

**HELLENIC SOCIETY
OF NEPHROLOGY**
MEETING & SEMINAR

Combined with:

**18th BANTAO
CONGRESS**

October 19-22, 2023

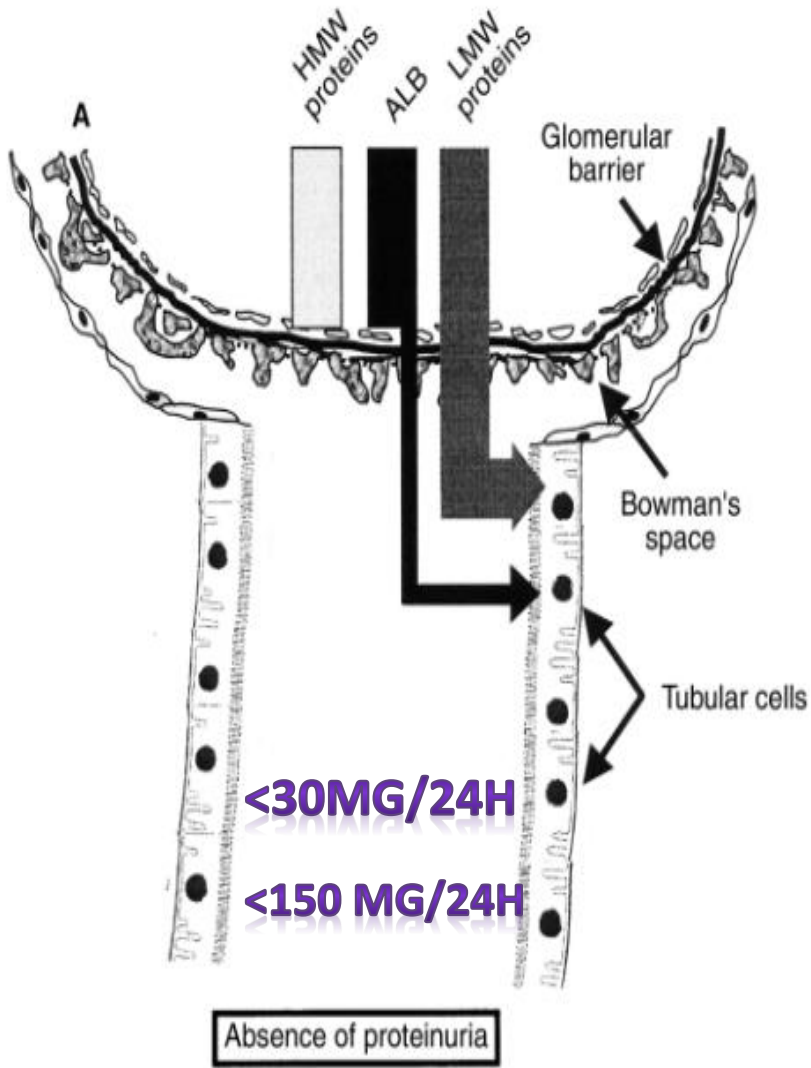
Makedonia Palace Hotel THESSALONIKI, GREECE



Σακχαρώδης Διαβήτης ΧΝΝ

Η λευκωματουρία ως θεραπευτικός στόχος

*Πελαγία Κρίκη
Νεφρολόγος
Π.Γ.Ν.Αλεξανδρούπολης*

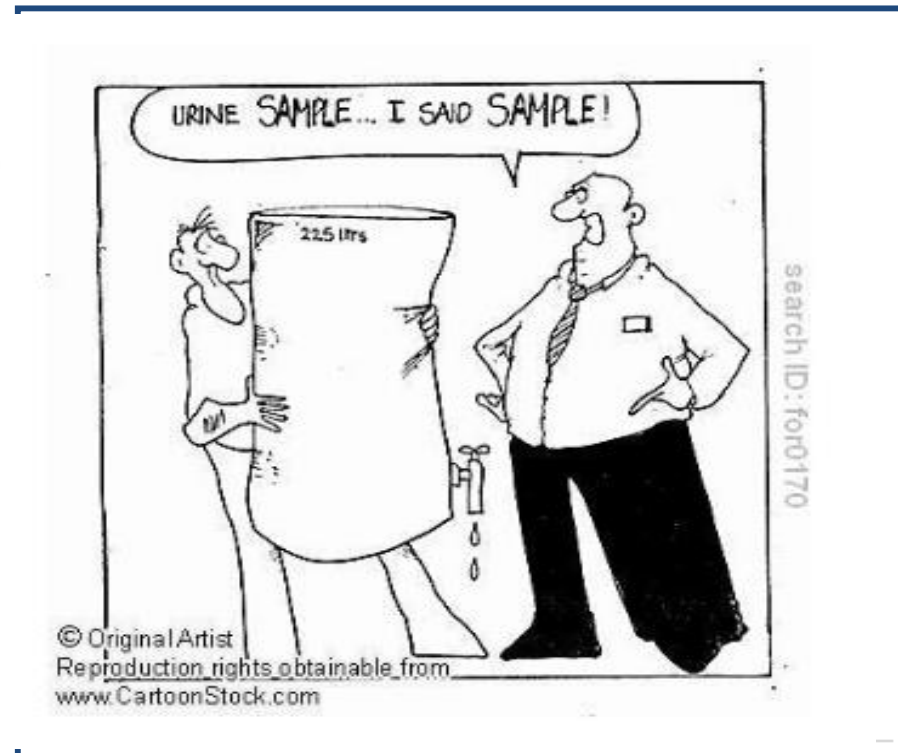


< 150 mg πρωτεΐνης /24ωρο

- ✓ αλβουμίνη : 20–40 %
- ✓ ανοσοσφαιρίνες :20%,
- ✓ β2-μικροσφαιρίνη
- ✓ πρωτεΐνη Tamm Horsfall

Πώς πρέπει να μετράται η αλβουμινουρία ;

Test	
Dipstick	Ημιποσοτική μέθοδος
24h συλλογή (AER,PER)	Δύσκολη Συχνά ανακριβής
PCR	Πρωινό δείγμα Καλύτερος τρόπος ελέγχου
ACR	Πρωινό δείγμα Καλύτερος τρόπος ελέγχου



$$\frac{\text{Urine albumin (mg/dL)}}{\text{Urine creatinine (g/dL)}} = \text{UACR in mg/g} \approx \text{Albumin excretion in mg/day}$$

How to screen?



Spot urine ACR

and



eGFR

Albumin / Protein mg/dL

Creatinine [mg/dL](#) ▼

Albumin : creatinine ratio

ACR / PCR mg/g

Albumin Creatinine Ratio Calculator

Created by [Dominika Śmiałek](#), MD, PhD candidate

Reviewed by [Dominik Czernia](#), PhD and [Jack Bowater](#)

Based on research by [Mattix HJ](#), [Hsu CY](#), [Shaykevich S](#), [Curhan G](#).

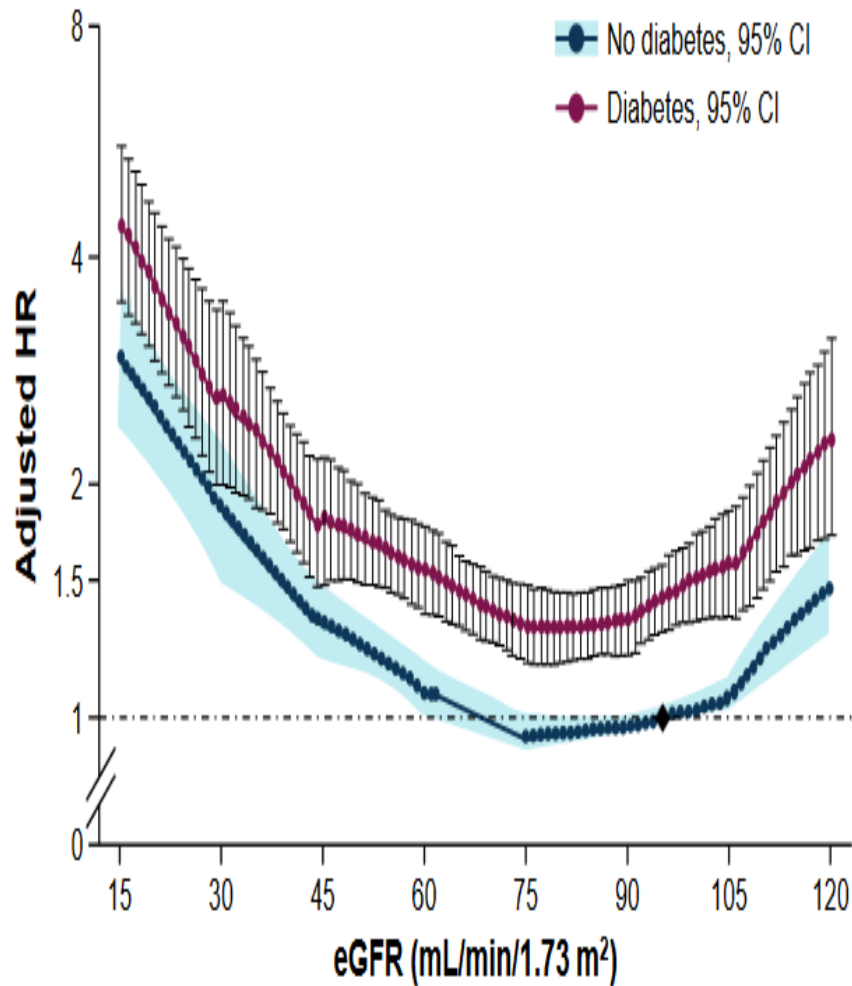
["Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race."](#) Journal of the American Society of Nephrology (April 2002)

KDIGO 2012 Clinical Practice Guideline: Albuminuria

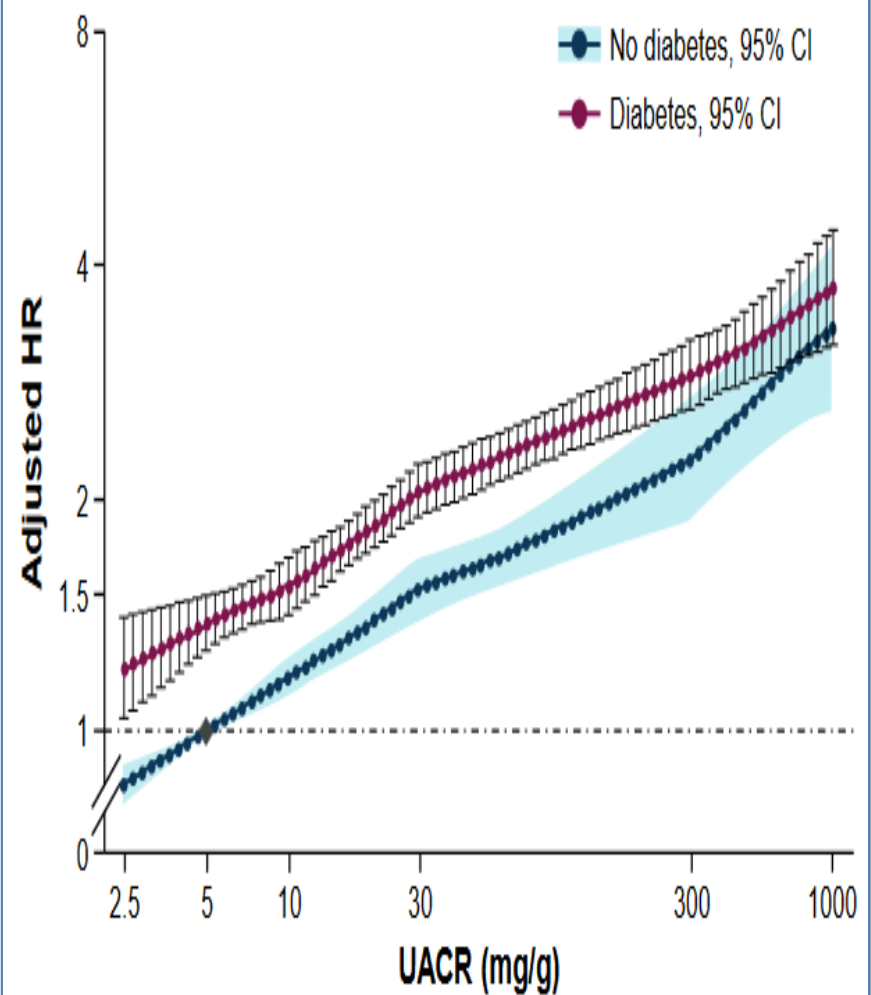


	A1- Normal to mildly increased	A2- Moderately increased	A3- Severely increased
AER	<30mg/24h	30-300mg	>300mg
PER	<150mg/24h	150-500mg	>500mg
ACR	<30mg/g Cr	30-300 mg/gr Cr	>300mg/gr Cr
PCR	<150 mg/g Cr	150-500 mg/g Cr	>500 mg/gr Cr

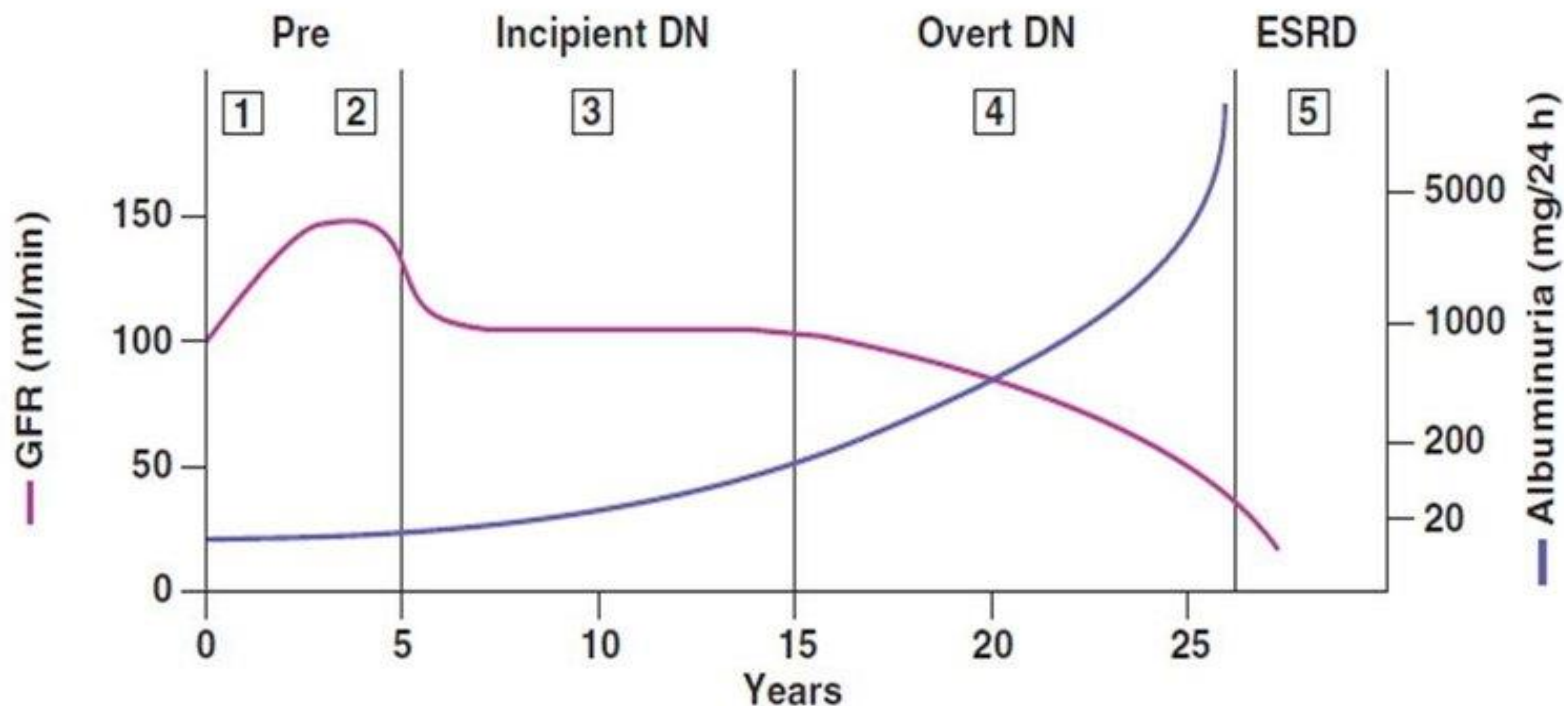
Risk of all-cause mortality according to eGFR in individuals with and without diabetes^{a-c}



Risk of all-cause mortality according to UACR in individuals with and without diabetes^{a-c}



Natural History of Type 1 Diabetic Nephropathy



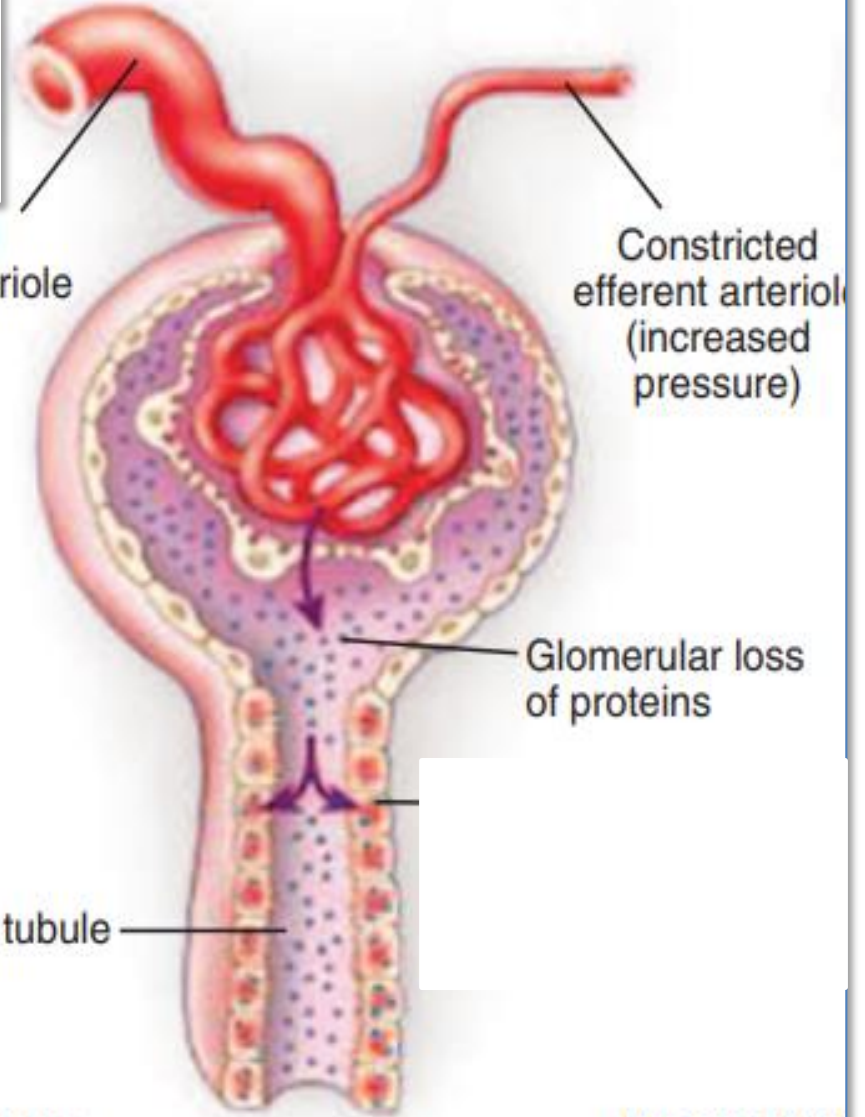
Stage	Pre	Incipient	Overt
Functional	GFR ↑ (25%–50%)	Microalbuminuria, hypertension	Proteinuria, nephrotic syndrome, GFR ↓
Structural	Renal hypertrophy	Mesangial expansion, GBM thickening, arteriolar hyalinosis	Mesangial nodules (Kimmelstiel-Wilson lesions) Tubulointerstitial fibrosis

Normal



↑ IGF-1
VEGF
PG
NO

Diabetes



Dilated afferent arteriole

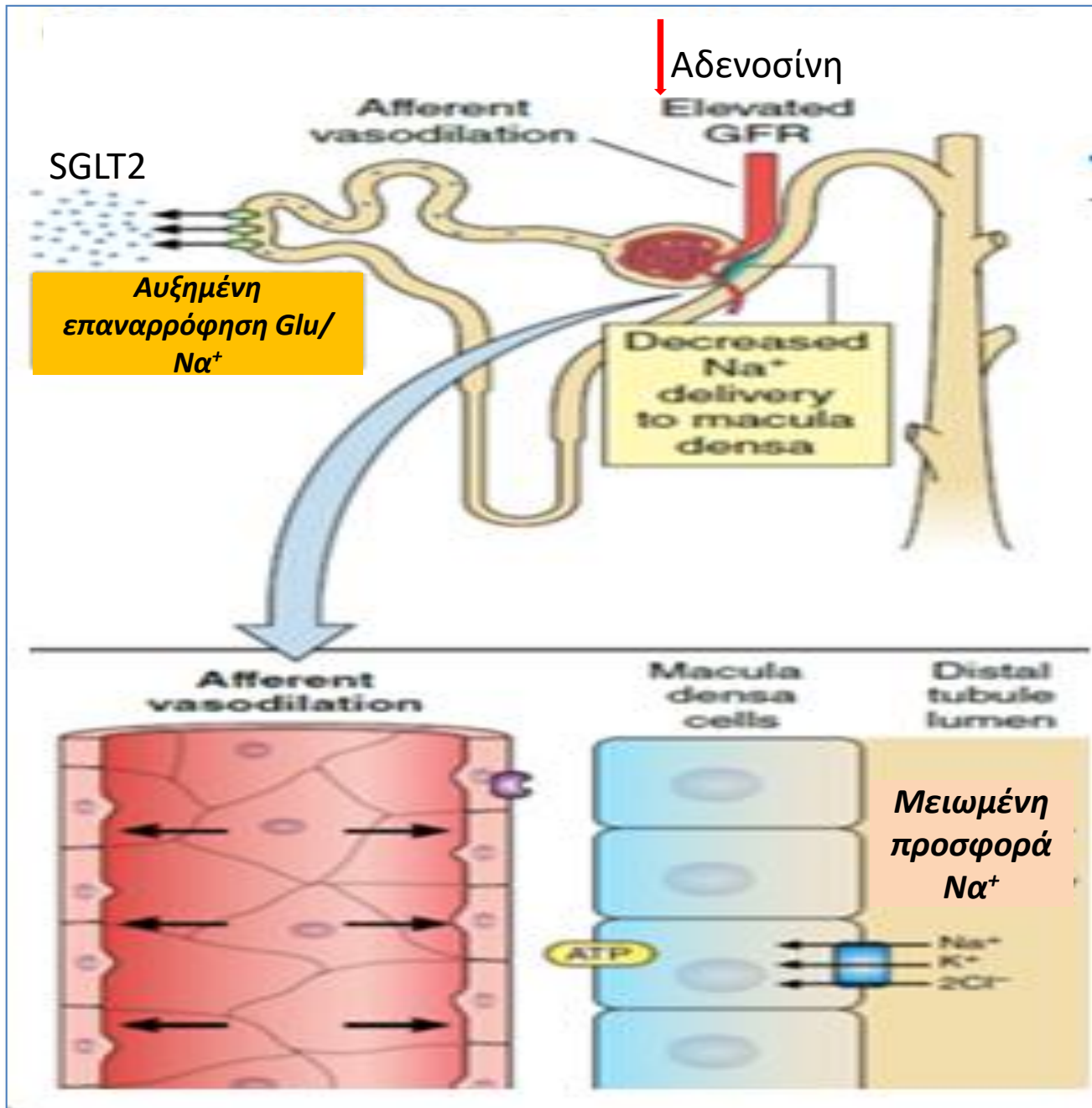
Constricted efferent arteriole (increased pressure)

Glomerular loss of proteins

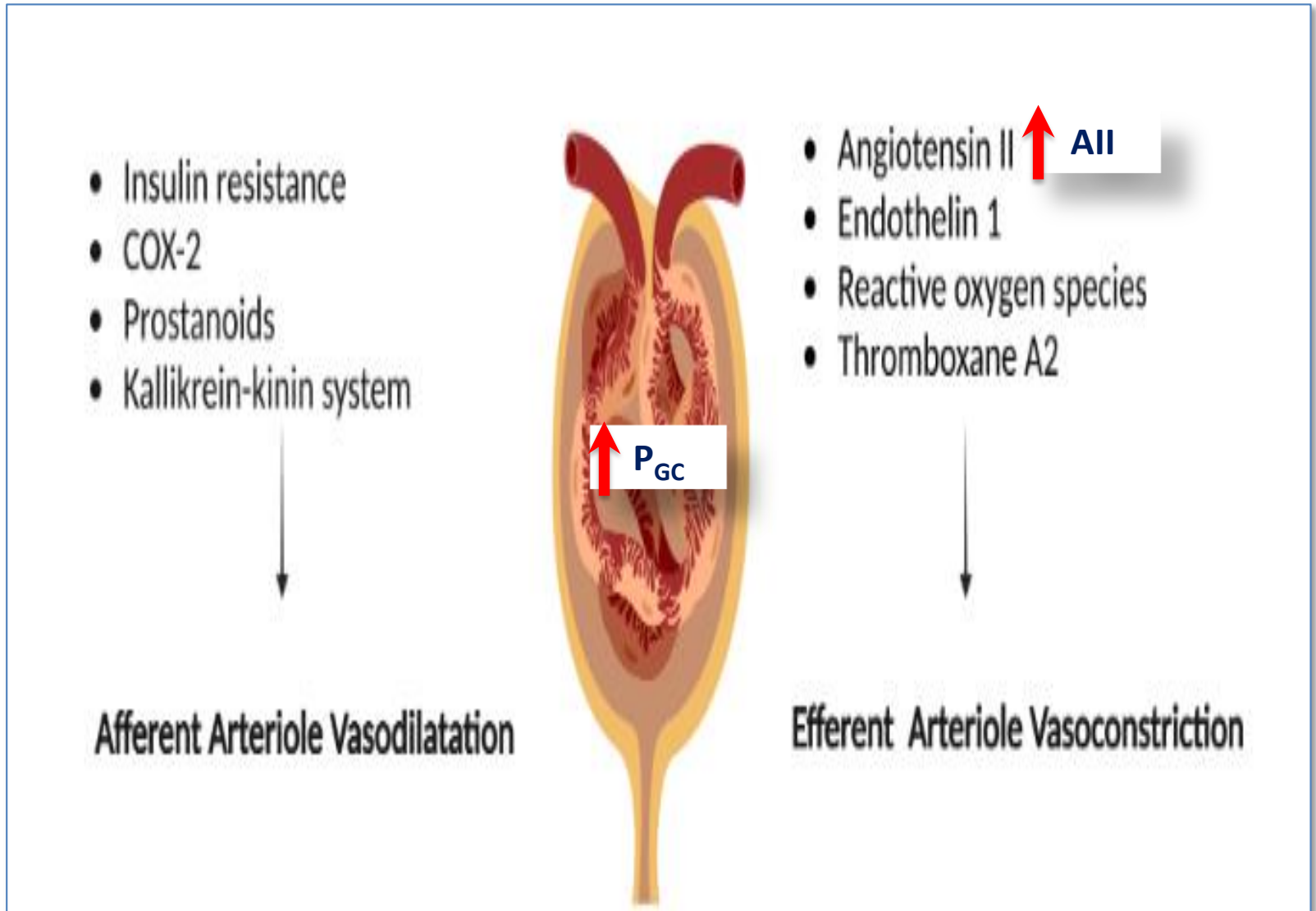
Proximal tubule

Glomerulus

Proximal tubule

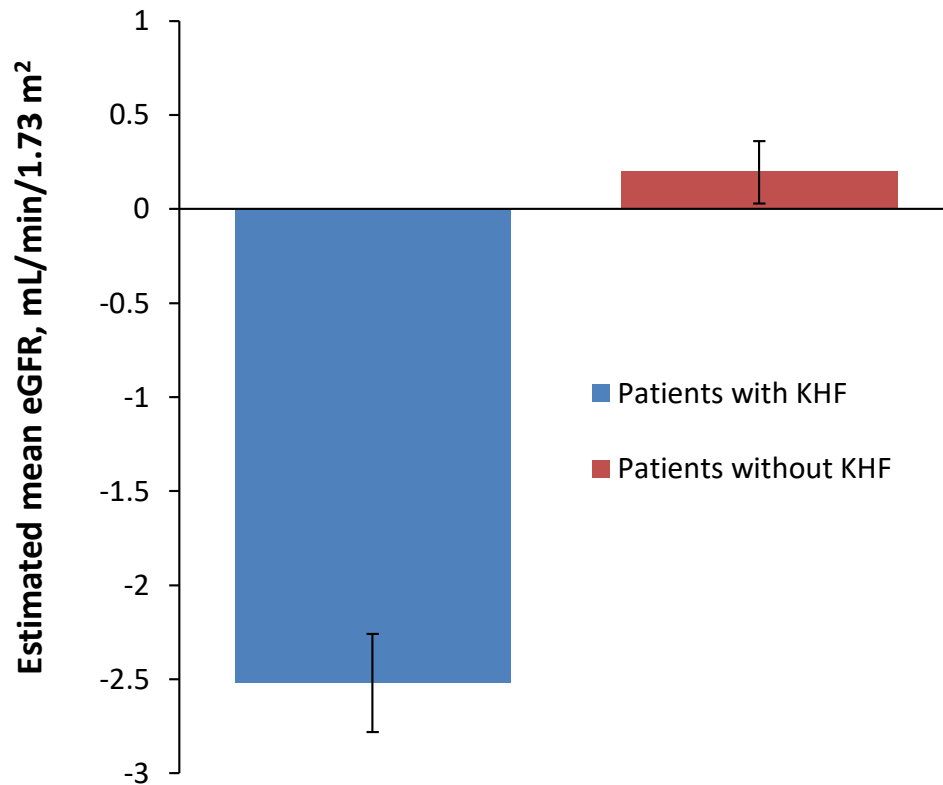


Αιμοδυναμική απορρύθμιση του σπειράματος

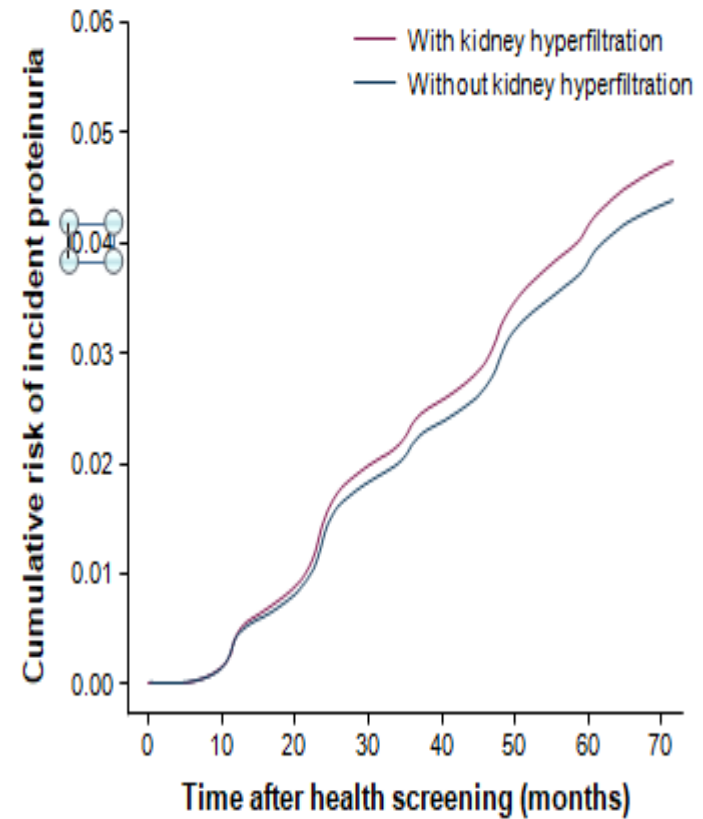


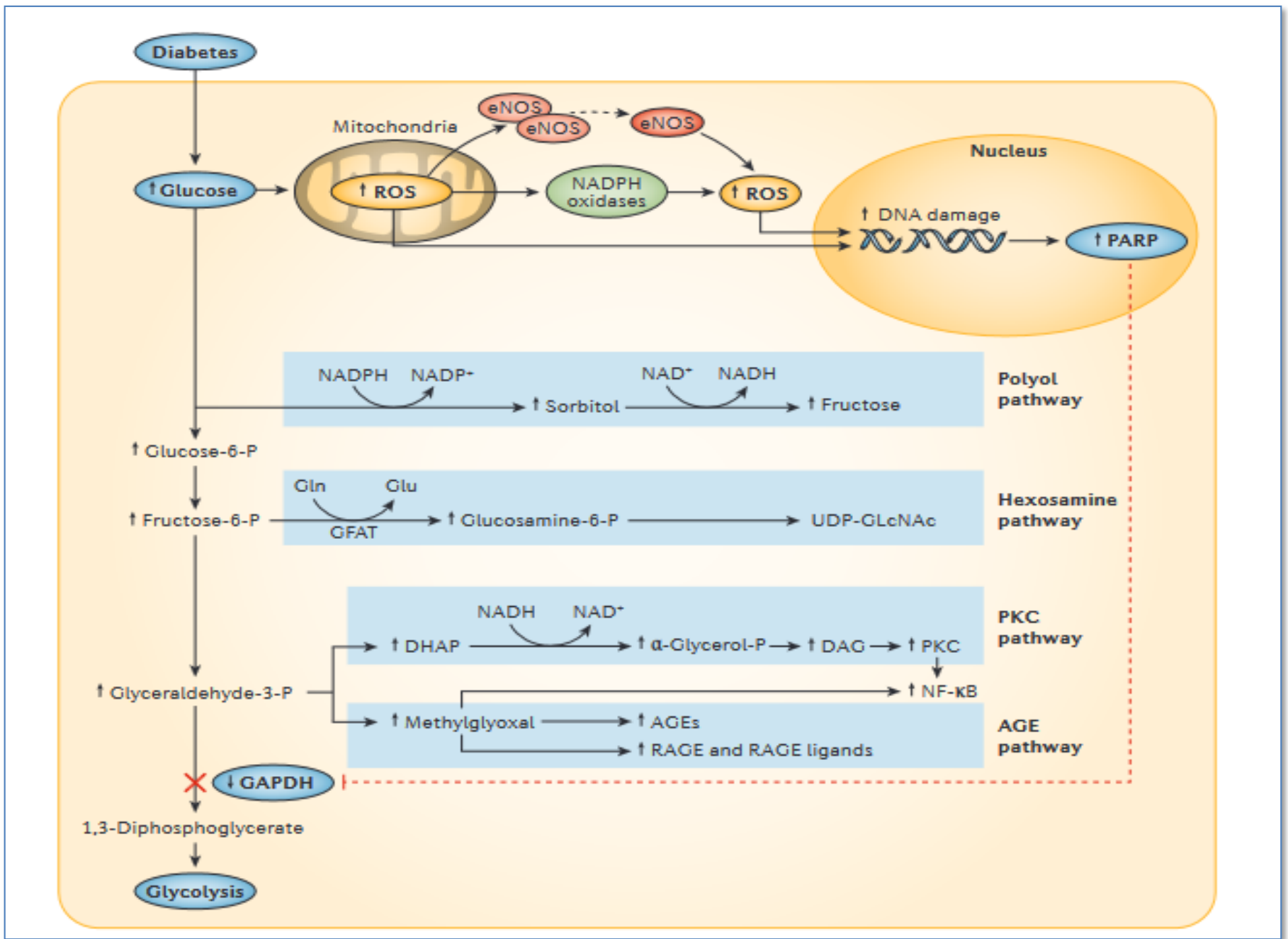
Αύξηση ενδοσπειραματικής πίεσης

Yearly change in eGFR in patients with and without kidney hyperfiltration¹

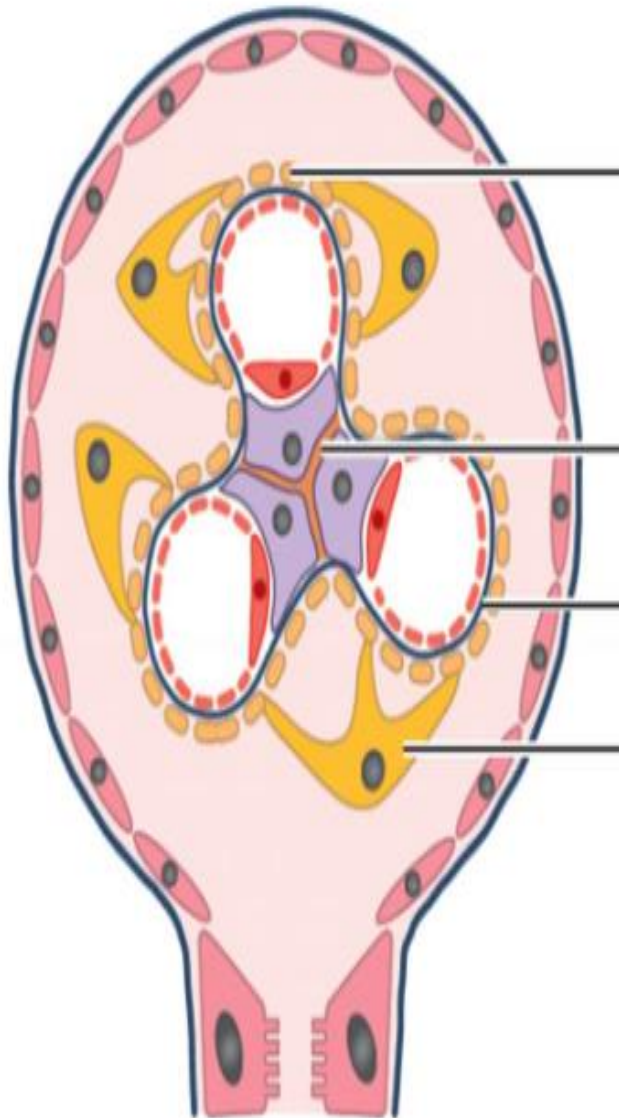


Risk of incident proteinuria in the general population, according to kidney hyperfiltration²

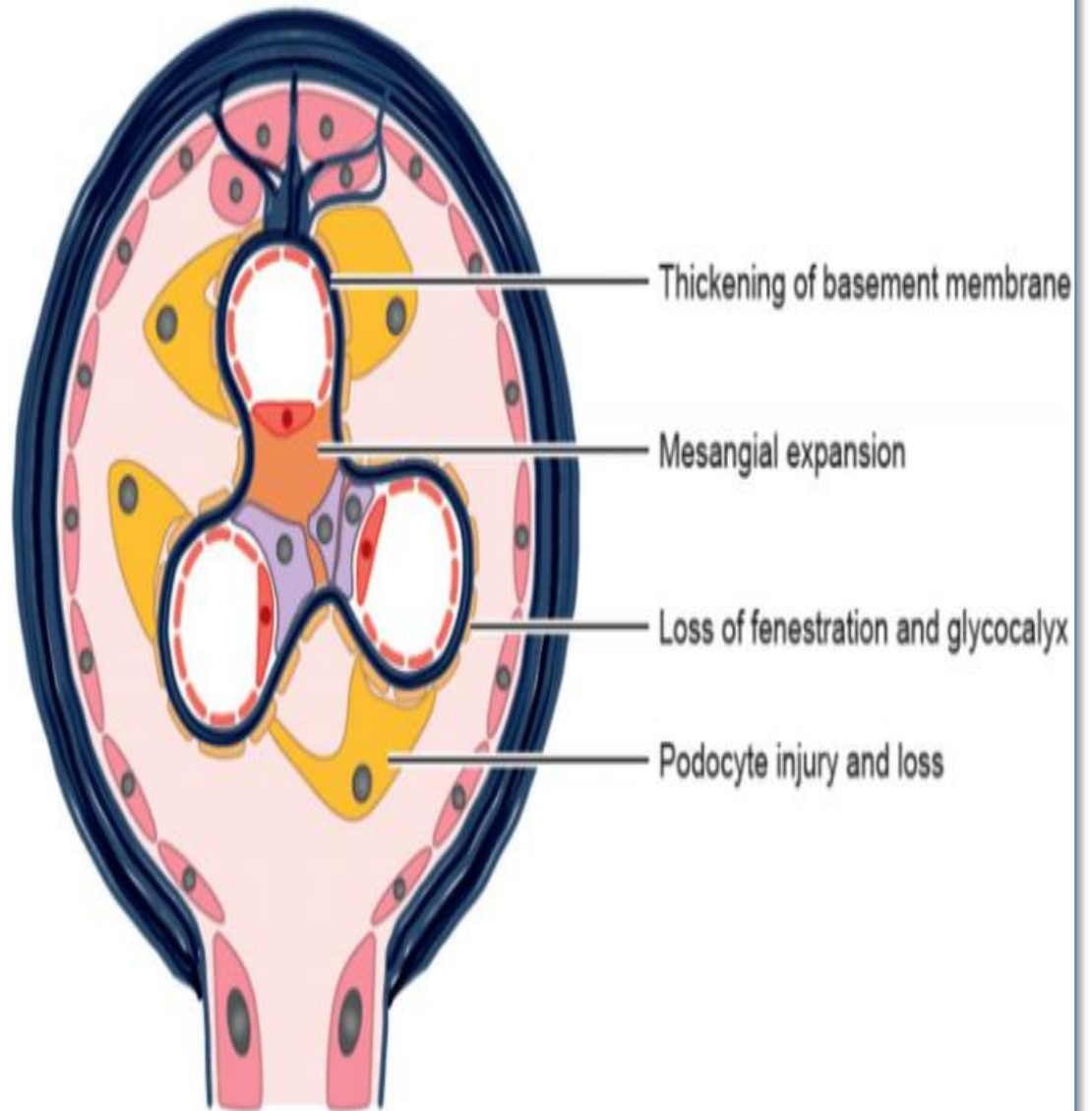


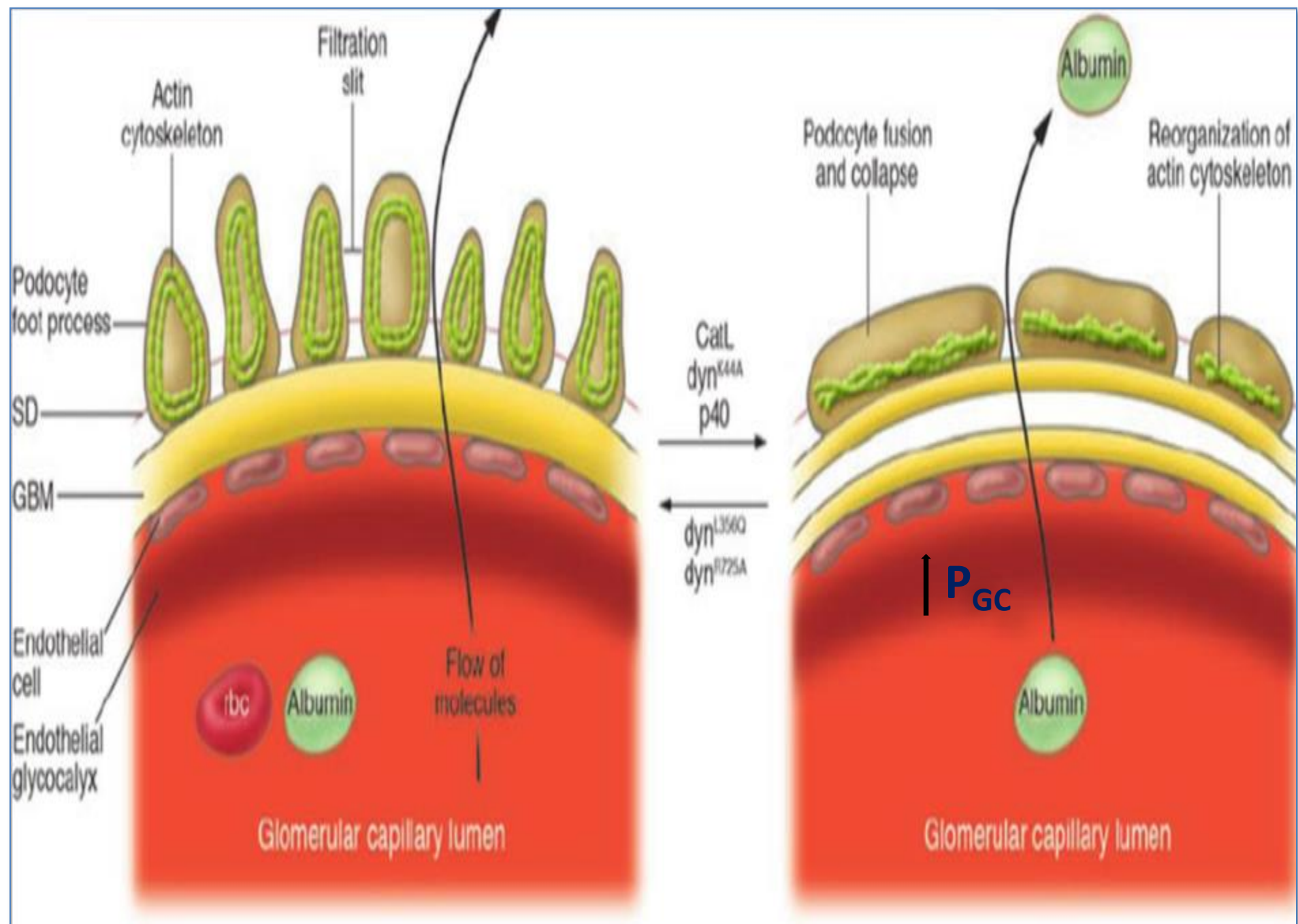


Healthy



Diabetic kidney disease

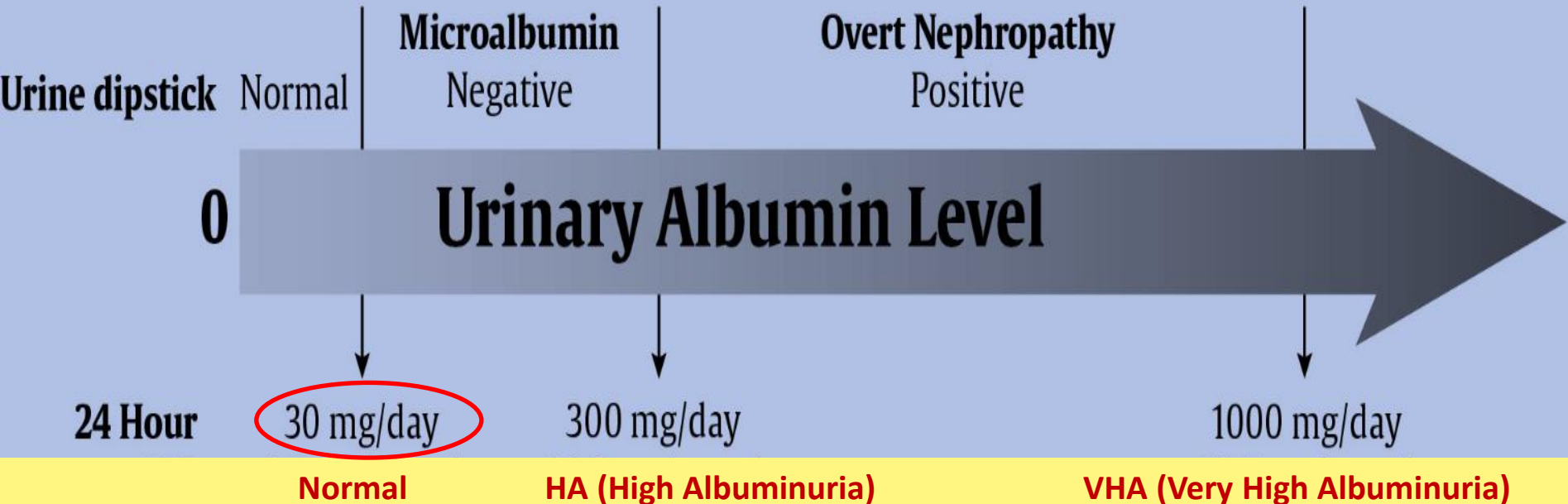




Αλβουμινουρία

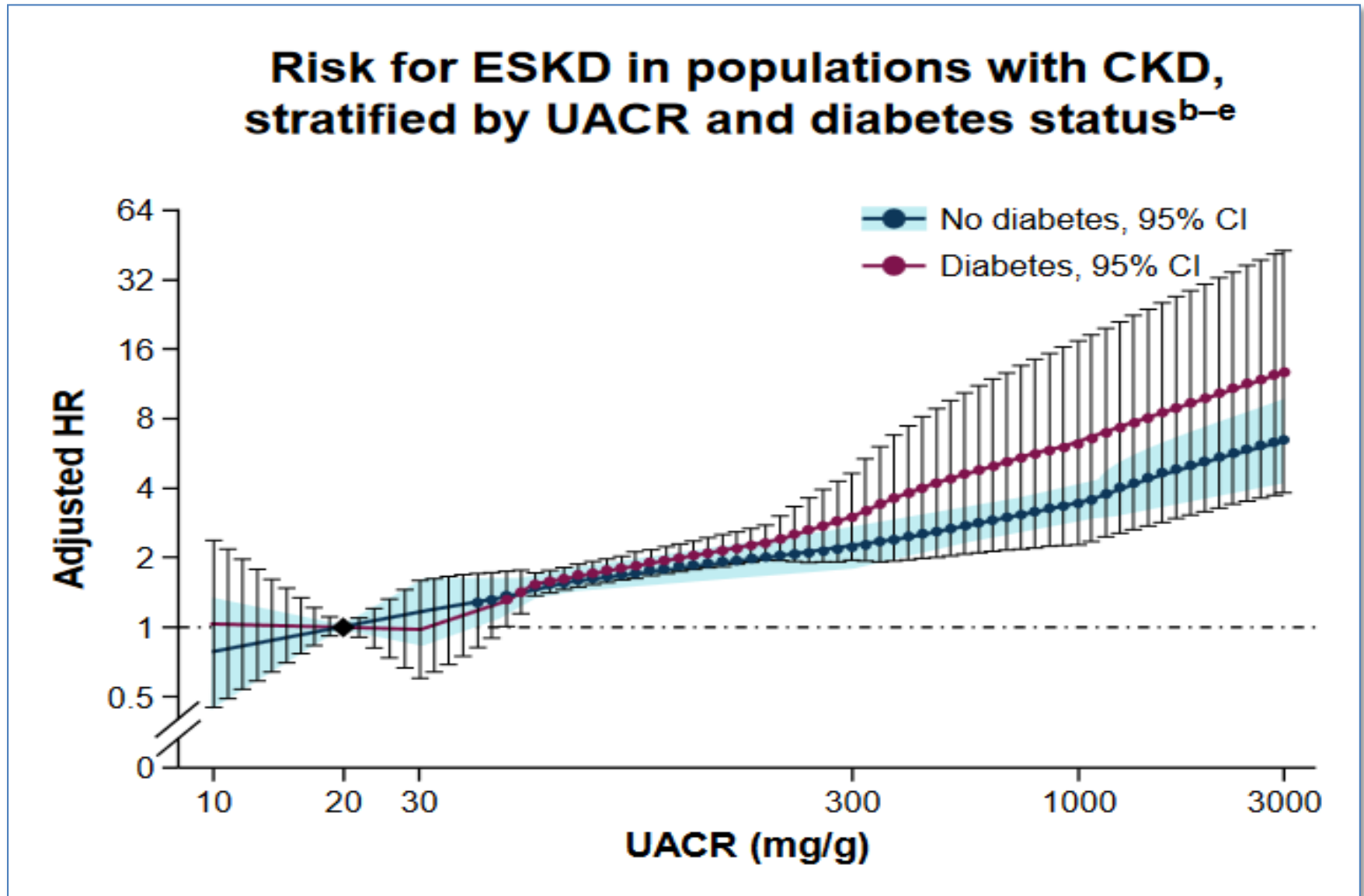


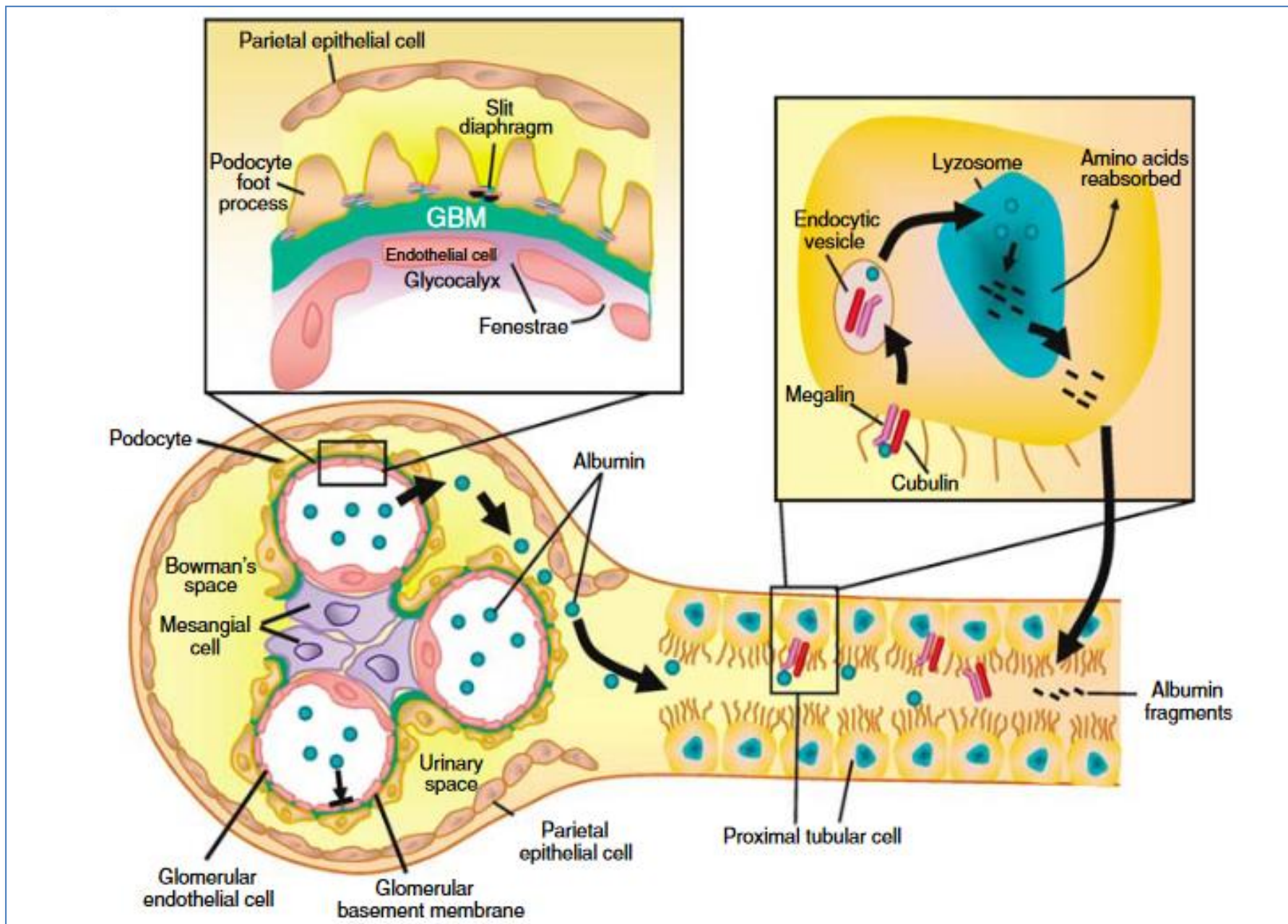
Stage of Nephropathy



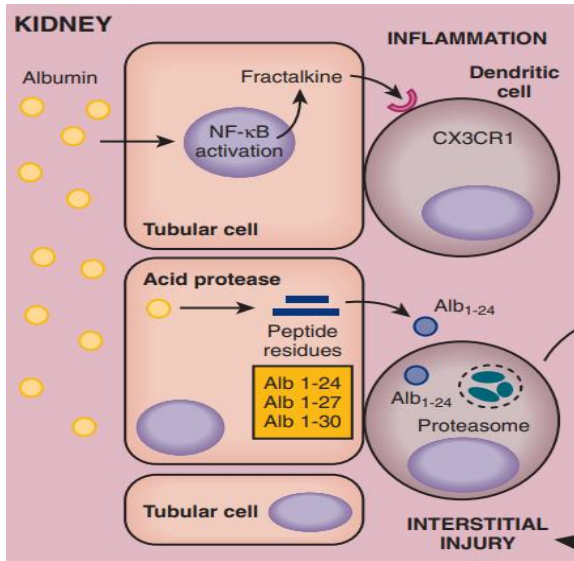
- ✓ Πρώτος δείκτης βλάβης- βασικό συστατικό της διαβητικής νεφρικής νόσου

✓ Παράγοντας κινδύνου εξέλιξης σε ΧΝΑΤΣ

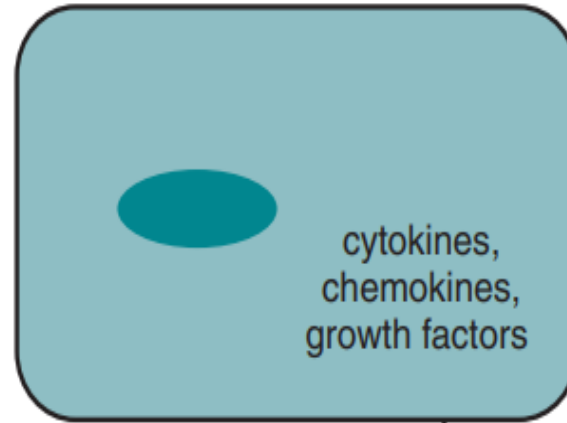




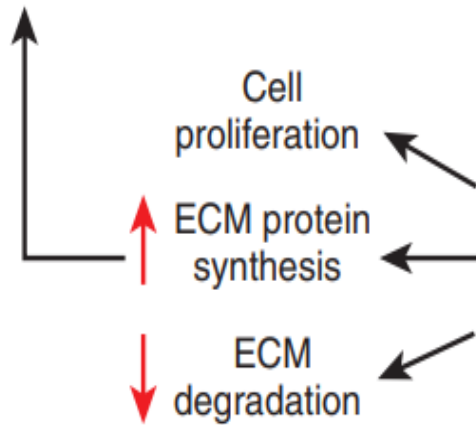
Mechanisms of Interstitial Damage Induced by Proteins



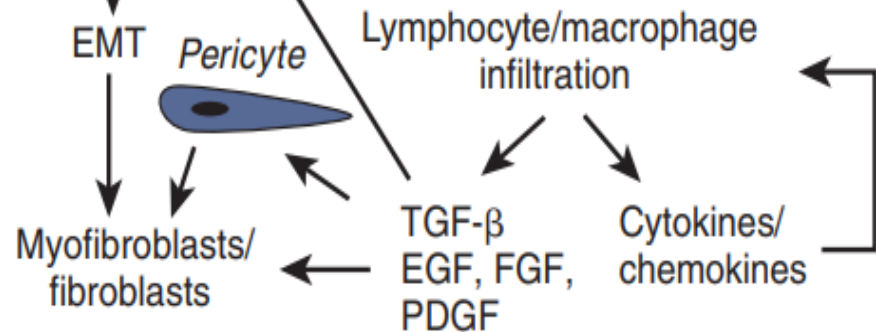
Activated proximal tubular cell



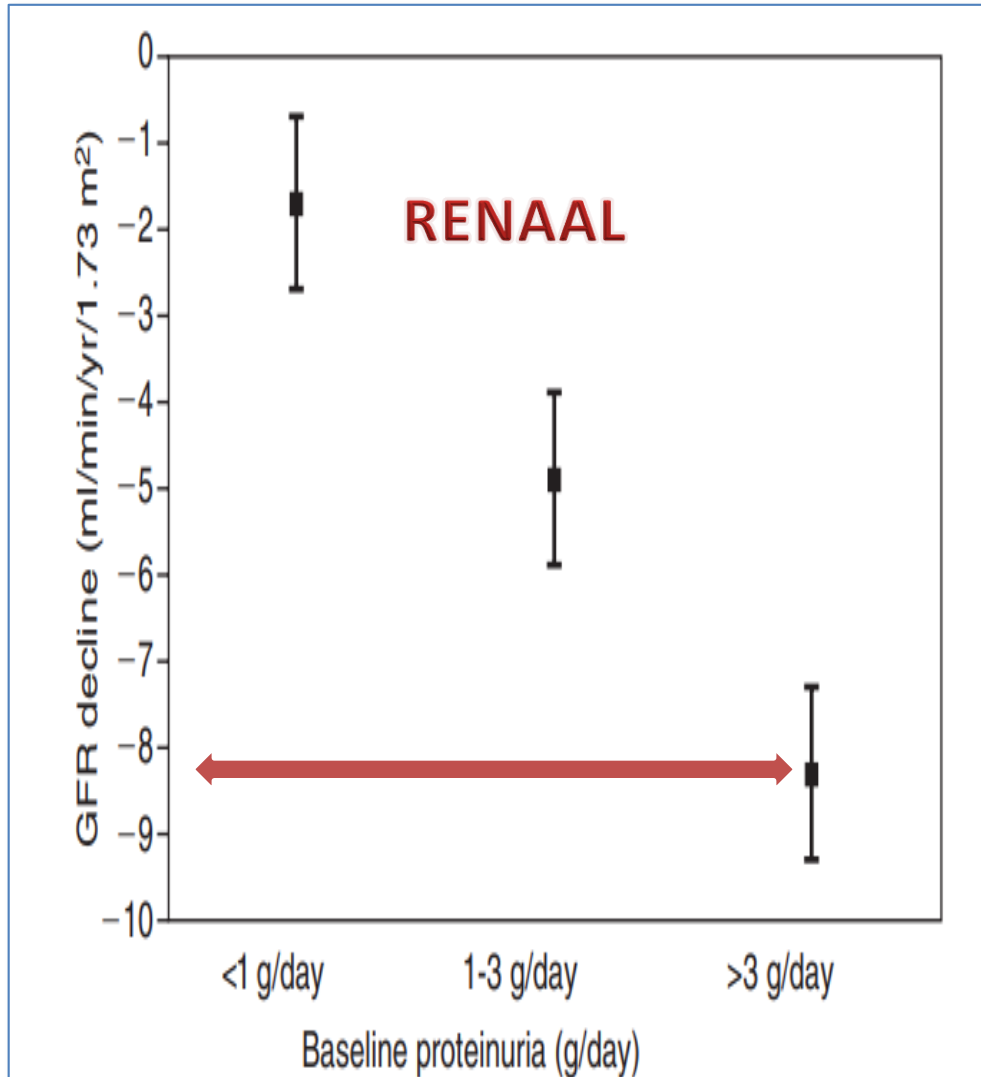
Interstitial fibrosis



Interstitialium



✓ Παράγοντας κινδύνου εξέλιξης σε ΧΝΑΤΣ



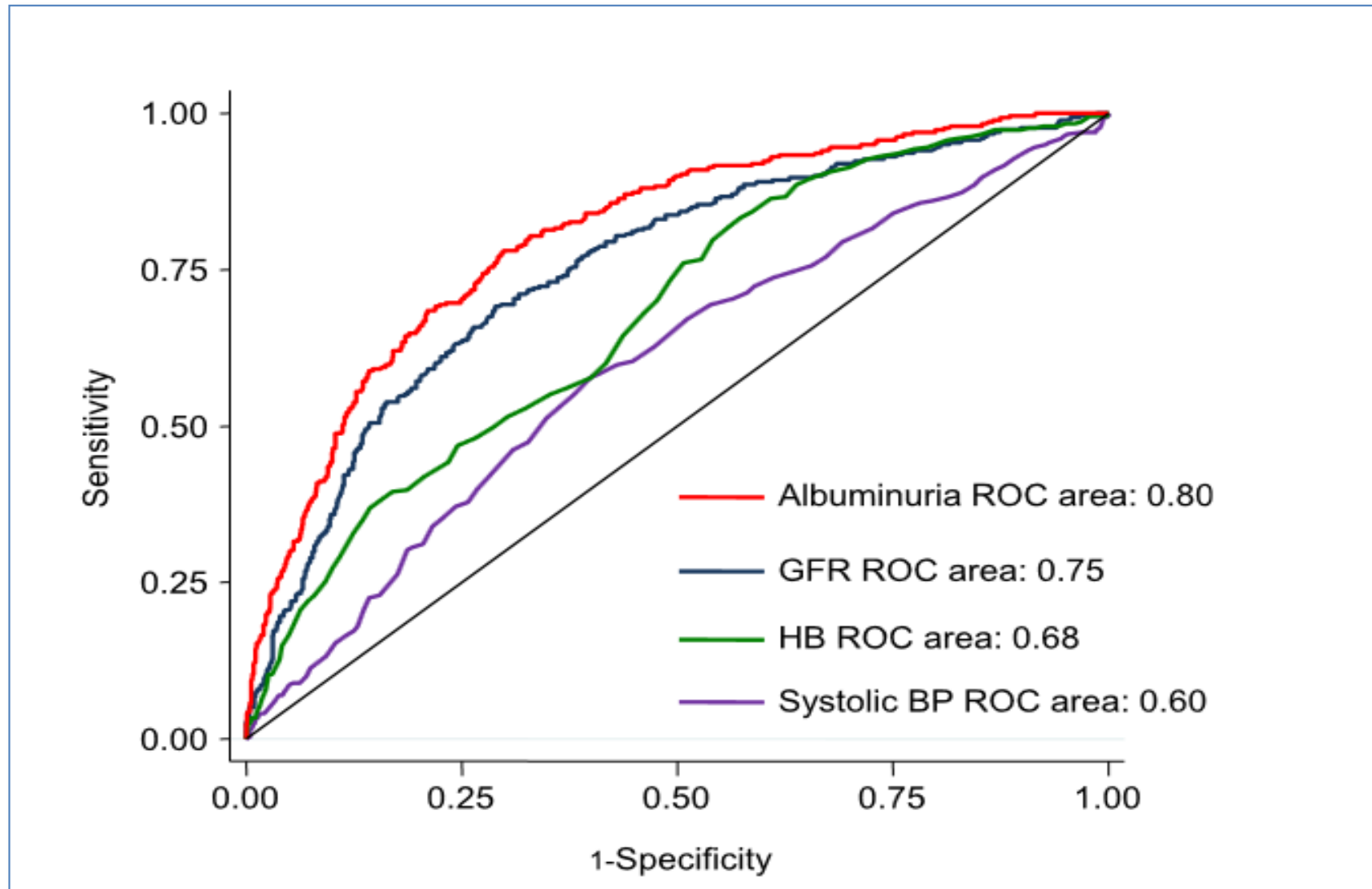
- 10πλασιασμός της αλβουμινουρίας αυξάνει τον κίνδυνο τελικού σταδίου κατά 39%

[Wachtell et al 2003](#)

- Ο διπλασιασμός της αλβουμινουρίας αύξησε κατά 40% τα νεφρικά συμβάματα

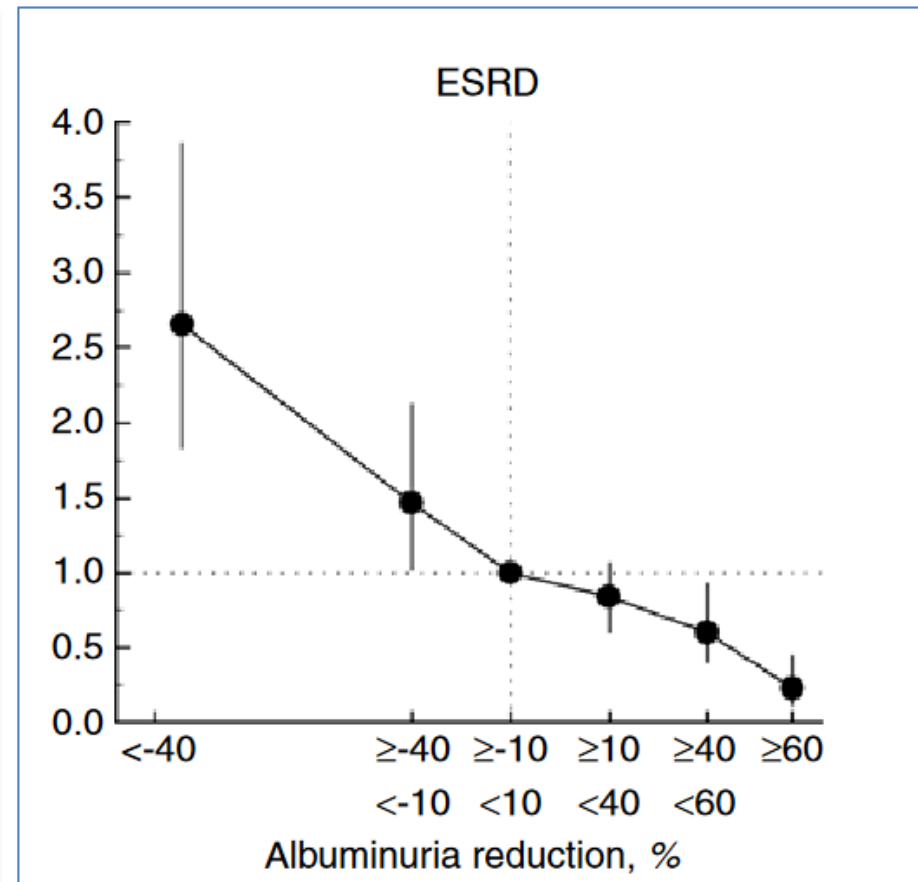
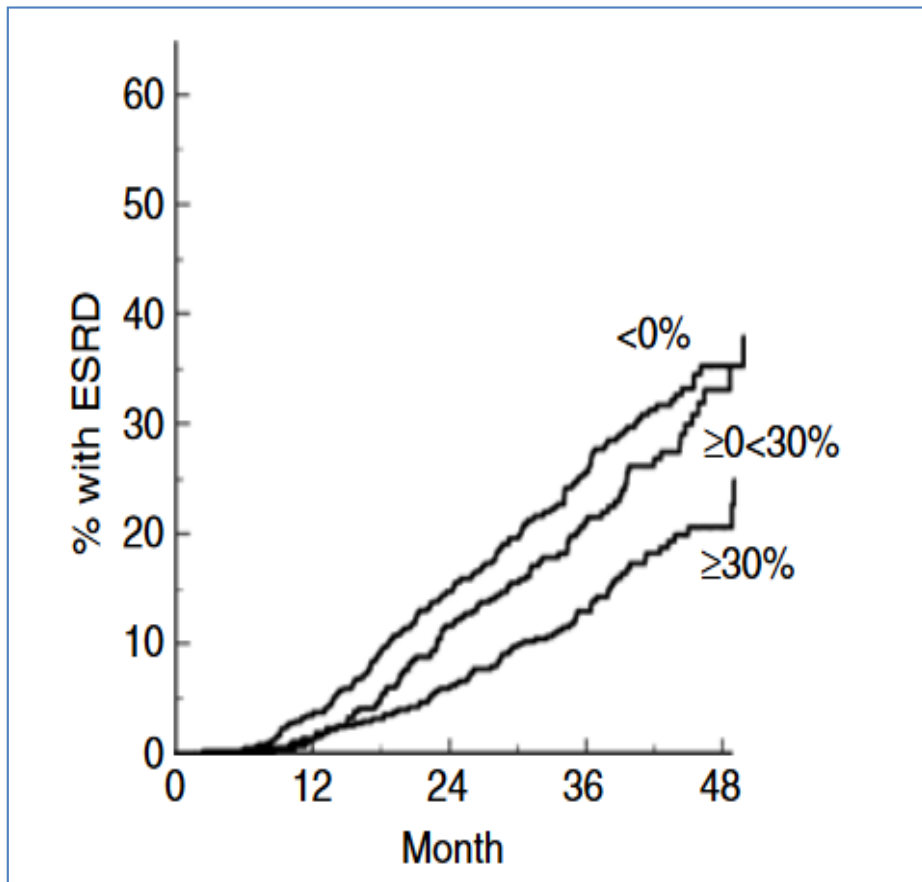
[Ruggenti and Remuzzi 2019](#)

✓ Παράγοντας κινδύνου εξέλιξης σε ΧΝΑΤΣ

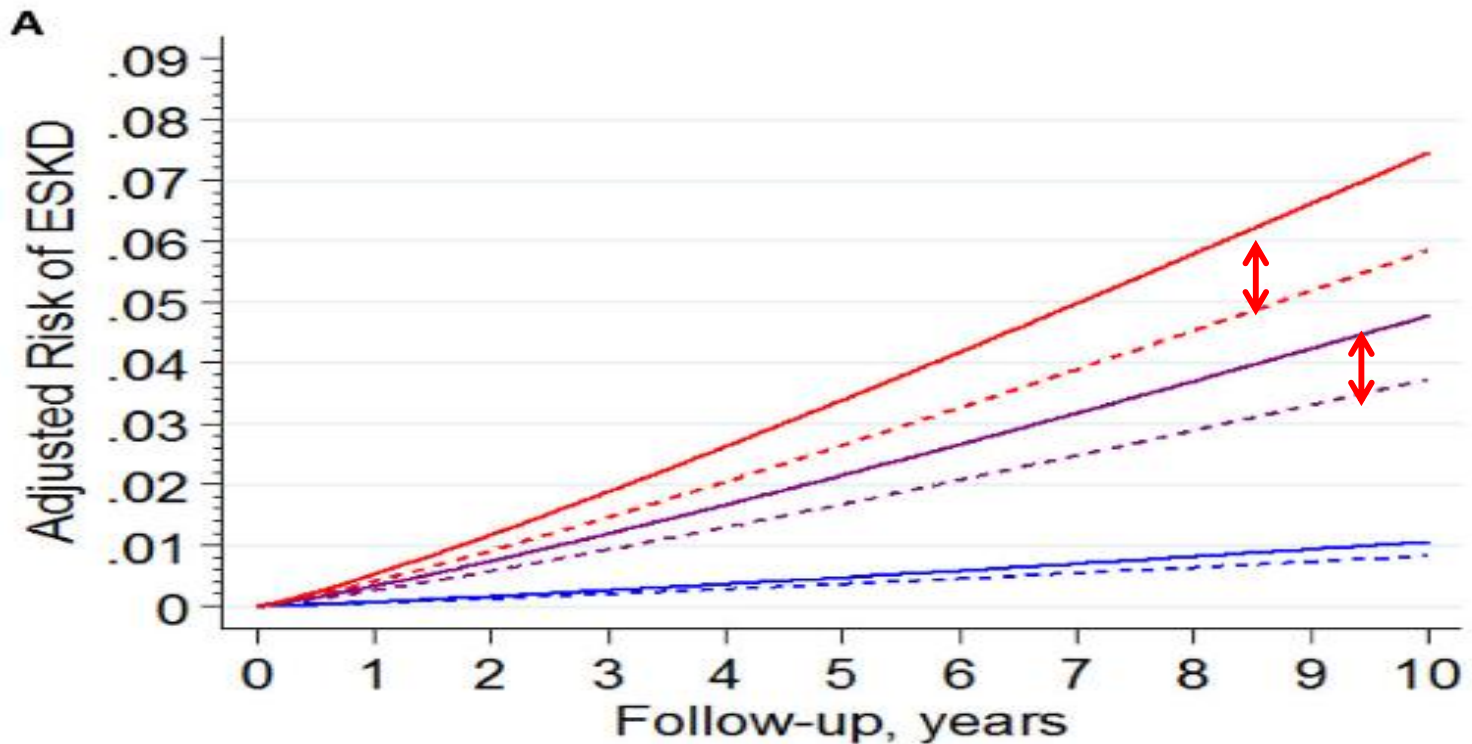


- ✓ Δείκτης νεφρικής βλάβης
- ✓ Παράγοντας κινδύνου εξέλιξης σε ΧΝΑΤΣ

Θεραπευτικός στόχος?



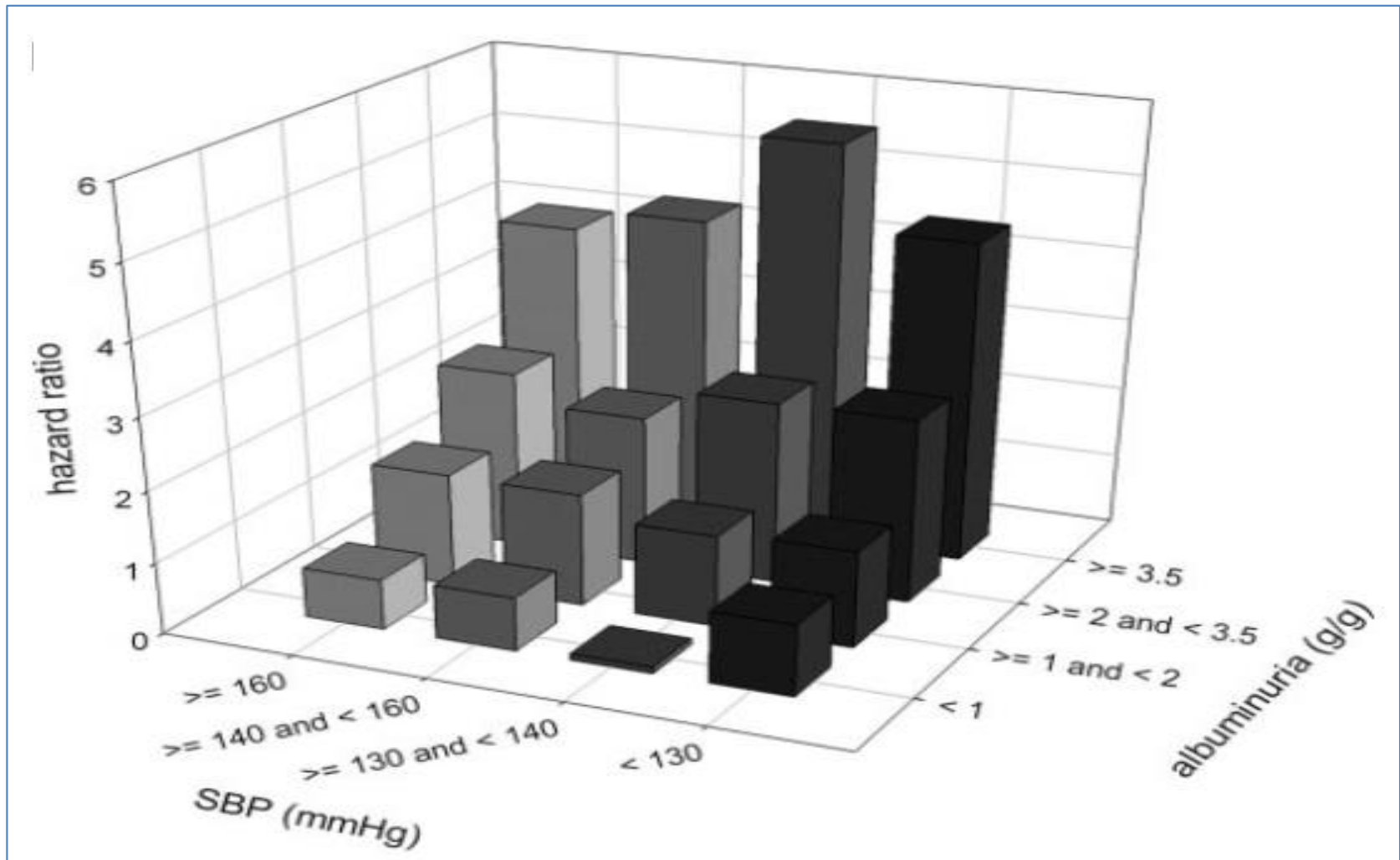
Change in albuminuria and subsequent risk of end-stage kidney disease: An individual participant-level consortium meta-analysis of observational studies



Baseline ACR, 2-year % change in ACR

— 30 mg/g, no change	- - - 30% decrease
— 300 mg/g, no change	- - - 30% decrease
— 600 mg/g, no change	- - - 30% decrease

Albuminuria Is a Target for Renoprotective Therapy Independent from Blood Pressure in Patients with Type 2 Diabetic Nephropathy: *Post Hoc* Analysis from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Trial



Σακχαρώδης διαβήτης

Αντίσταση στην ινσουλίνη

Μεταβολική απορρύθμιση

Συστηματική υπέρταση

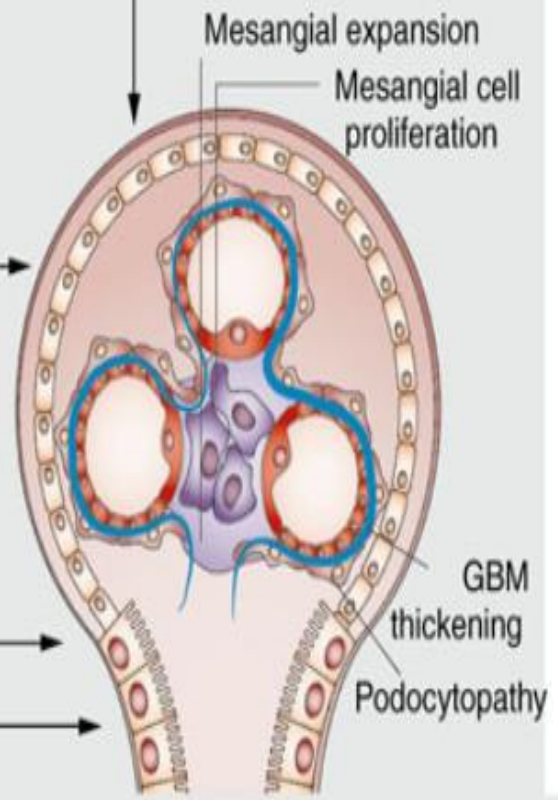
Ενδοσπειραματική υπέρταση

Dyslipidemia



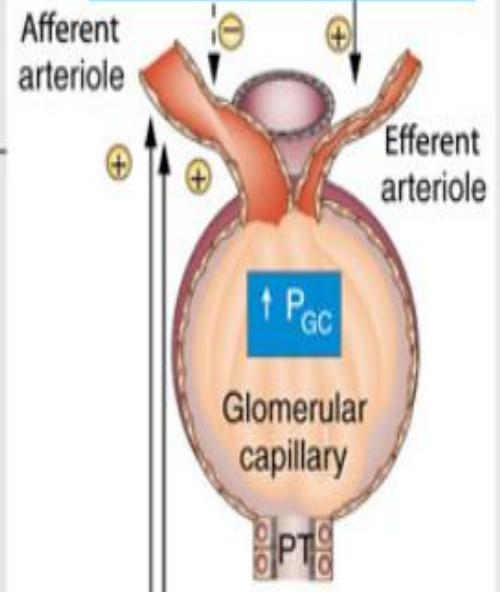
- Glucose-dependent pathways
- AGEs
- Polyol
- Hexosamine
- PKC

- AGE formation
- Growth factors TGF, VEGF
- Proinflammatory cytokines IL-1, IL-6, TNF
- Oxidative stress



Αιμοδυναμική απορρύθμιση

Vasoconstrictors Ang II, ET-1

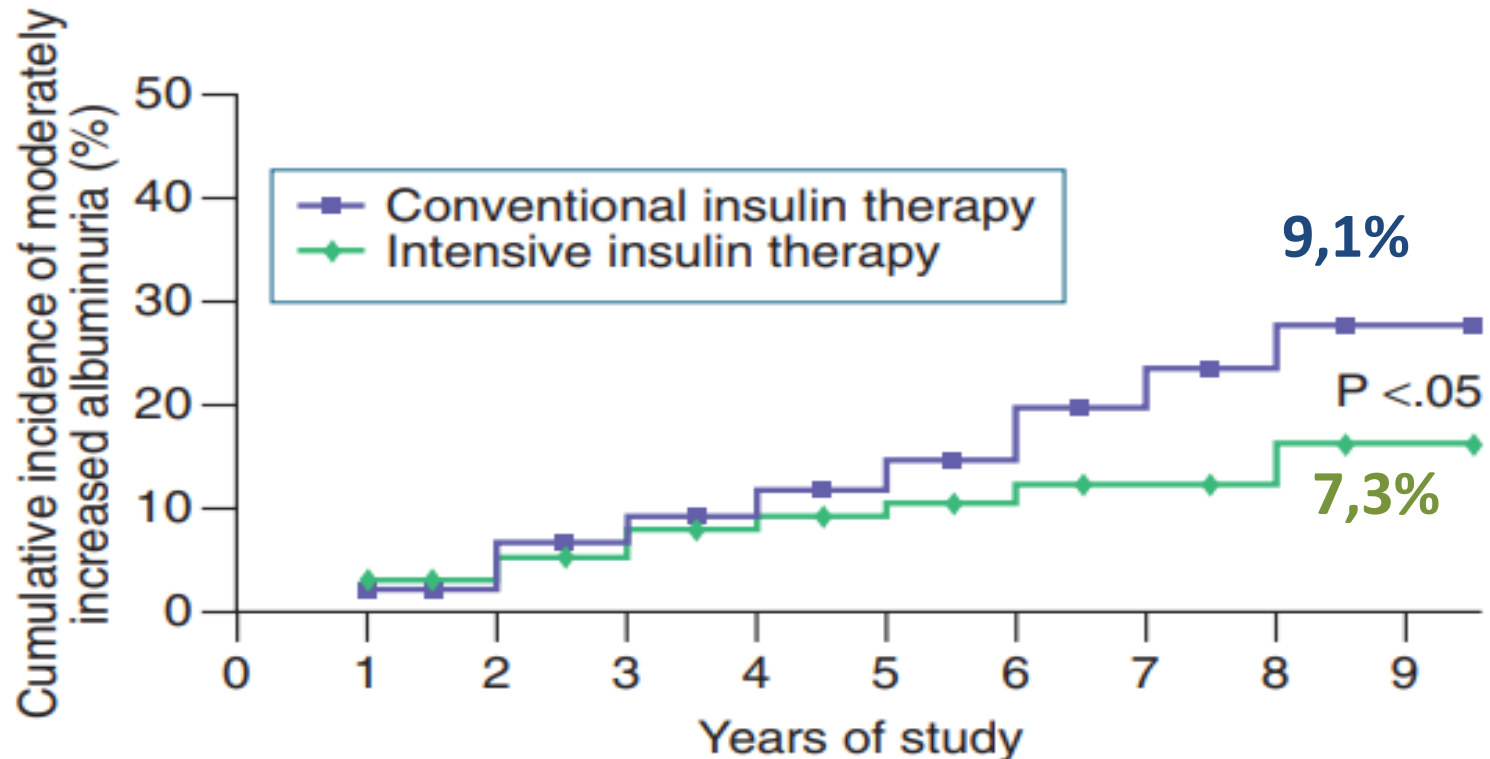


Afferent vasodilators ANP, NO, kinins COX, metabolites

Macula densa signals Tubuloglomerular feedback

Diabetes Control and Complications Trial (DCCT): Results of Feasibility Study

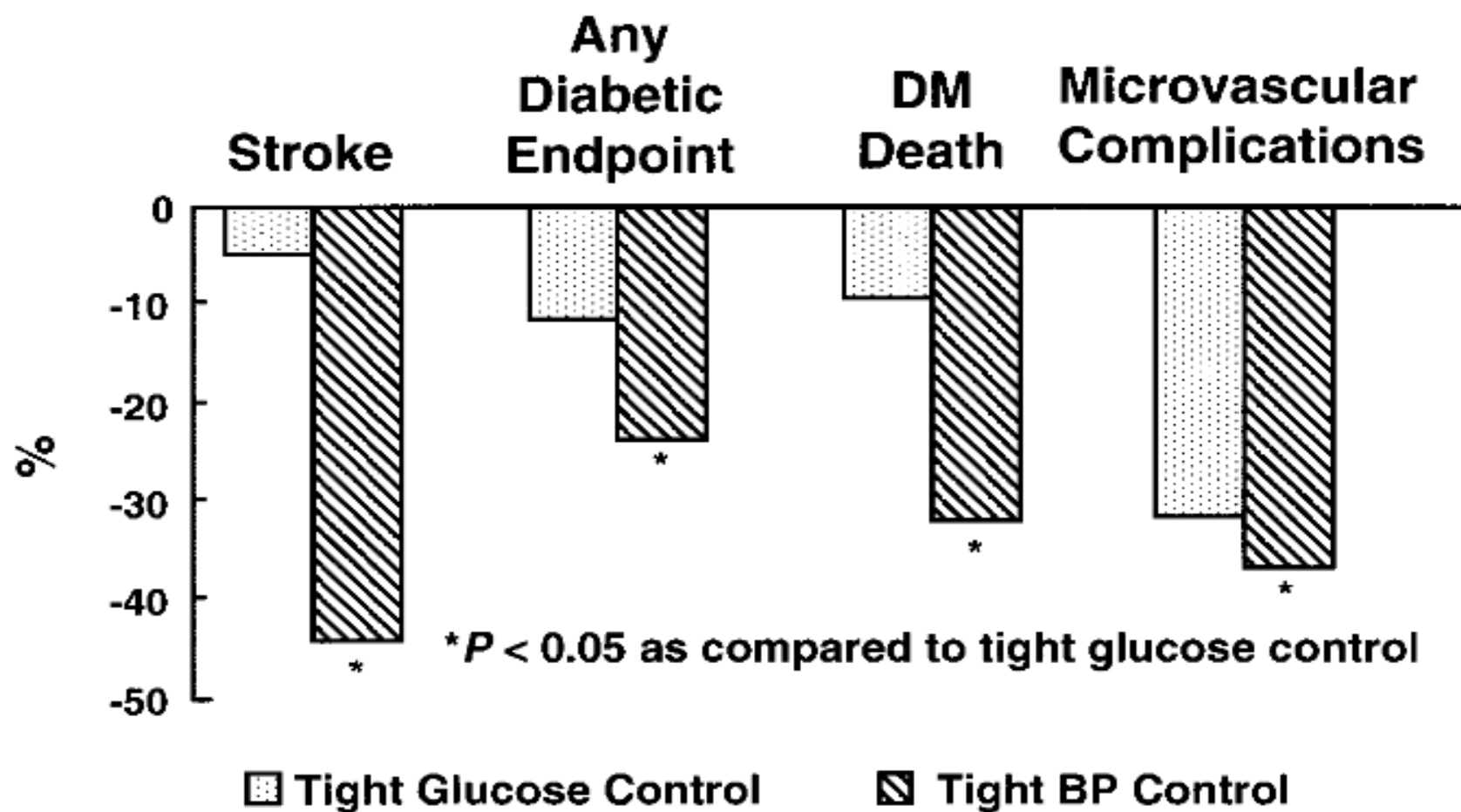
Intensive Glucose Control Reduces Development of Moderately Increased Albuminuria



Μελέτες γλυκαιμικού ελέγχου

DCCT	ΣΔτ1	1441pts	7,3% vs 9,1%	Μείωση εμφάνισης αλβουμινουρίας 39% Μείωση εμφάνισης πρωτεϊνουρίας 54%
EDIC	ΣΔτ1	1375pts	7,8% vs 7,9%	Μείωση της αλβουμινουρίας 59%, πρωτεϊνουρίας 84%
UKPDS	ΣΔτ2 νέα διάγνωση	3867pts	7% vs 7,9%	Μείωση της αλβουμινουρίας 24%, πρωτεϊνουρίας 33%
ACCORD	ΣΔτ2 και καρδ/κός κίνδυνος	10251pts	6,4% vs 7,5%	Όχι όφελος σε νεφρικά σημεία, αυξημένος καρδ/κός κίνδυνος
ADVANCE	ΣΔτ2 και καρδ/κός κίνδυνος	11140pts	6,3% vs 7,0%	21% μείωση της αλβουμινουρίας
VADT	ΣΔτ2 και ΑΥ	1791pts	6,9% vs 8,4%	Μείωση αλβουμινουρίας 32% Όχι συνολικό νεφρικό όφελος

Preserving Renal Function in Adults With Hypertension and Diabetes: A Consensus Approach



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

Patel et al Lancet 2007

	Number (%) of patients with event		Favours perindopril-indapamide	Favours placebo	Relative risk reduction (95% CI)
	Perindopril-indapamide (n=5569)	Placebo (n=5571)			
Total renal events	1243 (22.3%)	1500 (26.9%)			21% (15 to 27)
New or worsening nephropathy	181 (3.3%)	216 (3.9%)			18% (-1 to 32)
New microalbuminuria	1094 (19.6%)	1317 (23.6%)			21% (14 to 27)

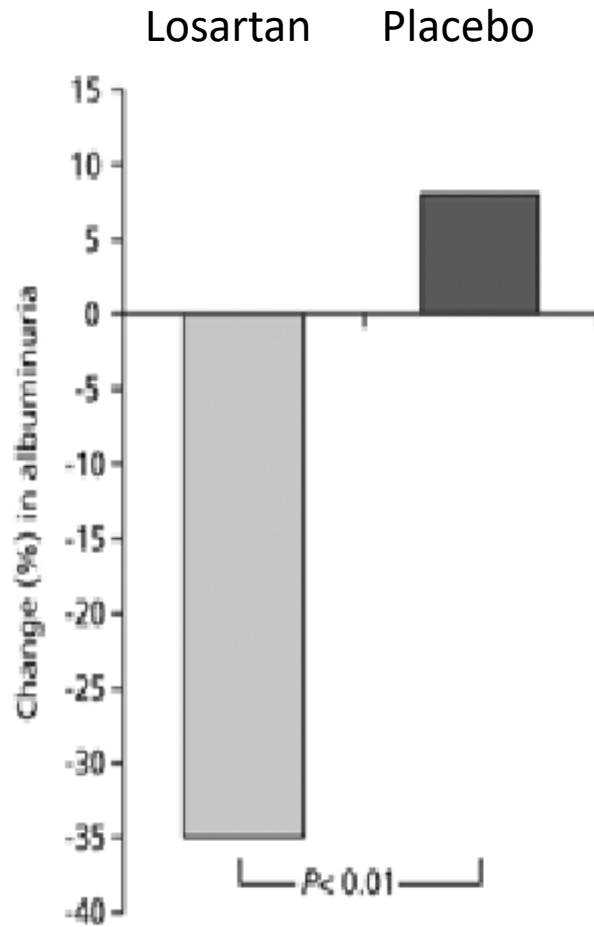
Blood Pressure Lowering in Type 2 Diabetes

A Systematic Review and Meta-analysis

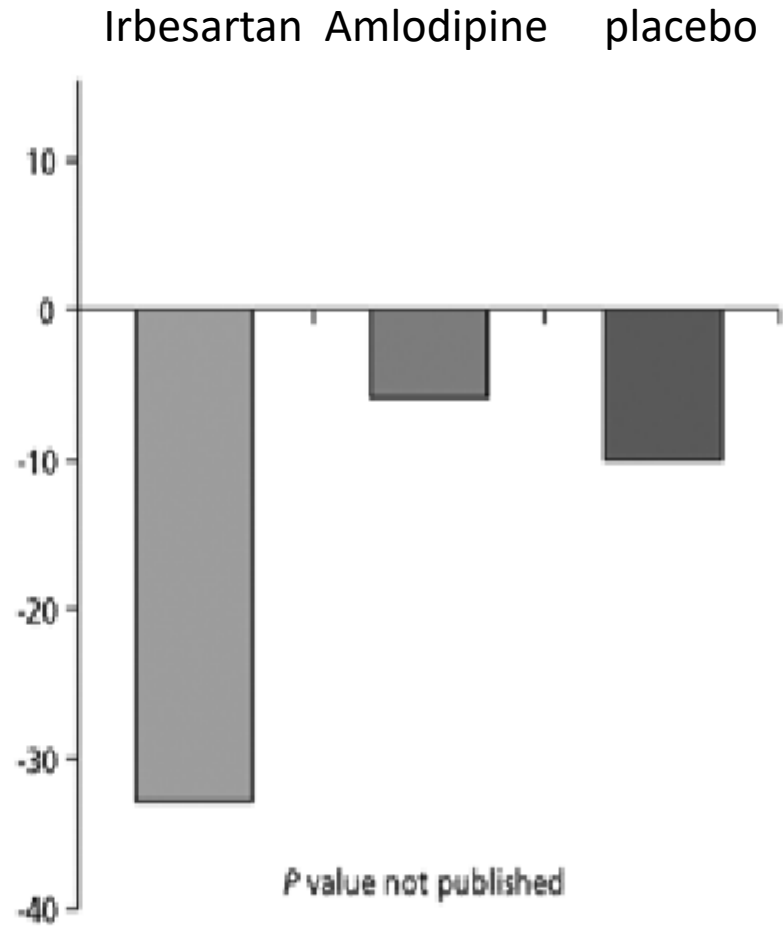
Outcome	No. of Studies	BP Lowering		Control		Relative Risk (95% CI)	Favors BP Lowering	Favors Control
		Events	Participants	Events	Participants			
Mortality	20	2334	27 693	2319	25 864	0.87 (0.78-0.96)		
Cardiovascular disease	17	3230	25 756	3280	24 862	0.89 (0.83-0.95)		
Coronary heart disease	17	1390	26 150	1449	24 761	0.88 (0.80-0.98)		
Stroke	19	1350	27 614	1475	26 447	0.73 (0.64-0.83)		
Heart failure	13	1235	21 684	1348	20 791	0.86 (0.74-1.00)		
Renal failure	9	596	19 835	560	18 912	0.91 (0.74-1.12)		
Retinopathy	7	844	9 781	905	9 566	0.87 (0.76-0.99)		
Albuminuria	7	2799	13 804	3163	12 821	0.83 (0.79-0.87)		

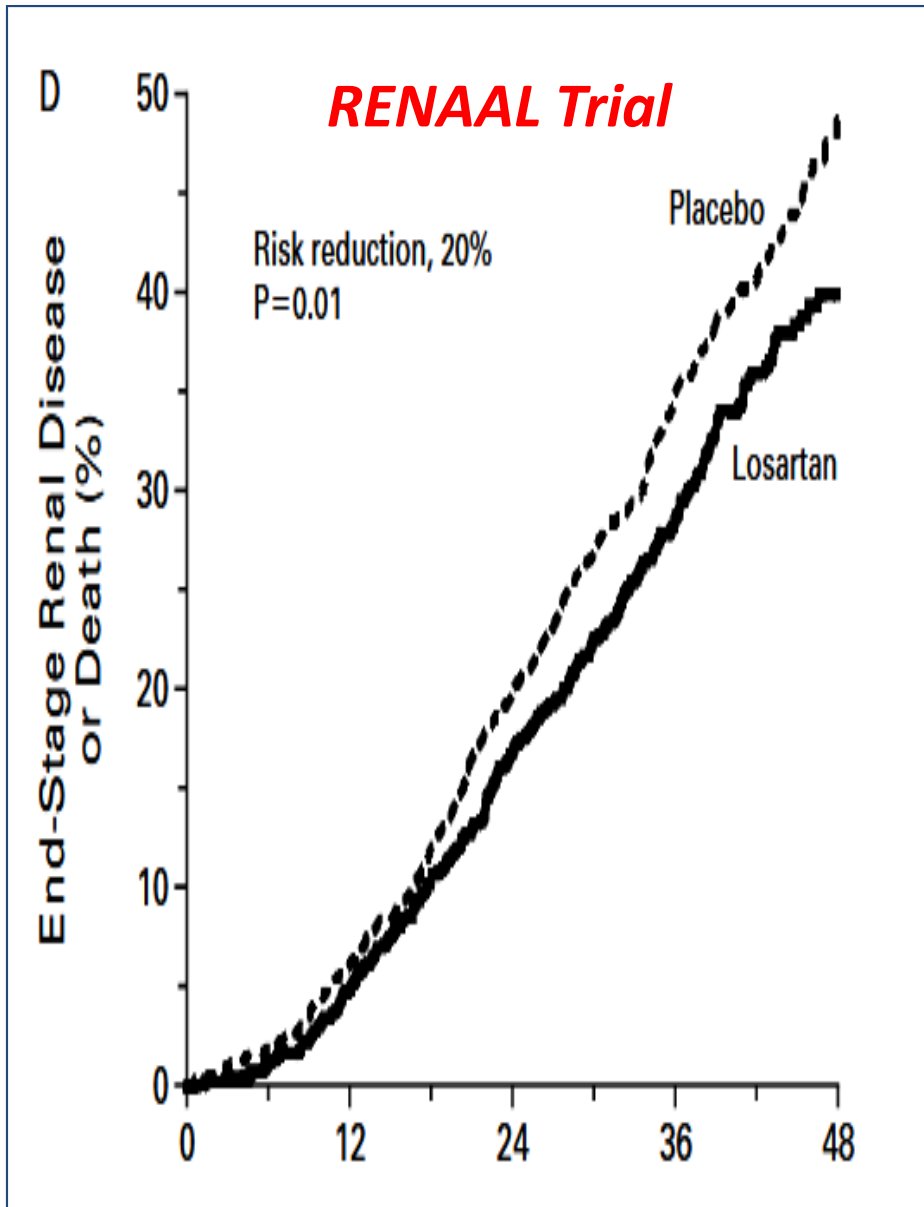
0.5 1.0 2.0
Relative Risk (95% CI)

RENAAL Trial

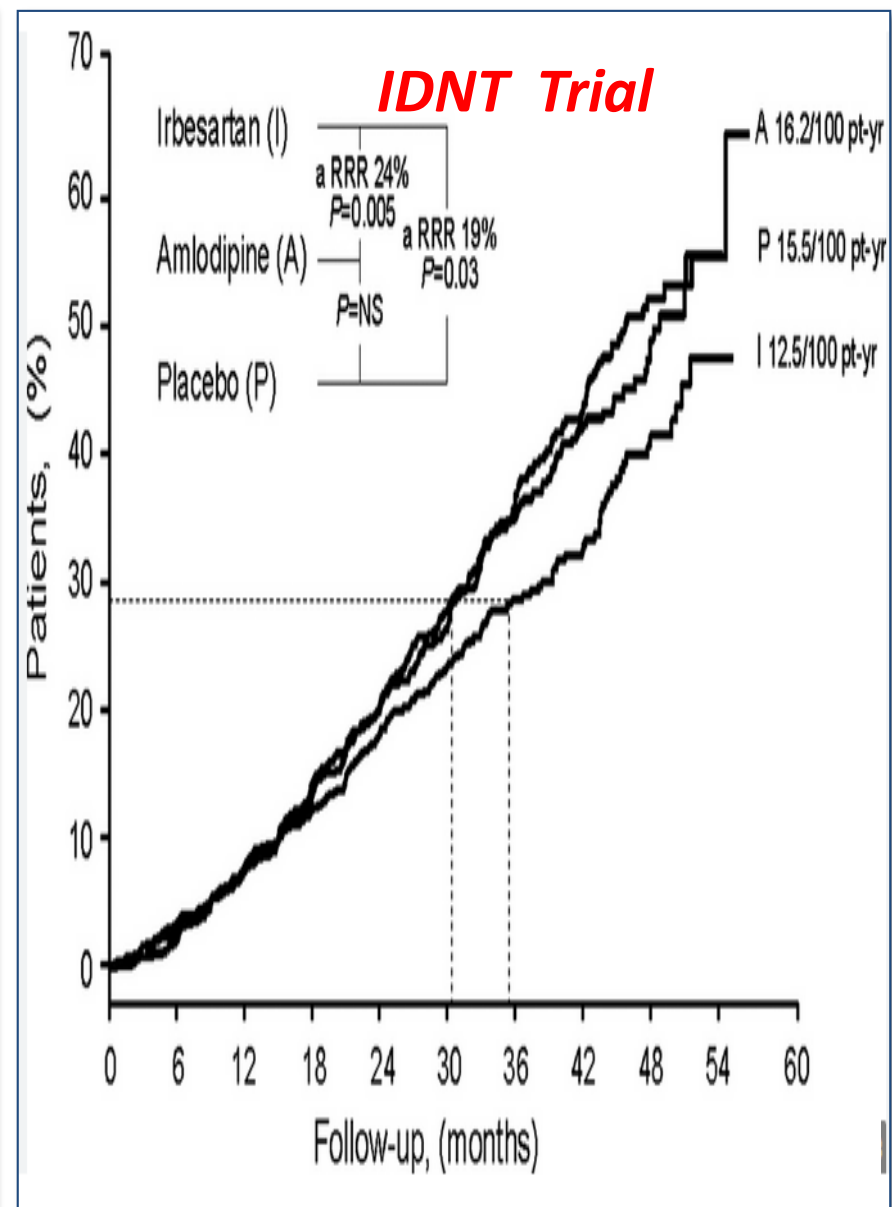


IDNT Trial





Barry M. Brenner *N Engl J Med* 2001



EJ Lewis *N Engl J Med* 2001

Μελέτες με χρήση RAASi (συστηματική και ενδοσπειραματική υπέρταση)

RENAAL	ΣΔτ2 και νεφρική νόσο	Losartan vs placebo	Μείωση αλβουμινουρίας κατά 35% Κάθε υποδιπλασιασμός αλβουμινουρίας μείωση του κινδύνου ΧΝΑΤΣ 50%
IDNT	ΣΔτ2 και νεφρική νόσο	Irbesartan vs amlodipine vs placebo	Για κάθε μείωση της αλβουμινουρίας κατά 50% τους πρώτους 12 μήνες, μείωση του κινδύνου ΧΝΑΤΣ
IRMA-2	ΣΔτ2 με αλβουμινουρία	Irbesartan vs placebo	Δοσοεξαρτώμενη μείωση του κινδύνου εμφάνισης πρωτεϊνουρίας Μειωμένος ρυθμός μείωσης του ΡΣΔ σε ασθενείς με >50% μείωση της αλβουμινουρίας
ROADMAP	ΣΔτ2 χωρίς αλβουμινουρία	Olmesartan vs placebo	Καθυστέρηση της εμφάνισης αλβουμινουρίας



Heerspink et al KI 2012

**6-Month response
(95% confidence interval)**

**24-h Urinary sodium/
creatinine ratio (mmol/g)**

**24-h ACR response
(%)**

**Systolic BP response
(mm Hg)**

< 121

−44 (−55 to −30)

−5.0 (−8.8 to −1.1)

121–153

−16 (−32 to +3)

−4.6 (−8.3 to −1.0)

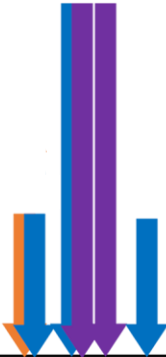
≥ 153

−21 (−35 to −2)

−3.5 (−7.4 to +0.4)

 SGLT2i

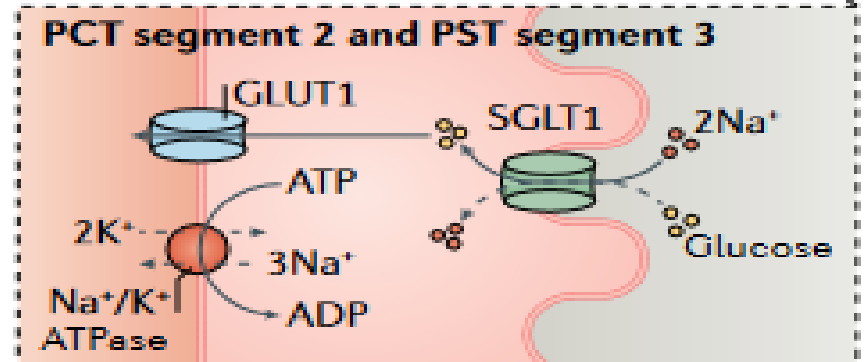
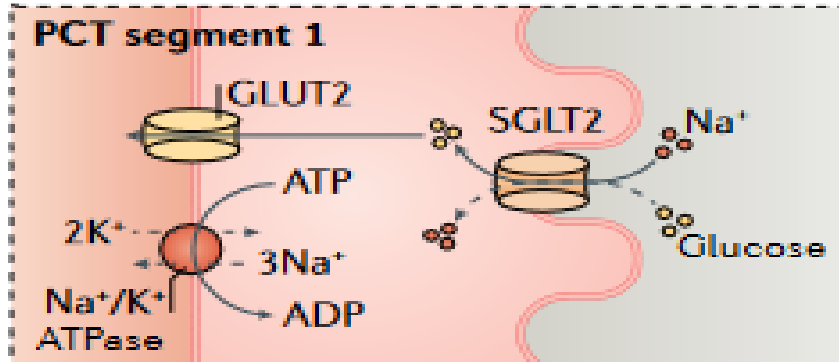
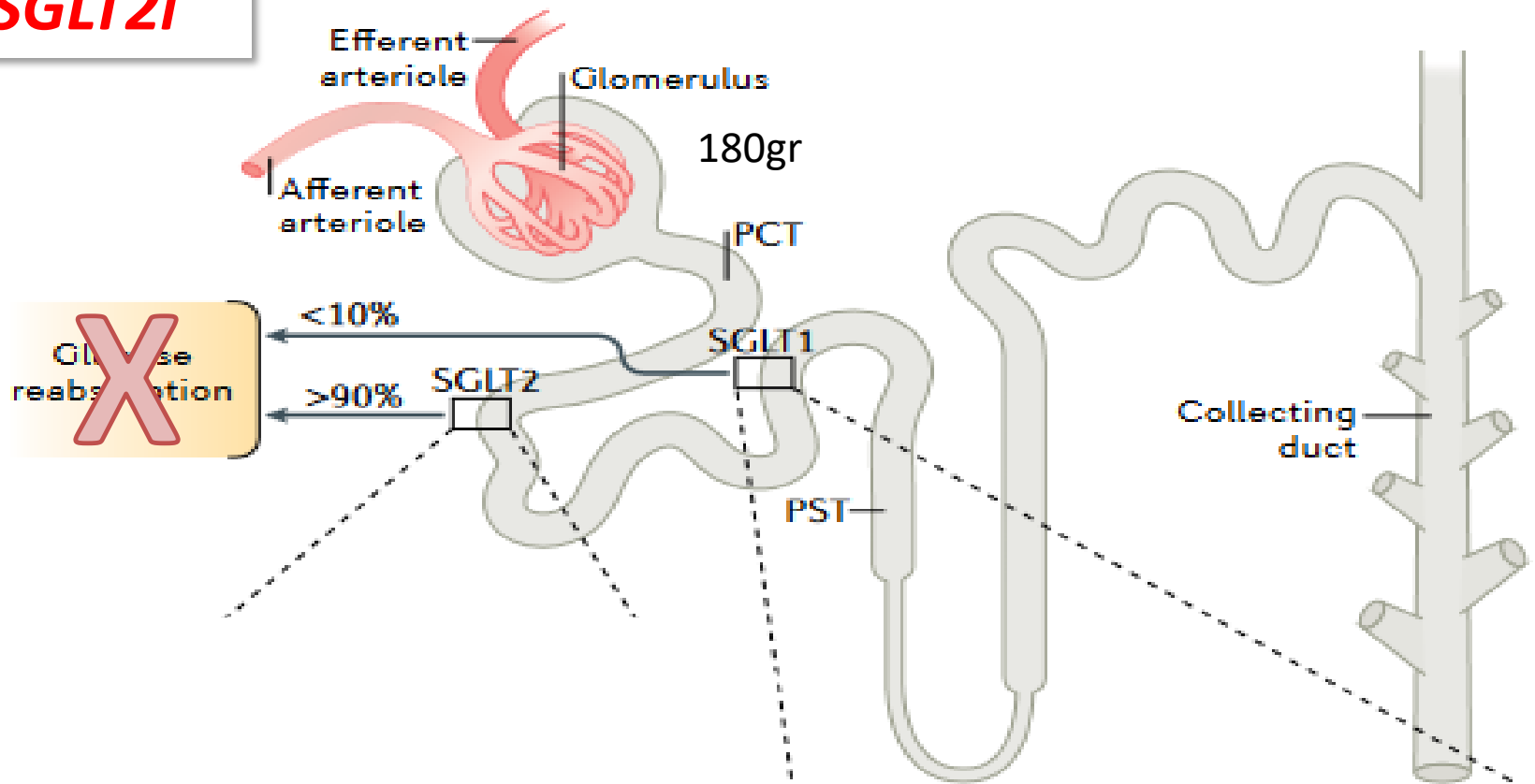
IDNT
RENAAL

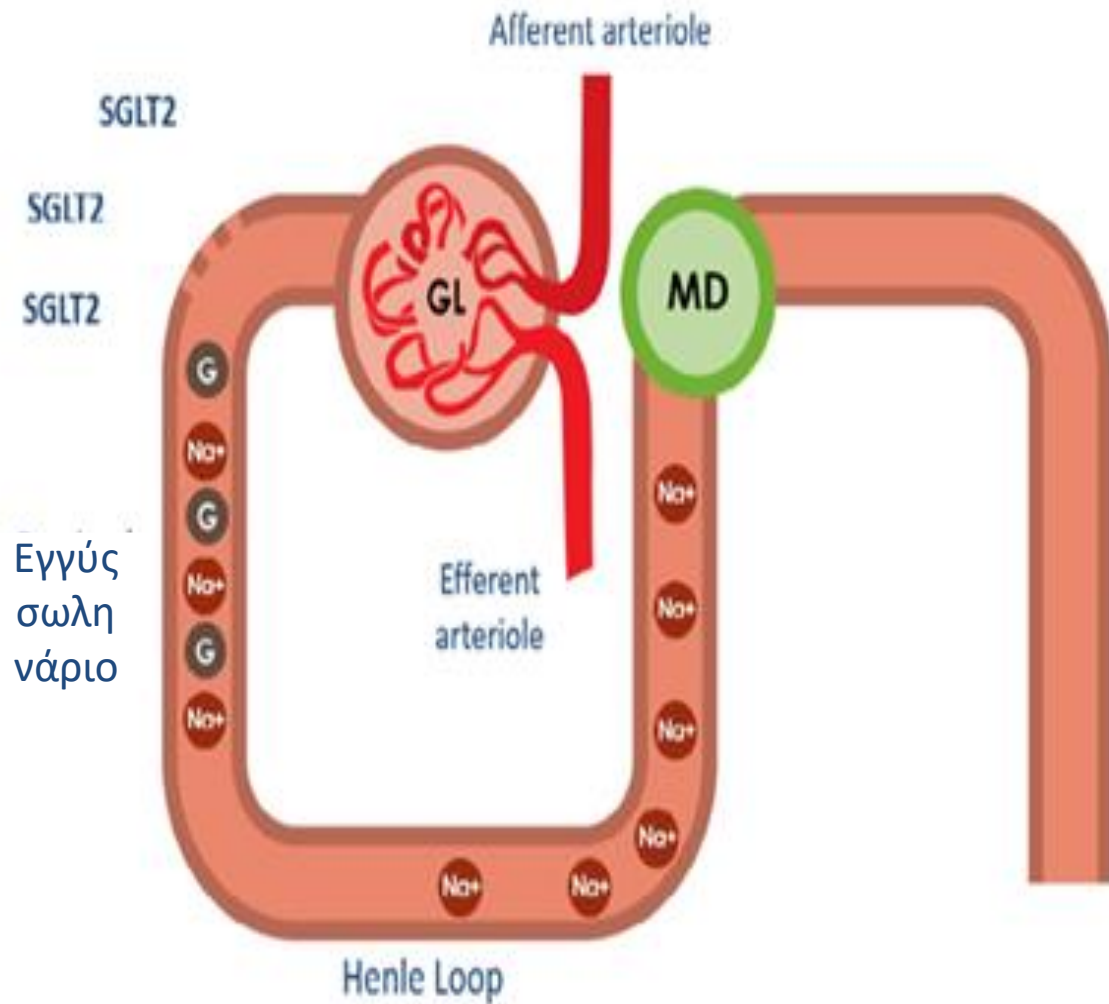


≈ 20-years

DOI: 10.4239/wjd.v13.i7.471 Copyright ©The Author(s) 2022.

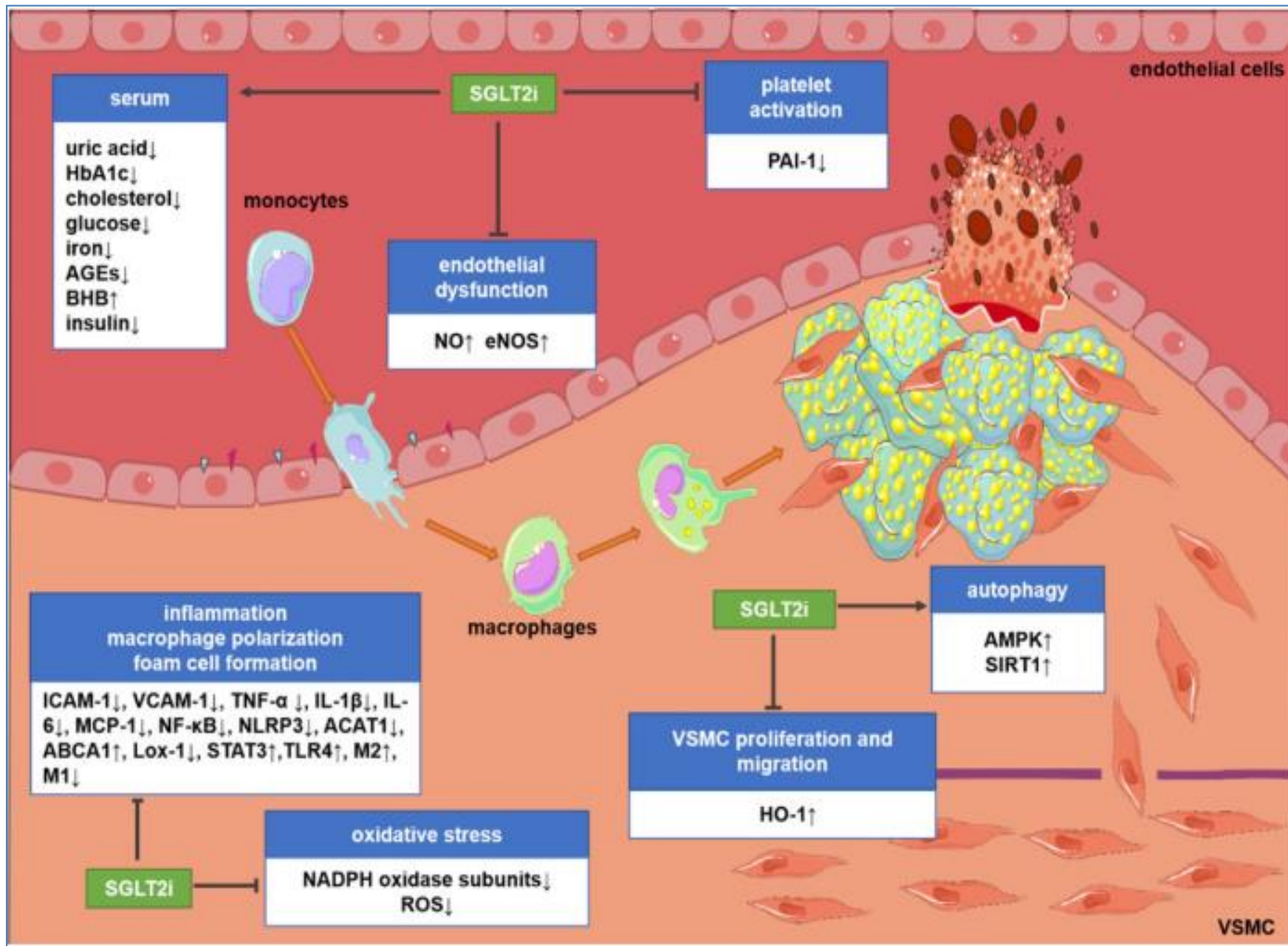
SGLT2i





Εγγύς
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ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Matthews, Dipl. Biomat., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Ulf C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

EMPA-REG¹

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*

CANVAS programme²

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE-TIMI 58 Investigators*

DECLARE-TIMI 58 trial³

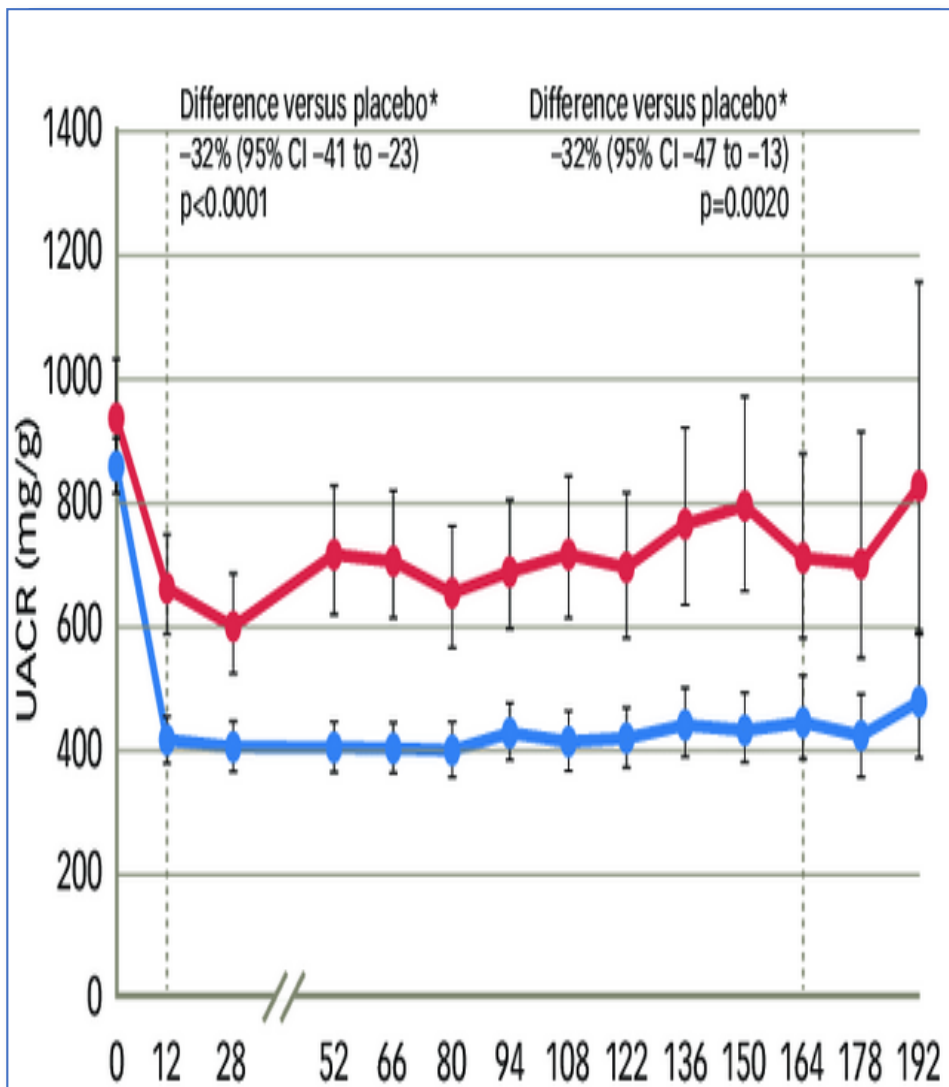
- New-onset macroalbuminuria
- Doubling of serum creatinine (+eGFR < 45 ml/min/1.73m²)
- Initiation of RRT
- Death due to renal disease

- Albuminuria progression
- Albuminuria regression
- 40% reduction in eGFR
- End-stage renal disease
- Renal death

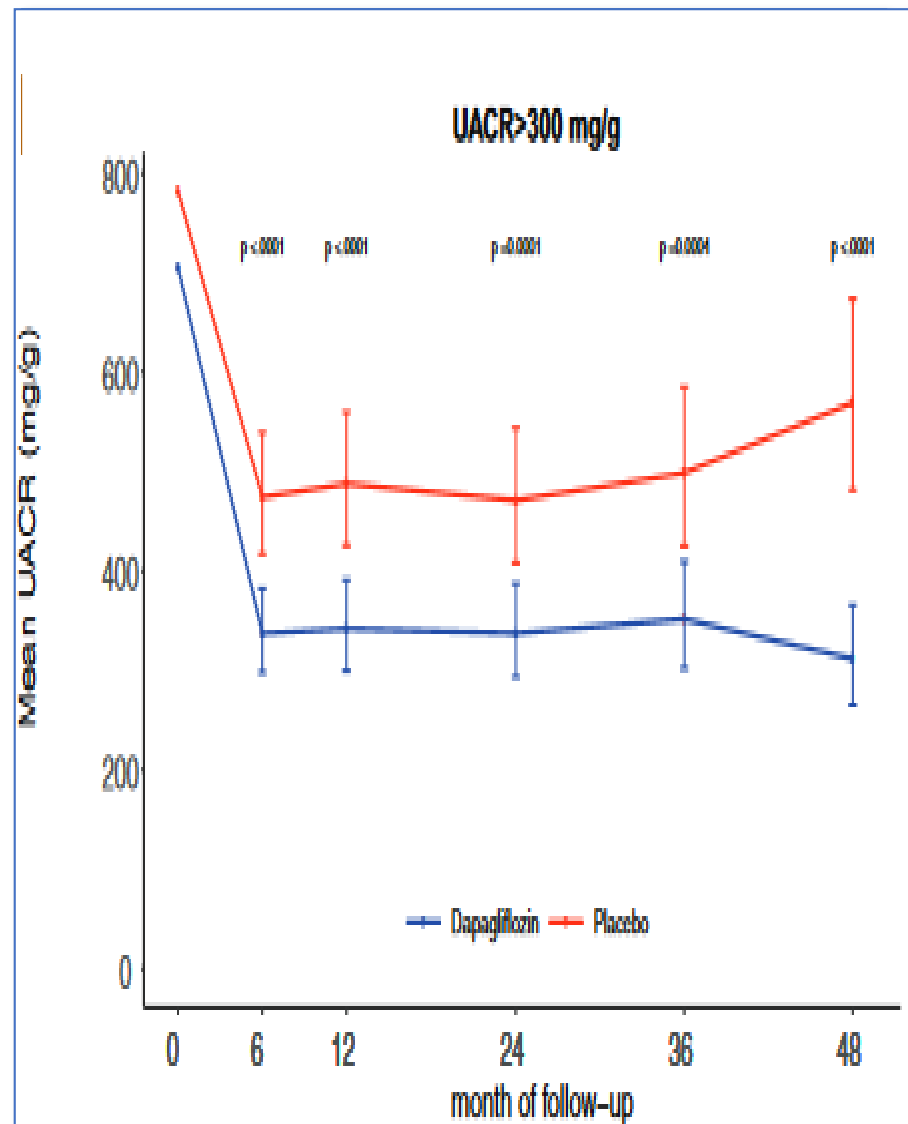
- Decrease of 40% or more eGFR
- eGFR drop to < 60ml/min/1.73m²
- New end-stage renal disease
- Death from renal or CV cause

↓ U_{ACR}

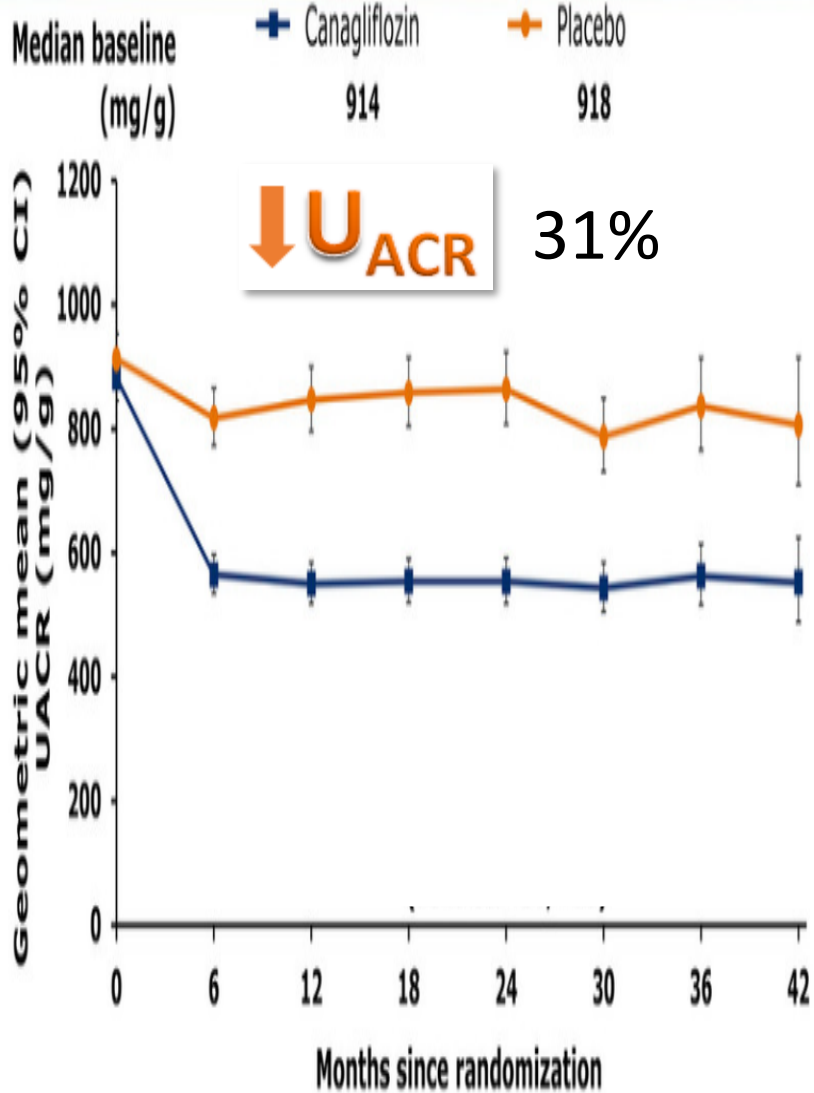
EMPA-REG



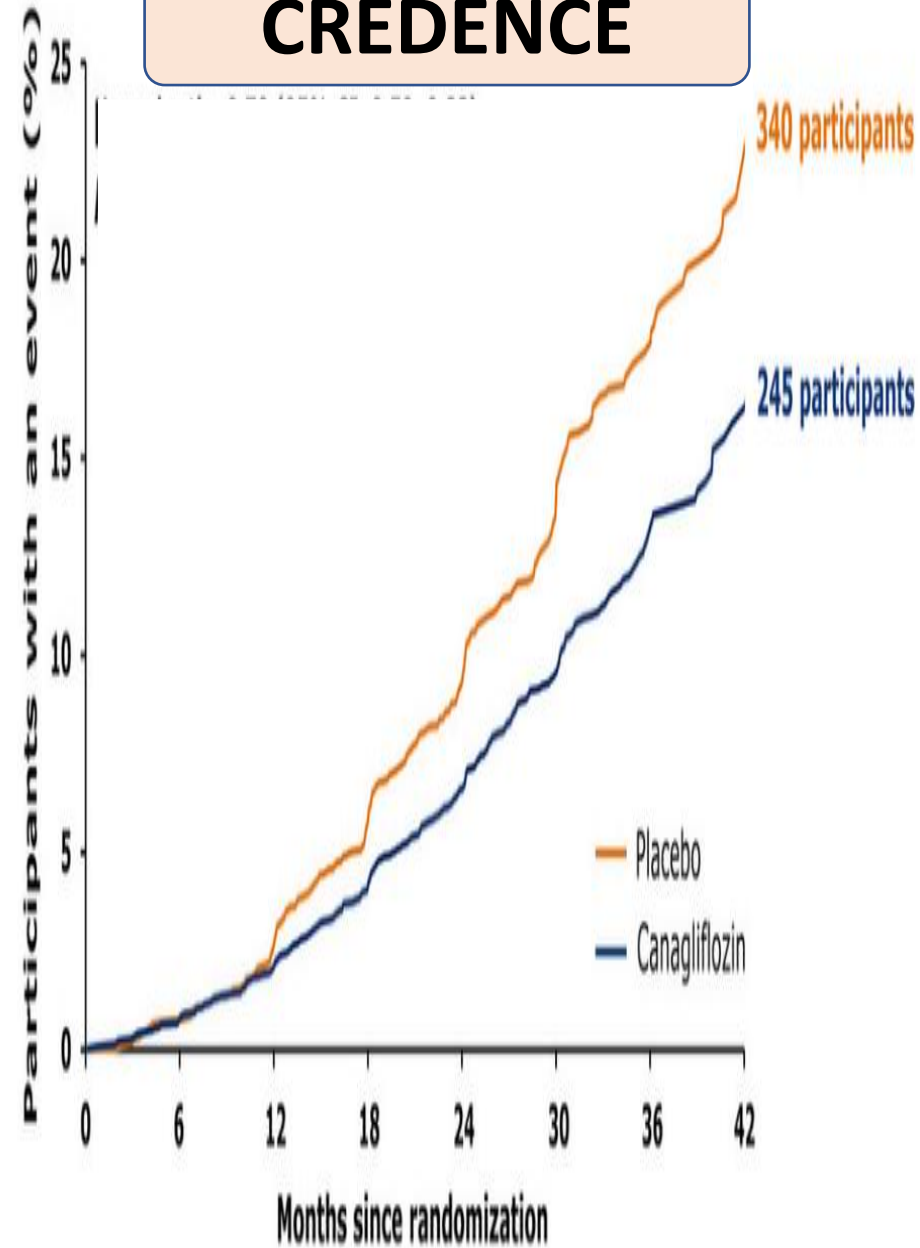
DECLARE-TIMI



Effects on Albuminuria (UACR)

