peter Rossing,⁷ Sophia Zoungas,⁸ and
George Bakris⁴

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes





Diabetic nephropathy in type 1 diabetes: has the outlook improved since the 1980s?



ΕΥΧΑΡΙΣΤΩ
ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ