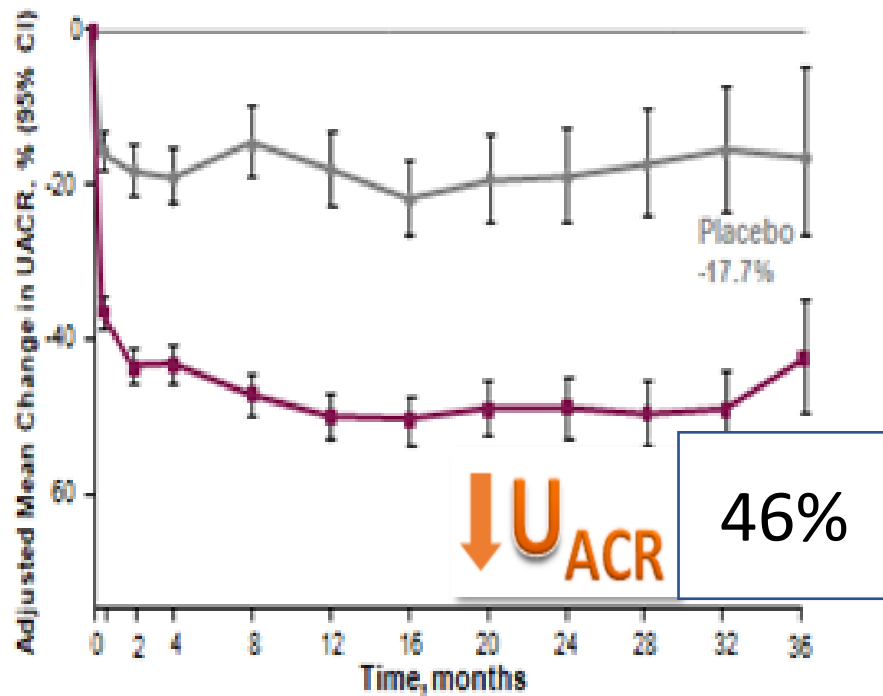


CREDESCENCE



DAPA-CKD

Patients with T2D



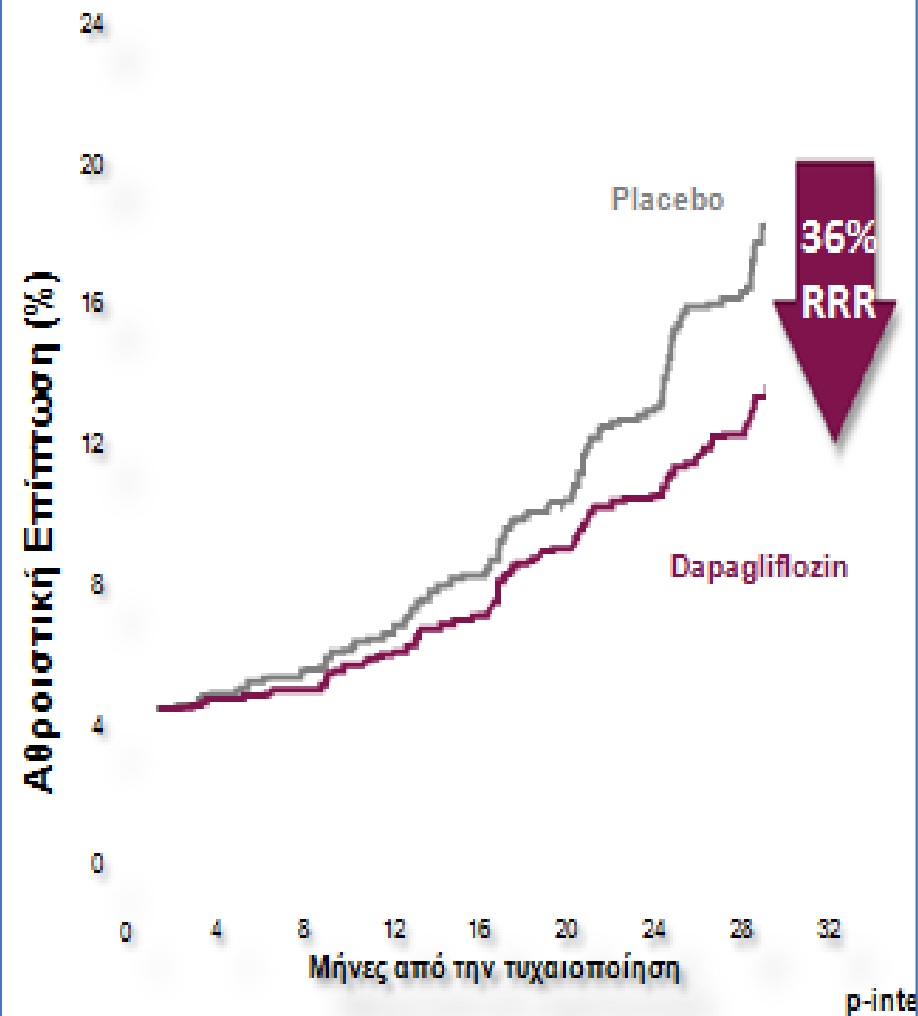
Dapagliflozin 1025 1111 1287 1366
Placebo 1051 1115 1365 1366

Median (IQR) baseline UACR, mg/g

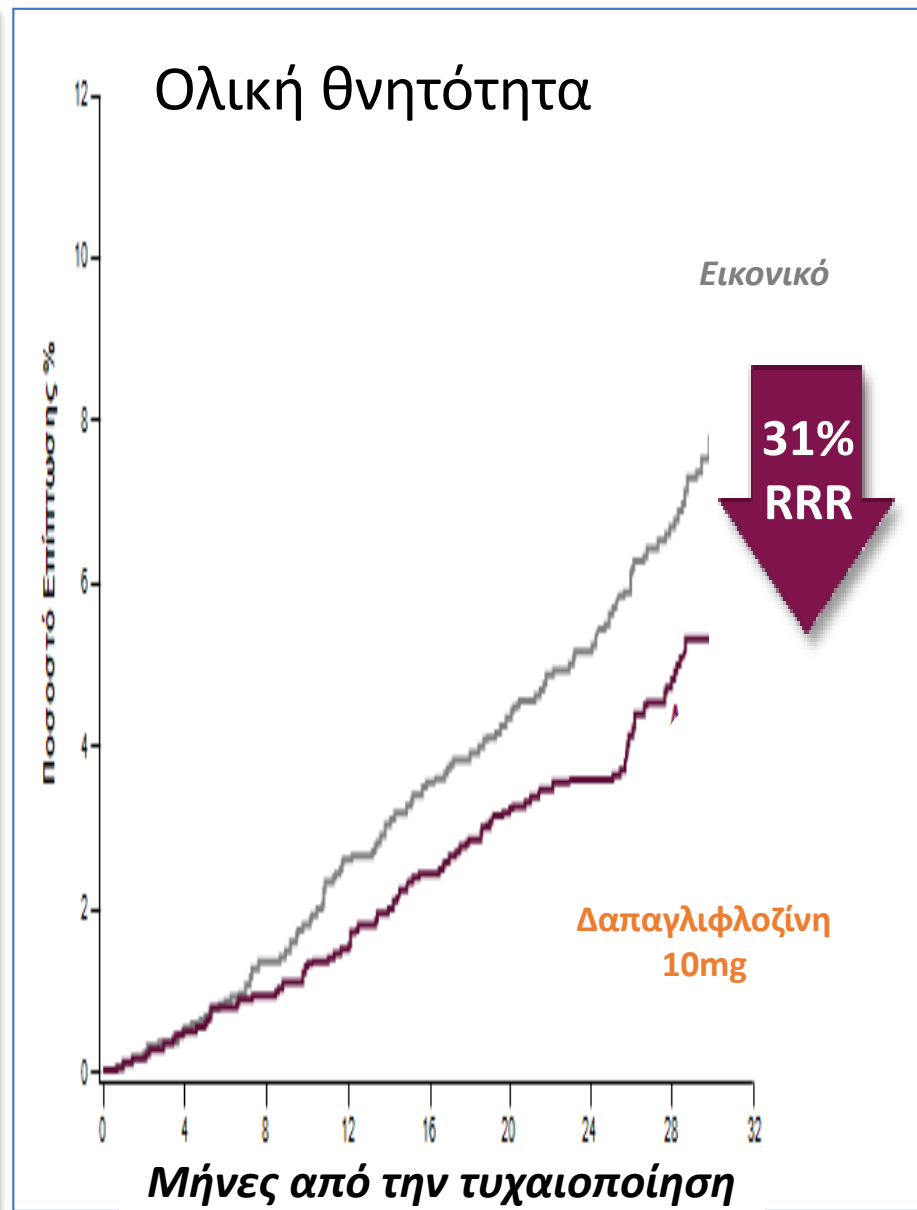
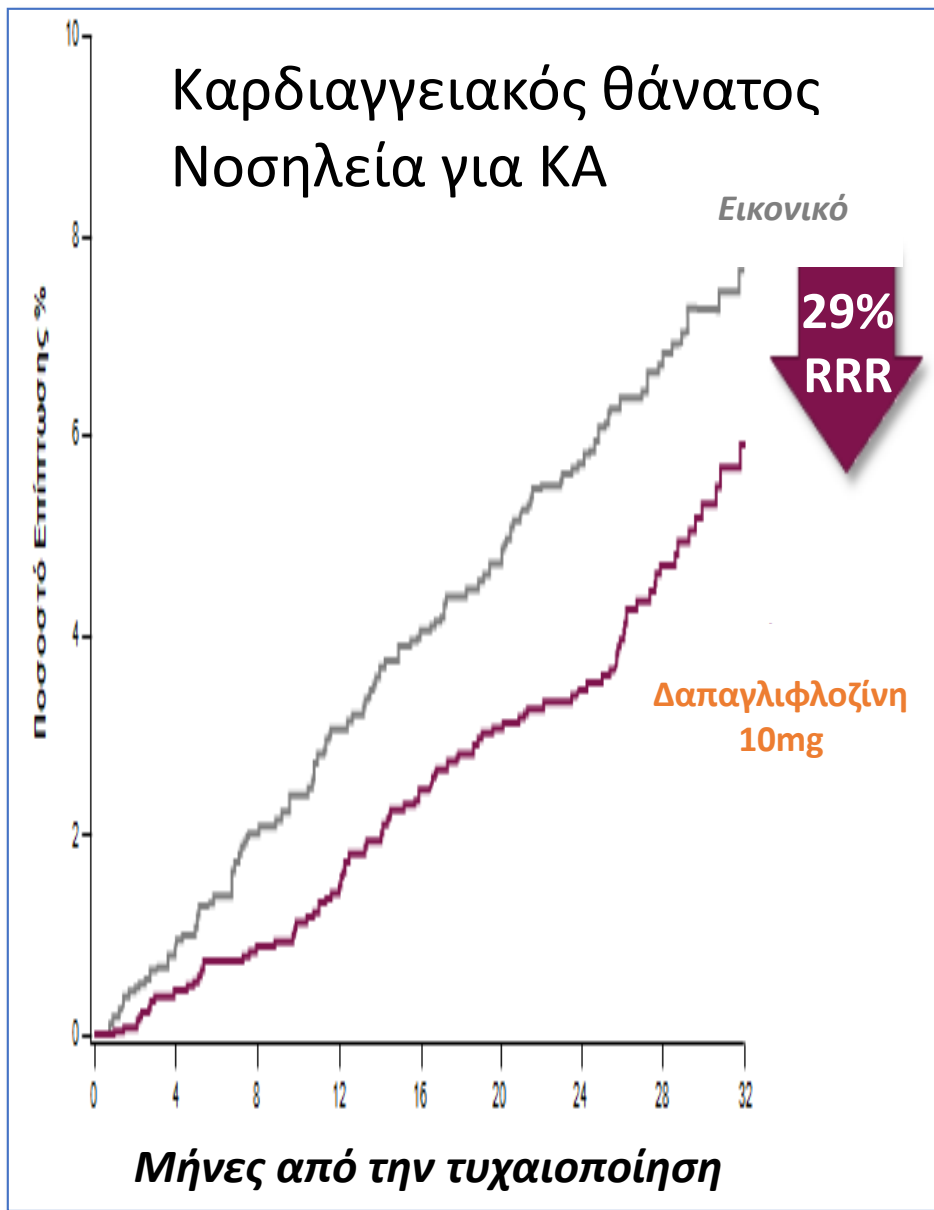
Dapagliflozin: 1025 (473–2111)

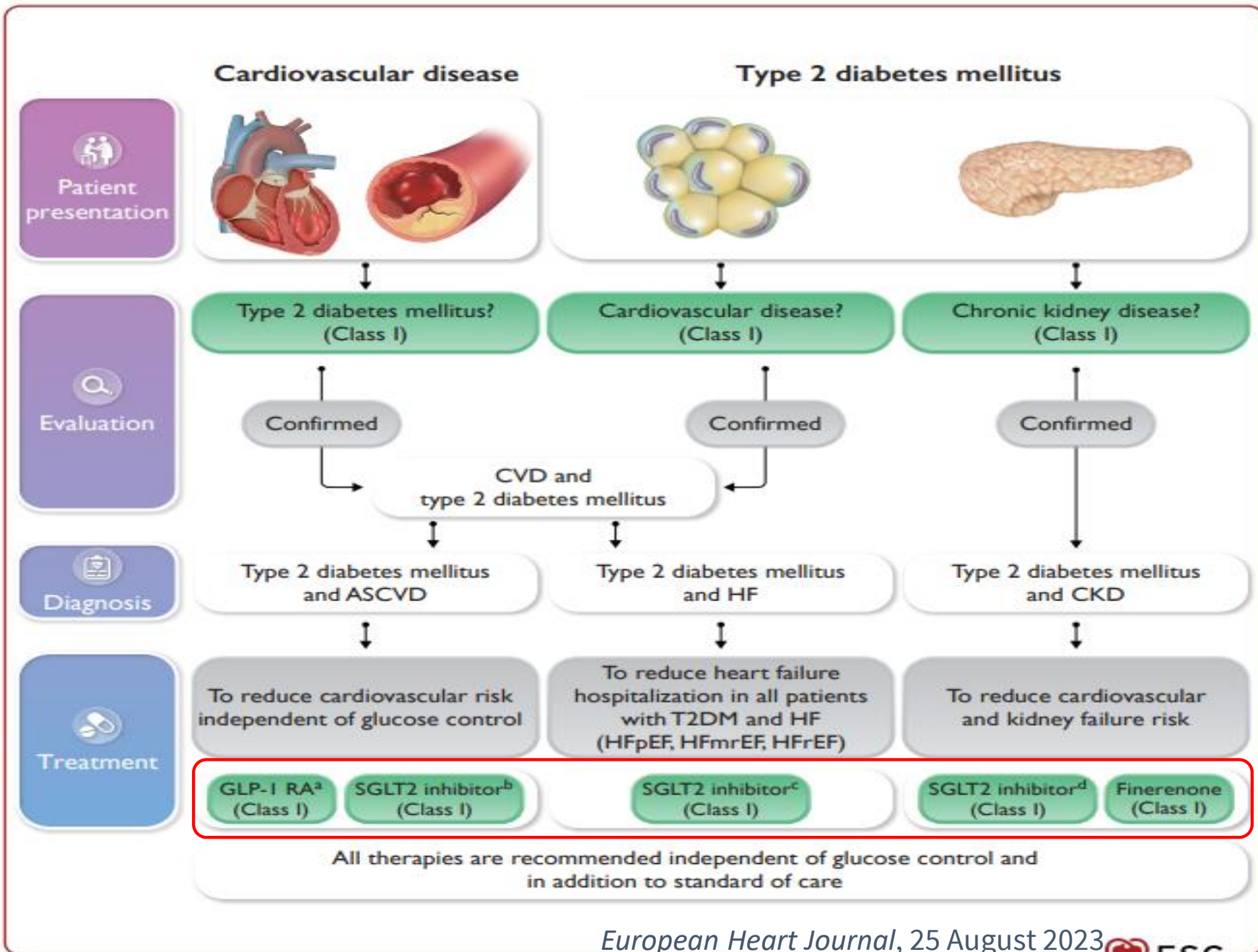
Placebo: 1005 (493–2017)

Ασθενείς με ΣΔτ2



Δευτερεύον καταληκτικό σημείο







MR and 11-BHSD2 expressed

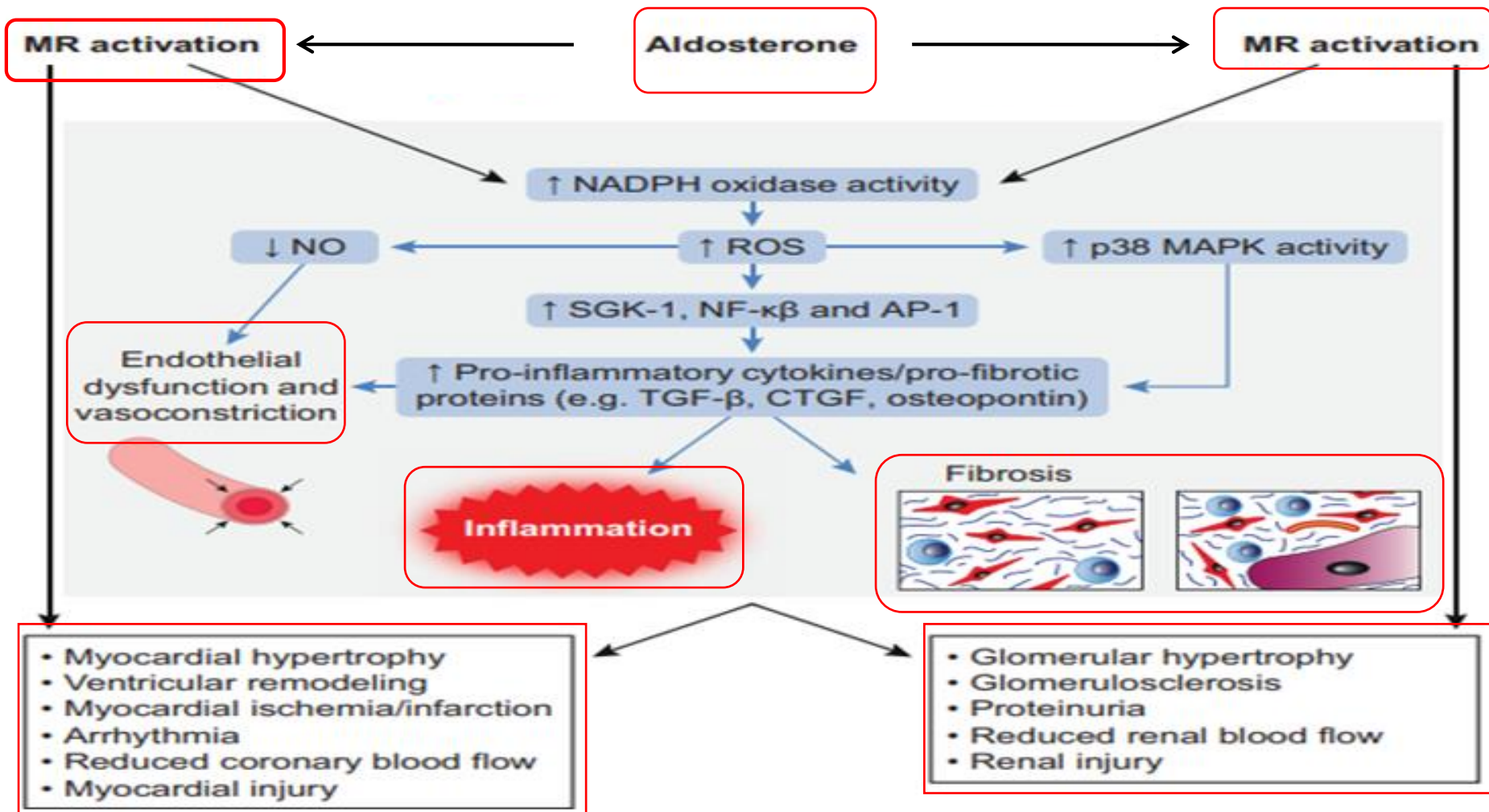
MR expression in disease states

Μηχανισμοί καρδιακής και νεφρικής βλάβης από την περίσσεια αλδοστερόνης



MR and 11-BHSD2 expressed

MR expression in disease states



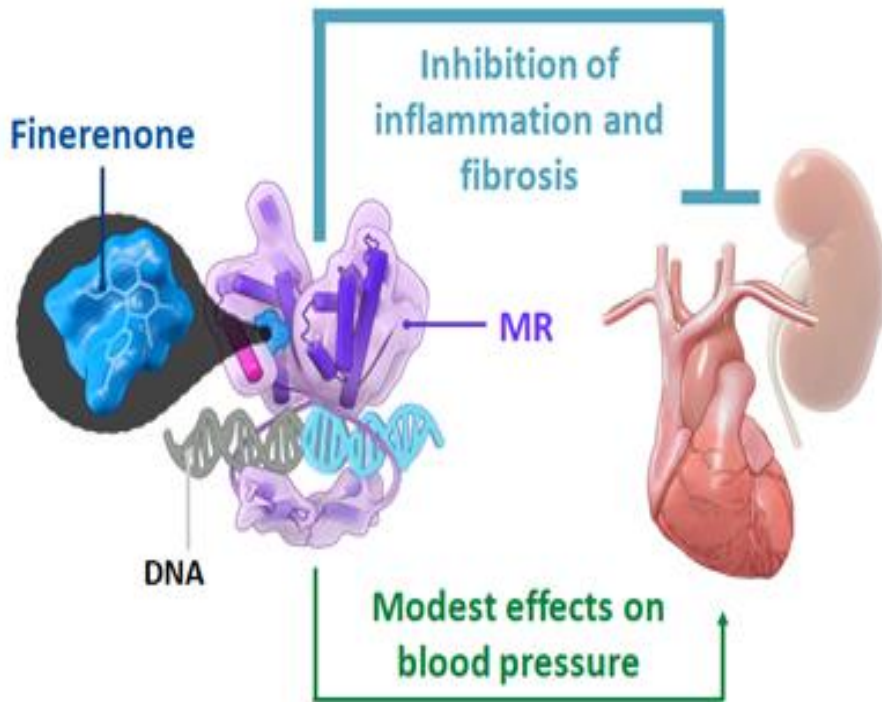
- Myocardial hypertrophy
- Ventricular remodeling
- Myocardial ischemia/infarction
- Arrhythmia
- Reduced coronary blood flow
- Myocardial injury

- Glomerular hypertrophy
- Glomerulosclerosis
- Proteinuria
- Reduced renal blood flow
- Renal injury

Sato et al	24wks	13pts	ΣΔτ2 Uacr 30-300 CLcr >60	Μείωση U_{ACR}
Rossing et al	8wks	21pts	ΣΔτ2 Uacr >300	Μείωση U_{ACR} 33%
Schoedt et al	8wks	20pts	ΣΔτ1 Uacr >300	Μείωση U_{ACR} 30%
Van den Meiracker et al	1year	59pts	ΣΔτ2 Uacr >300	Μείωση U_{ACR} 40%
Saklayen et al	7wks	30pts	ΣΔτ1ή ΣΔτ2 Κάθε επίπεδο αλβουμινου ρίας	Μείωση πρωτεϊνουρίας
Mehdi et al	48wks	81pts	ΣΔτ2 ή ΣΔτ1 Uacr >300	Μείωση U_{ACR} 34%

Finerenone

νέος, μη στεροειδής, εκλεκτικός αναστολέας των υποδοχέων των αλατοκορτικοειδών



Ογκώδες, μη στεροειδές μόριο

Μοναδική κατασκευή
Εκλεκτική, ισχυρή δράση με τον υποδοχέα MR και ρύθμιση της γονιδιακής έκφρασης

Αντιϊνωτική,
αντιπολλαπλασιαστική και
αντιφλεγμονώδη δράση

Finerenone in Chronic Kidney Disease

Phase 3 Clinical Trials



Estimated Enrollment²:

5734 pts

Estimated Study Completion Date:

May 25, 2020



Estimated Enrollment¹:

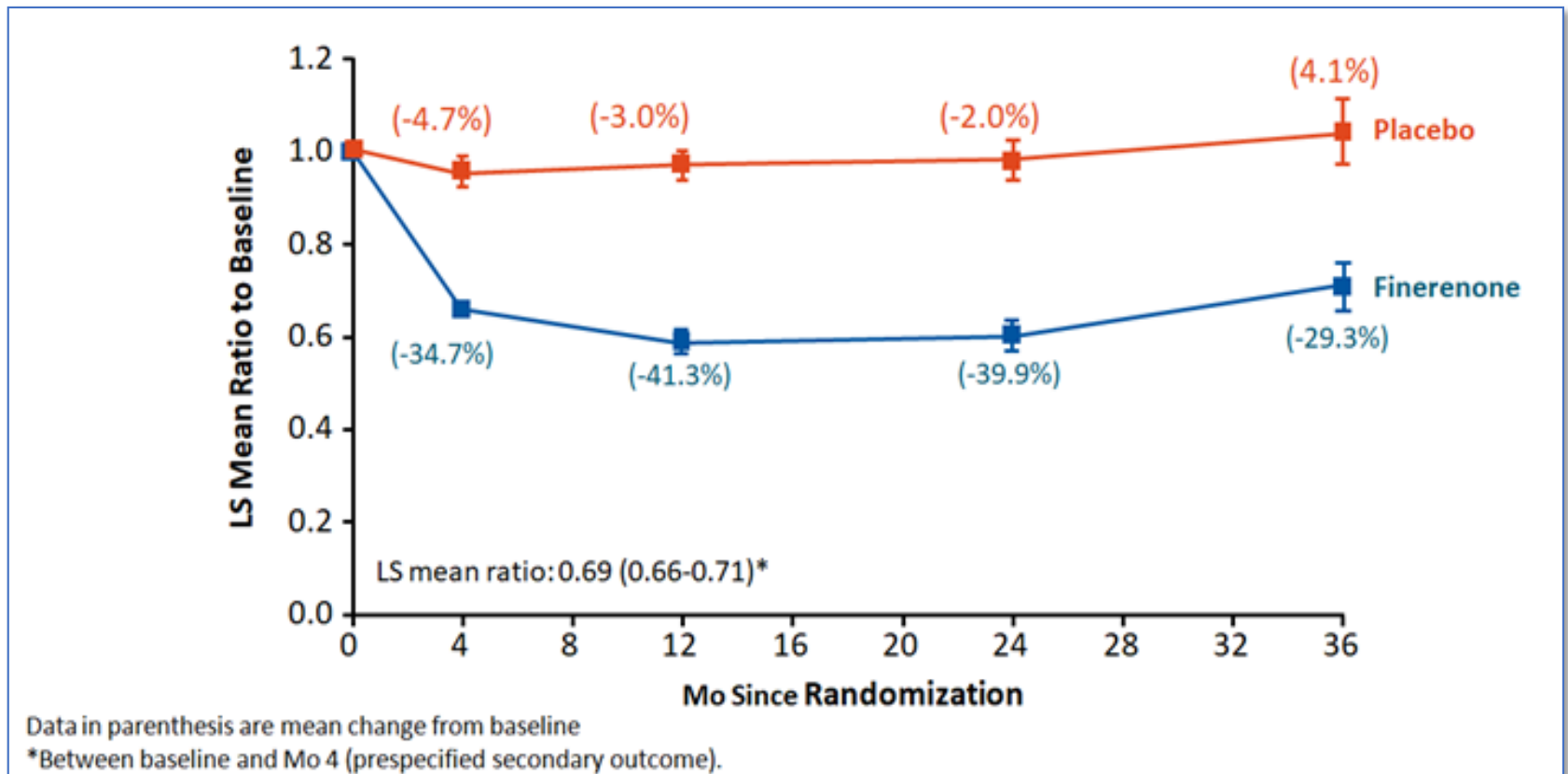
6400 pts

Estimated Study Completion Date:

July 21, 2021

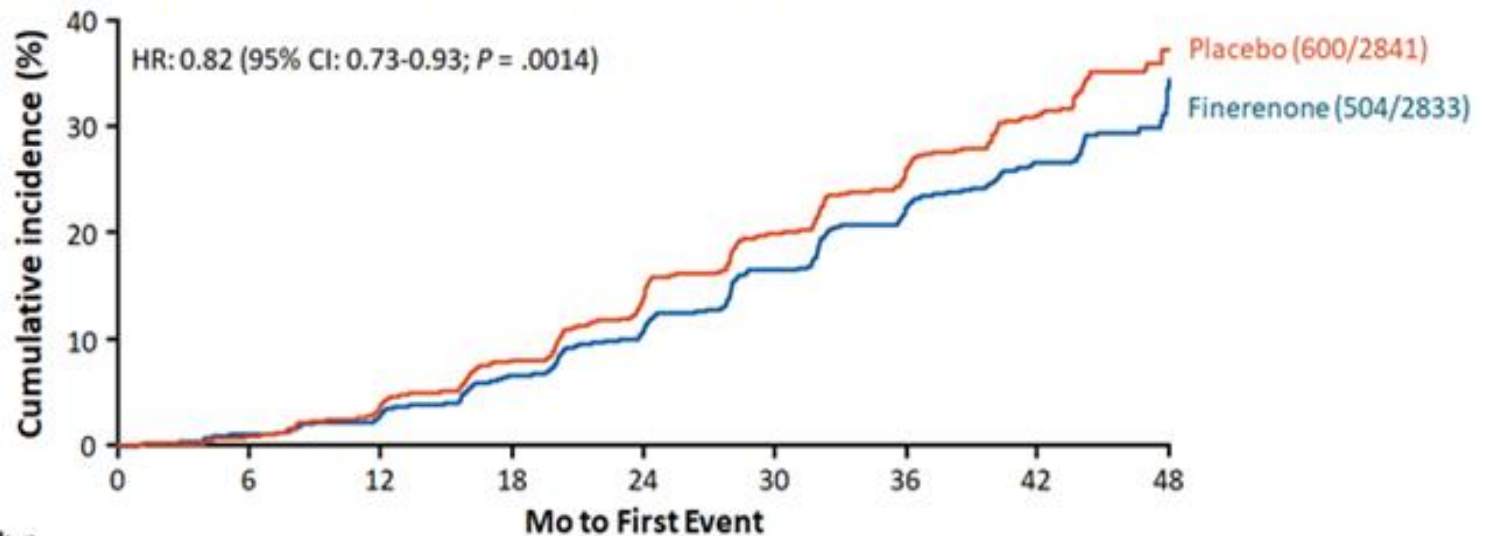
Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes FIDELIO-DKD

Μείωση λευκωματουρίας



Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes FIDELIO-DKD

Kidney failure, * sustained $\geq 40\%$ decrease in eGFR from baseline, or renal death

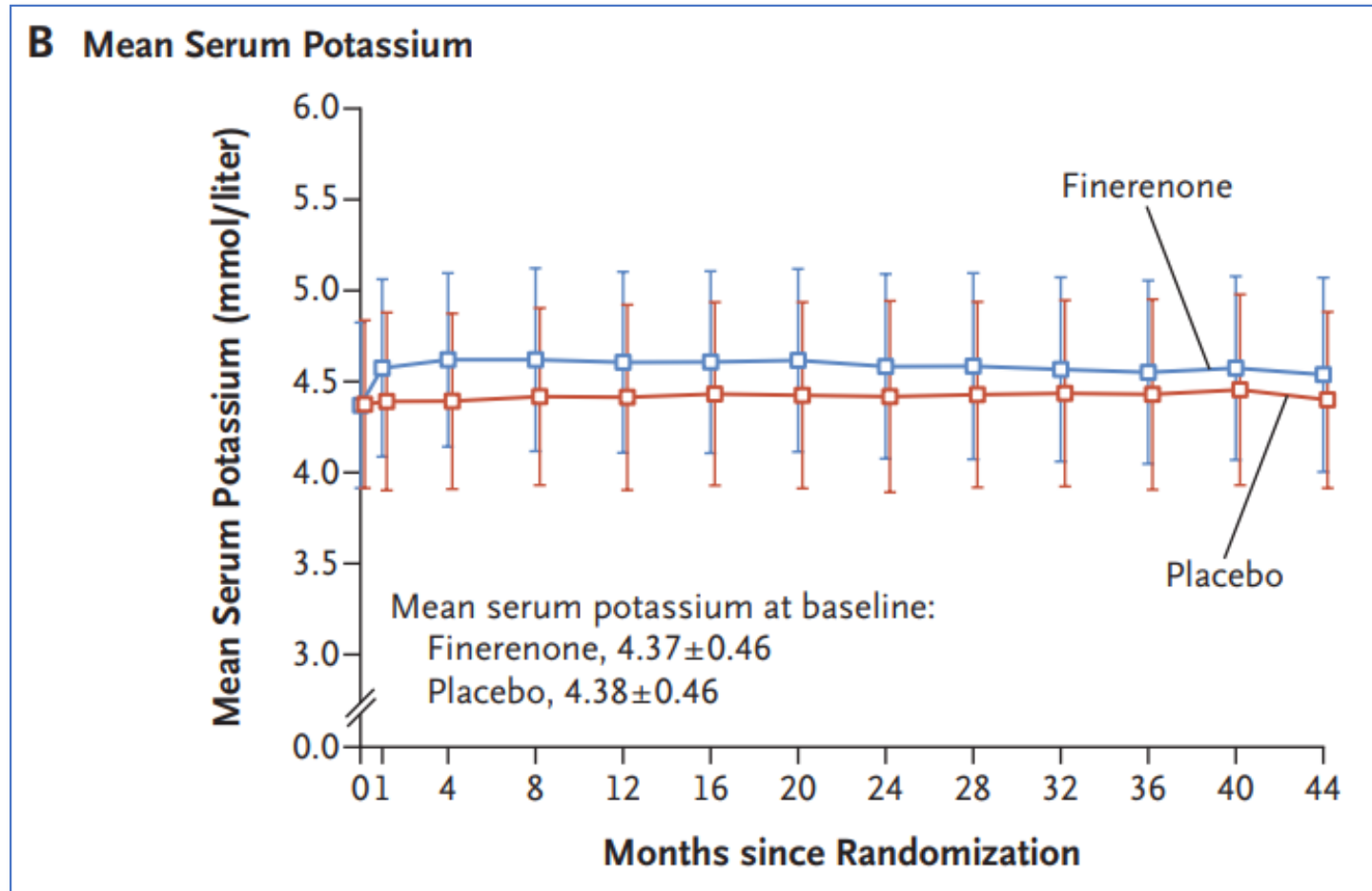


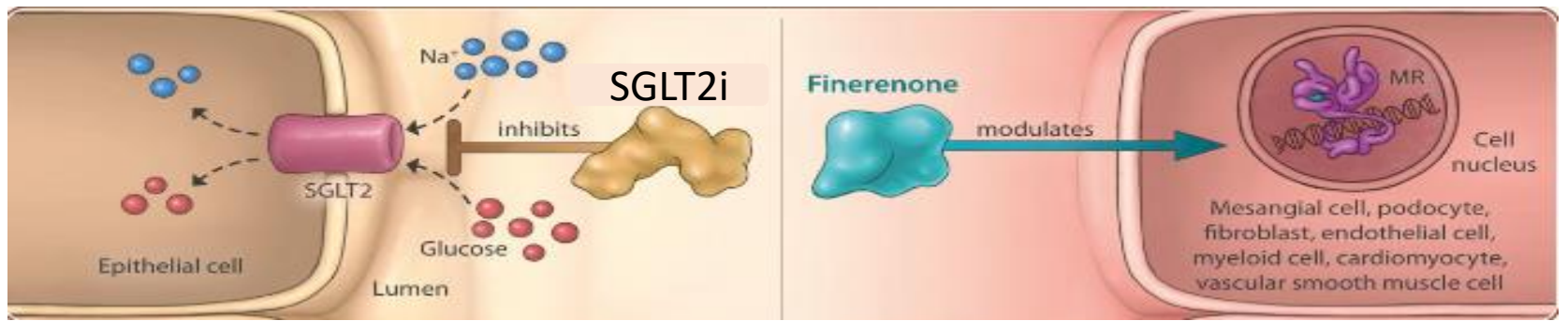
Patients at Risk, n

Placebo	2833	2607	1808	787	83
Finerenone	2841	2586	1758	792	82

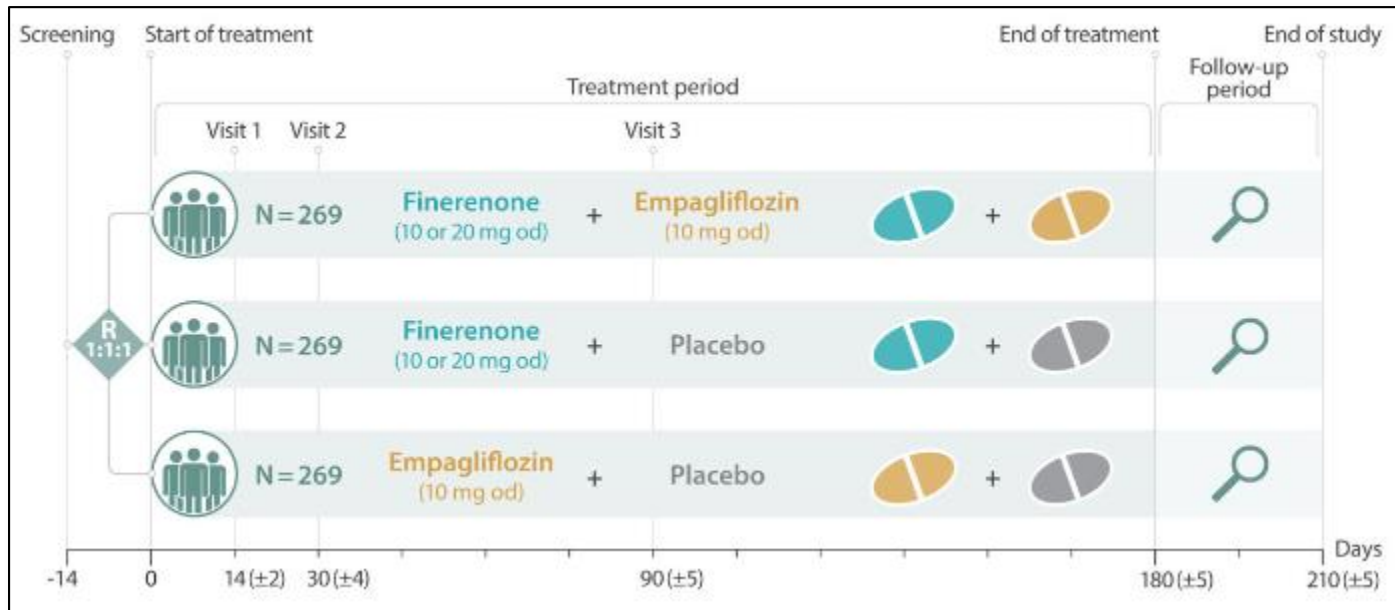
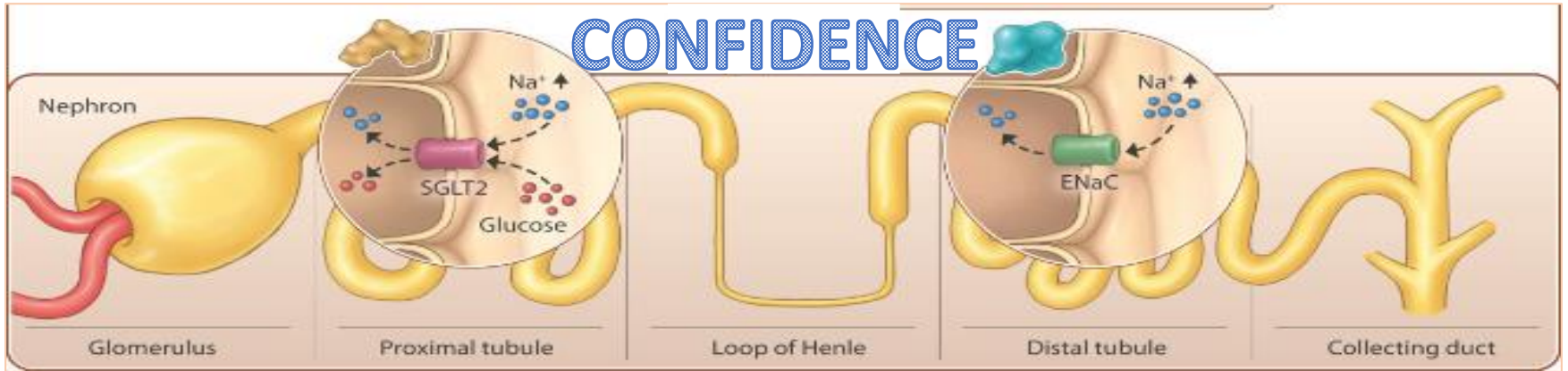
*End-stage kidney disease or an eGFR < 15 mL/min/1.73 m².

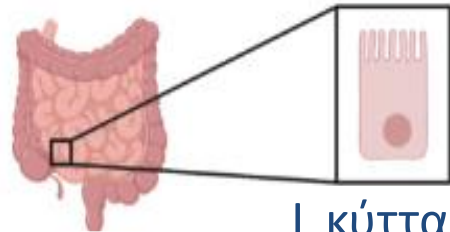
Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes FIDELIO-DKD





CONFIDENCE





Έντερο

L κύτταρα



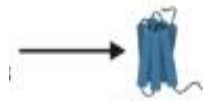
GLP-1



DPP-4

DPP4-I

GLP1-RA



GLP-1 R



πάγκρεας

Αύξηση στην έκκριση ινσουλίνης/μείωση γλουκαγόνου



Στομάχι

Καθυστέρηση στην κένωση του στομάχου



ΚΝΣ

Αίσθημα κορεσμού



Διάμεσος ιστός

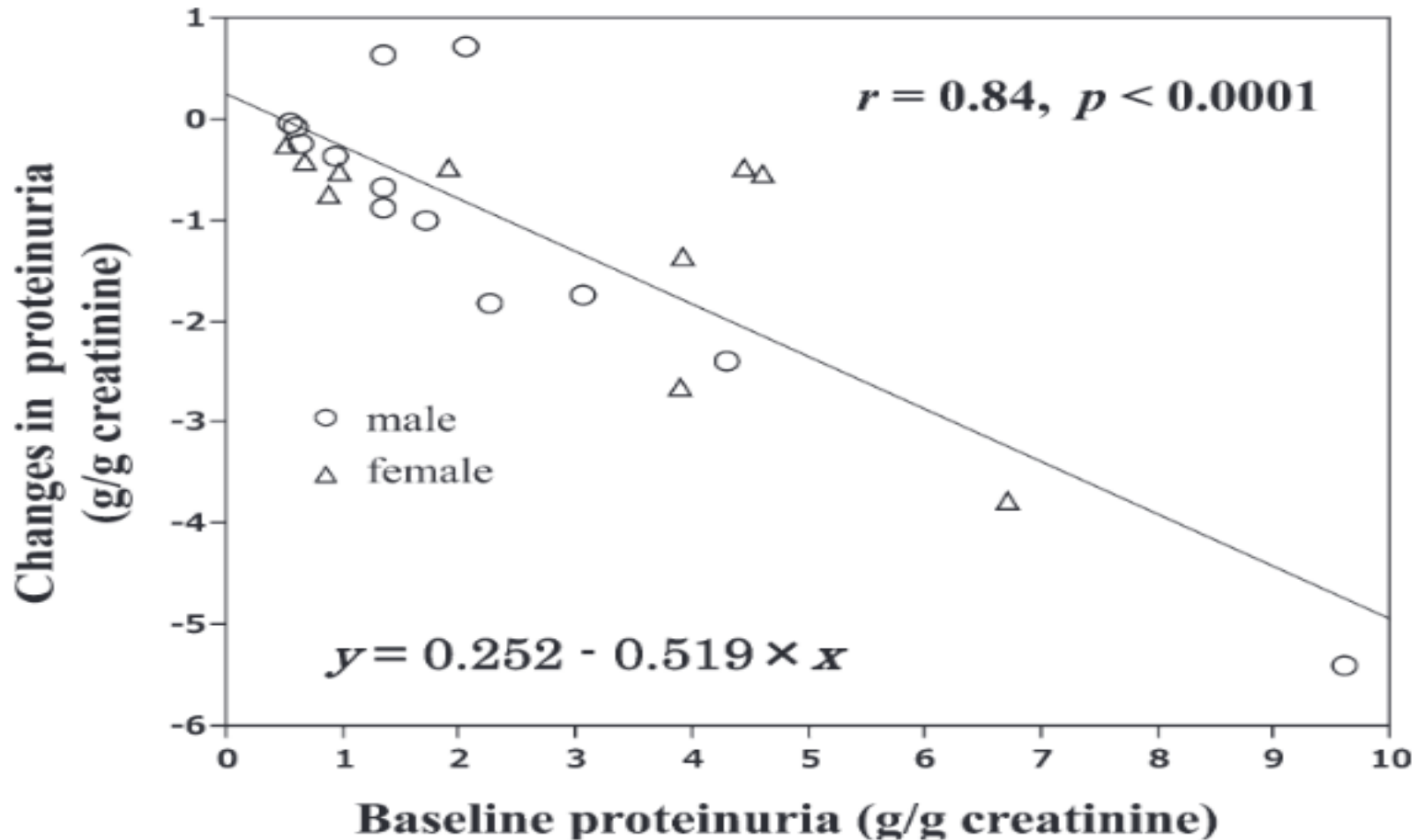
Μείωση φλεγμονής



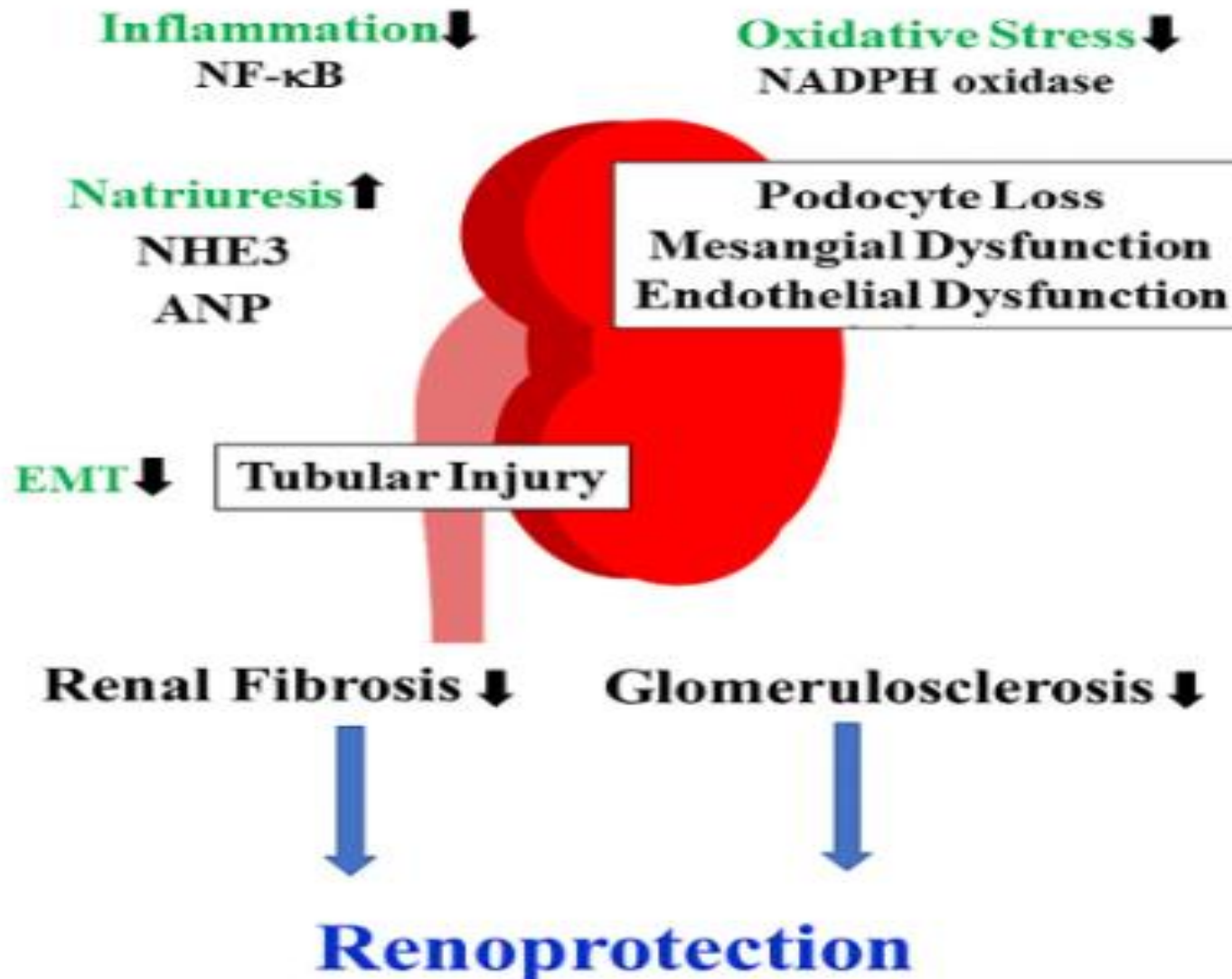
Νεφρός



The Glucagon-Like Peptide-1 Receptor Agonist, Liraglutide, Attenuates the Progression of Overt Diabetic Nephropathy in Type 2 Diabetic Patients

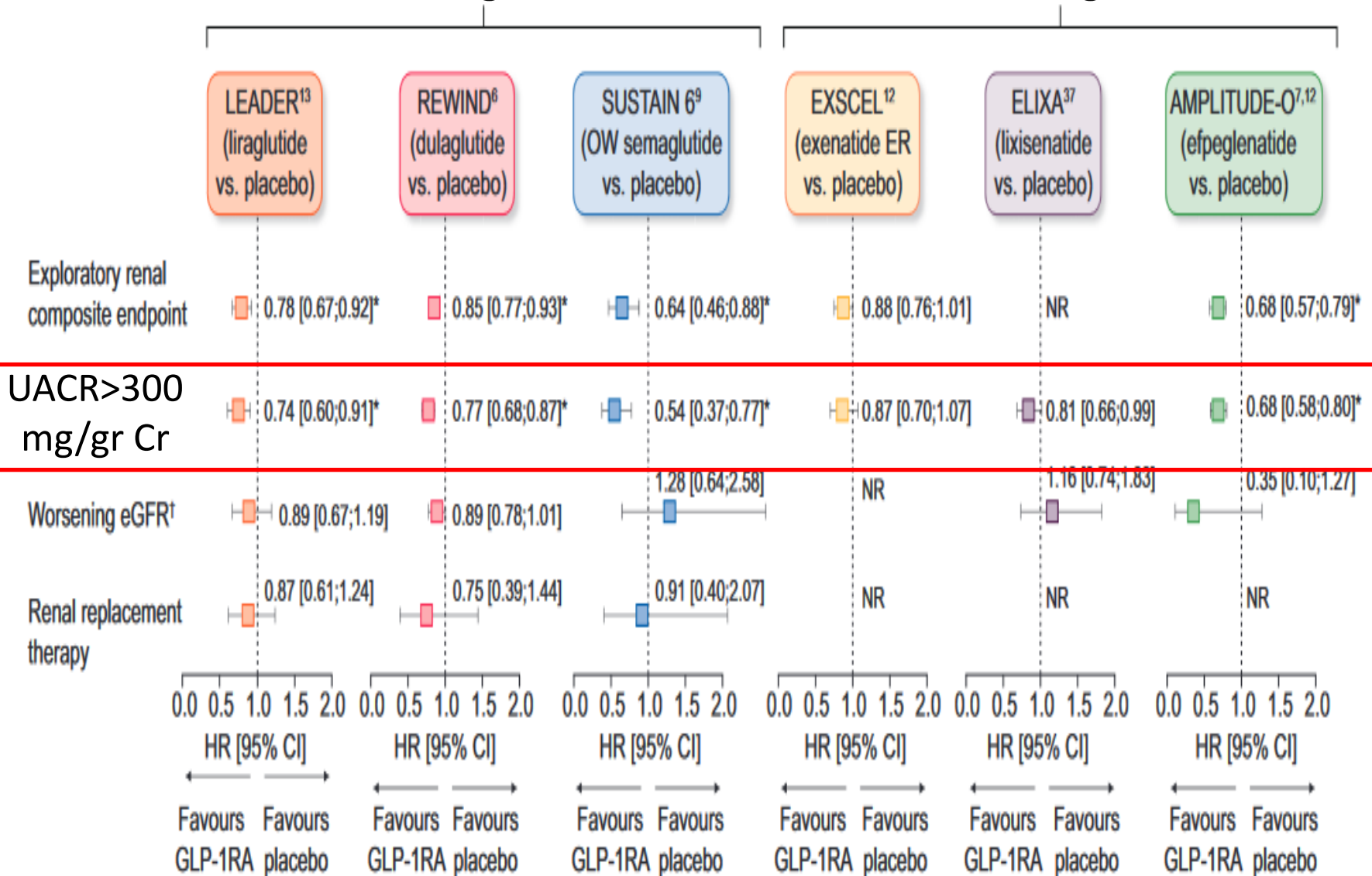


GLP-1



Trials with human GLP-1 based agents

Trials with exendin-4 based agents



The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease

Background

Evidence has emerged of potential kidney-protective effects of GLP-1RAs in people with T2D. FLOW is a dedicated kidney outcomes trial to assess semaglutide in a population with CKD and T2D at high risk of kidney disease progression.

Methods

Participants:

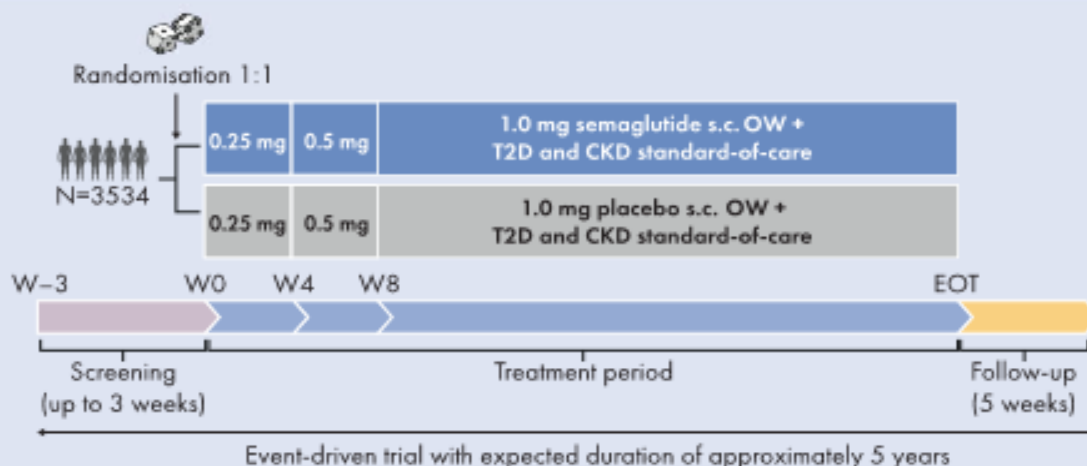


- Adults with T2D
- eGFR ≥ 50 to ≤ 75 ml/min/1.73 m² and UACR > 300 to < 5000 mg/g OR
- eGFR ≥ 25 to < 50 ml/min/1.73 m² and UACR > 100 to < 5000 mg/g

Composite primary endpoint:



- Time to first occurrence of:
- Kidney failure (persistent eGFR < 15 ml/min/1.73 m² or initiation of CKRT);
 - Persistent $\geq 50\%$ reduction in eGFR; or
 - Death from kidney or CV causes



Baseline characteristics



68.2% at very high risk for CKD progression according to KDIGO categorisation, eGFR of 47.0 (15) ml/min/1.73 m²; median UACR of 568 (range: 2–11 852) mg/g



Advanced type 2 diabetes:
Mean age 66.6 years
Mean diabetes duration 17.4 years
Mean HbA_{1c} 7.8%



15.5% receiving SGLT-2is

CKD, chronic kidney disease; CKRT, chronic kidney replacement therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOT, end of treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; OW, once weekly; s.c., subcutaneous; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio; W, week.

Conclusion

FLOW will evaluate the effect of semaglutide on kidney outcomes in participants with CKD and T2D, and is expected to complete in late 2024.

GLP-1-independent



**DPP-4
inhibitors**



GLP-1-dependent

TGF- β
• EMT \downarrow
• ECM production \downarrow
• NF- κ B \downarrow

SDF-1
• Tissue repair \uparrow
• Natriuresis \uparrow

micro RNAs
miR-29
• Integrin β \downarrow
• EndMT \downarrow
miR-200a
• Nrf2/Keap1 \uparrow



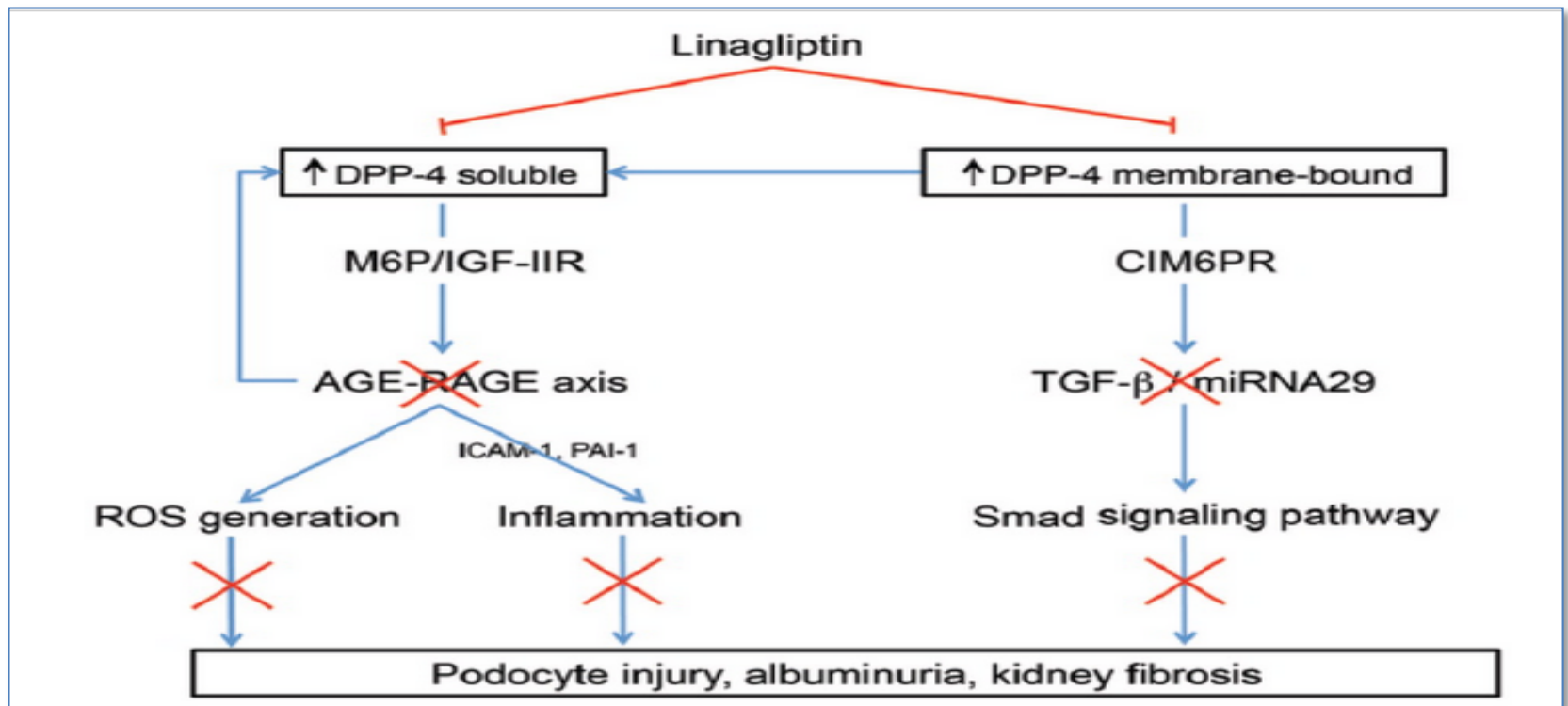
Oxidative Stress
Inflammation
Apoptosis
Fibrosis



GLP-1 receptor
• Hyperglycemia \downarrow
• NF- κ B \downarrow
• PKC- β \downarrow
• ROS generation \downarrow
• Cytokines \downarrow
• Chemokines \downarrow

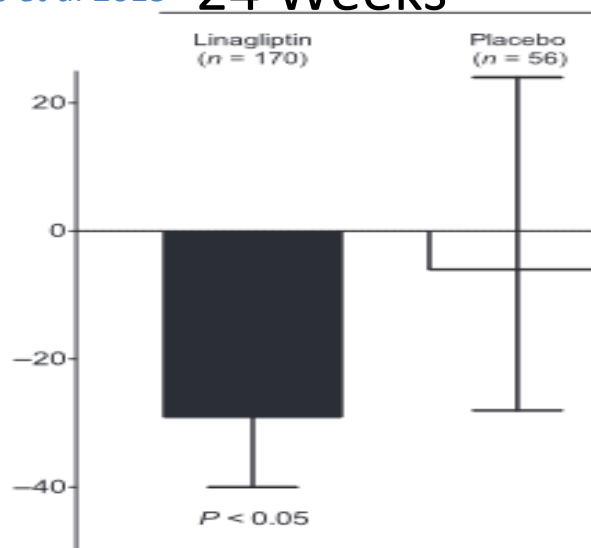


Renoprotection

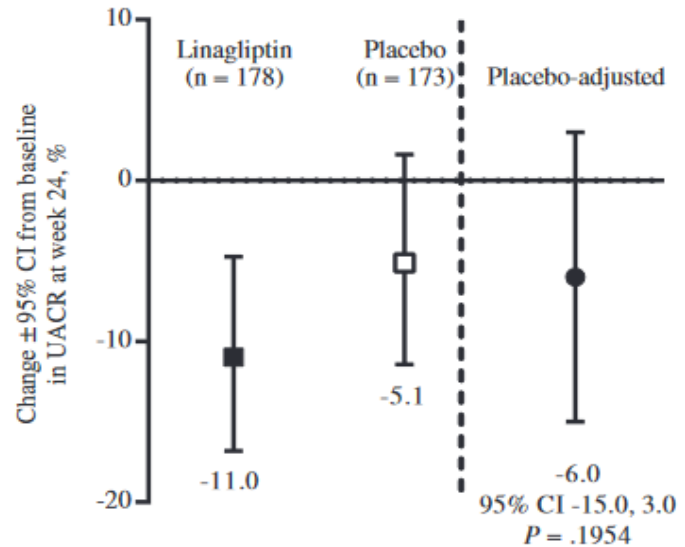


Groop et al 2013 **24 Weeks**

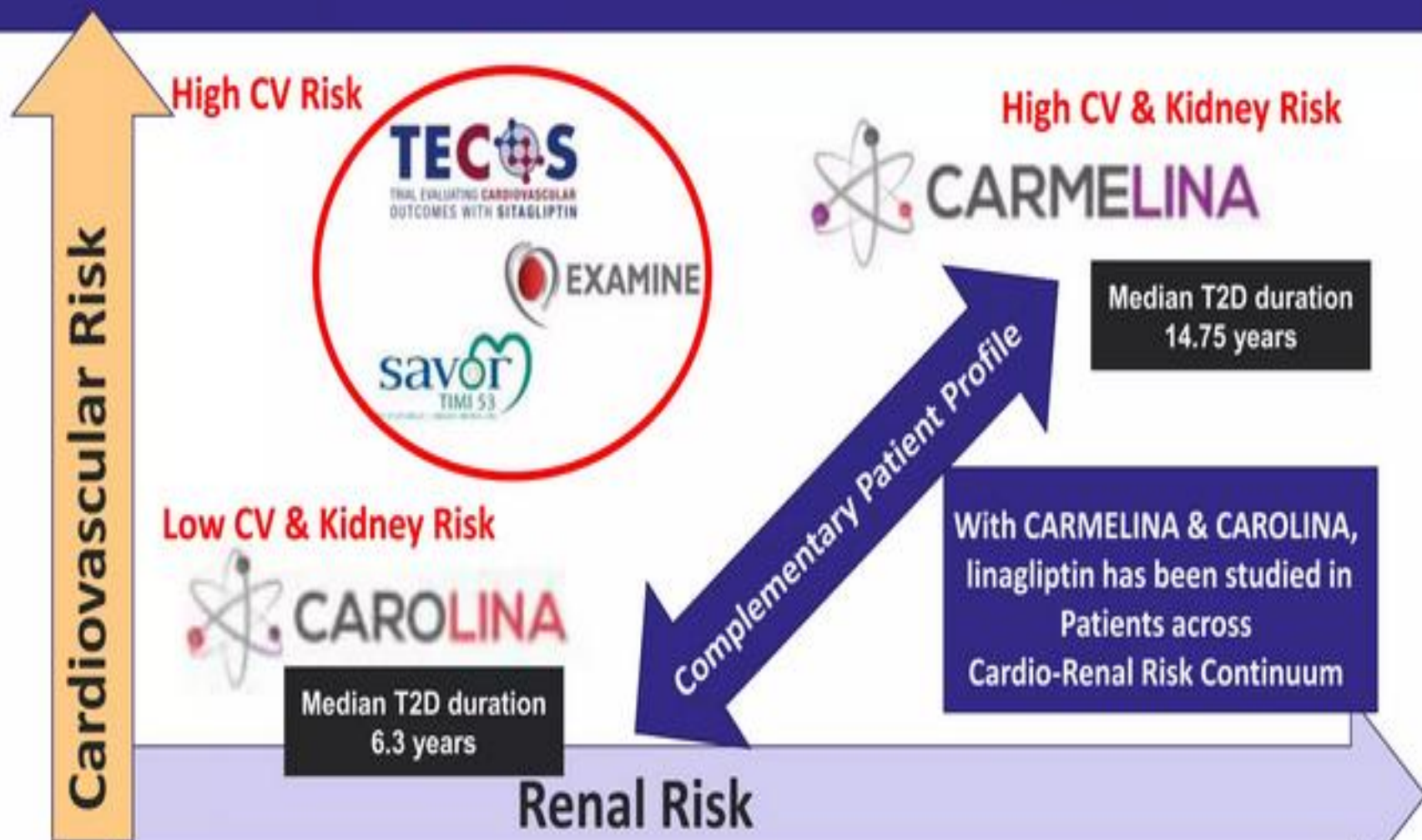
Change in Uacr



A



Baseline Characteristics of DPP-4i CVOTs

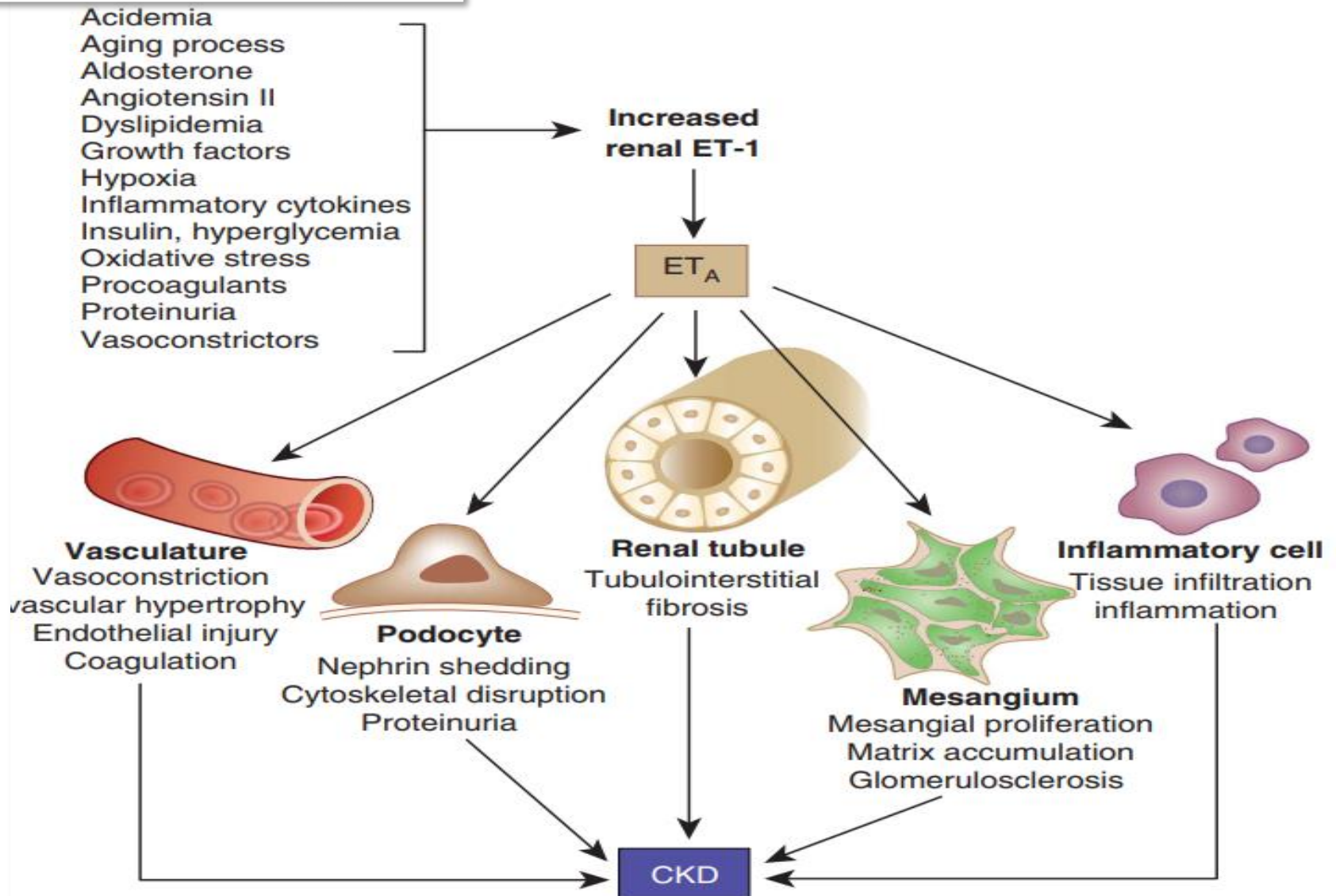


Effects of DPP4 Inhibitors on Renal Outcomes in Diabetes Mellitus: A Systematic Review and Meta-Analysis

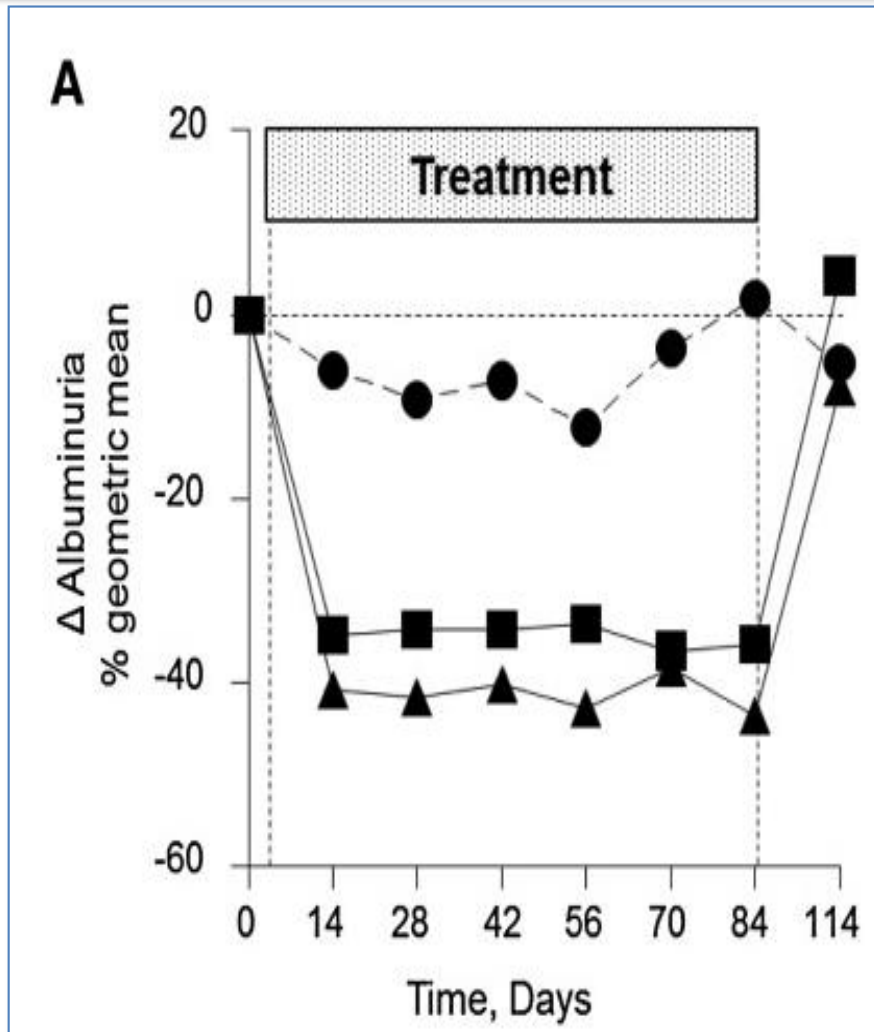
Table 2: Summary of findings of the results

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Plain language summary
	Risk with intervention	Risk with comparator				
A: Intervention: DPP4 inhibitors, Comparator: Placebo						
Μεταβολή GFR 24wk	MD 1.53 lower (3.34 lower to 0.29 higher)	The mean changes in eGFR at 24 weeks from baseline was 0	-	652 (3 RCTs)	⊕⊕○○ LOW ^{b,c}	We are uncertain of the effect of DPP4I on changes of eGFR at 24 weeks from baseline
Μεταβολή GFR 52wk	MD 0.08 higher (3.4 lower to 3.55 higher)	The mean changes in eGFR at 52 weeks was 0	-	14661 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c,d,e}	We are very uncertain of the effect of DPP4I on changes of eGFR at 52 weeks from baseline
Adverse events within 1 year	465 per 1,000	500 per 1,000	RR 0.93 (0.80 to 1.08)	700 (3 RCTs)	⊕⊕⊕○ MODERATE ^b	Probably there is little or no difference in adverse events within
Progression of UACR >1year	208 per 1000	236 per 1000	RR 0.88 (0,80 to 0,96)	14741 2RCTs	⊕⊕⊕⊕ HIGH	Καθυστερούν την εξέλιξη της UACR
Adverse events – long-term	483 per 1,000 (478 to 493)	493 per 1,000	RR 0.98 (0.97 to 1.00)	38011 (3 RCTs)	⊕⊕○○ LOW ^{b,c}	There may be little or no difference in adverse events
Θνητότητα	70 per 1,000 (65 to 76)	68 per 1,000	RR 1.04 (0.96 to 1.12)	38142 (3 RCTs)	⊕○○○ VERY LOW ^{b,c,f}	We are very uncertain of the effect of DPP4I on all-cause mortality

Endothelin Antagonists

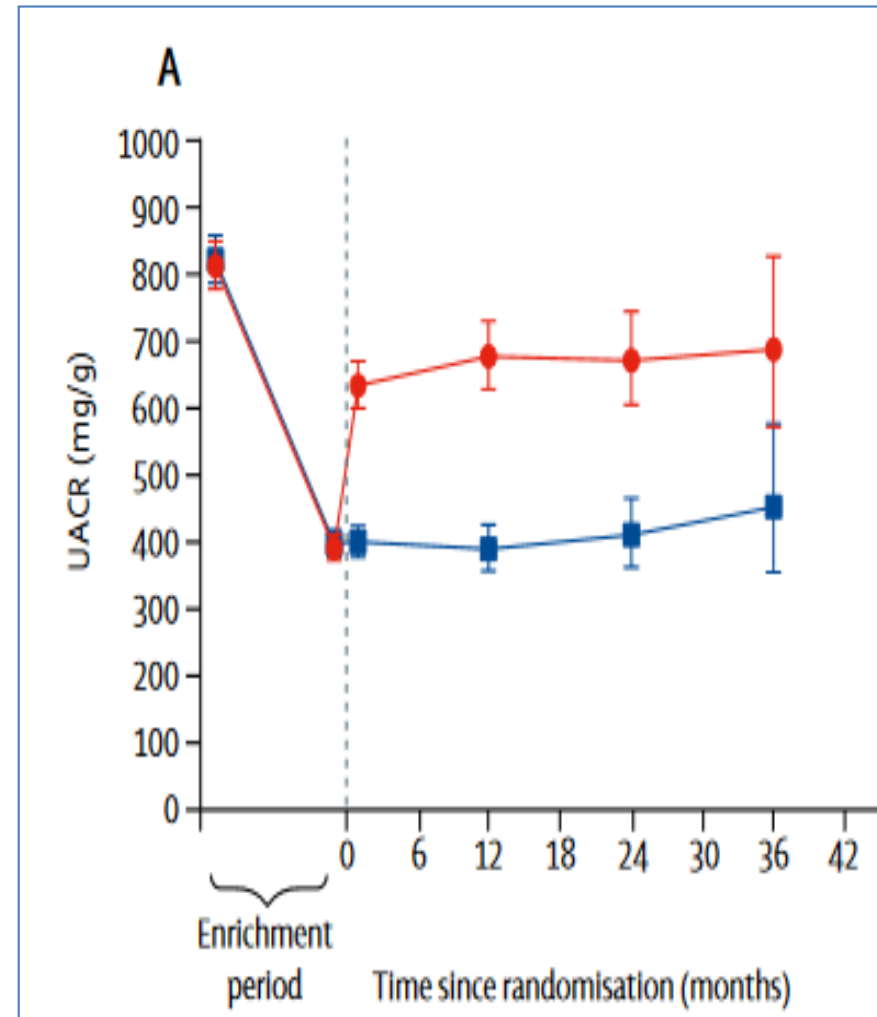


*The Endothelin Antagonist Atrasentan
Lowers Residual Albuminuria in Patients
with Type 2 Diabetic Nephropathy*



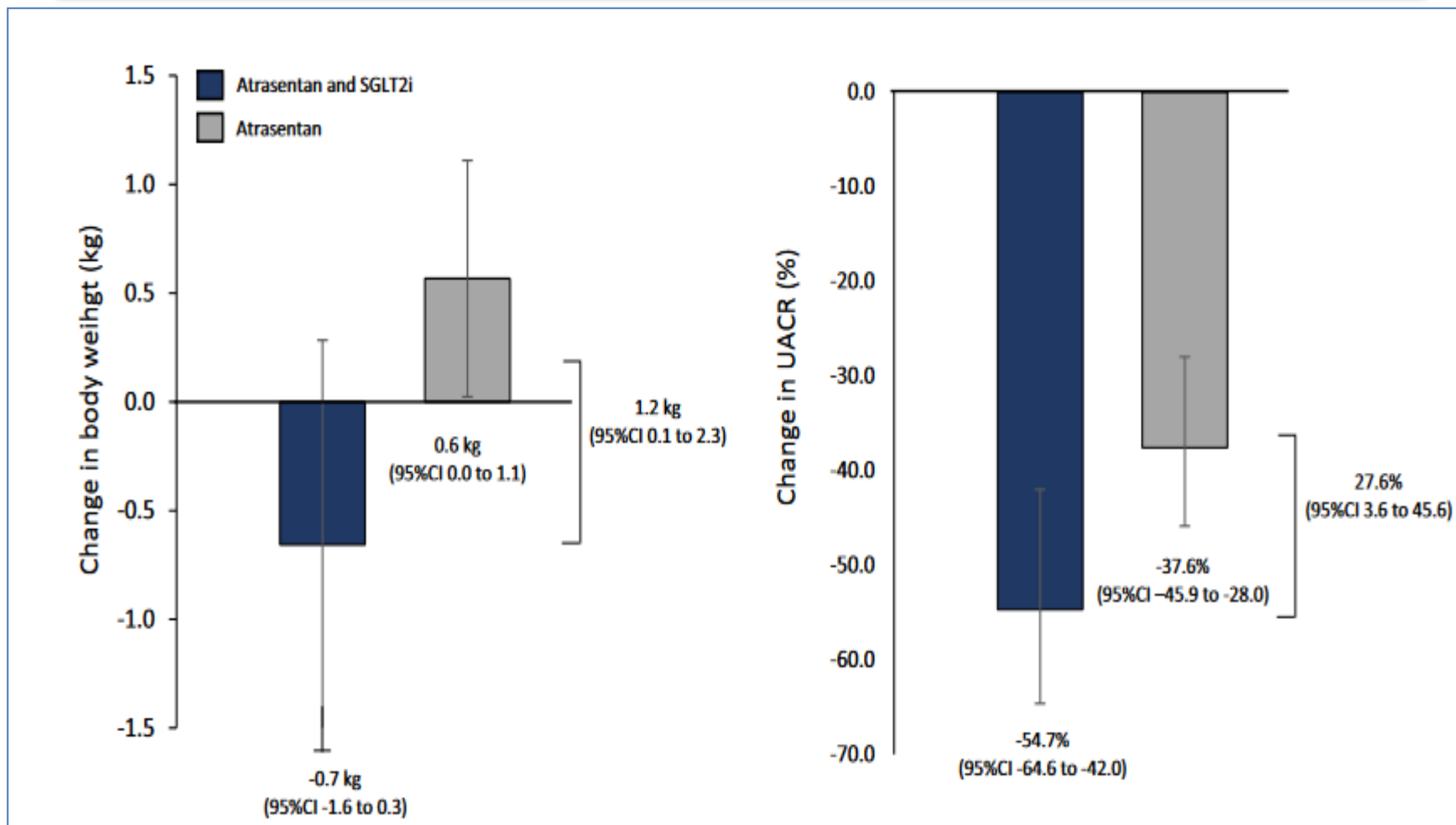
De Zeeuw et al JASN 2014

SONAR TRIAL



Heerspink et al The Lancet 2019

New insights from SONAR indicate adding sodium glucose co-transporter 2 inhibitors to an endothelin receptor antagonist mitigates fluid retention and enhances albuminuria reduction



Pentoxifylline

PREDIAN TRIAL

